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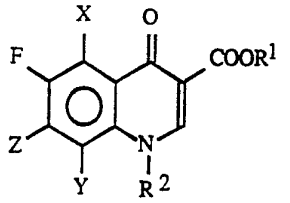
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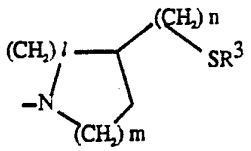
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**(54) Title:** A NOVEL QUINOLONE CARBOXYLIC ACID DERIVATIVE




(I)




(II)

**(57) Abstract**

The present invention relates to a novel quinolone carboxylic acid derivative of structural formula (I) and pharmaceutically acceptable salts thereof. These compounds also have a potent activity against both Gram-positive bacteria and Gram-negative bacteria; wherein $R^1$ is hydrogen or alkyl group having one to six carbon atoms, $R^2$ is alkyl group having one to four carbon atoms, haloalkyl group having one to four carbon atoms, cycloalkyl group having three to six carbon atoms, alkenyl group having two to four carbon atoms, or phenyl group which is optionally mono or disubstituted by fluorine atoms, X is hydrogen, amino, or halogen, Y is hydrogen or halogen, Z is (II) (wherein *l* is 1 or 2, m is 0, 1, or 2, and n is 0 or 1, $R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkyl group having one to three caroon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group).

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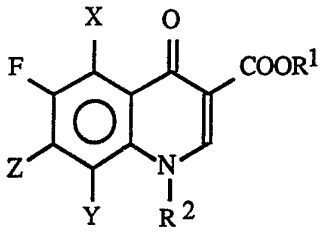
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# A NOVEL QUINOLONE CARBOXYLIC ACID DERIVATIVE

## BACKGROUND AND SUMMARY OF THE INVENTION

The present invention relates to a novel quinolone carboxylic acid derivatives of the following structural formula(I) and pharmaceutically acceptable salts thereof. These compounds also have a potent activity against both Gram-positive bacteria and Gram-negative bacteria :



( I )

Wherein,

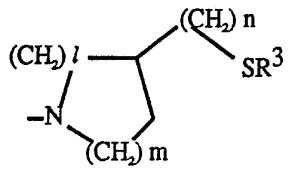
$R^1$ is hydrogen or alkyl group having one to six carbon atoms,

$R^2$ is alkyl group having one to four carbon atoms, haloalkyl group having one to four carbon atoms, cycloalkyl group having three to six carbon atoms, alkenyl group having two to four carbon atoms, or phenyl group which is optionally mono or disubstituted by fluorine atoms,

X is hydrogen, amino, or halogen,

Y is hydrogen or halogen,

Z is



( wherein

$l$ is 1 or 2, m is 0, 1, or 2, and n is 0 or 1,

$R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkylgroup

having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group).

In general, the antibacterial activity of quinolone compounds depends greatly upon the kinds of substituent groups at the 7 position. Quinolone antibacterial compounds are known with a 7-thiomorpholine substituent group having antibacterial properties(J. Med. Chem., V. 29, 394(1986)). But, there is no report on clinical use thereof yet.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel quinolone carboxylic acid derivatives having four, five, or six membered cyclic amines containing thio or thiomethyl group at the C-7 position. These compounds show a very excellent activity against Gram-positive bacteria including S. aureus. as well as against Gram-negative bacteria and a low toxicity.

Therefore, the purpose of the present invention is to provide a novel quinolone carboxylic acid derivatives and pharmaceutically acceptable salts thereof having excellent properties, for example, potent antibacterial activities against Gram-positive bacteria including S. aureus as well as against Gram-negative bacteria and high safety. Another the purpose of the present invention is to provide a process for producing a novel quinolone carboxylic acid derivatives and pharmaceutically acceptable salts thereof.

Detailed description of the present invention is as follows. The present invention relates to a novel quinolone carboxylic acid derivatives of the above described structural formula(I).

The preferred examples of the group represented by Z in the above described structural formula(I) are as follows :

3-mercaptopyrrolidinyl,

3- methylthiopyrrolidinyl,
3-ethylthiopyrrolidinyl,
3-propylthiopyrrolidinyl,
3-isopropylthiopyrrolidinyl,
3-mercaptomethylpyrrolidinyl,
3-methylthiomethylpyrrolidinyl,
3-ethylthiomethylpyrrolidinyl,
3-propylthiomethylpyrrolidinyl,
3-isopropylthiomethylpyrrolidinyl,
3-mercaptoazetidinyl,
3-methylthioazetidinyl,
3-ethylthioazetidinyl,
3-propylthioazetidinyl,
3-isopropylthioazetidinyl,
3-mercaptomethylazetidinyl,
3-methylthiomethylazetidinyl,
3-ethylthiomethylazetidinyl,
3-propylthiomethylazetidinyl,
3-isopropylthiomethylazetidinyl,
3-mercaptopiperidinyl,
3-methythiopiperidinyl,
3-ethylthiopiperidinyl,
3-propylthiopiperidinyl,
3-isopropylthiopiperidinyl,
3-mercaptomethylpiperidinyl,
3-methylthiomethylpiperidinyl,
3-ethylthiomethylpiperidinyl,
3-propylthiomethylpiperidinyl,

3-isopropylthiomethylpiperidinyl,
4-mercaptopiperidinyl,
4-methylthiopiperidinyl,
4-ethylthiopiperidinyl,
4-propylthiopiperidinyl,
4-isopropylthiopiperidinyl,
3-phenylthiopyrrolidinyl,
3-(2-pyridylthio)pyrrolidinyl,
3-phenylthiomethylpyrrolidinyl,
3-(2-pyridylthiomethyl)pyrrolidinyl,
3-phenylthioazetidinyl,
3-phenylthiopiperidinyl,
4-phenylthiopiperidinyl,
3-(2-pyridylthio)azetidinyl,
3-(2-pyridylthio)piperidinyl,
4-(2-pyridylthio)piperidinyl,
3-phenylthiomethylazetidinyl,
3-phenylthiomethylpiperidinyl,
4-phenylthiomethylpiperidinyl,
3-(2-pyridylthiomethyl)azetidinyl,
3-(2-pyridylthiomethyl)piperidinyl,
4-(2-pyridylthiomethyl)piperidinyl.

Also preferred group of compounds of this invention is compounds of the above formula(I) wherein $R^2$ is ethyl, fluoroethyl, cyclopropyl, tert-butyl, 2,4-difluorophenyl, and 4-fluorophenyl radical.

Other preferred compounds of this invention are those wherein X is hydrogen or amino, Y is hydrogen, fluorine, or chlorine, and $R^1$ is hydrogen.

Representative examples of the novel compound of the structural formula(I)

according to the present invention can be given as follows, but the present invention is not limited to the examples given as follows :

1-cyclopropyl-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-ethylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6-fluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(4-mercaptopiperidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthioazetidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-mercaptomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

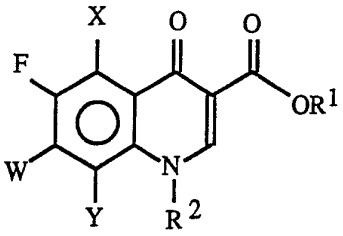
1-cyclopropyl-6,8-difluoro-7-[3-(2-pyridylthiomethyl)pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-[3-(2-pyridylthiomethyl)pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

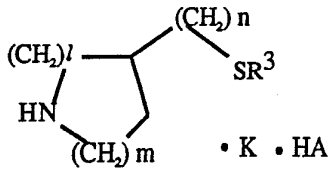
1-cyclopropyl-6,8-difluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

The compounds of the formula(I) of the present invention can be prepared by reacting a quinolone carboxylic acid of the following structural formula(II) with an amine of the following structural formula(III) in an inert solvent or a basic solvent.



