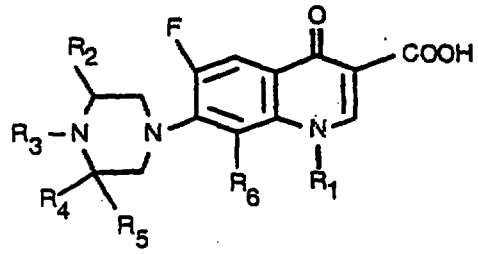
Description

Field of the Invention

The present invention relates to novel 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivatives which have an excellent antibacterial effect, and their pharmacologically acceptable salts and process for preparing the same.

More particularly, the present invention relates to novel 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivatives represented by the general formula (I),

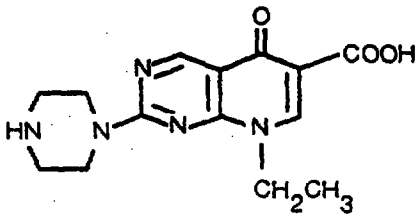


(I)

wherein R_1 is a lower alkyl group having 1 to 4 carbon atoms, a vinyl group, a 2-fluoroethyl group or a 2-hydroxyethyl group; R_2, R_3 and R_4 each is a hydrogen atom or a lower alkyl group having each 1 to 4 carbon atoms; R_5 is a lower alkyl group having 1 to 4 carbon atoms and R_6 is a hydrogen atom or a fluorine atom, and their pharmacologically acceptable salt and process for preparing the same.

Field of the Invention

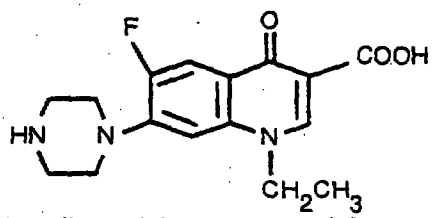
So far, as antibacterial medicines, those of pyridone carboxylic acids have been widely used. For example, nalidixic acid, piromidic acid, pipemidic acid and cinoxacine have been marketed for the clinical treatment of urinary tract infection, intestinal infection and cholangia infection. The most effective and widely used antibacterial among these is pipemidic acid (The Merck Index, 10th Edition, 7332) represented by the following formula (II):



(II)

Recently, norfloxacin (The Merck Index, 10th Edition, 6541) was synthesized to improve the antibacterial effect of pipe-midic acid and to expand its antibacterial spectrum. It has the chemical formula (III) as shown below and used for the clinical treatment of infections impetigo, phlegmon, subcutaneous abscess or tonsillitis.

EP—A—0 106 489 discloses among other things fluoroquinoline-3-carboxylic acid derivatives as antibacterial agents and a process for preparing same. Disclosed are also quinoline carboxylic acid derivatives that are substituted in their C-7 position with various N-alkylamines as 7-[3-(aminomethyl)-1-piperidinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.



(III)

However, such marketed antibacterials were unsatisfactory as they had to be applied in large quantities so that their continuous and long-term administration could cause adverse side-effects for example, gastrointestinal function disorder.

Summary of the Invention

The present inventors studied therefore for finding out a more effective antibacterial and discovered that the compounds represented by the above-mentioned general formula (I) are more effective as an antibacterial medicine compared with pipemidic acid (II) and norfloxacin (III) and excellent in its rate of urinary excretion as well as in its low toxicity.

The present invention is based on this finding.

Detailed Description of the Invention

In this invention the lower alkyl group represented by R_1—R_5 in the general formula (I) includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl groups, especially methyl and ethyl groups.

Pharmacologically acceptable salts of the compound having the said general formula (I) are acid addition salts or alkali addition salts. The former includes mineral acid salts such as hydrocloride, sulfate, nitrate, hydrobromide, hydroiodide, phosphate, etc.; or organic acid salts such as acetate, maleate, fumarate, citrate, or tartrate, etc. The latter includes inorganic alkali salts such as sodium, potassium, calcium or ammonium salt, etc.; or organic base salts such as ethanolamine salt or N,N-dialkyl ethanolamine salt, etc.

Non-limiting examples of the compounds of this invention include.

(1). 1-Ethyl-6, 8-difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

(2). 1-Ethyl-6, 8-difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

(3). 1-Ethyl-6-fluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

(4). 6-Fluoro-1-(2-fluoroethyl)-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

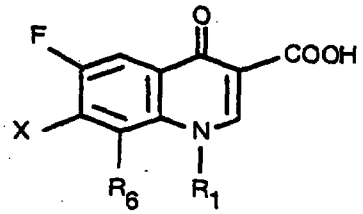
(5. 6, 8-Difluoro-1-(2-fluoroethyl)-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

(6). 6, 8-Difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-1-vinylquinoline-3-carboxylic acid.

(7). 6, 8-Difluoro-1, 4-dihydro-1-methyl-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

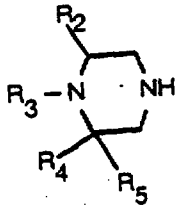
According to the present invention the novel compounds, 6-fluro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acids, represented by the general formula (I) can be prepared by various methods.

In the first method, the compound having the said formula (I) is obtained by reacting a 6-fluoro-7-halogeno-1, 4-dihy-dro-4-oxoquinoline-3-carboxylic acid having the following general formula (IV),



(IV)

wherein R_1 and R_6 each has the same meaning as that described above, while X is a chlorine atom or a fluorine atom, with a piperazine derivative represented by the following general formula (V),



(V)

wherein R_2, R_3, R_4 and R_5 each has the same meaning as that described above, in the presence or absence of a solvent.

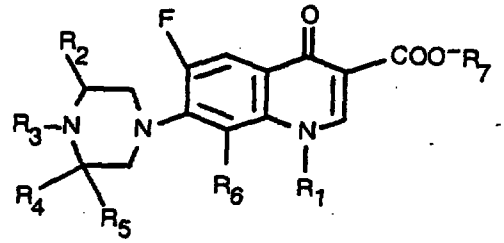
The solvent used in the process of this invention is, for example, water, alcohols such as butanol, 3-methoxy butanol or isoamyl alcohol; ethers such as ethylene glycol dimethyl ether (monoglyme), diethylene glycol dimethyl ether (diglyme), triethylene glycol dimethyl ether (triglyme); aprotic polar solvents such as dimethyl formamide, dimethyl sulfoxide or hexamethyl phosphoric triamide; aromatic hydrocarbons such as benzene or toluene; or organic bases such as pyridine, picoline, lutidine, collidine or triethyl-amine.

The above mentioned reaction is to be carried out within the temperature range from room temperature to 200°C, preferably from 100 to 180°C.

The starting material of this method, a 6-fluoro-7-halogeno-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid having the general formula (IV), is, for instance, those already disclosed in Japanese Patent Publication (unexamined) No. 141286/1978, Japanese Patent Publication (unexamined) No. 47658/1980 and Japanese Patent Publication (unexamined) No. 30964/1981.

The piperazine derivative having the general formula (V) are also known substances and are disclosed in, for example, U.S. Patent No. 2,780,625 and South Africa Patent No. 6,807,552.

According to the second method, the inventive compound represented by the general formula (I) is prepared by hydrolyzing a 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid ester derivative represented by the following general formula (VI),



(VI)

wherein R_1, R_2, R_3, R_4, R_5 and R_6 each has the same meaning as that described above and R_7 is a lower alkyl group having 1 to 4 carbon atoms.

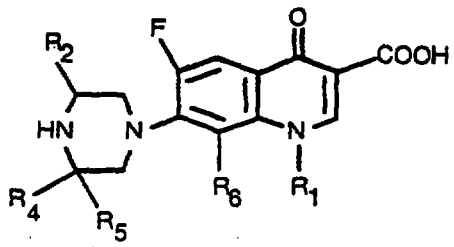
The hydrolysis is carried out according to the known method using an acid such as hydrochloric acid or sulfuric acid; or an alkali such as sodium hydroxide or potassium hydroxide.

These acids or alkalis can be used for the hydrolysis in the form of aqueous solutions, ethanol or methanol solutions or solutions of aqueous organic solvents.

The reaction is to be carried out at a temperature within the range from the room temperature to the reflux temperature of the solvent used.

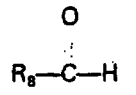
The starting materials of the said method, a 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid ester derivatives are novel substances and a method for their preparation is described in the following examples for reference.

