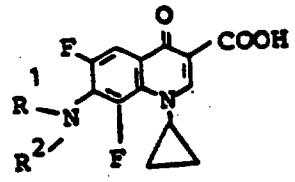
The invention relates to new 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids, processes for their preparation and also antibacterial agents containing these substances.

New 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain as ring members the atoms or groups -O-, -S-, -SO-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 - 3 carbon atoms, amino, methylamino or ethylamino, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 6 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms for an alkyl radical, the cyano group, or an alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical optionally mono- or disubstituted by hydroxyl,

methoxy, chlorine and fluorine, a phenacyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and also a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 is hydrogen, straight-chain or branched alkyl with 1 to 4 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 is straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl,

and their pharmaceutically acceptable salts, have been found.

DE-A1-3,106,013 and EP-A3-0,078,362 disclose quinolonecarboxylic acids with an antibacterial activity. Compared with these, the compounds according to the invention show improved species-specific antibacterial activities.

They are therefore suitable as active substances for human and veterinary medicine, where the prophylaxis and treatment of fish is also counted as veterinary medicine.

Those compounds of the formula (I) are preferred in which

R^1 and R^2 can be identical or different and represent a C_1-C_3-alkyl radical optionally substituted by a hydroxyl or amino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain as ring members the

atoms of the groups -O-, -S-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono- or disubstituted on the carbon atoms by C_1-C_3-alkyl, hydroxyl, amino or methylamino, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 4 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy or alkylmercapto group with 1 to 2 carbon atoms for an alkyl radical, the cyano group, or the alkoxycarbonyl group with 1 to 3 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group with up to 2 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenacyl radical, an oxoalkyl radical with up to 5 carbon atoms and also a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 2 carbon atoms in the acyclic part, furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 denotes hydrogen, straight-chain or branched alkyl with 1 to 3 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, methoxycarbonyl, carboxyl, alkoxy with 1 to 2 carbon atoms or trifluoromethylthio, phenyl optionally substituted by chlorine or hydroxyl, alkoxy with 1 to 3 C atoms, amino or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 2 C atoms in the alkyl part or carboxyl, and

R^5 denotes methyl, ethyl, phenyl or methylphenyl.

Particularly preferred are those compounds of the formula (I) in which

R^1 and R^2 can be identical or different and represent a C_1-C_2-alkyl radical optionally substituted by a hydroxyl group and furthermore, together with the nitrogen atom to which they are bonded, can form a 6-membered heterocyclic ring which can addition-

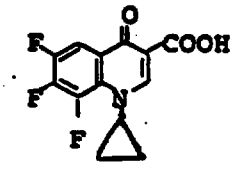
ally contain the group N-R^3 as a ring member and which can optionally be mono- or disubstituted on the carbon atoms by C_1-C_2-alkyl or hydroxyl, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 3 carbon atoms which can optionally be substituted by a hydroxyl group or the alkoxycarbonyl group with 1 to 2 carbon atoms in the alcohol part, a benzyl group optionally substituted in the phenyl radical by amino, a phenacyl radical, an oxoalkyl radical with up to 4 carbon atoms and also a cyclopropylmethyl radical, and furthermore denotes a radical COR^4 or SO_2R^5, wherein

R^4 denotes hydrogen, alkyl with 1 to 2 C atoms which is optionally substituted by a substituent from the series comprising alkoxy or carboxyl, alkoxy with 1 to 2 C atoms or benzyloxy and

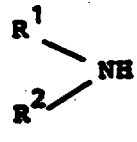
R^5 denotes methyl.

It has furthermore been found that 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acids of the formula (I) are obtained when the trifluoroquinolonecarboxylic acid of the formula (II)



(II)

is reacted with amines of the formula (III)



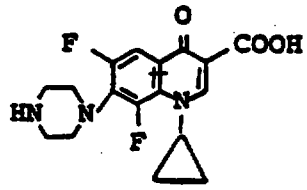
(III)

in which

R^1 and R^2 have the abovementioned meanings,

if appropriate in the presence of acid binders (Method A).

The compounds of the formula (I) according to the invention can also be obtained by reacting a 7-piperazinyl-quinolonecarboxylic acid of the formula (IV)



(IV)

in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent,

with compounds of the formula (V)

$$R^3X \qquad (V)$$

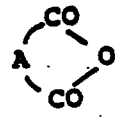
in which

R^3 has the abovementioned meaning, but cannot be hydrogen, and

X denotes fluorine, chlorine, bromine, iodine, acyloxy, ethoxy, phenoxy, 4-nitrophenoxy,

in the presence of acid binders (Method B).

