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OPTICALLY ACTIVE PYRIDONECARBOXYLIC ACID DERIVATIVES

FIELD OF THE INVENTION

This invention relates to an antimicrobial compound useful as human and veterinary medicines, fish medicines, agricultural chemicals, and antiseptics.

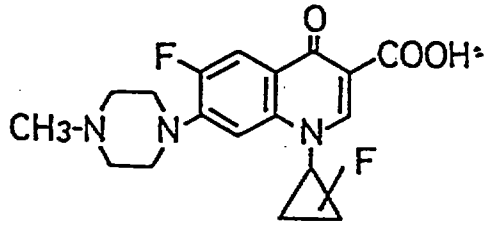
BACKGROUND OF THE INVENTION

Quinolone derivatives having a condensed pyridonecarboxylic acid skeleton are known as synthetic antimicrobial agents and to provide potent antimicrobial compounds on substitution of the 1-position thereof with a cyclopropyl group.

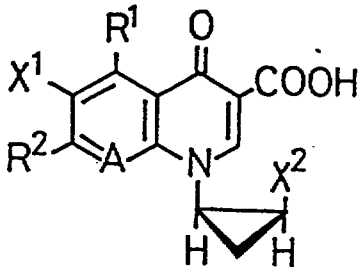
It is further known that the 1-cyclopropyl-quinolone derivatives having introduced a fluorine atom to the 2-position of the cyclopropyl group in a cis-configuration with the pyridonecarboxylic acid moiety also exhibit potent antimicrobial activity as disclosed in JP-A-87-12760 (the term "JP-A" as used herein means an "unexamined published Japanese patent application"). They are thought to have not only potent antimicrobial activity but improved safety. One example of the quinolone derivatives having a cis-fluorocyclopropyl group at the 1-position is shown below.

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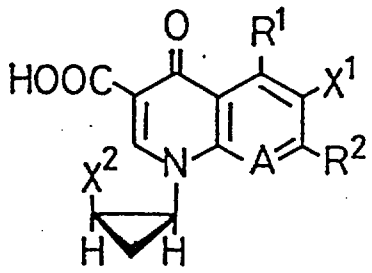
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Quinolone derivatives having a cis-halogeno-cyclopropyl group, inclusive of a cis-fluorocyclopropyl group, at the 1-position as stated above possess excellent properties in antimicrobial activity and safety. In these compounds, even when they have a substituent without stereo-isomerism at the 7-position of the pyridonecarboxylic acid moiety, the halogeno-cyclopropane ring of itself provides two enantiomers sttributed to the steric relationship between the pyridonecarboxylic acid moiety and the halogen atom with respect to the cyclopropane ring as illustrated below;



and



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wherein R^1, R^2, A, X^1, and X^2 are hereinafter defined. These quinolone derivatives are applicable as medicines as long as they are recemates. On the other hand, when there is stereoisomerism at the 7-positioned substituent of the pyridonecarboxylic acid moiety, such quinolone derivatives contain four kinds of diasteromers. With mixtures of the diasteromers, it is difficult to specify the excellent species and to supply them as medicines.

SUMMARY OF THE INVENTION

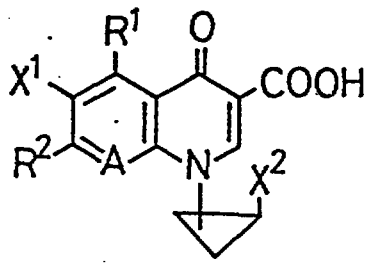
In the light of the aforesaid situation, the inventors have made extensive efforts to obtain the single isomers of 1-(1,2-cis-2-fluorocyclopropyl)-substituted quinolone derivatives within the diastereomers thereof. And they have succeeded in obtaining each of the enantiomers of a cis-2-fluorocyclopropyamine as a pure isomer. As a result of further investigations, they have also succeeded in synthesizing each of the enantiomers of a quinolone derivative which are attributed only to the steric configuration of the fluorocyclopropane ring by starting from the above-described amine.

The success of obtaining the enantiomeric quinolone derivatives useful as an intermediate has made it possible to synthesize an optically active quinolone derivative comprising one kind of diastereomer by

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reacting with a single isomer of the amine at introduction of a cyclic amino group to the 7-position. Each of these diastereomers was proved more potent in antimicrobial activity as compared with the corresponding quinolone derivatives substituted with a mere cyclopropyl group and, in addition, highly safe with markedly improved selective toxicity. The present invention has been completed based on these findings.

This invention relates to an N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a substituted or unsubstituted cyclic amino group which may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom, and a sulfur atom in its ring; A represents C-X^3

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or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group having from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom; provided that the case wherein R^1 is a hydrogen atom and R^2 is a piperazine or 4-alkyl-substituted piperazine residue is excluded, or a salt thereof.

Specifically implicit in the compounds represented by formula (I) and salts thereof are those wherein R^2 is a cyclic amino group which may be substituted; those wherein R^2 is a 4- to 7-membered cyclic amino group which may be substituted with a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, or a substituted or unsubstituted amino group; those wherein R^2 is a pyrrolidine, piperidine, piperazine, diazabicycloheptane or diazabicyclooctane residue; those wherein R^2 is a cyclic amino group comprising a single stereoisomer; those wherein R^2 is a 3-aminopyrrolidinyl group; those wherein R^2 in a 7-amino-5-azaspiro[2,4]-heptan-5-yl group; and those wherein X^2 is a fluorine atom. More specifically, the compounds according to the present invention include 7-[3-(S)-amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-

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dihydroquinoline-3-carboxylic acid, 7-[3-(S)-amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[7-amino-5-azaspiro[2,4]-heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

In formula (I), when X^3 represents a halogen atom, X^1 and X^3 each preferably represents a fluorine

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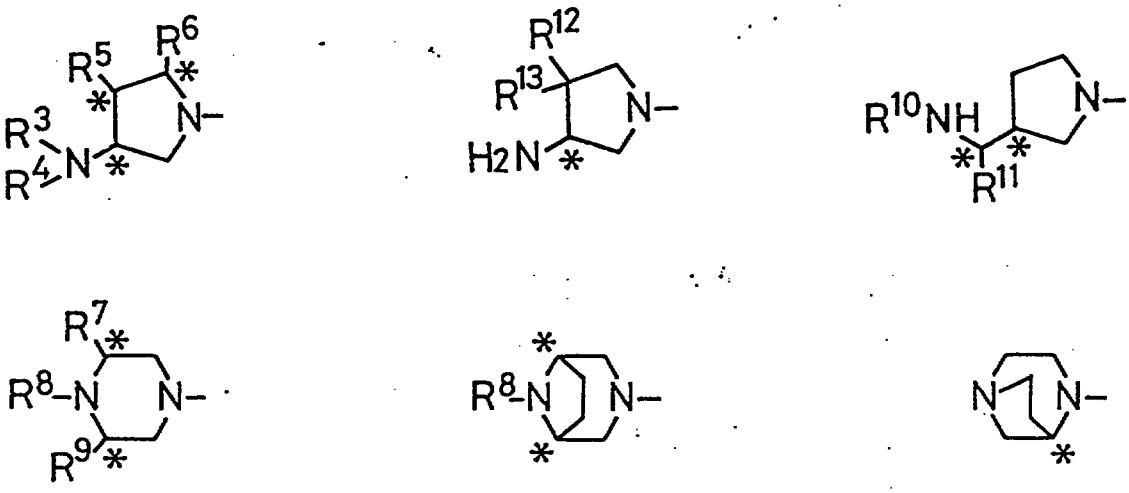
atom or a chlorine atom; and X^2 preferably represents a fluorine atom. R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom, preferably an unsubstituted amino group, a methylamino group, or a hydrogen atom.

R^2 represents a cyclic amino group, preferably a 4- to 7-membered, and more preferably 5- to 6-membered cyclic amino group. The cyclic amino group may further contain oxygen atom(s), sulfur atom(s) and/or nitrogen atom(s), as in oxazolidine, morpholine, thiazolidine, thiomorpholine, imidazolidine, pyrazolidine, and piperazine residues. Of these cyclic amino groups preferred are a pyrrolidine residue and a piperazine residue. The cyclic amino group may have substituents, such as a polar group (e.g., a substituted or unsubstituted amino group, a substituted or unsubstituted aminoalkyl group, a 5-substituted-2-oxo-1,3-dioxol-4-ylmethyl group, a hydroxyl group) and a straight chain, branched, or cyclic alkyl group having up to 6 carbon atoms. Preferred of the polar groups are an unsubstituted amino group, an aminomethyl group, a 1-aminoethyl group, and a hydroxyl group. Preferred of the alkyl group are methyl, ethyl, propyl, gem-dimethyl and gem-diethyl groups and further, these gem-alkyl groups may preferably form a cyclopropane or cyclobutane ring which is

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bonded through a spiro-union to the cyclic amine skeleton. The cyclic amino group further includes a bicyclic amino group composed of crosslinking to 4- to 7-membered cyclic amino groups.

Illustrative examples of these cyclic amino groups, particularly containing the second amino moiety, are shown below;



wherein R^3, R^4, R^5, R^6, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^7, R^8, and R^9, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, provided that the case wherein R^7, R^8, and R^9 each represents a hydrogen atom and the case wherein

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R^7 and R^9 each represents a hydrogen atom and R^8 represents an alkyl group having from 1 to 6 carbon atoms are excluded; R^{10} and R^{11}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^{12} and R^{13}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or they may be connected to each other to form a 3- to 6-membered ring composed of methylene chains; and the asterisk indicates an asymmetric center.

Examples of these cyclic amino groups are 3-aminopyrrolidinyl, 3-methylaminopyrrolidinyl, 3-dimethylaminopyrrolidinyl, 3-ethylaminopyrrolidinyl, 3-propylaminopyrrolidinyl, 3-isopropylaminopyrrolidinyl, 3-amino-4-methylpyrrolidinyl, 3-amino-5-methylpyrrolidinyl, 3-amino-4,5-dimethylpyrrolidinyl, 3-methylamino-4-methylpyrrolidinyl, 3-methylamino-5-methylpyrrolidinyl, 3-methylamino-4,5-dimethylpyrrolidinyl, 3-dimethylamino-4-methylpyrrolidinyl, 3-dimethylamino-5-methylpyrrolidinyl, 3-dimethylamino-4,5-dimethylpyrrolidinyl, 3-methylpiperzinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3,5-dimethylpiperazinyl, 3,4,5-trimethylpiperazinyl, 4-ethyl-3,5-dimethylpiperazinyl, 4-isopropyl-3,5-dimethylpiperazinyl, 3-aminomethylpyrrolidin-

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yl, 3-methylaminomethylpyrrolidinyl, 3-(1-amino)ethylpyrrolidinyl, 3-(1-methylamino)ethylpyrrolidinyl, 3-(1-ethylamino)ethylpyrrolidinyl, 3-(1-amino)propylpyrrolidinyl, 3-(1-methylamino)propylpiperizinyl, 3-aminopyrrolidinyl, 3-amino-4,4-dimethylpyrrolidinyl, 7-amino-5-azaspiro[2,4]heptan-5-yl, 8-amino-6-azaspiro[3,4]-octan-6-yl, 3,4-diazabicyclo[3,2,1]octan-3-yl, 9-methyl-3,9-diazabicyclo[3,2,1]octan-3-yl, and 9-ethyl-3,9-diazabicyclo[3,2,1]octan-3-yl.

The structure of the cyclic amino group at the 7-position have great influences on antimicrobial activity, toxicity, oral absorption, and physical properties such as water solubility. For instance, it is known that quinolones substituted by 3-aminopyrrolidinyl groups have strong antimicrobial spectra against a broad range of microorganisms covering Gram-positive to Gram-negative bacteria. Some quinolone derivatives of this type, however, are susceptible to metabolism or only show low water-solubility.

3-Aminopyrrolidinyl groups having a spiro ring at the carbon atom adjacent to the amine group thereof provide quinolone derivatives exhibit improved oral absorption rate and improved in vivo stability against metabolism while retaining potent antimicrobial activity. The compounds of this type have also been

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proved less causative of convulsion which is known as a side effect of quinolone type synthetic antimicrobials.

Further, 3-aminomethylpyrrolidinyl groups in which an amino group is bonded to a pyrrolidinyl group via a carbon atom provide quinolone derivatives exhibiting enhanced antimicrobial activity against Gram-positive bacteria. In particular, the quinolones of this type in which the carbon atom linking the amino and pyrrolidinyl groups is substituted with one or two alkyl group(s) were found to exhibit improved oral absorption rate, safety, and water solubility over those without such substituent(s).

Additionally preferred as cyclic amino groups are piperazine residues, such as alkylpiperazine residues and piperazine residues having a spiro ring.

Examples of cyclic amino groups having substituents other than an amino group are 3-hydroxypyrrolidinyl, 3-mercaptopyrrolidinyl, 3-hydroxy-4-methylpyrrolidinyl, 3-mercapto-4-methylpyrrolidinyl, morpholino, thiomorpholino, 2-methylmorpholino, 2-methylthiomorpholino, 2,6-dimethylmorpholino, 2,6-dimethylthiomorpholino, 2,2-dimethylmorpholino, and 2,2-dimethylthiomorpholino groups.

The cyclic amino group is bonded to the 7-position of the pyridonecarboxylic acid skeleton prefer-

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ably at the nitrogen atom of the cyclic amino group. As a matter of course, it may be bonded at the other atom.

The stereoisomerism of the cyclic amine moiety at the 7-position is explained below. In cases where a cyclic amine has isomers, if it is reacted in the form of an isomeric mixture with a 1-(1,2-cis-halogenocyclopropyl)quinolone derivative, the resulting quinolone derivative should be a mixture of diasteromers based on the steric relation with the 1,2-cis-2-halogenocyclopropyl group at the 1-position. In these cases, therefore, it is necessary that only one of the isomers of the starting amine should be reacted.

The functional group of the cyclic amino group at the 7-position such as amino, hydroxy and thiol groups may be protected by a conventional protective group prior to the substitution with the quinolone skeleton. The examples of such protective groups include alkoxycarbonyl groups such as t-butoxycarbonyl group, 2,2,2-trichloroethoxycarbonyl group and the like; aralkyloxycarbonyl groups such as benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, p-nitrobenzyloxycarbonyl group and the like; acyl groups such as acetyl group, methoxyacetyl group, trifluoroacetyl group, chloroacetyl group, pivaloyl group, fomyl group, benzoyl group and the like; alkyl or aralkyl groups

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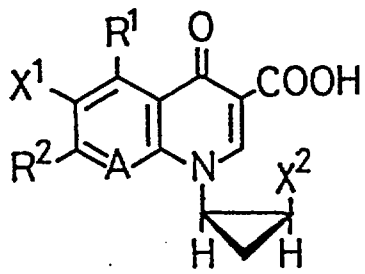
such as t-butyl group, benzyl group, p-nitrobenzyl group, p-methoxybenzyl group, triphenylmethyl group and the like; ethers such as methoxymethyl group, t-butoxymethyl group, 2,2,2-trichloroethoxymethyl group, tetrahydrofuran-2-yl group and the like; silyl groups such as trimethylsilyl group, isopropyldimethylsilyl group, t-butyldimethylsilyl group, t-butyldiphenylsilyl group, tribenzylsilyl group and the like.

The 1,2-cis-2-halogenocyclopropyl group at the N_1-position is described below. Introduction of a halogen atom to the cyclopropyl group particularly a fluorine atom, brings about an effect to reduce lipophilicity of the whole molecule. It is known that drugs are more likely to be distributed to the central nervous system as lipophilicity thereof increases. In this connection, introduction of the 1,2-cis-2-halogenocyclopropyl group yields quinolones having reduced toxicity while retaining excellent antimicrobial activity as compared with the corresponding 1-cyclopropylquinolones. The halogen atom to be introduced includes fluorine and chlorine atoms, with a fluorine atom being preferred.

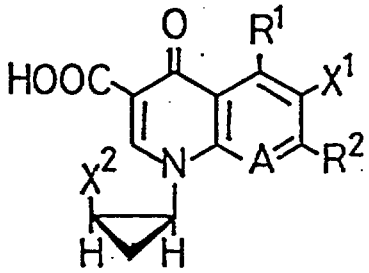
It is particularly preferable that the halogen atom and the pyridonecarboxylic acid moiety are cis with respect to the cyclopropane ring. Irrespective of

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whether the 7-cyclic amino group has stereoisomers or not, the quinolone derivatives of formula (I) have enantiometric pairs ascribed to the cis-2-halogenocyclopropyl moiety at the 1-position as illustrated below. Potent activity and high safety were observed in either of these enantiomers.



and



The pyridonecarboxylic acid derivatives according to the present invention include the respective free acids, acid-addition salts thereof, and the salts of the carboxyl group thereof. The acid-addition salts include inorganic acid salts, e.g., hydrochlorides, sulfates, nitrates, hydrobromides, hydroiodides, and phosphates; and organic acid salts, e.g., acetates, methanesulfonates, benzenesulfonates, toluenesulfonates, citrates, maleates, fumarates, and lactates.

The salts of the carboxyl group may be organic or inorganic and include alkali metal salts, e.g., lithium salts, sodium salts, and potassium salts,

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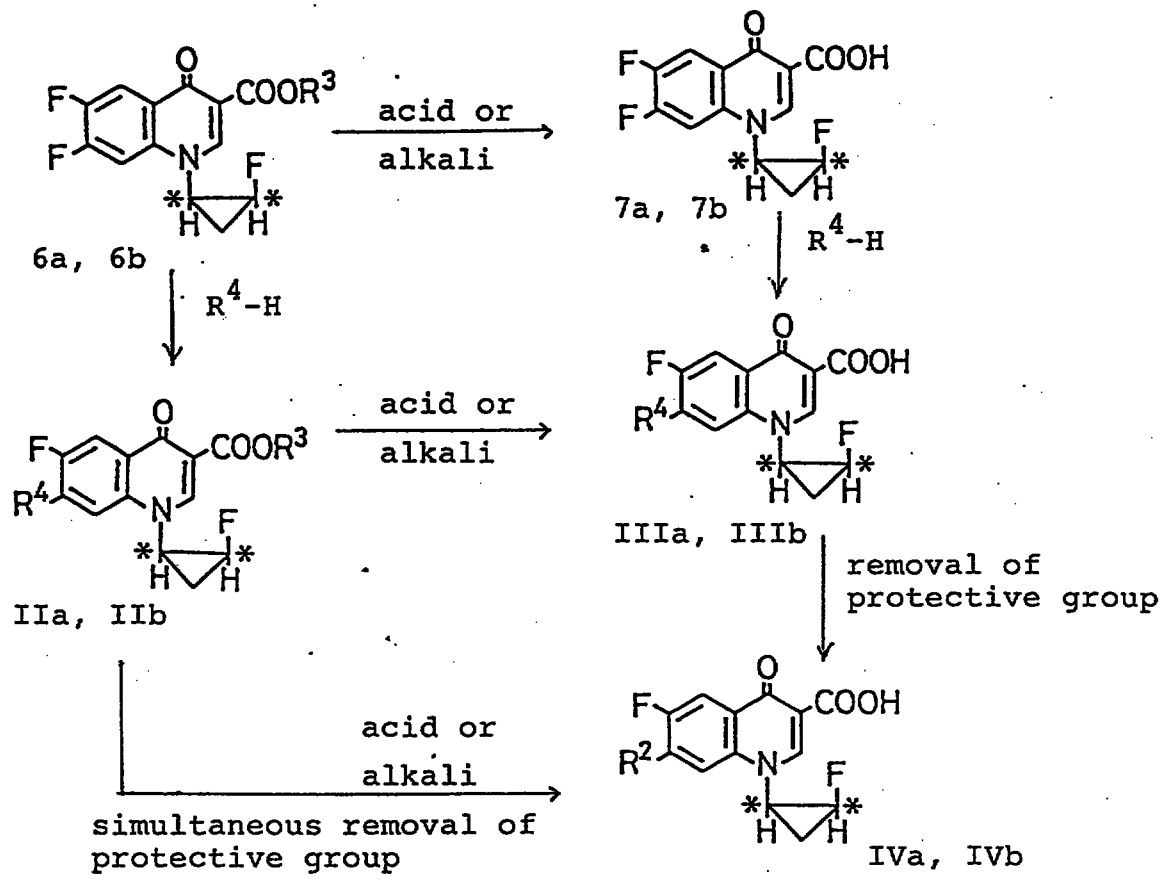
alkaline earth metal salts, e.g., magnesium salts and calcium salts; ammonium salts, triethylamine salts, N-methylglucamates, and tris(hydroxymethyl)aminomethane salts.

Some of these free acids and salts may exist as a hydrate.

Esterification of the carboxylic acid moiety of the pyridonecarboxylic acid derivatives of formula (I) gives compounds useful as synthesis intermediates or pro-drugs. For example, alkyl esters, benzyl esters, alkoxyalkyl esters, phenylaklyl esters and phenyl esters are useful as synthesis intermediates. Esters which are easily severed in the body to form free carboxylic acids are useful as pro-drugs. Examples of such esters are acetoxymethyl esters, pivaloyloxymethyl esters, ethoxy-carbonyloxy esters, chlorine esters, dimethylaminoethyl esters, 5-indanyl esters, phthalidinyl esters, and oxo-alkyl esters (e.g., 5-substituted-2-oxo-1,3-dioxol-4-yl-methyl esters and 3-acetoxy-2-oxobutyl esters).

A process for synthesizing the pyridone-carboxylic acid derivatives of formula (I) is illustrated below, taking the compound wherein A=C-H; R^1=H; X^1=X^2=F; and R^3=Et (ethyl group, hereinafter the same) for instance.

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wherein R^4 has the same meaning as R^2 or a cyclic amino group having the same structure as R^2 but being protected.

An optically active 1-(1,2-cis-2-fluoro-cyclopropyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (6a) or (6b) is hydrolyzed under acidic or alkaline conditions to give a free carboxylic acid derivative (7a) or (7b). The free acid (7a) or (7b) is reacted with a cyclic amine R^4-H to obtain a desired compound (IIIa) or (IIIb). If necessary, a protective group is removed from the resulting compound under proper conditions selected

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according to the protective group to obtain a desired compound (IVa) or (IVb).

The substitution reaction with the cyclic amine can be carried out in a solvent such as dimethyl sulfoxide, pyridine, acetonitrile and 3-methoxybutanol, at a temperature of from room temperature to 150°C, preferably from 40 to 120°C, for 0.5 to 5 hours, usually from 0.5 to 2 hours.

Alternatively, the compound (6a) or (6b) is reacted with a cyclic amine under the same conditions as recited above, and the resulting compound (IIa) or (IIb) as is produced is then hydrolyzed under acidic or alkaline conditions and, if necessary, a protective group is removed, to obtain a desired compound (IIIa) or (IIIb) or (IVa) or (IVb).

The optically active cis-2-fluorocyclopropylamine can be synthesized as follows. 2-Fluorocyclopropanecarboxylic acid is reacted with (R)-(+)-α-methylbenzylamine to yield N-[1-(R)-phenylethyl]-1,2-cis-fluorocyclopropanecarboxamide. The reaction can be carried out in tetrahydrofuran in the presence of N,N-carbonyldiimidazole. The reaction may also be effected in accordance with a mixed anhydride procedure, in which the carboxylic acid is dissolved in an aprotic solvent and reacted with a halogenoformic ester in the presence

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of a base at low temperatures and then reacted with the benzylamine to obtain the carboxamide. The resulting carboxamide can be separated into each isomer by chromatographic techniques.

The aprotic solvent to be used in the mixed anhydride procedure is not particularly limited and includes ethers, e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, and 1,2-dimethoxyethyane; halogenated hydrocarbons, e.g., dichloromethane, chloroform, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane; aromatic hydrocarbons, e.g., benzene, toluene, and xylene; and aliphatic hydrocarbons, e.g., pentane, hexane, heptane, and cyclohexane. Commonly employed of them is tetrahydrofuran or chloroform. The water contained in the solvent to be used is usually removed beforehand.

The halogen atom in the halogenoformic ester is normally a chlorine atom. The halogenoformic ester includes methyl, ethyl, 2,2,2-trichloroethyl, phenyl, p-nitrophenyl and benzyl esters.

The base to be used may be either an organic or an inorganic. The inorganic base includes alkali metal hydroxides, carbonates and hydrogencarbonates, e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate,

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potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate. The organic base includes trialkylamines, e.g., triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine; dialkylanilines, e.g., diethylaniline and dimethylaniline; and heterocyclic compounds, e.g., N-methylmorpholine, pyridine, and N,N-dimethylaminopyridine.

Separation of the carboxamide into optical isomers can be effected by known techniques, such as silica gel column chromatography under normal pressure or under pressure, preparative thin layer chromatography, and high performance liquid chromatography (HPLC). Separation into optical isomers can also be performed by other separation techniques generally employed, such as recrystallization and reprecipitation.

The thus separated optionally active carboxamide can be led to an optically active cis-2-fluorocyclopropanecarboxylic acid by hydrolysis. The reaction can be carried out by dissolving the carboxamide in, for example, concentrated hydrochloric acid, followed by heating. The hydrochloric acid may be replaced with sulfuric acid or nitric acid. A solvent, such as acetic acid and a lower alcohol, may be used.

The resulting carboxylic acid can be converted at once by Curtius reaction in the presence of a t-butanol

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to a protected cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane. The reaction can be carried out conveniently by use of diphenylphosphorylazide, but the synthesis of the intermediate azide compound is not limited thereto, and general methods of synthesis can be applied.

The resulting optically active cis-2-fluorocyclopropylamine derivative can be made use of in obtaining a quinolone derivative having a cis-fluorocyclopropyl group at the 1-position as a single isomer. The quinolone derivative according to the present invention can then be obtained by reacting this isomer with the cyclic amine as described above.

The pyridonecarboxylic acid derivatives according to the present invention exhibit potent antimicrobial activity and thus can be used as human and veterinary medicines, fish medicines, agricultural chemicals, and food preservatives.

The dose of the pyridonecarboxylic acid derivatives for use as human medicines ranges from 50 mg to 1 g, preferably from 100 mg to 300 mg, per day for adult. The dose for use as veterinary medicines generally ranges from 1 mg to 200 mg, preferably from 5 mg to 100 mg, per kg of body weight per day, though more or less verying depending on the purpose of administra-

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tion (therapeutic use or preventive use, etc.), the kind and size of the animal, the kind of pothogenic organisms, and the symptoms. The daily dose recited above may be divided into 2 to 4 doses per day. If necessary, the daily dose may be sometimes deviated from the above-recited range.

The pyridonecarboxylic acid derivatives of this invention are active against a wide variety of microorganisms causing various infectious diseases and capable of curing or alleviating and/or preventing the diseases caused by such phthogenes.

Illustrative examples of bacteria or bacterium-like microorganisms on which the pyridonecarboxylic acid derivatives of the invention are effective are Staphylococcus sp., Streptococcus pyogenes, Streptococcus Haemolyticus, enterococci, Streptococcus pneumoniae, Peptostreptococcus sp., Neisseria gonorrhoeae, Escherichia coli, Citrobacter sp., Shigella sp., Klebsiella pneumoniae, Enterobacter sp., Serratia sp., Proteus sp., Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter sp., Campylobacter sp., and Chlamidiae.

Examples of diseases caused by these pathogenes include folliculitis, furuncle, carbuncle, erysipelas, phlegmon, lymphangitis/lymphadenitis, felon, subcutaneous abscess, spiradenitis, acne conglobata,

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infectious atheroma, perianal abscess, mastadenitis, superficial secondary infections after trauma, burn or surgery trauma, pharyngolaryngitis, acute bronchitis, tonsillitis, chronic bronchitis, bonchiectasis, diffuse panbronchiolitis, secondary infections of chronic respiratory diseases, pneumonia, pyelonephritis, cystitis, prostatitis, epididymitis, gonococcal urethritis, non-gonococcal urethritis, cholecystitis, cholangitis, bacillary dysentery, enteritis, adnexitis, intrauterine infections, Bartholinitis, blepharitis, hordeolum, dacryocystitis, tarsadenitis, keratohelcosis, otitis media, sinusitis, paradentitis, pericoronitis circumcoronitis, gnathitis, peritonitis, endocarditis, septicemia, meningitis, and skin infectious.

Examples of susceptible microorganisms causing veterinary infectious diseases include those of fowl, such as Escherichia sp., Salmonella sp., Pasteurella sp., Haemophilus sp., Bordetella sp., Staphylococcus sp., and Mycoplasma sp. Specific examples of veneterinary diseases caused by these microorganisms include colibacillosis, pullorum disease, avian paratyphosis, fowl chlera, infectious coryza, staphylococcal infections, and mycoplasmal diseases; those of swin, such as colibacillosis, malmonelosis, pasteurellosis, haemophylus infection, atrophic rhintis,

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exduadative epidermitis, and mycoplasmal diseases; those for cattle, such as colibacillosis, salmonellosis, hemorrhagic septicemia, mycoplasmal diseases, bovine contageous pleurponeumonia, and bovine mastesis; those of dogs, such as coliform sepsis, salmonelosis, hemorrhagic septicemia, pyometra, and cystitis; and those of cats, such as hemorrhagic pleuritis, cystitis, chronic rhiniti, haemophylus infection, kitten diarrhea, and mycoplasmal diseases.

The compound of the present invention can be formulated into antimicrobial preparations in an appropriate dose form according to administration route selected by the conventional preparation methods. The dose form for oral administration includes tablets, powders, granules, capsules, solutions, syrups, elixiers, and oily or aqueous suspensions. Injections may contain, in addition to the active ingredient, stabilizers, antiseptics, and solubilizing agents. The solution which may contain such excipients is put in a container and further, the solution may be subjected to lyophilization or the like means to prepare solid preparations which can be dissolved on use. The container may contain either a single dose or several doses.

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Dose forms for external administration include solutions, suspensions, emulsions, ointments, gels, creams, lotions, and sprays.

In the preparation of solid preparations, the active ingredient may be mixed with appropriately selected pharmaceutically acceptable excipients, such as fillers, extenders, binders, disintegrators, dissolution accelerators, wetting agents, and lubricants.

Liquid preparations include solutions, suspensions, and emulsions. They may contain excipients, such as suspension stabilizers and emulsifiers.

The compound of the present invention can be administered to animals orally either directly or as admixed to feedstuff, or its solution may be given either directly or as admixed to water or feedstuff. The compound may also be administered non-orally by, for example, injection.

The compound of the invention can be formulated into preparations for animals, such as powders, fine granules, solubilized powders, syrups, solutions, and injections, by commonly employed preparation methods.

Formulation Examples are given below for illustrative purposes only but not for limitation.

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FORMULATION EXAMPLE 1

Capsule:

Compound of Example 8	100.0 mg
Corn starch	23.0 mg
Calcium carboxymethyl cellulose	22.5 mg
Hydroxypropylmethyl cellulose	3.0 mg
Magnesium stearate	1.5 mg
total:	150.0 mg

FORMULATION EXAMPLE 2

Solution:

Compound of Example 7	1 to 10 g
Acetic acid or sodium hydroxide	0.5 to 2 g
Ethyl p-hydroxybenzoate	0.1 g
Purified water	88.9 to 98.4 g
total:	100 g

FORMULATION EXAMPLE 3

Powder for Admixture with Feedstuff:

Compound of Example 6	1 to 10 g
Corn starch	98.5 to 98.5 g
Light anhydrous silicic acid	0.5 g
total:	100 g

The present invention is now illustrated in greater detail by way of the following Examples and Reference Examples, but it should be understood that the

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present invention is not deemed to be limited thereto. Reference Examples describe the syntheses of optically active skeletons from an optically active cis-2-fluorocyclopropanecarboxylic acid.

Antimicrobial activity of the optically active compounds prepared in Examples was evaluated in accordance with the standard method specified by Nippon Kagakuryoho gakkai, and results obtained are shown in Table 1 below in terms of minimum inhibitory concentration (MIC: $\mu g/m^2$).

REFERENCE EXAMPLE 1

N-[1-(R)-Phenylethyl]-1,2-cis-2-fluorocyclopropanecarboxamide (2a, 2b):

1-1. Carbonyldiimidazole Method:

One gram of cis-2-fluorocyclopropanecarboxylic acid was dissolved in 30 ml of tetrahydrofuran (THF), and 1.78 g of N,N'-carbonyldiimidazole was added thereto, and the mixture was stirred at room temperature for 1 hour. To the solution was added 1.45 g of (R)-(+)-α-methylbenzylamine, and the stirring was continued for 2 hours. The solvent was removed under reduced pressure, and the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced

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pressure. From the residual viscous oily substance, each stereoisomer was isolated by HPLC under conditions shown below. Each isomer was recrystallized from diisopropyl ether to yield the titled compound (2a) or (2b).

HPLC Conditions:

Column: Nucleosil 50-5 (20 mm ID × 250 mm L) (senshu Pack SSC Silica, 782-IN, produced by Senshu Kagaku)

Solvent: ethyl acetate-THF (9:1 by volume)

Flow Rate: 9.0 ml/min

Retention Time: 11 mins, for Compound (2a)

13 mins. for Compound (2b)

Compound (2a):

Melting point: 108°C

Elementary Analysis for $C_{12}H_{14}FNO$:

Calcd. (%): C 69.55; H 6.81; N 6.76

Found (%): C 69.31; H 7.01; N 6.65

$[\alpha]_D$: +61.96° (c=0.965, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.92-1.34 (2H, m), 1.50 (3H, d, J=7Hz), 1.50-1.96 (1H, m), 4.68 (1H, dm, J=64Hz), 5.14 (1H, m), 7.40 (5H, s)

Physiochemical Properties of Compound (2b):

Melting point: 102°C

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Elementary Analysis for $C_{12}H_{14}FNO$:

Calcd. (%): C 69.55; H 6.81; N 6.76

Found (%): C 69.45; H 6.87; N 6.70

$[\alpha]_D$: +143.61° (c=0.830, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.98=1.34 (2H, m), 1.52 (3H, d, J=7Hz), 1.64-1.96 (1H, m), 4.58 (1H, dm, J=66Hz), 5.24 (1H, m), 7.40 (5H, m)

1-2. Mixed Anhydride Method:

In 50 ml of THF were dissolved 4.19 g of 2-fluorocyclopropanecarboxylic acid (cis-trans mixture) and 4.07 g of triethylamine, and the solution was cooled to -10°C. To this was added a solution of 4.73 g of ethyl chloroformate in 20 ml of THF and the mixture was stirred for 10 minutes. To the solution was then added dropwise a solution of 4.88 g of (R)-(+)-α-methyl-benzylamine in 30 ml of THF at that temperature, and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure, and the residue was extracted with benzene. The extract was washed successively with a 10% citric acid aqueous solution, a 1N sodium hydroxide aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting pale yellow oily substance was purified by

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silica gel column chromatography using a mixed solvent of benzene and ethyl acetate as an eluent to each of the titled compounds (2a) and (2b).

REFERENCE EXAMPLE 2

(+)-cis-2-Fluorocyclopropanecarboxylic acid (3a):

In 15 ml of concentrated hydrochloric acid was dissolved 530 mg of the amide compound (2a) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. To the reaction mixture was added 20 ml of water, and the mixture was extracted with ethyl acetate. The extract was then extracted with a sodium hydrogencarbonate aqueous solution and this aqueous extract was washed with ethyl acetate. The aqueous extract was adjusted to a pH of 5 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield the titled compound (3a) as a pale yellow oil.

$[\alpha]_D$: -23.13° (c=1.020, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.60-2.10 (2H, m), 4.82 (1H, dm, J=65Hz), 12.0 (1H, s)

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REFERENCE EXAMPLE 3

(+)-cis-2-Fluorocyclopropanecarboxylic acid (3b):

In 30 ml of concentrated hydrochloric acid was dissolved 1.65 g of amide compound (2b) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. The pH of the reaction mixture was adjusted between 8 and 9 with sodium hydrogencarbonate and then washed with chloroform. The pH of aqueous layer was adjusted to 4 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the titled compound (3b) as a pale yellow oil.

$[\alpha]_D$: +21.56° (c=1.113, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.56-1.98 (2H, m), 4.76 (1H, dm, J=66Hz), 11.32 (1H, s)

REFERENCE EXAMPLE 4

(+)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4a):

In 5 ml of t-butanol were dissolved 200 mg of the carboxylic acid (3a) as obtained in Reference Example 2, 603 mg of diphenylphosphorylazide, and 203 mg of triethylamine, and the solution was heated under

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reflux for 4.5 hours. After removing the solvent under reduced pressure, the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution, a 2% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using chloroform as an eluent to obtain the titled compound (4a) as a colorless crystal.

Melting Point: 73°C

$[\alpha]_D$: +65.57° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.62 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 5

(-)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4b):

In 6 ml of t-butanol were added 265 mg of the carboxylic acid (3b) as obtained in Reference Example 3, 800 mg of diphenylphosphorylazide, and 270 mg of triethylamine. The solution was allowed to react and worked up in the same manner as in Reference Example 4 to obtain the titled compound (4b).

Melting Point: 63°C

$[\alpha]_D$: -60.27 (c=0.740, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.66-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.58 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 6

(-)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)amino-methylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5a):

Ethyl 2,4,5-trifluorobenzoylacetate (234 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Compound (4a) as obtained in Reference Example 4 (167 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for 20 minutes and concentrated to dryness under reduced pressure (the resulting amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloromethane and cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was added dropwise thereto. Thereafter, the above prepared dichloromethane solution was added dropwise to the mixture, followed by stirring at room temperature over-night. The solvent was evaporated to dryness under reduced pressure, and the residue was subjected to

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silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after the removed of the solvent. The product was recrystallized from diisopropyl ether-n-hexane to yield the titled compound (5a) as a colorless crystals.

Melting Point: 69-70°C

$[\alpha]_D$: -10.29° (c=1.088, chloroform)

REFERENCE EXAMPLE 7

(+)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)amino-methylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5b):

Ethyl 2,4,5-trifluorobenzoylacetate (337 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Compound (4b) as obtained in reference Example 5 (240 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for 1 hour, followed by concentration under reduced pressure (the amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloroethane, and the solution was cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was

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added thereto dropwise, and the above-prepared dichloromethane solution was further added to the mixture, followed by stirring at room temperature over-night. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after the removal of solvent. Recrystallization from diisopropyl ether-n-hexane gave the titled compound (5b) as a colorless crystal.

Melting Point: 69-70°C

$[\alpha]_D$: +12.09 (c=0.645, chloroform)

REFERENCE EXAMPLE 8

(+)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6a):

In 15 ml of anhydrous dioxane was dissolved 180 mg of Compound (5a) as obtained in Reference Example 6, and 200 mg of 60% sodium hydride was added to the solution, followed by stirring at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel

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preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing solvent to yield the titled compound (6a) as a colorless crystal.

Melting Point: 231-232°C

$[\alpha]_D$: +27.20° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.20 (3H, t, J=7Hz), 1.6-1.9 (2H, m), 3.28-3.56 (1H, m), 4.42 (2H, q, J=7Hz), 5.11 (1H, dm, J=63Hz), 7.60 (1H, dd, J=11Hz & 7Hz), 8.28 (1H, dd, J=10Hz & 11Hz), 8.58 (1H, s)

REFERENCE EXAMPLE 9

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6b):

In 15 ml of anhydrous dioxane was dissolved 267 mg of Compound (5b) as obtained in Reference Example 7, and 200 mg of 60% sodium hydride was added thereto, and the mixture was stirred at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing

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solvent to yield the titled compound (6b) as a colorless crystal.

Melting Point: 226-227°C

$[\alpha]_D$: -31.36° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.22 (3H, t, J=7Hz), 1.5-1.9 (2H, m), 3.26-3.52 (1H, m), 4.40 (2H, q, J=7Hz), 5.10 (1H, dm, J=63Hz), 7.58 (1H, dd, J=11Hz & 7Hz), 8.26 (1H, dd, J=10Hz & 11Hz), 8.55 (1H, s)

REFERENCE EXAMPLE 10

(+)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7a):

In 15 ml of concentrated hydrochloric acid was dissolved 106 mg of the ester (6a) as obtained in Reference Example 8, and the solution was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture was added 15 ml of water, and the precipitate was collected by filtration to obtain the titled compound (7a) as a colorless crystal.

Melting Point: 265-270°C

$[\alpha]_D$: +3.66° (c=0.383, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H, dm, J=64Hz), 7.82 (1H, dd, J=12Hz, & 7Hz), 8.37 (1H, dd, J=18Hz & 8Hz), 8.94 (1H, s)

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REFERENCE EXAMPLE 11

(-)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7b):

In 10 ml of concentrated hydrochloric acid was dissolved 150 mg of the ester (6b) as obtained in Reference Example 9, and the solution was heated at 110°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to yield the titled compound (7b) as a colorless crystal.

Melting Point: 261-264°C

$[\alpha]_D$: -4.08° (c=0.343, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H, dm, J=64Hz), 7.82 (1H, dd, J=12Hz & 7Hz), 8.37 (1H, dd, J=12Hz & 8 Hz), 8.94 (1H s)

EXAMPLE 1

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (8a):

Seventy milligrams of the carboxylic acid (7a) as obtained in Reference Example 10, 150 mg of (S)-3-(t-butoxycarbonylamino)pyrrolidine, 200 mg of triethyl-

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amine, and 20 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to obtain the titled compound (8a) as a yellow crystal.

Melting Point: 236-239°C

$[\alpha]_D$: +1.0°(c=0.200, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.7 (2H, m), 1.46 (9H, s), 1.7-1.9 (1H, m), 2.0-2.36 (1H, m), 3.3-4.0 (5H, m), 4.2-4.4 (1H, m), 5.06 (1H, dm, J=68Hz), 6.68 (1H, d, J=7Hz), 7.84 (1H, d, J=14Hz), 8.46 (1H, s)

EXAMPLE 2

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (8b):

The carboxylic acid as obtained in Reference Example 11 (7b) (112 mg), 200 mg of (S)-3-(t-butoxycarboxylamino)pyrrolidine, 220 mg of triethylamine, and 15 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the

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residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to yield the titled compound (8b) as a yellow crystal.

Melting Point: 242-243°C

$[\alpha]_D$: -4.0°(c=0.448, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.7 (2H, m), 1.40 (9H, s), 1.6-1.8 (1H, m), 1.9-2.1 (1H, m), 3.3-3.9 (5H, m), 4.2-4.5 (1H, m), 5.00 (1H, dm, J=68Hz), 6.58 (1H, d, J=7Hz), 7.72 (1H, d, J=14Hz), 8.32 (1H, s)

EXAMPLE 3

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

In 10 ml of trifluoroacetic acid was dissolved 80 mg of the carboxylic acid (8a) as obtained in Example 1. After stirring for 20 minutes, the reaction mixture was evaporated under reduced pressure to dryness. To the residue was added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of aqueous layer was adjusted to 7.5 with 1N hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous

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sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from ethanol yielded the titled compound as a colorless crystal.

Melting Point: 248-252°C

$[\alpha]_D$: -31.35° (c=0.370, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.52-1.68 (2H, m), 1.68-1.80 (1H, m), 2.05-2.15 (1H, m), 3.13-3.22 (1H, m), 3.25-3.45 (2H, m), 3.45-3.65 (3H, m), 5.12 (1H, dm, J=65Hz), 6.58 (1H, d, J=7Hz), 7.58 (1H, d, J=14Hz), 8.29 (1H, s)

EXAMPLE 4

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

In 10 ml of trifluoroacetic acid was added 80 mg of the carboxylic acid (8b) as obtained in Example 2. After stirring for 20 minutes, the reaction mixture was evaporated to dryness under reduced pressure. To the residue was added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of aqueous layer was adjusted to 7.5 with 1N hydrochloric acid and followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed therefrom

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under reduced pressure. Recrystallization of the residue from ethanol gave the titled compound (9b) as a colorless crystal.

Melting Point: 236-240°C

$[\alpha]_D$: +23.72 (c=0.413, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.55-1.69 (2H, m), 1.69-1.77 (1H, m), 2.07-2.15 (1H, m), 3.15-3.22 (1H, m), 3.37-3.47 (2H, m), 3.52-3.58 (2H, m), 3.58-3.66 (1H, m), 5.13 (1H, dm, J=65Hz), 6.62 (1H, d, J=7Hz), 7.61 (1H, d, J=14Hz), 8.30 (1H, s)

REFERENCE EXAMPLE 12

(-)-Ethyl 2-[[1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)-propionate (10a):

Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 5 ml of dichloromethane.

Seven milliliters of trifluoroacetic acid was cooled with ice, and 480 mg of (+)-cis-1-(t-butoxy-carbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature

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for 20 minutes, followed by evaporation under reduced pressure to dryness. The residue was suspended in 10 ml of dichloromethane, and 3 ml of triethylamine was added thereto under ice-cooling. After stirring for 20 minutes, the above-prepared dichloromethane solution was added thereto, and the mixture was stirred for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using a mixed solvent of benzene and ethyl acetate (5:1 by volume) as an eluent. The solvent was removed under reduced pressure, and the residue was washed with diisopropyl ether to obtain 620 mg of the titled compound (10a).

Melting Point: 98-100°C

$[\alpha]_D$: -6.66° (c=0.998, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 49.26; H 3.31; N 3.83

Found (%): C 49.39; H 3.22; N 3.86

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

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REFERENCE EXAMPLE 13

(+)-2-[[1,2-cis-2-Fluoro-1-cyclopropyl)amino]methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)propionate (10b):

Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid were ice-cooled, and 1.12 g of (-)-cis-1-(t-butoxycarbonyl-amino)-2-fluorocyclopropane (4b) was dissolved therein. After stirring at room temperature for 20 minutes, the mixture was evaporated to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine was added to the suspension under ice-cooling. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography which was eluted with a mixed solvent of benzene and ethyl acetate (4:1 by volume) The solvent

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of the eluent was removed under reduced pressure. The residue was washed with diisopropyl ether-n-hexane to obtain 1.74 g of crystals of the titled compound (10b).

Melting Point: 99-100°C

$[\alpha]_D$: +6.70° (c=0.895, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 49.26; H 3.31; N 3.83

Found (%): C 49.41; H 3.60; N 4.06

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

REFERENCE EXAMPLE 14

(+)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11a):

In 7 ml of anhydrous dioxane was dissolved 620 mg of Compound (10a) as prepared in Reference Example 12, and 80 mg of 60% sodium hydride was added to the solution, followed by stirring at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the

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solvent was removed therefrom under reduced pressure. The residue was washed with n-hexane to obtain 551 mg of the titled compound (11a) as a colorless crystal.