( II )



( III )

wherein :

$R^1$, $R^2$, $R^3$, X, Y, Z, $l$ , m, and n are as defined above,

W is halogen (preferably, fluorine or chlorine),

HA is an inorganic or organic acid capable of forming a salt with amines,

K is 0 or 1.

Convenient solvents for this reaction are non-reactive solvents such as tetrahydrofuran, pyridine, ethanol, propanol, butanol, chloroform, dimethyl-sulfoxide, dimethylformamide, water, acetonitrile, dioxane, and the like.

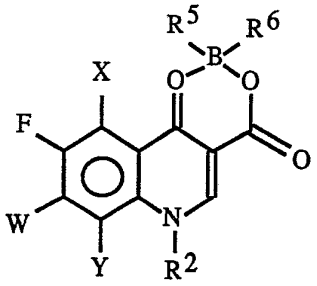
Solvent mixtures may also be utilized. The reaction is preferably carried out in the presence of an acid acceptor such as an alkali metal or alkaline earth metal carbonate, alkali metal or alkaline earth metal bicarbonate, or a tertiary amine such as triethylamine, 1,8-diazabicyclo [5.4.0]undec-7-ene(DBU), pyridine, and the like.

According to the present invention, the preferred solvent is acetonitrile and the preferred base is 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU), triethylamine, and mixture thereof.

The reaction temperature ranges from 50 ℃ to 190℃, preferably from 50 ℃ to 120℃ at atmospheric pressure. The reaction is usually carried out for about 1 hour to about 48 hours.

According to another method, the compound of the formula(I) can be prepared by reacting a boron complex, the formula(IV), with the compound of the

above-described formula(III) and then hydrolyzing the reaction product.



( IV )

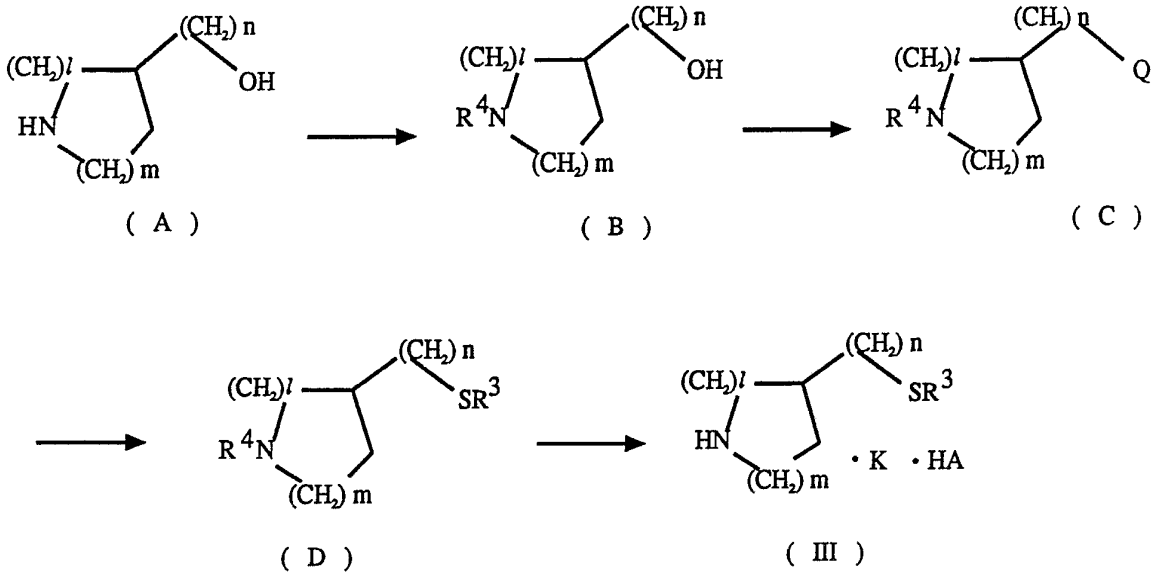
wherein,

$R^2$, X, Y, and W are as defined above,

$R^5$ and $R^6$ is aliphatic acyloxy group having two to six carbon atoms or aromatic acyloxy group having seven to eleven carbon atoms.

The starting compounds having structural formula(II) are known in the article (European Patent Application No. 78362, No. 106489, No. 113091, No. 131839, No. 153580, No. 154780, No. 202763, No. 221463, No. 235762, No. 350950, and No. 360258).

The amine compound of the above-described structural formula(III) can be prepared through the following reaction sequence from the known starting materials, for example, 3-pyrrolidinol(Aldrich's reagent), 3-piperidinol(Aldrich's reagent), 4-piperidinol(Aldrich's reagent), 3-hydroxymethyl piperidine (Aldrich's reagent), 3-hydroxymethyl pyrrolidine (J. Org. Chem., V. 26, 1519(1961)), 3-azetidinol(Chem. Commun., 93(1966)), and 3-hydroxymethylazetidine(Chem. Pharm. Bull., V. 32, 4907(1984)) :




( A ) ( B ) ( C )

( D ) ( III )

wherein,

$R^3$ is alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group,

$R^4$ is amine protecting group,

Q is alkylsulfonyloxy group, arylsulfonyloxy group, or halide,

HA is organic acid or inorganic acid,

K is 0 or 1,

*l* is 1 or 2,

m is 0, 1, or 2,

n is 0 or 1.

Thus compound(A) may be converted to compound(B) by treatment with an appropriate amine protection reagent. For example, a known amine protection reagent, preferably, acetic anhydride, alkoxycarbonyl anhydride, acetyl halide, or alkoxycarbonyl halide may be utilized.

The hydroxyl function of the compound(B) may next be converted to an appropriate leaving group of compound(C) by treatment with convinient reagents, for example, methanesulfonyl chloride or p-toluenesulfonyl chloride in the presence

of a base(for example, triethylamine, pyridine), or thionylchloride or phosphorous trihalide, etc.

Compound(C) may also be converted to compound(D) by treatment with thioalkoxide or mercapto compound in the presence of an appropriate base (for example, sodium hydride, potassium tert-butoxide).

Finally, compound(D) may be deprotected to produce compound of the above described structural formula(III) in the state of an acid salt or a free base by various well known reagents, for example, hydrochloric acid, trifluoroacetic acid, methanesulfonic acid, iodotrimethylsilane, sodium hydroxide, etc.

On the other hand, pharmaceutically acceptable acid addition salts of the above-described structural formula(I) are formed with organic acid or inorganic acids.

Examples of suitable acids for salt formation are acetic acid, lactic acid, succinic acid, maleic acid, tartaric acid, citric acid, gluconic acid, ascorbic acid, benzoic acid, methanesulfonic acid, cinnamic acid, fumaric acid, phosphoric acid, hydrochloric acid, hydroiodic acid, sulfuric acid, and the like.

The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce either a mono or di, etc. salt in the conventional manner.

Pharmaceutically acceptable base salts of the above-described structural formula(I) are formed with metals such as alkali and alkaline earth metals , or amines including ammonia and organic amines.

Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are diethanolamine, N-methylglucamine, arginine, and the like.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms.

For preparing pharmaceutical compositions from the compounds described

by this invention, inert and pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, suppositories, and ointments. A solid carriers can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablets disintegrating agents ; it can also be an encapsulating material.