The compounds of the formula (I) according to the invention are also obtained when a 7-piperazinyl-quinolonecarboxylic acid of the formula (IV) in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent, is reacted with anhydrides of the formula (VI)

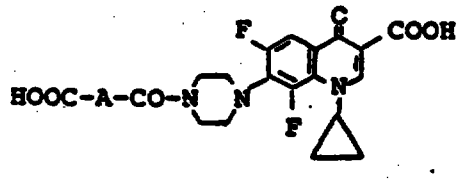


(VI)

in which

A denotes an optionally substituted alkylene chain with 2 or 3 carbon atoms or an arylene radical,

to give the compounds according to the invention of the formula (Ia) (Method C),



(Ia)

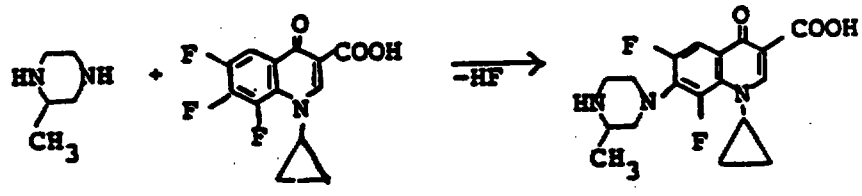
in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent.

Compounds according to the invention of the formula (I) are also obtained when a 7-piperazinyl-quinolonecarboxylic acid of the formula (IV) in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent, is reacted with Michael acceptors of the formula (VII)

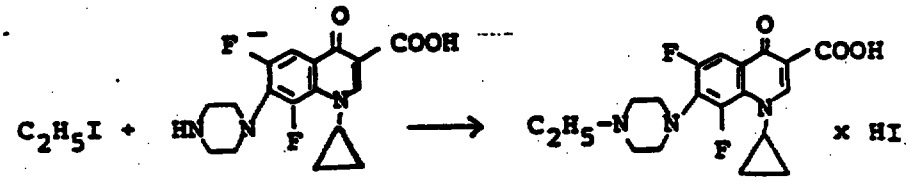
$$B\text{-}CH=CH_2 \qquad (VII)$$

in which B represents CN, $CO\text{-}R^6$ or $COOR^7$, wherein
R^6 represents methyl or ethyl and
R^7 represents methyl, ethyl, n- or i-propyl or benzyl (Method D).

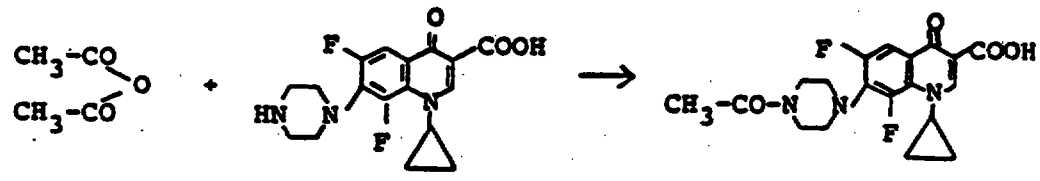
If 2-methyl-piperazine and 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (II) are used as starting substances in the reaction according to Method A, then the course of the reaction can be represented by the following scheme:



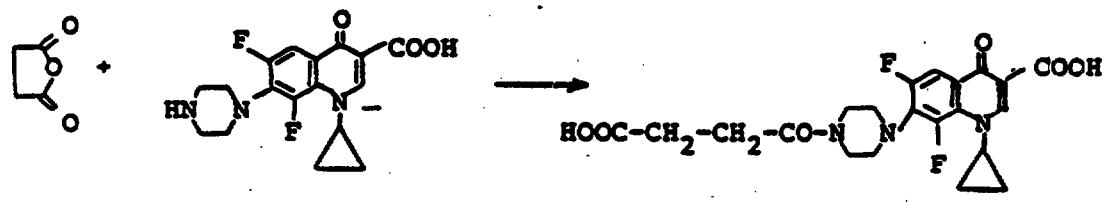
If ethyl iodide and 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid are used as starting substances in the reaction according to Method B, then the course of the reaction can be represented by the following scheme:



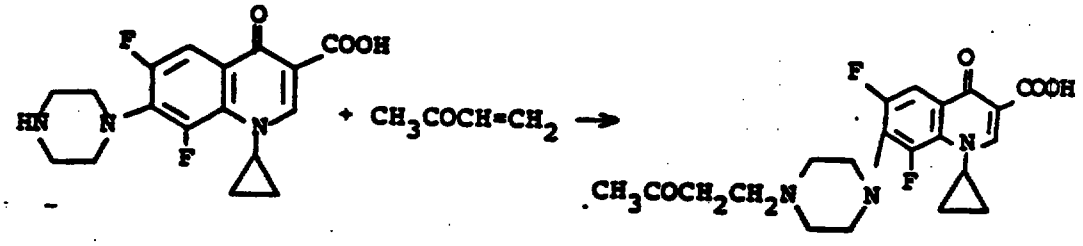
If, for example, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid and acetic anhydride are used as starting compounds in the reaction of (IV) with (V) according to Method B, then the course of the reaction can be represented by the following scheme:



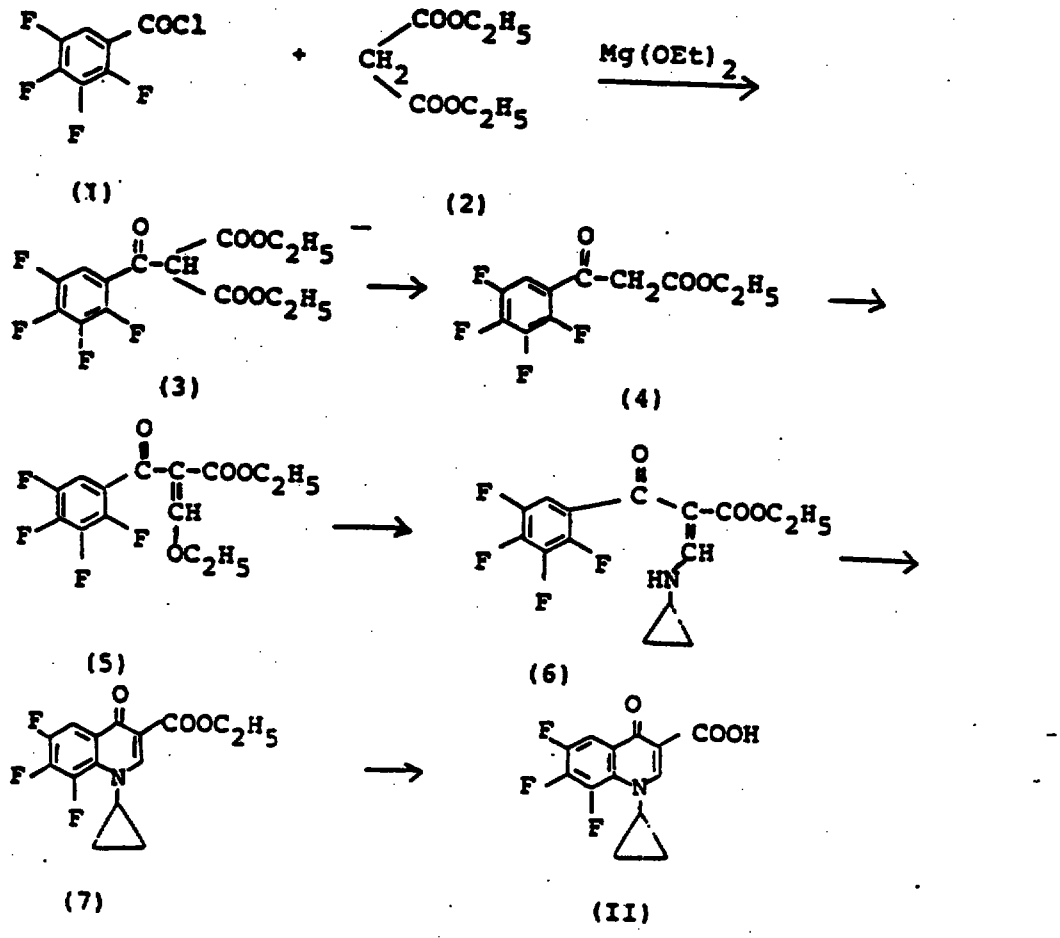
If, for example, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid and succinic anhydride are used as starting compounds in the reaction of (I) with (VI) according to Method C, then the course of the reaction can be represented by the following scheme:



If, for example, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid and methyl vinyl ketone are used as starting compounds in the reaction of (I) with (VII) according to Method D, then the course of the reaction can be represented by the following scheme:



The 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid of the formula (II) which can be used as starting substances according to Method A can be prepared according to the following reaction scheme:



(I) (2) (3) (4) (5) (6) (7) (II)

Thus diethyl malonate (2) is acylated using 2,3,4,5-tetrafluorobenzoyl chloride (1) in the presence of magnesium ethylate to give the aroyl malonic ester (3) (Organicum, 3rd edition, 1964, p. 438).