Melting Point: 181-184°C

$[\alpha]_D$: +45.1° (c=1.18, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 52.12; H 3.21; N 4.05

Found (%): C 52.09; H 3.33; N 4.01

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

REFERENCE EXAMPLE 15

(-)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11b):

In 10 ml of anhydrous dioxane was suspended 560 mg of 60% sodium hydride having been washed twice with anhydrous n-hexane. The suspension was added to a solution of 1.70 g of Compound (10b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 2 hours. The solvent was removed under reduced pressure, and 0.1N hydrochloric acid was added to the residue. The precipitated crystals were collected by filtration, washed successively with water and diethyl

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ether, and dried under reduced pressure to obtain 1.44 g of the entitled compound (11b) as a colorless crystal.

Melting Point: 174°C

$[\alpha]_D$: -45.3° (c=1.05, chloroform)

Elementary Analysis for $C_{15}H_{11}ClF_4NO_3$:

Calcd. (%): C 52.12; H 3.21; N 4.05

Found (%): C 51.80; H 3.45; N 4.15

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

IR(KBr); ν_{max} cm^{-1}: 3100, 2998, 1731, 1638, 1614, 1470, 1317

REFERENCE EXAMPLE 16

(+)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12a):

The ester (11a) (540 mg), 5 ml of concentrated hydrochloric acid, and 5 ml of acetic acid were mixed, and the mixture was heated at 120-130°C for 2 hours while stirring. To the reaction mixture was added 50 ml of water, and the precipitated crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to

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obtain 420 mg of the titled compound (12a) as a colorless crystal.

Melting Point: 170-171°C

$[\alpha]_D$: +30.4° (c=0.54, chloroform)

Elementary Analysis for $C_{13}H_7ClF_3NO_3$:

Calcd. (%): C 49.16; H 2.22; N 4.41

Found (%): C 49.21; H 2.49; N 4.27

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

REFERENCE EXAMPLE 17

(-)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b)

The ester (11b) (1.40 g) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 110°C for 2.5 hours under stirring. To the reaction mixture was added 50 ml of water, and the precipitated crystals were collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to obtain 1.16 g of the titled compound (12b) as a colorless crystal.

Melting Point: 177-182°C

$[\alpha]_D$: -26.8° (c=0.90, chloroform)

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Elementary Analysis for $C_{13}H_7ClF_3NO_3$:

Calcd. (%): C 49.16; H 2.22; N 4.41

Found (%): C 49.28; H 2.40; N 4.66

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

EXAMPLE 5

(+)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (13a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12a) and 400 mg of triethylamine, followed by refluxing for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure, and to the residue was added 1N hydrochloric acid. The mixture was washed with chloroform. The pH of the aqueous layer was adjusted to 12 with a 1N sodium hydroxide aqueous solution and washed with chloroform. The pH of the aqueous layer was readjusted to 7.6 with

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hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 138 mg of the titled compound (13a) as a colorless crystal.

Melting Point: 214-217°C (with decomposition)

$[\alpha]_D$: +120.8° (c=0.475, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot 1/2H_2O$:

Calcd. (%): C 51.98; H 4.36; N 10.70

Found (%): C 52.07; H 4.71; N 10.72

^{1}H-NMR (NaOD) δ ppm:

1.28 (1H, dm, J=27Hz), 1.69-1.78 (2H, m), 3.39-3.42 (1H, m), 3.51-3.61 (3H, m), 3.69-3.72 (1H, m), 4.13-4.17 (1H, m), 4.99 (1H, dm, J=70Hz), 7.72 (1H, d, J=14Hz), 8.44, 8.45 (1H, each s, split, 1:1)

EXAMPLE 6

(-)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (13a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in

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15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12b) and 400 mg of triethylamine, and the mixture was heated under reflux for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure. A 1N hydrochloric acid was added to the residue, and the mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, and the aqueous layer was adjusted to a pH of 7.6 with hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to give 158 mg of the titled compound (13b) as a colorless crystal.

Melting Point: 247-252°C (with decomposition)

$[\alpha]_D$: -94.7° (c=0.378, 0.1N HaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot H_2O$:

Calcd. (%): C 50.82; H 4.52; N 10.46

Found (%): C 50.97; H 5.14; N 10.42

^{1}H-NMR (NaOD) δ ppm:

1.32 (1H, dm, J=27Hz), 1.73-1.80 (2H, m), 2.15-2.19 (1H, m), 3.19-3.22 (1H, m), 3.45-3.50 (1H, m), 3.58-3.62 (1H, m), 3.85-3.88 (2H, m), 4.16-4.20 (1H, m), 4.99 (1H, dm, J=63Hz), 7.76 (1H, d, J=14Hz), 8.54, 8.44 (1H, each s, split, 1:1)

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REFERENCE EXAMPLE 18

(-)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)-propionate (14a):

Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 120°C for 2 hours. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 1.1 g of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporating to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling, followed by stirring for 20 minutes. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 30 minutes. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the compound (14a) were combined, and the solvent was removed under reduced

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pressure. The residue was washed with n-hexane to yield 1.57 g of crystals of the titled compound (14a).

Melting Point: 99-100°C

$[\alpha]_D$: -10.3° (c=1.25, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$

Calcd. (%): C 45.70; H 2.81; N 7.10

Found (%): C 45.60; H 3.01; N 7.03

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.55 (2H, m), 2.88-3.16 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.29 (1H, d, J=14Hz)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521, 1482

REFERENCE EXAMPLE 19

(+)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)-propionate (14b):

Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1 hour while stirring. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was ice-cooled, and 1.10 g of (-)-cis-1-(t-butoxycarbonyl-

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amino)-2-fluorocyclopropane (4b) was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was suspended in 20 ml of dichloromethane. To the suspension was added 1.8 g of triethylamine under ice-cooling, followed by stirring for 20 minutes. To the mixture was added the above-prepared dichloromethane solution, followed by stirring for 2 hours. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the product (14b) were combined, and the solvent was removed under reduced pressure. The residue was washed with n-hexane to yield 1.50 g of crystals of the titled compound (14b).

Melting Point: 98-100°C

$[\alpha]_D$: -10.1° (c=2.09, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$

Calcd. (%): C 45.70; H 2.81; N 7.10

Found (%): C 45.77; H 3.38; N 7.18

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.5 (2H, m), 2.88-3.12 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.30 (1H, d, J=14Hz)

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IR(KBr): ν_{max} cm^{-1}: 3454 1695, 1638, 1554, 1515

REFERENCE EXAMPLE 20

(+)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15a):

In 20 ml of anhydrous dioxane was suspended 580 mg of 60% sodium hydride having been washed twice with n-hexane. The suspension was added to a solution of 1.90 g of Compound (14a) in 20 ml of anhydrous dioxane. The mixture was stirred at room temperature for 1 hour, and the solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid. The crystals thus formed were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.65 g of the titled compound (15a) as a colorless crystal.

Melting Point: 172-176°C

$[\alpha]_D$: +10.7° (c=1.12, chloroform)

Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$

Calcd. (%): C 48.14; H 2.69; N 7.49

Found (%): C 48.29; H 2.78; N 7.20

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.80-4.08 (1H, m), 4.34 (2H, q, J=7Hz), 4.99 (1H, dm, J=63Hz), 8.55 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521 1482

REFERENCE EXAMPLE 21

(-)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15b):

In 10 ml of anhydrous dioxane was suspended 440 mg of 60% sodium hydride having been washed twice with n-hexane. The suspension was added to a solution of 1.45 g of Compound (14b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 30 minutes. The solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid, and the formed crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.18 g of the titled compound (15b) as a colorless crystal.

Melting Point: 171-175°C

$[\alpha]_D$: -11.1° (c=0.27, chloroform)

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Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$

Calcd. (%): C 48.14; H 2.69; N 7.49

Found (%): C 48.44; H 3.17; N 7.48

^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.74-4.02 (1H, m), 4.36 (2H, q, J=7Hz), 4.94 (1H, dm, J=62Hz), 8.54 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 1731, 1626, 1566, 1485, 1323, 1275

REFERENCE EXAMPLE 22

(+)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16a):

The nitro compound (15a) (1.60 g), 6 ml of Raney nickel, and 200 ml of ethanol were mixed, and the mixture was shaken for 2.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16a) were combined, and the solvent was removed therefrom under reduced pressure. The residue was recrystallized from ethanol to obtain 770 mg of the titled compound (16a) as a pale yellow crystal.

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Melting Point: 190-191°C

$[\alpha]_D$: +26.0° (c=0.76, chloroform)

Elementary Analysis for $C_{15}H_{12}F_4N_2O_3$

Calcd. (%): C 52.33; H 3.51; N 8.14

Found (%): C 52.13; H 3.95; N 8.13

^{1}H-NMR ($CDCl_3$) δ ppm:

1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.37 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1557, 1461, 1284

REFERENCE EXAMPLE 23

(-)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (16b):

The nitro compound (15b) (1.60 g), 3 ml of Raney nickel, and 120 ml of ethanol were mixed, and the mixture was shaken for 4.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16b) were combined, and the solvent was removed under reduced pressure. The residue

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was recrystallized from ethanol to obtain 620 mg of the titled compound (16b) as a pale yellow crystal.

Melting Point: 191-193°C

$[\alpha]_D$: -25.9° (c=0.65, chloroform)

Elementary analysis for $C_{15}H_{12}F_4N_2O_3$

Calcd. (%): C 52.33; H 3.51; N 8.14

Found (%): C 52.16; H 3.54; N 8.08

^{1}H-NMR ($CDCl_3$) δ ppm:

1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.38 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1593, 1464, 1284

REFERENCE EXAMPLE 24

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17a):

The ester (16a) (750 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 610 mg of the titled compound (17a) as a colorless crystal.

Melting Point: 297-300°C

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Elementary Analysis for $C_{13}H_8F_4N_2O_3$

Calcd. (%): C 49.38; H 2.55; N 8.86

Found (%): C 49.43; H 2.91; N 8.84

^{1}H-NMR (DMSO-d_6) δ ppm:

1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

REFERENCE EXAMPLE 25

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17b):

The ester (16b) (588 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 514 mg of the titled compound (17b) as a colorless crystal.

Melting Point: 295-300°C

Elementary Analysis for $C_{13}H_8F_4N_2O_3$

Calcd. (%): C 49.38; H 2.55; N 8.86

Found (%): C 49.41; H 2.81; N 8.88

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)

IR: ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

EXAMPLE 7

(-)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (18a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17a) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid,

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followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 128 mg of the titled compound (18a) as a colorless crystal.

Melting Point: 224-230°C

$[\alpha]_D$: -4.72° (c=0.888, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{17}F_3N_4O_3$

Calcd. (%): C 53.40; H 4.48; N 14.65

Found (%): C 53.28; H 4.08; N 14.54

^{1}H-NMR (NaOD)) δ ppm:

1.47-1.58 (1H, m), , 1.67-1.78 (2H, m), 2.07-2.11 (1H, m), 3.28-3.44 (1H, m), 3.48-3.52(1H, m), 3.60-3.66 (1H, m), 3.71-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.18 (1H, s)

IR: ν_{max} cm^{-1}: 3400, 1728, 1635, 1605, 1518, 1433, 1350, 1308

EXAMPLE 8

(+)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (18b):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved

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therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17b) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 68 mg of the titled compound (18b) as a colorless crystal.

Melting Point: 214-217°C

$[\alpha]_D$: +31.3° (c=0.268, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{17}F_3N_4O_3 \cdot 1/2H_2O$:

Calcd. (%): C 52.18; H 4.64; N 14.32

Found (%): C 52.22; H 4.93; N 14.23

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^{1}H-NMR (NaOD) δ ppm:

1.48-1.58 (1H, m), , 1.66-1.79 (2H, m), 2.06-2.12 (1H, m), 3.29-3.32 (1H, m), 3.48-3.52(1H, m), 3.60-3.64 (1H, m), 3.70-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.19 (1H, s)

IR: ν_{max} cm^{-1}: 3490, 1716, 1635, 1521, 1437, 1356, 1305

REFERENCE EXAMPLE 26

Synthesis of Optically Active 7-Amino-5-azaspiro-[2,4]-heptane:

1) 5-[(1R)-Phenylethyl]-4.7-dioxo-5-azaspiro[2,4]-heptane (19):

To 10.4 g of ethyl acetoacetate were added 15 g of 1,2-dibromoethane, 23 g of potassium carbonate, and 150 ml of N,N-dimethylformamide (DMF), and the mixture was stirred at room temperature for 2 days. Any insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. To the residue was added water, and the mixture was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting pale yellow oily substance was subjected to distillation under reduced pressure to obtain 7.5 g of

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ethyl 1-acetyl-1-cyclopropanecarboxylate having a boiling point of 70 to 71°C/2 to 3 mmHg.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.30 (3H, t, J=7Hz), 1.48 (4H, s), 2.49 (3H, s), 4.24 (2H, q, J=7Hz)

In 200 ml of ethanol was dissolved 35.7 g of the above obtained compound, and 40 g of bromine was added dropwise to the solution at room temperature while stirring. After the stirring was continued at room temperature for 2 hours, the excess bromine and the solvent were removed under reduced pressure to obtain ethyl 1-bromoacetyl-1-cyclopropanecarboxylate, which was then, without further purification, dissolved in 200 ml of ethanol. To the solution were simultaneously added dropwise 33 g of R-(+)-1-phenylethylamine and 27 g of triethylamine over a period of 1 hour while stirring under ice-cooling. After the addition, the reaction temperature was raised to room temperature, and the stirring was continued at room temperature for 2 days. Any insoluble matter was removed by filtration, and ethanol was removed from the filtrate under reduced pressure. The residue was dissolved in 300 ml of ethyl acetate, and the solution was washed successively with 1N hydrochloric acid, a saturated sodium hydrogen-carbonate aqueous solution, and a saturated sodium

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chloride aqueous solution in this order. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to 200 g of silica gel column which was eluted with 0 to 2% methanolic chloroform to obtain the titled compound (19) as a colorless crystal.

Melting Point: 98-103°C

^{1}H-NMR ($CDCl_3$) δ ppm:

1.62 (3H, d, J=7.2Hz), 3.5 (1H, d, J=18Hz), 3.9 (1H, d, J=18Hz), 5.82 (1H, q, J=7.2Hz), 7.36 (5H, s)

2) 5-[(1R)-Phenylethyl]-7-hydroxyimino-4-oxo-5-aza-spiro[2,4]heptane (20):

To 3.35 g of Compound (19) were added 1.6 g of hydroxylamine hydrochloride, 2.3 g of triethylamine, and 80 ml of ethanol, and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and chloroform was added to the residue. The mixture was washed successively with a 10% citric acid aqueous solution and a saturated sodium chloride aqueous solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain 3.5 g of the titled compound (20) as a colorless crystal.

Melting Point: 188-194°C

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.4 (2H, m), 1.53 (3H, d, J=7.2Hz & 2H, m), 3.8 (1H, d, J=18Hz), 4.16 (1H, d, J=18Hz), 5.63 (1H, q, J=7.2Hz), 7.32 (5H, s)

3) 7-Amino-4-oxo-5-[(1R)-Phenylethyl]-5-azaspiro[2,4]-heptane (21a, 21b):

To 150 ml of methanol were added 3.5 g of Compound (20) and 7.5 ml of Raney nickel, and catalytic reduction was carried out at room temperature for 12 hours. After the catalyst was removed by filtration, the solvent was removed from the filtrate under reduced pressure. The residue was subjected to a 100 g of silica gel column eluted with a mixed solvent of 5% methanol/chloroform which was to yield 1.0 g of the entitled compound (21b) from the earlier fraction and 0.8 g of the titled compound (21a) from the later fraction each as a colorless oily substance.

Compound (21b):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.8-1.4 (4H, m), 1.52 (3H, d, J=7Hz), 2.87 (1H, dd, J=10, & 3Hz), 3.3-3.9 (2H, m), 4.27 (2H, br. s), 5.42 (1H, q, J=7Hz), 7.29 (5H, s)

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Compound (21a):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (4H, m), 1.40 (2H, s), 1.53 (3H, d, J=7.2Hz), 2.99 (1H, dd, J=12.8, & 7.2Hz), 3.15-3.45 (2H, m), 5.52 (1H, q, J=7.2Hz), 7.30 (5H, s)

4) 7-Amino-5-[(1R)-Phenylethyl]-5-azaspiro[2,4]heptane (22a, 22b):

To 50 ml of anhydrous tetrahydrofuran were added 1.0 g of Compound (21b) and 500 mg of lithium aluminum hydride, and the mixture was refluxed for 17 hours. After cooling, 0.5 ml of water, 0.5 ml of a 15% sodium hydroxide aqueous solution, and 1.5 ml of water were successively added to the reaction mixture in this order, followed by stirring well at room temperature for 30 minutes. Any insoluble matter was removed by filtration and thoroughly washed with tetrahydrofuran. The filtrate and the washing were combined and dried. The solvent was removed under reduced pressure to obtain 940 mg of the titled compound (22b) as a pale yellow oily substance. In the same manner, 755 mg of the titled compound (22a) was obtained from 800 mg of Compound (21a).

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Compound (21b):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.2-0.8 (4H, m), 1.35(3H, d, J=6.6Hz), 1.6-2.0 (2H, br. m), 2.2-3.1 (4H, m), 3.24 (1H, q, J=6.6Hz), 3.5-3.9 (1H, m), 7.28 (5H, br. s)

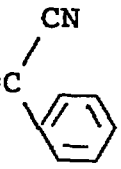
Compound (22a):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.3-0.9 (4H, m), 1.36 (3H, d, J=6.7Hz), 1.8-2.2 (2H, m), 2.2-3.2 (4H, m), 3.24 (1H, q, J=6.7Hz), 3.6-3.9 (1H, m), 7.28 (5H, br. s)

5) 7-(t-Butoxycarbonylamino)-5-[(1R)-phenylethyl]-5-azaspiro[2,4]heptane (23a, 23b):

To 20 ml of anhydrous tetrahydrofuran were added 764 mg of Compound (22b) and 1.3 g of Boc-ON [Boc-ON; 2-(t-Butoxycarbonyloxyimino]-2-phenylacetonitrile



], and the mixture was stirred at room temperature for 4 hours. Ethyl acetate was added to the reaction mixture, and the mixture was washed twice with a 1N sodium hydroxide aqueous solution and then once with water, followed by extraction with a 10% citric acid aqueous solution. The aqueous extract was washed once with ethyl acetate, and a 15% sodium hydroxide aqueous solution was added to the aqueous

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layer under cooling to make it alkaline. The mixture was extracted three times with chloroform, and the organic layer was washed with a saturated sodium chloride aqueous solution and then dried. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (silica gel: 20 g; eluent: chloroform:methanol=20:1, 10:1) to obtain 690 mg of the titled compound (23b). This compound was allowed to stand to crystallize, followed by washing with n-hexane. The titled compound (23a) was obtained in the same manner.

Compound (23b) (colorless crystal):

Melting Point: 103-105°C

$[\alpha]_D$: -15.2° (c=1.475, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-0.9 (4H, m), 1.36 (3H, d, J=7.2Hz), 1.44 (9H, s), 2.42 (2H, AB q, J=10.2 Hz), 2.79 (2H, d, J=5.6 Hz), 3.24 (1H, q, J=7.2Hz), 3.6-4.0 (1H, m), 4.6-5.1 (1H, br. d), 7.28 (5H, s)

Elementary qAnalysis for $C_{19}H_{28}N_2O_2$:

Calcd. (%): C 72.12; H 8.92; N 8.85

Found (%): C 71.63; H 9.07; N 8.64

Compound (23a) (colorless crystal):

Melting Point: 94-97°C

$[\alpha]_D$: +47.6° (c=0.89, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-0.9 (4H, m), 1.33 (3H, d, J=6.6Hz), 1.40 (9H, s), 2.29 (1H, d, J=9Hz), 2.44 (1H, dd, J=10.8 & 3.6Hz), 2.77 (1H, d, J=9Hz), 2.88 (1H, dd, J=10.8 & 5.3Hz), 3.22 (1H, q, J=6.6Hz), 3.6-3.9 (1H, m), 4.7-5.2 (1H, br. d), 7.27 (5H, s)

Elementary aAnalysis for $C_{19}H_{28}N_2O_2$:

Calcd. (%): C 72.12; H 8.92; N 8.85

Found (%): C 71.86; H 9.36; N 8.68

6) 7-t-Butoxycarbonylamino-5-azaspiro[2,4]heptane (24a, 24b)

To 30 ml of ethanol were added 650 mg of Compound (23b) and 500 mg of 50% hydrated palladium-on-carbon, and catalytic reduction was effected under heating at a pressure of 4.2 atoms. After 6 hours, the catalyst was removed by filtration, and the solvent was removed under reduced pressure. To the oily residue was added ethyl acetate, followed by extracting twice with a 10% citric acid aqueous solution. The aqueous extract was made alkaline with a 15% sodium hydroxide aqueous solution and then extracted three times with chloroform. The chloroform layer was washed with water and dried. The solvent was removed under reduced pressure to yield 440 mg of the titled compound (24b) as a crude product. The titled compound (24a) was obtained in the same

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manner as above. The NMR spectra of Compounds 24b) and (24a) were in complete agreement with each other.

Compound (24)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-1.0 (4H, m), 1,42 (9H, s), 2.71 (1H, d, J=10.2Hz), 2.92 (1H, dd, J=10.8 & 3.6 Hz), 3.01 (1H, d, J=10.2Hz), 3.33 (1H, dd, J=10.8 & 5.4 Hz), 3.5-3.9 (1H, m), 5.0-5.4 (1H, br, d)

EXAMPLE 9

7-(7-t-Butoxycarbonylamino-5-azaspiro[2,4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (25bb):

In 0.6 ml of acetonitrile were dissolved 160 mg of 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cylopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (12b), 150 mg of the amine compound (24b), and 0.5 ml of triethylamine, and the solution was heated under reflux for 5 hours. After cooling, the precipitated colorless crystals were collected by filtration. The solvent of the mother liquor was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using a developing solvent of chloroform-methanol (5:1 by volume). The purified product and the above-obtained crystals were combined to give 255 mg of the titled compound (25bb).

Melting Point: 213-218°C

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.0 (6H, m), 1,45 (9H, s), 7.99 (1H, d, J=13.1Hz), 8.74, 8.78 (each 0.5H, s)

EXAMPLE 10

(-)-7-(7-Amino-5-azaspiro[2,4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cylcopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (26bb):

To 255 mg of the Boc-compound (25bb) as obtained in Example 9 were added 0.5 ml of anisole and 10 ml of trifluoroacetic acid under ice-cooling. After warming to room temperature, the mixture was stirred for 30 minutes. The solvent was removed under reduced pressure, a 1N sodium hydroxide aqueous solution was added to the residue adjusting a pH of 11 to 12. The alkaline aqueous solution was washed twice with chloroform. The aqueous layer was adjusted to a pH of about 7 with concentrated hydrochloric acid and a 10% citric acid aqueous solution and extracted three times with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting solid was recrystallized from ethanol-concentrated aqueous ammonia to obtain 142 mg of the titled compound (26bb) as a colorless crystal.

Melting Point: 127-140°C (with decomposition)

$[\alpha]_D$: -199.2° (c=0.24, 1N NaOH)

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Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/4H_2O$:

Calcd. (%): C 55.08; H 4.50; N 10.14

Found (%): C 54.86; H 4.80; N 10.03

EXAMPLE 11

Synthesis of Compound (26ab)

Compound (26ab) was obtained from Compound (12a) and Compound (24b) in the same manner as described in Examples 9 and 10.

Melting Point: 123-128°C (with decomposition)

$[\alpha]_D$: +21.5° (c=0.195, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/2H_2O$:

Calcd. (%): C 54.49; H 4.57; N 10.03

Found (%): C 54.33; H 4.73; N 9.81

EXAMPLE 12

Synthesis of Compound (26a)

Compound (26a) was synthesized from Compound (12b) and Compound (24a) in the same manner as described in Examples 9 and 10.

Melting Point: 121-127°C (with decomposition)

$[\alpha]_D$: -21.1° (c=0.275, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/2H_2O$:

Calcd. (%): C 54.49; H 4.57; N 10.03

Found (%): C 54.77; H 4.43; N 9.86

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EXAMPLE 13

Synthesis of Compound (26aa)

Compound (26aa) was synthesized from Compound (12a) and Compound (24a) in the same manner as in Examples 9 and 10.

Melting Point: 126-145°C (with decomposition)

$[\alpha]_D$: +186.6° (c=0.228, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 3/4H_2O$:

Calcd. (%): C 53.91; H 4.64; N 9.93

Found (%): C 53.80; H 4.47; N 9.82

REFERENCE EXAMPLE 27

(-)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29a)

A mixture of 1 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (27), 3 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 1 hour while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 750 mg of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of

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dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, followed by stirring at room temperature for 30 minutes.

The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to column chromatography using 50 g of silica gel using chloroform as an eluent to yield 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (28a) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.06 (3H, t, J=7Hz), 1.1-1.6 (2H, m), 2.86-3.18 (1H, m), 4.05 (2H, q, J=7Hz), 4,78 (1H, dm, J=63Hz), 7.36 (1H, d, J=7Hz), 8.31 (1H, d, J=14 Hz)

In 25 ml of anhydrous dioxane was dissolved 1.29 g of Compound (28a), and 300 mg of 60% sodium hydride was added to the solution, followed by stirring for 1 hour. The reaction mixture was concentrated under reduced pressure, and to the residue was added 0.1N hydrochloric acid. The precipitated crystals were collected by filtration and washed successively with

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water and diethyl ether to obtain 860 mg of the titled compound (29a) as a colorless crystal.

Melting Point: 184-185°C

$[\alpha]_D$: -1.26° (c=0.793, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$

Calcd. (%): C 51.16; H 3.37; N 8.52

Found (%): C 51.12; H 3.26; N 8.52

^{1}H-NMR ($CDCl_3$) δ ppm:

1.41 (3H, t, J=7Hz), 1.4-1.84 (2H, m), 3.50 (1H, m), 4.40 (2H, q, J=7Hz), 5.02 (1H, dm, J=65Hz), 8.43 (1H, d, J=7Hz), 8.66 (1H, s)

REFERENCE EXAMPLE 28

(+)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29b):

A mixture of 1.0 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (27), 3 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 1.5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 750 mg of (-)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4b) was dissolved therein. The solution was stirred at room temperature

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for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 30 ml of dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 30 minutes.

The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography using 50 g of silica gel and chloroform as an eluent to obtain 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)-acrylate (28b) as a colorless oil.

Compound (28b) (1.29 g) was reacted in the same manner as for Compound (28a) to obtain 936 mg of the titled compound (29b) as a colorless crystal.

Melting Point: 183-185°C

$[\alpha]_D$: +1.12° (c=1.07, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$

Calcd. (%): C 51.16; H 3.37; N 8.52

Found (%): C 51.39; H 3.24; N 8.49

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REFERENCE EXAMPLE 29

(-)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30a):

A mixture of 800 mg of Compound (29a) and 15 ml of concentrated hydrochloric acid was heated at 100°C for 1.5 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 610 mg of the titled compound (30a) as a colorless crystal.

Melting Point: 215-219°C

$[\alpha]_D$: -20.65° (c=0.910, chloroform)

REFERENCE EXAMPLE 30

(+)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30b):

A mixture of 870 mg of Compound (29b) and 20 ml of concentrated hydrochloric acid was heated at 100°C for 2 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 715 mg of the titled compound (30b) as a colorless crystal.

Melting Point: 218-220°C

$[\alpha]_D$: +22.34° (c=0.555, chloroform)

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EXAMPLE 14

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (31a):

In 15 ml of trifluoroacetic acid was dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methyl-pyrrolidine (32) (cf. Terry Ronson, et al., J. Med. Chem., Vol. 31, p.1598 (1988)), and the solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of acetonitrile, and 150 mg of Compound (30a) and 2 ml of triethylamine were added to the solution, followed by refluxing for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 13 with sodium hydroxide and washed with chloroform. The aqueous layer was adjusted to a pH of 7.5 and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from aqueous ammonia-ethanol yielded 150 mg of the titled compound (31a) as a colorless crystal.

Melting Point: 255-258°C

$[\alpha]_D$: -14.52° (c=0.413, 0.1N NaOH)

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Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$:

Calcd. (%): C 55.36; H 5.06; N 15.19

Found (%): C 55.09; H 5.40; N 15.04

EXAMPLE 15

(-)-7-[3-(R)-[1-(S)-Aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (34b):

A mixture of 159 mg of (-)-8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b), 160 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine (cf. JP-A-61-311992), 400 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in chloroform. The organic solution was washed successively with a 10% citric acid aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was recrystallized from ethyl acetate-isopropyl ether to yield 220 mg of (-)-7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (33b).

Melting Point: 189-193°C

$[\alpha]_D$: -205° (c=0.985, chloroform)

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Elementary Analysis for $C_{24}H_{28}ClF_2N_3O_5$

Calcd. (%): C 56.31; H 5.51; N 8.21

Found (%): C 56.16; H 5.48; N 8.21

In 10 ml of trifluoroacetic acid was dissolved 200 mg of Compound (33b), and the solution was stirred for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in a 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 with hydrochloric acid and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 140 mg of the titled compound (34b) as a colorless crystal.

Melting Point: 204-207°C

$[\alpha]_D$: -160.0° (c=0.605, 0.1N NaOH)

Elementary Analysis for $C_{19}H_{20}ClF_2N_3O_3 \cdot H_2O$:

Calcd. (%): C 53.09; H 5.38; N 9.77

Found (%): C 53.20; H 5.17; N 9.66

REFERENCE EXAMPLE 31

Ethyl 2-(3-acetoxy-2,4,5-trifluorobenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (36b):

A mixture of 1.0 g of ethyl 3-acetoxy-2,4,5-trifluorobenzoylacetate (35) (cf. JP-A-87-175485), 6 ml

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of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 3 hours under stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

In 5 ml of trifluoroacetic acid was dissolved 467 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 5 ml of a dichloromethane solution containing 500 mg of triethylamine was added dropwise thereto under ice-cooling, followed by stirring for 10 minutes. To the solution was added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure to obtain 1.25 g of the titled compound (36b).

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REFERENCE EXAMPLE 32

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (37b):

In 40 ml of dioxane was dissolved 1.25 g of Compound (36b), and 440 mg of potassium carbonate and 10 ml of water were added thereto, followed by stirring at room temperature for 19 hours. The reaction mixture was neutralized with hydrochloric acid, concentrated under reduced pressure, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in 40 ml of anhydrous dioxane, and 300 mg of 60% sodium hydride and 1 ml of ethyl iodide were added thereto, followed by stirring at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was recrystallized from isopropyl ether to obtain 235 mg of the titled compound (37b) as a colorless crystal.

Melting Point: 163-64°C

$[\alpha]_D$: -22.9° (c=0.490, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7Hz), 1.3-1.8 (2H, m), 3.7-4.0 (1H, m), 4.10 (3H, d, J=2Hz), 4.38 (2H, q, J=7Hz), 4.85 (1H, dm, J=63Hz), 8.02 (1H, dd, J=9Hz, & 8.5Hz), 8.55 (1H, s)

Elementary Analysis for $C_{16}H_{14}F_3NO_4$

Calcd. (%): C 56.31; H 4.13; N 4.10

Found (%): C 56.62; H 4.18; N 4.11

REFERENCE EXAMPLE 33-1

(±)-cis-4-Amino-1-benzyl-3-methyl-2-oxopyrrolidine (45):

A mixture of 5.13 g of ethyl 1-benzyl-3-methyl-2-oxo-3-pyrrolidinecarboxylate (42, cf. JP-A-62-4284), 40 ml of 50% ethanol, and 2 g of sodium hydroxide was stirred at room temperature for 42 hours. To the reaction mixture was added 100 ml of water, and the mixture was washed with chloroform. The aqueous layer was neutralized with hydrochloric acid, extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated to obtain 3.40 g of (±)-1-benzyl-2-oxo-3-pyrrolidinecarboxylic acid (43) as a colorless crystal.

Compound (43) (3.40 g), 4.45 g of diphenylphosphorylazide, 1.9 g of triethylamine, and 50 ml of t-butyl alcohol were mixed and the mixture was heated under reflux for 12 hours. The reaction mixture was

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concentrated under reduced pressure, and the residue was dissolved in chloroform. The solution was washed successively with a 10% citric acid aqueous solution, a 2% sodium hydroxide aqueous solution, and water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography using chloroform-methanol (97.5:2.5 by volume) as an eluent to obtain 1.76 g of (±)-cis-1-benzyl-4-t-butoxycarbonylamino-3-methyl-4-oxopyrrolidine (44) as a colorless oil.

In 15 ml of trifluoroacetic acid was dissolved 1.76 g of Compound (44). After 1 hour, the solution was concentrated under reduced pressure. To the residue was added 100 ml of water, and the mixture was washed with benzene. The aqueous layer was adjusted to a pH of 12 with sodium hydroxide and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain the titled compound (45) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.25 (3H, d, J=7Hz), 1.44 (2H, s), 2.16 (1H, dt, J=7Hz), 2.83 (1H, dd, J=6.7Hz, & 8Hz), 3.14 (1H, m), 3.38 (1H, dd, J=6.7Hz, & 8Hz), 4.48 (2H, s), 7.28 (5H, s)

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REFERENCE EXAMPLE 33-2

Optical Resolution of cis-4-Amino-1-benzyl-3-methyl-2-oxopyrrolidine (45):

In 40 ml of dichloromethane were dissolved 4.17 g of Compound (45) and 3.3 ml of pyridine, and a solution of 7.7 g of (S)-N-p-toluenesulfonylprolyl chloride in 50 ml of dichloromethane was added thereto dropwise, followed by stirring for 4 hours.

The reaction mixture was washed successively with 1N hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution, and water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate as an eluent to isolate the isomers. Each of the isomers was recrystallized from ethyl acetate to obtain 3.3 g and 3.6 g of cis-1-benzyl-3-methyl-4-[(S)-N-p-toluenesulfonylprolylamino]-2-oxopyrrolidine (46a) and (46b), respectively.

Compound (46a):

Rf (silica gel TLC; ethyl acetate): 0.69

Melting Point: 162°C

$[\alpha]_D$: -87.3° (c=0.735, chloroform)

Compound (46b):

Rf (silica gel TLC; ethyl acetate): 0.61

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Melting Point: 175-177°C

$[\alpha]_D$: -148.6° (c=0.665, chloroform)

REFERENCE EXAMPLE 33-3

(+)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methyl-pyrrolidine (47a):

A mixture of 3.23 g of Compound (46a) and 50 ml of concentrated hydrochloric acid as heated under reflux for 5 hours, followed by concentration under reduced pressure. To the residue was added a 1N sodium hydroxide aqueous solution, and the solution was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain 1.48 g of Compound (45a) as a colorless oil.

The product was dissolved in 10 ml of tetrahydrofuran, and the solution was added dropwise to a suspension of 2.0 g of lithium aluminum hydride in 50 ml of tetrahydrofuran. The mixture was heated under reflux for 24 hours. To the reaction mixture was added dropwise 10 ml of water under ice-cooling, and, after stirring for 30 minutes, any insoluble matter was removed by filtration. To the filtrate was added 1.92 g of Boc-ON, followed by stirring for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform.

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The extract was washed successively with a 5% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was then evaporated.

The residue was purified by silica gel column chromatography using chloroform-methanol (1:0 to 9:1 by volume) as an eluent to obtain 1.76 g of a crystal. To the product was added n-hexane, and the mixture was stirred thereby precipitating a dℓ compound. The crystals were collected by filtration, and the filtrate was concentrated. This procedure was repeated twice. One hundred milligrams of the dℓ compound was obtained from the filter cake and 1.61 g of the titled optically active compound (47a) from the mother liquor.

Melting Point: 48-52°C

$[\alpha]_D$: +27.2° (c=2.33, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.07 (3H, d, J=7Hz), 1.43 (9H, s), 1.78-2.02 (2H, m), 2.62 (2H, d, J=5Hz), 2.84-3.10 (1H, m), 3.55 (2H, s), 3.5-3.8 (1H, m), 4.8-5.2 (1H, broad), 7.23 (5H, s)

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REFERENCE EXAMPLE 33-4

(-)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methyl-pyrrolidine (47b):

In the same manner as for the synthesis of Compound (47a) but starting with 3.52 g of Compound (46b), 1.72 g of the titled compound (47b) was obtained.

Melting Point: 57-61°C

$[\alpha]_D$: -31.21°

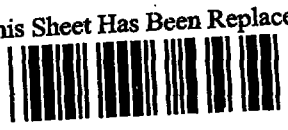
REFERENCE EXAMPLE 33-5

cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (39a), (39b):

Compound (47a) (1.61 g), 1.5 g of 5% palladium-on-carbon, and 80 ml of ethanol were mixed, and catalytic reduction was carried out for 5 hours while irradiating the mixture with an infrared lamp in a hydrogen atmosphere at a pressure of 4 atoms. After the reaction, the catalyst was removed by filtration, and the filtrate was concentrated to obtain 1.09 g of a crude product as a colorless oil. The product solidified as a carbonate on standing, which was used without purification.

In the same manner as for the synthesis of Compound (39a), 1.1 g of Compound (39b) was obtained as a colorless oil from 1.70 g of Compound (47b).

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REFERENCE EXAMPLE 34

Ethyl 2-(2,4,5-trifluoro-3-methylbenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (50b):

A mixture of 710 mg of ethyl 2,4,5-trifluoro-3-methylbenzoylacetate (prepared from 2,4,5-trifluoro-3-methylbenzxoic acid (48), cf. JP-A-62-215572), 6 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 2 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

In 5 ml of trifluoroacetic acid was dissolved 580 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 700 mg of triethylamine was added thereto under ice-cooling. After stirring for 10 minutes, the above-prepared dichloromethane solution was added thereto, followed by allowing to stand overnight. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was crystallized from n-hexane to obtain 787 mg of the titled compound (50b) as a pale yellow crystal.

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REFERENCE EXAMPLE 35

(-)-Ethyl 6.7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (51b):

In 20 ml of anhydrous dioxane was dissolved 600 mg of Compound (50b), and a suspension of 100 mg of 60% sodium hydride having been washed with n-hexane in a small amount of anhydrous dioxane was added to the solution. The mixture was stirred at room temperature for 1 hour, and 10 ml of a 10% citric acid aqueous solution was added thereto, followed by concentration under reduced pressure. The precipitated crystals were collected by filtration, washed successively with water, a small amount of ethanol, and diethyl ether to obtain 480 mg of the titled compound (51b) as a colorless crystal.

Melting Point: 230-231°C

$[\alpha]_D$: -80.0° (c=0.350, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7Hz), 1.1-1.7 (2H, m), 2.71 (3H, d, J=3.3Hz), 3.77-3.98 (1H, m), 4.38 (2H, q, J=7Hz), 4.85 (2H, dm, J=64Hz), 8.12 (1H, dd, J=10Hz), 8.54 (1H, d, J=3Hz)

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REFERENCE EXAMPLE 36

(-)-6,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (52b):

A mixture of 480 mg of the ester compound (51b) and 10 ml of concentrated hydrochloric acid was heated at 120°C for 75 minutes while stirring. After cooling, the precipitated crystals were collected by filtration and washed with water and ethanol to obtain 380 mg of the titled compound (52b) as a colorless crystal.

Melting Point: 204°C

$[\alpha]_D$: -60.0° (c=0.100, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-1.9 (2H, m), 2.80 (3H, d, J=5.8Hz), 4.1-4.4 (1H, m), 4.15 (1H, dm, J=64Hz), 8.17 (1H, dd, J=16Hz), 8.82 (1H, d, J=4Hz), 14.2 (1H, s)

EXAMPLE 16

(-)-6-[3-(R)-(1-(S)-Aminoethyl)-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (54b):

A mixture of 198 mg of Compound (52b), 350 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine, 5 ml of dimethyl sulfoxide, and 1.5 g of triethylamine was heated at 110 to 120°C for 5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in chloro-

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form and the solution was washed with a 10% citric acid aqueous solution and then with water, and dried over anhydrous sodium sulfate. The solvent was evaporated.

The residue was subjected to preparative TLC which was developed with a mixed solvent of chloroform-methanol (95:5 by volume) to obtain 110 mg of 7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidinyl]-6,7-difluoro-8-methyl-4-dihydroquinoline-3-carboxylic acid (53b) as a pale yellow powder.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.24 (3H, d, J=7Hz), 1.45 (9H, s), 1.2-1.9 (2H, m), 2.52 (3H, s), 1.9-2.7 (3H, m), 3.2-4.2 (6H, m), 4.73 (1H, d, J=8Hz), 4.98 (1H, dm, J=65Hz), 7.77 (1H, d, J=13Hz), 8.70 (1H, d, J=3.5Hz)

To 110 mg of Compound (53b) was added 5 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 10 minutes, followed by evaporation to dryness under reduced pressure. The residue was recrystallized from ethanol-diethyl ether to obtain 62 mg of the titled compound (54b) as a yellow crystal.

Melting Point: 149-153°C

$[\alpha]_D$: -34.4° (c=0.168, 1N HCℓ)

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EXAMPLE 17

5-Amino-7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (56b):

A mixture of 100 mg of (-)-5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17b), 100 mg of 7-t-butoxycarbonylamino-5-azaspiro[2,4]heptane (24b), 300 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 23 hours.

The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 100 ml of chloroform. The solution was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from acetonitrile to obtain 120 mg of 5-amino-7-[7-t-butoxycarbonylamino-5-azaspiro[2,4]-heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (55bb) as a yellow needle-like crystal.

Melting Point: 250-253°C

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-0.8 (2H, m), 0.8-1.0 (2H, m), 1.45 (9H, s), 1.3-1.8 (2H, m), 3.2-3.4 (1H, m), 3.6-3.9 (3H,

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m), 3.9-4.3 (2H, m), 4.85 (1H, dm, J=63Hz), 4.7-5.0 (1H, broad), 8.51 (1H, s)

In 5 ml of trifluoroacetic acid was dissolved 120 mg of Compound (55bb), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in hydrochloric acid and the solution was washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 65 mg of the titled compound (56bb) as a yellow crystal.

Melting Point: 213-217°C

$[\alpha]_D$: -96.7° (c=0.120, DMF)

EXAMPLE 18

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylic acid (31b):

In 15 ml of trifluoroacetic acid was dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methyl-pyrrolidine (32), and the solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of anhydrous acetonitrile, and 150 mg of Compound (30b) and 2 ml of triethylamine were added

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to the solution, followed by refluxing for 15 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was made alkaline with 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7 and extracted with chloroform. The organic layer was dried and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to yield 130 mg of the titled compound (31b).

Melting Point: 247-255°C (with decomposition)

$[\alpha]_D$: +120° (c=0.950, 1N NaOH)

Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$

Calcd. (%): C 55.36; H 5.06; N 15.19

Found (%): C 55.50; H 5.25; N 14.97

EXAMPLE 19

5-Amino-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-7-piperzinyl-4-oxo-quinoline-3-carboxylic acid (57b)

A mixture of 75 mg of Compound (17b), 45 mg of anhydrous piperazine in 5 ml of acetonitrile was heated under reflux for 2 hours. The reaction mixture was evaporated under reduced pressure and the residue was recrystallized from ethanol to yield 72 mg of the titled compound (57b) as a yellow crystal.

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Melting Point: 230-239°C

$[\alpha]_D$: +8.00° (c=0.225, 1N NaOH)

REFERENCE EXAMPLE 37

8,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid BF_2-chelate (38b):

A mixture of 230 mg of the ester compound (37b) and 5 ml of 42% borofluoric acid was heated at 110°C with stirring for 2 hours. After cooling, precipitated crystal was collected by filtration and washed with water to yield 210 mg of colorless crystal of the titled compound.

Melting Point: 281-271°C

By the reaction of cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (38a) and the chelate compound (38b), 7-(cis-3-amino-4-methylpyrrolidinyl)-8-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (40ba) is obtained. And further, by the reaction of the amine compound (24b) and the chelate comound (38b), 7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (41bb) is obtained.