Suitable solid carriers are magnesium carbonate, magnesium sterate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, and the like.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Such solutions are prepared so as to be acceptable to biological systems(isotonicity, pH, etc.). Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

Reference Example 1

Preparation of N-tert-butoxycarbonyl-3-hydroxymethylpyrrolidine

A mixture of 3.5g (0.035 mole) of 3-hydroxymethylpyrrolidine[J. Org. Chem., 26, 1519(1961)] in 90*ml* of dioxane, 40*ml* of 1N NaOH, and 20*ml* of water was cooled to 0℃, treated dropwise with a solution of 9g (0.041 mole) of di-tert-butyldicarbonate in 30*ml* of dioxane, and warmed to room temperature. The resulting solution was stirred for 12 hours and extracted with 40*ml* of ethyl acetate over three times. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford 5.0g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.56 ~ 2.47(m, 3H), 2.97 ~ 3.61(m, 6H).

Reference Example 2

Preparation of N-tert-butoxycarbonyl-3-hydroxypyrrolidine

In the same manner as described in Reference Example 1, except that 3-hydroxypyrrolidine was used in place of 3-hydroxymethylpyrrolidine, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.44(s, 9H), 1.85 ~ 1.94(m, 2H), 3.35 ~ 3.54(m, 4H), 3.74(s, 1H), 4.40(m, 1H).

Reference Example 3

Preparation of N-tert-butoxycarbonyl-3-hydroxyazetidine

In the same manner as described in Reference Example 1, except that 3-hydroxyazetidine [Chem. Commun., 93(1968)] was used in place of 3-hydroxymethylpyrrolidine, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.43(s, 9H), 3.10 ~ 3.95(m, 4H), 3.95 ~ 4.40(m, 1H).

Reference Example 4

Preparation of N-tert-butoxycarbonyl-4-hydroxypiperidine

In the same manner as described in Reference Example 1, except that 4-hydroxypiperidine was used in place of 3-hydroxymethylpyrrolidine, the title compound was prepared as pale yellow oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.22 ~ 2.95(m, 4H), 2.35(s, 1H), 2.85 ~ 3.14(m, 2H), 3.69 ~ 3.98(m, 3H).

Reference Example 5

Preparation of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl]pyrrolidine

A solution of 5g(0.025 mole) of N-tert-butoxycarbonyl-3-hydroxymethylpyrrolidine in 80*ml* of dichloromethane was treated with 4*ml* (0.029mole) of triethylamine and cooled to -5℃ to -10℃.

A solution of 3.3g(0.029 mole) of methanesulfonyl chloride in 20*ml* of dichloromethane was added dropwise to the reaction mixture, stirred for 10 hours at room temperature, and then treated with 80*ml* of water. After 30 minutes, the organic layer was separated, washed with 10% $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give the crude product. This was purified by column chromatography using ethyl acetate : dichloromethane (1 : 1) as an eluent to afford 5.9g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.48 ~ 2.70(m, 3H), 3.03(s, 3H), 3.10 ~ 3.57(m, 4H), 4.20(dd, 2H).

Reference Example 6

Preparation of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxy]pyrrolidine

In the same manner as described in Reference Example 5, except that N-tert-butoxycarbonyl-3-hydroxypyrrolidine was used in place of N-tert-butoxycarbonyl-3-hydroxymethylpyrrolidine, the title compound was prepared as pale yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.46(s, 9H), 1.99 ~ 2.31(m, 2H), 3.04(s, 3H), 3.36 ~ 3.64(m, 4H), 5.17 ~ 5.30(m, 1H).

Reference Example 7

Preparation of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxy]azetidine

In the same manner as described in Reference Example 5, except that N-tert-butoxycarbonyl-3-hydroxyazetidine was used in place of N-tert-butoxycarbonyl-3-hydroxymethylpyrrolidine, the title compound was prepared as pale yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.44(s, 9H), 3.08(s, 3H), 3.30 ~ 4.15(m, 4H), 5.2 ~ 5.4(m, 1H).

Reference Example 8

Preparation of N-tert-butoxycarbonyl-4-[(methylsulfonyl)-oxy]piperidine

In the same manner as described in Reference Example 5, except that N-tert-butoxycarbonyl-4-hydroxypiperidine was used in place of N-tert-butoxycarbonyl-3-hydroxymethylpyrrolidine, the title compound was prepared as pale yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.46(s, 9H), 1.64 ~ 2.00(m, 4H), 3.02(s, 3H), 3.12 ~ 3.87(m, 4H), 4.79 ~ 4.97(m, 1H).

Reference Example 9

Preparation of 3-methylthiomethylpyrrolidine hydroiodide

A solution of 2.8g(0.01 mole) of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl] pyrrolidine and 0.74g(0.01 mole) of sodium thiomethoxide in 30*ml* of anhydrous dimethylformamide was stirred for 4 hours at 80℃ and cooled to room temperature. The reaction mixture was poured into 50*ml* of water and extracted with 50*ml* of diethyl ether over twice. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give the crude product. This was purified by column chromatography using diethyl ether : n-hexane (4 : 1) as an eluent to afford 2.05g of N-tert-butoxycarbonyl-3-methylthiomethylpyrrolidine as yellowish oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.61 ~ 2.36(m, 3H), 2.12(s, 3H), 2.51(d, 2H), 2.81 ~ 3.82(m, 4H).

A solution of 2.05g (8.64 mmole) of N-tert-butoxycarbonyl-3-methylthiomethylpyrrolidine in 20*ml* of chloroform was added dropwise with 1.6*ml* (11.2 mmole) of iodotrimethylsilane at 5℃ under $N_2$.

The resulting solution was stirred at room temperature. After 2 hours, 10 *ml* of methanol was added to the reaction mixture. Then the removal of solvent under reduced pressure was afforded 2.34g of the title compound as brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.52 ~ 2.46(m, 3H), 2.13(s, 3H), 2.59(d, 2H), 2.62 ~ 3.41(m, 4H), 7.02(br, 2H).

Reference Example 10

Preparation of 3-methylthiopyrrolidine hydroiodide

In the same manner as described in Reference Example 9, except that N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxy]pyrrolidine was used in place of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl]pyrrolidine, the title compound was prepared as reddish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.83 ~ 2.69(m, 2H), 2.24(s, 3H), 3.0 ~ 3.99(m, 5H), 8.59(br, 2H).

Reference Example 11

Preparation of 3-methylthioazetidine hydroiodide

In the same manner as described in Reference Example 9, except that N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxy]azetidine was used in place of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl]pyrrolidine, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 2.25(s, 3H), 3.30 ~4.10(m, 5H), 7.85(br, 2H)

Reference Example 12

Preparation of 3-ethylthiomethylpyrrolidine hydroiodide

In the same manner as described in Reference Example 9, except that sodium thioethoxide was used in place of sodium thiomethoxide, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.28(t, 3H), 1.51 ~ 2.60(m, 5H), 2.59(d, 2H), 2.63 ~ 3.51(m, 4H), 8.86(br, 2H).

Reference Example 13

Preparation of 3-ethylthiopyrrolidine hydroiodide

In the same manner as described in Reference Example 9, except that sodium thioethoxide and N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxy]pyrrolidine were used in place of sodium thiomethoxide and N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl]pyrrolidine, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.26(t, 3H), 1.82 ~ 2.69(m, 4H), 2.96 ~ 3.87(m, 5H), 8.86(br, 2H).

Reference Example 14

Preparation of N-tert-butoxycarbonyl-4-acetylthiopiperidine

A solution of 1*ml* (0.014 mole) of thioacetic acid in 10*ml* of anhydrous dimethylformamide was added dropwise to a suspended solution of 0.6g(0.015 mole) of 60% sodium hydride in 20*ml* of anhydrous dimethylformamide at -5℃ to -10℃. After 1 hour of stirring at this temperature, the reaction mixture was treated with 3.6g(0.013 mole) of N-tert-butoxycarbonyl-4-[(methylsulfonyl-oxy]piperidine and 1.92g (0.013 mole) of sodium iodide in 20*ml* of anhydrous dimethylformamide. The resulting solution was stirred for 12 hours at 70℃, cooled to room temperature, added 50*ml* of water, stirred for 30 minutes, and extracted with 50*ml* of diethyl ether over three times.