In the third method of the present invention, the compound represented by the general formula (I) is prepared by alkylating a 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinyl-quinoline-3-carboxylic acid derivative having the following general formula (VII),



(VII)

wherein R_1, R_2, R_4, R_5 and R_6 each has the same meaning as that described above. This formula is the same as the said formula (I) except that R_3 is replaced with a hydrogen atom. The above derivative may be reacted with a carbonyl compound represented by the following general formula (VIII),



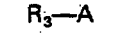
(VIII)

wherein R_8 is a hydrogen atom or a lower alkyl group having 1 through 3 carbon atoms, in the presence of formic acid.

Examples of the carbonyl compound having the general formula (VIII) are formaldehyde, acetaldehyde and propionaldehyde. Formaldehyde is used preferably in the form of its aqueous solution (formalin). In case of acetaldehyde or propionaldehyde, it is desirable to use nitrobenzene as a solvent for the reaction.

The reaction is carried out at a temperature within the range of 100 to 200°C, preferably at the reflux temperature of the reaction solvent used.

Alternatively the 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivatives having the general formula (VII) may be reacted with an alkyl halogenide represented by the general formula (IX).



(IX)

wherein R_3 has the same meaning as that described above and A is a halogen atom, in a solvent in the presence or absence of a base as an acid-binding agent.

The solvent used in this reaction can be any kind so far it does not inhibit the reaction. The examples are acetone, ethanol, ether, tetrahydrofuran, dimethylformamide, dioxane, benzene, toluene or chloroform.

As an acid-binding agent that can be used in the present invention is, for example, triethylamine, pyridine or potassium carbonate.

The reaction is carried out at a temperature within the range from the room temperature to the reflux temperature of the solvent used, preferably at 50 to 100°C.

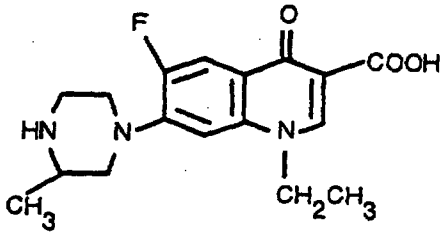
The novel compound, a 6-fluoro-1, 4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivatives represented by the general formula (I) and its pharmacologically acceptable salt, that are obtained according to the methods described so far, have an antibacterial effect against both gram-positive and gram-negative microorganisms and are very useful as medicines.

The effect of antimicrobiological activity, antibacterial spectrum and urinary excretion are shown in Table 1 and 2 respectively as examples for representing the potentating pharmacological effect of the inventive compounds.

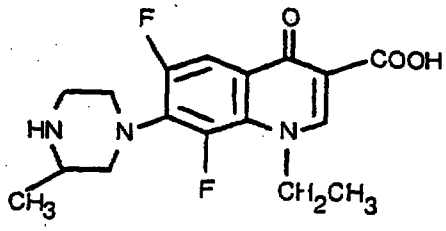
The acute toxicity has been determined as shown in Table 3, whereby as a reference drug, norfloxacin, market product represented by formula (III), is used.

Test Compounds:

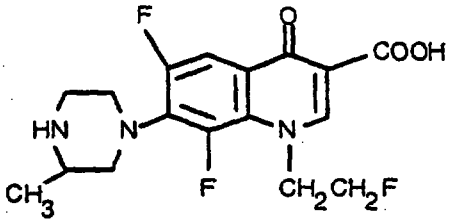
Compound of Invention (Example 1)



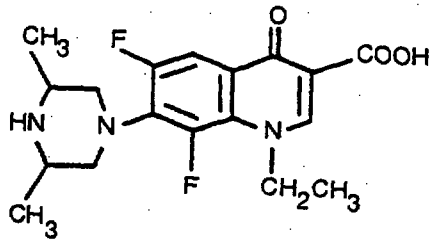
Compound of Invention (Example 4)



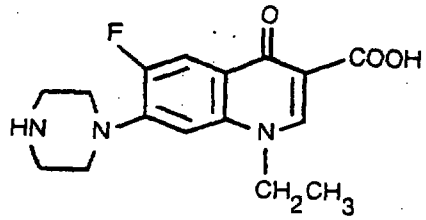
Compound of Invention (Example 16)



Compound of Invention (Example 20)



Reference Drug (norfloxacin)



1. Antibacterial Spectrum

Experiment:

Minimum inhibitory concentrations (MIC) were determined by the twofold agar dilution method (Chemotherapy, *29*(1), 76(1981)). Over night cultures in Mueller-Hinton broth were suspended by buffered saline gelatine. One loopful of the bacterial suspension (10^6 or 10^8 colony-forming units/ml) was inocubated onto the test compound containing plates. The plates were incubated for 18hrs. at 37°C. The MIC was the lowest concentration of the drug that inhibited visible growth. The results are shown in Table 1.

TABLE 1

Antibacterial Spectrum (Minimum concentration causing growth inhibition, μg/ml. 10^6 cells/ml)

Bacteria	Gram	Example 1	Example 4 *	Example 16	Example 20	Ref. Drug
Bacillus subtilis ATCC6633	+	0.10	0.10	0.30	0.20	0.10
Micrococcus luteus ATCC9341	+	25	6.25	6.25	12.5	6.25
Staphylococcus aureus FAD209PJC-1	+	0.20	0.39	0.39	0.78	0.20
Staphylococcus aureus Terajima	+	0.39	0.78	0.78	1.56	0.39
Staphylococcus aureus MS-353	+	0.39	0.78	1.56	1.56	6.25
Streptococcus pyogenes Cook	+	3.13	3.13	3.13	6.25	1.56
Escherichia coli NIHJ-JC-2	−	0.10	0.05	0.10	0.39	0.05
Escherichia coli K-12 C600	−	0.10	0.05	0.20	0.20	0.05
Klebsiella pneumoniae PCI-602	−	0.025	0.0125	0.025	0.20	0.025
Salmonella typhimurium IID971	−	0.10	0.05	0.20	0.20	0.05
Salmonella typhi 901	−	0.05	0.0125	0.10	0.10	0.025
Salmonella paratyphi 1015	−	0.0125	0.025	0.05	0.10	0.025
Salmonella schottmulleri 8006	−	0.025	0.025	0.10	0.10	0.025
Salmonella enteritidis G14	−	0.10	0.05	0.20	0.39	0.05
Serratia marcescens IAM1184	−	0.20	0.10	0.20	0.78	0.10
Pseudomonas aeruginosa ATCC9027	−	0.10	0.05	0.10	0.20	0.05
Pseudomonas aeruginosa IFO3445	−	0.78	0.78	0.78	3.13	0.78
Pseudomonas aeruginosa NCTC10490	−	0.39	0.78	0.39	0.78	0.78
Pseudomonas aeruginosa PAOL	−	0.78	1.56	1.56	3.13	0.39
Proteus morganii IFO3848	−	0.025	0.025	0.05	0.20	0.025
Proteus mirabilis IFO3849	−	0.39	0.20	0.39	1.56	0.10
Proteus vulgaris OX-19	−	0.05	0.05	0.20	0.10	0.05
Proteux vulgarix HX-19	−	0.025	0.025	0.05	0.20	0.025
Proteus rettgeri IFO3850	−	0.10	0.05	0.20	0.39	0.05
Enterobacter aerogenes ATCC13048	−	0.10	0.10	0.20	0.20	0.10
Enterobacter cloaceae 963	−	0.10	0.10	0.20	0.20	0.05

* Free.

2. Urinary Excretion

Experiment:

Male rats of SD strain, weighing 180-210g, were used at 8 animals at a group. Test compounds suspended in 0.5% carboxymethyl cellulose were administered per os to 24 hr-fasted rats at dose of 20mg/Kg. Urine was pooled from 0 to 6hrs. and 6 to 24hrs, and urinary excretion was measured by bioassay using Escherichia coli NIHJ-JC-2. The results are shown in Table 2.

Bioassay:

The assay method employed was the cup-plate method using Escherichia coli NIHJ-JC-2. Urine was appropriately diluted with 1/15M phosphate buffer pH 7.0, before assay if necessary. Standard calibration lines were made in 1/15M phosphate buffer pH 7.0.

TABLE 2
Urinary Excretion

Drug	Drug Concentration in Urine (μg/ml)		Rate of Urinary Excretion(%)
	0—6	6—24 (hr)	0—24 (hr)
Example 1	514	28	30
Example 4*	659	87	75
Example 16	344	46	41
Reference Drug	63	9	10

* Free.