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Table. Antimicrobial activity (M I C, μg/ml)

bacteria ＼ Compound	9a	9b	13a	13b	18a	18b	26bb	26aa
E. coli., NIHJ	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Ser. marcescens, 10100	0.20	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
Ps. aeruginosa, 32104	0.39	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.39
Ps. aeruginosa, 32121	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
S. aureus, 209 P	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
S. epidermidis, 56500	0.39	0.39	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.20
Str. faecalis, ATCC 19433	1.57	0.79	0.20	0.20	0.20	0.10	0.20	0.39

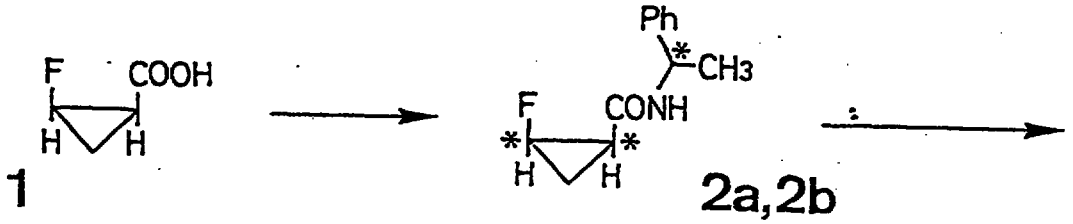
bacteria ＼ Compound	26ba	26ab	31a	31b	34b	54b	56b	
E. coli., NIHJ	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	
Ser. marcescens, 10100	< 0.1	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1	
Ps. aeruginosa, 32104	0.20	0.20	0.20	0.20	0.10	0.20	< 0.1	
Ps. aeruginosa, 32121	0.10	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1	
S. aureus, 209 P	< 0.1	< 0.1	0.10	< 0.1	< 0.1	< 0.1	< 0.1	
S. epidermidis, 56500	0.20	0.10	0.20	0.20	< 0.1	< 0.1	< 0.1	
Str. faecalis, ATCC 19433	0.39	0.20	0.78	0.39	< 0.1	0.10	0.10	

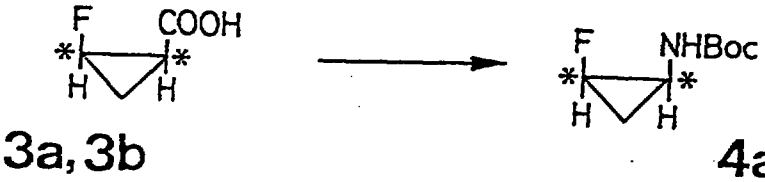
While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

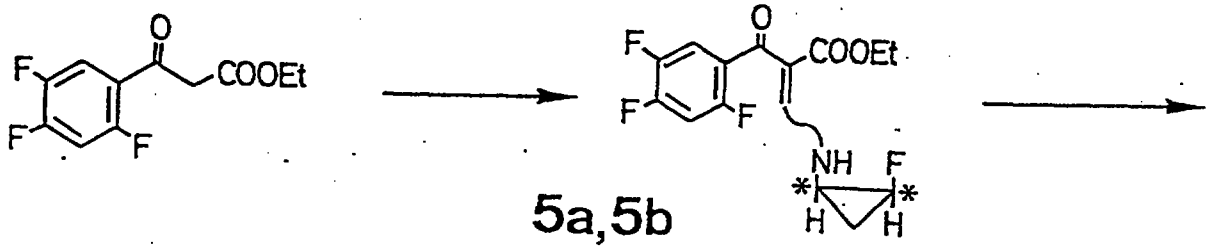
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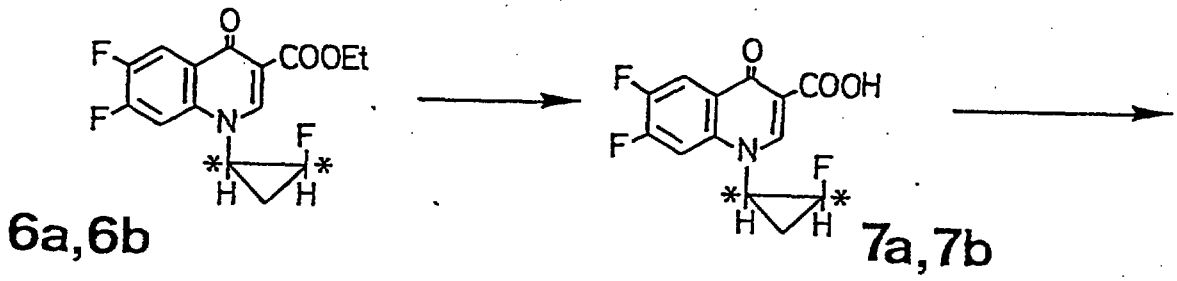
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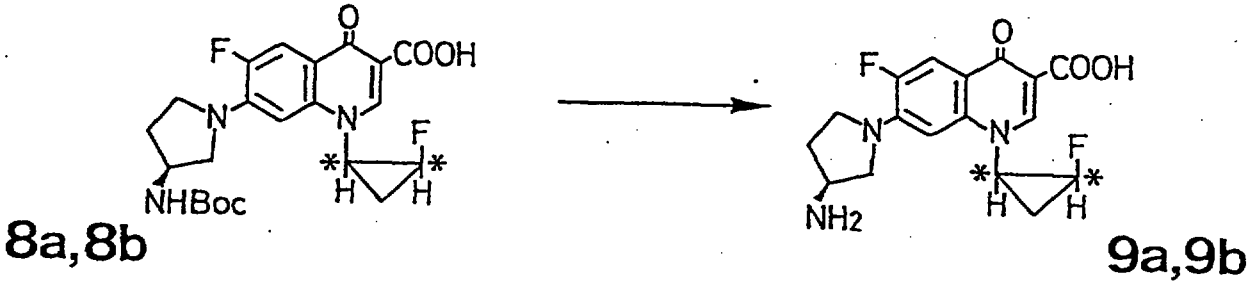
REACTION SCHEME



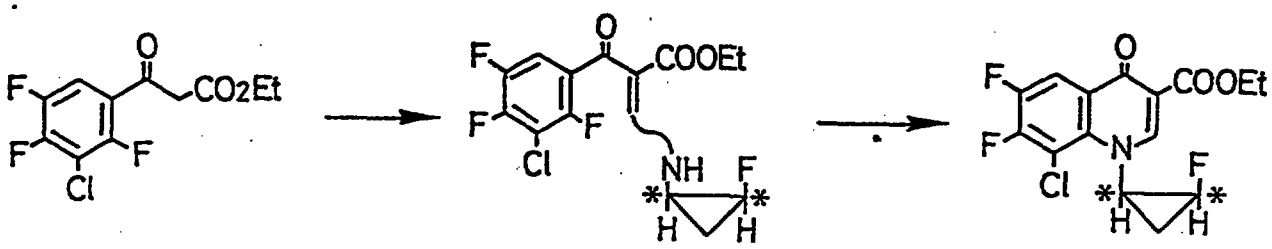




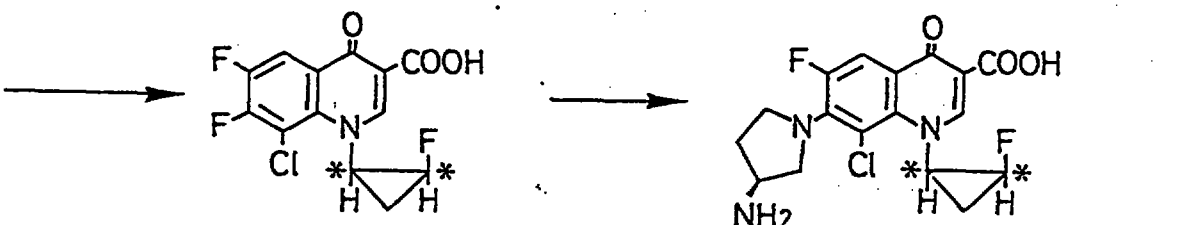




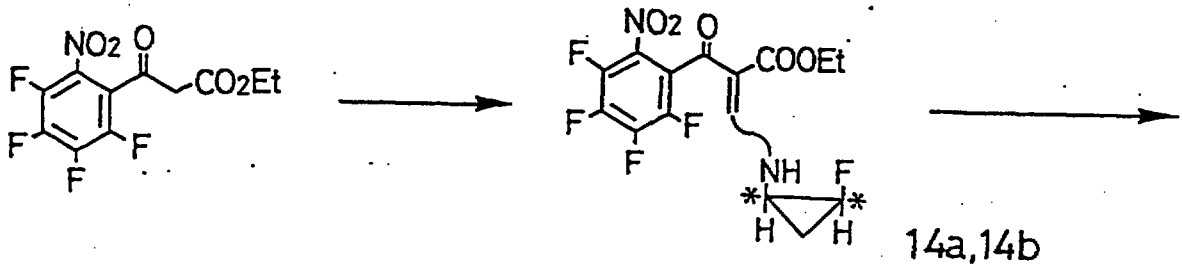
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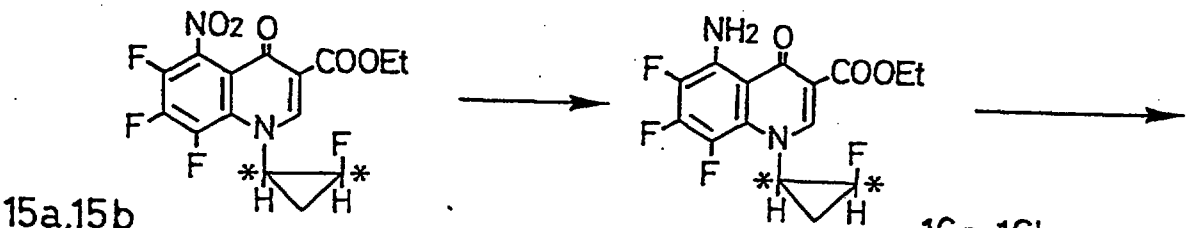
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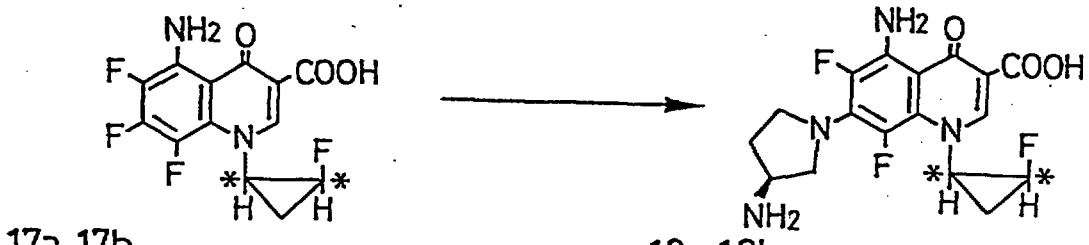
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14a,14b

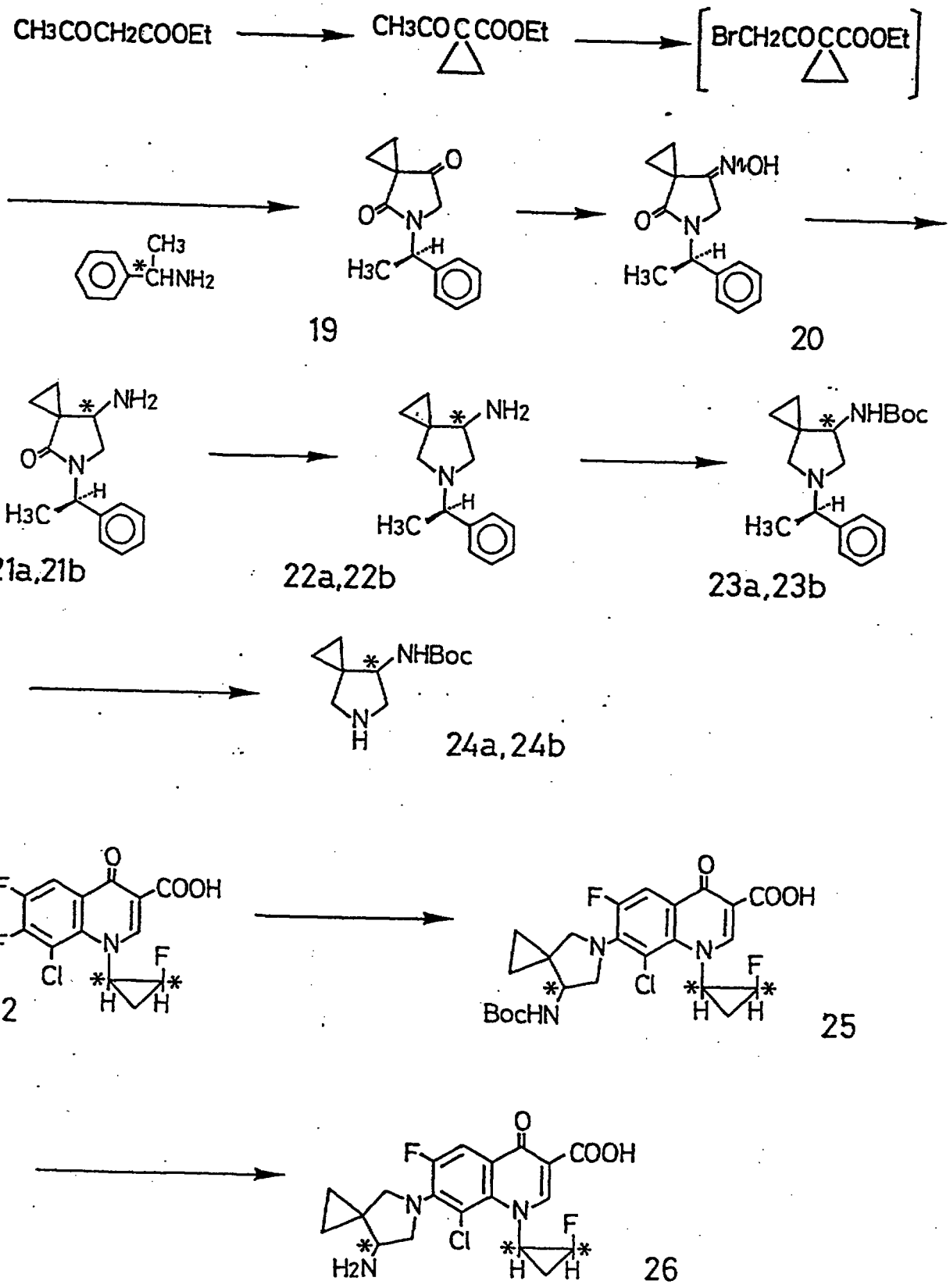


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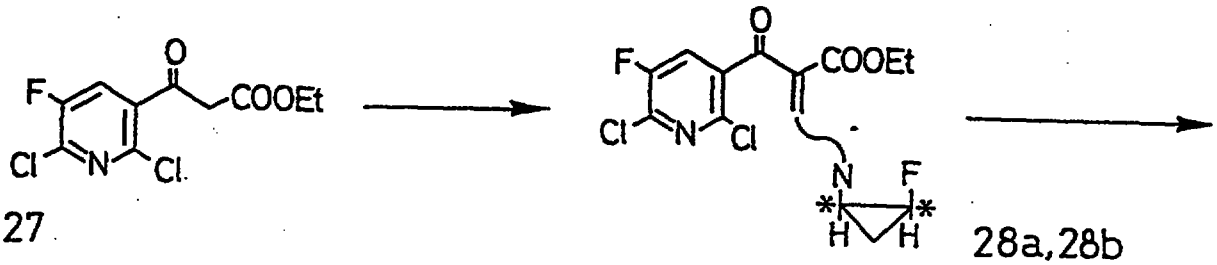


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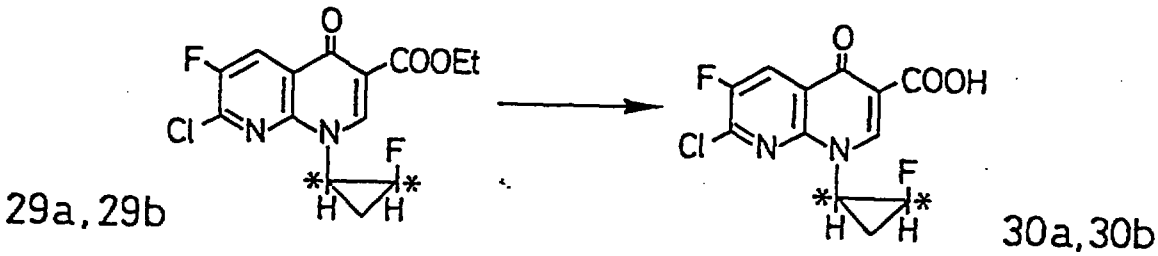
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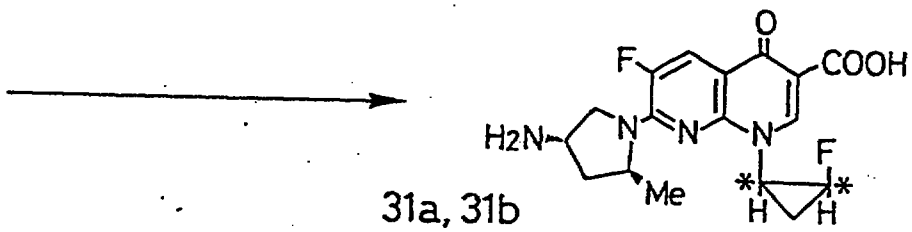
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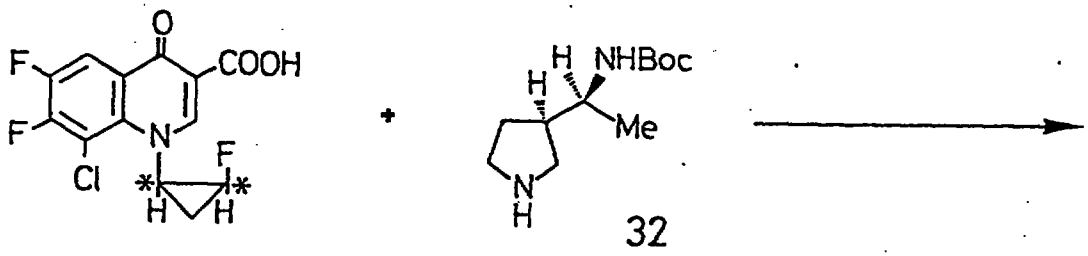
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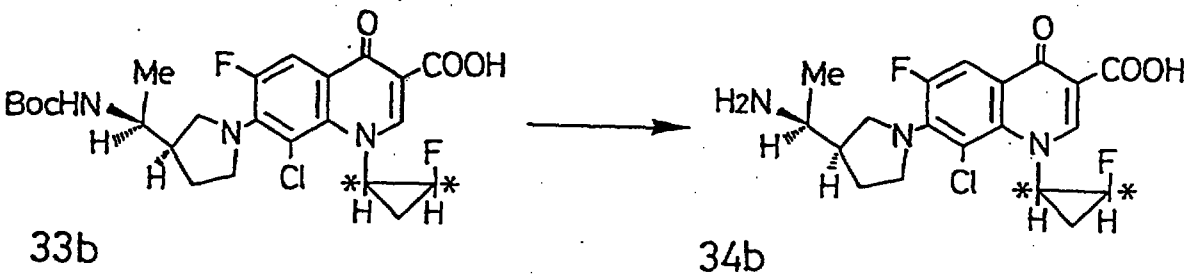
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31a, 31b

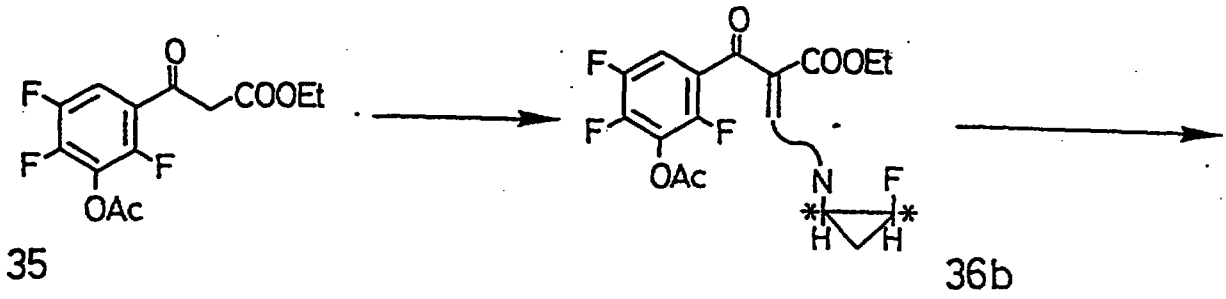


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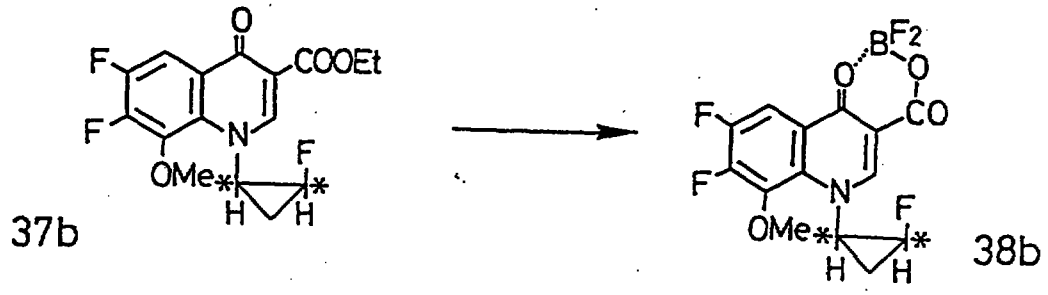


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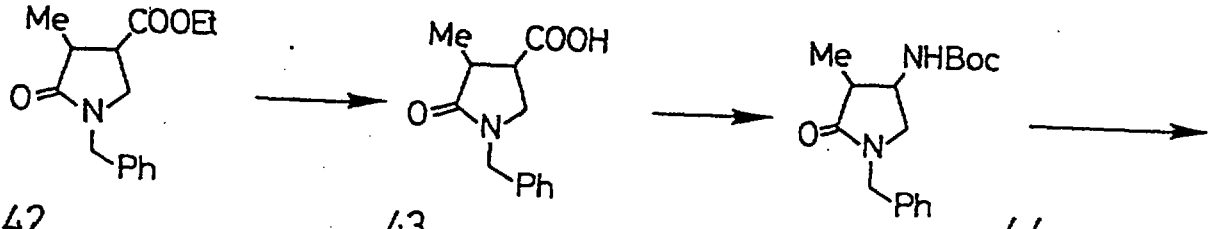
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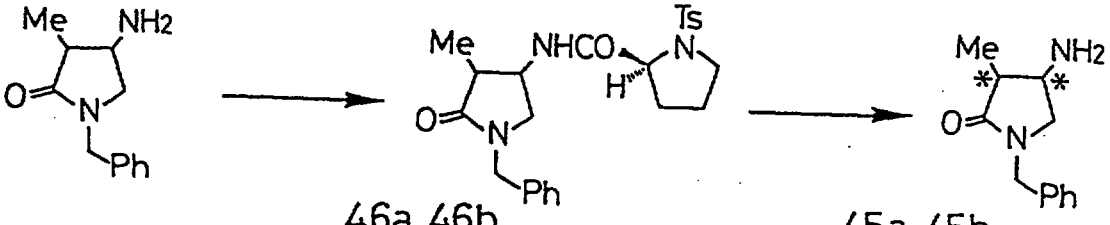
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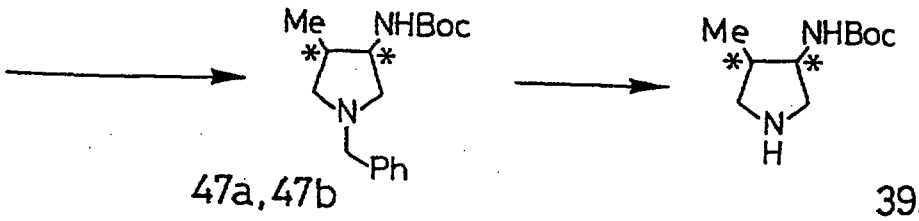
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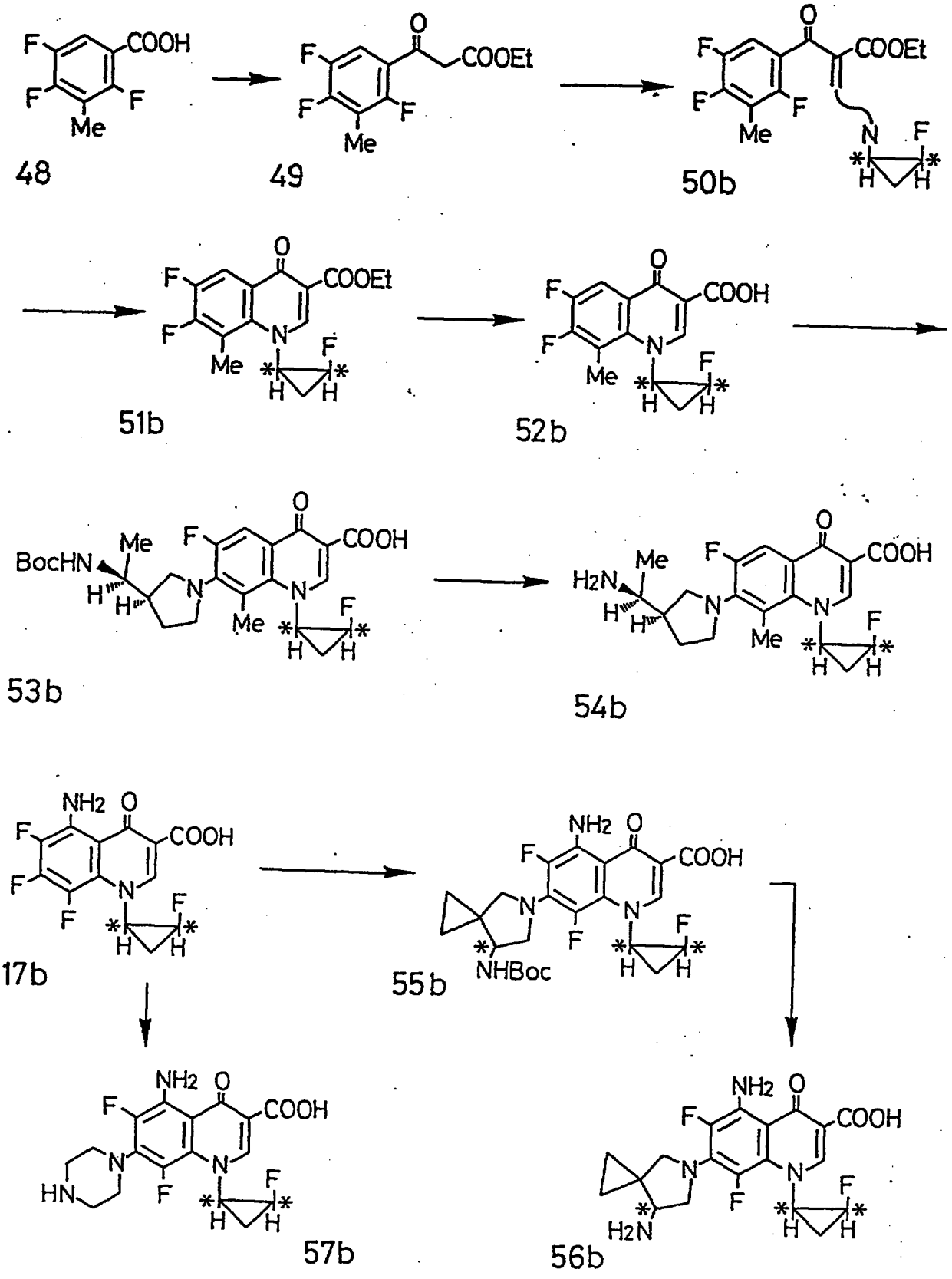


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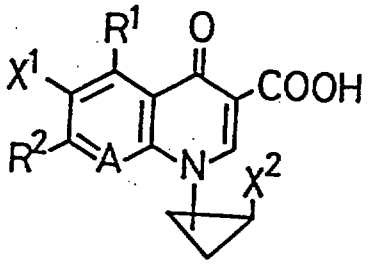
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* C L M S *

WHAT IS CLAIMED IS:

1. An N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a substituted or unsubstituted cyclic amino group which may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom in its ring; A represents $C-X^3$ or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group having from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom; provided that the case wherein R^1 is a hydrogen atom and R^2 is a piperazine or 4-alkyl-

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substituted piperazine residue is excluded, or a salt thereof.

2. A compound as claimed in claim 1, wherein R^2 is a 4- to 7-membered cyclic amino group which may be substituted with a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, or a substituted or unsubstituted amino group; or a salt thereof.

3. A compound as claimed in claim 1, wherein R^2 is a pyrrolidone, piperidine piperazine, diazabicycloheptane or diazabicyclooctane residue; or a salt thereof.

4. A compound as claimed in claim 1, wherein R^2 is a cyclic amino group comprising a single stereoisomer; or a salt thereof.

5. A compound as claimed in claim 4, wherein R^2 is a 3-aminopyrrolidinyl group; or a salt thereof.

6. A compound as claimed in claim 4, wherein R^2 is a 7-amino-5-azaspiro[2,4]heptan-5-yl group; or a salt thereof.

7. A compound as claimed in claim 1, wherein X^2 is a fluorine atom.

8. A compound as claimed in claim, wherein said compound is 7-[3-(S)-amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-(S)-amino-1-pyrrolidinyl]-8-

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chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline 3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid; or a salt thereof.

9. An antibacterial agent comprising, as an active ingredient, at least one N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I) or a salt thereof as claimed in claim 1.

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ABSTRACT OF THE DISCLOSURE

N_1-(1,2-cis-2-halogenocydopropyl)-substituted pyridonecarboxylic acid derivatives represented by formula (I) and the salts thereof are disclosed. These compounds have patent antibacterial activities against a wide variety of infectious bacteria, and are useful as antibacterial agents by oral or parenteral administration.

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OPTICALLY ACTIVE PYRIDONECARBOXYLIC ACID DERIVATIVES

FIELD OF THE INVENTION

This invention relates to an antimicrobial compound useful as human and veterinary medicines, fish medicines, agricultural chemicals, and antiseptics.

BACKGROUND OF THE INVENTION

Quinolone derivatives having a condensed pyridonecarboxylic acid skeleton are known as synthetic antimicrobial agents and to provide potent antimicrobial compounds on substitution of the 1-position thereof with a cyclopropyl group.

It is further known that the 1-cyclopropyl-quinolone derivatives having introduced a fluorine atom to the 2-position of the cyclopropyl group in a cis-configuration with the pyridonecarboxylic acid moiety also exhibit potent antimicrobial activity as disclosed in JP-A-87-12760 (the term "JP-A" as used herein means an "unexamined published Japanese patent application"). They are thought to have not only potent antimicrobial activity but improved safety. One example of the quinolone derivatives having a cis-fluorocyclopropyl group at the 1-position is shown below.

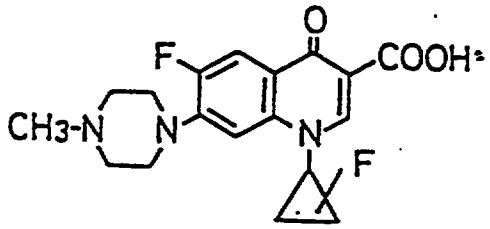
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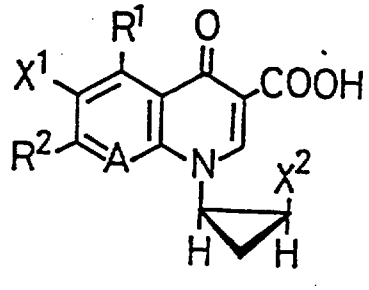
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☑ Claim(s)	: paged 106 to paged 108
☐ Drawing(s)	: paged ..... to paged .....
☑ Abstract	: paged 109 to paged 109

REPLACEMENT SHEETS	SG
☑ Description	: paged 1 to paged 105
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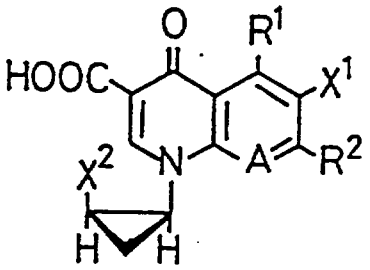
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Quinolone derivatives having a cis-halogeno-cyclopropyl group, inclusive of a cis-fluorocyclopropyl group, at the 1-position as stated above possess excellent properties in antimicrobial activity and safety. In these compounds, even when they have a substituent without stereo-isomerism at the 7-position of the pyridonecarboxylic acid moiety, the halogeno-cyclopropane ring of itself provides two enantiomers sttributed to the steric relationship between the pyridonecarboxylic acid moiety and the halogen atom with respect to the cyclopropane ring as illustrated below;



and



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wherein R^1, R^2, A, X^1, and X^2 are hereinafter defined. These quinolone derivatives are applicable as medicines as long as they are recemates. On the other hand, when there is stereoisomerism at the 7-positioned substituent of the pyridonecarboxylic acid moiety, such quinolone derivatives contain four kinds of diasteromers. With mixtures of the diasteromers, it is difficult to specify the excellent species and to supply them as medicines.

SUMMARY OF THE INVENTION

In the light of the aforesaid situation, the inventors have made extensive efforts to obtain the single isomers of 1-(1,2-cis-2-fluorocyclopropyl)-substituted quinolone derivatives within the diastereomers thereof. And they have succeeded in obtaining each of the enantiomers of a cis-2-fluorocyclopropyamine as a pure isomer. As a result of further investigations, they have also succeeded in synthesizing each of the enantiomers of a quinolone derivative which are attributed only to the steric configuration of the fluorocyclopropane ring by starting from the above-described amine.

The success of obtaining the enantiomeric quinolone derivatives useful as an intermediate has made it possible to synthesize an optically active quinolone derivative comprising one kind of diastereomer by

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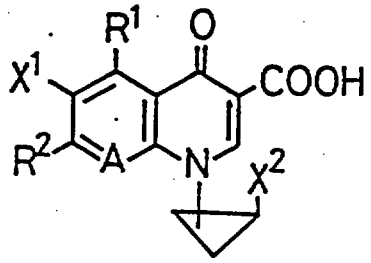
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reacting with a single isomer of the amine at introduction of a cyclic amino group to the 7-position. Each of these diastereomers was proved more potent in antimicrobial activity as compared with the corresponding quinolone derivatives substituted with a mere cyclopropyl group and, in addition, highly safe with markedly improved selective toxicity. The present invention has been completed based on these findings.

This invention relates to an N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a substituted or unsubstituted cyclic amino group which may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom, and a sulfur atom in its ring; A represents C-X^3

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or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group having from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom; provided that the case wherein R^1 is a hydrogen atom and R^2 is a piperazine or 4-alkyl-substituted piperazine residue is excluded, or a salt thereof.

Specifically implicit in the compounds represented by formula (I) and salts thereof are those wherein R^2 is a cyclic amino group which may be substituted; those wherein R^2 is a 4- to 7-membered cyclic amino group which may be substituted with a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, or a substituted or unsubstituted amino group; those wherein R^2 is a pyrrolidine, piperidine, piperazine, diazabicycloheptane or diazabicyclooctane residue; those wherein R^2 is a cyclic amino group comprising a single stereoisomer; those wherein R^2 is a 3-aminopyrrolidinyl group; those wherein R^2 in a 7-amino-5-azaspiro[2,4]-heptan-5-yl group; and those wherein X^2 is a fluorine atom. More specifically, the compounds according to the present invention include 7-[3-(S)-amino-1-pyrrolidin-yl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-

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dihydroquinoline-3-carboxylic acid, 7-[3-(S)-amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[7-amino-5-azaspiro[2,4]-heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

In formula (I), when X^3 represents a halogen atom, X^1 and X^3 each preferably represents a fluorine

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atom or a chlorine atom; and X^2 preferably represents a fluorine atom. R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom, preferably an unsubstituted amino group, a methylamino group, or a hydrogen atom.

R^2 represents a cyclic amino group, preferably a 4- to 7-membered, and more preferably 5- to 6-membered cyclic amino group. The cyclic amino group may further contain oxygen atom(s), sulfur atom(s)and/or nitrogen atom(s), as in oxazolidine, morpholine, thiazolidine, thiomorpholine, imidazolidine, pyrazolidine, and piperazine residues. Of these cyclic amino groups preferred are a pyrrolidine residue and a piperazine residue. The cyclic amino group may have substituents, such as a polar group (e.g., a substituted or unsubstituted amino group, a substituted or unsubstituted aminoalkyl group, a 5-substituted-2-oxo-1,3-dioxol-4-ylmethyl group, a hydroxyl group) and a straight chain, branched, or cyclic alkyl group having up to 6 carbon atoms. Preferred of the polar groups are an unsubstituted amino group, an aminomethyl group, a 1-aminoethyl group, and a hydroxyl group. Preferred of the alkyl group are methyl, ethyl, propyl, gem-dimethyl and gem-diethyl groups and further, these gem-alkyl groups may preferably form a cyclopropane or cyclobutane ring which is

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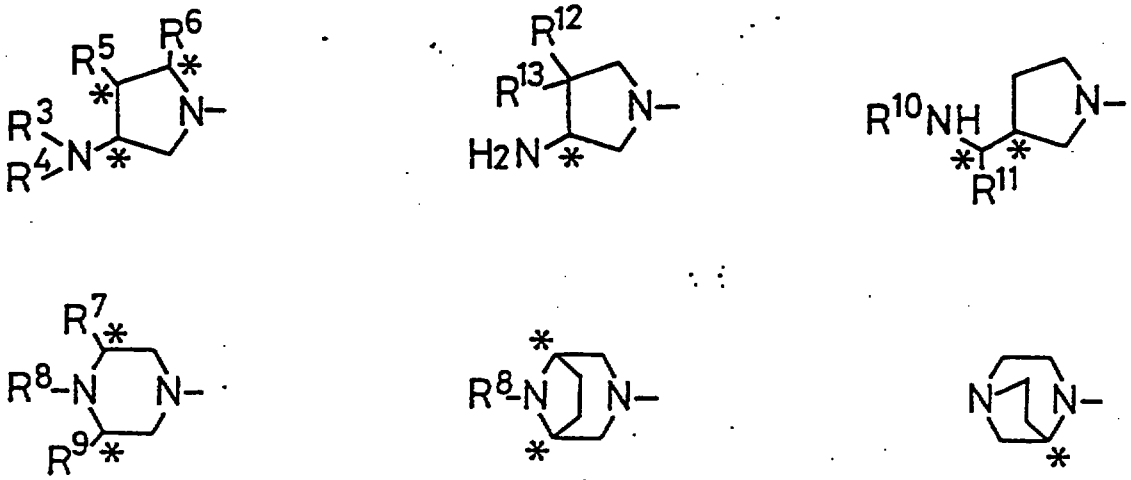


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bonded through a spiro-union to the cyclic amine skeleton. The cyclic amino group further includes a bicyclic amino group composed of crosslinking to 4- to 7-membered cyclic amino groups.

Illustrative examples of these cyclic amino groups, particularly containing the second amino moiety, are shown below;



wherein R^3, R^4, R^5, R^6, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^7, R^8, and R^9, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, provided that the case wherein R^7, R^8, and R^9 each represents a hydrogen atom and the case wherein

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R^7 and R^9 each represents a hydrogen atom and R^8 represents an alkyl group having from 1 to 6 carbon atoms are excluded; R^{10} and R^{11}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^{12} and R^{13}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or they may be connected to each other to form a 3- to 6-membered ring composed of methylene chains; and the asterisk indicates an asymmetric center.

Examples of these cyclic amino groups are 3-aminopyrrolidinyl, 3-methylaminopyrrolidinyl, 3-dimethylaminopyrrolidinyl, 3-ethylaminopyrrolidinyl, 3-propylaminopyrrolidinyl, 3-isopropylaminopyrrolidinyl, 3-amino-4-methylpyrrolidinyl, 3-amino-5-methylpyrrolidinyl, 3-amino-4,5-dimethylpyrrolidinyl, 3-methylamino-4-methylpyrrolidinyl, 3-methylamino-5-methylpyrrolidinyl, 3-methylamino-4,5-dimethylpyrrolidinyl, 3-dimethylamino-4-methylpyrrolidinyl, 3-dimethylamino-5-methylpyrrolidinyl, 3-dimethylamino-4,5-dimethylpyrrolidinyl, 3-methylpiperzinyl, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3,5-dimethylpiperazinyl, 3,4,5-trimethylpiperazinyl, 4-ethyl-3,5-dimethylpiperazinyl, 4-isopropyl-3,5-dimethylpiperazinyl, 3-aminomethylpyrrolidin-

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yl, 3-methylaminomethylpyrrolidinyl, 3-(1-amino)ethyl-pyrrolidinyl, 3-(1-methylamino)ethylpyrrolidinyl, 3-(1-ethylamino)ethylpyrrolidinyl, 3-(1-amino)propylpyrrolidinyl, 3-(1-methylamino)propylpiperizinyl, 3-amino-pyrrolidinyl, 3-amino-4,4-dimethylpyrrolidinyl, 7-amino-5-azaspiro[2,4]heptan-5-yl, 8-amino-6-azaspiro[3,4]-octan-6-yl, 3,4-diazabicyclo[3,2,1]octan-3-yl, 9-methyl-3,9-diazabicyclo[3,2,1]octan-3-yl, and 9-ethyl-3,9-diazabicyclo[3,2,1]octan-3-yl.

The structure of the cyclic amino group at the 7-position have great influences on antimicrobial activity, toxicity, oral absorption, and physical properties such as water solubility. For instance, it is known that quinolones substituted by 3-aminopyrrolidinyl groups have strong antimicrobial spectra against a broad range of microorganisms covering Gram-positive to Gram-negative bacteria. Some quinolone derivatives of this type, however, are susceptible to metabolism or only show low water-solubility.

3-Aminopyrrolidinyl groups having a spiro ring at the carbon atom adjacent to the amine group thereof provide quinolone derivatives exhibit improved oral absorption rate and improved in vivo stability against metabolism while retaining potent antimicrobial activity. The compounds of this type have also been

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proved less causative of convulsion which is known as a side effect of quinolone type synthetic antimicrobials.

Further, 3-aminomethylpyrrolidinyl groups in which an amino group is bonded to a pyrrolidinyl group via a carbon atom provide quinolone derivatives exhibiting enhanced antimicrobial activity against Gram-positive bacteria. In particular, the quinolones of this type in which the carbon atom linking the amino and pyrrolidinyl groups is substituted with one or two alkyl group(s) were found to exhibit improved oral absorption rate, safety, and water solubility over those without such substituent(s).

Additionally preferred as cyclic amino groups are piperazine residues, such as alkylpiperazine residues and piperazine residues having a spiro ring.

Examples of cyclic amino groups having substituents other than an amino group are 3-hydroxypyrrolidinyl, 3-mercaptopyrrolidinyl, 3-hydroxy-4-methylpyrrolidinyl, 3-mercapto-4-methylpyrrolidinyl, morpholino, thiomorpholino, 2-methylmorpholino, 2-methylthiomorpholino, 2,6-dimethylmorpholino, 2,6-dimethylthiomorpholino, 2,2-dimethylmorpholino, and 2,2-dimethylthiomorpholino groups.

The cyclic amino group is bonded to the 7-position of the pyridonecarboxylic acid skeleton prefer-

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ably at the nitrogen atom of the cyclic amino group. As a matter of course, it may be bonded at the other atom.

The stereoisomerism of the cyclic amine moiety at the 7-position is explained below. In cases where a cyclic amine has isomers, if it is reacted in the form of an isomeric mixture with a 1-(1,2-cis-halogenocyclopropyl)quinolone derivative, the resulting quinolone derivative should be a mixture of diasteromers based on the steric relation with the 1,2-cis-2-halogenocyclopropyl group at the 1-position. In these cases, therefore, it is necessary that only one of the isomers of the starting amine should be reacted.

The functional group of the cyclic amino group at the 7-position such as amino, hydroxy and thiol groups may be protected by a conventional protective group prior to the substitution with the quinolone skeleton. The examples of such protective groups include alkoxycarbonyl groups such as t-butoxycarbonyl group, 2,2,2-trichloroethoxycarbonyl group and the like; aralkyloxycarbonyl groups such as benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, p-nitrobenzyloxycarbonyl group and the like; acyl groups such as acetyl group, methoxyacetyl group, trifluoroacetyl group, chloroacetyl group, pivaloyl group, fomyl group, benzoyl group and the like; alkyl or aralkyl groups

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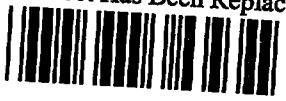
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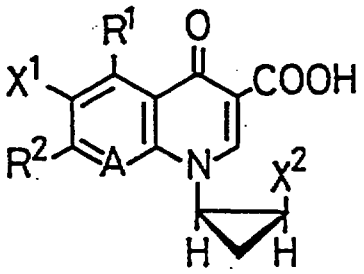
such as t-butyl group, benzyl group, p-nitrobenzyl group, p-methoxybenzyl group, triphenylmethyl group and the like; ethers such as methoxymethyl group, t-butoxymethyl group, 2,2,2-trichloroethoxymethyl group, tetrahydrofuran-2-yl group and the like; silyl groups such as trimethylsilyl group, isopropyldimethylsilyl group, t-butyldimethylsilyl group, t-butyldiphenylsilyl group, tribenzylsilyl group and the like.

The 1,2-cis-2-halogenocyclopropyl group at the N_1-position is described below. Introduction of a halogen atom to the cyclopropyl group particularly a fluorine atom, brings about an effect to reduce lipophilicity of the whole molecule. It is known that drugs are more likely to be distributed to the central nervous system as lipophilicity thereof increases. In this connection, introduction of the 1,2-cis-2-halogenocyclopropyl group yields quinolones having reduced toxicity while retaining excellent antimicrobial activity as compared with the corresponding 1-cyclopropylquinolones. The halogen atom to be introduced includes fluorine and chlorine atoms, with a fluorine atom being preferred.

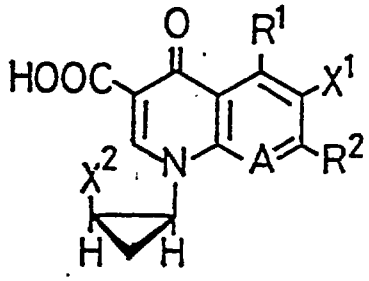
It is particularly preferable that the halogen atom and the pyridonecarboxylic acid moiety are cis with respect to the cyclopropane ring. Irrespective of

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whether the 7-cyclic amino group has stereoisomers or not, the quinolone derivatives of formula (I) have enantiometric pairs ascribed to the cis-2-halogenocyclopropyl moiety at the 1-position as illustrated below. Potent activity and high safety were observed in either of these enantiomers.



and



The pyridonecarboxylic acid derivatives according to the present invention include the respective free acids, acid-addition salts thereof, and the salts of the carboxyl group thereof. The acid-addition salts include inorganic acid salts, e.g., hydrochlorides, sulfates, nitrates, hydrobromides, hydroiodides, and phosphates; and organic acid salts, e.g., acetates, methanesulfonates, benzenesulfonates, toluenesulfonates, citrates, maleates, fumarates, and lactates.

The salts of the carboxyl group may be organic or inorganic and include alkali metal salts, e.g., lithium salts, sodium salts, and potassium salts,

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alkaline earth metal salts, e.g., magnesium salts and calcium salts; ammonium salts, triethylamine salts, N-methylglucamates, and tris(hydroxymethyl)aminomethane salts.

Some of these free acids and salts may exist as a hydrate.

Esterification of the carboxylic acid moiety of the pyridonecarboxylic acid derivatives of formula (I) gives compounds useful as synthesis intermediates or pro-drugs. For example, alkyl esters, benzyl esters, alkoxyalkyl esters, phenylaklyl esters and phenyl esters are useful as synthesis intermediates. Esters which are easily severed in the body to form free carboxylic acids are useful as pro-drugs. Examples of such esters are acetoxymethyl esters, pivaloyloxymethyl esters, ethoxy-carbonyloxy esters, chlorine esters, dimethylaminoethyl esters, 5-indanyl esters, phthalidinyl esters, and oxo-alkyl esters (e.g., 5-substituted-2-oxo-1,3-dioxol-4-yl-methyl esters and 3-acetoxy-2-oxobutyl esters).

A process for synthesizing the pyridone-carboxylic acid derivatives of formula (I) is illustrated below, taking the compound wherein A=C-H; R^1=H; X^1=X^2=F; and R^3=Et (ethyl group, hereinafter the same) for instance.