The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give the crude product. This was purified by column chromatography using isopropyl ether : n-hexane (1 : 1) as an eluent to afford 1.6g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.49 ~ 2.02(m, 4H), 2.31(s, 3H), 2.89 ~ 3.22(m, 2H), 3.49 ~ 3.99(m, 3H).

Reference Example 15

Preparation of 4-acetylthiopiperidine trifluoroacetate

To a mixture of 1*ml* of anisole and 0.7g(2.7 mmole) of N-tert-butoxycarbonyl-4-acetylthiopiperidine was added 2*ml* of trifluoroacetic acid at 0℃. The mixture was stirred for 1 hour at room temperature. To the resulting solution was added 30*ml* of diethyl ether and the precipitates were filtered to give 0.64g of the title compound as white solid.

m.p. : 118 ~ 120℃

$^1$H NMR(ppm, $CDCl_3$) : 1.82 ~ 2.19(m, 4H), 2.32(s, 3H), 3.03 ~ 3.41(m, 4H), 3.62 ~ 3.67(m, 1H), 8.49(br, 2H).

Reference Example 16

Preparation of N-tert-butoxycarbonyl-3-methylcarbothiomethylpyrrolidine

A solution of 0.25g(0.9 mmole) of N-tert-butoxycarbonyl-3-[(methyl-sulfonyl)-oxymethyl]pyrrolidine in 10*ml* of anhydrous dimethylformamide was added dropwise to a solution of 0.16g(1.4 mmole) of potassium thioacetate in 20*ml* of anhydrous dimethylformamide at 0 ℃. The mixture was stirred for 6 hours at 80℃ and cooled to room temperature. The reaction mixture was poured into 30*ml* of water and extracted with 20*ml* of diethyl ether over twice. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give 0.234g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.50 ~ 2.64(m, 3H), 2.34(s, 3H), 2.90(d, 2H), 3.13 ~ 3.62(m, 4H).

Reference Example 17

Preparation of N-tert-butoxycarbonyl-3-mercaptomethylpyrrolidine

To a solution of 0.3g(1.16 mmole) of N-tertbutoxycarbonyl-3-methyl-carbonylthiomethylpyrrolidine in 10*ml* of ethanol was added 10*ml* of 1N

NaOH. The resulting mixture was stirred for 6 hours at 60℃, cooled to room temperature, evaporated under reduced pressure, and treated 20*ml* of water. Then the resulting solution was extracted with 20*ml* of diethyl ether over twice. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford 0.23g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.46(s, 9H), 1.73 ~ 2.72(m, 3H), 2.70(s, 2H), 2.84 ~ 3.90(m, 4H).

Reference Example 18

Preparation of 3-mercaptomethylpyrrolidine trifluoroacetate

To a mixture of 0.1g of anisole and 0.25g of N-tert-butoxycarbonyl-3-mercaptomethylpyrrolidine was added 1*ml* of trifluoroacetic acid at 0℃. The mixture was stirred for 2 hours at room temperature. The reaction mixture was evaporated under reduced pressure followed by washing with 20*ml* of n-hexane over twice. This was concentrated under reduced pressure to afford 0.25g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.54 ~ 2.42(m, 3H), 2.72(d, 2H), 2.92 ~ 3.64(m, 5H), 8.24(br, 2H).

Reference Example 19

Preparation of N-tert-butoxycarbonyl-3-(2-pyridylthiomethyl)pyrrolidine

A solution of 0.42g(3.77 mmole) of 2-mercaptopyridine in 10*ml* of anhydrous dimethyl formamide was added dropwise to a solution of 0.15g(3.75 mmole) of 60% sodium hydride in 20*ml* of anhydrous dimethylformamide at -5℃ to 0℃ and stirred for 1 hour at room temperature. To the resulting solution was added a solution of 1g(3.58 mmole) of N-tert-butoxycarbonyl-3-[(methylsulfonyl)-oxymethyl]pyrrolidine in 10*ml* of dimethylformamide. The reaction mixture was stirred for 6 hours at 80℃ to 100℃, cooled to room temperature, added 80*ml* of

water, and extracted with 50*ml* of diethyl ether over twice. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give the crude product. This was purified by column chromatography using isopropyl ether as an eluent to afford 0.94g of the title compound as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.45(s, 9H), 1.64 ~ 2.70(m, 3H), 2.95(d, 2H), 3.0 ~ 3.70(m, 4H), 6.90 ~ 7.18(m, 3H), 8.43(dd, 1H).

Reference Example 20

Preparation of N-tert-butoxycarbonyl-3-phenylthiomethylpyrrolidine

In the same manner as described in Reference Example 19, except that thiophenol was used in place of 2-mercaptopyridine, the title compound was prepared as yellowish brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.44(s, 9H), 1.60 ~ 2.62(m, 3H), 2.97(d, 2H), 3.10 ~ 3.72(m, 4H), 7.30(s, 5H).

Reference Example 21

Preparation of 3-(2-pyridylthiomethyl)pyrrolidine trifluoroacetate

In the same manner as described in Reference Example 18, except that N-tert-butoxycarbonyl-3-(2-pyridylthiomethyl)pyrrolidine was used in place of N-tert-butoxycarbonyl-3-mercaptomethylpyrrolidine, the title compound was prepared as brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.51 ~ 2.62(m, 3H), 3.04(d, 2H), 3.16 ~ 4.01(m, 4H), 7.20 ~ 9.20(m, 4H), 9.12(br, 2H).

Reference Example 22

Preparation of 3-phenylthiomethylpyrrolidine trifluoroacetate

In the same manner as described in Reference Example 18, except that N-tert-butoxycarbonyl-3-phenylthiomethylpyrrolidine was used in place of N-tert-

butoxycarbonyl-3-mercaptomethylpyrrolidine, the title compound was prepared as brown oil.

$^1$H NMR(ppm, $CDCl_3$) : 1.54 ~ 2.70(m, 3H), 2.95(d, 2H), 3.01 ~ 3.70(m, 4H), 7.30(s, 5H), 8.77(br, 2H).

Example 1

Preparation of 1-cyclopropyl-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.71 mmole) of 1-cyclopropyl-6-fluoro-7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.8g (3.24 mmole) of 3-methylthio-pyrrolidine hydroiodide, and 0.4g(3.96 mmole) of triethylamine in 6*ml* of dimethylsulfoxide was stirred for 6 hours at 110℃ and cooled to room temperature. The reaction mixture was diluted with 10*ml* of water, adjusted at pH 7.4 with 1N HCl, and then allowed to stand for 1 day. The precipitated product was filtered, washed with water and methanol, and recrystallized from methanol : dichloromethane (1 : 1) to afford 0.15g of the title compound as pale yellow solid.

m.p. : 230 ~ 234℃

$^1$H NMR(ppm, $NaOD/D_2O$) : 0.60 ~ 1.00(m, 4H), 1.41 ~ 2.50(m, 2H), 2.10(s, 3H), 2.60 ~ 4.21(m, 6H), 6.22(d, 1H), 7.30(d, 1H), 8.09(s, 1H)

Example 2

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.1g(0.35 mmole) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.06g(0.39 mmole) of 1,8-diazabicyclo [5.4.0]undec-7-ene, 0.04g(0.39 mmole) of triethylamine, and 0.09g(0.37 mmole) of 3-methylthiopyrrolidine hydroiodide in 6*ml* of acetonitrile was stirred for 2 hours at

60℃, cooled to room temperature, and stirred for 2 hours. The precipitate was filtered, washed with acetonitrile and diethyl ether, and dried to afford 0.11g of the title compound as pale yellow solid.

m.p. : 214 ~ 218℃

$^1$H NMR(ppm, $CDCl_3$) : 1.09 ~ 1.27(m, 4H), 1.93 ~ 2.37(m, 2H), 2.20(s, 3H), 3.29 ~ 3.45(m, 1H), 3.71 ~ 4.68(m, 5H), 7.73(dd, 1H), 8.71(s, 1H), 14.78(br, 1H).