2,3,4,5-Tetrafluorobenzoyl fluoride can also be used in place of (1).

Ethyl aroylacrylate (4) is obtained in a good yield by partial saponification and decarboxylation of (3) in aqueous medium with catalytic amounts of sulphuric acid or p-toluenesulphonic acid, and is converted into ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxy-acrylate (5) with triethyl orthoformate/acetic anhydride. Reaction of (5) with cyclopropylamine in a solvent such as, for example, methylene chloride, alcohol, chloroform, cyclohexane or toluene leads by means of a slightly exothermic reaction to the desired intermediate (6).

The cyclization reaction (6) ---> (7) is carried out in a temperature range of about 60 to 300°C, preferably 80 to 180°C.

Dioxane, dimethylsulphoxide, N-methylpyrrolidone, sulpholane, hexamethylphosphoric acid triamide and preferably N,N-dimethylformamide can be employed as diluents.

Potassium tert-butanolate, butyl-lithium, phenyl-lithium, phenyl magnesium bromide, sodium methylate, sodium hydride, sodium carbonate or potassium carbonate and particularly preferably potassium fluoride or sodium fluoride can be used as acid binders in this reaction step. The use of a 10 mol % excess of base can be advantageous.

The ester hydrolysis of (7) occurring under basic or acidic conditions in the last step leads to 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (II).

The 2,3,4,5-tetrafluorobenzoyl chloride (1) used as a starting material for this synthetic route was obtained in a customary manner from the known 2,3,4,5-tetrafluorobenzoic acid [G.G. Yakobson, V.N. Odinokov and N.N. Vorozhtsov Jr., Zh. Obsh. Khim. 36, 139 (1966)] using thionyl chloride. It possesses a boiling point of 75-80°C/17 mbar. 2,3,4,5-Tetrafluorobenzoyl fluoride possesses a boiling point of 46 to 47°C/20 mbar (n_D^{20}: 1.4375).

The amines (III) used as starting substances are known or can be obtained by processes which are known from the literature. Examples which may be mentioned are: morpholine, piperidine, thiomorpholine, pyrrolidine, dimethylamine, ethylmethylamine, piperazine, N-methylpiperazine, N-ethylpiperazine, N-β-hydroxyethylpiperazine, N-formylpiperazine, 2-methylpiperazine, 1,2-dimethylpiperazine, cis- and trans-2,5-dimethylpiperazine, cis- and trans-2,6-dimethylpiperazine, 2-ethylpiper-azine, 2-propylpiperazine, 2-isopropylpiperazine, 2-iso-butylpiperazine.

The compounds of the formula (V) used as starting materials are known. Examples which may be mentioned are:

methyl iodide, methyl bromide, ethyl iodide, ethyl bromide, ethyl chloride, 2-hydroxyethyl chloride, 3-hydroxypropyl chloride, 4-hydroxybutyl chloride, n-propyl bromide, i-propyl iodide, n-butyl bromide, i-butyl bromide, sec-butyl chloride, n-pentyl chloride, 3-methylbutyl chloride, n-hexyl bromide.

Formic acetic anhydride, acetic anhydride, propionic anhydride, acetyl chloride, chloroacetyl chloride, dichloroacetyl chloride, bromoacetyl bromide, butyryl chloride, 4-chlorobutyryl chloride, isobutyryl chloride, 3-methylbutyryl chloride, benzoyl chloride, 3-chlorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-nitrobenzoyl chloride, 4-methylbenzoyl chloride, monomethyl succinate chloride, trifluoromethylthioacetyl fluoride, N-(tert-butoxycarbonyl)-glycine 4-nitrophenyl ester, N-(tert-butoxycarbonyl)-L-alanine 4-nitrophenyl ester, N-(tert-butoxycarbonyl)-L-leucine 4-nitrophenyl ester, N-(tert-butoxycarbonyl)-L-valine 4-nitrophenyl ester, 3-methoxypropionyl chloride, methyl chloroformate, ethyl chloroformate, n-butyl chloroformate, diethyl carbonate, cyanogen chloride, diphenyl carbonate, cyanogen bromide, dimethyl carbamoyl chloride, methanesulphonyl chloride, ethanesulphonyl chloride, propane-1-sulphonyl chloride, benzenesulphonyl chloride, 4-toluenesulphonyl chloride, butane-1-sulphonyl chloride and dichlorofluoromethanesulphonyl chloride.

The anhydrides (VI) which may be used according to the invention are known. Examples which may be mentioned are:

succinic anhydride, methylsuccinic anhydride, glutaric anhydride, phthalic anhydride and tetrachlorophthalic anhydride.