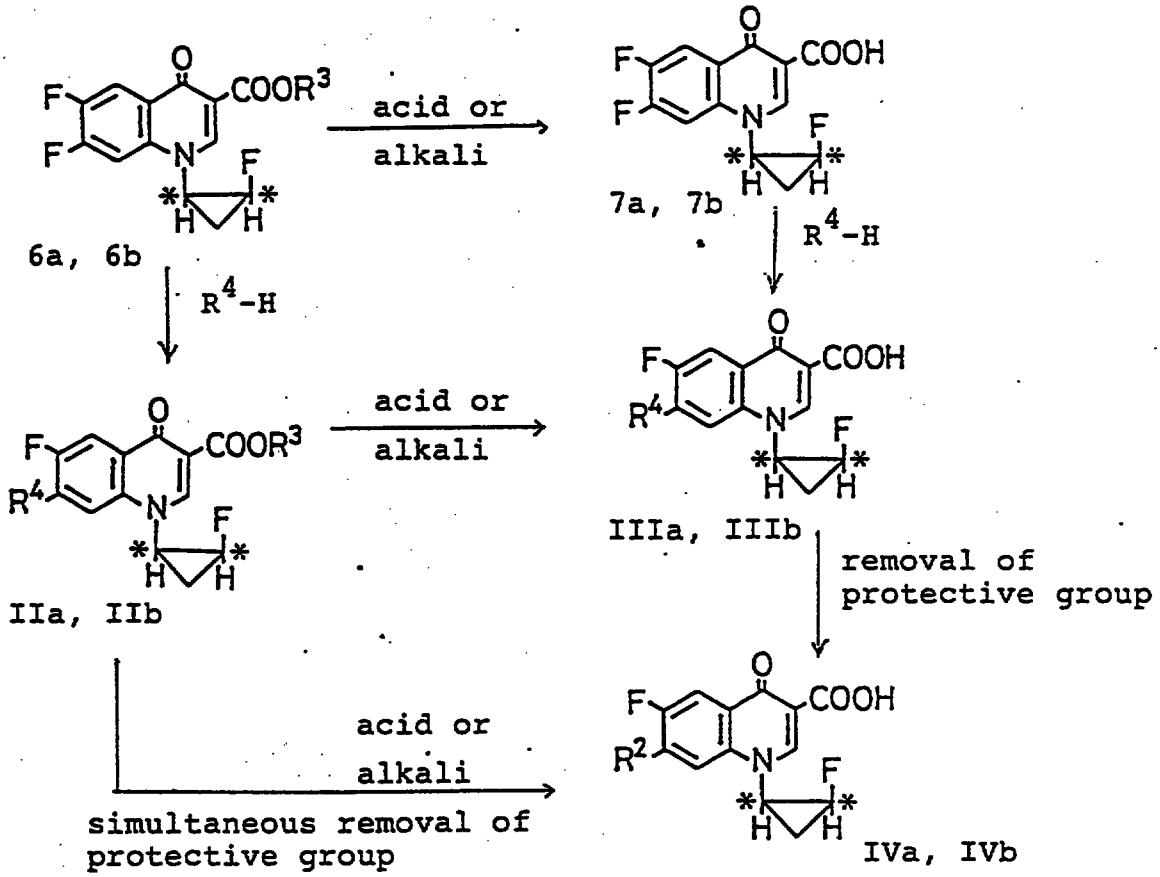
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wherein R^4 has the same meaning as R^2 or a cyclic amino group having the same structure as R^2 but being protected.

An optically active 1-(1,2-cis-2-fluoro-cyclopropyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (6a) or (6b) is hydrolyzed under acidic or alkaline conditions to give a free carboxylic acid derivative (7a) or (7b). The free acid (7a) or (7b) is reacted with a cyclic amine R^4-H to obtain a desired compound (IIIa) or (IIIb). If necessary, a protective group is removed from the resulting compound under proper conditions selected

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according to the protective group to obtain a desired compound (IVa) or (IVb).

The substitution reaction with the cyclic amine can be carried out in a solvent such as dimethyl sulfoxide, pyridine, acetonitrile and 3-methoxybutanol, at a temperature of from room temperature to 150°C, preferably from 40 to 120°C, for 0.5 to 5 hours, usually from 0.5 to 2 hours.

Alternatively, the compound (6a) or (6b) is reacted with a cyclic amine under the same conditions as recited above, and the resulting compound (IIa) or (IIb) as is produced is then hydrolyzed under acidic or alkaline conditions and, if necessary, a protective group is removed, to obtain a desired compound (IIIa) or (IIIb) or (IVa) or (IVb).

The optically active cis-2-fluorocyclopropylamine can be synthesized as follows. 2-Fluorocyclopropanecarboxylic acid is reacted with (R)-(+)-α-methylbenzylamine to yield N-[1-(R)-phenylethyl]-1,2-cis-fluorocyclopropanecarboxamide. The reaction can be carried out in tetrahydrofuran in the presence of N,N-carbonyldiimidazole. The reaction may also be effected in accordance with a mixed anhydride procedure, in which the carboxylic acid is dissolved in an aprotic solvent and reacted with a halogenoformic ester in the presence

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of a base at low temperatures and then reacted with the benzylamine to obtain the carboxamide. The resulting carboxamide can be separated into each isomer by chromatographic techniques.

The aprotic solvent to be used in the mixed anhydride procedure is not particularly limited and includes ethers, e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, and 1,2-dimethoxyethyane; halogenated hydrocarbons, e.g., dichloromethane, chloroform, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane; aromatic hydrocarbons, e.g., benzene, toluene, and xylene; and aliphatic hydrocarbons, e.g., pentane, hexane, heptane, and cyclohexane. Commonly employed of them is tetrahydrofuran or chloroform. The water contained in the solvent to be used is usually removed beforehand.

The halogen atom in the halogenoformic ester is normally a chlorine atom. The halogenoformic ester includes methyl, ethyl, 2,2,2-trichloroethyl, phenyl, p-nitrophenyl and benzyl esters.

The base to be used may be either an organic or an inorganic. The inorganic base includes alkali metal hydroxides, carbonates and hydrogencarbonates, e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate,

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potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate. The organic base includes trialkylamines, e.g., triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine; dialkylanilines, e.g., diethylaniline and dimethylaniline; and heterocyclic compounds, e.g., N-methylmorpholine, pyridine, and N,N-dimethylaminopyridine.

Separation of the carboxamide into optical isomers can be effected by known techniques, such as silica gel column chromatography under normal pressure or under pressure, preparative thin layer chromatography, and high performance liquid chromatography (HPLC). Separation into optical isomers can also be performed by other separation techniques generally employed, such as recrystallization and reprecipitation.

The thus separated optionally active carboxamide can be led to an optically active cis-2-fluorocyclopropanecarboxylic acid by hydrolysis. The reaction can be carried out by dissolving the carboxamide in, for example, concentrated hydrochloric acid, followed by heating. The hydrochloric acid may be replaced with sulfuric acid or nitric acid. A solvent, such as acetic acid and a lower alcohol, may be used.

The resulting carboxylic acid can be converted at once by Curtius reaction in the presence of a t-butanol

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to a protected cis-1-(t-butoxycarbonylamino)-2-fluoro-cyclopropane. The reaction can be carried out conveniently by use of diphenylphosphorylazide, but the synthesis of the intermediate azide compound is not limited thereto, and general methods of synthesis can be applied.

The resulting optically active cis-2-fluoro-cyclopropylamine derivative can be made use of in obtaining a quinolone derivative having a cis-fluoro-cyclopropyl group at the 1-position as a single isomer. The quinolone derivative according to the present invention can then be obtained by reacting this isomer with the cyclic amine as described above.

The pyridonecarboxylic acid derivatives according to the present invention exhibit potent antimicrobial activity and thus can be used as human and veterinary medicines, fish medicines, agricultural chemicals, and food preservatives.

The dose of the pyridonecarboxylic acid derivatives for use as human medicines ranges from 50 mg to 1 g, preferably from 100 mg to 300 mg, per day for adult. The dose for use as veterinary medicines generally ranges from 1 mg to 200 mg, preferably from 5 mg to 100 mg, per kg of body weight per day, though more or less verying depending on the purpose of administra-

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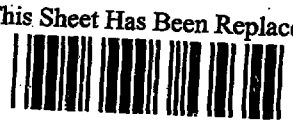
tion (therapeutic use or preventive use, etc.), the kind and size of the animal, the kind of pothogenic organisms, and the symptoms. The daily dose recited above may be divided into 2 to 4 doses per day. If necessary, the daily dose may be sometimes deviated from the above-recited range.

The pyridonecarboxylic acid derivatives of this invention are active against a wide variety of micro-organisms causing various infectious diseases and capable of curing or alleviating and/or preventing the diseases caused by such phthogenes.

Illustrative examples of bacteria or bacterium-like microorganisms on which the pyridonecarboxylic acid derivatives of the invention are effective are Staphylococcus sp., Streptococcus pyogenes, Streptococcus Haemolyticus, enterococci, Streptococcus pneumoniae, Peptostreptococcus sp., Neisseria gonorrhoeae, Escherichia coli, Citrobacter sp., Shigella sp., Klebsiella pneumoniae, Enterobacter sp., Serratia sp., Proteus sp., Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter sp., Campylobacter sp., and Chlamidiae.

Examples of diseases caused by these pathogenes include folliculitis, furuncle, carbuncle, erysipelas, phlegmon, lymphangitis/lymphadenitis, felon, subcutaneous abscess, spiradenitis, acne conglobata,

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infectious atheroma, perianal abscess, mastadenitis, superficial secondary infections after trauma, burn or surgery trauma, pharyngolaryngitis, acute bronchitis, tonsillitis, chronic bronchitis, bonchiectasis, diffuse panbronchiolitis, secondary infections of chronic respiratory diseases, pneumonia, pyelonephritis, cystitis, prostatitis, epididymitis, gonococcal urethritis, non-gonococcal urethritis, cholecystitis, cholangitis, bacillary dysentery, enteritis, adnexitis, intrauterine infections, Bartholinitis, blepharitis, hordeolum, dacryocystitis, tarsadenitis, keratohelcosis, otitis media, sinusitis, paradentitis, pericoronitis circumcoronitis, gnathitis, peritonitis, endocarditis, septicemia, meningitis, and skin infectious.

Examples of susceptible microorganisms causing veterinary infectious diseases include those of fowl, such as Escherichia sp., Salmonella sp., Pasteurella sp., Haemophilus sp., Bordetella sp., Staphylococcus sp., and Mycoplasma sp. Specific examples of veneterinary diseases caused by these microorganisms include colibacillosis, pullorum disease, avian paratyphosis, fowl chlera, infectious coryza, staphylococcal infections, and mycoplasmal diseases; those of swin, such as colibacillosis, malmonelosis, pasteurellosis, haemophylus infection, atrophic rhintis,

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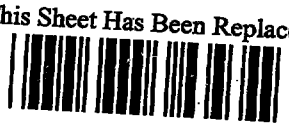
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exduadative epidermitis, and mycoplasmal diseases; those for cattle, such as colibacillosis, salmonellosis, hemorrhagic septicemia, mycoplasmal diseases, bovine contageous pleurponeumonia, and bovine mastesis; those of dogs, such as coliform sepsis, salmonelosis, hemorrhagic septicemia, pyometra, and cystitis; and those of cats, such as hemorrhagic pleuritis, cystitis, chronic rhiniti, haemophylus infection, kitten diarrhea, and mycoplasmal diseases.

The compound of the present invention can be formulated into antimicrobial preparations in an appropriate dose form according to administration route selected by the conventional preparation methods. The dose form for oral administration includes tablets, powders, granules, capsules, solutions, syrups, elixiers, and oily or aqueous suspensions. Injections may contain, in addition to the active ingredient, stabilizers, antiseptics, and solubilizing agents. The solution which may contain such excipients is put in a container and further, the solution may be subjected to lyophilization or the like means to prepare solid preparations which can be dissolved on use. The container may contain either a single dose or several doses.

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Dose forms for external administration include solutions, suspensions, emulsions, ointments, gels, creams, lotions, and sprays.

In the preparation of solid preparations, the active ingredient may be mixed with appropriately selected pharmaceutically acceptable excipients, such as fillers, extenders, binders, disintegrators, dissolution accelerators, wetting agents, and lubricants.

Liquid preparations include solutions, suspensions, and emulsions. They may contain excipients, such as suspension stabilizers and emulsifiers.

The compound of the present invention can be administered to animals orally either directly or as admixed to feedstuff, or its solution may be given either directly or as admixed to water or feedstuff. The compound may also be administered non-orally by, for example, injection.

The compound of the invention can be formulated into preparations for animals, such as powders, fine granules, solubilized powders, syrups, solutions, and injections, by commonly employed preparation methods.

Formulation Examples are given below for illustrative purposes only but not for limitation.

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FORMULATION EXAMPLE 1

Capsule:

Compound of Example 8	100.0 mg
Corn starch	23.0 mg
Calcium carboxymethyl cellulose	22.5 mg
Hydroxypropylmethyl cellulose	3.0 mg
Magnesium stearate	1.5 mg
total:	150.0 mg

FORMULATION EXAMPLE 2

Solution:

Compound of Example 7	1 to 10 g
Acetic acid or sodium hydroxide	0.5 to 2 g
Ethyl p-hydroxybenzoate	0.1 g
Purified water	88.9 to 98.4 g
total:	100 g

FORMULATION EXAMPLE 3

Powder for Admixture with Feedstuff:

Compound of Example 6	1 to 10 g
Corn starch	98.5 to 98.5 g
Light anhydrous silicic acid	0.5 g
total:	100 g

The present invention is now illustrated in greater detail by way of the following Examples and Reference Examples, but it should be understood that the

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present invention is not deemed to be limited thereto. Reference Examples describe the syntheses of optically active skeletons from an optically active cis-2-fluorocyclopropanecarboxylic acid.

Antimicrobial activity of the optically active compounds prepared in Examples was evaluated in accordance with the standard method specified by Nippon Kagakuryoho gakkai, and results obtained are shown in Table 1 below in terms of minimum inhibitory concentration (MIC: $\mu g/m^2$).

REFERENCE EXAMPLE 1

N-[1-(R)-Phenylethyl]-1,2-cis-2-fluorocyclopropanecarboxamide (2a, 2b):

1-1. Carbonyldiimidazole Method:

One gram of cis-2-fluorocyclopropanecarboxylic acid was dissolved in 30 ml of tetrahydrofuran (THF), and 1.78 g of N,N'-carbonyldiimidazole was added thereto, and the mixture was stirred at room temperature for 1 hour. To the solution was added 1.45 g of (R)-(+)-α-methylbenzylamine, and the stirring was continued for 2 hours. The solvent was removed under reduced pressure, and the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced

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pressure. From the residual viscous oily substance, each stereoisomer was isolated by HPLC under conditions shown below. Each isomer was recrystallized from diisopropyl ether to yield the titled compound (2a) or (2b).

HPLC Conditions:

Column: Nucleosil 50-5 (20 mm ID × 250 mm L) (senshu Pack SSC Silica, 782-IN, produced by Senshu Kagaku)

Solvent: ethyl acetate-THF (9:1 by volume)

Flow Rate: 9.0 ml/min

Retention Time: 11 mins, for Compound (2a)

13 mins. for Compound (2b)

Compound (2a):

Melting point: 108°C

Elementary Analysis for $C_{12}H_{14}FNO$:

Calcd. (%): C 69.55; H 6.81; N 6.76

Found (%): C 69.31; H 7.01; N 6.65

$[\alpha]_D$: +61.96° (c=0.965, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.92-1.34 (2H, m), 1.50 (3H, d, J=7Hz), 1.50-1.96 (1H, m), 4.68 (1H, dm, J=64Hz), 5.14 (1H, m), 7.40 (5H, s)

Physiochemical Properties of Compound (2b):

Melting point: 102°C

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Elementary Analysis for $C_{12}H_{14}FNO$:

Calcd. (%): C 69.55; H 6.81; N 6.76

Found (%): C 69.45; H 6.87; N 6.70

$[\alpha]_D$: +143.61° (c=0.830, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.98=1.34 (2H, m), 1.52 (3H, d, J=7Hz), 1.64-1.96 (1H, m), 4.58 (1H, dm, J=66Hz), 5.24 (1H, m), 7.40 (5H, m)

1-2. Mixed Anhydride Method:

In 50 ml of THF were dissolved 4.19 g of 2-fluorocyclopropanecarboxylic acid (cis-trans mixture) and 4.07 g of triethylamine, and the solution was cooled to -10°C. To this was added a solution of 4.73 g of ethyl chloroformate in 20 ml of THF and the mixture was stirred for 10 minutes. To the solution was then added dropwise a solution of 4.88 g of (R)-(+)-α-methyl-benzylamine in 30 ml of THF at that temperature, and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure, and the residue was extracted with benzene. The extract was washed successively with a 10% citric acid aqueous solution, a 1N sodium hydroxide aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting pale yellow oily substance was purified by

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silica gel column chromatography using a mixed solvent of benzene and ethyl acetate as an eluent to each of the titled compounds (2a) and (2b).

REFERENCE EXAMPLE 2

(+)-cis-2-Fluorocyclopropanecarboxylic acid (3a):

In 15 ml of concentrated hydrochloric acid was dissolved 530 mg of the amide compound (2a) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. To the reaction mixture was added 20 ml of water, and the mixture was extracted with ethyl acetate. The extract was then extracted with a sodium hydrogencarbonate aqueous solution and this aqueous extract was washed with ethyl acetate. The aqueous extract was adjusted to a pH of 5 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield the titled compound (3a) as a pale yellow oil.

$[\alpha]_D$: -23.13° (c=1.020, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.60-2.10 (2H, m), 4.82 (1H, dm, J=65Hz), 12.0 (1H, s)

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REFERENCE EXAMPLE 3

(+)-cis-2-Fluorocyclopropanecarboxylic acid (3b):

In 30 ml of concentrated hydrochloric acid was dissolved 1.65 g of amide compound (2b) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. The pH of the reaction mixture was adjusted between 8 and 9 with sodium hydrogencarbonate and then washed with chloroform. The pH of aqueous layer was adjusted to 4 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the titled compound (3b) as a pale yellow oil.

$[\alpha]_D$: +21.56° (c=1.113, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.56-1.98 (2H, m), 4.76 (1H, dm, J=66Hz), 11.32 (1H, s)

REFERENCE EXAMPLE 4

(+)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4a):

In 5 ml of t-butanol were dissolved 200 mg of the carboxylic acid (3a) as obtained in Reference Example 2, 603 mg of diphenylphosphorylazide, and 203 mg of triethylamine, and the solution was heated under

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reflux for 4.5 hours. After removing the solvent under reduced pressure, the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution, a 2% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using chloroform as an eluent to obtain the titled compound (4a) as a colorless crystal.

Melting Point: 73°C

$[\alpha]_D$: +65.57° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.62 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 5

(-)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4b):

In 6 ml of t-butanol were added 265 mg of the carboxylic acid (3b) as obtained in Reference Example 3, 800 mg of diphenylphosphorylazide, and 270 mg of triethylamine. The solution was allowed to react and worked up in the same manner as in Reference Example 4 to obtain the titled compound (4b).

Melting Point: 63°C

$[\alpha]_D$: -60.27 (c=0.740, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.66-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.58 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 6

(-)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)amino-methylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5a):

Ethyl 2,4,5-trifluorobenzoylacetate (234 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Compound (4a) as obtained in Reference Example 4 (167 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for 20 minutes and concentrated to dryness under reduced pressure (the resulting amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloromethane and cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was added dropwise thereto. Thereafter, the above prepared dichloromethane solution was added dropwise to the mixture, followed by stirring at room temperature over-night. The solvent was evaporated to dryness under reduced pressure, and the residue was subjected to

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silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after the removed of the solvent. The product was recrystallized from diisopropyl ether-n-hexane to yield the titled compound (5a) as a colorless crystals.

Melting Point: 69-70°C

$[\alpha]_D$: -10.29° (c=1.088, chloroform)

REFERENCE EXAMPLE 7

(+)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)amino-methylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5b):

Ethyl 2,4,5-trifluorobenzoylacetate (337 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Compound (4b) as obtained in reference Example 5 (240 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for 1 hour, followed by concentration under reduced pressure (the amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloroethane, and the solution was cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was

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added thereto dropwise, and the above-prepared dichloromethane solution was further added to the mixture, followed by stirring at room temperature over-night. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after the removal of solvent. Recrystallization from diisopropyl ether-n-hexane gave the titled compound (5b) as a colorless crystal.

Melting Point: 69-70°C

$[\alpha]_D$: +12.09 (c=0.645, chloroform)

REFERENCE EXAMPLE 8

(+)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6a):

In 15 ml of anhydrous dioxane was dissolved 180 mg of Compound (5a) as obtained in Reference Example 6, and 200 mg of 60% sodium hydride was added to the solution, followed by stirring at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel

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preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing solvent to yield the titled compound (6a) as a colorless crystal.

Melting Point: 231-232°C

$[\alpha]_D$: +27.20° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.20 (3H, t, J=7Hz), 1.6-1.9 (2H, m), 3.28-3.56 (1H, m), 4.42 (2H, q, J=7Hz), 5.11 (1H, dm, J=63Hz), 7.60 (1H, dd, J=11Hz & 7Hz), 8.28 (1H, dd, J=10Hz & 11Hz), 8.58 (1H, s)

REFERENCE EXAMPLE 9

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6b):

In 15 ml of anhydrous dioxane was dissolved 267 mg of Compound (5b) as obtained in Reference Example 7, and 200 mg of 60% sodium hydride was added thereto, and the mixture was stirred at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing

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solvent to yield the titled compound (6b) as a colorless crystal.

Melting Point: 226-227°C

$[\alpha]_D$: -31.36° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.22 (3H, t, J=7Hz), 1.5-1.9 (2H, m), 3.26-3.52 (1H, m), 4.40 (2H, q, J=7Hz), 5.10 (1H, dm, J=63Hz), 7.58 (1H, dd, J=11Hz & 7Hz), 8.26 (1H, dd, J=10Hz & 11Hz), 8.55 (1H, s)

REFERENCE EXAMPLE 10

(+)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7a):

In 15 ml of concentrated hydrochloric acid was dissolved 106 mg of the ester (6a) as obtained in Reference Example 8, and the solution was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture was added 15 ml of water, and the precipitate was collected by filtration to obtain the titled compound (7a) as a colorless crystal.

Melting Point: 265-270°C

$[\alpha]_D$: +3.66° (c=0.383, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H, dm, J=64Hz), 7.82 (1H, dd, J=12Hz, & 7Hz), 8.37 (1H, dd, J=18Hz & 8Hz), 8.94 (1H, s)

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REFERENCE EXAMPLE 11

(-)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7b):

In 10 ml of concentrated hydrochloric acid was dissolved 150 mg of the ester (6b) as obtained in Reference Example 9, and the solution was heated at 110°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to yield the titled compound (7b) as a colorless crystal.

Melting Point: 261-264°C

$[\alpha]_D$: -4.08° (c=0.343, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H, dm, J=64Hz), 7.82 (1H, dd, J=12Hz & 7Hz), 8.37 (1H, dd, J=12Hz & 8 Hz), 8.94 (1H s)

EXAMPLE 1

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (8a):

Seventy milligrams of the carboxylic acid (7a) as obtained in Reference Example 10, 150 mg of (S)-3-(t-butoxycarbonylamino)pyrrolidine, 200 mg of triethyl-

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amine, and 20 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to obtain the titled compound (8a) as a yellow crystal.

Melting Point: 236-239°C

$[\alpha]_D$: +1.0°(c=0.200, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.7 (2H, m), 1.46 (9H, s), 1.7-1.9 (1H, m), 2.0-2.36 (1H, m), 3.3-4.0 (5H, m), 4.2-4.4 (1H, m), 5.06 (1H, dm, J=68Hz), 6.68 (1H, d, J=7Hz), 7.84 (1H, d, J=14Hz), 8.46 (1H, s)

EXAMPLE 2

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (8b):

The carboxylic acid as obtained in Reference Example 11 (7b) (112 mg), 200 mg of (S)-3-(t-butoxycarboxylamino)pyrrolidine, 220 mg of triethylamine, and 15 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the

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residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to yield the titled compound (8b) as a yellow crystal.

Melting Point: 242-243°C

$[\alpha]_D$: -4.0°(c=0.448, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.7 (2H, m), 1.40 (9H, s), 1.6-1.8 (1H, m), 1.9-2.1 (1H, m), 3.3-3.9 (5H, m), 4.2-4.5 (1H, m), 5.00 (1H, dm, J=68Hz), 6.58 (1H, d, J=7Hz), 7.72 (1H, d, J=14Hz), 8.32 (1H, s)

EXAMPLE 3

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

In 10 ml of trifluoroacetic acid was dissolved 80 mg of the carboxylic acid (8a) as obtained in Example 1. After stirring for 20 minutes, the reaction mixture was evaporated under reduced pressure to dryness. To the residue was added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of aqueous layer was adjusted to 7.5 with 1N hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous

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sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from ethanol yielded the titled compound as a colorless crystal.

Melting Point: 248-252°C

$[\alpha]_D$: -31.35° (c=0.370, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.52-1.68 (2H, m), 1.68-1.80 (1H, m), 2.05-2.15 (1H, m), 3.13-3.22 (1H, m), 3.25-3.45 (2H, m), 3.45-3.65 (3H, m), 5.12 (1H, dm, J=65Hz), 6.58 (1H, d, J=7Hz), 7.58 (1H, d, J=14Hz), 8.29 (1H, s)

EXAMPLE 4

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

In 10 ml of trifluoroacetic acid was added 80 mg of the carboxylic acid (8b) as obtained in Example 2. After stirring for 20 minutes, the reaction mixture was evaporated to dryness under reduced pressure. To the residue was added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of aqueous layer was adjusted to 7.5 with 1N hydrochloric acid and followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed therefrom

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under reduced pressure. Recrystallization of the residue from ethanol gave the titled compound (9b) as a colorless crystal.

Melting Point: 236-240°C

$[\alpha]_D$: +23.72 (c=0.413, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.55-1.69 (2H, m), 1.69-1.77 (1H, m), 2.07-2.15 (1H, m), 3.15-3.22 (1H, m), 3.37-3.47 (2H, m), 3.52-3.58 (2H, m), 3.58-3.66 (1H, m), 5.13 (1H, dm, J=65Hz), 6.62 (1H, d, J=7Hz), 7.61 (1H, d, J=14Hz), 8.30 (1H, s)

REFERENCE EXAMPLE 12

(-)-Ethyl 2-[[1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)-propionate (10a):

Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 5 ml of dichloromethane.

Seven milliliters of trifluoroacetic acid was cooled with ice, and 480 mg of (+)-cis-1-(t-butoxy-carbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature

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for 20 minutes, followed by evaporation under reduced pressure to dryness. The residue was suspended in 10 ml of dichloromethane, and 3 ml of triethylamine was added thereto under ice-cooling. After stirring for 20 minutes, the above-prepared dichloromethane solution was added thereto, and the mixture was stirred for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using a mixed solvent of benzene and ethyl acetate (5:1 by volume) as an eluent. The solvent was removed under reduced pressure, and the residue was washed with diisopropyl ether to obtain 620 mg of the titled compound (10a).

Melting Point: 98-100°C

$[\alpha]_D$: -6.66° (c=0.998, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 49.26; H 3.31; N 3.83

Found (%): C 49.39; H 3.22; N 3.86

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

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REFERENCE EXAMPLE 13

(+)-2-[[1,2-cis-2-Fluoro-1-cyclopropyl)amino]methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)propionate (10b):

Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid were ice-cooled, and 1.12 g of (-)-cis-1-(t-butoxycarbonyl-amino)-2-fluorocyclopropane (4b) was dissolved therein. After stirring at room temperature for 20 minutes, the mixture was evaporated to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine was added to the suspension under ice-cooling. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography which was eluted with a mixed solvent of benzene and ethyl acetate (4:1 by volume) The solvent

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of the eluent was removed under reduced pressure. The residue was washed with diisopropyl ether-n-hexane to obtain 1.74 g of crystals of the titled compound (10b).

Melting Point: 99-100°C

$[\alpha]_D$: +6.70° (c=0.895, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 49.26; H 3.31; N 3.83

Found (%): C 49.41; H 3.60; N 4.06

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

REFERENCE EXAMPLE 14

(+)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11a):

In 7 ml of anhydrous dioxane was dissolved 620 mg of Compound (10a) as prepared in Reference Example 12, and 80 mg of 60% sodium hydride was added to the solution, followed by stirring at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the

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solvent was removed therefrom under reduced pressure. The residue was washed with n-hexane to obtain 551 mg of the titled compound (11a) as a colorless crystal.

Melting Point: 181-184°C

$[\alpha]_D$: +45.1° (c=1.18, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:

Calcd. (%): C 52.12; H 3.21; N 4.05

Found (%): C 52.09; H 3.33; N 4.01

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

REFERENCE EXAMPLE 15

(-)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11b):

In 10 ml of anhydrous dioxane was suspended 560 mg of 60% sodium hydride having been washed twice with anhydrous n-hexane. The suspension was added to a solution of 1.70 g of Compound (10b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 2 hours. The solvent was removed under reduced pressure, and 0.1N hydrochloric acid was added to the residue. The precipitated crystals were collected by filtration, washed successively with water and diethyl

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ether, and dried under reduced pressure to obtain 1.44 g of the entitled compound (11b) as a colorless crystal.

Melting Point: 174°C

$[\alpha]_D$: -45.3° (c=1.05, chloroform)

Elementary Analysis for $C_{15}H_{11}ClF_4NO_3$:

Calcd. (%): C 52.12; H 3.21; N 4.05

Found (%): C 51.80; H 3.45; N 4.15

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

IR(KBr); ν_{max} cm^{-1}: 3100, 2998, 1731, 1638, 1614, 1470, 1317

REFERENCE EXAMPLE 16

(+)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12a):

The ester (11a) (540 mg), 5 ml of concentrated hydrochloric acid, and 5 ml of acetic acid were mixed, and the mixture was heated at 120-130°C for 2 hours while stirring. To the reaction mixture was added 50 ml of water, and the precipitated crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to

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obtain 420 mg of the titled compound (12a) as a colorless crystal.

Melting Point: 170-171°C

$[\alpha]_D$: +30.4° (c=0.54, chloroform)

Elementary Analysis for $C_{13}H_7ClF_3NO_3$:

Calcd. (%): C 49.16; H 2.22; N 4.41

Found (%): C 49.21; H 2.49; N 4.27

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

REFERENCE EXAMPLE 17

(-)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b)

The ester (11b) (1.40 g) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 110°C for 2.5 hours under stirring. To the reaction mixture was added 50 ml of water, and the precipitated crystals were collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to obtain 1.16 g of the titled compound (12b) as a colorless crystal.

Melting Point: 177-182°C

$[\alpha]_D$: -26.8° (c=0.90, chloroform)

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Elementary Analysis for $C_{13}H_7ClF_3NO_3$:

Calcd. (%): C 49.16; H 2.22; N 4.41

Found (%): C 49.28; H 2.40; N 4.66

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

EXAMPLE 5

(+)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (13a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12a) and 400 mg of triethylamine, followed by refluxing for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure, and to the residue was added 1N hydrochloric acid. The mixture was washed with chloroform. The pH of the aqueous layer was adjusted to 12 with a 1N sodium hydroxide aqueous solution and washed with chloroform. The pH of the aqueous layer was readjusted to 7.6 with

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hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 138 mg of the titled compound (13a) as a colorless crystal.

Melting Point: 214-217°C (with decomposition)

$[\alpha]_D$: +120.8° (c=0.475, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot 1/2H_2O$:

Calcd. (%): C 51.98; H 4.36; N 10.70

Found (%): C 52.07; H 4.71; N 10.72

^{1}H-NMR (NaOD) δ ppm:

1.28 (1H, dm, J=27Hz), 1.69-1.78 (2H, m), 3.39-3.42 (1H, m), 3.51-3.61 (3H, m), 3.69-3.72 (1H, m), 4.13-4.17 (1H, m), 4.99 (1H, dm, J=70Hz), 7.72 (1H, d, J=14Hz), 8.44, 8.45 (1H, each s, split, 1:1)

EXAMPLE 6

(-)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (13a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in

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15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12b) and 400 mg of triethylamine, and the mixture was heated under reflux for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure. A 1N hydrochloric acid was added to the residue, and the mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, and the aqueous layer was adjusted to a pH of 7.6 with hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to give 158 mg of the titled compound (13b) as a colorless crystal.

Melting Point: 247-252°C (with decomposition)

$[\alpha]_D$: -94.7° (c=0.378, 0.1N HaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot H_2O$:

Calcd. (%): C 50.82; H 4.52; N 10.46

Found (%): C 50.97; H 5.14; N 10.42

^{1}H-NMR (NaOD) δ ppm:

1.32 (1H, dm, J=27Hz), 1.73-1.80 (2H, m), 2.15-2.19 (1H, m), 3.19-3.22 (1H, m), 3.45-3.50 (1H, m), 3.58-3.62 (1H, m), 3.85-3.88 (2H, m), 4.16-4.20 (1H, m), 4.99 (1H, dm, J=63Hz), 7.76 (1H, d, J=14Hz), 8.54, 8.44 (1H, each s, split, 1:1)

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REFERENCE EXAMPLE 18

(-)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)-propionate (14a):

Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 120°C for 2 hours. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 1.1 g of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporating to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling, followed by stirring for 20 minutes. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 30 minutes. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the compound (14a) were combined, and the solvent was removed under reduced

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pressure. The residue was washed with n-hexane to yield 1.57 g of crystals of the titled compound (14a).

Melting Point: 99-100°C

$[\alpha]_D$: -10.3° (c=1.25, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$

Calcd. (%): C 45.70; H 2.81; N 7.10

Found (%): C 45.60; H 3.01; N 7.03

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.55 (2H, m), 2.88-3.16 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.29 (1H, d, J=14Hz)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521, 1482

REFERENCE EXAMPLE 19

(+)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)-propionate (14b):

Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1 hour while stirring. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was ice-cooled, and 1.10 g of (-)-cis-1-(t-butoxycarbonyl-

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amino)-2-fluorocyclopropane (4b) was dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was suspended in 20 ml of dichloromethane. To the suspension was added 1.8 g of triethylamine under ice-cooling, followed by stirring for 20 minutes. To the mixture was added the above-prepared dichloromethane solution, followed by stirring for 2 hours. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the product (14b) were combined, and the solvent was removed under reduced pressure. The residue was washed with n-hexane to yield 1.50 g of crystals of the titled compound (14b).

Melting Point: 98-100°C

$[\alpha]_D$: -10.1° (c=2.09, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$

Calcd. (%): C 45.70; H 2.81; N 7.10

Found (%): C 45.77; H 3.38; N 7.18

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.5 (2H, m), 2.88-3.12 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.30 (1H, d, J=14Hz)

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IR(KBr): ν_{max} cm^{-1}: 3454 1695, 1638, 1554, 1515

REFERENCE EXAMPLE 20

(+)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15a):

In 20 ml of anhydrous dioxane was suspended 580 mg of 60% sodium hydride having been washed twice with n-hexane. The suspension was added to a solution of 1.90 g of Compound (14a) in 20 ml of anhydrous dioxane. The mixture was stirred at room temperature for 1 hour, and the solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid. The crystals thus formed were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.65 g of the titled compound (15a) as a colorless crystal.

Melting Point: 172-176°C

$[\alpha]_D$: +10.7° (c=1.12, chloroform)

Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$

Calcd. (%): C 48.14; H 2.69; N 7.49

Found (%): C 48.29; H 2.78; N 7.20

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.80-4.08 (1H, m), 4.34 (2H, q, J=7Hz), 4.99 (1H, dm, J=63Hz), 8.55 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521 1482

REFERENCE EXAMPLE 21

(-)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15b):

In 10 ml of anhydrous dioxane was suspended 440 mg of 60% sodium hydride having been washed twice with n-hexane. The suspension was added to a solution of 1.45 g of Compound (14b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 30 minutes. The solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid, and the formed crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.18 g of the titled compound (15b) as a colorless crystal.

Melting Point: 171-175°C

$[\alpha]_D$: -11.1° (c=0.27, chloroform)

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Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$

Calcd. (%): C 48.14; H 2.69; N 7.49

Found (%): C 48.44; H 3.17; N 7.48

^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.74-4.02 (1H, m), 4.36 (2H, q, J=7Hz), 4.94 (1H, dm, J=62Hz), 8.54 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 1731, 1626, 1566, 1485, 1323, 1275

REFERENCE EXAMPLE 22

(+)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16a):

The nitro compound (15a) (1.60 g), 6 ml of Raney nickel, and 200 ml of ethanol were mixed, and the mixture was shaken for 2.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16a) were combined, and the solvent was removed therefrom under reduced pressure. The residue was recrystallized from ethanol to obtain 770 mg of the titled compound (16a) as a pale yellow crystal.

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Melting Point: 190-191°C

$[\alpha]_D$: +26.0° (c=0.76, chloroform)

Elementary Analysis for $C_{15}H_{12}F_4N_2O_3$

Calcd. (%): C 52.33; H 3.51; N 8.14

Found (%): C 52.13; H 3.95; N 8.13

^{1}H-NMR ($CDCl_3$) δ ppm:

1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.37 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1557, 1461, 1284

REFERENCE EXAMPLE 23

(-)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (16b):

The nitro compound (15b) (1.60 g), 3 ml of Raney nickel, and 120 ml of ethanol were mixed, and the mixture was shaken for 4.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16b) were combined, and the solvent was removed under reduced pressure. The residue

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was recrystallized from ethanol to obtain 620 mg of the titled compound (16b) as a pale yellow crystal.

Melting Point: 191-193°C

$[\alpha]_D$: -25.9° (c=0.65, chloroform)

Elementary analysis for $C_{15}H_{12}F_4N_2O_3$

Calcd. (%): C 52.33; H 3.51; N 8.14

Found (%): C 52.16; H 3.54; N 8.08

^{1}H-NMR ($CDCl_3$) δ ppm:

1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.38 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1593, 1464, 1284

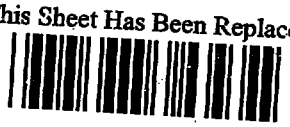
REFERENCE EXAMPLE 24

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17a):

The ester (16a) (750 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 610 mg of the titled compound (17a) as a colorless crystal.

Melting Point: 297-300°C

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Elementary Analysis for $C_{13}H_8F_4N_2O_3$

Calcd. (%): C 49.38; H 2.55; N 8.86

Found (%): C 49.43; H 2.91; N 8.84

^{1}H-NMR (DMSO-d_6) δ ppm:

1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

REFERENCE EXAMPLE 25

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17b):

The ester (16b) (588 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 514 mg of the titled compound (17b) as a colorless crystal.

Melting Point: 295-300°C

Elementary Analysis for $C_{13}H_8F_4N_2O_3$

Calcd. (%): C 49.38; H 2.55; N 8.86

Found (%): C 49.41; H 2.81; N 8.88

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)

IR: ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

EXAMPLE 7

(-)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (18a):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17a) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid,

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followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 128 mg of the titled compound (18a) as a colorless crystal.

Melting Point: 224-230°C

$[\alpha]_D$: -4.72° (c=0.888, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{17}F_3N_4O_3$

Calcd. (%): C 53.40; H 4.48; N 14.65

Found (%): C 53.28; H 4.08; N 14.54

^{1}H-NMR (NaOD)) δ ppm:

1.47-1.58 (1H, m), , 1.67-1.78 (2H, m), 2.07-2.11 (1H, m), 3.28-3.44 (1H, m), 3.48-3.52(1H, m), 3.60-3.66 (1H, m), 3.71-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.18 (1H, s)

IR: ν_{max} cm^{-1}: 3400, 1728, 1635, 1605, 1518, 1433, 1350, 1308

EXAMPLE 8

(+)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (18b):

Five milliliters of trifluoroacetic acid was cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine was dissolved

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therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17b) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 68 mg of the titled compound (18b) as a colorless crystal.

Melting Point: 214-217°C

$[\alpha]_D$: +31.3° (c=0.268, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{17}F_3N_4O_3 \cdot 1/2H_2O$:

Calcd. (%): C 52.18; H 4.64; N 14.32

Found (%): C 52.22; H 4.93; N 14.23

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^{1}H-NMR (NaOD) δ ppm:

1.48-1.58 (1H, m), , 1.66-1.79 (2H, m), 2.06-2.12 (1H, m), 3.29-3.32 (1H, m), 3.48-3.52(1H, m), 3.60-3.64 (1H, m), 3.70-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.19 (1H, s)

IR: ν_{max} cm^{-1}: 3490, 1716, 1635, 1521, 1437, 1356, 1305

REFERENCE EXAMPLE 26

Synthesis of Optically Active 7-Amino-5-azaspiro-[2,4]-heptane:

1) 5-[(1R)-Phenylethyl]-4.7-dioxo-5-azaspiro[2,4]-heptane (19):

To 10.4 g of ethyl acetoacetate were added 15 g of 1,2-dibromoethane, 23 g of potassium carbonate, and 150 ml of N,N-dimethylformamide (DMF), and the mixture was stirred at room temperature for 2 days. Any insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. To the residue was added water, and the mixture was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting pale yellow oily substance was subjected to distillation under reduced pressure to obtain 7.5 g of

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ethyl 1-acetyl-1-cyclopropanecarboxylate having a boiling point of 70 to 71°C/2 to 3 mmHg.

^{1}H-NMR ($CDCl_3$) δ ppm:

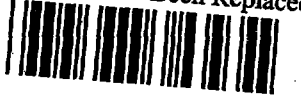
1.30 (3H, t, J=7Hz), 1.48 (4H, s), 2.49 (3H, s), 4.24 (2H, q, J=7Hz)

In 200 ml of ethanol was dissolved 35.7 g of the above obtained compound, and 40 g of bromine was added dropwise to the solution at room temperature while stirring. After the stirring was continued at room temperature for 2 hours, the excess bromine and the solvent were removed under reduced pressure to obtain ethyl 1-bromoacetyl-1-cyclopropanecarboxylate, which was then, without further purification, dissolved in 200 ml of ethanol. To the solution were simultaneously added dropwise 33 g of R-(+)-1-phenylethylamine and 27 g of triethylamine over a period of 1 hour while stirring under ice-cooling. After the addition, the reaction temperature was raised to room temperature, and the stirring was continued at room temperature for 2 days. Any insoluble matter was removed by filtration, and ethanol was removed from the filtrate under reduced pressure. The residue was dissolved in 300 ml of ethyl acetate, and the solution was washed successively with 1N hydrochloric acid, a saturated sodium hydrogen-carbonate aqueous solution, and a saturated sodium

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chloride aqueous solution in this order. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to 200 g of silica gel column which was eluted with 0 to 2% methanolic chloroform to obtain the titled compound (19) as a colorless crystal.

Melting Point: 98-103°C

^{1}H-NMR ($CDCl_3$) δ ppm:

1.62 (3H, d, J=7.2Hz), 3.5 (1H, d, J=18Hz), 3.9 (1H, d, J=18Hz), 5.82 (1H, q, J=7.2Hz), 7.36 (5H, s)

2) 5-[(1R)-Phenylethyl]-7-hydroxyimino-4-oxo-5-aza-spiro[2,4]heptane (20):

To 3.35 g of Compound (19) were added 1.6 g of hydroxylamine hydrochloride, 2.3 g of triethylamine, and 80 ml of ethanol, and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and chloroform was added to the residue. The mixture was washed successively with a 10% citric acid aqueous solution and a saturated sodium chloride aqueous solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain 3.5 g of the titled compound (20) as a colorless crystal.

Melting Point: 188-194°C

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.4 (2H, m), 1.53 (3H, d, J=7.2Hz & 2H, m), 3.8 (1H, d, J=18Hz), 4.16 (1H, d, J=18Hz), 5.63 (1H, q, J=7.2Hz), 7.32 (5H, s)

3) 7-Amino-4-oxo-5-[(1R)-Phenylethyl]-5-azaspiro[2,4]-heptane (21a, 21b):

To 150 ml of methanol were added 3.5 g of Compound (20) and 7.5 ml of Raney nickel, and catalytic reduction was carried out at room temperature for 12 hours. After the catalyst was removed by filtration, the solvent was removed from the filtrate under reduced pressure. The residue was subjected to a 100 g of silica gel column eluted with a mixed solvent of 5% methanol/chloroform which was to yield 1.0 g of the entitled compound (21b) from the earlier fraction and 0.8 g of the titled compound (21a) from the later fraction each as a colorless oily substance.

Compound (21b):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.8-1.4 (4H, m), 1.52 (3H, d, J=7Hz), 2.87 (1H, dd, J=10, & 3Hz), 3.3-3.9 (2H, m), 4.27 (2H, br. s), 5.42 (1H, q, J=7Hz), 7.29 (5H, s)

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Compound (21a):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (4H, m), 1.40 (2H, s), 1.53 (3H, d, J=7.2Hz), 2.99 (1H, dd, J=12.8, & 7.2Hz), 3.15-3.45 (2H, m), 5.52 (1H, q, J=7.2Hz), 7.30 (5H, s)

4) 7-Amino-5-[(1R)-Phenylethyl]-5-azaspiro[2,4]heptane (22a, 22b):

To 50 ml of anhydrous tetrahydrofuran were added 1.0 g of Compound (21b) and 500 mg of lithium aluminum hydride, and the mixture was refluxed for 17 hours. After cooling, 0.5 ml of water, 0.5 ml of a 15% sodium hydroxide aqueous solution, and 1.5 ml of water were successively added to the reaction mixture in this order, followed by stirring well at room temperature for 30 minutes. Any insoluble matter was removed by filtration and thoroughly washed with tetrahydrofuran. The filtrate and the washing were combined and dried. The solvent was removed under reduced pressure to obtain 940 mg of the titled compound (22b) as a pale yellow oily substance. In the same manner, 755 mg of the titled compound (22a) was obtained from 800 mg of Compound (21a).