Example 3

Preparation of 1-cyclopropyl-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.66 mmole) of 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.1g(0.66 mmole) of 1,8-diazabicyclo [5.4.0]undec-7-ene, 0.07g(0.69 mmole) of triethylamine, and 0.17g(0.69 mmole) of 3-methylthiopyrrolidine hydroiodide in 6*ml* of acetonitrile was stirred for 3 hours at 60℃, cooled to room temperature, and stirred for 2 hours. The precipitate was filtered, washed with acetonitrile and diethyl ether, and dried to afford 0.2g of the title compound as pale yellow solid.

m.p. : 220 ~ 222℃

$^1$H NMR(ppm, $CDCl_3$) : 1.09 ~ 1.25(m, 4H), 1.93 ~ 2.39(m, 2H), 2.16(s, 3H), 3.39 ~ 3.47(m, 1H), 3.73 ~ 4.08(m, 5H), 8.67(s, 1H), 14.63(br, 1H).

Example 4

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-ethylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 2, except that 3-ethylthio-pyrrolidine hydroiodide was used in place of 3-methylthiopyrrolidine hydroiodide,

the title compound was prepared as pale yellow solid.

$^1$H NMR(ppm, $CDCl_3$) : 1.16 ~ 1.41(m, 7H), 1.87 ~ 2.76(m, 4H),
3.69 ~ 4.72(m, 6H), 7.74(dd, 1H), 8.70(s, 1H),
14.65(br, 1H).

Example 5

Preparation of 1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.56 mmole) of 1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.09g (0.56 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene, 0.06g(0.59 mmole) of triethylamine, and 0.14g(0.57 mmole) of 3-methylthiopyrrolidine hydroiodide in 10*ml* of acetonitrile was stirred for 3 hours at 60℃, cooled to room temperature, stirred for 2 hours, and evaporated under reduced pressure. The mixture was diluted with 20*ml* of water. The precipitate was filtered and recrystallized from methanol : dichloromethane (1:1) to afford 0.18g of the title compound as pale yellow solid.

m.p. : 188 ~ 192℃

$^1$H NMR(ppm, $CDCl_3$) : 1.78 ~ 2.28(m, 2H), 2.14(s, 3H), 3.29 ~ 3.37(m, 1H),
3.45 ~ 3.85(m, 4H), 7.02 ~ 7.79(m, 3H),
7.96(dd, 1H), 8.42(s, 1H), 14.38(br, 1H).

Example 6

Preparation of 1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.54 mmole) of 1-(2,4-difluororphenyl)-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.09g(0.59 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene, 0.06g(0.59 mmole) of triethylamine, and 0.14g(0.57 mmole) of 3-methylthiopyrrolidine hydroiodide in 6*ml* of acetonitrile

was stirred for 4 hours at 60℃, cooled to room temperature, stirred for 2 hours, and evaporated under reduced pressure. The mixture was diluted with 20*ml* of water. The precipitate was filtered and recrystallized from methanol : dichloromethane(1 : 1) to afford 0.20g of the title compound as pale yellow solid.

m.p. : 206 ~ 208℃

$^1$H NMR(ppm, $CDCl_3$) : 1.78 ~ 2.37(m, 2H), 2.14(s, 3H), 3.16 ~ 3.45(m, 1H), 3.54 ~ 4.00(m, 4H), 6.94 ~ 7.63(m, 3H), 8.36(s, 1H), 14.4 (br, 1H).

Example 7

Preparation of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.57 mmole) of 1-(2,4-difluorophenyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.8g(3.24 mmole) of 3-methylthio-pyrrolidine hydroiodide, and 0.4g(3.96 mmole) of triethylamine in 8*ml* of dimethylsulfoxide was stirred for 7 hours at 110℃ and cooled to room temperature. The reaction mixture was diluted with 20*ml* of water, adjusted at pH 7.4 with 1N HCl, and then allowed to stand for 1 day. The precipitated product was filtered, washed with water and methanol, and recrystallized from methanol : dichloromethane(1:1) to afford 0.15g of the title compound as pale yellow solid.

m.p. : 210 ~ 212℃

$^1$H NMR(ppm, $CDCl_3$) : 1.78 ~ 2.28(m, 2H), 2.14(s, 3H), 3.29 ~ 4.10(m, 5H), 6.95 ~ 7.79(m, 5H), 8.60(s, 1H), 14.64(br, 1H).

Example 8

Preparation of 1-cyclopropyl-6-fluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.71 mmole) of 1-cyclopropyl-7-chloro-6-fluoro-1,4-

dihydro-4-oxo-3-quinolinecarboxylic acid, 0.9g(3.5 mmole) of 3-methylthiomethylpyrrolidine hydroiodide, and 0.4g(3.96 mmole) of triethylamine in 6*ml* of dimethylsulfoxide was stirred for 6 hours at 110℃ and cooled to room temperature.

The reaction mixture was diluted with 15*ml* of water, adjusted at pH 7.4 with 1N HCl, and then allowed to stand for 1 day. The precipitated product was filtered, washed with water and methanol, and recrystallized from methanol : dichloromethane(1:1) to afford 0.19g of the title compound as pale yellow solid.

m.p. : 196 ~ 198℃

$^1$H NMR(ppm, $CDCl_3$) : 1.19 ~ 1.31(m, 4H), 1.50 ~ 2.50(m, 3H), 2.17(s, 3H), 2.67(d, 2H), 3.20 ~ 4.01(m, 5H), 6.84(d, 1H), 7.80(d, 1H), 8.59(s, 1H), 15.29(br, 1H).

Example 9

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.1g(0.35 mmole) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.06g(0.39 mmole) of 1,8-diazabicyclo [5.4.0]undec-7-ene, 0.04g(0.39 mmole) of triethylamine, and 0.1g(0.39 mmole) of 3-methylthiomethylpyrrolidine hydroiodide in 6*ml* of acetonitrile was stirred for 3 hours at 60℃, cooled to room temperature, and stirred for 2 hours. The precipitate was filtered, washed with acetonitrile and diethyl ether, and dried to afford 0.12g of the title compound as pale yellow solid.

m.p. : 166 ~ 168℃

$^1$H NMR(ppm, $CDCl_3$) : 1.10 ~ 1.30(m, 4H), 1.54 ~ 2.42(m, 3H), 2.16(s, 3H), 2.62(d, 2H), 3.34 ~ 4.20(m, 5H), 7.80(dd, 1H), 8.68(s, 1H), 14.01(br, 1H)

Example 10

Preparation of 1-cyclpropyl-5,6,8-trifluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.66 mmole) of 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.1g(0.66 mmole) of 1,8-diazabicyclo [5.4.0]undec-7-ene, 0.07g(0.67 mmole) of triethylamine, and 0.18g(0.69 mmole) of 3-methylthiomethylpyrrolidine hydroiodide in 6*ml* of acetonitrile was stirred for 3 hours at 60℃, cooled to room temperature, and stirred for 3 hours.