3. Acute Toxicity

Experiment:

Male mice of ddY strain, 4 weeks old, were used at 10 animals at a group. Test compounds suspended in 0.5% carboxymethyl cellulose were administered per os(p.o.) in mice. In the case of intravenous (i.v.) administration, test compounds were solved in 0.1N-HCl solution and neutralized with 0.1N-NaOH solution. LD_{50} was determined by the Probit method from dead animals with 10 days. The results are shown in Table 3.

TABLE 3
Acute Toxicity

Drug	LD_{50} (mg/kg)	
	p.o.	i.v.
Example 1	>4000	348.5 (326.6—372.0)*1
Example 4*2	>4000	245.6 (223.7—269.6)
Reference Drug	>4000	229.5 (211.1—252.7)

*1 ( ) = 95% Confidence Limit

*2 Free.

It is clearly seen from the results above that the compounds of this invention exhibit potent effect of urinary excretion and excellent lower toxicity as compared to reference drug.

Further, the antibacterial spectrum shows that the compounds of the invention exhibit approximately the same activity as the reference drug.

Therefore, it is clear that the compounds of the invention are very useful as medicines for clinical usage because of their superior pharmaceutical effects, such as excellent absorption, and lower toxity.

Thus, the present compounds are much safer than traditionally marketed medicines and are considered to be highly useful as a clinical medicines.

Necessary amount for treatment : Normally, a total of 150—1000 mg is to be orally administered by dividing the amount into 2-4 doses per day per adult.

This preparation of the compounds of the invention is further explained hereinbelow with the help of examples, which are given by way of illustration only and are not to be considered as limiting.

Example 1

1-Ethyl-6-fluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 15.00 g of 7-chloro-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid, 16.70 g of 2-methylpiperazine and 70 ml of pyridine was heated for 14 hours under reflux. The solvent of the reaction mixture was evaporated and the residue was acidified with 50% aqueous acetic acid. The solution was treated with activated carbon and neutralized with 20% aqueous sodium hydroxide. Then, the solution was again treated with activated carbon, and concentrated. The precipitate was filtered and dissolved in ethanol. The solution was acidified with ethanolic hydrogen chloride and concentrated. The precipitate was filtered and recrystallized from aqueous ethanol to give 8.19g of hydrochloride of the title compound as pale yellow needles, M.p. >300°C.

Analysis for $C_{17}H_{20}FN_3O_3 \cdot HCl$
Calculated %: C, 55.21 H, 5.72; N, 11.36
Found %: C, 55.13; H, 5.72; N, 11.17

Example 2

7-(3,4-Dimethyl-1-piperazinyl)-1-ethyl-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid

A mixture of 2.69 g of 1-ethyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride, 5.4 ml 90% formic acid, 3.5 ml of 37% formalin and 0.70 g of potassium carbonate was heated for 5 hours under reflux. The reaction mixture was neutralized with 20% aqueous sodium hydroxide. The precipitate was filtered and recrystallized from a mixture of chloroform and methanol to give 1.70g of the title compound as colorless needles, M.p. 244—246°C.

Analysis for $C_{18}H_{22}FN_3O_3$
Calculated %: C, 62.24; H, 6.38; N, 12.10
Found %: C, 62.02; H, 6.37; N, 12.05

Example 3

1-Ethyl-7-(4-ethyl-3-methyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid

A solution of 1.00 g of 1-ethyl-6-fluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride, 1.29 g of ethyl iodide and 1.09 g of triethylamine in 20 ml of N,N-dimethylformamide was heated at 70 to 80°C for 1.5 hours. The solvent of the reaction mixture was evaporated and the residue was acidified with 50% aqueous acetic acid. The solution was neutralized with 20% aqueous sodium hydroxide and the precipitate was filtered. The precipitate was chromatographed on silica gel using chloroform-methanol (9:1) as eluent to give 0.47 g of the title compound as colorless crystals, which were recrystallized from a mixture of chloroform and methanol as colorless needles, M.p. 203—205°C.

Analysis for $C_{19}H_{24}FN_3O_3$
Calculated %: C, 63.14; H, 6.69; N, 11.63
Found %: C, 62.82; H, 6.78; N, 11.66

Example 4

1-Ethyl-6,8-difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 1.00 g of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 1.10 g of 2-methylpiperazine and 10 ml of pyridine was heated for 15 minutes under reflux. The reaction mixture was evaporated and methanol was added to the residue. The precipitate was filtered and recrystallized from ethanol to give 0.36 g of the title compound as colorless needles, M.p. 239—240.5°C.

Analysis for $C_{17}H_{19}F_2N_3O_3$
Calculated %: C, 58.11; H, 5.45; N, 11.96
Found %: C, 57.98; H, 5.47; N, 12.18

In the usual manner the hydrochloride was prepared and recrystallized from water as colorless needles, M.p. 290—300°C (decom.).

Analysis for $C_{17}H_{19}F_2N_3O_3 \cdot HCl$
Calculated %: C, 52.65; H, 5.20; N, 10.84
Found %: C, 52.78; H, 5.32; N, 10.65

Example 5

7-(3,4-Dimethyl-1-piperazinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

A mixture of 1.40 g of 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid, 2.8 ml of 90% formic acid and 2.2 ml of 37% formalin was heated for 4 hours under reflux. The reaction mixture was evaporated and the residue was dissolved in water. The solution was neutralized

with aqueous sodium bicarbonate. The precipitate was filtered and recrystallized from ethanol to give 0.32 g of the title compound as colorless needles, M.p. 211.5—212°C.

Analysis for $C_{18}H_{21}F_2N_3O_3$
Calculated %: C, 59.17; H, 5.79; N, 11.50
Found %: C, 59.29; H, 5.87; N, 11.55

Example 6

1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

a) To a solution of 0.55 g of ethyl 1-ethyl-6, 8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylate in 5.5 ml of ethanol 11 ml of 18% hydrochloric acid were added and the mixture was heated for 4 hours under reflux. The precipitate was filtered and washed with ethanol and ether. Recrystallization from water gave 0.43 g of hydrochloride of the title compound as colorless needles. The NMR and IR spectra of this compound were identical with those of the compound prepared in example 4.

b) Ethyl 1-ethyl-6, 8-difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylate used above was prepared as follow.

A mixture of 1.50 g of ethyl 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate, 1.50 g of 2-methylpiperazine and 5 ml of pyridine was heated for 3 hours under reflux. The solvent of the reaction mixture was evaporated and the residue was dissolved in chloroform. The solution was washed with water, dried and evaporated. The residue was recrystallized from a mixture of benzene and isopropyl ether to give 1.00 g of the title compound as colorless needles, M.p. 126.5—127.5°C.

Analysis for $C_{19}H_{23}F_2N_3O_3$
Calculated %: C, 60.15; H, 6.11; N, 11.08
Found %: C, 60.30; H, 6.34; N, 10.84

Example 7

6,8-Difluoro-1,4-dihydro-1-isopropyl-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

a) A mixture of 0.68 g of 6,7,8-trifluoro-1,4-dihydro-1-isopropyl-4-oxoquinoline-3-carboxylic acid, 0.72 g of 2-methyl piperazine and 10 ml of pyridine was treated in the same manner as that described in example 4 to give 0.42 g of the title compound as colorless crystals. M.p. 217—218°C.

Analysis for $C_{18}H_{21}F_2N_3O_3 \cdot 1/2H_2O$
Calculated %: C, 57.75; H, 5.92; N, 11.22
Found %: C, 57.53; H, 5.97; N, 11.13

b) 6,7,8-Trifluoro-1,4-dihydro-1-isopropyl-4-oxoquinoline-3-carboxylic acid used above was prepared as follows.

7.70 g of sodium borohydride were added to a mixture of 3.70 g of 2,3,4-trifluoroaniline, 10.30 g of sodium acetate, 20 ml of acetone, 19.6 ml of acetic acid and 39 ml of water under stirring and ice-cooling. After 2 hours, the reaction mixture was made alkaline with sodium carbonate and extracted with benzene. The extract was washed with NaCl saturated water and dried and the solvent was evaporated to give 3.17 g of 2,3,4-trifluoro-N-isopropyl aniline as a colorless oil.

IR ν_{max}^{film} cm^{-1}: 3450 (NH)

A mixture of 2.50 g of 2,3,4-trifluoro-N-isopropylaniline and 2.80 g of diethyl 2-ethoxymethylenemalonate was heated for 1 hour at 160—170°C. Hexane was added to the reaction mixture which was then cooled. The crystals were filtered to give 2.45 g of diethyl 2-(2,3,4-trifluoro-N-isopropylanilino) methylene malonate, which was recrystallized from hexane as colorless needles, M.p. 92.5—93°C.