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Compound (21b):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.2-0.8 (4H, m), 1.35(3H, d, J=6.6Hz), 1.6-2.0 (2H, br. m), 2.2-3.1 (4H, m), 3.24 (1H, q, J=6.6Hz), 3.5-3.9 (1H, m), 7.28 (5H, br. s)

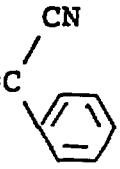
Compound (22a):

^{1}H-NMR ($CDCl_3$) δ ppm:

0.3-0.9 (4H, m), 1.36 (3H, d, J=6.7Hz), 1.8-2.2 (2H, m), 2.2-3.2 (4H, m), 3.24 (1H, q, J=6.7Hz), 3.6-3.9 (1H, m), 7.28 (5H, br. s)

5) 7-(t-Butoxycarbonylamino)-5-[(1R)-phenylethyl]-5-azaspiro[2,4]heptane (23a, 23b):

To 20 ml of anhydrous tetrahydrofuran were added 764 mg of Compound (22b) and 1.3 g of Boc-ON [Boc-ON; 2-(t-Butoxycarbonyloxyimino]-2-phenylacetonitrile



], and the mixture was stirred at room temperature for 4 hours. Ethyl acetate was added to the reaction mixture, and the mixture was washed twice with a 1N sodium hydroxide aqueous solution and then once with water, followed by extraction with a 10% citric acid aqueous solution. The aqueous extract was washed once with ethyl acetate, and a 15% sodium hydroxide aqueous solution was added to the aqueous

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layer under cooling to make it alkaline. The mixture was extracted three times with chloroform, and the organic layer was washed with a saturated sodium chloride aqueous solution and then dried. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (silica gel: 20 g; eluent: chloroform:methanol=20:1, 10:1) to obtain 690 mg of the titled compound (23b). This compound was allowed to stand to crystallize, followed by washing with n-hexane. The titled compound (23a) was obtained in the same manner.

Compound (23b) (colorless crystal):

Melting Point: 103-105°C

$[\alpha]_D$: -15.2° (c=1.475, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-0.9 (4H, m), 1.36 (3H, d, J=7.2Hz), 1.44 (9H, s), 2.42 (2H, AB q, J=10.2 Hz), 2.79 (2H, d, J=5.6 Hz), 3.24 (1H, q, J=7.2Hz), 3.6-4.0 (1H, m), 4.6-5.1 (1H, br. d), 7.28 (5H, s)

Elementary qAnalysis for $C_{19}H_{28}N_2O_2$:

Calcd. (%): C 72.12; H 8.92; N 8.85

Found (%): C 71.63; H 9.07; N 8.64

Compound (23a) (colorless crystal):

Melting Point: 94-97°C

$[\alpha]_D$: +47.6° (c=0.89, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-0.9 (4H, m), 1.33 (3H, d, J=6.6Hz), 1.40 (9H, s), 2.29 (1H, d, J=9Hz), 2.44 (1H, dd, J=10.8 & 3.6Hz), 2.77 (1H, d, J=9Hz), 2.88 (1H, dd, J=10.8 & 5.3Hz), 3.22 (1H, q, J=6.6Hz), 3.6-3.9 (1H, m), 4.7-5.2 (1H, br. d), 7.27 (5H, s)

Elementary aAnalysis for $C_{19}H_{28}N_2O_2$:

Calcd. (%): C 72.12; H 8.92; N 8.85

Found (%): C 71.86; H 9.36; N 8.68

6) 7-t-Butoxycarbonylamino-5-azaspiro[2,4]heptane (24a, 24b)

To 30 ml of ethanol were added 650 mg of Compound (23b) and 500 mg of 50% hydrated palladium-on-carbon, and catalytic reduction was effected under heating at a pressure of 4.2 atoms. After 6 hours, the catalyst was removed by filtration, and the solvent was removed under reduced pressure. To the oily residue was added ethyl acetate, followed by extracting twice with a 10% citric acid aqueous solution. The aqueous extract was made alkaline with a 15% sodium hydroxide aqueous solution and then extracted three times with chloroform. The chloroform layer was washed with water and dried. The solvent was removed under reduced pressure to yield 440 mg of the titled compound (24b) as a crude product. The titled compound (24a) was obtained in the same

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manner as above. The NMR spectra of Compounds 24b) and (24a) were in complete agreement with each other.

Compound (24)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.4-1.0 (4H, m), 1,42 (9H, s), 2.71 (1H, d, J=10.2Hz), 2.92 (1H, dd, J=10.8 & 3.6 Hz), 3.01 (1H, d, J=10.2Hz), 3.33 (1H, dd, J=10.8 & 5.4 Hz), 3.5-3.9 (1H, m), 5.0-5.4 (1H, br, d)

EXAMPLE 9

7-(7-t-Butoxycarbonylamino-5-azaspiro[2,4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (25bb):

In 0.6 ml of acetonitrile were dissolved 160 mg of 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cylopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (12b), 150 mg of the amine compound (24b), and 0.5 ml of triethylamine, and the solution was heated under reflux for 5 hours. After cooling, the precipitated colorless crystals were collected by filtration. The solvent of the mother liquor was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using a developing solvent of chloroform-methanol (5:1 by volume). The purified product and the above-obtained crystals were combined to give 255 mg of the titled compound (25bb).

Melting Point: 213-218°C

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^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.0 (6H, m), 1,45 (9H, s), 7.99 (1H, d, J=13.1Hz), 8.74, 8.78 (each 0.5H, s)

EXAMPLE 10

(-)-7-(7-Amino-5-azaspiro[2,4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cylcopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (26bb):

To 255 mg of the Boc-compound (25bb) as obtained in Example 9 were added 0.5 ml of anisole and 10 ml of trifluoroacetic acid under ice-cooling. After warming to room temperature, the mixture was stirred for 30 minutes. The solvent was removed under reduced pressure, a 1N sodium hydroxide aqueous solution was added to the residue adjusting a pH of 11 to 12. The alkaline aqueous solution was washed twice with chloroform. The aqueous layer was adjusted to a pH of about 7 with concentrated hydrochloric acid and a 10% citric acid aqueous solution and extracted three times with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting solid was recrystallized from ethanol-concentrated aqueous ammonia to obtain 142 mg of the titled compound (26bb) as a colorless crystal.

Melting Point: 127-140°C (with decomposition)

$[\alpha]_D$: -199.2° (c=0.24, 1N NaOH)

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Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/4H_2O$:

Calcd. (%): C 55.08; H 4.50; N 10.14

Found (%): C 54.86; H 4.80; N 10.03

EXAMPLE 11

Synthesis of Compound (26ab)

Compound (26ab) was obtained from Compound (12a) and Compound (24b) in the same manner as described in Examples 9 and 10.

Melting Point: 123-128°C (with decomposition)

$[\alpha]_D$: +21.5° (c=0.195, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/2H_2O$:

Calcd. (%): C 54.49; H 4.57; N 10.03

Found (%): C 54.33; H 4.73; N 9.81

EXAMPLE 12

Synthesis of Compound (26a)

Compound (26a) was synthesized from Compound (12b) and Compound (24a) in the same manner as described in Examples 9 and 10.

Melting Point: 121-127°C (with decomposition)

$[\alpha]_D$: -21.1° (c=0.275, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 1/2H_2O$:

Calcd. (%): C 54.49; H 4.57; N 10.03

Found (%): C 54.77; H 4.43; N 9.86

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EXAMPLE 13

Synthesis of Compound (26aa)

Compound (26aa) was synthesized from Compound (12a) and Compound (24a) in the same manner as in Examples 9 and 10.

Melting Point: 126-145°C (with decomposition)

$[\alpha]_D$: +186.6° (c=0.228, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl \cdot 3/4H_2O$:

Calcd. (%): C 53.91; H 4.64; N 9.93

Found (%): C 53.80; H 4.47; N 9.82

REFERENCE EXAMPLE 27

(-)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29a)

A mixture of 1 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (27), 3 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 1 hour while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 750 mg of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) was dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of

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dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, followed by stirring at room temperature for 30 minutes.

The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to column chromatography using 50 g of silica gel using chloroform as an eluent to yield 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (28a) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.06 (3H, t, J=7Hz), 1.1-1.6 (2H, m), 2.86-3.18 (1H, m), 4.05 (2H, q, J=7Hz), 4,78 (1H, dm, J=63Hz), 7.36 (1H, d, J=7Hz), 8.31 (1H, d, J=14 Hz)

In 25 ml of anhydrous dioxane was dissolved 1.29 g of Compound (28a), and 300 mg of 60% sodium hydride was added to the solution, followed by stirring for 1 hour. The reaction mixture was concentrated under reduced pressure, and to the residue was added 0.1N hydrochloric acid. The precipitated crystals were collected by filtration and washed successively with

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water and diethyl ether to obtain 860 mg of the titled compound (29a) as a colorless crystal.

Melting Point: 184-185°C

$[\alpha]_D$: -1.26° (c=0.793, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$

Calcd. (%): C 51.16; H 3.37; N 8.52

Found (%): C 51.12; H 3.26; N 8.52

^{1}H-NMR ($CDCl_3$) δ ppm:

1.41 (3H, t, J=7Hz), 1.4-1.84 (2H, m), 3.50 (1H, m), 4.40 (2H, q, J=7Hz), 5.02 (1H, dm, J=65Hz), 8.43 (1H, d, J=7Hz), 8.66 (1H, s)

REFERENCE EXAMPLE 28

(+)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29b):

A mixture of 1.0 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (27), 3 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 1.5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

Ten milliliters of trifluoroacetic acid was cooled with ice, and 750 mg of (-)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4b) was dissolved therein. The solution was stirred at room temperature

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for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 30 ml of dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 30 minutes.

The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography using 50 g of silica gel and chloroform as an eluent to obtain 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)-acrylate (28b) as a colorless oil.

Compound (28b) (1.29 g) was reacted in the same manner as for Compound (28a) to obtain 936 mg of the titled compound (29b) as a colorless crystal.

Melting Point: 183-185°C

$[\alpha]_D$: +1.12° (c=1.07, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$

Calcd. (%): C 51.16; H 3.37; N 8.52

Found (%): C 51.39; H 3.24; N 8.49

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REFERENCE EXAMPLE 29

(-)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30a):

A mixture of 800 mg of Compound (29a) and 15 ml of concentrated hydrochloric acid was heated at 100°C for 1.5 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 610 mg of the titled compound (30a) as a colorless crystal.

Melting Point: 215-219°C

$[\alpha]_D$: -20.65° (c=0.910, chloroform)

REFERENCE EXAMPLE 30

(+)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30b):

A mixture of 870 mg of Compound (29b) and 20 ml of concentrated hydrochloric acid was heated at 100°C for 2 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 715 mg of the titled compound (30b) as a colorless crystal.

Melting Point: 218-220°C

$[\alpha]_D$: +22.34° (c=0.555, chloroform)

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EXAMPLE 14

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (31a):

In 15 ml of trifluoroacetic acid was dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methyl-pyrrolidine (32) (cf. Terry Ronson, et al., J. Med. Chem., Vol. 31, p.1598 (1988)), and the solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of acetonitrile, and 150 mg of Compound (30a) and 2 ml of triethylamine were added to the solution, followed by refluxing for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 13 with sodium hydroxide and washed with chloroform. The aqueous layer was adjusted to a pH of 7.5 and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from aqueous ammonia-ethanol yielded 150 mg of the titled compound (31a) as a colorless crystal.

Melting Point: 255-258°C

$[\alpha]_D$: -14.52° (c=0.413, 0.1N NaOH)

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Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$:

Calcd. (%): C 55.36; H 5.06; N 15.19

Found (%): C 55.09; H 5.40; N 15.04

EXAMPLE 15

(-)-7-[3-(R)-[1-(S)-Aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (34b):

A mixture of 159 mg of (-)-8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b), 160 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine (cf. JP-A-61-311992), 400 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in chloroform. The organic solution was washed successively with a 10% citric acid aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was recrystallized from ethyl acetate-isopropyl ether to yield 220 mg of (-)-7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (33b).

Melting Point: 189-193°C

$[\alpha]_D$: -205° (c=0.985, chloroform)

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Elementary Analysis for $C_{24}H_{28}ClF_2N_3O_5$

Calcd. (%): C 56.31; H 5.51; N 8.21

Found (%): C 56.16; H 5.48; N-8.21

In 10 ml of trifluoroacetic acid was dissolved 200 mg of Compound (33b), and the solution was stirred for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in a 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 with hydrochloric acid and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 140 mg of the titled compound (34b) as a colorless crystal.

Melting Point: 204-207°C

$[\alpha]_D$: -160.0° (c=0.605, 0.1N NaOH)

Elementary Analysis for $C_{19}H_{20}ClF_2N_3O_3 \cdot H_2O$:

Calcd. (%): C 53.09; H 5.38; N 9.77

Found (%): C 53.20; H 5.17; N 9.66

REFERENCE EXAMPLE 31

Ethyl 2-(3-acetoxy-2,4,5-trifluorobenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (36b):

A mixture of 1.0 g of ethyl 3-acetoxy-2,4,5-trifluorobenzoylacetate (35) (cf. JP-A-87-175485), 6 ml

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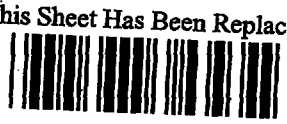
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of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 3 hours under stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

In 5 ml of trifluoroacetic acid was dissolved 467 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 5 ml of a dichloromethane solution containing 500 mg of triethylamine was added dropwise thereto under ice-cooling, followed by stirring for 10 minutes. To the solution was added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure to obtain 1.25 g of the titled compound (36b).

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REFERENCE EXAMPLE 32

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (37b):

In 40 ml of dioxane was dissolved 1.25 g of Compound (36b), and 440 mg of potassium carbonate and 10 ml of water were added thereto, followed by stirring at room temperature for 19 hours. The reaction mixture was neutralized with hydrochloric acid, concentrated under reduced pressure, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in 40 ml of anhydrous dioxane, and 300 mg of 60% sodium hydride and 1 ml of ethyl iodide were added thereto, followed by stirring at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was recrystallized from isopropyl ether to obtain 235 mg of the titled compound (37b) as a colorless crystal.

Melting Point: 163-64°C

$[\alpha]_D$: -22.9° (c=0.490, chloroform)

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^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7Hz), 1.3-1.8 (2H, m), 3.7-4.0 (1H, m), 4.10 (3H, d, J=2Hz), 4.38 (2H, q, J=7Hz), 4.85 (1H, dm, J=63Hz), 8.02 (1H, dd, J=9Hz, & 8.5Hz), 8.55 (1H, s)

Elementary Analysis for $C_{16}H_{14}F_3NO_4$

Calcd. (%): C 56.31; H 4.13; N 4.10

Found (%): C 56.62; H 4.18; N 4.11

REFERENCE EXAMPLE 33-1

(±)-cis-4-Amino-1-benzyl-3-methyl-2-oxopyrrolidine (45):

A mixture of 5.13 g of ethyl 1-benzyl-3-methyl-2-oxo-3-pyrrolidinecarboxylate (42, cf. JP-A-62-4284), 40 ml of 50% ethanol, and 2 g of sodium hydroxide was stirred at room temperature for 42 hours. To the reaction mixture was added 100 ml of water, and the mixture was washed with chloroform. The aqueous layer was neutralized with hydrochloric acid, extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated to obtain 3.40 g of (±)-1-benzyl-2-oxo-3-pyrrolidinecarboxylic acid (43) as a colorless crystal.

Compound (43) (3.40 g), 4.45 g of diphenylphosphorylazide, 1.9 g of triethylamine, and 50 ml of t-butyl alcohol were mixed and the mixture was heated under reflux for 12 hours. The reaction mixture was

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concentrated under reduced pressure, and the residue was dissolved in chloroform. The solution was washed successively with a 10% citric acid aqueous solution, a 2% sodium hydroxide aqueous solution, and water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography using chloroform-methanol (97.5:2.5 by volume) as an eluent to obtain 1.76 g of (±)-cis-1-benzyl-4-t-butoxycarbonylamino-3-methyl-4-oxopyrrolidine (44) as a colorless oil.

In 15 ml of trifluoroacetic acid was dissolved 1.76 g of Compound (44). After 1 hour, the solution was concentrated under reduced pressure. To the residue was added 100 ml of water, and the mixture was washed with benzene. The aqueous layer was adjusted to a pH of 12 with sodium hydroxide and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain the titled compound (45) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.25 (3H, d, J=7Hz), 1.44 (2H, s), 2.16 (1H, dt, J=7Hz), 2.83 (1H, dd, J=6.7Hz, & 8Hz), 3.14 (1H, m), 3.38 (1H, dd, J=6.7Hz, & 8Hz), 4.48 (2H, s), 7.28 (5H, s)

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REFERENCE EXAMPLE 33-2

Optical Resolution of cis-4-Amino-1-benzyl-3-methyl-2-oxopyrrolidine (45):

In 40 ml of dichloromethane were dissolved 4.17 g of Compound (45) and 3.3 ml of pyridine, and a solution of 7.7 g of (S)-N-p-toluenesulfonylprolyl chloride in 50 ml of dichloromethane was added thereto dropwise, followed by stirring for 4 hours.

The reaction mixture was washed successively with 1N hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution, and water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate as an eluent to isolate the isomers. Each of the isomers was recrystallized from ethyl acetate to obtain 3.3 g and 3.6 g of cis-1-benzyl-3-methyl-4-[(S)-N-p-toluenesulfonylprolylamino]-2-oxopyrrolidine (46a) and (46b), respectively.

Compound (46a):

Rf (silica gel TLC; ethyl acetate): 0.69

Melting Point: 162°C

$[\alpha]_D$: -87.3° (c=0.735, chloroform)

Compound (46b):

Rf (silica gel TLC; ethyl acetate): 0.61

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Melting Point: 175-177°C

$[\alpha]_D$: -148.6° (c=0.665, chloroform)

REFERENCE EXAMPLE 33-3

(+)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methyl-pyrrolidine (47a):

A mixture of 3.23 g of Compound (46a) and 50 ml of concentrated hydrochloric acid as heated under reflux for 5 hours, followed by concentration under reduced pressure. To the residue was added a 1N sodium hydroxide aqueous solution, and the solution was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain 1.48 g of Compound (45a) as a colorless oil.

The product was dissolved in 10 ml of tetrahydrofuran, and the solution was added dropwise to a suspension of 2.0 g of lithium aluminum hydride in 50 ml of tetrahydrofuran. The mixture was heated under reflux for 24 hours. To the reaction mixture was added dropwise 10 ml of water under ice-cooling, and, after stirring for 30 minutes, any insoluble matter was removed by filtration. To the filtrate was added 1.92 g of Boc-ON, followed by stirring for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform.

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The extract was washed successively with a 5% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was then evaporated.

The residue was purified by silica gel column chromatography using chloroform-methanol (1:0 to 9:1 by volume) as an eluent to obtain 1.76 g of a crystal. To the product was added n-hexane, and the mixture was stirred thereby precipitating a dℓ compound. The crystals were collected by filtration, and the filtrate was concentrated. This procedure was repeated twice. One hundred milligrams of the dℓ compound was obtained from the filter cake and 1.61 g of the titled optically active compound (47a) from the mother liquor.

Melting Point: 48-52°C

$[\alpha]_D$: +27.2° (c=2.33, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.07 (3H, d, J=7Hz), 1.43 (9H, s), 1.78-2.02 (2H, m), 2.62 (2H, d, J=5Hz), 2.84-3.10 (1H, m), 3.55 (2H, s), 3.5-3.8 (1H, m), 4.8-5.2 (1H, broad), 7.23 (5H, s)

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REFERENCE EXAMPLE 33-4

(-)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methyl-pyrrolidine (47b):

In the same manner as for the synthesis of Compound (47a) but starting with 3.52 g of Compound (46b), 1.72 g of the titled compound (47b) was obtained.

Melting Point: 57-61°C

$[\alpha]_D$: -31.21°

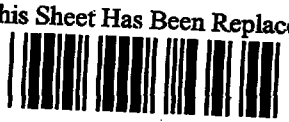
REFERENCE EXAMPLE 33-5

cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (39a), (39b):

Compound (47a) (1.61 g), 1.5 g of 5% palladium-on-carbon, and 80 ml of ethanol were mixed, and catalytic reduction was carried out for 5 hours while irradiating the mixture with an infrared lamp in a hydrogen atmosphere at a pressure of 4 atoms. After the reaction, the catalyst was removed by filtration, and the filtrate was concentrated to obtain 1.09 g of a crude product as a colorless oil. The product solidified as a carbonate on standing, which was used without purification.

In the same manner as for the synthesis of Compound (39a), 1.1 g of Compound (39b) was obtained as a colorless oil from 1.70 g of Compound (47b).

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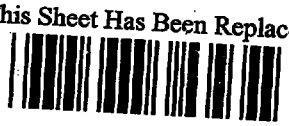
REFERENCE EXAMPLE 34

Ethyl 2-(2,4,5-trifluoro-3-methylbenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (50b):

A mixture of 710 mg of ethyl 2,4,5-trifluoro-3-methylbenzoylacetate (prepared from 2,4,5-trifluoro-3-methylbenzxoic acid (48), cf. JP-A-62-215572), 6 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 2 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

In 5 ml of trifluoroacetic acid was dissolved 580 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 700 mg of triethylamine was added thereto under ice-cooling. After stirring for 10 minutes, the above-prepared dichloromethane solution was added thereto, followed by allowing to stand overnight. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was crystallized from n-hexane to obtain 787 mg of the titled compound (50b) as a pale yellow crystal.

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REFERENCE EXAMPLE 35

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (51b):

In 20 ml of anhydrous dioxane was dissolved 600 mg of Compound (50b), and a suspension of 100 mg of 60% sodium hydride having been washed with n-hexane in a small amount of anhydrous dioxane was added to the solution. The mixture was stirred at room temperature for 1 hour, and 10 ml of a 10% citric acid aqueous solution was added thereto, followed by concentration under reduced pressure. The precipitated crystals were collected by filtration, washed successively with water, a small amount of ethanol, and diethyl ether to obtain 480 mg of the titled compound (51b) as a colorless crystal.

Melting Point: 230-231°C

$[\alpha]_D$: -80.0° (c=0.350, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7Hz), 1.1-1.7 (2H, m), 2.71 (3H, d, J=3.3Hz), 3.77-3.98 (1H, m), 4.38 (2H, q, J=7Hz), 4.85 (2H, dm, J=64Hz), 8.12 (1H, dd, J=10Hz), 8.54 (1H, d, J=3Hz)

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REFERENCE EXAMPLE 36

(-)-6,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (52b):

A mixture of 480 mg of the ester compound (51b) and 10 ml of concentrated hydrochloric acid was heated at 120°C for 75 minutes while stirring. After cooling, the precipitated crystals were collected by filtration and washed with water and ethanol to obtain 380 mg of the titled compound (52b) as a colorless crystal.

Melting Point: 204°C

$[\alpha]_D$: -60.0° (c=0.100, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-1.9 (2H, m), 2.80 (3H, d, J=5.8Hz), 4.1-4.4 (1H, m), 4.15 (1H, dm, J=64Hz), 8.17 (1H, dd, J=16Hz), 8.82 (1H, d, J=4Hz), 14.2 (1H, s)

EXAMPLE 16

(-)-6-[3-(R)-(1-(S)-Aminoethyl)-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (54b):

A mixture of 198 mg of Compound (52b), 350 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine, 5 ml of dimethyl sulfoxide, and 1.5 g of triethylamine was heated at 110 to 120°C for 5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in chloro-

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form and the solution was washed with a 10% citric acid aqueous solution and then with water, and dried over anhydrous sodium sulfate. The solvent was evaporated.

The residue was subjected to preparative TLC which was developed with a mixed solvent of chloroform-methanol (95:5 by volume) to obtain 110 mg of 7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidinyl]-6,7-difluoro-8-methyl-4-dihydroquinoline-3-carboxylic acid (53b) as a pale yellow powder.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.24 (3H, d, J=7Hz), 1.45 (9H, s), 1.2-1.9 (2H, m), 2.52 (3H, s), 1.9-2.7 (3H, m), 3.2-4.2 (6H, m), 4.73 (1H, d, J=8Hz), 4.98 (1H, dm, J=65Hz), 7.77 (1H, d, J=13Hz), 8.70 (1H, d, J=3.5Hz)

To 110 mg of Compound (53b) was added 5 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 10 minutes, followed by evaporation to dryness under reduced pressure. The residue was recrystallized from ethanol-diethyl ether to obtain 62 mg of the titled compound (54b) as a yellow crystal.

Melting Point: 149-153°C

$[\alpha]_D$: -34.4° (c=0.168, 1N HCℓ)

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EXAMPLE 17

5-Amino-7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (56b):

A mixture of 100 mg of (-)-5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17b), 100 mg of 7-t-butoxycarbonylamino-5-azaspiro[2,4]heptane (24b), 300 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 23 hours.

The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 100 ml of chloroform. The solution was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from acetonitrile to obtain 120 mg of 5-amino-7-[7-t-butoxycarbonylamino-5-azaspiro[2,4]-heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (55bb) as a yellow needle-like crystal.

Melting Point: 250-253°C

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-0.8 (2H, m), 0.8-1.0 (2H, m), 1.45 (9H, s), 1.3-1.8 (2H, m), 3.2-3.4 (1H, m), 3.6-3.9 (3H,

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m), 3.9-4.3 (2H, m), 4.85 (1H, dm, J=63Hz), 4.7-5.0 (1H, broad), 8.51 (1H, s)

In 5 ml of trifluoroacetic acid was dissolved 120 mg of Compound (55bb), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in hydrochloric acid and the solution was washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 65 mg of the titled compound (56bb) as a yellow crystal.

Melting Point: 213-217°C

$[\alpha]_D$: -96.7° (c=0.120, DMF)

EXAMPLE 18

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylic acid (31b):

In 15 ml of trifluoroacetic acid was dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methyl-pyrrolidine (32), and the solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of anhydrous acetonitrile, and 150 mg of Compound (30b) and 2 ml of triethylamine were added

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to the solution, followed by refluxing for 15 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was made alkaline with 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7 and extracted with chloroform. The organic layer was dried and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to yield 130 mg of the titled compound (31b).

Melting Point: 247-255°C (with decomposition)

$[\alpha]_D$: +120° (c=0.950, 1N NaOH)

Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$

Calcd. (%): C 55.36; H 5.06; N 15.19

Found (%): C 55.50; H 5.25; N 14.97

EXAMPLE 19

5-Amino-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-7-piperzinyl-4-oxo-quinoline-3-carboxylic acid (57b)

A mixture of 75 mg of Compound (17b), 45 mg of anhydrous piperazine in 5 ml of acetonitrile was heated under reflux for 2 hours. The reaction mixture was evaporated under reduced pressure and the residue was recrystallized from ethanol to yield 72 mg of the titled compound (57b) as a yellow crystal.

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Melting Point: 230-239°C

$[\alpha]_D$: +8.00° (c=0.225, 1N NaOH)

REFERENCE EXAMPLE 37

8,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid BF_2-chelate (38b):

A mixture of 230 mg of the ester compound (37b) and 5 ml of 42% borofluoric acid was heated at 110°C with stirring for 2 hours. After cooling, precipitated crystal was collected by filtration and washed with water to yield 210 mg of colorless crystal of the titled compound.

Melting Point: 281-271°C

By the reaction of cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (38a) and the chelate compound (38b), 7-(cis-3-amino-4-methylpyrrolidinyl)-8-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (40ba) is obtained. And further, by the reaction of the amine compound (24b) and the chelate comound (38b), 7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (41bb) is obtained.

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Table. Antimicrobial activity (M I C, $\mu g/ml$)

bacteria \ Compound	9a	9b	13a	13b	18a	18b	26bb	26aa
E. coli., NIHJ	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Ser. marcescens, 10100	0.20	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
Ps. aeruginosa, 32104	0.39	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.39
Ps. aeruginosa, 32121	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
S. aureus, 209 P	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
S. epidermidis, 56500	0.39	0.39	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.20
Str. faecalis, ATCC 19433	1.57	0.79	0.20	0.20	0.20	0.10	0.20	0.39

bacteria \ Compound	26ba	26ab	31a	31b	34b	54b	56b	
E. coli., NIHJ	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	
Ser. marcescens, 10100	< 0.1	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1	
Ps. aeruginosa, 32104	0.20	0.20	0.20	0.20	0.10	0.20	< 0.1	
Ps. aeruginosa, 32121	0.10	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1	
S. aureus, 209 P	< 0.1	< 0.1	0.10	< 0.1	< 0.1	< 0.1	< 0.1	
S. epidermidis, 56500	0.20	0.10	0.20	0.20	< 0.1	< 0.1	< 0.1	
Str. faecalis, ATCC 19433	0.39	0.20	0.78	0.39	< 0.1	0.10	0.10	

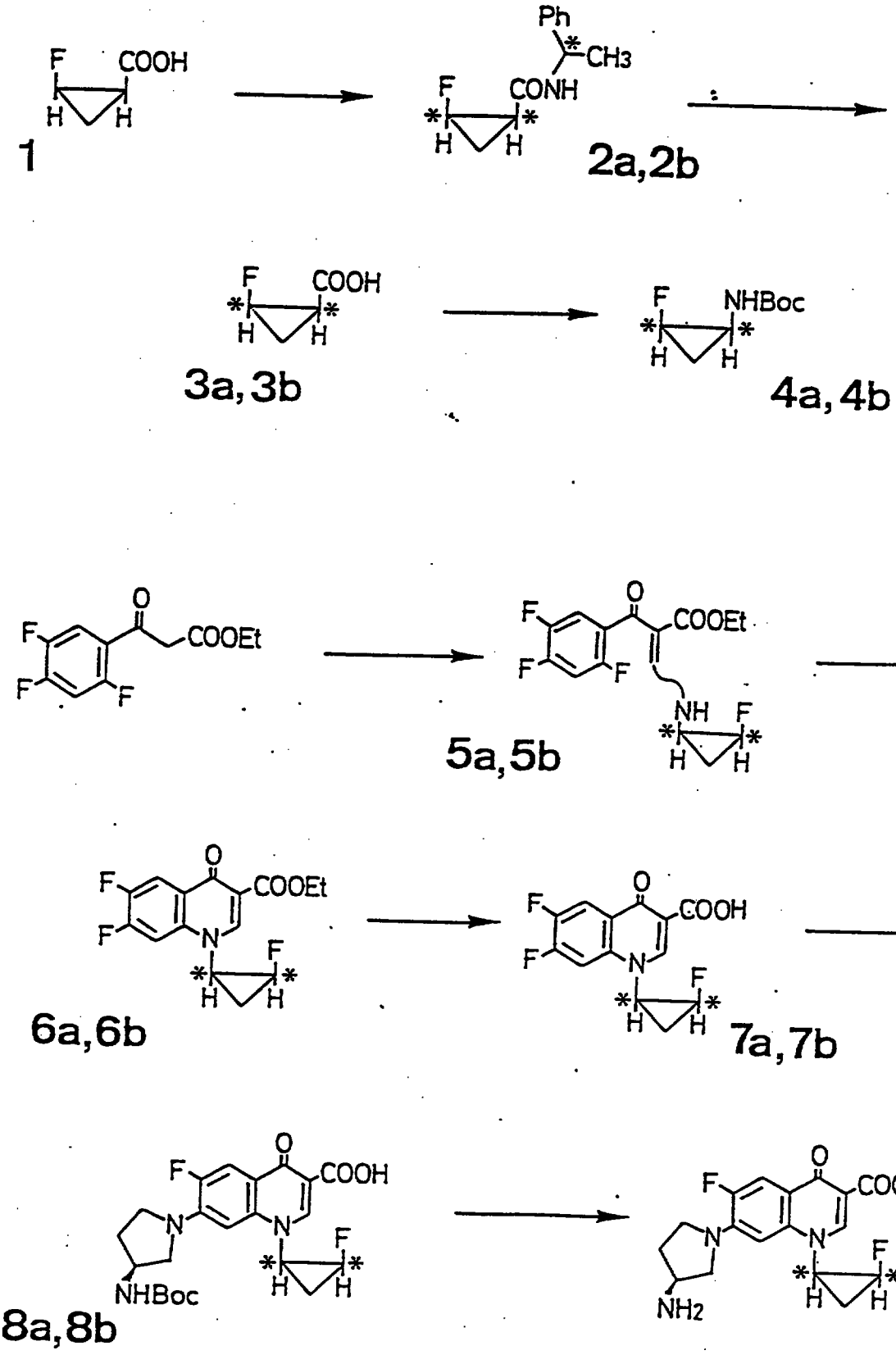
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While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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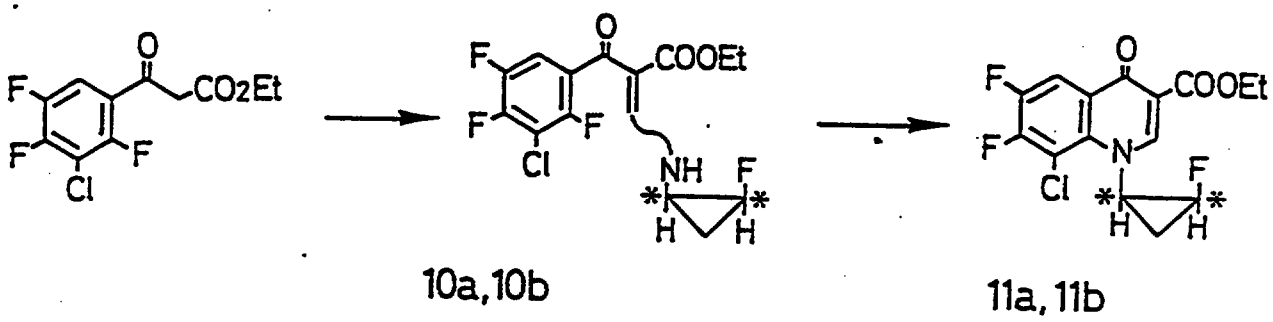
REACTION SCHEME



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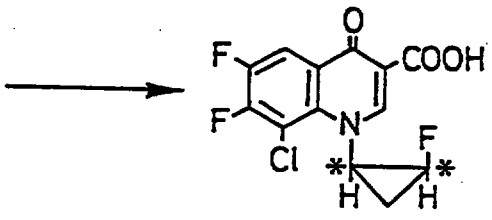
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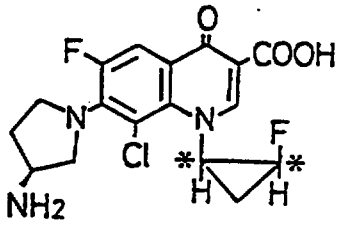


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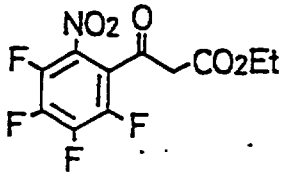
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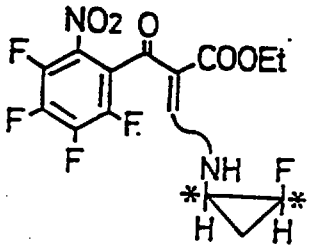


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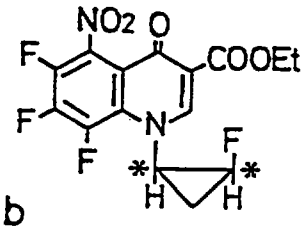


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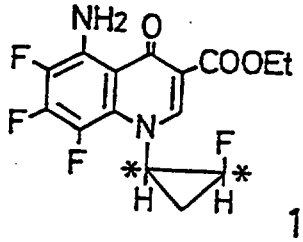




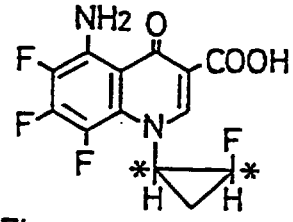
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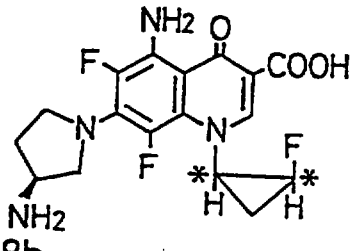
15a,15b



16a,16b



17a,17b

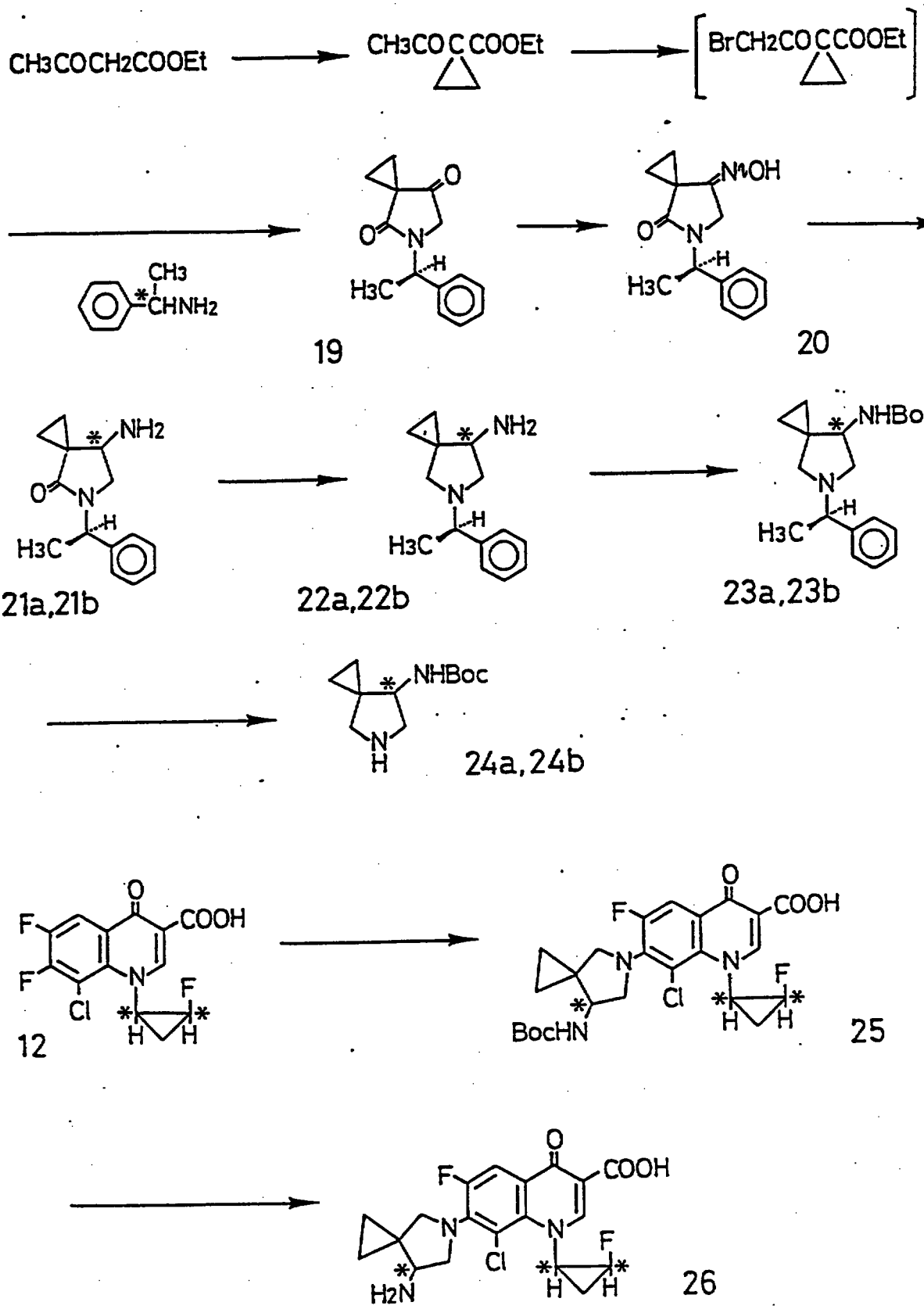


18a,18b

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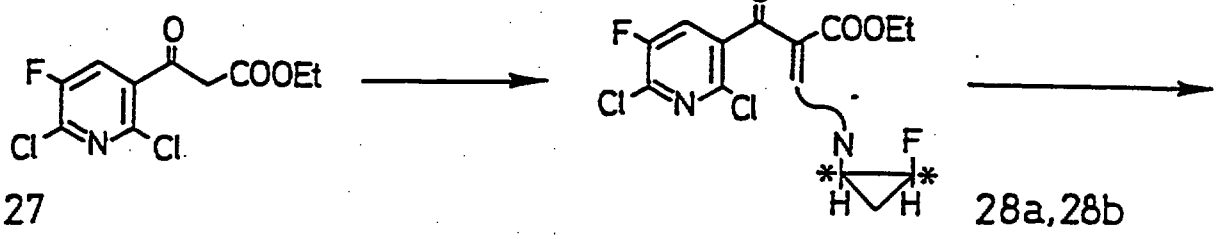
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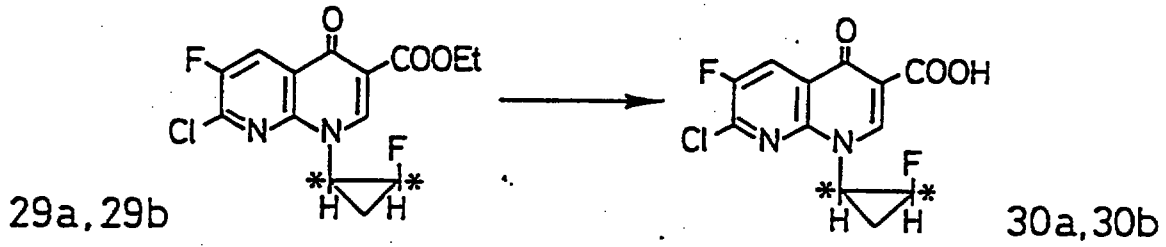
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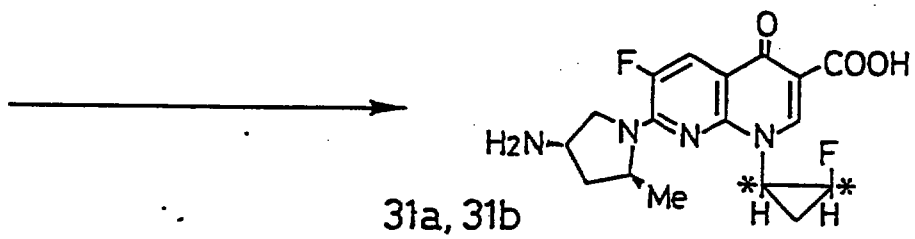
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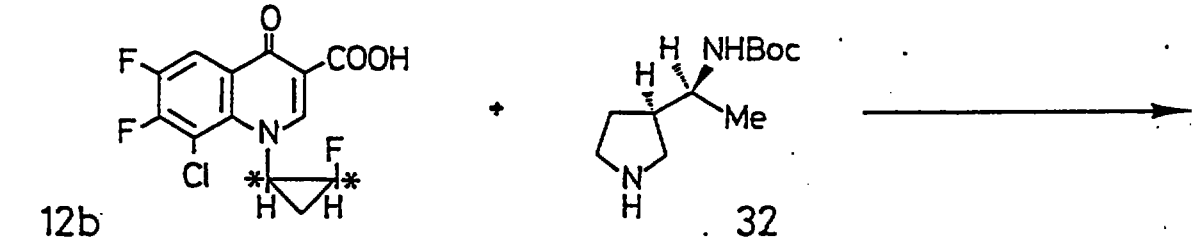
27 28a,28b



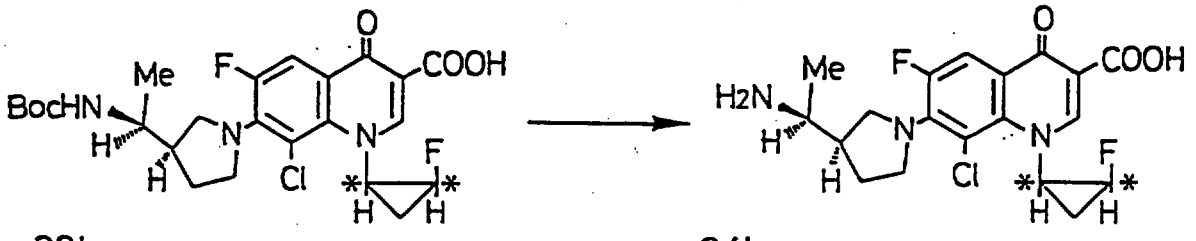
29a,29b 30a,30b



31a, 31b



12b 32

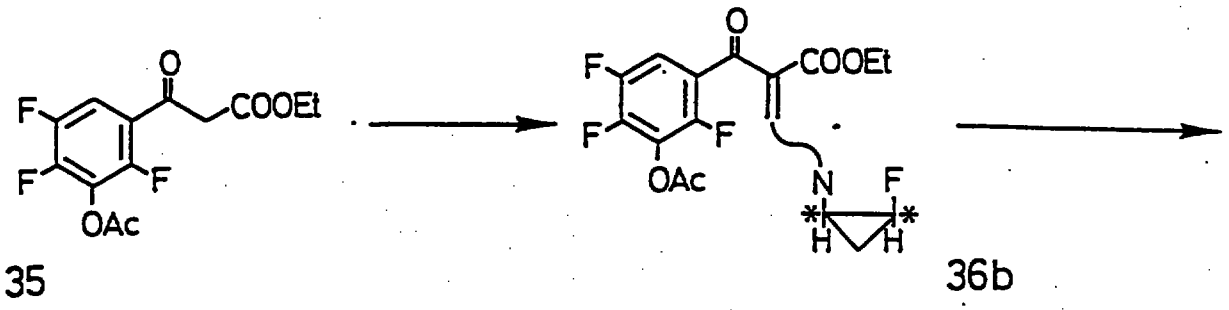


33b 34b

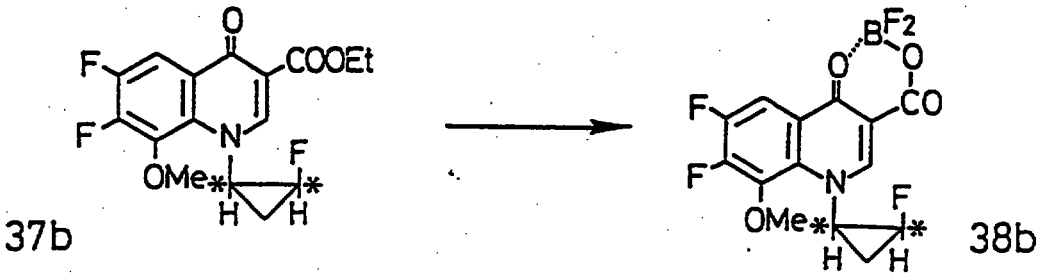
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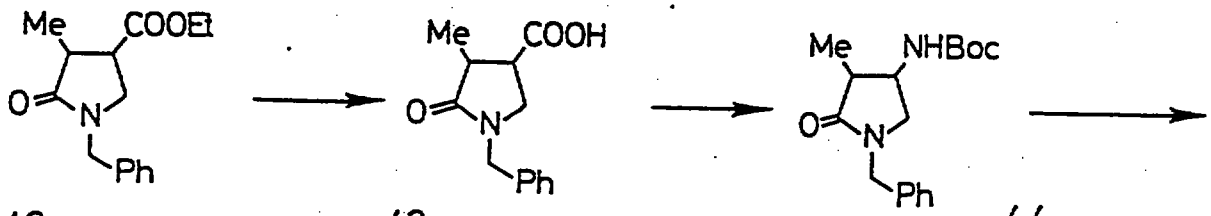
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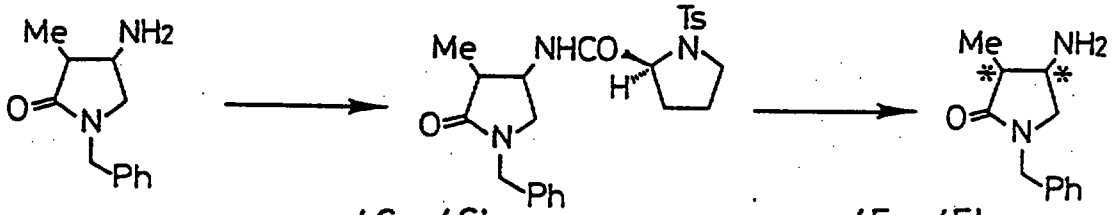
35 36b



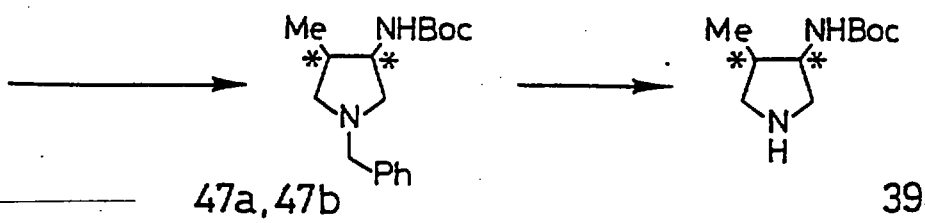
37b 38b



42 43 44



45 46a,46b 45a,45b

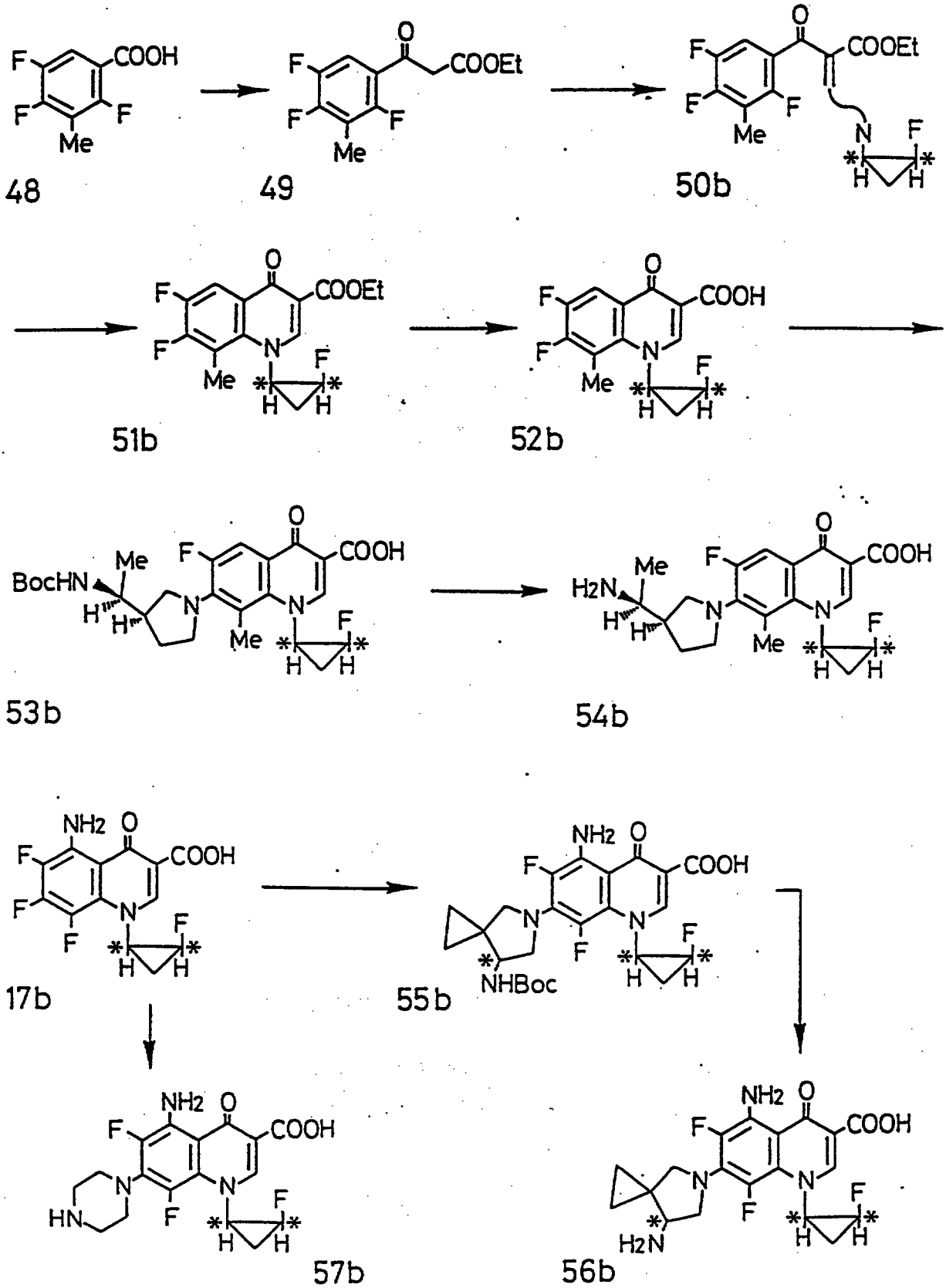


47a,47b 39a,39b

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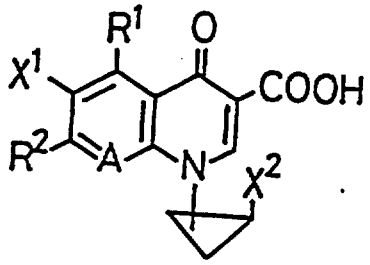
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WHAT IS CLAIMED IS:

1. An N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted amino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a substituted or unsubstituted cyclic amino group which may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom in its ring; A represents C-X^3 or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group having from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom; provided that the case wherein R^1 is a hydrogen atom and R^2 is a piperazine or 4-alkyl-

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substituted piperazine residue is excluded, or a salt thereof.