The compounds of the formula (VII) which may be used according to the invention are known. Examples which may be mentioned are:

acrylonitrile, methyl vinyl ketone, methyl acrylate, ethyl acrylate and benzyl acrylate.

The reaction of (II) with (III) according to Method A is preferably performed in a diluent such as dimethyl sulphoxide, N,N-dimethylformamide, hexamethylphosphoric triamide, sulpholane, water, an alcohol such as methanol, ethanol, n-propanol, isopropanol or glycol monomethyl ether, or pyridine. Mixtures of these diluents can also be used.

All the usual inorganic and organic acid binding

agents can be used as acid binders. These preferably include the alkali metal hydroxides, alkali metal carbonates, organic amines and amidines. Examples which may be mentioned separately as particularly suitable are: triethylamine, 1,4-diazabicyclo-[2,2,2]octane (DABCO), excess amine (III) or 1,8-diaza-bicyclo[5,4,0]undec-7-ene (DBU).

The reaction temperatures can be varied over a relatively wide range. In general, temperatures between about 20 and 200°C are used, preferably between 80 and 180°C.

The reaction can be performed at atmospheric pressure or alternatively at elevated pressure. In general, it is performed at pressures between about 1 and about 100 bar, preferably between 1 and 10 bar.

In performing the process according to the invention, 1 to 15 mol, preferably 1 to 6 mol, of the amine (III) are employed per mol of the carboxylic acid (II).

The reaction of (IV) with (V) is preferably performed in a diluent such as dimethyl sulphoxide, dioxane, N,N-dimethylformamide, hexamethylphosphoric triamide, sulpholane, water, an alcohol such as methanol, ethanol, n-propanol, isopropanol or glycol monomethyl ether or pyridine. Mixtures of these diluents can also be used.

All the usual inorganic and organic acid binding agents can be used as acid binders. In these are included preferably the alkali metal hydroxides, alkali metal carbonates, organic amines and amidines. Examples which may be mentioned separately as particularly suitable are: triethylamine, 1,4-diazabicyclo-[2,2,2]octane (DABCO) or 1,8-diaza-bicyclo[5,4,0]undec-7-ene (DBU).

The reaction temperatures can be varied over a relatively wide range. In general, temperatures between about 20 and about 180°C are used, preferably between 40 and 110°C.

The reaction can be performed at atmospheric pressure or alternatively at elevated pressure. In general, it is performed at pressures between about 1 and about 100 bar, preferably between 1 and 10 bar.

In performing the process according to the invention according to Method B, 1 to 4 mol, preferably 1 to 1.5 mol, of the compound (V) are employed per mol of the

compound (IV).

The reaction of (IV) with (VI) (Method C) is performed in a diluent such as N,N-dimethylformamide, dioxane, tetrahydrofuran, pyridine or water or also in mixtures of these diluents. The reaction temperatures can be varied over a relatively wide range. In general, temperatures between about 0° and about 140°C, preferably between 10 and 100°C, are used.

The reaction can be performed at atmospheric pressure or alternatively at elevated pressure. In general, it is performed at pressures between about 1 and about 100 bar, preferably between 1 and 10 bar.

All the usual inorganic and organic acid binding agents can be used as acid binders. These preferably include the alkali metal hydroxides, alkali metal carbonates, pyridine and tertiary amines such as triethylamine, 1,4-diazabicyclo[2,2,2]octane.

In carrying out the method according to the invention, 1 to 3 mol, preferably 1 to 1.3 mol, of the compound (VI) are employed per mol of the compound (IV).

The reaction of (IV) with (VII) (Method D) is preferably performed in a diluent such as dioxane, dimethyl sulphoxide, N,N-dimethylformamide, methanol, ethanol, isopropanol, n-propanol, glycol monomethyl ether or also in mixtures of these diluents.

The reaction temperatures can be varied over a relatively wide range. In general, temperatures between about 20°C and about 150°C, preferably between 50°C and 100°C, are used.

The reaction can be performed at atmospheric pressure or alternatively at elevated pressure. In general, it is performed at pressures between about 1 and about 100 bar, preferably between 1 and 10 bar.

In carrying out the method according to the invention, 1 to 5 mol, preferably 1 to 2 mol, of the compound (VII) are employed per mol of the compound (IV).