Analysis for $C_{17}H_{20}F_3NO_4$
Calculated %: C, 56.82; H, 5.61; N, 3.90
Found %: C, 56.83; H, 5.67; N, 3.91

A mixture of 9.00 g of diethyl 2-(2,3,4-trifluoro-N-isopropylanilino)methylenemalonate and 90.0 g of polyphosphoric acid was heated for 1 hour at 80—85°C under stirring. The reaction mixture was poured to ice-water and extracted with chloroform. The extract was washed with water and dried and the solvent was evaporated. A mixture of 90 ml of 18% hydrochloric acid and 45 ml of ethanol was added to the residue and the mixture was refluxed for 1.5 hours.

The precipitate was filtered and washed with ethanol to give 1.40 g of the title compound, which was recrystallized from a mixture of chloroform and ethanol as pale brown needles, M.p. 261—262.5°C.

Analysis for $C_{17}H_{10}F_3NO_3$
Calculated %: C, 54.74; H, 3.53; N, 4.91
Found %: C, 54.64; H, 3.47; N, 4.93

Example 8

(R)-(+)-1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 2.00 g of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 1.50 g of (R)-(−)-2-methylpiperazine ($[\alpha]_D^{21°}$ −6.4° (c=1, ethanol)) and 15 ml of pyridine was heated for 15 minutes under

reflux. After completion of the reaction, the solvent was evaporated and the residue was dissolved in 10% hydrochloric acid. The solution was neutralized with aqueous sodium bicarbonate. The precipitate was filtered, dried and dissolved in a mixture of chloroform and methanol. The solution was acidified with ethanolic hydrogen chloride. The precipitate was filtered and dissolved in water. The solution was neutralized with aqueous sodium bicarbonate and the precipitate was filtered to give 1.72 g of the title compound, which was recrystallized from a mixture of chloroform and ethanol as colorless needles, M.p. 244.5—245.5°C, $[\alpha]_D^{21°}$ +39.5° (c=1, chloroform).

Analysis for $C_{17}H_{19}F_2N_3O_3$

Calculated %: C, 58.11 H, 5.45; N, 11.96

Found %: C, 58.12; H, 5.72; N, 12.07

Example 9

6-Fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 1.50 g of 7-chloro-6-fluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 1.60 g of 2-methylpiperazine and 8 ml of pyridine was heated for 11 hours under reflux. The solvent of the reaction mixture was evaporated and the residue was dissolved in hot water. After cooling of the solution, the precipitate was filtered and recrystallized from ethanol to give 0.62 g of the title compound as colorless needles, M.p. 226—227°C.

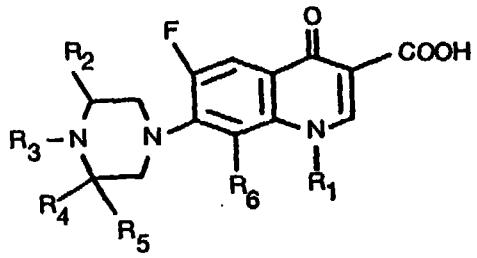
Analysis for $C_{17}H_{19}F_2N_3O_3$

Calculated %: C, 58.11 H, 5.45; N, 11.96

Found %: C, 58.14; H, 5.80; N, 11.61

According to the same manner as described in the examples 1 to 9, the compounds of the examples 10 to 29 below were prepared.

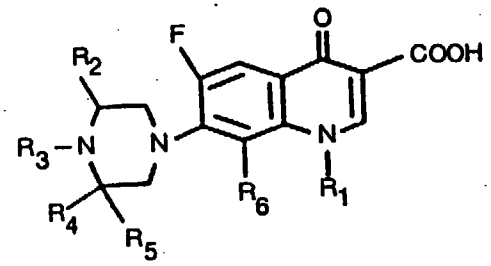
TABLE 4



(I)

Example No.	Structure Date R_1	R_2	R_3	R_4	R_5	R_6	Crystal	m.p.	(solvent)
10*1	Et	H	H	H	Et	H	colorless crystals	>300°	(H_2O-acetone)
11	Et	H	Me	H	Et	H	colorless needles	213—215°	($CHCl_3$-MeOH)
12*1	Me	H	H	H	Me	H	colorless needles	>300°	(H_2O-EtOH)
13	Me	H	H	H	Me	F	colorless scales	249—250°	($CHCl_3$-EtOH)
14*2	Et	H	H	H	Me	F	colorless needles	242.5—243.5°	($CHCl_3$-EtOH)
15	—$CH=CH_2$	H	H	H	Me	F	pale yellow crystals	245—255° (decompn.)	(H_2O)
16	—$(CH_2)_2F$	H	H	H	Me	F	colorless needles	262—263°	($CHCl_3$-EtOH)
17*1	—$(CH_2)_2OH$	H	H	H	Me	H	colorless needles	295—298° (decompn.)	(H_2O-EtOH)
18	—$(CH_2)_2OH$	H	Me	H	Me	H	colorless needles	258—260° (decompn.)	($CHCl_3$-MeOH)

TABLE 4 (continued)



(I)

Example No.	R_1	Structure Date R_2	R_3	R_4	R_5	R_6	Crystal	m.p.	(solvent)
19*1	Et	Me	H	H	Me	H	colorless crystals	>300°	(MeOH)
20	Et	Me	H	H	Me	F	colorless crystals	233—234°	($CHCl_3$-EtOH)
21	Et	H	H	Me	Me	H	colorless crystals	208.5—209.5°	(EtOH)
22	Et	H	H	Me	Me	F	pale yellow needles	207—208°	(EtOH)
23	Et	Me	Me	H	Me	F	colorless needles	216—217°	(EtOH)
24	Me	H	Me	H	Me	H	colorless needles	262—263°	(CH_2Cl_2-EtOH)
25	Pr	H	H	H	Me	H	pale yellow crystals	163—164°	(EtOH-C_5H_6)
26	Pr	H	Me	H	Me	H	pale yellow needles	157—158°	(C_6H_6-hexane)
27	iPr	H	Me	H	Me	F	pale yellow needles	190.5—191.5°	(C_6H_6-hexane)
28	Pr	H	H	H	Me	F	pale yellow needles	211—212°	($CHCl_3$-EtOH)
29	Pr	H	Me	H	Me	F	pale yellow scales	186.5—187.5°	(EtOH)

*1 Hydrochloride
*2 (S)-(−)-, $(\alpha)_D^{20}$ −34.1° (C=1, $CHCL_3$)

Example No.	Formula	Analysis Calculated C;	Calculated H;	Calculated N;	Found C;	Found H;	Found N;
10*1	$C_{18}H_{22}FN_3O_3 \cdot HCl$	56.32	6.04	10.95	56.10	6.01	10.89
11	$C_{19}H_{24}FN_3O_3$	63.14	6.69	11.63	63.11	7.01	11.54
12*1	$C_{16}H_{18}FN_3O_3 \cdot HCl \cdot 1/4H_2O$	53.34	5.45	11.66	53.31	5.75	11.56
13	$C_{16}H_{17}F_2N_3O_3$	56.98	5.08	12.46	56.86	5.36	12.17
14*2	$C_{17}H_{19}F_2N_3O_3$	58.11	5.45	11.96	58.01	5.64	11.77
15	$C_{17}H_{17}F_2N_3O_3 \cdot 1/2H_2O$	56.98	5.06	11.73	57.04	5.18	11.46
16	$C_{17}H_{18}F_3N_3O_3$	55.28	4.91	11.38	55.10	5.02	11.41
17*1	$C_{17}H_{20}FN_3O_4 \cdot HCl$	52.92	5.49	10.89	52.57	5.72	10.72
18	$C_{18}H_{22}FN_3O_4$	59.40	6.10	11.56	59.14	6.39	11.49
19*1	$C_{18}H_{22}FN_3O_3 \cdot HCl$	56.32	6.04	10.95	56.05	6.27	10.84
20	$C_{18}H_{21}F_2N_3O_3$	59.17	5.79	11.50	59.23	5.95	11.49
21	$C_{18}H_{22}FN_3O_3$	62.23	6.38	12.10	62.10	6.62	11.86
22	—	—	—	—	—	—	—
23	$C_{19}H_{23}F_2N_3O_3$	60.15	6.11	11.08	60.09	6.49	11.09
24	$C_{17}H_{20}FN_3O_3$	61.25	6.05	12.60	60.94	6.38	12.51
25	$C_{18}H_{22}FN_3O_3 \cdot 1/4H_2O$	61.43	6.44	11.94	61.20	6.58	11.73
26	$C_{19}H_{24}FN_3O_3$	63.14	6.69	11.63	62.98	6.98	11.61
27	$C_{19}H_{23}F_2N_3O_3$	60.15	6.11	11.08	60.00	6.35	11.13
28	$H_{18}H_{21}F_2N_3O_3$	59.17	5.79	11.50	58.86	6.14	11.38
29	$H_{19}H_{23}F_2N_3O_3$	60.15	6.11	11.08	59.85	6.31	10.92