2. A compound as claimed in claim 1, wherein R^2 is a 4- to 7-membered cyclic amino group which may be substituted with a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, or a substituted or unsubstituted amino group; or a salt thereof.

3. A compound as claimed in claim 1, wherein R^2 is a pyrrolidone, piperidine piperazine, diazabicycloheptane or diazabicyclooctane residue; or a salt thereof.

4. A compound as claimed in claim 1, wherein R^2 is a cyclic amino group comprising a single stereoisomer; or a salt thereof.

5. A compound as claimed in claim 4, wherein R^2 is a 3-aminopyrrolidinyl group; or a salt thereof.

6. A compound as claimed in claim 4, wherein R^2 is a 7-amino-5-azaspiro[2,4]heptan-5-yl group; or a salt thereof.

7. A compound as claimed in claim 1, wherein X^2 is a fluorine atom.

8. A compound as claimed in claim, wherein said compound is 7-[3-(S)-amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-(S)-amino-1-pyrrolidinyl]-8-

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* C L M S *

chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline 3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid; or a salt thereof.

9. An antibacterial agent comprising, as an active ingredient, at least one N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I) or a salt thereof as claimed in claim 1.

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OPTICALLY ACTIVE PYRIDONECARBOXYLIC ACID DERIVATIVES

ABSTRACT OF THE DISCLOSURE

N_1-(1,2-cis-2-halogenocydopropyl)-substituted pyridonecarboxylic acid derivatives represented by formula (I) and the salts thereof are disclosed. These compounds have patent antibacterial activities against a wide variety of infectious bacteria, and are useful as antibacterial agents by oral or parenteral administration.

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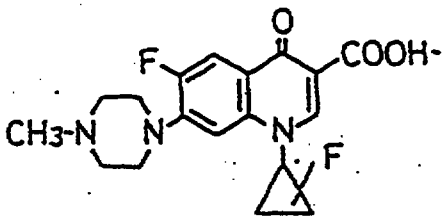
OPTICALLY ACTIVE PYRIDONECARBOXYLIC ACID DERIVATIVES

Description

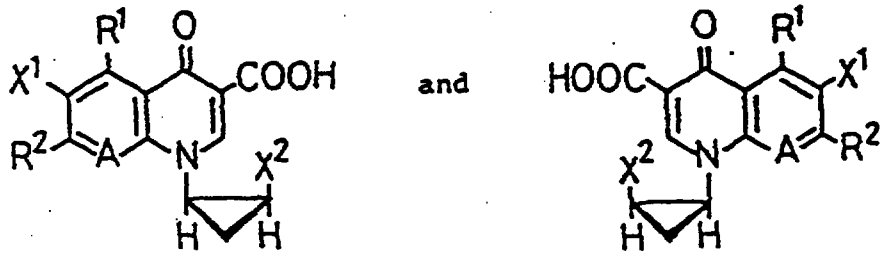
[0001] This invention relates to antimicrobial compounds useful as human and veterinary medicines, fish medicines, agricultural chemicals, and antiseptics.

[0002] Quinolone derivatives having a condensed pyridonecarboxylic acid skeleton are known as synthetic antimicrobial agents and to provide potent antimicrobial compounds on substitution of the 1-position thereof with a cyclopropyl group, as disclosed in GB-A-2 188 317.

[0003] It is further known that the 1-cyclopropylquinolone derivatives having introduced a fluorine atom to the 2-position of the cyclopropyl group in a cis-configuration with the pyridonecarboxylic acid moiety also exhibit potent antimicrobial activity as disclosed in EP-A-191 185. They are thought to have not only potent antimicrobial activity but improved safety. One example of the quinolone derivatives having a cis-fluorocyclopropyl group at the 1-position is shown below.



[0004] Quinolone derivatives having a cis-halogeno-cyclopropyl group, inclusive of a cis-fluorocyclopropyl group, at the 1-position as stated above possess excellent antimicrobial activity and safety. In these compounds, even when they have an a chiral substituent at the 7-position of the pyridonecarboxylic acid moiety, the halogeno-cyclopropane ring of itself provides two enantiomers attributed to the steric relationship between the pyridonecarboxylic acid moiety and the halogen atom with respect to the cyclopropane ring as illustrated below;



wherein R^1, R^2, A, X^1, and X^2 are hereinafter defined. These quinolone derivatives are applicable as medicines as long as they are racemates. On the other hand, when there is a chiral substituent in 7-position of the pyridonecarboxylic acid moiety, such quinolone derivatives contain four kinds of diastereomers. With mixtures of the diastereomers, it is difficult to specify the excellent species and to supply them as medicines.

[0005] In the light of the aforesaid situation, the inventors now obtained the single isomers of 1-(1,2-cis-2-fluorocyclopropyl)-substituted quinolone derivatives within the diastereomers thereof. And they have succeeded in obtaining each of the enantiomers of a cis-2-fluorocyclopropylamine as a pure isomer. As a result of further investigations, they have also succeeded in synthesizing each of the enantiomers of a quinolone derivative which are attributed only to the steric configuration of the fluorocyclopropane ring by starting from the above-described amine.

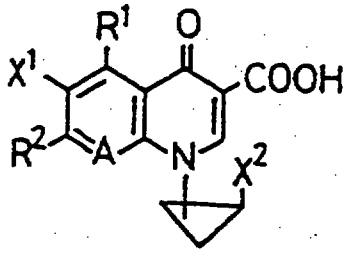
[0006] The success of obtaining the enantiomeric quinolone derivatives useful as intermediates has made it possible to synthesize an optically active quinolone derivative comprising one kind of diastereomer by reacting with a single isomer of the amine at introduction of a cyclic amino group to the 7-position. Each of these diastereomers was proved more potent in antimicrobial activity as compared with the corresponding quinolone derivatives substituted with a mere cyclopropyl group and, in addition, highly safe with markedly improved selective toxicity.

[0007] This invention relates to N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivatives

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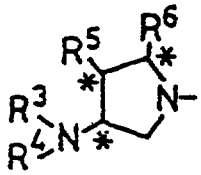
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represented by formula (I):

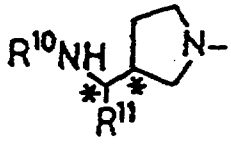


(I)

wherein R^1 represents an amino group, a methylamino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a 4-, 5- or 7-membered cyclic amino group having at least one substituent selected from a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, a polymethylene group having from 2 to 5 carbon atoms which together with the ring atom to which it is attached forms a spiro unit, an aminoalkyl group or an amino group, and which cyclic amino group may contain a bridging unit to form a bicyclic amino group and may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom in its ring, or R^2 represents a cyclic amino group represented by formula



or



wherein R^3, R^4, R^5, R^6, R^{10}, and R^{11}, which may be the same or different, represent an alkyl group having 1 to 6 carbon atoms or a hydrogen atom; A represents C - X^3 or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom, or a salt or ester thereof.

[0008] Specifically preferred compounds represented by formula (I) are those wherein R^2 is a substituted pyrrolidine, di-azabicycloheptane or diazabicyclooctane residue; those wherein R^2 is a cyclic amino group comprising a single stereoisomer; those wherein R^2 is a 3-aminopyrrolidinyl group; those wherein R^2 is a 7-amino-5-azaspiro[2,4]-heptan-5-yl group; and those wherein X^2 is a fluorine atom. More specifically, the compounds according to the present invention include 7-[3-(S)-amino-1-pyrrolidin-yl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-(S)-amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, 7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 5-amino-7-[7-amino-5-azaspiro[2,4]-heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, and salts thereof.

[0009] In formula (I), when X^3 represents a halogen atom, X^1 and X^3 each preferably represents a fluorine atom or a chlorine atom; and X^2 preferably represents a fluorine atom. R^1 represents preferably an unsubstituted amino group, a methylamino group, or a hydrogen atom.

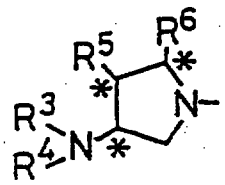
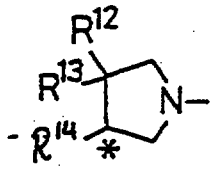
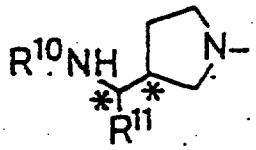
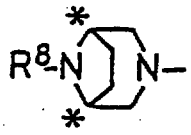
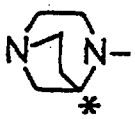
[0010] R^2 represents preferably a 5-membered cyclic amino group. The cyclic amino group may further contain oxygen atom(s), sulfur atom(s)and/or nitrogen atom(s), as in oxazolidine, thiazolidine, imidazolidine and pyrazolidine residues. Of these cyclic amino groups preferred is a pyrrolidine residue. The cyclic amino group may have substituents, such as a polar group (e.g., a substituted or unsubstituted amino group, a substituted or unsubstituted aminoalkyl group, a 5-substituted-2-oxo-1,3-dioxol-4-ylmethyl group, a hydroxyl group) and a straight chain, branched, or cyclic

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alkyl group having up to 6 carbon atoms. Preferred of the polar groups are an unsubstituted amino group, an aminomethyl group, a 1-aminoethyl group, and a hydroxyl group. Preferred of the alkyl groups are methyl, ethyl, propyl, gem-dimethyl and gem-diethyl groups and further, these gem-alkyl groups may preferably form a cyclopropane or cyclobutane ring which is bonded through a spiro-union to the cyclic amine skeleton. The cyclic amino group further includes a bicyclic amino group composed of crosslinking to 4- to 7-membered cyclic amino groups.

[0011] Illustrative examples of these cyclic amino groups, particularly containing the second amino moiety, are shown below:

wherein R^3, R^4, R^5, R^6, which may be the same or different, represent a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^8 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^{10} and R^{11}, which may be the same or different, represent a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; R^{12} and R^{13}, which may be the same or different, represent a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or they may be connected to each other to form a 3- to 6-membered ring composed of methylene chains; R^{14} is hydroxy or amino and the asterisk indicates an asymmetric center.

[0012] Examples of these cyclic amino groups are 3-aminopyrrolidinyl, 3-methylaminopyrrolidinyl, 3-dimethylaminopyrrolidinyl, 3-ethylaminopyrrolidinyl, 3-propylaminopyrrolidinyl, 3-isopropylaminopyrrolidinyl, 3-amino-4-methylpyrrolidinyl, 3-amino-5-methylpyrrolidinyl, 3-amino-4,5-dimethylpyrrolidinyl, 3-methylamino-4-methylpyrrolidinyl, 3-methylamino-5-methylpyrrolidinyl, 3-methylamino-4,5-dimethylpyrrolidinyl, 3-dimethylamino-4-methylpyrrolidinyl, 3-dimethylamino-5-methylpyrrolidinyl, 3-dimethylamino-4,5-dimethylpyrrolidinyl, 3-aminomethylpyrrolidinyl, 3-methylaminomethylpyrrolidinyl, 3-(1-amino)ethylpyrrolidinyl, 3-(1-methylamino)ethylpyrrolidinyl, 3-(1-ethylamino)ethylpyrrolidinyl, 3-(1-amino)propylpyrrolidinyl, 3-aminopyrrolidinyl, 3-amino-4,4-dimethylpyrrolidinyl, 7-amino-5-azaspiro[2,4]heptan-5-yl, 8-amino-6-azaspiro[3,4]octan-6-yl, 3,4-diazabicyclo[3,2,1]octan-3-yl, -3-yl, 9-methyl-3,9-diazabicyclo[3,2,1]octan-3-yl, -3-yl, and 9-ethyl-3,9-diazabicyclo[3,2,1]octan-3-yl.

[0013] The structure of the cyclic amino group at the 7-position greatly influences the antimicrobial activity, toxicity, oral absorption, and physical properties such as water solubility. For instance, it is known that quinolones substituted by 3-aminopyrrolidinyl groups have strong antimicrobial spectra against a broad range of microorganisms covering Gram-positive to Gram-negative bacteria. Some quinolone derivatives of this type, however, are susceptible to metabolism or only show low water-solubility.

[0014] 3-Aminopyrrolidinyl groups having a spiro ring at the carbon atom adjacent to the amine group thereof provide quinolone derivatives which exhibit improved oral absorption rate and improved in vivo stability against metabolism while retaining potent antimicrobial activity. The compounds of this type have also been proved less causative of convulsion which is known as a side effect of quinolone type synthetic antimicrobials.

[0015] Further, 3-aminomethylpyrrolidinyl groups in which an amino group is bonded to a pyrrolidinyl group via a carbon atom provide quinolone derivatives exhibiting enhanced antimicrobial activity against Gram-positive bacteria. In particular, the quinolones of this type in which the carbon atom linking the amino and pyrrolidinyl groups is substituted with one or two alkyl group(s) were found to exhibit improved oral absorption rate, safety, and water solubility over those without such substituent(s).

[0016] Examples of cyclic amino groups having substituents other than an amino group are 3-hydroxypyrrolidinyl, 3-mercaptopyrrolidinyl, 3-hydroxy-4-methylpyrrolidinyl and 3-mercapto-4-methylpyrrolidinyl.

[0017] The cyclic amino group is bonded to the 7-position of the pyridonecarboxylic acid skeleton preferably at the

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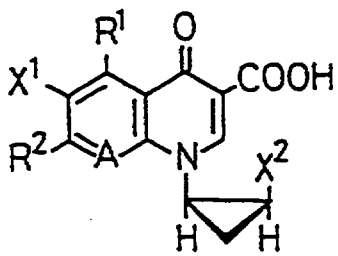
nitrogen atom of the cyclic amino group. As a matter of course, it may be bonded at another atom.

[0018] The stereoisomerism of the cyclic amine moiety at the 7-position is explained below. In case an asymmetric cyclic amine is reacted in the form of an isomeric mixture with a 1-(1,2-cis-halogenocyclopropyl)quinolone derivative, the resulting quinolone derivative should be a mixture of diasteromers based on the steric relation with the 1,2-cis-2-halogenocyclopropyl group at the 1-position. In these cases, therefore, it is necessary that only one of the isomers of the starting amine should be reacted.

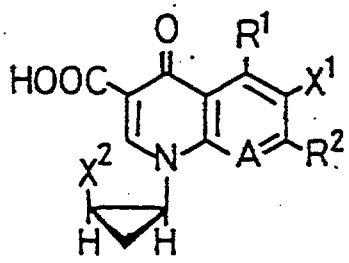
[0019] The functional group of the cyclic amino group at the 7-position such as amino, hydroxy and thiol groups may be protected by a conventional protective group prior to the substitution with the quinolone skeleton. The examples of such protective groups include alkoxycarbonyl groups such as t-butoxycarbonyl group, 2,2,2-trichloroethoxycarbonyl group and the like; aralkyloxycarbonyl groups such as benzyloxycarbonyl group, p-methoxybenzyloxycarbonyl group, p-nitrobenzyloxycarbonyl group and the like; acyl groups such as acetyl group, methoxyacetyl group, trifluoroacetyl group, chloroacetyl group, pivaloyl group, formyl group, benzoyl group and the like; alkyl or aralkyl groups such as t-butyl group, benzyl group, p-nitrobenzyl group, p-methoxybenzyl group, triphenylmethyl group and the like; ethers such as methoxymethyl group, t-butoxymethyl group, 2,2,2-trichloroethoxymethyl group, tetra-hydrofuran-2-yl group and the like; silyl groups such as trimethylsilyl group, isopropyldimethylsilyl group, t-butyldimethylsilyl group, t-butyldiphenylsilyl group, tribenzylsilyl group and the like.

[0020] The 1,2-cis-2-halogenocyclopropyl group at the N_1-position is described below. Introduction of a halogen atom to the cyclopropyl group, particularly a fluorine atom, brings about an effect to reduce lipophilicity of the whole molecule. It is known that drugs are more likely to be distributed to the central nervous system as lipophilicity thereof increases. In this connection, introduction of the 1,2-cis-2-halogenocyclopropyl group yields quinolones having reduced toxicity while retaining excellent antimicrobial activity as compared with the corresponding 1-cyclopropyl-quinolones. The halogen atom to be introduced includes fluorine and chlorine atoms, with a fluorine atom being preferred.

[0021] It is particularly preferable that the halogen atom and the pyridonecarboxylic acid moiety are cis with respect to the cyclopropane ring. Irrespective of whether the 7-cyclic amino group has stereoisomers or not, the quinolone derivatives of formula (I) have enantiomeric pairs ascribed to the cis-2-halogenocyclopropyl moiety at the 1-position as illustrated below. Potent activity and high safety were observed in either of these enantiomers.



and



[0022] The pyridonecarboxylic acid derivatives according to the present invention include the respective free acids, acid-addition salts thereof, and the salts of the carboxyl group thereof. The acid-addition salts include inorganic acid salts, e.g., hydrochlorides, sulfates, nitrates, hydrobromides, hydroiodides, and phosphates; and organic acid salts, e.g., acetates, methanesulfonates, benzenesulfonates, toluenesulfonates, citrates, maleates, fumarates, and lactates.

[0023] The salts of the carboxyl group may be organic or inorganic and include alkali metal salts, e.g., lithium salts, sodium salts, and potassium salts, alkaline earth metal salts, e.g., magnesium salts and calcium salts; ammonium salts, triethylamine salts, N-methylglucamates, and tris(hydroxymethyl)aminomethane salts.

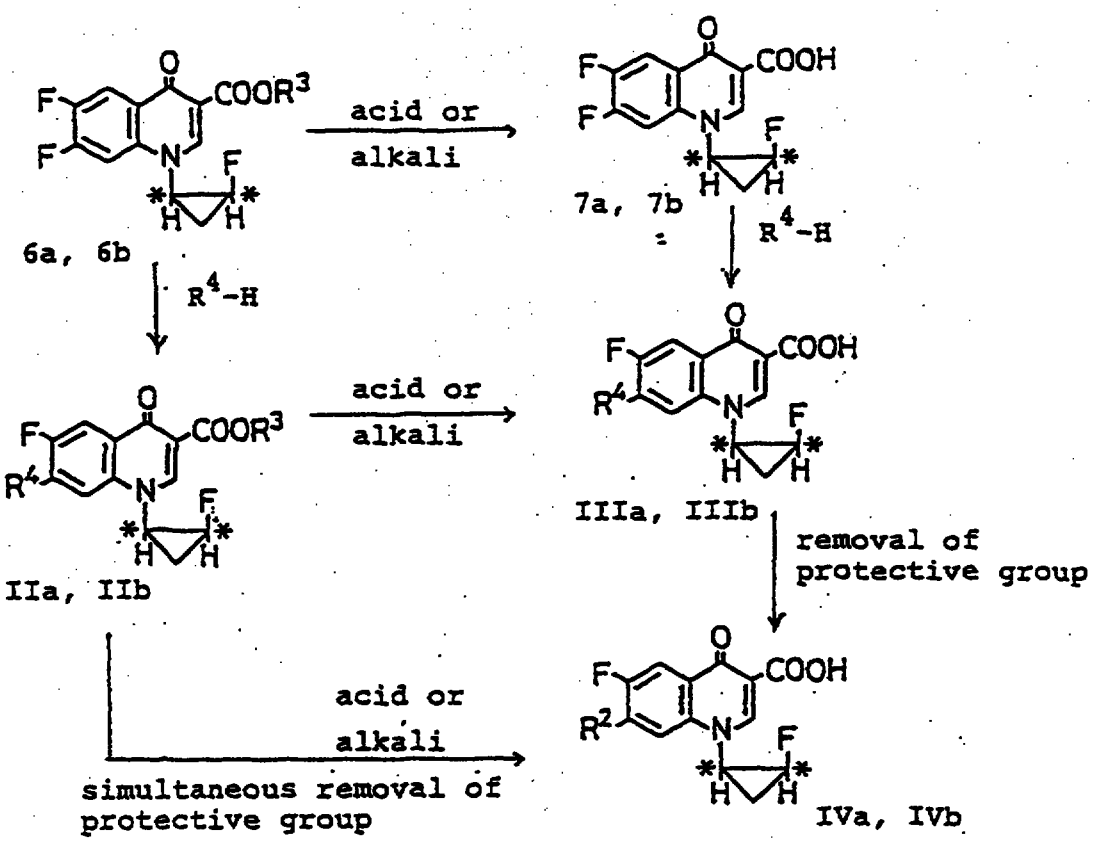
[0024] Some of these free acids and salts may exist as a hydrate.

[0025] Esterification of the carboxylic acid moiety of the pyridonecarboxylic acid derivatives of formula (I) gives compounds useful as synthesis intermediates or pro-drugs. For example, alkyl esters, benzyl esters, alkoxyalkyl esters, phenylalkyl esters and phenyl esters are useful as synthesis intermediates. Esters which are easily severed in the body to form free carboxylic acids are useful as pro-drugs. Examples of such esters are acetoxymethyl esters, pivaloyloxymethyl esters, ethoxy-carbonyloxy esters, chlorine esters, dimethylaminoethyl esters, 5-indanyl esters, phthalidinyl esters, and oxo-alkyl esters (e.g., 5-substituted-2-oxo-1,3-dioxol-4-yl-methyl esters and 3-acetoxy-2-oxobutyl esters).

[0026] A process for synthesizing the pyridonecarboxylic acid derivatives of formula (I) is illustrated below, taking the compound wherein A=C-H; R^1=H; X^1=X^2=F; and R^3=Et (ethyl group, hereinafter the same) for instance.

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wherein R^4 has the same meaning as R^2 or a cyclic amino group having the same structure as R^2 but being protected.

[0027] An optically active 1-(1,2-cis-2-fluorocyclopropyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (6a) or (6b) is hydrolyzed under acidic or alkaline conditions to give a free carboxylic acid derivative (7a) or (7b). The free acid (7a) or (7b) is reacted with a cyclic amine R^4-H to obtain a desired compound (IIIa) or (IIIb). If necessary, a protective group is removed from the resulting compound under proper conditions selected according to the protective group to obtain a desired compound (IVa) or (IVb).

[0028] The substitution reaction with the cyclic amine can be carried out in a solvent such as dimethyl sulfoxide, pyridine, acetonitrile and 3-methoxybutanol, at a temperature from room temperature to 150°C, preferably from 40 to 120°C, for 0.5 to 5 hours, usually from 0.5 to 2 hours.

[0029] Alternatively, the compound (6a) or (6b) is reacted with a cyclic amine under the same conditions as recited above, and the resulting compound (IIa) or (IIb) is then hydrolyzed under acidic or alkaline conditions and, if necessary, a protective group is removed, to obtain a desired compound (IIIa) or (IIIb) or (IVa) or (IVb).

[0030] The optically active cis-2-fluorocyclopropylamine can be synthesized as follows. 2-Fluorocyclopropanecarboxylic acid is reacted with (R)-(+)-α-methylbenzylamine to yield N-[1-(R)-phenylethyl]-1,2-cis-fluorocyclopropanecarboxamide. The reaction can be carried out in tetrahydrofuran in the presence of N,N-carbonyldiimidazole. The reaction may also be effected in accordance with a mixed anhydride procedure, in which the carboxylic acid is dissolved in an aprotic solvent and reacted with a halogenoformic ester in the presence of a base at low temperatures and then reacted with the benzylamine to obtain the carboxamide. The resulting carboxamide can be separated into each isomer by chromatographic techniques.

[0031] The aprotic solvent to be used in the mixed anhydride procedure is not particularly limited and includes ethers, e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, 1,4-dioxane, and 1,2-dimethoxyethane; halogenated hydrocarbons, e.g., dichloromethane, chloroform, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane; aromatic hydrocarbons, e.g., benzene, toluene, and xylene; and aliphatic hydrocarbons, e.g., pentane, hexane, heptane, and cyclohexane. Commonly employed of them is tetrahydrofuran or chloroform. The water contained in the solvent to be used is usually removed beforehand.

[0032] The halogen atom in the halogenoformic ester is normally a chlorine atom. The halogenoformic ester includes methyl, ethyl, 2,2,2-trichloroethyl, phenyl, p-nitrophenyl and benzyl esters.

[0033] The base to be used may be either organic or inorganic. The inorganic base includes alkali metal hydroxides,

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carbonates and hydrogencarbonates, e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate. The organic base includes trialkylamines, e.g., triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine; dialkylanilines, e.g., diethylaniline and dimethylaniline; and heterocyclic compounds, e.g., N-methylmorpholine, pyridine, and N,N-dimethylaminopyridine.

[0034] Separation of the carboxamide into optical isomers can be effected by known techniques, such as silica gel column chromatography under normal pressure or under pressure, preparative thin layer chromatography, and high performance liquid chromatography (HPLC). Separation into optical isomers can also be performed by other separation techniques generally employed, such as recrystallization and reprecipitation.

[0035] The thus separated optically active carboxamide can be led to an optically active cis-2-fluorocyclopropanecarboxylic acid by hydrolysis. The reaction can be carried out by dissolving the carboxamide in, for example, concentrated hydrochloric acid, followed by heating. The hydrochloric acid may be replaced with sulfuric acid or nitric acid. A solvent, such as acetic acid and a lower alcohol, may be used.

[0036] The resulting carboxylic acid can be converted at once by Curtius reaction in the presence of t-butanol to a protected cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane. The reaction can be carried out conveniently by use of diphenylphosphorylazide, but the synthesis of the intermediate azide compound is not limited thereto, and general methods of synthesis can be applied.

[0037] The resulting optically active cis-2-fluorocyclopropylamine derivative can be used for obtaining a quinolone derivative having a cis-fluorocyclopropyl group at the 1-position as a single isomer. The quinolone derivative according to the present invention can then be obtained by reacting this isomer with the cyclic amine as described above.

[0038] The pyridonecarboxylic acid derivatives according to the present invention exhibit potent antimicrobial activity and thus can be used as human and veterinary medicines, fish medicines, agricultural chemicals, and food preservatives.

[0039] The dose of the pyridonecarboxylic acid derivatives for use as human medicines ranges from 50 mg to 1 g, preferably from 100 mg to 300 mg, per day for adults. The dose for use as veterinary medicines generally ranges from 1 mg to 200 mg, preferably from 5 mg to 100 mg, per kg of body weight per day, though more or less varying depending on the purpose of administration (therapeutic use or preventive use, etc.), the kind and size of the animal, the kind of pathogenic organisms, and the symptoms. The daily dose recited above may be divided into 2 to 4 doses per day. If necessary, the daily dose may sometimes deviate from the above-recited range.

[0040] The pyridonecarboxylic acid derivatives of this invention are active against a wide variety of microorganisms causing various infectious diseases and capable of curing or alleviating and/or preventing the diseases caused by such pathogenes.

[0041] Illustrative examples of bacteria or bacterium-like microorganisms on which the pyridonecarboxylic acid derivatives of the invention are effective are Staphylococcus sp., Streptococcus pyogenes, Streptococcus Haemolyticus, enterococci, Streptococcus pneumoniae, Peptostreptococcus sp., Neisseria gonorrhoeae, Escherichia coli, Citrobacter sp., Shigella sp., Klebsiella pneumoniae, Enterobacter sp., Serratia sp., Proteus sp., Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter sp., Campylobacter sp., and Chlamidiae.

[0042] Examples of diseases caused by these pathogenes include folliculitis, furuncle, carbuncle, erysipelas, phlegmon, lymphangitis/lymphadenitis, felon, subcutaneous abscess, spiradenitis, acne conglobata, infectious atheroma, perianal abscess, mastadenitis, superficial secondary infections after trauma, burn or surgery trauma, pharyngolaryngitis, acute bronchitis, tonsillitis, chronic bronchitis, bronchiectasis, diffuse panbronchiolitis, secondary infections of chronic respiratory diseases, pneumonia, pyelonephritis, cystitis, prostatitis, epididymitis, gonococcal urethritis, nongonococcal urethritis, cholecystitis, cholangitis, bacillary dysentery, enteritis, adnexitis, intrauterine infections, bartholinitis, blepharitis, hordeolum, dacryocystitis, tarsadenitis, keratohelcosis, otitis media, sinusitis, paradentitis, pericoronitis circumcoronitis, gnathitis, peritonitis, endocarditis, septicemia, meningitis, and skin infections.

[0043] Examples of susceptible microorganisms causing veterinary infectious diseases include those of fowl, such as Escherichia sp., Salmonella sp., Pasteurella sp., Haemophilus sp., Bordetella sp., Staphylococcus sp., and Mycoplasma sp. Specific examples of veterinary diseases caused by these microorganisms include colibacillosis, pullorum disease, avian paratyphosis, fowl chlera, infectious coryza, staphylococcal infections, and mycoplasmal diseases; those of swin, such as colibacillosis, salmonellosis, pasteurellosis, haemophylus infection, atrophic rhinitis, exudative epidermitis, and mycoplasmal diseases; those for cattle, such as colibacillosis, salmonellosis, hemorrhagic septicemia, mycoplasmal diseases, bovine contageous pleuropneumonia, and bovine mastesis; those of dogs, such as coliform sepsis, salmonellosis, hemorrhagic septicemia, pyometra, and cystitis; and those of cats, such as hemorrhagic pleuritis, cystitis, chronic rhinitis, haemophylus infection, kitten diarrhea, and mycoplasmal diseases.

[0044] The compound of the present invention can be formulated into antimicrobial preparations in an appropriate dose form according to the administration route selected by the conventional preparation methods. The dose form for oral administration includes tablets, powders, granules, capsules, solutions, syrups, elixiers, and oily or aqueous suspensions. Injections may contain, in addition to the active ingredient, stabilizers, antiseptics, and solubilizing agents.

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The solution which may contain such excipients is put in a container and further, the solution may be subjected to lyophilization or the like means to prepare solid preparations which can be dissolved on use. The container may contain either a single dose or several doses.

[0045] Dose forms for external administration include solutions, suspensions, emulsions, ointments, gels, creams, lotions, and sprays.

[0046] In the preparation of solid preparations, the active ingredient may be mixed with appropriately selected pharmaceutically acceptable excipients, such as fillers, extenders, binders, disintegrators, dissolution accelerators, wetting agents, and lubricants.

[0047] Liquid preparations include solutions, suspensions, and emulsions. They may contain excipients, such as suspension stabilizers and emulsifiers.

[0048] The compound of the present invention can be administered to animals orally either directly or admixed to feedstuff, or its solution may be given either directly or admixed to water or feedstuff. The compound may also be administered non-orally by, for example, injection.

[0049] The compound of the invention can be formulated into preparations for animals, such as powders, fine granules, solubilized powders, syrups, solutions, and injections, by commonly employed preparation methods.

[0050] Formulation Examples are given below for illustrative purposes.

FORMULATION EXAMPLE 1	
Capsule:	
Compound of Example 8	100.0 mg
Corn starch	23.0 mg
Calcium carboxymethyl cellulose	22.5 mg
Hydroxypropylmethyl cellulose	3.0 mg
Magnesium stearate	1.5 mg
total:	150.0 mg

FORMULATION EXAMPLE 2	
Solution:	
Compound of Example 7	1 to 10 g
Acetic acid or sodium hydroxide	0.5 to 2 g
Ethyl p-hydroxybenzoate	0.1 g
Purified water	88.9 to 98.4 g
total:	100 g

FORMULATION EXAMPLE 3	
Powder for Admixture with Feedstuff:	
Compound of Example 6	1 to 10 g
Corn starch	98.5 to 98.5 g
Light anhydrous silicic acid	0.5 g
total:	100 g

[0051] The present invention is now illustrated in greater detail by way of the following Examples and Reference Examples. Reference Examples describe the syntheses of optically active skeletons from an optically active cis-2-fluorocyclopropanecarboxylic acid.

[0052] Antimicrobial activity of the optically active compounds prepared in Examples was evaluated in accordance with the standard method specified by Nippon Kagakuryoho gakkai, and results obtained are shown in Table 1 below in terms of minimum inhibitory concentration (MIC: μg/ml).

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REFERENCE EXAMPLE 1

N-[1-(R)-Phenylethyl]-1.2-cis-2-fluorocyclopropane-carboxamide (2a. 2b):

1-1. Carbonyldiimidazole Method:

[0053] One gram of cis-2-fluorocyclopropanecarboxylic acid was dissolved in 30 ml of tetrahydrofuran (THF), and 1.78 g of N,N'-carbonyldiimidazole was added thereto, and the mixture was stirred at room temperature for 1 hour. To the solution was added 1.45 g of (R)-(+)-α-methylbenzylamine, and the stirring was continued for 2 hours. The solvent was removed under reduced pressure, and the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. From the residual viscous oily substance, each stereoisomer was isolated by HPLC under conditions shown below. Each isomer was recrystallized from diisopropyl ether to yield the title compound (2a) or (2b). HPLC Conditions:

Column:	Nucleosil 50-5 (20 mm ID × 250 mm L) (senshu Pack SSC Silica, 782-IN, produced by Senshu Kagaku)
Solvent:	ethyl acetate-THF (9:1 by volume)
Flow Rate:	9.0 ml/min
Retention Time:	11 mins, for Compound (2a)
	13 mins. for Compound (2b)

Compound (2a):

[0054] Melting Point: 108°C

Elementary Analysis for $C_{12}H_{14}FNO$			
Calcd. (%)	C 69.55;	H 6.81;	N 6.76
Found (%)	C 69.31;	H 7.01;	N 6.65

$[\alpha]_D$: +61.96° (c=0.965, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.92-1.34 (2H, m), 1.50 (3H, d, J=7Hz), 1.50-1.96 (1H, m), 4.68 (1H, dm, J=64Hz), 5.14 (1H, m), 7.40 (5H, s)

Physiochemical Properties of Compound (2b):

[0055] Melting point: 102°C

Elementary Analysis for $C_{12}H_{14}FNO$			
Calcd. (%)	C 69.55;	H 6.81;	N 6.76
Found (%)	C 69.45;	H 6.87;	N 6.70

$[\alpha]_D$: +143.61° (c=0.830, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.98=1.34 (2H, m), 1.52 (3H, d, J=7Hz), 1.64-1.96 (1H, m), 4.58 (1H, dm, J=66Hz), 5.24 (1H, m), 7.40 (5H, m)

1-2. Mixed Anhydride Method:

[0056] In 50 ml of THF were dissolved 4.19 g of 2-fluorocyclopropanecarboxylic acid (cis-trans mixture) and 4.07 g of triethylamine, and the solution was cooled to -10°C. To this was added a solution of 4.73 g of ethyl chloroformate in 20 ml of THF and the mixture was stirred for 10 minutes. To the solution was then added dropwise a solution of 4.88 g of (R)-(+)-α-methylbenzylamine in 30 ml of THF at that temperature, and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure, and the residue was extracted with benzene. The extract was washed successively with a 10% citric acid aqueous solution, a 1N sodium hydroxide aqueous solution and water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the re-

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sulting pale yellow oily substance was purified by silica gel column chromatography using a mixed solvent of benzene and ethyl acetate as an eluent to each of the title compounds (2a) and (2b).

REFERENCE EXAMPLE 2

(+)-cis-2-Fluorocyclopropanecarboxylic acid (3a):

[0057] In 15 ml of concentrated hydrochloric acid were dissolved 530 mg of the amide compound (2a) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. To the reaction mixture was added 20 ml of water, and the mixture was extracted with ethyl acetate. The extract was then extracted with a sodium hydrogencarbonate aqueous solution and this aqueous extract was washed with ethyl acetate. The aqueous extract was adjusted to a pH of 5 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield the title compound (3a) as a pale yellow oil.

$[\alpha]_D$: -23.13° (c=1.020, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.60-2.10 (2H, m), 4.82 (1H, dm, J=65Hz), 12.0 (1H, s)

REFERENCE EXAMPLE 3

(+)-cis-2 -Fluorocyclopropanecarboxylic acid (3b):

[0058] In 30 ml of concentrated hydrochloric acid were dissolved 1.65 g of amide compound (2b) as prepared in Reference Example 1, and the solution was heated at 100 to 110°C for 5 hours while stirring. The pH of the reaction mixture was adjusted between 8 and 9 with sodium hydrogencarbonate and then washed with chloroform. The pH of the aqueous layer was adjusted to 4 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the title compound (3b) as a pale yellow oil.

$[\alpha]_D$: +21.56° (c=1.113, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.42 (1H, m), 1.56-1.98 (2H, m), 4.76 (1H, dm, J=66Hz), 11.32 (1H, s)

REFERENCE EXAMPLE 4

(+)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4a):

[0059] In 5 ml of t-butanol were dissolved 200 mg of the carboxylic acid (3a) as obtained in Reference Example 2, 603 mg of diphenylphosphorylazide, and 203 mg of triethylamine, and the solution was heated under reflux for 4.5 hours. After removing the solvent under reduced pressure, the residue was extracted with chloroform. The extract was washed successively with a 10% citric acid aqueous solution, a 2% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using chloroform as an eluent to obtain the title compound (4a) as colorless crystals.

Melting Point: 73°C

$[\alpha]_D$: +65.57° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.62 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 5

(-)-cis-1-(t-Butoxycarbonylamino)-2-fluorocyclopropane (4b):

[0060] To 6 ml of t-butanol were added 265 mg of the carboxylic acid (3b) as obtained in Reference Example 3, 800 mg of diphenylphosphorylazide, and 270 mg of triethylamine. The solution was allowed to react and worked up in the same manner as in Reference Example 4 to obtain the title compound (4b).

Melting Point: 63°C

$[\alpha]_D$: -60.27 (c=0.740, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

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0.66-1.3 (2H, m), 1.46 (9H, s), 2.48-2.74 (1H, m), 4.58 (1H, dm, J=65Hz), 4.6-5.1 (1H, broad)

REFERENCE EXAMPLE 6

(-)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)aminomethylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5a):

[0061] Ethyl 2,4,5-trifluorobenzoylacetate (234 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0062] Compound (4a) as obtained in Reference Example 4 (167 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for 20 minutes and concentrated to dryness under reduced pressure (the resulting amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloromethane and cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was added dropwise thereto. Thereafter, the above prepared dichloromethane solution was added dropwise to the mixture, followed by stirring at room temperature overnight. The solvent was evaporated to dryness under reduced pressure, and the residue was subjected to silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after removal of the solvent. The product was recrystallized from diisopropyl ether-n-hexane to yield the title compound (5a) as colorless crystals.

Melting Point: 69-70°C

$[\alpha]_D$: -10.29° (c=1.088, chloroform)

REFERENCE EXAMPLE 7

(+)-Ethyl-2-[(1,2-cis-2-fluorocyclopropan-1-yl)aminomethylene]-3-oxo-3-(2,4,5-trifluorophenyl)propionate (5b):

[0063] Ethyl 2,4,5-trifluorobenzoylacetate (337 mg), 2 ml of ethyl orthoformate, and 4 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 2 hours while stirring. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0064] Compound (4b) as obtained in reference Example 5 (240 mg) and 5 ml of trifluoroacetic acid were mixed and the mixture was stirred at room temperature for I hour, followed by concentration under reduced pressure (the amine trifluoroacetate was used without purification). The residue was dissolved in 10 ml of dichloroethane, and the solution was cooled to -10°C. A solution of 230 mg of triethylamine in 10 ml of dichloromethane was added thereto dropwise, and the above-prepared dichloromethane solution was further added to the mixture, followed by stirring at room temperature overnight. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography using a mixed solvent of benzene and ethyl acetate (2:1 by volume). A yellow oily substance was obtained from the eluent after removal of the solvent. Recrystallization from diisopropyl ether-n-hexane gave the title compound (5b) as colorless crystals.

Melting Point: 69-70°C

$[\alpha]_D$: +12.09 (c=0.645, chloroform)

REFERENCE EXAMPLE 8

(+)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6a):

[0065] In 15 ml of anhydrous dioxane were dissolved 180 mg of Compound (5a) as obtained in Reference Example 6, and 200 mg of 60% sodium hydride were added to the solution, followed by stirring at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform, and the extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing solvent to yield the title compound (6a) as colorless crystals.