Examples of new active substances which may be mentioned separately are:

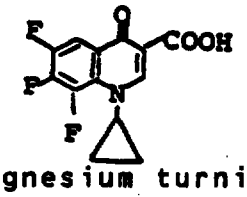
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piper-

azinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-ethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-methyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3,4-dimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-ethyl-3-methyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[4-(2-hydroxyethyl)-3-methyl-1-piperazinyl]-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[4-(3-hydroxypropyl)-3-methyl-1-piperazinyl]-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(2,5-dimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-ethyl-2,5-dimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3,5-dimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3,4,5-trimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-ethyl-3,5-dimethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-ethyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-n-propyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-isopropyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-isobutyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-(3-methyl-4-n-propyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(3-methyl-4-isopropyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(4-n-

butyl-3-methyl-1-piperazinyl)-3-quinolinecarboxylic acid,
1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-morpholinyl-3-quinolinecarboxylic acid,
and their pharmaceutically acceptable acid addition salts, alkali metal salts, alkaline earth metal salts or hydrates.

Preparation examples

Example A (Preparation of starting substance II):



24.3 g of magnesium turnings are suspended in 50 ml of anhydrous ethanol. 5 ml of tetrachloromethane are added and, when the reaction has begun, a mixture of 160 g of diethyl malonate, 100 ml of absolute ethanol and 400 ml of anhydrous toluene is added dropwise at 50-60°C. The mixture is then heated to 50-60°C for 1 hour, cooled to between -5°C and -10°C using dry ice/acetone, and a solution of 212.5 g of 2,3,4,5-tetrafluorobenzoyl chloride (1) in 80ml of absolute toluene is slowly added dropwise at this temperature. The mixture is then stirred for 1 hour at 0 to -5°C and allowed to come to room temperature overnight, and a mixture of 400 ml of ice-water and 25 ml of conc. sulphuric acid is run in with ice cooling. The phases are separated and extracted twice more with toluene. The combined toluene solutions are washed with saturated NaCl solution and dried using Na_2SO_4 and the solvent is stripped off in vacuo. 335 g of diethyl 2,3,4,5-tetrafluorobenzoylmalonate (3) are obtained as a crude product.

An emulsion of 284.8 g of crude diethyl 2,3,4,5-tetrafluorobenzoylmalonate (3) in 300 ml of water is treated with 0.3 g of p-toluenesulphonic acid. The mixture is heated to boiling with vigorous stirring for 5 hours, the cooled emulsion is extracted several times with methylene chloride, the combined CH_2Cl_2 solutions are washed once with saturated NaCl solution and dried using Na_2SO_4 and the solvent is distilled off in vacuo. Fractionation of the residue under high vacuum yields 160.2 g of ethyl 2,3,4,5-tetrafluorobenzoylacetate (4) of boiling point 100-110°C/0.90-0.1 mbar. Melting point 47-49°C.

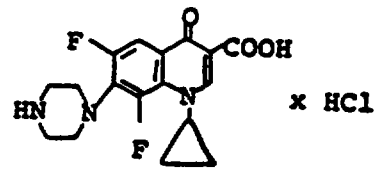
A mixture of 110.7 g of ethyl 2,3,4,5-tetrafluorobenzoylacetate (4), 93.5 g of ethyl orthoformate and 107 g of acetic anhydride is heated for 2 hours at 150°C. The volatile constituents are then distilled off at a bath temperature of ~ 120°C under a water pump vacuum and finally under high vacuum. 123.9 g of crude ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate (5) remain behind. This product is sufficiently pure for further reactions.

23.2 g of cyclopropylamine are added dropwise to a solution of 123.9 g of ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate (5) in 250 ml of ethanol with ice cooling and stirring. When the exothermic reaction has subsided, the mixture is stirred for 1 hour at room temperature, the solvent is stripped off in vacuo and the residue is recrystallized from cyclohexane/petroleum ether. 115 g of ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-cyclopropylaminoacrylate (6) of melting point 63-65°C are obtained.

A solution of 107.8 g of ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-cyclopropylaminoacrylate (6) in 400 ml of anhydrous dimethylformamide is treated with 21.2 g of sodium fluoride. It is then stirred for 2 hours under reflux and the hot reaction mixture is poured onto ice. The precipitate is filtered off with suction, washed well with water and dried in vacuo over calcium chloride at 100°C. 91.2 g of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (7) of melting point 167-168°C are obtained.

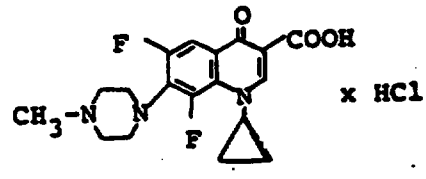
A mixture of 94 g of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (7), 600 ml of glacial acetic acid, 450 ml of water and 70 ml of conc. sulphuric acid is heated to reflux for 1.5 hours. The hot suspension is then poured onto ice and the precipitate is filtered off with suction, then washed well with water and dried in vacuo at 100°C. In this way 88.9 g of pure 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid II of melting point 228-230°C (decomposition) are obtained.