Example 30

7-(3,4-Dimethyl-1-piperazinyl)-6,8-dihydro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylic acid

A mixture of 700 mg of 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylic acid, 930 mg of 1,2-dimethylpiperazine and 5 ml of pyridine was heated for 20 minutes under reflux. The reaction mixture was evaporated and the residue was dissolved in a mixture of chloroform and methanol. The solution was acidified with ethanolic hydrogen chloride. Then the precipitate was filtered and dissolved in water. The solution was neutralized with sodium bicarbonate and extracted with chloroform. The extract was washed with water, dried and evaporated. Methanol was added to the residue and the precipitate was filtered to give 730 mg of the desired compound, which was recrystallized from a mixture of chloroform and ethanol as colorless needles, M.p. 231—232.5°C.

Analysis for $C_{17}H_{19}F_2N_3O_3$

Calculated %: C, 58.11 H, 5.45; N, 11.96

Found %: C, 58.13; H, 5.54; N, 11.99

The following compounds were obtained in the same manner as that described in Example 30.

Example 31

7-(3,4-Dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-1-vinylquinoline-3-carboxylic acid

Yellow needles, M.p. 178—179°C (EtOH).

Analysis for $C_{18}H_{19}F_2N_3O_3$

Calculated %: C, 59.50 H, 5.27; N, 11.56

Found %: C, 59.20; H, 5.57; N, 11.58

Example 32

7-(3,4-Dimethyl-1-piperazinyl)-6-fluoro-1-(2-fluoroethyl)-1,4-oxoquinoline-3-carboxylic acid

Pale yellow needles, M.p. 238.5—239.5°C ($CHCl_3$-EtOH).

Analysis for $C_{18}H_{21}F_2N_3O_3$

Calculated %: C, 59.17 H, 5.79; N, 11.50

Found %: C, 58.99; H, 5.97; N, 11.49

Example 33

7-(3,4-Dimethyl-1-piperazinyl)-6,8-difluoro-1-(2-fluoroethyl)1,4-dihydro-4-oxoquinoline-3-carboxylic acid

Colorless scales, M.p. 224.5—225°C ($CHCl_3$-EtOH).

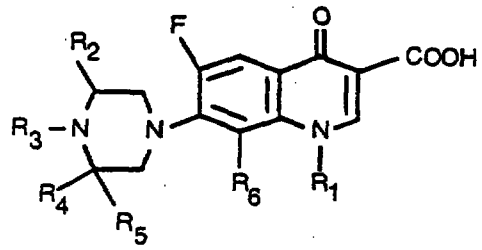
Analysis for $C_{18}H_{20}F_3N_3O_3$

Calculated %: C, 56.39 H, 5.26; N, 10.96

Found %: C, 56.41; H, 5.38; N, 10.98

Claims for the Contracting States: BE CH GB IT LI NL SE

1. A 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivative represented by the general formula (I)



(I)

wherein R_1 is a lower alkyl group having 1 to 4 carbon atoms, a vinyl group, a 2-fluoroethyl group or a 2-hydroxy-ethyl group; R_2, R_3 and R_4 each is a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; R_5 is a lower alkyl group having 1 to 4 carbon atoms and R_6 is a hydrogen atom or a fluorine atom and a pharmacologically acceptable salt thereof.

2. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

3. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

4. 1-Ethyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

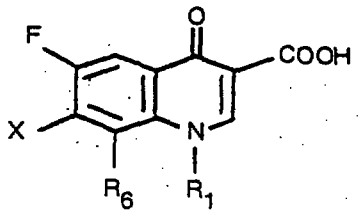
5. 6-Fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

6. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

7. 6,8-Difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-1-vinylquinoline-3-carboxylic acid.

8. 6,8-Difluoro-1,4-dihydro-1-methyl-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

9. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises reacting 6-fluoro-7-halogeno-1,4-dihydro-4-oxoquinoline-3-carboxylic acid represented by the general formula,



(IV)

wherein R_1 and R_6 each has the same meanings as that described above and X is a chlorine atom or a fluorine atom, with a piperazine derivative represented by the following formula,

Example 31

7-(3,4-Dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-1-vinylquinoline-3-carboxylic acid
Yellow needles, M.p. 178—179°C (EtOH).
Analysis for $C_{18}H_{19}F_2N_3O_3$
Calculated %: C, 59.50 H, 5.27; N, 11.56
Found %: C, 59.20; H, 5.57; N, 11.58

Example 32

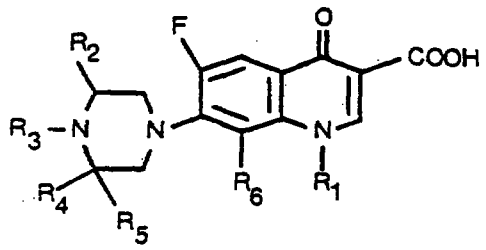
7-(3,4-Dimethyl-1-piperazinyl)-6-fluoro-1-(2-fluoroethyl)-1,4-oxoquinoline-3-carboxylic acid
Pale yellow needles, M.p. 238.5—239.5°C ($CHCl_3$-EtOH).
Analysis for $C_{18}H_{21}F_2N_3O_3$
Calculated %: C, 59.17 H, 5.79; N, 11.50
Found %: C, 58.99; H, 5.97; N, 11.49

Example 33

7-(3,4-Dimethyl-1-piperazinyl)-6,8-difluoro-1-(2-fluoroethyl)1,4-dihydro-4-oxoquinoline-3-carboxylic acid
Colorless scales, M.p. 224.5—225°C ($CHCl_3$-EtOH).
Analysis for $C_{18}H_{20}F_3N_3O_3$
Calculated %: C, 56.39 H, 5.26; N, 10.96
Found %: C, 56.41; H, 5.38; N, 10.98

Claims for the Contracting States: BE CH GB IT LI NL SE

1. A 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivative represented by the general formula (I)



(I)

wherein R_1 is a lower alkyl group having 1 to 4 carbon atoms, a vinyl group, a 2-fluoroethyl group or a 2-hydroxy-ethyl group; R_2, R_3 and R_4 each is a hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; R_5 is a lower alkyl group having 1 to 4 carbon atoms and R_6 is a hydrogen atom or a fluorine atom and a pharmacologically acceptable salt thereof.

2. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

3. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

4. 1-Ethyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

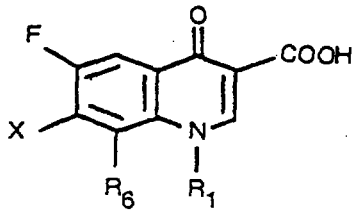
5. 6-Fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

6. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

7. 6,8-Difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-1-vinylquinoline-3-carboxylic acid.

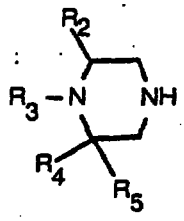
8. 6,8-Difluoro-1,4-dihydro-1-methyl-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid.

9. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises reacting 6-fluoro-7-halogeno-1,4-dihydro-4-oxoquinoline-3-carboxylic acid represented by the general formula,



(IV)

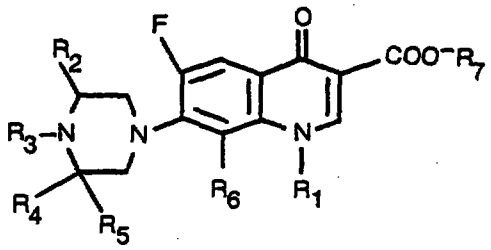
wherein R_1 and R_5 each has the same meanings as that described above and X is a chlorine atom or a fluorine atom, with a piperazine derivative represented by the following formula,



(V)

wherein R_2, R_3, R_4 and R_5 each has the same meanings as that described above.