The precipitate was filtered, washed with acetonitrile and diethyl ether, and dried to afford 0.21g of the title compound as pale yellow solid.

m.p. : 200 ~ 204℃

$^1$H NMR(ppm, $CDCl_3$) : 1.17 ~ 1.27(m, 4H), 1.76 ~ 2.49(m, 3H), 2.17(s, 3H), 2.63(d, 2H), 3.54 ~ 4.04(m, 5H), 8.63(s, 1H), 14.31(br, 1H)

Example 11

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 3-ethylthiomethylpyrrolidine hydroiodide was used in place of 3-methylthio-methylpyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

$^1$H NMR(ppm, $CDCl_3$) : 1.12 ~ 1.43(m, 7H), 1.64 ~ 2.38(m, 3H), 2.42 ~ 2.78(m, 4H), 3.32 ~ 4.26(m, 5H), 7.82(dd, 1H), 8.67(s, 1H), 14.26(br, 1H)

Example 12

Preparation of 1-cyclopropyl-5,6,8-trifluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-

dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 10, except that 3-ethylthiomethylpyrrolidine hydroiodide was used in place of 3-methylthiomethylpyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

$^1$H NMR(ppm, $CDCl_3$) : 1.17 ~ 1.46(m, 7H), 1.58 ~ 2.42(m, 3H),
2.41 ~ 2.80(m, 4H), 3.26 ~ 4.24(m, 5H),
8.63(s, 1H), 14.42(br, 1H)

Example 13

Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 1-cyclopropyl-6,7-difluoro-8-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid was used in place of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, the title compound was prepared as pale yellow solid.

$^1$H NMR(ppm, $CDCl_3$) : 1.12 ~ 1.32(m, 4H), 1.52 ~ 2.43(m, 3H), 2.16(s, 3H),
2.61(d, 2H), 3.32 ~ 4.16(m, 5H), 7.84(dd, 1H),
8.64(s, 1H), 14.38(br, 1H)

Example 14

Preparation of 1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.56 mmole) of 1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.09g(0.59 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene, 0.06g(0.59 mmole) of triethylamine, and 0.15g(0.58 mmole) of 3-methylthiomethylpyrrolidine hydroiodide in 8*ml* of acetonitrile was stirred for 4 hours at 60℃, cooled to room temperature, stirred for 2 hours, and evaporated under reduced pressure.

The mixture was diluted with 20*ml* of water. The precipitate was filtered and recrystallized from methanol : dichloromethane(1:1) to afford 0.2g of the title compound as pale yellow solid.

m.p. : 178 ~ 182℃

$^1$H NMR(ppm, $CDCl_3$) : 1.47 ~ 2.34(m, 3H), 2.14(s, 3H), 2.60(d, 2H), 3.60 ~ 3.78(m, 4H), 6.95 ~ 7.52(m, 3H), 7.75(dd, 1H), 8.41(s, 1H), 14.54(br, 1H)

Example 15

Preparation of 1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.2g(0.54 mmole) of 1-(2,4-difluorophenyl)-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.09g(0.59 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene, 0.06g(0.59 mmole) of triethylamine, and 0.15g(0.58 mmole) of 3-methylthiomethylpyrrolidine hydroiodide in 10*ml* of acetonitrile was stirred for 4 hours at 60℃, cooled to room temperature, stirred for 3 hours, and evaporated under reduced pressure.

The mixture was diluted with 20*ml* of water. The precipitate was filtered and recrystallized from methanol : dichloromethane(1 : 1) to afford 0.2g of the title compound as pale yellow solid.

m.p. : 190 ~ 194℃

$^1$H NMR(ppm, $CDCl_3$) : 1.48 ~ 2.43(m, 3H), 2.12(s, 3H), 2.64(d, 2H), 3.43 ~ 3.99(m, 4H), 6.94 ~ 7.50(m, 3H), 8.36(s, 1H), 14.49(br, 1H)

Example 16

Preparation of 1-cyclopropyl-6,8-difluoro-7-(4-mercaptopiperidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

A mixture of 0.1g(0.35 mmole) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.48g(1.75 mmole) of 4-acetylthiopiperidine trifluoroacetate, and 0.18g(1.78 mmole) of triethylamine in 6 *ml* of dimethylsulfoxide was stirred for 3 hours at 180℃ and then added with 10*ml* of 1N HCl.

The resulting solution was stirred for 2 hours at 110℃, cooled to room temperature, adjusted at pH 7.4 with 1N NaOH, and then allowed to stand for 1 day. The precipitated product was filtered, dried, and recrystallized from methanol : dichloromethane(1:1) to afford 0.08g of the title compound as pale yellow solid.

$^1$H NMR(ppm, NaOD/$D_2O$) : 0.92 ~ 1.18(m, 4H), 1.34 ~ 2.10(m, 4H), 2.23 ~ 3.12(m, 4H), 3.30 ~ 3.56(m, 1H), 3.56 ~ 3.64(m, 1H), 7.84(dd, 1H), 8.41(s, 1H)

Example 17

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-methylthioazetidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 2, except that 3-methylthioazetidine hydroiodide was used in place of 3-methylthiopyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

$^1$H NMR(ppm, NaOD/$D_2O$) : 1.10 ~ 1.30(m, 4H), 2.14(s, 3H), 3.35 ~ 3.60(m, 1H), 3.70 ~ 4.70(m, 5H), 7.81(dd, 1H), 8.70(s, 1H)

Example 18

Preparation of 1-cyclopropyl-5-amino-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 2, except that 3-methylthiomethylpyrrolidine hydroiodide and 1-cyclopropyl-5-amino-6,7,8-

trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid were used in place of 3-methylthiopyrrolidine hydroiodide and 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, the title compound was prepared as yellow solid.

m.p. : 158 ~ 163℃

$^1$H NMR(ppm, $CDCl_3$) : 0.94 ~ 1.20(m, 4H), 1.43 ~ 2.53(m, 3H), 2.14(s, 3H), 2.59(s, 2H), 3.47 ~ 4.21(m, 5H), 6.36(br, 2H), 8.54(s, 1H), 14.83(br, 1H)

Example 19

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-mercaptomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 2, except that 3-mercaptomethylpyrrolidine trifluoroacetate was used in place of 3-methylthio-pyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

m.p. : 238 ~ 243℃ (decomp.)

$^1$H NMR(ppm, $NaOD/D_2O$) : 0.94 ~ 1.23(m, 4H), 1.63 ~ 3.01(m, 5H), 2.14(s, 3H), 3.23 ~ 4.01(m, 5H), 7.50(d, 1H), 8.37(s, 1H)

Example 20

Preparation of 1-cyclopropyl-6,8-difluoro-7-[3-(2-pyridylthiomethyl)pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 3-(2-pyridylthiomethyl)pyrrolidine trifluoroacetate was used in place of 3-methylthio-methylpyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

m.p. : 196 ~ 200℃

$^1$H NMR(ppm, $CDCl_3$) : 0.91 ~ 1.46(m, 4H), 1.50 ~ 2.82(m, 3H), 3.39(d, 2H), 3.30 ~ 4.24(m, 5H), 6.72 ~ 7.94(m, 4H), 8.42(d, 1H), 8.67(s, 1H), 14.83(br, 1H)

Example 21

Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 3-phenylthiomethylpyrrolidine trifluoroacetate was used in place of 3-methylthiomethylpyrrolidine hydroiodide, the title compound was prepared as pale yellow solid.

m.p. : 160 ~ 164℃

$^1$H NMR(ppm, $CDCl_3$) : 0.90 ~ 1.24(m, 4H), 1.32 ~ 2.80(m, 3H), 3.10(d, 2H), 3.30 ~ 4.32(m, 5H), 7.30(s, 5H), 7.80(dd, 1H), 8.69(s, 1H), 14.80(br, 1H)