Example 1



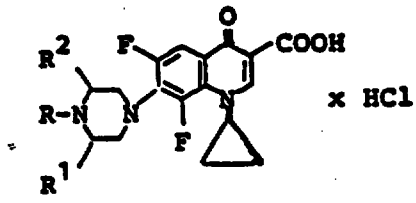
A mixture of 2.83 g (0.01 mol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (II), 4.4 g (0.051 mol) of anhydrous piperazine and 30 ml of dry pyridine is refluxed for 6 hours. The solvent is stripped off in vacuo, the residue is taken up in 25 ml of water and adjusted to pH 1 with concentrated hydrochloric acid with ice cooling, and the precipitate is filtered off under suction while cold and washed with cold 10% hydrochloric acid and ethanol. After drying in vacuo at 100°C, 3.05 g of 1-cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride of decomposition point 354-355°C are obtained.

Example 2



2.83 g (0.01 mol) of II are reacted with 4 g (0.04 mol) of N-methylpiperazine analogously to Example 1, and 3.6 g of 1-cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride of decomposition point 300-303°C are isolated.

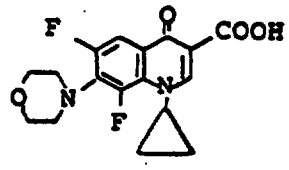
The following compounds are obtained analogously to Example 1 or 2:



61

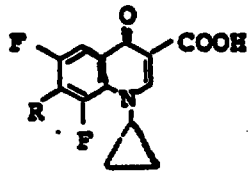
Example	R	R^1	R^2	Decomposition point (°C)
3	H	CH_3	H	325-330
4	H	C_2H_5	H	330-335
5	H	CH_3	CH_3	310-315
6	$HO(CH_2)_2$-	H	H	290-293

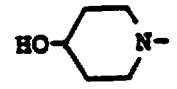
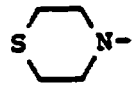
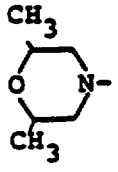
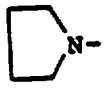
Example 7



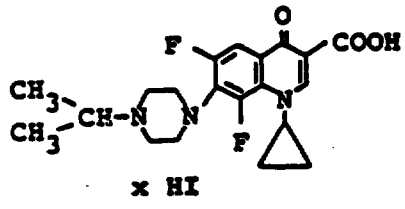
A mixture of 2.83 g (0.01 mol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 0.9 g (0.01 mol) of morpholine and 2.3 g of diazabicyclo-[2,2,2]octane (0.02 mol) in 35 ml of dimethyl sulphoxide is heated for 5 hours at 140°C. The solvent is then distilled off in vacuo and the residue is treated with 50 ml of water, acidified with 1:1 hydrochloric acid, filtered off under suction while cold, washed with water, dried in vacuo and recrystallized from glycol monomethyl ether. 2.4 g of 1-cyclopropyl-6,8-difluoro-7-(4-morpholinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of decomposition point 257-260°C are obtained.

The following compounds are obtained analogously to Example 7:



Example	R	Decomposition point (°C)
8		277-280
9		291-294
10		241-245
11		280-285

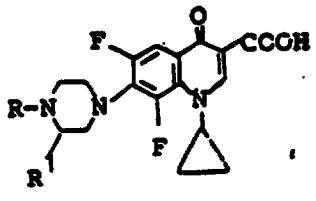
Example 12



x HI

A mixture of 3.5 g (0.01 mol) of 1-cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 3.4 g (0.02 mol) of isopropyl iodide and 2.1 g (0.02 mol) of triethylamine in 50 ml of dimethylformamide is heated to 80°C for 6 hours. After evaporation of the solvent, the residue is stirred with 30 ml of water, filtered off under suction, washed with water and recrystallized from methanol. 2.3 g of 1-cyclopropyl-6,8-difluoro-7-(4-isopropyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydroiodide with a decomposition point of 306-308°C are obtained.