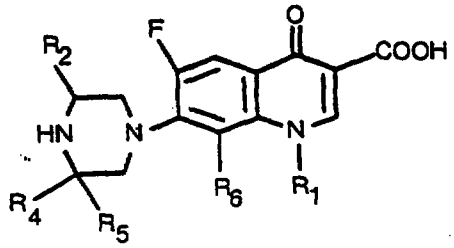
10. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises hydrolysing 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid ester derivative represented by the general formula,



(VI)

wherein R_1, R_2, R_3, R_4, R_5 and R_6 each has the same meanings as that described in claim 1 and R_7 is a lower alkyl group having 1 to 4 carbon atoms, with a hydrolysing agent.

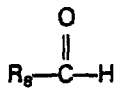
11. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises alkylating a 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinyl-quinoline-3-carboxylic acid derivative represented by the general formula,



(VII)

wherein R_1, R_2, R_4, R_5 and R_6 each has the same meanings as that described in claim 1 with an alkylating agent.

12. A process according to claim 11 wherein a carbonyl compound represented by the general formula,



wherein R_8 is a hydrogen atom or a lower alkyl group having 1 to 3 carbon atoms is used for alkylation in the presence of formic acid,

13. A process according to claim 11 wherein an alkyl halogenide represented by the general formula,

$$R_3—A$$

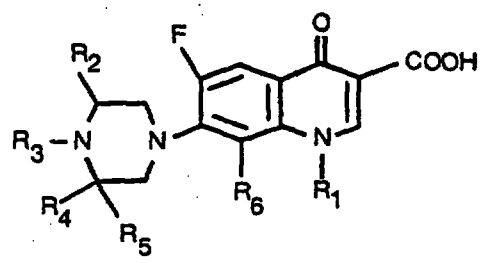
wherein R_3 is a lower alkyl group having 1 to 4 carbon atoms and A is a halogen atoms is used as an alkylating agent, in a solvent and in the presence or absence of a base.

14. Pharmaceutical compositions for use in the treatment of bacterial desease, comprising an effective amount of one or more compounds as claimed in claims 1—8, together which compatible, pharmaceutical by-acceptable carrier or coating.

* C L M S *

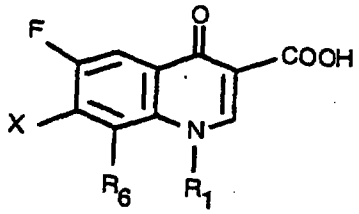
Claims for the Contracting State: AT

1. A process for preparing a 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivative represented by the general formula (I) and a pharmacologically acceptable salt thereof,



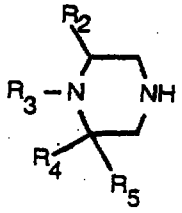
(I)

wherein R_1 is a lower alkyl group having 1 to 4 carbon atoms, a vinyl group, a 2-fluoroethyl group or a 2-hydroxyethyl group; R_2, R_3 and R_4 each is a hydrogen atom or a lower alkyl group having each 1 to 4 carbon atoms; R_5 is a lower alkyl group having 1 to 4 carbon atoms and R_6 is a hydrogen atom or a fluorine atom, which comprises reacting 6-fluoro-7-halogeno-1,4-dihydro-4-oxoquinoline-3-carboxylic acid represented by the general formula,



(IV)

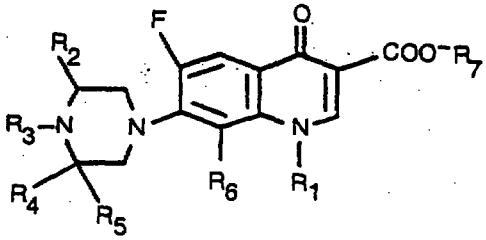
wherein R_1 and R_6 each has the same meanings as that described above and X is a chlorine atom or a fluorine atom, with a piperazine derivative represented by the following formula,



(V)

wherein R_2, R_3, R_4 and R_5 each has the same meanings as that described above.

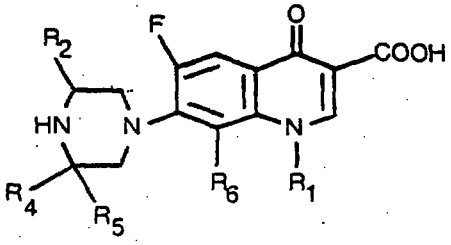
2. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises hydrolysing 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid ester derivative represented by the general formula,



(VI)

wherein R_1, R_2, R_3, R_4, R_5 and R_6 each has the same meanings as that described in claim 1 and R_7 is a lower alkyl group having 1 to 4 carbon atoms, with a hydrolysing agent.

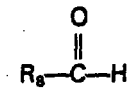
3. A process for preparing the compound of claim 1 represented by the general formula (I) and a pharmacologically acceptable salt thereof, which comprises alkylating a 6-fluoro-1,4-dihydro-4-oxo-7-substituted piperazinylquinoline-3-carboxylic acid derivative represented by the general formula,



(VII)

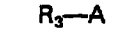
wherein R_1, R_2, R_4, R_5 and R_6 each has the same meanings as that described above, with an alkylating agent.

4. A process according to claim 3 wherein a carbonyl compound represented by the general formula,



wherein R_8 is a hydrogen atom or a lower alkyl group having 1 to 3 carbon atoms is used for alkylation in the presence of formic acid.

5. A process according to claim 3 wherein an alkyl halogenide represented by the general formula,

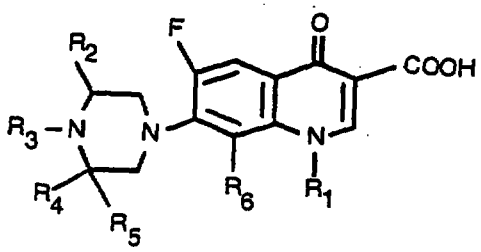


wherein R_3 is a lower alkyl group having 1 to 4 carbon atoms and A is a halogen atoms is used as an alkylating agent, in a solvent and in the presence or absence of a base.

6. A process for the preparation of pharmaceutical compositions for use in the treatment of bacterial desease, comprising an effective amount of one or more compounds obtainable by the processes as claimed in claims 1—5, together which compatible, pharmaceutical by-acceptable carrier or coating.

Patentansprüche für die Vertragsstaaten: BE CH GB IT LI NL SE

1. 6-Fluoro-1,4-dihydro-4-oxo-7-substituiertes Piperazinyl-chinolin-3-carbonsäure-Derivat der allgemeinen Formel (I)



(I)

in der R_1 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen, eine Vinyl-Gruppe, eine 2-Fluoroethyl-Gruppe oder eine 2-Hydroxyethyl-Gruppe ist, R_2, R_3 und R_4 jeweils ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen sind, R_5 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist und R_6 ein Wasserstoff-Atom oder ein Fluor-Atom ist, und deren pharmakologisch unbedenkliche Salze.

2. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure.

3. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure-hydrochlorid.

4. 1-Ethyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure-hydrochlorid.

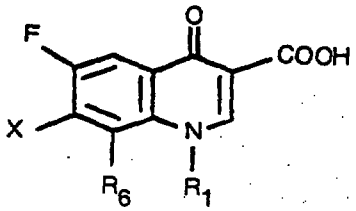
5. 6-Fluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure.

6. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure.

7. 6,8-Difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-1-vinylchinolin-3-carbonsäure.

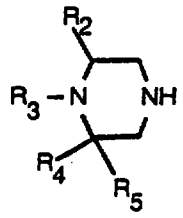
8. 6,8-Difluoro-1,4-dihydro-1-methyl-7-(3-methyl-1-piperazinyl)-4-oxochinolin-3-carbonsäure.

9. Verfahren zur Herstellung der Verbindung nach Anspruch 1 der allgemeinen Formel (I) und deren pharmakologisch unbedenklicher Salze dadurch gekennzeichnet, daß 6-Fluoro-7-halogeno-1,4-dihydro-4-oxo-chinolin-3-carbonsäure der allgemeinen Formel



(IV)

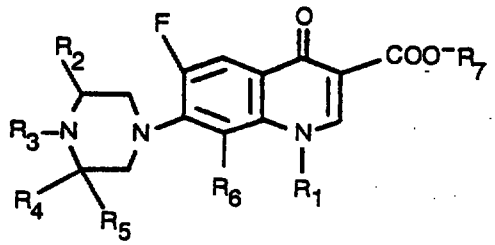
in der R_1 und R_6 jeweils die oben angegebenen Bedeutengen haben und X ein Chlor-Atom oder ein Fluor-Atom ist, mit einem Piperazin-Derivat der allgemeinen Formel



(V)

in der R_2, R_3, R_4 und R_5 jeweils die oben angegebenen Bedeutungen haben, umgesetzt wird.