Melting Point: 231-232°C

$[\alpha]_D$: +27.20° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.20 (3H, t, J=7Hz), 1.6-1.9 (2H, m), 3.28-3.56 (1H, m), 4.42 (2H, q, J=7Hz), 5.11 (1H, dm, J=63Hz), 7.60 (1H, dd, J=11Hz & 7Hz), 8.28 (1H, dd, J=10Hz & 11Hz), 8.58 (1H, s)

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REFERENCE EXAMPLE 9

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (6b):

[0066] In 15 ml of anhydrous dioxane were dissolved 267 mg of Compound (5b) as obtained in Reference Example 7, and 200 mg of 60% sodium hydride were added thereto, and the mixture was stirred at room temperature for 2 days. The reaction mixture was added to a 10% citric acid aqueous solution, followed by concentration under reduced pressure. The residue was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using benzene-ethyl acetate (1:2 by volume) as a developing solvent to yield the title compound (6b) as colorless crystals.

Melting Point: 226-227°C

$[\alpha]_D$: -31.36° (c=0.610, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.22 (3H, t, J=7Hz), 1.5-1.9 (2H, m), 3.26-3.52 (1H, m), 4.40 (2H, q, J=7Hz), 5.10 (1H, dm, J=63Hz), 7.58 (1H, dd, J=11Hz & 7Hz), 8.26 (1H, dd, J=10Hz & 11Hz), 8.55 (1H, s)

REFERENCE EXAMPLE 10

(+)-6,7-Difluoro-1-(1,2-cis -2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7a):

[0067] In 15 ml of concentrated hydrochloric acid were dissolved 106 mg of the ester (6a) as obtained in Reference Example 8, and the solution was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture were added 15 ml of water, and the precipitate was collected by filtration to obtain the title compound (7a) as colorless crystals.

Melting Point: 265-270°C

$[\alpha]_D$: +3.66° (c=0.383, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H; dm, J=64Hz), 7.82 (1H, dd, J=12Hz, & 7Hz), 8.37 (1H, dd, J=18Hz & 8Hz), 8.94 (1H, s)

REFERENCE EXAMPLE 11

(-)-6,7-Difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7b):

[0068] In 10 ml of concentrated hydrochloric acid were dissolved 150 mg of the ester (6b) as obtained in Reference Example 9, and the solution was heated at 110°C for 2 hours while stirring. To the reaction mixture were added 20 ml of water, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to yield the title compound (7b) as colorless crystals.

Melting Point: 261-264°C

$[\alpha]_D$: -4.08° (c=0.343, acetic acid)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.75-1.95 (2H, m), 3.58 (1H, m), 5.18 (1H, dm, J=64Hz), 7.82 (1H, dd, J=12Hz & 7Hz), 8.37 (1H, dd, J=12Hz & 8 Hz), 8.94 (1H s)

EXAMPLE 1

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8a):

[0069] Seventy milligrams of the carboxylic acid (7a) as obtained in Reference Example 10, 150 mg of (S)-3-(t-butoxycarbonylamino)pyrrolidine, 200 mg of triethylamine, and 20 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to obtain the title compound (8a) as yellow crystals.

Melting Point: 236-239°C

$[\alpha]_D$: +1.0°(c=0.200, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.7 (2H, m), 1.46 (9H, s), 1.7-1.9 (1H, m), 2.0-2.36 (1H, m), 3.3-4.0 (5H, m), 4.2-4.4 (1H, m), 5.06 (1H, dm, J=68Hz), 6.68 (1H, d, J=7Hz), 7.84 (1H, d, J=14Hz), 8.46 (1H, s)

EXAMPLE 2

7-[3-(S)-t-Butoxycarbonylamino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (8b):

[0070] The carboxylic acid as obtained in Reference Example 11 (7b) (112 mg), 200 mg of (S)-3-(t-butoxycarboxylamino)pyrrolidine, 220 mg of triethylamine, and 15 ml of acetonitrile were mixed, and the mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure, and to the residue was added a 10% citric acid aqueous solution, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to yield the title compound (8b) as yellow crystals.

Melting Point: 242-243°C

$[\alpha]_D$: -4.0° (c=0.448, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.0-1.7 (2H, m), 1.40 (9H, s), 1.6-1.8 (1H, m), 1.9-2.1 (1H, m), 3.3-3.9 (5H, m), 4.2-4.5 (1H, m), 5.00 (1H, dm, J=68Hz), 6.58 (1H, d, J=7Hz), 7.72 (1H, d, J=14Hz), 8.32 (1H, s)

EXAMPLE 3

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

[0071] In 10 ml of trifluoroacetic acid were dissolved 80 mg of the carboxylic acid (8a) as obtained in Example 1. After stirring for 20 minutes, the reaction mixture was evaporated under reduced pressure to dryness. To the residue were added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of the aqueous layer was adjusted to 7.5 with 1N hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from ethanol yielded the title compound as colorless crystals.

Melting Point: 248-252°C

$[\alpha]_D$: -31.35° (c=0.370, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.52-1.68 (2H, m), 1.68-1.80 (1H, m), 2.05-2.15 (1H, m), 3.13-3.22 (1H, m), 3.25-3.45 (2H, m), 3.45-3.65 (3H, m), 5.12 (1H, dm, J=65Hz), 6.58 (1H, d, J=7Hz), 7.58 (1H, d, J=14Hz), 8.29 (1H, s)

EXAMPLE 4

7-[3-(S)-Amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (9a):

[0072] To 10 ml of trifluoroacetic acid were added 80 mg of the carboxylic acid (8b) as obtained in Example 2. After stirring for 20 minutes, the reaction mixture was evaporated to dryness under reduced pressure. To the residue were added 5 ml of water, and was further added a 1N sodium hydroxide aqueous solution to dissolve the residue. The pH of the aqueous layer was adjusted to 7.5 with 1N hydrochloric acid and followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed therefrom under reduced pressure. Recrystallization of the residue from ethanol gave the title compound (9b) as colorless crystals.

Melting Point: 236-240°C

$[\alpha]_D$: +23.72 (c=0.413, 1N NaOH aqueous solution)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.55-1.69 (2H, m), 1.69-1.77 (1H, m), 2.07-2.15 (1H, m), 3.15-3.22 (1H, m), 3.37-3.47 (2H, m), 3.52-3.58 (2H, m), 3.58-3.66 (1H, m), 5.13 (1H, dm, J=65Hz), 6.62 (1H, d, J=7Hz), 7.61 (1H, d, J=14Hz), 8.30 (1H, s)

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REFERENCE EXAMPLE 12

(-)-Ethyl 2-[[1.2-cis-2-fluoro-1-cyclopropyl)amino]-methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)-propionate (10a):

[0073] Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 5 ml of dichloromethane.

[0074] Seven milliliters of trifluoroacetic acid was cooled with ice, and 480 mg of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) were dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporation under reduced pressure to dryness. The residue was suspended in 10 ml of dichloromethane, and 3 ml of triethylamine were added thereto under ice-cooling. After stirring for 20 minutes, the above-prepared dichloromethane solution was added thereto, and the mixture was stirred for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using a mixed solvent of benzene and ethyl acetate (5:1 by volume) as an eluent. The solvent was removed under reduced pressure, and the residue was washed with diisopropyl ether to obtain 620 mg of the title compound (10a).

Melting Point: 98-100°C

$[\alpha]_D$: -6.66° (c=0.998, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:			
Calcd. (%)	C 49.26;	H 3.31;	N 3.83
Found (%)	C 49.39;	H 3.22;	N 3.86

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

REFERENCE EXAMPLE 13

(+)-2-[[1,2-cis-2-Fluoro-1-cyclopropyl)amino]methylene]-3-oxo-3-(3-chloro-2,4,5-trifluorophenyl)propionate (10b):

[0075] Ethyl 3-chloro-2,4,5-trifluorobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1.5 hours while stirring. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0076] Ten milliliters of trifluoroacetic acid were ice-cooled, and 1.12 g of (-)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4b) were dissolved therein. After stirring at room temperature for 20 minutes, the mixture was evaporated to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine were added to the suspension under ice-cooling. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 1 hour. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography which was eluted with a mixed solvent of benzene and ethyl acetate (4:1 by volume). The solvent of the eluent was removed under reduced pressure. The residue was washed with diisopropyl ether-n-hexane to obtain 1.74 g of crystals of the title compound (10b).

Melting Point: 99-100°C

$[\alpha]_D$: +6.70° (c=0.895, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:			
Calcd. (%)	C 49.26:	H 3.31:	N 3.83
Found (%)	C 49.41:	H 3.60:	N 4.06

^{1}H-NMR ($CDCl_3$) δ ppm:

0.95, 1.08 (3H, 1:2.5, each t, J=7HZ), 1.0-1.5 (2H, m), 2.8-3.15 (1H, m), 4.03, 4.07 (2H, 1:2.5, each q, J=7Hz), 4.78 (1H, dm, J=65Hz), 7.13 (1H, ddd, J=5.9, 8.6, & 9.5Hz), 8.20, 8.25 (1H, 1:2.5, each d, J=14HZ)

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REFERENCE EXAMPLE 14

(+)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11a):

[0077] In 77 ml of anhydrous dioxane were dissolved 620 mg of Compound (10a) as prepared in Reference Example 12, and 80 mg of 60% sodium hydride were added to the solution, followed by stirring at room temperature for 1 hour. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed therefrom under reduced pressure. The residue was washed with n-hexane to obtain 551 mg of the title compound (11a) as colorless crystals.

Melting Point: 181-184°C

$[\alpha]_D$: +45.1° (c=1.18, chloroform)

Elementary Analysis for $C_{15}H_{12}ClF_4NO_3$:			
Calcd. (%)	C 52.12;	H 3.21;	N 4.05
Found (%)	C 52.09;	H 3.33;	N 4.01

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

REFERENCE EXAMPLE 15

(-)-Ethyl 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (11b):

[0078] In 10 ml of anhydrous dioxane were suspended 560 mg of 60% sodium hydride having been washed twice with anhydrous n-hexane. The suspension was added to a solution of 1.70 g of Compound (10b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 2 hours. The solvent was removed under reduced pressure, and 0.1N hydrochloric acid was added to the residue. The precipitated crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.44 g of the title compound (11b) as colorless crystals.

Melting Point: 174°C

$[\alpha]_D$: -45.3° (c=1.05, chloroform)

Elementary Analysis for $C_{15}H_{11}ClF_4NO_3$:			
Calcd. (%)	C 52.12;	H 3.21;	N 4.05
Found (%)	C 51.80;	H 3.45;	N 4.15

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7HZ), 1.4-1.9 (2H, m), 4.08 (1H, m), 4.39 (2H, q, J=7HZ), 4.90 (1H, dm, J=65Hz), 8.24 (1H, dd, J=10 & 11 Hz)

IR(KBr); ν_{max} cm^{-1}: 3100, 2998, 1731, 1638, 1614, 1470, 1317

REFERENCE EXAMPLE 16

(+)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12a):

[0079] The ester (11a) (540 mg), 5 ml of concentrated hydrochloric acid, and 5 ml of acetic acid were mixed, and the mixture was heated at 120-130°C for 2 hours while stirring. To the reaction mixture were added 50 ml of water, and the precipitated crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 420 mg of the title compound (12a) as colorless crystals.

Melting Point: 170-171°C

$[\alpha]_D$: +30.4° (c=0.54, chloroform)

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Elementary Analysis for $C_{13}H_7ClF_3NO_3$:			
Calcd. (%)	C 49.16;	H 2.22;	N 4.41
Found (%)	C 49.21;	H 2.49;	N 4.27

^{1}H-NMR ($CDCl_3$) δ ppm:
1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

REFERENCE EXAMPLE 17

(-)-8-Chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b)

[0080] The ester (11b) (1.40 g) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 110°C for 2.5 hours under stirring. To the reaction mixture were added 50 ml of water, and the precipitated crystals were collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to obtain 1.16 g of the title compound (12b) as colorless crystals.
Melting Point: 177-182°C
$[\alpha]_D$: -26.8° (c=0.90, chloroform)

Elementary Analysis for $C_{13}H_7ClF_3NO_3$:			
Calcd. (%)	C 49.16;	H 2.22;	N 4.41
Found (%)	C 49.28;	H 2.40;	N 4.66

^{1}H-NMR ($CDCl_3$) δ ppm:
1.3-2.0 (2H, m), 4.12-4.34 (1H, m), 4.95 (1H, dm, J=63Hz), 8.27 (1H, dd, J=8 & 8Hz), 8.87, 8.89 (1H, each s, split 1:1)

EXAMPLE 5

(+)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (13a):

[0081] Five milliliters of trifluoroacetic acid were cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine were dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12a) and 400 mg of triethylamine, followed by refluxing for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure, and to the residue was added 1N hydrochloric acid. The mixture was washed with chloroform. The pH of the aqueous layer was adjusted to 12 with a 1N sodium hydroxide aqueous solution and washed with chloroform. The pH of the aqueous layer was readjusted to 7.6 with hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 138 mg of the title compound (13a) as colorless crystals.
Melting Point: 214-217°C (with decomposition)
$[\alpha]_D$: +120.8° (c=0.475, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot 1/2H_2O$:			
Calcd. (%)	C 51.98;	H 4.36;	N 10.70
Found (%)	C 52.07;	H 4.71;	N 10.72

^{1}H-NMR (NaOD) δ ppm:
1.28 (1H, dm, J=27Hz), 1.69-1.78 (2H, m), 3.39-3.42 (1H, m), 3.51-3.61 (3H, m), 3.69-3.72 (1H, m), 4.13-4.17 (1H, m), 4.99 (1H, dm, J=70Hz), 7.72 (1H, d, J=14Hz), 8.44, 8.45 (1H, each s, split, 1:1)

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EXAMPLE 6

(-)-7-[3-(S)-Amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (13b):

[0082] Five milliliters of trifluoroacetic acid were cooled with ice, and 230 mg of 3-(S)-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine were dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 15 ml of acetonitrile. To the solution were added 170 mg of the carboxylic acid (12b) and 400 mg of triethylamine, and the mixture was heated under reflux for 6.5 hours. The reaction mixture was evaporated to dryness under reduced pressure. A 1N hydrochloric acid was added to the residue, and the mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, and the aqueous layer was adjusted to a pH of 7.6 with hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to give 158 mg of the title compound (13b) as colorless crystals.

Melting Point: 247-252°C (with decomposition)

$[\alpha]_D$: -94.7° (c=0.378, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{16}ClF_2N_3O_3 \cdot H_2O$:			
Calcd. (%)	C 50.82;	H 4.52;	N 10.46
Found (%)	C 50.97;	H 5.14;	N 10.42

^{1}H-NMR (NaOD) δ ppm:

1.32 (1H, dm, J=27Hz), 1.73-1.80 (2H, m), 2.15-2.19 (1H, m), 3.19-3.22 (1H, m), 3.45-3.50 (1H, m), 3.58-3.62 (1H, m), 3.85-3.88 (2H, m), 4.16-4.20 (1H, m), 4.99 (1H, dm, J=63Hz), 7.76 (1H, d, J=14Hz), 8.54, 8.44 (1H, each s, split, 1:1)

REFERENCE EXAMPLE 18

(-)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)propionate (14a):

[0083] Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 120°C for 2 hours. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

[0084] Ten milliliters of trifluoroacetic acid were cooled with ice, and 1.1 g of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) were dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporating to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine were added thereto under ice-cooling, followed by stirring for 20 minutes. The above-prepared dichloromethane solution was then added thereto, followed by stirring for 30 minutes. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the compound (14a) were combined, and the solvent was removed under reduced pressure. The residue was washed with n-hexane to yield 1.57 g of crystals of the title compound (14a).

Melting Point: 99-100°C

$[\alpha]_D$: -10.3° (c=1.25, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$			
Calcd. (%)	C 45.70;	H 2.81;	N 7.10
Found (%)	C 45.60;	H 3.01;	N 7.03

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.55 (2H, m), 2.88-3.16 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.29 (1H, d, J=14Hz)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521, 1482

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REFERENCE EXAMPLE 19

(+)-Ethyl 2-[[(1,2-cis-2-fluoro-1-cyclopropyl)amino]methylene]-3-oxo-3-(2,3,4,5-tetrafluoro-6-nitrophenyl)propionate (14b):

[0085] Ethyl 2,3,4,5-tetrafluoro-6-nitrobenzoylacetate (1.5 g), 6 ml of ethyl orthoformate, and 10 ml of acetic anhydride were mixed, and the mixture was heated at 110 to 120°C for 1 hour while stirring. The reaction mixture was concentrated to dryness, and the residue was dissolved in 10 ml of dichloromethane.

[0086] Ten milliliters of trifluoroacetic acid were ice-cooled, and 1.10 g of (-)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4b) were dissolved therein, followed by stirring at room temperature for 20 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was suspended in 20 ml of dichloromethane. To the suspension were added 1.8 g of triethylamine under ice-cooling, followed by stirring for 20 minutes. To the mixture was added the above-prepared dichloromethane solution, followed by stirring for 2 hours. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography using benzene as an eluent. The fractions of the product (14b) were combined, and the solvent was removed under reduced pressure. The residue was washed with n-hexane to yield 1.50 g of crystals of the title compound (14b).

Melting Point: 98-100°C

$[\alpha]_D$: -10.1° (c=2.09, chloroform)

Elementary Analysis for $C_{15}H_{11}F_5N_2O_5$			
Calcd. (%)	C 45.70;	H 2.81;	N 7.10
Found (%)	C 45.77;	H 3.38;	N 7.18

^{1}H-NMR ($CDCl_3$) δ ppm:

1.10 (3H, t, J=7Hz), 1.2-1.5 (2H, m), 2.88-3.12 (1H, m), 4.09 (2H, q, J=7Hz), 4.45 (1H, dm, J=63Hz), 8.30 (1H, d, J=14Hz)

IR(KBr): ν_{max} cm^{-1}: 3454 1695, 1638, 1554, 1515

REFERENCE EXAMPLE 20

(+)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15a):

[0087] In 20 ml of anhydrous dioxane were suspended 580 mg of 60% sodium hydride having been washed twice with n-hexane. The suspension was added to a solution of 1.90 g of Compound (14a) in 20 ml of anhydrous dioxane. The mixture was stirred at room temperature for 1 hour, and the solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid. The crystals thus formed were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.65 g of the title compound (15a) as colorless crystals.

Melting Point: 172-176°C

$[\alpha]_D$: +10.7° (c=1.12, chloroform)

Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$			
Calcd. (%)	C 48.14;	H 2.69;	N 7.49
Found (%)	C 48.29;	H 2.78;	N 7.20

^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.80-4.08 (1H, m), 4.34 (2H, q, J=7Hz), 4.99 (1H, dm, J=63Hz), 8.55 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3454 1734, 1626, 1566, 1521 1482

REFERENCE EXAMPLE 21

(-)-Ethyl 6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-5-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (15b):

[0088] In 10 ml of anhydrous dioxane were suspended 440 mg of 60% sodium hydride having been washed twice

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with n-hexane. The suspension was added to a solution of 1.45 g of Compound (14b) in 20 ml of anhydrous dioxane, followed by stirring at room temperature for 30 minutes. The solvent was removed from the reaction mixture under reduced pressure. To the residue was added 0.1N hydrochloric acid, and the formed crystals were collected by filtration, washed successively with water and diethyl ether, and dried under reduced pressure to obtain 1.18 g of the title compound (15b) as colorless crystals.

Melting Point: 171-175°C

$[\alpha]_D$: -11.1° (c=0.27, chloroform)

Elementary Analysis for $C_{15}H_{10}F_4N_2O_5$			
Calcd. (%)	C 48.14;	H 2.69;	N 7.49
Found (%)	C 48.44;	H 3.17;	N 7.48

^{1}H-NMR ($CDCl_3$) δ ppm:

1.36 (3H, t, J=7Hz), 1.4-1.92 (2H, m), 3.74-4.02 (1H, m), 4.36 (2H, q, J=7Hz), 4.94 (1H, dm, J=62Hz), 8.54 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 1731, 1626, 1566, 1485, 1323, 1275

REFERENCE EXAMPLE 22

(+)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (16a):

[0089] The nitro compound (15a) (1.60 g), 6 ml of Raney nickel, and 200 ml of ethanol were mixed, and the mixture was shaken for 2.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16a) were combined, and the solvent was removed therefrom under reduced pressure. The residue was recrystallized from ethanol to obtain 770 mg of the title compound (16a) as pale yellow crystals.

Melting Point: 190-191°C

$[\alpha]_D$: +26.0° (c=0.76, chloroform)

Elementary Analysis for $C_{15}H_{12}F_4N_2O_3$			
Calcd. (%)	C 52.33;	H 3.51;	N 8.14
Found (%)	C 52.13;	H 3.95;	N 8.13

^{1}H-NMR ($CDCl_3$) δ ppm:

1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.37 (1H, s)

IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1557, 1461, 1284

REFERENCE EXAMPLE 23

(-)-Ethyl 5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (16b):

[0090] The nitro compound (15b) (1.60 g), 3 ml of Raney nickel, and 120 ml of ethanol were mixed, and the mixture was shaken for 4.5 hours in a hydrogen atmosphere. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using chloroform as an eluent. The fractions of product (16b) were combined, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to obtain 620 mg of the title compound (16b) as pale yellow crystals.

Melting Point: 191-193°C

$[\alpha]_D$: -25.9° (c=0.65, chloroform)

Elementary analysis for $C_{15}H_{12}F_4N_2O_3$			
Calcd. (%)	C 52.33;	H 3.51;	N 8.14
Found (%)	C 52.16;	H 3.54;	N 8.08

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^{1}H-NMR ($CDCl_3$) δ ppm:
1.39 (3H, t, J=7Hz), 1.4-1.8 (2H, m), 3.60-3.88 (1H, m), 4.38 (2H, q, J=7Hz), 4.87 (1H, dm, J=63Hz), 6.8-7.1 (2H, m), 8.38 (1H, s)
IR(KBr): ν_{max} cm^{-1}: 3436, 1683, 1653, 1593, 1464, 1284

REFERENCE EXAMPLE 24

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17a):

[0091] The ester (16a) (750 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100°C for 2 hours while stirring. To the reaction mixture was added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 610 mg of the title compound (17a) as colorless crystals.
Melting Point: 297-300°C

Elementary Analysis for $C_{13}H_8F_4N_2O_3$			
Calcd. (%)	C 49.38;	H 2.55;	N 8.86
Found (%)	C 49.43;	H 2.91;	N 8.84

^{1}H-NMR (DMSO-d_6) δ ppm:
1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)
IR(KBr): ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

REFERENCE EXAMPLE 25

5-Amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (17b):

[0092] The ester (16b) (588 mg) and 10 ml of concentrated hydrochloric acid were mixed and the mixture was heated at 100 to 110°C for 2 hours while stirring. To the reaction mixture were added 20 ml of water, and the precipitated crystals were collected by filtration to obtain 514 mg of the title compound (17b) as colorless crystals.
Melting Point: 295-300°C

Elementary Analysis for $C_{13}H_8F_4N_2O_3$			
Calcd. (%)	C 49.38;	H 2.55;	N 8.86
Found (%)	C 49.41;	H 2.81;	N 8.88

^{1}H-NMR ($CDCl_3$) δ ppm:
1.4-2.1 (2H, m), 3.9-4.2 (1H, m), 5.08 (1H, dm, J=65Hz), 7.72 (1H, s), 8.62 (1H, s)
IR: ν_{max} cm^{-1}: 3448, 3334, 1725, 1656, 1596, 1566, 1518

EXAMPLE 7

(-)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (18a):

[0093] Five milliliters of trifluoroacetic acid were cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine were dissolved therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17a) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 128 mg of the titled compound (18a) as colorless crystals.
Melting Point: 224-230°C
$[\alpha]_D$: -4.72° (c=0.888, 0.1N NaOH aqueous solution)

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Elementary Analysis for $C_{17}H_{17}F_3N_4O_3$			
Calcd. (%)	C 53.40;	H 4.48;	N 14.65
Found (%)	C 53.28;	H 4.08;	N 14.54

^{1}H-NMR (NaOD)) δ ppm:
1.47-1.58 (1H, m), , 1.67-1.78 (2H, m), 2.07-2.11 (1H, m), 3.28-3.44 (1H; m), 3.48-3.52(1H, m), 3.60-3.66 1H, m), 3.71-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.18 (1H, s)
IR: ν_{max} cm^{-1}: 3400, 1728, 1635, 1605, 1518, 1433, 1350, 1308

EXAMPLE 8

(+)-5-Amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (18b):

[0094] Five milliliters of trifluoroacetic acid were cooled with ice, and 230 mg of 3-(S)-1-t-butoxycarbonyl-3-(t-butoxycarbonylamino)pyrrolidine were dissolved therein, followed by stirring at room temperature for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 25 ml of acetonitrile. To the solution were added 160 mg of the carboxylic acid (17b) and 400 mg of triethylamine, and the mixture was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. After washing the mixture with chloroform, the aqueous layer was adjusted to a pH of 12 with a 1N sodium hydroxide aqueous solution, followed by washing with chloroform. The aqueous layer was then adjusted to a pH of 7.6 with hydrochloric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 68 mg of the title compound (18b) as colorless crystals.
Melting Point: 214-217°C
$[\alpha]_D$: +31.3° (c=0.268, 0.1N NaOH aqueous solution)

Elementary Analysis for $C_{17}H_{17}F_3N_4O_3 \cdot 1/2H_2O$:			
Calcd. (%)	C 52.18;	H 4.64;	N 14.32
Found (%)	C 52.22;	H 4.93;	N 14.23

^{1}H-NMR (NaOD) δ ppm:
1.48-1.58 (1H, m), , 1.66-1.79 (2H, m), 2.06-2.12 (1H, m), 3.29-3.32 (1H, m), 3.48-3.52(1H, m), 3.60-3.64 (1H, m), 3.70-3.78 (2H, m), 4.92 (1H, dm, J=72Hz), 8.19 (1H, s)
IR: ν_{max} cm^{-1}: 3490, 1716, 1635, 1521, 1437, 1356, 1305

REFERENCE EXAMPLE 26

Synthesis of Optically Active 7-Amino-5-azaspiro-[2,4]heptane:

1) 5-[(1R)-Phenylethyl]-4,7-dioxo-5-azaspiro[2,4]heptane (19):

[0095] To 10.4 g of ethyl acetoacetate were added 15 g of 1,2-dibromoethane, 23 g of potassium carbonate, and 150 ml of N,N-dimethylformamide (DMF), and the mixture was stirred at room temperature for 2 days. Any insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. To the residue was added water, and the mixture was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting pale yellow oily substance was subjected to distillation under reduced pressure to obtain 7.5 g of ethyl 1-acetyl-1-cyclopropanecarboxylate having a boiling point of 70 to 71°C/2 to 3 mmHg.
^{1}H-NMR ($CDCl_3$) δ ppm:
1.30 (3H, t, J=7Hz), 1.48 (4H, s), 2.49 (3H, s), 4.24 (2H, q, J=7Hz)
[0096] In 200 ml of ethanol were dissolved 35.7 g of the above obtained compound, and 40 g of bromine were added dropwise to the solution at room temperature while stirring. After the stirring was continued at room temperature for 2 hours, the excess bromine and the solvent were removed under reduced pressure to obtain ethyl l-bromoacetyl-1-cyclopropanecarboxylate, which was then, without further purification, dissolved in 200 ml of ethanol. To the solution

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were simultaneously added dropwise 33 g of R-(+)-1-phenylethylamine and 27 g of triethylamine over a period of 1 hour while stirring under ice-cooling. After the addition, the reaction temperature was raised to room temperature, and the stirring was continued at room temperature for 2 days. Any insoluble matter was removed by filtration, and ethanol was removed from the filtrate under reduced pressure. The residue was dissolved in 300 ml of ethyl acetate, and the solution was washed successively with 1N hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution, and a saturated sodium chloride aqueous solution in this order. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to 200 g of silica gel column which was eluted with 0 to 2% methanolic chloroform to obtain the title compound (19) as colorless crystals.

Melting Point: 98-103°C

^{1}H-NMR ($CDCl_3$) δ ppm:

1.62 (3H, d, J=7.2Hz), 3.5 (1H, d, J=18Hz), 3.9 (1H, d, J=18Hz), 5.82 (1H, q, J=7.2Hz), 7.36 (5H, s)

2) 5-[(1R)-Phenylethyl]-7-hydroxyimino-4-oxo-5-azaspiro[2.4]heptane (20):

[0097] To 3.35 g of Compound (19) were added 1.6 g of hydroxylamine hydrochloride, 2.3 g of triethylamine, and 80 ml of ethanol, and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and chloroform was added to the residue. The mixture was washed successively with a 10% citric acid aqueous solution and a saturated sodium chloride aqueous solution. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain 3.5 g of the title compound (20) as colorless crystals.

Melting Point: 188-194°C

^{1}H-NMR ($CDCl_3$) δ ppm:

1.2-1.4 (2H, m), 1.53 (3H, d, J=7.2Hz & 2H, m), 3.8 (1H, d, J=18Hz), 4.16 (1H, d, J=18Hz), 5.63 (1H, q, J=7.2Hz), 7.32 (5H, s)

3) 7-Amino-4-oxo-5-[(1R)-Phenylethyl]-5-azaspiro[2.4]heptane (21a, 21b):

[0098] To 150 ml of methanol were added 3.5 g of Compound (20) and 7.5 ml of Raney nickel, and catalytic reduction was carried out at room temperature for 12 hours. After the catalyst was removed by filtration, the solvent was removed from the filtrate under reduced pressure. The residue was subjected to a 100 g silica gel column eluted with a mixed solvent of 5% methanol/chloroform which was to yield 1.0 g of the title compound (21b) from the earlier fraction and 0.8 g of the title compound (21a) from the later fraction, each as a colorless oily substance.

Compound (21b):

[0099] ^{1}H-NMR ($CDCl_3$) δ ppm:

0.8-1.4 (4H, m), 1.52 (3H, d, J=7Hz), 2.87 (1H, dd, J=10, & 3Hz), 3.3-3.9 (2H, m), 4.27 (2H, br. s), 5.42 (1H, q, J=7Rz), 7.29 (5H, s)

Compound (21a):

[0100] ^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-1.3 (4H, m), 1.40 (2H, s), 1.53 (3H, d, J=7.2Hz), 2.99 (1H, dd, J=12.8, & 7.2Hz), 3.15-3.45 (2H, m), 5.52 (1H, q, J=7.2Hz), 7.30 (5H, s)

4) 7-Amino-5-[(1R)-Phenylethyl]-5-azaspiro[2.4]heptane (22a, 22b):

[0101] To 50 ml of anhydrous tetrahydrofuran were added 1.0 g of Compound (21b) and 500 mg of lithium aluminum hydride, and the mixture was refluxed for 17 hours. After cooling, 0.5 ml of water, 0.5 ml of a 15% sodium hydroxide aqueous solution, and 1.5 ml of water were successively added to the reaction mixture in this order, followed by stirring well at room temperature for 30 minutes. Any insoluble matter was removed by filtration and thoroughly washed with tetrahydrofuran. The filtrate and the washing were combined and dried. The solvent was removed under reduced pressure to obtain 940 mg of the title compound (22b) as a pale yellow oily substance. In the same manner, 755 mg of the title compound (22a) were obtained from 800 mg of Compound (21a).

Compound (22b):

[0102] ^{1}H-NMR ($CDCl_3$) δ ppm:

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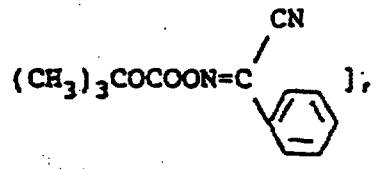
0.2-0.8 (4H, m), 1.35(3H, d,: J=6.6Hz), 1.6-2.0 (2H, br. m), 2.2-3.1 (4H, m), 3.24 (1H, q, J=6.6Hz), 3.5-3.9 (1H, m), 7.28 (5H, br. s)

Compound (22a):

[0103] ^{1}H-NMR ($CDCl_3$) δ ppm:
0.3-0.9 (4H, m), 1.36 (3H, d, J=6.7Hz), 1.8-2.2 (2H, m), 2.2-3.2 (4H, m), 3.24 (1H, q, J=6.7Hz), 3.6-3.9 (1H, m), 7.28 (5H, br. s)

5) 7-(t-Butoxycarbonylamino)-5-[(1R)-phenylethyl]-5-azaspiro[2.4]heptane (23a, 23b):

[0104] To 20 ml of anhydrous tetrahydrofuran were added 764 mg of Compound (22b) and 1.3 g of Boc-ON [Boc-ON; 2-(t-Butoxycarbonyloxyimino]-2-phenylacetonitrile



and the mixture was stirred at room temperature for 4 hours. Ethyl acetate was added to the reaction mixture, and the mixture was washed twice with a 1N sodium hydroxide aqueous solution and then once with water, followed by extraction with a 10% citric acid aqueous solution. The aqueous extract was washed once with ethyl acetate, and a 15% sodium hydroxide aqueous solution was added to the aqueous layer under cooling to make it alkaline. The mixture was extracted three times with chloroform, and the organic layer was washed with a saturated sodium chloride aqueous solution and then dried. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (silica gel: 20 g; eluent: chloroform:methanol=20:1, 10:1) to obtain 690 mg of the title compound (23b). This compound was allowed to stand to crystallize, followed by washing with n-hexane. The title compound (23a) was obtained in the same manner.

Compound (23b) (colorless crystals):

[0105] Melting Point: 103-105°C
$[\alpha]_D$: -15.2° (c=1.475, chloroform)
^{1}H-NMR ($CDCl_3$) δ ppm:
0.4-0.9 (4H, m), 1.36 (3H, d, J=7.2Hz), 1.44 (9H, s), 2.42 (2H, AB q, J=10.2 Hz), 2.79 (2H, d, J=5.6 Hz), 3.24 (1H, q, J=7.2Hz), 3.6-4.0 (1H, m), 4.6-5.1 (1H, br. d), 7.28 (5H, s)

Elementary Analysis for $C_{19}H_{26}N_2O_2$:			
Calcd. (%)	C 72.12;	H 8.92;	N 8.85
Found (%)	C 71.63;	H 9.07;	N 8.64

Compound (23a) (colorless crystals):

[0106] Melting Point: 94-97°C
$[\alpha]_D$: +47.6° (c=0.89, chloroform)
^{1}H-NMR ($CDCl_3$) δ ppm:
0.4-0.9 (4H, m), 1.33 (3H, d, J=6.6Hz), 1.40 (9H, s), 2.29 (1H, d, J=9Hz), 2.44 (1H, dd, J=10.8 & 3.6Hz), 2.77 (1H, d, J=9Hz), 2.88 (1H, dd, J=10.8 & 5.3Hz), 3.22 (1H, q, J=6.6Hz), 3.6-3.9 (1H, m), 4.7-5.2 (1H, br. d), 7.27 (5H, s)

Elementary Analysis for $C_{19}H_{26}N_2O_2$:			
Calcd. (%)	C 72.12;	H 8.92;	N 8.85
Found (%)	C 71.86;	H 9.36;	N 8.68

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6) 7-t-Butoxycarbonylamino-5-azaspiro[2.4]heptane (24a, 24b)

[0107] To 30 ml of ethanol were added 650 mg of Compound (23b) and 500 mg of 50% hydrated palladium-on-carbon, and catalytic reduction was effected under heating at a pressure of 4.2 atm. After 6 hours, the catalyst was removed by filtration, and the solvent was removed under reduced pressure. To the oily residue was added ethyl acetate, followed by extracting twice with a 10% citric acid aqueous solution. The aqueous extract was made alkaline with a 15% sodium hydroxide aqueous solution and then extracted three times with chloroform. The chloroform layer was washed with water and dried. The solvent was removed under reduced pressure to yield 440 mg of the titled compound (24b) as a crude product. The titled compound (24a) was obtained in the same manner as above. The NMR spectra of Compounds (24b) and (24a) were in complete agreement with each other.

Compound (24)

[0108] ^{1}H-NMR ($CDCl_3$) δ ppm:
0.4-1.0 (4H, m), 1.42 (9H, s), 2.71 (1H, d, J=10.2Hz), 2.92 (1H, dd, J=10.8 & 3.6 Hz), 3.01 (1H, d, J=10.2Hz), 3.33 (1H, dd, J=10.8 & 5.4 Hz), 3.5-3.9 (1H, m), 5.0-5.4 (1H, br, d)

EXAMPLE 9

7-(7-t-Butoxycarbonylamino-5-azaspiro[2.4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (25bb):

[0109] In 0.6 ml of acetonitrile were dissolved 160 mg of 8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cylopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (12b), 150 mg of the amine compound (24b), and 0.5 ml of triethylamine, and the solution was heated under reflux for 5 hours. After cooling, the precipitated colorless crystals were collected by filtration. The solvent of the mother liquor was removed under reduced pressure, and the residue was purified by silica gel preparative TLC using a developing solvent of chloroform-methanol (5:1 by volume). The purified product and the above-obtained crystals were combined to give 255 mg of the title compound (25bb).

Melting Point: 213-218°C

^{1}H-NMR ($CDCl_3$) δ ppm:
0.6-1.0 (6H, m), 1.45 (9H, s), 7.99 (1H, d, J=13.1Hz), 8.74, 8.78 (each 0.5H, s)

EXAMPLE 10

(-)-7-(7-Amino-5-azaspiro[2.4]heptan-5-yl)-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cylcopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (26bb):

[0110] To 255 mg of the Boc-compound (25bb) as obtained in Example 9 were added 0.5 ml of anisole and 10 ml of trifluoroacetic acid under ice-cooling. After warming to room temperature, the mixture was stirred for 30 minutes. The solvent was removed under reduced pressure, a 1N sodium hydroxide aqueous solution was added to the residue adjusting a pH of 11 to 12. The alkaline aqueous solution was washed twice with chloroform. The aqueous layer was adjusted to a pH of about 7 with concentrated hydrochloric acid and a 10% citric acid aqueous solution and extracted three times with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting solid was recrystallized from ethanol-concentrated aqueous ammonia to obtain 142 mg of the title compound (26bb) as colorless crystals.

Melting Point: 127-140°C (with decomposition)

$[\alpha]_D$: -199.2° (c=0.24, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl\cdot 1/4H_2O$:			
Calcd. (%)	C 55.08;	H 4.50;	N 10.14
Found (%)	C 54.86;	H 4.80;	N 10.03

EXAMPLE 11

Synthesis of Compound (26ab)

[0111] Compound (26ab) was obtained from Compound (12a) and Compound (24b) in the same manner as described

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in Examples 9 and 10.

Melting Point: 123-128°C (with decomposition)

$[\alpha]_D$: +21.5° (c=0.195, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl\cdot 1/2H_2O$:			
Calcd. (%)	C 54.49;	H 4.57;	N 10.03
Found (%)	C 54.33;	H 4.73;	N 9.81

EXAMPLE 12

Synthesis of Compound (26ba)

[0112] Compound (26ba) was synthesized from Compound (12b) and Compound (24a) in the same manner as described in Examples 9 and 10.

Melting Point: 121-127°C (with decomposition)

$[\alpha]_D$: -21.1° (c=0.275, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl\cdot 1/2H_2O$:			
Calcd. (%)	C 54.49;	H 4.57;	N 10.03
Found (%)	C 54.77;	H 4.43;	N 9.86

EXAMPLE 13

Synthesis of Compound (26aa)

[0113] Compound (26aa) was synthesized from Compound (12a) and Compound (24a) in the same manner as in Examples 9 and 10.

Melting Point: 126-145°C (with decomposition)

$[\alpha]_D$: +186.6° (c=0.228, 1N NaOH)

Elementary Analysis for $C_{19}H_{18}N_3O_3F_2Cl\cdot 3/4H_2O$			
Calcd. (%)	C 53.91;	H 4.64;	N 9.93
Found (%)	C 53.80;	H 4.47;	N 9.82

REFERENCE EXAMPLE 27

(-)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29a)

[0114] A mixture of 1 g of ethyl 2,6-dichloro-5-fluoro-nicotinoylacetate (27), 3 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 1 hour while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0115] Ten milliliters of trifluoroacetic acid were cooled with ice, and 750 mg of (+)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4a) were dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 2.0 g of triethylamine was added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, followed by stirring at room temperature for 30 minutes.

[0116] The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was subjected to column chromatography using 50 g of silica gel using chloroform as an eluent to yield 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (28a) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.06 (3H, t, J=7Hz), 1.1-1.6 (2H, m), 2.86-3.18 (1H, m), 4.05 (2H, q, J=7Hz), 4.78 (1H, dm, J=63Hz), 7.36 (1H, d, J=7Hz), 8.31 (1H, d, J=14 Hz)

[0117] In 25 ml of anhydrous dioxane were dissolved 1.29 of Compound (28a), and 300 mg of 60% sodium hydride were added to the solution, followed by stirring for 1 hour. The reaction mixture was concentrated under reduced

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pressure, and to the residue was added 0.1N hydrochloric acid. The precipitated crystals were collected by filtration and washed successively with water and diethyl ether to obtain 860 mg of the title compound (29a) as colorless crystals.

Melting Point: 184-185°C

$[\alpha]_D$: -1.26° (c=0.793, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$			
Calcd. (%)	C 51.16;	H 3.37;	N 8.52
Found (%)	C 51.12;	H 3.26;	N 8.52

^{1}H-NMR ($CDCl_3$) δ ppm:

1.41 (3H, t, J=7Hz), 1.4-1.84 (2H, m), 3.50 (1H, m), 4.40 (2H, q, J=7Hz), 5.02 (1H, dm, J=65Hz), 8.43 (1H, d, J=7Hz), 8.66 (1H, s)

REFERENCE EXAMPLE 28

(+)-Ethyl 8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (29b):

[0118] A mixture of 1.0 g of ethyl 2,6-dichloro-5-fluoronicotinoylacetate (27), 3 ml of ethyl ortho-formate, and 6 ml of acetic anhydride was heated at 120°C for 1.5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0119] Ten milliliters of trifluoroacetic acid were cooled with ice, and 750 mg of (-)-cis-1-(t-butoxycarbonylamino)-2-fluorocyclopropane (4b) were dissolved therein. The solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 30 ml of dichloromethane, and 2.0 g of triethylamine were added thereto under ice-cooling. To the suspension was further added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 30 minutes.

[0120] The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by column chromatography using 50 g of silica gel and chloroform as an eluent to obtain 1.29 g of ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (28b) as a colorless oil.

[0121] Compound (28b) (1.29 g) was reacted in the same manner as for Compound (28a) to obtain 936 mg of the title compound (29b) as colorless crystals.

Melting Point: 183-185°C

$[\alpha]_D$: +1.12° (c=1.07, chloroform)

Elementary Analysis for $C_{14}H_{11}F_2N_2O_3$			
Calcd. (%)	C 51.16;	H 3.37;	N 8.52
Found (%)	C 51.39;	H 3.24;	N 8.49

REFERENCE EXAMPLE 29

(-)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30a):

[0122] A mixture of 800 mg of Compound (29a) and 15 ml of concentrated hydrochloric acid was heated at 100°C for 1.5 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 610 mg of the title compound (30a) as colorless crystals.

Melting Point: 215-219°C

$[\alpha]_D$: -20.65° (c=0.910, chloroform)

REFERENCE EXAMPLE 30

(+)-8-chloro-7-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (30b):

[0123] A mixture of 870 mg of Compound (29b) and 20 ml of concentrated hydrochloric acid was heated at 100°C for 2 hours while stirring. Water was added to the reaction mixture, and the precipitated crystals were collected by filtration to yield 715 mg of the title compound (30b) as colorless crystals.

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Melting Point: 218-220°C
$[\alpha]_D$: +22.34° (c=0.555, chloroform)

EXAMPLE 14

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis -2 -fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (31a):

[0124] In 15 ml of trifluoroacetic acid were dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methylpyrrolidine (32) (cf. Terry Ronson, et al., J. Med. Chem., Vol. 31, p.1598 (1988)), and the solution was stirred at room temperature for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of acetonitrile, and 150 mg of Compound (30a) and 2 ml of triethylamine were added to the solution, followed by refluxing for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was adjusted to a pH of 13 with sodium hydroxide and washed with chloroform. The aqueous layer was adjusted to a pH of 7.5 and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Recrystallization of the residue from aqueous ammonia-ethanol yielded 150 mg of the title compound (31a) as colorless crystals.

Melting Point: 255-258°C
$[\alpha]_D$: -14.52° (c=0.413, 0.1N NaOH)

Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$			
Calcd. (%)	C 55.36;	H 5.06;	N 15.19
Found (%)	C 55.09;	H 5.40;	N 15.04

EXAMPLE 15

(-)-7-[3-(R)-[1-(S)-Aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (34b):

[0125] A mixture of 159 mg of (-)-8-chloro-6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (12b), 160 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine (cf. JP-A-61-311992), 400 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in chloroform. The organic solution was washed successively with a 10% citric acid aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was recrystallized from ethyl acetate-isopropyl ether to yield 220 mg of (-)-7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (33b).

Melting Point: 189-193°C
$[\alpha]_D$: -205° (c=0.985, chloroform)

Elementary Analysis for $C_{24}H_{28}ClF_2N_3O_5$			
Calcd. (%)	C 56.31;	H 5.51;	N 8.21
Found (%)	C 56.16;	H 5.48;	N 8.21

[0126] In 10 ml of trifluoroacetic acid were dissolved 200 mg of Compound (33b), and the solution was stirred for 30 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in a 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 with hydrochloric acid and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to obtain 140 mg of the title compound (34b) as colorless crystals.

Melting Point: 204-207°C
$[\alpha]_D$: -160.0° (c=0.605, 0.1N NaOH)

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Elementary Analysis for $C_{19}H_{20}ClF_2N_3O_3 \cdot H_2O$:			
Calcd. (%)	C 53.09;	H 5.38;	N 9.77
Found (%)	C 53.20;	H 5.17;	N 9.66

REFERENCE EXAMPLE 31

Ethyl 2-(3-acetoxy-2,4,5-trifluorobenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (36b):

[0127] A mixture of 1.0 g of ethyl 3-acetoxy-2,4,5-trifluorobenzoylacetate (35) (cf. JP-A-87-175485), 6 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 3 hours under stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.