Example 22

Preparation of 1-(2,4-difluorophenyl)-6,8-difluoro-7-[3-(2-pyridylthiomethyl) pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 3-(2-pyridylthiomethyl)pyrrolidine trifluoroacetate and 1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid were used in place of 3-methylthiomethylpyrrolidine hydroiodide and 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, the title compound was prepared as pale yellow solid.

m.p. : 202 ~ 206℃

$^1$H NMR(ppm, $CDCl_3$) : 1.84 ~ 2.72(m, 3H), 3.32(d, 2H),

3.24 ~ 4.12(m, 5H), 6.81 ~ 8.34(m, 8H),
8.39(s, 1H), 14.66(br, 1H)

Example 23

Preparation of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

In the same manner as described in Example 9, except that 3-phenylthiomethylpyrrolidine trifluoroacetate and 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid were used in place of 3-methylthiomethylpyrrolidine hydroiodide and 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, the title compound was prepared as pale yellow solid.

m.p. : 180 ~ 184℃

$^1$H NMR(ppm, $CDCl_3$) : 1.56 ~ 2.82(m, 3H), 3.02(d, 2H), 3.10 ~ 4.12(m, 4H),
5.76(d, 1H), 6.90 ~ 8.20(m, 4H), 7.27(s, 5H),
8.42(s, 1H), 15.05(br, 1H)

The typical examples of the present compounds were tested for antimicrobial activity in vitro against twenty strains of Gram-positive and Gram-negative microorganisms.

The antibacterial activity in vitro is shown in Table 1. The numerals in the table 1 show minimum inhibitory concentrations(MIC in $\mu g/ml$). The minimum inhibitory concentrations were determined according to the agar dilution method recommended by Japan Society of Chemotherapy[Chemotherapy., 29, 76 (1981)].

Table 1. In vitro Antibacterial Activity, MIC ($\mu g/ml$)

| No. | example compound | | 1 | 2 | 8 | 9 | 10 | 18 | CIP |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *S. pyogenes* | A 308 | 1.563 | 0.781 | 1.563 | 0.195 | 0.781 | 0.195 | 1.563 |
| 2 | *S. pyogenes* | A 77 | 0.781 | 0.391 | 0.781 | 0.098 | 1.563 | 0.391 | 0.195 |
| 3 | *S. faecium* | MD 86 | 0.781 | 0.391 | 0.781 | 0.195 | 0.781 | 1.195 | 0.781 |
| 4 | *S. aureus* | SG 511 | 0.025 | 0.002 | 0.025 | 0.002 | 0.008 | 0.004 | 0.195 |
| 5 | *S. aureus* | 285 | 0.025 | 0.002 | 0.025 | 0.002 | 0.013 | 0.025 | 0.195 |
| 6 | *S. aureus* | 503 | 0.025 | 0.002 | 0.025 | 0.002 | 0.007 | 0.007 | 0.391 |
| 7 | *E. coli* | O 55 | 0.098 | 0.049 | 0.025 | 0.013 | 0.195 | 0.013 | 0.013 |
| 8 | *E. coli* | DC 0 | 6.25 | 0.781 | 3.125 | 0.781 | 6.25 | 3.125 | 0.195 |
| 9 | *E. coli* | DC 2 | 3.125 | 0.781 | 0.781 | 0.781 | 3.125 | 0.195 | 0.098 |
| 10 | *E. coli* | TEM | 3.125 | 0.781 | 0.391 | 0.391 | 3.125 | 0.025 | 0.098 |
| 11 | *E. coli* | 1507E | 1.563 | 0.781 | 1.563 | 0.391 | 3.125 | 0.025 | 0.049 |
| 12 | *P. aeruginosa* | 9027 | 1.563 | 0.781 | 1.563 | 0.781 | 3.125 | 3.125 | 0.098 |
| 13 | *P. aeruginosa* | 1592E | 1.563 | 0.781 | 1.563 | 0.781 | 3.125 | 3.125 | 0.195 |
| 14 | *P. aeruginosa* | 1771 | 0.781 | 0.195 | 0.781 | 0.391 | 1.563 | 1.563 | 0.195 |
| 15 | *P. aeruginosa* | 1771M | 0.391 | 0.195 | 0.391 | 0.098 | 1.563 | 0.781 | 0.049 |
| 16 | *S. typhimurium* | | 0.391 | 0.049 | 0.195 | 0.049 | 0.391 | 0.049 | 0.013 |
| 17 | *K. oxytoca* | 1082E | 0.098 | 0.007 | 0.098 | 0.007 | 0.098 | 1.563 | 0.002 |
| 18 | *K. aerogenes* | 1522E | 0.195 | 0.195 | 0.391 | 0.098 | 0.781 | 3.125 | 0.013 |
| 19 | *E. cloacae* | P99 | 0.195 | 0.195 | 0.195 | 0.098 | 0.391 | 0.049 | 0.013 |
| 20 | *E. cloacae* | 1321E | 0.098 | 0.098 | 0.195 | 0.025 | 0.391 | 0.049 | 0.007 |

CIP = Ciprofloxacin

The compound of example 9 was orally administered to determine the $LD_{50}$ for a group of male mice. The result was proved to be $LD_{50} > 3000$ mg/kg. The antibacterial activity for MRSA(Methicillin Resistant Staphyloccocus Aureus) was tested by the compound of example 9. The results are shown in Table 2.

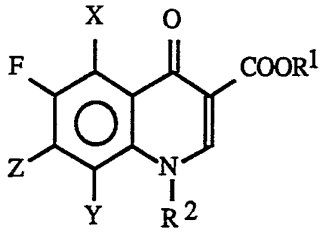
Table 2. Antibacterial Activity for MRSA ($\mu g/ml$)

| No. | Fungus | example 9 | CIP. |
|---|---|---|---|
| 1 | *Staphylococcus aureus* 88 E | 0.004 | 0.391 |
| 2 | *Staphylococcus aureus* 121E | 0.013 | 0.391 |
| 3 | *Staphylococcus aureus* 208E | 0.025 | 0.195 |
| 4 | *Staphylococcus aureus* 256E | 0.013 | 0.391 |
| 5 | *Staphylococcus aureus* 690E | 0.004 | 0.195 |
| 6 | *Saphylococcus aureus* 692E | 0.004 | 0.195 |
| 7 | *Staphylococcus aureus* 693E | 0.007 | 0.391 |
| 8 | *Staphylococcus aureus* 694E | 0.013 | 0.391 |
| 9 | *Staphylococcus aureus* 695E | 0.013 | 0.391 |
| 10 | *Staphylococcus aureus* 697E | 0.013 | 0.195 |
| 11 | *Staphylococcus aureus* 701E | 0.013 | 0.391 |
| 12 | *Staphylococcus aureus* 703E | 0.007 | 0.195 |
| 13 | *Staphylococcus aureus* 705E | 0.013 | 0.391 |
| 14 | *Staphylococcus aureus* 706E | 0.013 | 0.391 |
| 15 | *Staphylococcus aureus* 707E | 0.007 | 0.391 |
| 16 | *Staphylococcus aureus* 708E | 0.007 | 0.098 |
| 17 | *Staphylococcus aureus* 711E | 0.013 | 0.098 |
| 18 | *Staphylococcus aureus* 714E | 0.007 | 0.195 |
| 19 | *Staphylococcus aureus* 752E | 0.013 | 0.195 |

CIP = Ciprofloxacin

WHAT IS CLAIMED IS ;

1. A compound of following structural formula(I) or pharmaceutically acceptable salts thereof.



( I )

wherein,

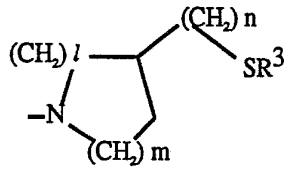
$R^1$ is hydrogen or alkyl group having one to six carbon atoms,

$R^2$ is alkyl group having one to four carbon atoms, haloalkyl group having one to four carbon atoms, cycloalkyl group having three to six carbon atoms, alkenyl group having two to four carbon atoms, or phenyl group which is optionally mono or disubstituted by fluorine atoms,

X is hydrogen, amino, or halogen,

Y is hydrogen, or halogen,

Z is



(wherein,

*l* is 1 or 2, m is 0, 1, or 2, and n is 0 or 1,

$R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group).