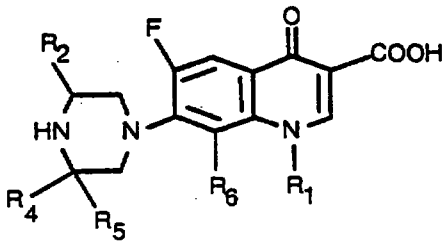
10. Verfahren zur Herstellung der Verbindung nach Anspruch 1 der allgemeinen Formel (I) und deren pharmakologisch unbedenklicher Salze dadurch gekennzeichnet, daß ein 6-Fluoro-1,4-dihydro-4-oxo-7-substituiertes Piperazinyl-chinolin-3-carbonsäure-ester-Derivat der allgemeinen Formel



(VI)

in der R_1, R_2, R_3, R_4, R_5 und R_6 jeweils die oben angegebenen Bedeutungen haben und R_7 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist, mit Hilfe eines hydrolysierenden Mittels hydrolysiert wird.

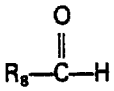
11. Verfahren zur Herstellung der Verbindung nach Anspruch 1 der allgemeinen Formel (I) und deren pharmakologisch unbedenklicher Salze dadurch gekennzeichnet, daß ein 6-Fluoro-1,4-dihydro-4-oxo-7-substituiertes Piperazinyl-chinolin-3-carbonsäure-Derivat der allgemeinen Formel



(VII)

in der R_1, R_2, R_4, R_5 und R_6 jeweils die oben angegebenen Bedeutungen haben, mit Hilfe eines Alkylierungsmittels alkyliert wird.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß eine Carbonyl-Verbindung der allgemeinen Formel



in der R_8 ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe mit 1 bis 3 Kohlenstoff-Atomen ist, zur Alkylierung in Gegenwart von Ameisensäure verwendet wird.

13. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß ein Alkylhalogenid der allgemeinen Formel

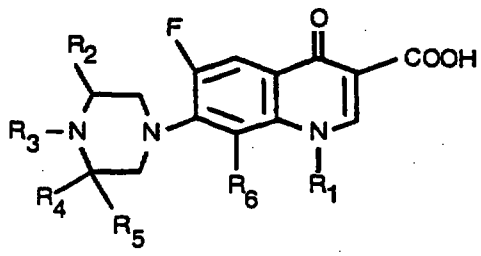
$$R_3—A$$

in der R_3 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist und A ein Halogen-Atom ist, als Alkylierungsmittel verwendet wird.

14. Pharmazeutische Zusammensetzungen zur Verwendung bei der Behandlung bakterieller Erkrankungen, enthaltend eine wirksame Menge einer oder mehrerer Verbindungen nach Anspruch 1 bis 8 zusammen mit einem verträglichen, pharmazeutische unbedenklichen Träger oder Überzug.

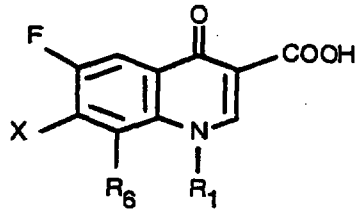
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines 6-Fluoro-1,4-dihydro-4-oxo-7-substituierten Piperazinyl-chinolin-3-carbonsäure-Derivats der allgemeinen Formel (I)



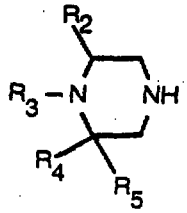
(I)

in der R_1 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen, eine Vinyl-Gruppe, eine 2-Fluoroethyl-Gruppe oder eine 2-Hydroxyethyl-Gruppe ist, R_2, R_3 und R_4 jeweils ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen sind, R_5 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist und R_6 ein Wasserstoff-Atom oder ein Fluor-Atom ist, und der pharmakologisch unbedenkliche Salze desselben, 6-Fluoro-7-halogeno-1,4-dihydro-4-oxo-chinolin-3-carbonsäure der allgemeinen Formel



(IV)

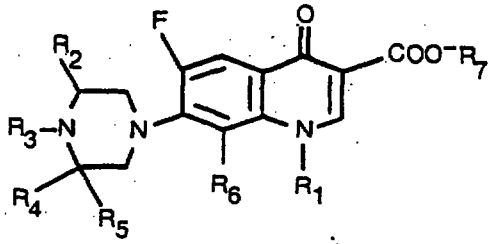
in der R_1 und R_6 jeweils die oben angegebenen Bedeutungen haben und X ein Chlor-Atom oder ein Fluor-Atom ist, mit einem Piperazin-Derivat der allgemeinen Formel



(V)

in der R_2, R_3, R_4 und R_5 jeweils die oben angegebenen Bedeutungen haben, umgesetzt wird.

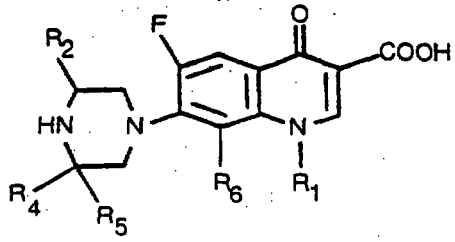
2. Verfahren zur Herstellung der Verbindung nach Anspruch 1 der allgemeinen Formel (I) und deren pharmakologisch unbedenklicher Salze dadurch gekennzeichnet, daß ein 6-Fluoro-1,4-dihydro-4-oxo-7-substituiertes Piperazinyl-chinolin-3-carbonsäure-ester-Derivat der allgemeinen Formel



(VI)

in der R_1, R_2, R_3, R_4, R_5 und R_6 jeweils die oben angegebenen Bedeutungen haben und R_7 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist, mit Hilfe eines hydrolysierenden Mittels hydrolysiert wird.

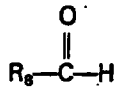
3. Verfahren zur Herstellung der Verbindung nach Anspruch 1 der allgemeinen Formel (I) und deren pharmakologisch unbedenklicher Salze dadurch gekennzeichnet, daß ein 6-Fluoro-1,4-dihydro-4-oxo-7-substituiertes Piperazinyl-chinolin-3-carbonsäure-Derivat der allgemeinen Formel



(VII)

in der R_1, R_2, R_4, R_5 und R_6 jeweils die oben angegebenen Bedeutungen haben, mit Hilfe eines Alkylierungsmittels alkyliert wird.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß eine Carbonyl-Verbindung der allgemeinen Formel



in der R_8 ein Wasserstoff-Atom oder eine niedere Alkyl-Gruppe mit 1 bis 3 Kohlenstoff-Atomen ist, zur Alkylierung in Gegenwart von Ameisensäure verwendet wird.

5. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß ein Alkylhalogenid der allgemeinen Formel

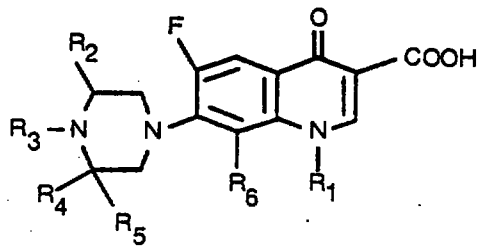
$$R_3—A$$

in der R_3 eine niedere Alkyl-Gruppe mit 1 bis 4 Kohlenstoff-Atomen ist und A ein Halogen-Atom ist, als Alkylierungsmittel verwendet wird.

4. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen zur Verwendung bei der Behandlung bakterieller Erkrankungen, enthaltend eine wirksame Menge einer oder mehrerer Verbindungen nach Anspruch 1 bis 5 zusammen mit einem verträglichen, pharmazeutisch unbedenklichen Träger oder Überzug.

Revendications pour les Etats contractants: BE CH GB IT LI NL SE

1. Dérivé de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3, représenté par la formule générale (I):



(I)

dans laquelle R_1 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone, un groupe vinyle, un groupe fluoro-2 éthyle ou un groupe hydroxy-2 éthyle; R_2, R_3 et R_4 sont chacun un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone; R_5 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone et R_6 est un atome d'hydrogène ou un atome de fluor, ainsi que ses sels pharmacologiquement acceptables.