[0128] In 5 ml of trifluoroacetic acid were dissolved 467 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 20 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 5 ml of a dichloromethane solution containing 500 mg of triethylamine was added dropwise thereto under ice-cooling, followed by stirring for 10 minutes. To the solution was added the above-prepared dichloromethane solution, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure to obtain 1.25 g of the title compound (36b).

REFERENCE EXAMPLE 32

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl) -8 -methoxy -4 -oxo-1,4-dihydroquinoline-3-carboxylate (37b):

[0129] In 40 ml of dioxane were dissolved 1.25 g of Compound (36b), and 440 mg of potassium carbonate and 10 ml of water were added thereto, followed by stirring at room temperature for 19 hours. The reaction mixture was neutralized with hydrochloric acid, concentrated under reduced pressure, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in 40 ml of anhydrous dioxane, and 300 mg of 60% sodium hydride and 1 ml of ethyl iodide were added thereto, followed by stirring at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated. The residue was recrystallized from isopropyl ether to obtain 235 mg of the title compound (37b) as colorless crystals.

Melting Point: 163-64°C

$[\alpha]_D$: -22.9° (c=0.490, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.40 (3H, t, J=7Hz), 1.3-1.8 (2H, m), 3.7-4.0 (1H, m), 4.10 (3H, d, J=2Hz), 4.38 (2H, q, J=7Hz), 4.85 (1H, dm, J=63Hz), 8.02 (1H, dd, J=9Hz, & 8.5Hz), 8.55 (1H, s)

Elementary Analysis for $C_{16}H_{14}F_3NO_4$			
Calcd. (%)	C 56.31;	H 4.13;	N 4.10
Found (%)	C 56.62;	H 4.18;	N 4.11

REFERENCE EXAMPLE 33-1

(±)-cis-4-Amino-1-benzyl-3-methyl-2-oxopyrrolidine (45):

[0130] A mixture of 5.13 g of ethyl 1-benzyl-3-methyl-2-oxo-3-pyrrolidinecarboxylate (42, cf. JP-A-62-4284), 40 ml of 50% ethanol, and 2 g of sodium hydroxide was stirred at room temperature for 42 hours. To the reaction mixture were added 100 ml of water, and the mixture was washed with chloroform. The aqueous layer was neutralized with hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The solvent was evaporated to obtain 3.40 g of (±)-1-benzyl-2-oxo-3-pyrrolidinecarboxylic acid (43) as colorless crystals.

[0131] Compound (43) (3.40 g), 4.45 g of diphenylphosphorylazide, 1.9 g of triethylamine, and 50 ml of t-butyl alcohol were mixed and the mixture was heated under reflux for 12 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in chloroform. The solution was washed successively with a 10% citric acid

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aqueous solution, a 2% sodium hydroxide aqueous solution, and water and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography using chloroform-methanol (97.5:2.5 by volume) as an eluent to obtain 1.76 g of (±)-cis-1-benzyl-4-t-butoxycarbonylamino-3-methyl-4-oxopyrrolidine (44) as a colorless oil.

[0132] In 15 ml of trifluoroacetic acid were dissolved 1.76 g of Compound (44). After 1 hour, the solution was concentrated under reduced pressure. To the residue were added 100 ml of water, and the mixture was washed with benzene. The aqueous layer was adjusted to a pH of 12 with sodium hydroxide and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain the title compound (45) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.25 (3H, d, J=7Hz), 1.44 (2H, s), 2.16 (1H, dt, J=7Hz), 2.83 (1H, dd, J=6.7Hz, & 8Hz), 3.14 (1H, m), 3.38 (1H, dd, J=6.7Hz, & 8Hz), 4.48 (2H, s), 7.28 (5H, s)

REFERENCE EXAMPLE 33-2

Optical Resolution of cis -4 -Amino -l -benzyl-3 -methyl -2-oxopyrrolidine (45):

[0133] In 40 ml of dichloromethane were dissolved 4.17 g of Compound (45) and 3.3 ml of pyridine, and a solution of 7.7 g of (S)-N-p-toluenesulfonylprolyl chloride in 50 ml of dichloromethane was added thereto dropwise, followed by stirring for 4 hours.

[0134] The reaction mixture was washed successively with 1N hydrochloric acid, a saturated sodium hydrogencarbonate aqueous solution, and water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate as an eluent to isolate the isomers. Each of the isomers was recrystallized from ethyl acetate to obtain 3.3 g and 3.6 g of cis-1-benzyl-3-methyl-4-[(S)-N-p-toluene-sulfonylprolylamino]-2-oxopyrrolidine (46a) and (46b), respectively.

Compound (46a):

[0135] Rf (silica gel TLC; ethyl acetate): 0.69
Melting Point: 162°C
$[\alpha]_D$: -87.3° (c=0.735, chloroform)

Compound (46b):

[0136] Rf (silica gel TLC; ethyl acetate): 0.61
Melting Point: 175-177°C
$[\alpha]_D$: -148.6° (c=0.665, chloroform)

REFERENCE EXAMPLE 33-3

(+)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methylpyrrolidine (47a):

[0137] A mixture of 3.23 g of Compound (46a) and 50 ml of concentrated hydrochloric acid was heated under reflux for 5 hours, followed by concentration under reduced pressure. To the residue was added a 1N sodium hydroxide aqueous solution, and the solution was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain 1.48 g of Compound (45a) as a colorless oil.

[0138] The product was dissolved in 10 ml of tetrahydrofuran, and the solution was added dropwise to a suspension of 2.0 g of lithium aluminum hydride in 50 ml of tetrahydrofuran. The mixture was heated under reflux for 24 hours. To the reaction mixture were added dropwise 10 ml of water under ice-cooling, and, after stirring for 30 minutes, any insoluble matter was removed by filtration. To the filtrate were added 1.92 g of Boc-ON, followed by stirring for 24 hours. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with chloroform. The extract was washed successively with a 5% sodium hydroxide aqueous solution and water, and dried over anhydrous sodium sulfate. The solvent was then evaporated.

[0139] The residue was purified by silica gel column chromatography using chloroform-methanol (1:0 to 9:1 by volume) as an eluent to obtain 1.76 g of crystals. To the product was added n-hexane, and the mixture was stirred thereby precipitating the dℓ compound. The crystals were collected by filtration, and the filtrate was concentrated. This procedure was repeated twice. One hundred milligrams of the dℓ compound was obtained from the filter cake and 1.61 g of the optically active title compound (47a) from the mother liquor.

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Melting Point: 48-52°C
$[\alpha]_D$: +27.2° (c=2.33, chloroform)
^{1}H-NMR ($CDCl_3$) δ ppm:
1.07 (3H, d, J=7Hz), 1.43 (9H, s), 1.78-2.02 (2H, m), 2.62 (2H, d, J=5Hz), 2.84-3.10 (1H, m), 3.55 (2H, s), 3.5-3.8 (1H, m), 4.8-5.2 (1H, broad), 7.23 (5H, s)

REFERENCE EXAMPLE 33-4

(-)-cis-1-Benzyl-3-t-butoxycarbonylamino-4-methylpyrrolidine (47b):

[0140] In the same manner as for the synthesis of Compound (47a) but starting with 3.52 g of Compound (46b), 1.72 g of the title compound (47b) were obtained.
Melting Point: 57-61°C
$[\alpha]_D$: -31.21°

REFERENCE EXAMPLE 33-5

cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (39a), (39b):

[0141] Compound (47a) (1.61 g), 1.5 g of 5% palladium-on-carbon, and 80 ml of ethanol were mixed, and catalytic reduction was carried out for 5 hours while irradiating the mixture with an infrared lamp in a hydrogen atmosphere at a pressure of 4 atm. After the reaction, the catalyst was removed by filtration, and the filtrate was concentrated to obtain 1.09 g of a crude product as a colorless oil. The product solidified as a carbonate on standing, which was used without purification.
[0142] In the same manner as for the synthesis of Compound (39a), 1.1 g of Compound (39b) were obtained as a colorless oil from 1.70 g of Compound (47b).

REFERENCE EXAMPLE 34

Ethyl 2-(2,4,5-trifluoro-3-methylbenzoyl)-3-(1,2-cis-2-fluoro-1-cyclopropyl)acrylate (50b):

[0143] A mixture of 710 mg of ethyl 2,4,5-trifluoro-3-methylbenzoylacetate (prepared from 2,4,5-trifluoro-3-methylbenzxoic acid (48), cf. JP-A-62-215572), 6 ml of ethyl orthoformate, and 6 ml of acetic anhydride was heated at 120°C for 2 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane.
[0144] In 5 ml of trifluoroacetic acid were dissolved 580 mg of (-)-cis-1-t-butoxycarbonylamino-2-fluorocyclopropane (4b), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was suspended in 20 ml of dichloromethane, and 700 mg of triethylamine was added thereto under ice-cooling. After stirring for 10 minutes, the above-prepared dichloromethane solution was added thereto, followed by allowing to stand overnight. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was crystallized from n-hexane to obtain 787 mg of the title compound (50b) as pale yellow crystals.

REFERENCE EXAMPLE 35

(-)-Ethyl 6,7-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (51b):

[0145] In 20 ml of anhydrous dioxane were dissolved 600 mg of Compound (50b), and a suspension of 100 mg of 60% sodium hydride having been washed with n-hexane in a small amount of anhydrous dioxane was added to the solution. The mixture was stirred at room temperature for 1 hour, and 10 ml of a 10% citric acid aqueous solution was added thereto, followed by concentration under reduced pressure. The precipitated crystals were collected by filtration, washed successively with water, a small amount of ethanol, and diethyl ether to obtain 480 mg of the title compound (51b) as colorless crystals.
Melting Point: 230-231°C
$[\alpha]_D$: -80.0° (c=0.350, chloroform)
^{1}H-NMR ($CDCl_3$) δ ppm:
1.40 (3H, t, J=7Hz), 1.1-1.7 (2H, m), 2.71 (3H, d, J=3.3Hz), 3.77-3.98 (1H, m), 4.38 (2H, q, J=7Hz), 4.85 (2H, dm, J=64Hz), 8.12 (1H, dd, J=10Hz), 8.54 (1H, d, J=3Hz)

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REFERENCE EXAMPLE 36

(-)-6,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (52b):

[0146] A mixture of 480 mg of the ester compound (51b) and 10 ml of concentrated hydrochloric acid was heated at 120°C for 75 minutes while stirring. After cooling, the precipitated crystals were collected by filtration and washed with water and ethanol to obtain 380 mg of the title compound (52b) as colorless crystals.

Melting Point: 204°C

$[\alpha]_D$: -60.0° (c=0.100, chloroform)

^{1}H-NMR ($CDCl_3$) δ ppm:

1.3-1.9 (2H, m), 2.80 (3H, d, J=5.8Hz), 4.1-4.4 (1H, m), 4.15 (1H, dm, J=64Hz), 8.17 (1H, dd, J=16Hz), 8.82 (1H, d, J=4Hz), 14.2 (1H, s)

EXAMPLE 16

(-)-6-[3-(R)-(1-(S)-Aminoethyl)-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (54b):

[0147] A mixture of 198 mg of Compound (52b), 350 mg of 3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidine, 5 ml of dimethyl sulfoxide, and 1.5 g of triethylamine was heated at 110 to 120°C for 5 hours while stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and the solution was washed with a 10% citric acid aqueous solution and then with water, and dried over anhydrous sodium sulfate. The solvent was evaporated.

[0148] The residue was subjected to preparative TLC which was developed with a mixed solvent of chloroform-methanol (95:5 by volume) to obtain 110 mg of 7-[3-(R)-[1-(S)-t-butoxycarbonylaminoethyl]pyrrolidinyl]-6,7-difluoro-8-methyl-4-dihydroquinoline-3-carboxylic acid (53b) as a pale yellow powder.

^{1}H-NMR ($CDCl_3$) δ ppm:

1.24 (3H, d, J=7Hz), 1.45 (9H, s), 1.2-1.9 (2H, m), 2.52 (3H, s), 1.9-2.7 (3H, m), 3.2-4.2 (6H, m), 4.73 (1H, d, J=8Hz), 4.98 (1H, dm, J=65Hz), 7.77 (1H, d, J=13Hz), 8.70 (1H, d, J=3.5Hz)

[0149] To 110 mg of Compound (53b) were added 5 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 10 minutes, followed by evaporation to dryness under reduced pressure. The residue was recrystallized from ethanol-diethyl ether to obtain 62 mg of the title compound (54b) as yellow crystals.

Melting Point: 149-153°C

$[\alpha]_D$: -34.4° (c=0.168, 1N HCℓ)

EXAMPLE 17

5-Amino-7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (56b):

[0150] A mixture of 100 mg of (-)-5-amino-6,7,8-trifluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-di-hydroquinoline-3-carboxylic acid (17b), 100 mg of 7-t-butoxycarbonylamino-5-azaspiro[2,4]heptane (24b), 300 mg of triethylamine, and 20 ml of acetonitrile was heated under reflux for 23 hours.

[0151] The reaction mixture was evaporated to dryness under reduced pressure, and the residue was dissolved in 100 ml of chloroform. The solution was washed successively with a 10% citric acid aqueous solution and water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from acetonitrile to obtain 120 mg of 5-amino-7-[7-t-butoxycarbonylamino-5-azaspiro[2,4]heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (55bb) as yellow needle-like crystals.

Melting Point: 250-253°C

^{1}H-NMR ($CDCl_3$) δ ppm:

0.6-0.8 (2H, m), 0.8-1.0 (2H, m), 1.45 (9H, s), 1.3-1.8 (2H, m), 3.2-3.4 (1H, m), 3.6-3.9 (3H, m), 3.9-4.3 (2H, m), 4.85 (1H, dm, J=63Hz), 4.7-5.0 (1H, broad), 8.51 (1H, s)

[0152] In 5 ml of trifluoroacetic acid were dissolved 120 mg of Compound (55bb), and the solution was stirred for 30 minutes, followed by evaporation to dryness under reduced pressure. The residue was dissolved in hydrochloric acid and the solution was washed with chloroform. The aqueous layer was adjusted to a pH of 7.4 and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was recrystallized from aqueous ammonia-ethanol to obtain 65 mg of the title compound (56bb) as yellow crystals.

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Melting Point: 213-217°C
$[\alpha]_D$: -96.7° (c=0.120, DMF)

EXAMPLE 18

7-[4-(S)-Amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphtyridine-3-carboxylic acid (31b):

[0153] In 15 ml of trifluoroacetic acid were dissolved 300 mg of 4-(S)-amino-1-t-butoxycarbonyl-2-(S)-methylpyrrolidine (32), and the solution was stirred at room temperature for 20 minutes; followed by evaporation to dryness under reduced pressure. The residue was dissolved in 20 ml of anhydrous acetonitrile, and 150 mg of Compound (30b) and 2 ml of triethylamine were added to the solution, followed by refluxing for 15 minutes. The reaction mixture was evaporated to dryness under reduced pressure, and 1N hydrochloric acid was added to the residue. The mixture was washed with chloroform. The aqueous layer was made alkaline with 1N sodium hydroxide aqueous solution and washed with chloroform. The aqueous layer was adjusted to a pH of 7 and extracted with chloroform. The organic layer was dried and the solvent was evaporated. The residue was recrystallized from aqueous ammonia-ethanol to yield 130 mg of the title compound (31b).

Melting Point: 247-255°C (with decomposition)
$[\alpha]_D$: +120° (c=0.950, 1N NaOH)

Elementary Analysis for $C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$			
Calcd. (%)	C 55.36;	H 5.06;	N 15.19
Found (%)	C 55.50;	H 5.25;	N 14.97

REFERENCE EXAMPLE 37

8,7-Difluoro-1-(1,2-cis-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid BF_2-chelate (38b):

[0154] A mixture of 230 mg of the ester compound (37b) and 5 ml of 42% borofluoric acid was heated at 110°C with stirring for 2 hours. After cooling, precipitated crystals were collected by filtration and washed with water to yield 210 mg of colorless crystals of the title compound.

Melting Point: 281-271°C

[0155] By the reaction of cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (38a) and the chelate compound (38b), 7-(cis-3-amino-4-methylpyrrolidinyl)-8-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (40ba) is obtained. And further, by the reaction of the amine compound (24b) and the chelate compound (38b), 7-(7-amino-5-azaspiro[2,4]heptan-5-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (41bb) is obtained.

Table. Antimicrobial activity (M I C, μg/ml)

bacteria \ Compound	9a	9b	13a	13b	16a	16b	26bb	26aa
E. coli., NIHJ	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Ser. marcescens, 10100	0.20	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
Ps. aeruginosa, 32104	0.39	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.39
Ps. aeruginosa, 32121	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.10
S. aureus, 209 P	0.10	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
S. epidermidis, 56500	0.39	0.39	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.20
Str. faecalis, ATCC 19433	1.57	0.79	0.20	0.20	0.20	0.10	0.20	0.39

bacteria \ Compound	26ba	26ab	31a	31b	34b	54b	56b
E. coli., NIHJ	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Pr. vulgaris, 08601	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Ser. marcescens, 10100	< 0.1	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1
Ps. aeruginosa, 32104	0.20	0.20	0.20	0.20	0.10	0.20	< 0.1
Ps. aeruginosa, 32121	0.10	< 0.1	0.20	0.10	< 0.1	0.10	< 0.1
S. aureus, 209 P	< 0.1	< 0.1	0.10	< 0.1	< 0.1	< 0.1	< 0.1
S. epidermidis, 56500	0.20	0.10	0.20	0.20	< 0.1	< 0.1	< 0.1
Str. faecalis, ATCC 19433	0.39	0.20	0.78	0.39	< 0.1	0.10	0.10

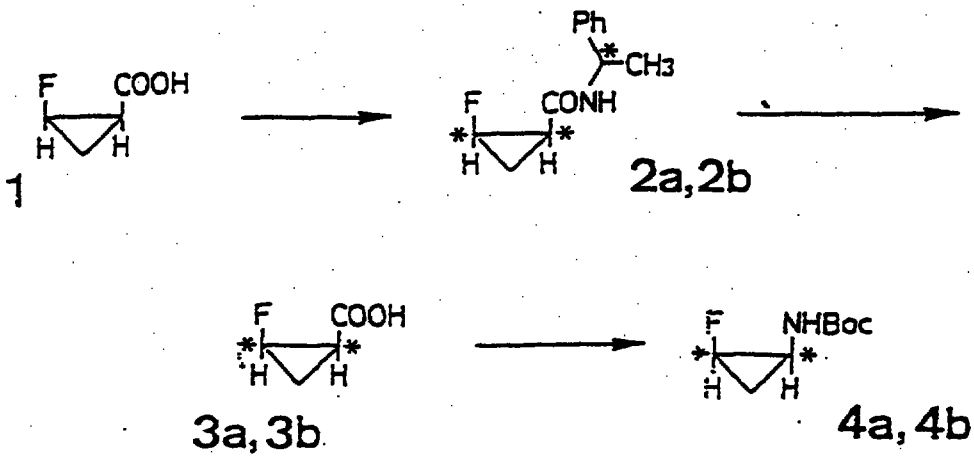
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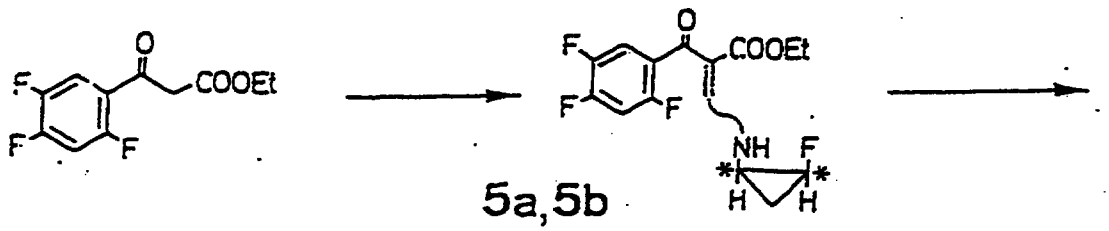
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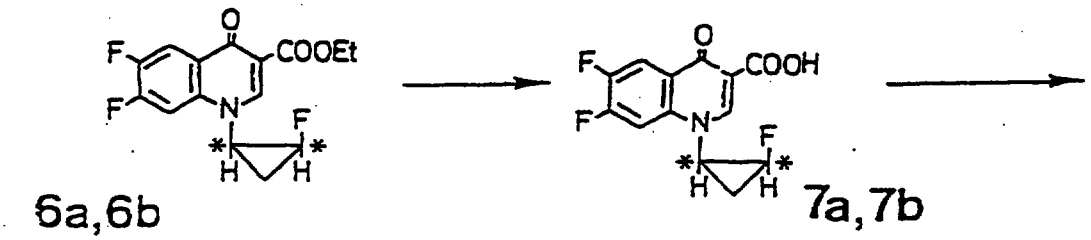
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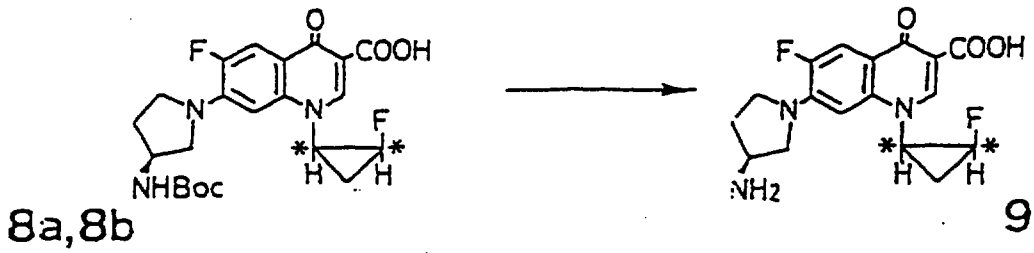
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REACTION SCHEME



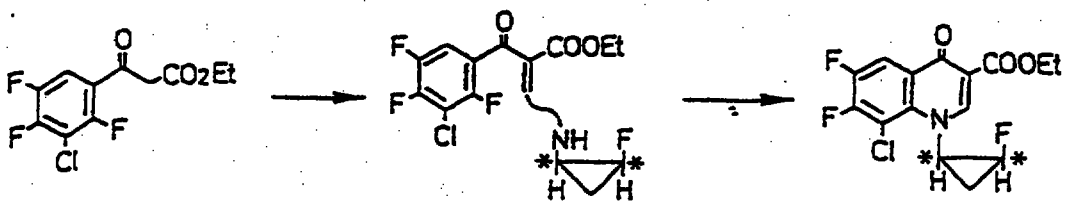




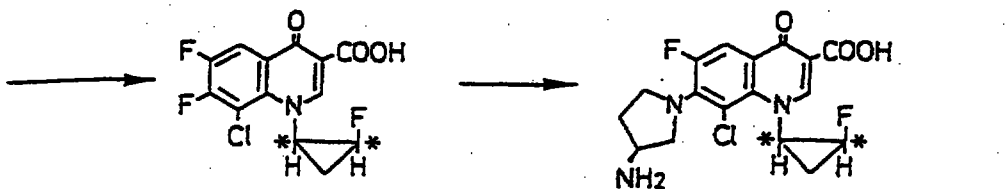


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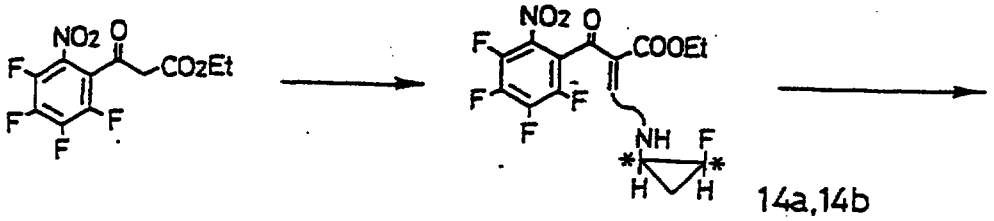
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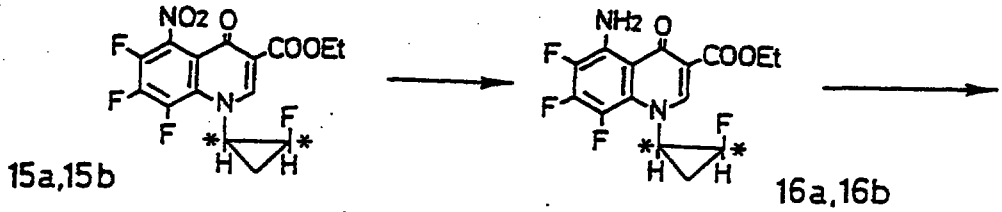
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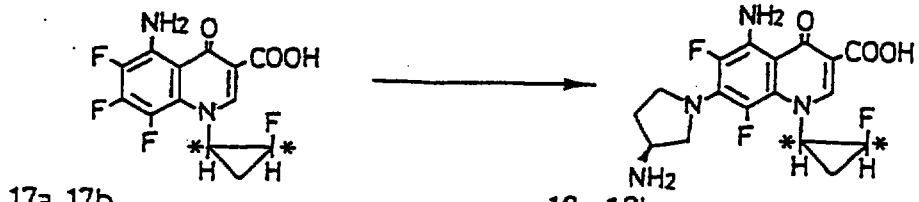
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14a,14b



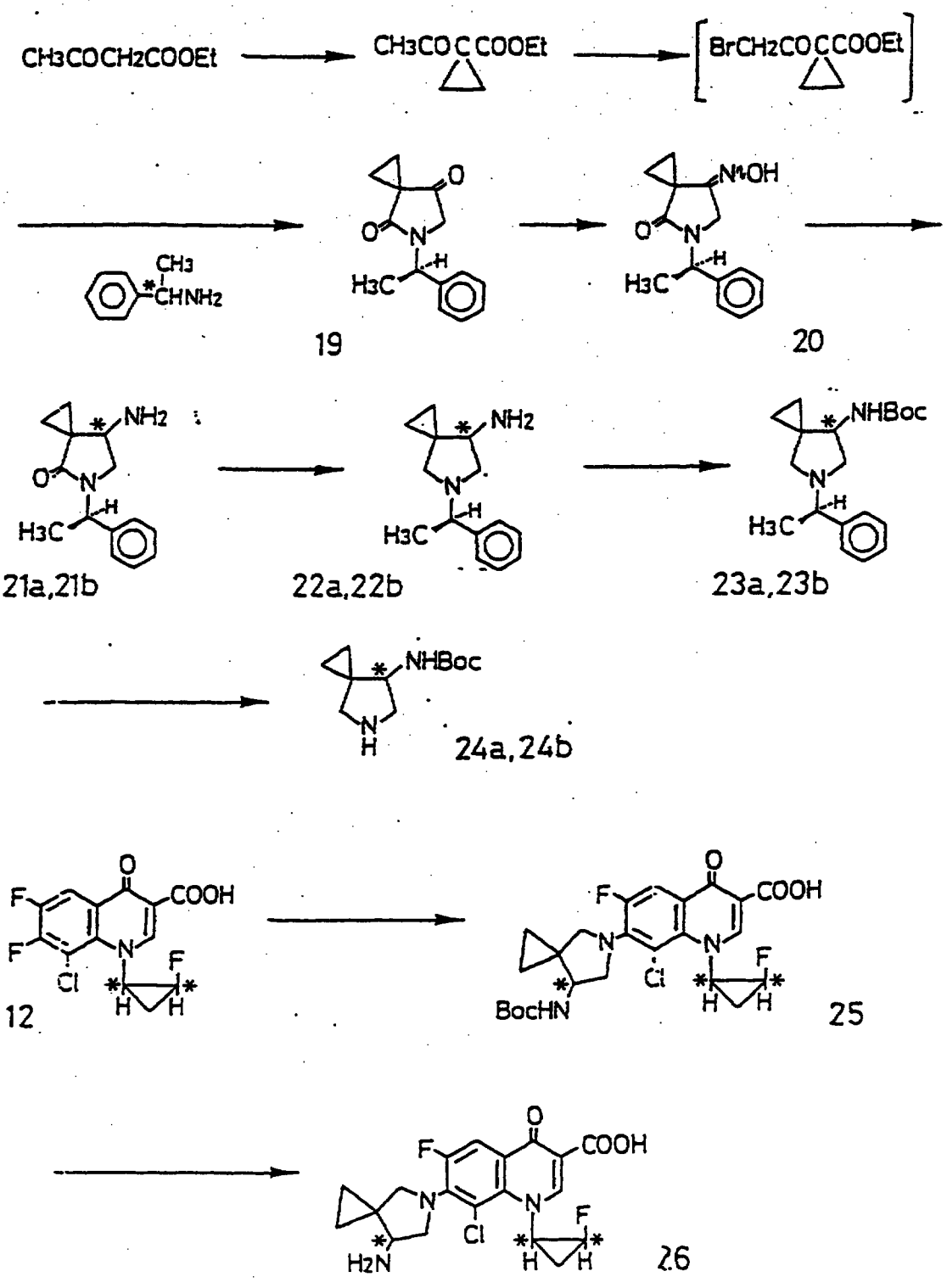
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17a,17b 18a,18b

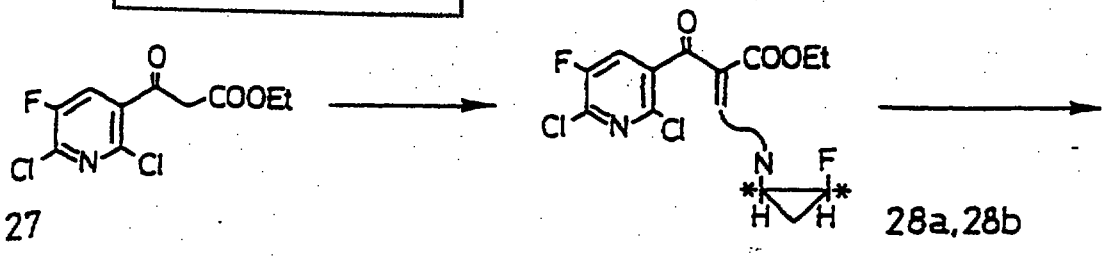
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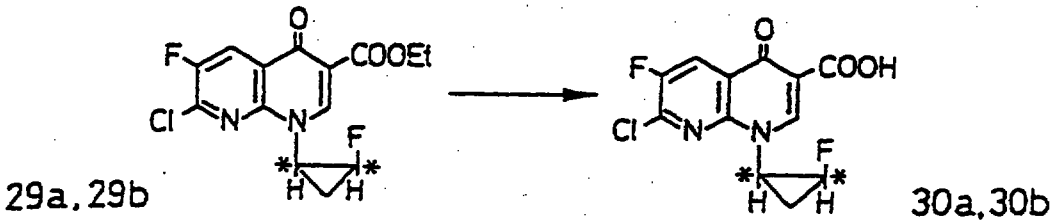


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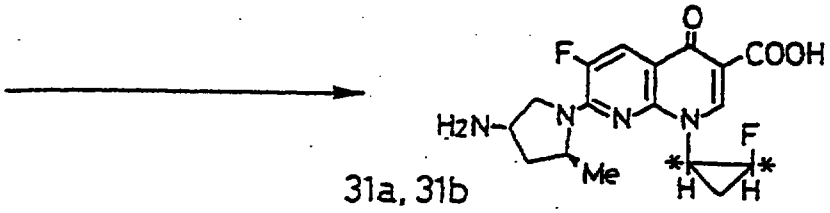
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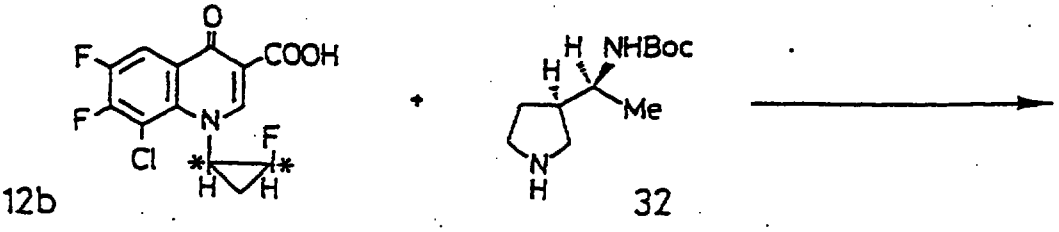
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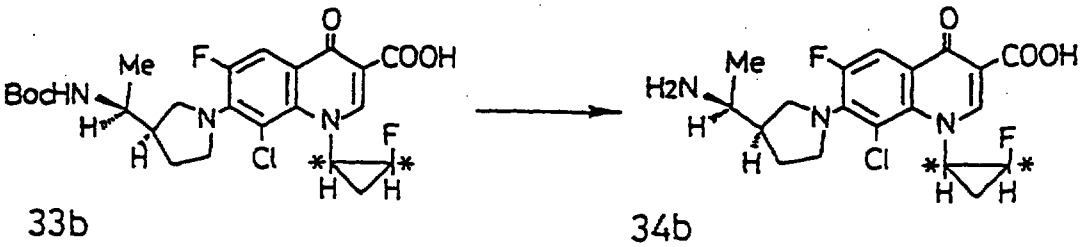
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31a, 31b



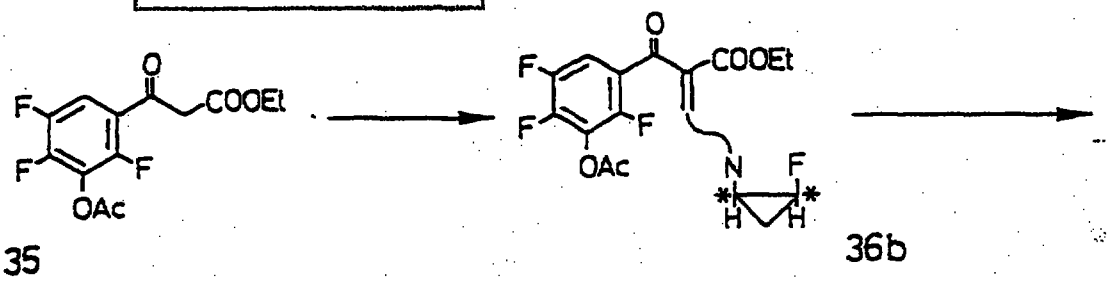
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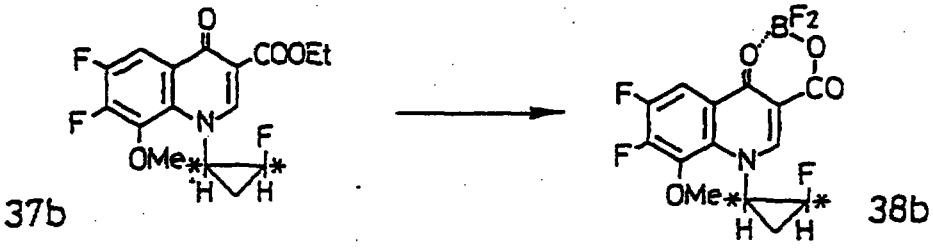
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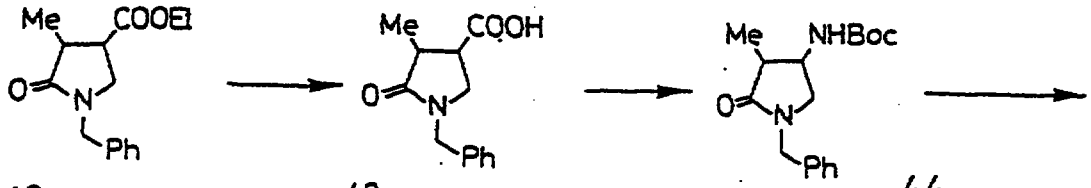
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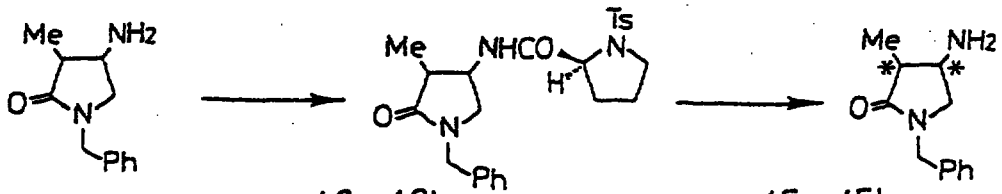
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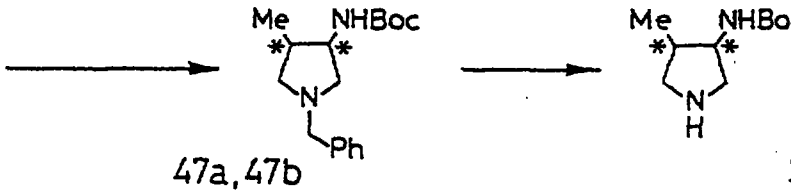
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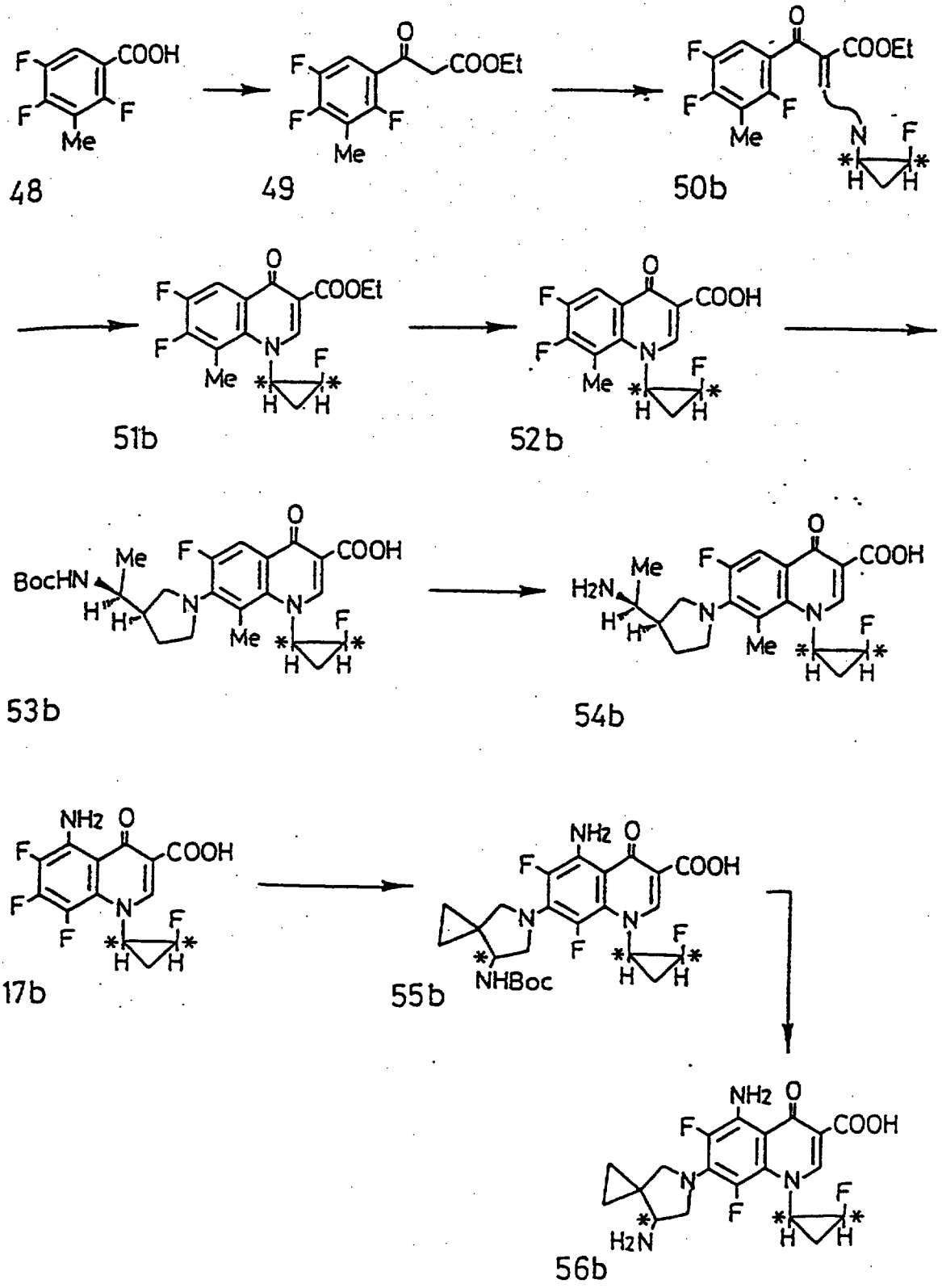


47a,47b 39a,39b

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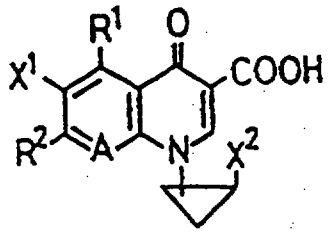
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* C L M S *

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. An N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



I

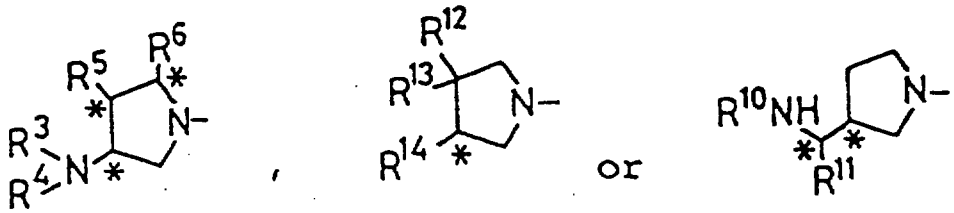
wherein R^1 represents an amino group, a methylamino group, a hydroxyl group, a thiol group, or a hydrogen atom; R^2 represents a 4-, 5- or 7-membered cyclic amino group having at least one substituent selected from a hydroxyl group, an alkyl group having from 1 to 6 carbon atoms, a polymethylene group having from 2 to 5 carbon atoms which together with the ring atom to which it is attached forms a spiro unit, an aminoalkyl group or an amino group, and which cyclic amino group may contain a bridging unit to form a bicyclic amino group and may contain at least one hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom in its ring, or R^2 represents a cyclic amino group represented by formula:



wherein R^3, R^4, R^5, R^6, R^{10}, and R^{11}, which may be the same or different, represent an alkyl group having 1 to 6 carbon atoms or a hydrogen atom; A represents C-X^3 or a nitrogen atom; X^1 and X^2, which may be the same or different, each represents a halogen atom; and X^3 represents a halogen atom, an alkyl group having from 1 to 6 carbon atoms, an alkoxyl group from 1 to 6 carbon atoms, a cyano group, a trifluoromethyl group, or a hydrogen atom, or a salt or ester thereof.

2. A compound as claimed in claim 1, wherein R^2 is a pyrrolidine, diazabicycloheptane, or a diazabicyclooctane residue; or a salt thereof.

3. A compound as claimed in claim 1, wherein R^2 represents a cyclic amino group represented by formula:



wherein R^3, R^4, R^5, R^6; R^{10}, R^{11}, which may be the same or different, each represents an alkyl group of from 1 to 6 carbon atoms or a hydrogen atom; R^{12} and R^{13}, which may be the same or different, each represents an alkyl group of from 1 to 6 carbon atoms or a hydrogen atom, or they may be connected to each other to form a polymethylene chain of 2 to 5 carbon atoms; R^{14} represents an amino group or a hydroxy; or a pharmaceutically acceptable salt thereof, optionally in a stereoisomerically pure form.

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4. A compound as claimed in any one of claims 1 to 3, wherein R^2 is a cyclic amino group derived from a cyclic amine comprising a single stereoisomer: or a salt thereof.

5. A compound as claimed in claim 4, wherein R^2 is a 3-aminopyrrolidinyl group; or a salt thereof.

6. A compound as claimed in claim 5, wherein R^2 is a 7-amino-5-azaspiro[2.4]heptan-5-yl group: or a salt thereof.

7. A compound as claimed in anyone of claims 1 to 6, wherein X^2 is a fluorine atom.

8. A compound as claimed in claim 1, which is

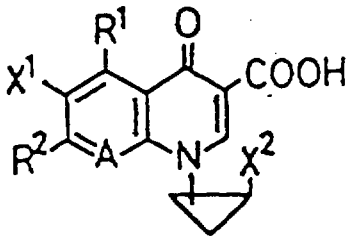
7-[3-(S)-amino-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
7-[3-(S)-amino-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
5-amino-7-[3-(S)-amino-1-pyrrolidinyl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid;
7-[3-(R)-[1-(S)-aminoethyl]-1-pyrrolidinyl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
7-[3-amino-4-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid;
7-[4-(S)-amino-2-(S)-methyl-1-pyrrolidinyl]-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid; or
5-amino-7-[7-amino-5-azaspiro[2.4]heptan-5-yl]-6,8-difluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid; or a salt thereof.

9. A compound as claimed in anyone of claims 1 to 8, wherein said compound is a single stereoisomer; or a salt thereof.

10. A compound as claimed in claim 1, which is
7-[7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-(1,2-cis-2-fluorocyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid; or a single stereoisomer thereof; or a salt thereof.

11. An antibacterial composition comprising, as an active ingredient, at least one N1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I) or a single stereoisomer thereof or a salt thereof as claimed in any one of claims 1 to 10.

12. A process for preparing a N_1-(1,2-cis-2-halogenocyclopropyl)-substituted pyridonecarboxylic acid derivative represented by formula (I):



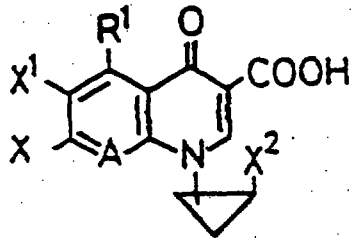
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as defined in any one of claims 1 to 10, which comprises reacting 7-halogeno-1-(1,2-cis-2-halogenocyclopropyl)-pyridonecarboxylic acid of the following formula:

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wherein R^1, X^1, X^2 and A are as defined above, and X represents a halogen atom, or an ester thereof with a cyclic amine compound of R^2-H which may be protected by a conventional protective group, wherein R^2 is as defined above, and the protective group is removed by a conventional method, if desired, and the ester residue is removed under acidic or alkaline conditions, if desired.

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OPTICALLY ACTIVE PYRIDONECARBOXYLIC ACID DERIVATIVES

ABSTRACT OF THE DISCLOSURE

N_1-(1,2-cis-2-halogenocydopropyl)-substituted pyridonecarboxylic acid derivatives represented by formula (I) and the salts thereof are disclosed. These compounds have patent antibacterial activities against a wide variety of infectious bacteria, and are useful as antibacterial agents by oral or parenteral administration.