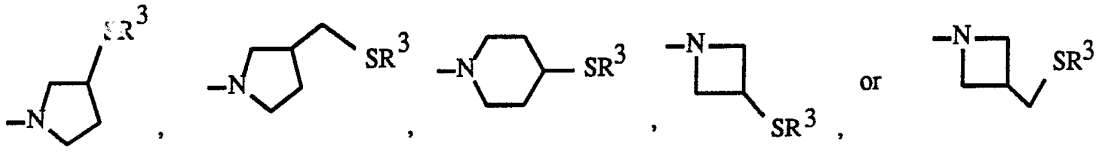
2. A compound according to claim 1, wherein $R^1$ is hydrogen.

3. A compound according to claim 1, wherein X is hydrogen, or amino.

4. A compound according to claim 1, wherein Y is hydrogen, fluorine, or chlorine.

5. A compound according to claim 1, wherein $R^2$ is cyclopropyl, or 2,4-difluorophenyl.

6. A compound according to claim 1, wherein Z is



(wherein, $R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group).

7. A compound according to calim 6, wherein $R^3$ is methyl, ethyl, phenyl, or 2-pyridyl.

8. A compound to according to claim 1 and selected from the groups consisting of :

1-cyclopropyl-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylicacid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-

oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-ethylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylthiopyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6-fluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-5,6,8-trifluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(4-mercaptopiperidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-5,6,8-trifluoro-7-(3-ethylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-methylthioazetidinyl)-1,4-dihydro-4-oxo-3-

quinolinecarboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-(3-methylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-cyclopropyl-6,8-difluoro-7-(3-mercaptomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

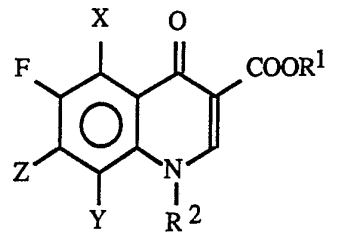
1-cyclopropyl-6,8-difluoro-7-[3-(2-pyridylthiomethyl)pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6,8-difluoro-7-[3-(2-pyridylthiomethyl)pyrrolidinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

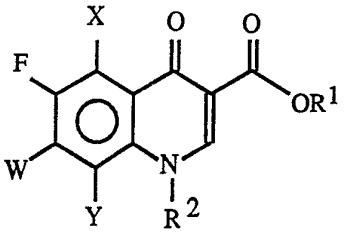
1-cyclopropyl-6,8-difluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-(3-phenylthiomethylpyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, and pharmaceutically acceptable salts thereof.

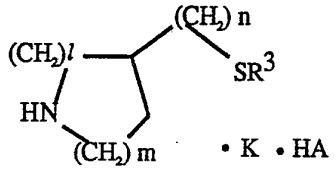
9. A process for the preparation of compounds of structural formula(I) by reacting a compound of structural formula(II) with a compound of structural formula(III).



( I )



( II )



( III )

wherein,

$R^1$ is hydrogen or alkyl group having one to six carbon atoms,

$R^2$ is alkyl group having one to four carbon atoms, haloalkyl group having one to four carbon atoms, cycloalkyl group having three to six carbon atoms, alkenyl group having two to four carbon atoms, or phenyl group which is optionally mono or disubstituted by fluorine atoms,

X is hydrogen, amino, or halogen,

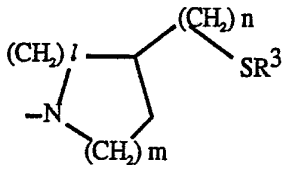
Y is hydrogen or halogen,

W is halogen,

HA is organic acid or inorganic acid,

K is 0 or 1,

Z is

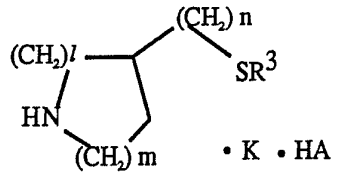


(wherein,

*l* is 1 or 2, m is 0, 1, or 2, and n is 0 or 1,

$R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroarylgroup).

10. A compound of following structural formula(III)




( III )

wherein,

$R^3$ is hydrogen, alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group,

HA is organic acid or inorganic acid,

K is 0 or 1,

*l* is 1 or 2,

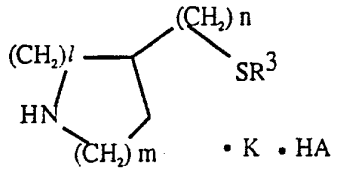
m is 0, 1, or 2,

n is 0 or 1.

11. A pharmaceutical composition comprising an antibacterially effective amount of compound according to claim 1 together with a pharmaceutically acceptable carrier.

AMENDED CLAIMS
[received by the International Bureau on 17 December 1991 (17.12.91);
original claim 10 amended;
other claims unchanged (1page)]

10. A compound of following structural formula(III)



( III )

wherein,

$R^3$ is alkyl group having one to four carbon atoms, haloalkyl group having one to three carbon atoms, acyl group, cycloalkyl group having three to six carbon atoms, aryl, or heteroaryl group,

HA is organic acid or inorganic acid,

K is 0 or 1,

*l* is 1 or 2,

m is 0, 1, or 2,

n is 0 or 1.

11. A pharmaceutical composition comprising an antibacterially effective amount of compound according to claim 1 together with a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/KR 91/00018

**I. CLASSIFIC... OF SU...ECT MATTER** (if several classification symbols apply, indicate all) [6]

According to In... nal Pat... assification (IPC) or to both National Classification and IPC

Int.Cl.[5]: C 07 D .../04, 203/06, 207/08, 207/12, 211/20, 211/54; A 61 K 31/445

**II. FIELDS SEARCHED**

**Minimum Documentation Searched [7]**

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.[5] | C 07 D 401/04, 207/08, 211/00, 203/06, 207/12, 211/54; A 61 K 31/445 |

**Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]**

Chemical Abstracts (Columbus, Ohio, USA); AT

**III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]**

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| A | DE, A1, 3 906 365 (BAYER) 18 January 1990 (18.01.90), see claims 1,8; table 1; page 24. | (1,11) |
| P,A | EP, A1, 0 401 623 (BAYER) 12 December 1990 (12.12.90), see claims 1,7; page 11, line 24; example 34. | (1,11) |
| A | DE, A1, 3 517 535 (BAYER) 20 November 1986 (20.11.86), see claim 1. | (1) |
| A | EP, A2, 0 366 643 (NORWICH EATON) 02 May 1990 (02.05.90), see claim 1. | (1) |
| X | Chemical Abstracts, Volume 104, no. 11, issued 1986, March 17 (Columbus, Ohio, U.S.A.), Barrera, Heribert et al. "Synthesis and spectroscopic characterization of some $\gamma$-mercaptoalkylpiperidines" see page 644, column 1, the abstract no. 88 398k, J. Chem. Res., Synop. 1985, (8), 270-1. | (10) |

* Special categories of cited documents: [10]

"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 referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

**IV. CERTIFICATION**

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 01 October 1991 (01.10.91) | 23 October 1991 (23.10.91) |
| **International Searching Authority** | **Signature of Authorized Officer** |
| AUSTRIAN PATENT OFFICE | i.A. Pal |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No |
|---|---|---|
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In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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