2. Acide éthyl-1 difluoro-6,8 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

3. Chlorhydrate de l'acide éthyl-1 difluoro-6,8 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

4. Chlorhydrate de l'acide éthyl-1 fluoro-6,8 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

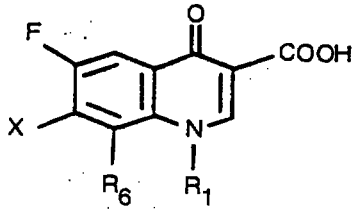
5. Acide fluoro-6 (fluoro-2 éthyl)-1 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

6. Acide difluoro-6,8 (fluoro-2 éthyl)-1 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

7. Acide difluoro-6,8 dihydro-1,4 (méthyl-3 pipérazinyl-1)-7 oxo-4 vinyl-1 quinoléine-carboxylique-3.

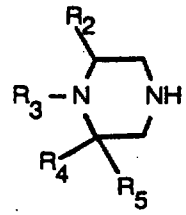
8. Acide difluoro-6,8 dihydro-1,4 méthyl-1 (méthyl-3 pipérazinyl-1)-7 oxo-4 quinoléine-carboxylique-3.

9. Procédé de préparation du composé tel que défini à la revendication 1 représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables qui consiste à faire réagir l'acide fluoro-6 halogéno-7 dihydro-1,4 oxo-4 quinoléine-carboxylique-3, représenté par la formule générale:



(IV)

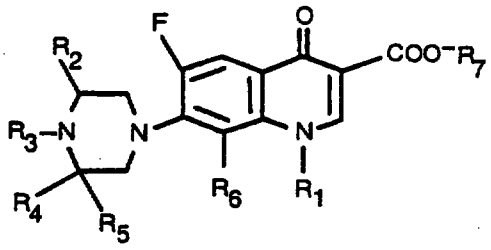
dans laquelle R_1 et R_6 ont chacun la même signification que celle décrite ci-dessus et X est un atome de chlore ou un atome de fluor, avec un dérivé de pipérazine, représenté par la formule suivante:



(V)

dans laquelle R_2, R_3, R_4 et R_5 ont chacun la même signification que celle décrite ci-dessus.

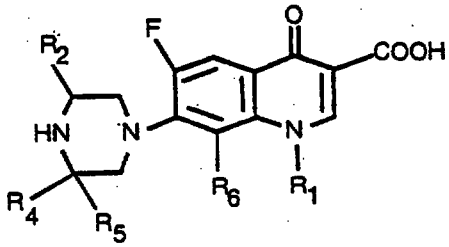
10. Procédé de préparation du composé tel que défini à la revendication 1 représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables, qui consiste à hydrolyser le dérivé ester de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3, représenté par la formule générale:



(VI)

dans laquelle R_1, R_2, R_3, R_4, R_5 et R_6 ont chacun la même significations que celle décrite à la revendication 1, et R_7 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone, avec un agent d'hydrolysation.

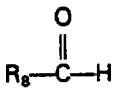
11. Procédé de préparation du composé tel que défini à la revendication 1 représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables qui consiste à alkyler un dérivé de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3 représenté par la formule générale:



(VII)

dans laquelle R_1, R_2, R_4, R_5 et R_6 ont chacun la même signification que celle décrite à la revendication 1, avec un agent d'alkylation.

12. Procédé selon la revendication 11, dans lequel on utilise, pour l'alkylation en présence d'acide formique, un composé du carbonyle, représenté par la formule générale:



dans laquelle R_8 est un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 3 atomes de carbone.

13. Procédé selon la revendication 11, dans lequel on utilise en tant qu'agent d'alkylation un halogénure d'alkyle, représenté par la formule générale:

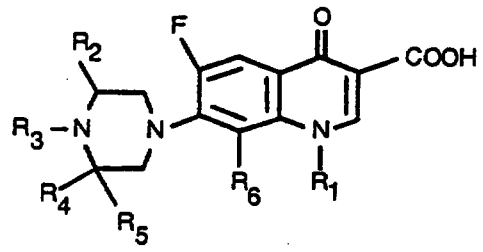
$$R_3—A$$

dans laquelle R_3 est u8n groupe alkyle inférieur ayant de 1 à 4 atomes de carbone et A est un atome d'halogène, dans un solvant et en présence ou en l'absence d'une base.

14. Des compositions pharmaceutiques destinées à être utilisées dans le traitement des maladies bactériennes, comprenant une quantité efficace d'un ou plusieurs composés tels que définis aux revendications 1 à 8, conjointement avec un support ou revêtement compatible, acceptable pharmaceutiquement.

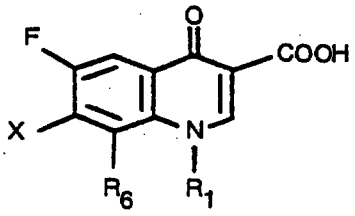
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un dérivé de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3, représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables,



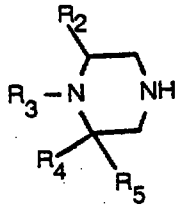
(I)

dans laquelle R_1 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone, un groupe vinyle, un groupe fluoro-2 éthyle ou un groupe hydroxy-2 éthyle; R_2, R_3 et R_4 sont chacun un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone; R_5 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone et R_6 est un atome d'hydrogène ou un atome de fluor, qui consiste à faire réagir l'acide fluoro-6 halogéno-7 dihydro-1,4 oxo-4 quinoléine-carboxylique-3, représenté par la formule générale:



(IV)

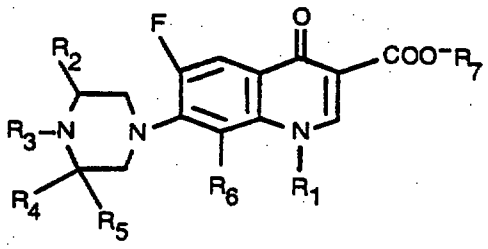
dans laquelle R_1 et R_6 ont chacun la même signification que celle décrite ci-dessus et X est un atome de chlore ou un atome de fluor, avec un dérivé de pipérazine, représenté par la formule suivante:



(V)

dans laquelle R_2, R_3, R_4 et R_5 ont chacun la même signification que celle décrite ci-dessus.

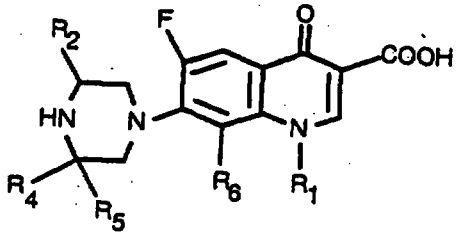
2. Procédé de préparation du composé tel que défini à la revendication 1, représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables, qui consiste à hydrolyser le dérivé ester de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3, représenté par la formule générale:



(VI)

dans laquelle R_1, R_2, R_3, R_4, R_5 et R_6 ont chacun la même signification que celle décrite à la revendication 1, et R_7 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone, avec un agent hydrolysant.

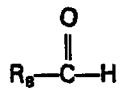
3. Procédé de préparation du composé tel que défini à la revendication 1, représenté par la formule générale (I) et de ses sels pharmacologiquement acceptables qui consiste à alkyler un dérivé de l'acide fluoro-6 dihydro-1,4 oxo-4 pipérazinyl substitué-7 quinoléine-carboxylique-3 représenté par la formule générale:



(VII)

dans laquelle R_1, R_2, R_4, R_5 et R_6 ont chacun la même signification que celle décrite à la revendication 1, avec un agent d'alkylant.

4. Procédé selon la revendication 3, dans lequel on utilise pour l'alkylation, en présence d'acide formique, un composé du carbonyle, représenté par la formule générale:



dans laquelle R_8 est un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 3 atomes de carbone.

5. Procédé selon la revendication 3, dans lequel on utilise en tant qu'agent alkylant un halogénure d'alkyle, représenté par la formule générale:

$$R_3—A$$

dans laquelle R_3 est un groupe alkyle inférieur ayant de 1 à 4 atomes de carbone et A est un atome d'halogène, dans un solvant et en présence ou en l'absence d'une base.

6. Procédé de préparation de compositions pharmaceutiques destinées à être utilisées dans le traitement des maladies bactériennes, comprenant une quantité efficace d'un ou plusieurs composés que l'on peut obtenir par les procédés tels que définis aux revendications 1 à 5, conjointement avec un support ou revêtement compatible, acceptable pharmaceutiquement.