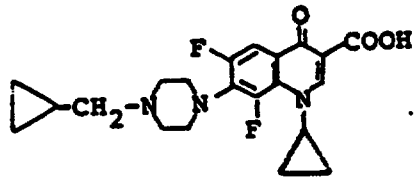
The following compounds are obtained analogously to Example 12:



x HI

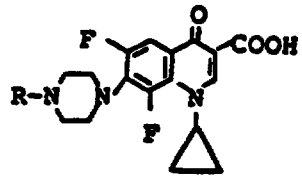
Example	R	R^1	Decomposition point (°C)
13	C_2H_5	H	289-291
14	C_2H_5	CH_3	252-258

Example 15

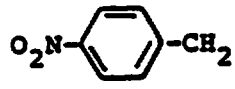
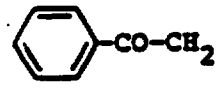


A mixture of 3.5 g (0.01 mol) of 1-cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 2.1 g of triethylamine, 1.8 g of cyclopropylmethyl chloride and 3.3 g of potassium iodide is heated for 6 hours at 80°C. The mixture is then concentrated in vacuo, treated with 30 ml of water and adjusted to pH 5, and the precipitate is filtered off under suction, washed with water and methanol and recrystallized from glycol monomethyl ether. 1.8 g of 1-cyclopropyl-7-(4-cyclopropylmethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid with a decomposition point of 246-248°C are obtained.

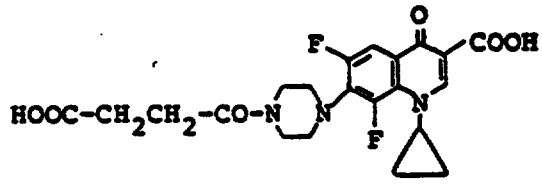
The following compounds are obtained analogously to Example 15:



64

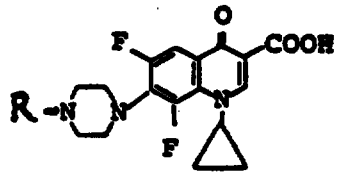
Example	R	Decomposition point (°C)
16		210-212
17	$CH_3-CO-CH_2$	201-204
18		210-212
19	$CH_2=CH-CH_2$	172-175
20	$HC\equiv C-CH_2$	228-232 (hydrochloride)

Example 21



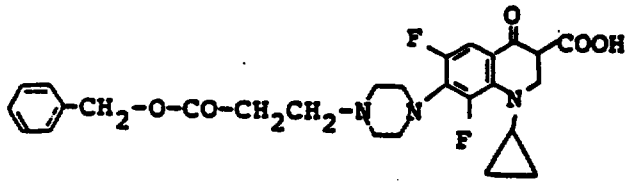
3.5 g (0.01 mol) of 1-cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are dissolved in a mixture of 0.4 g sodium hydroxide and 20 ml of water, and a solution of 1 g of succinic anhydride in 10 ml of dioxane and a solution of 0.4 g of sodium hydroxide in 10 ml of water are simultaneously added dropwise at 20°C. After standing for 12 hours, the pH is adjusted to 5 with 2N hydrochloric acid, and the precipitate is filtered off under suction, washed with water, heated with methanol, filtered off with suction and dried. 2.5 g of 7-[4-(3-carboxypropionyl)-1-piperazinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid with a decomposition point of 217-219°C are obtained.

Analogously to Example 21, the following are obtained:



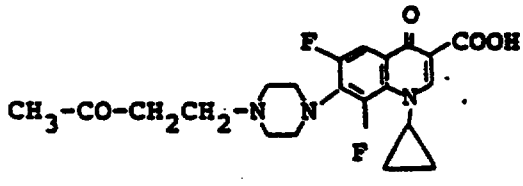
Example	R	Acylating agent	Decomposition point (°C)
22	H-CO	$HCO-O-COCH_3$	295-300
23	CH_3-CO	$CH_3-CO-Cl$	248-251
24	n-C_3H_7-CO	$C_3H_7-CO-Cl$	182-186
25	C_2H_5O-CO	$C_2H_5O-CO-Cl$	204-208
26	CH_3-SO_2	CH_3-SO_2-Cl	295-296

Example 27



3.5 g (0.01 mol) of 1-cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are heated under reflux for 5 hours with 4 g of benzyl acrylate. The solution is filtered while hot, and the precipitate is filtered off under suction, washed with ethanol and dried. 2.3 g of 7-[4-(2-benzyloxycarbonylethyl)-1-piperazinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid with a decomposition point of 132-135°C are obtained.

Example 28



By the use of methyl vinyl ketone analogously to Example 27, 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[4-(3-oxobutyl)-1-piperazinyl]-3-quinolinecarboxylic acid with a decomposition point of 155-158°C is obtained.

The compounds according to the invention show, with reduced toxicity, a broad antibacterial spectrum against Gram-positive and Gram-negative organisms,

especially against Enterobacteriaceae; and also in particular against those which are resistant to various antibiotics such as, for example, penicillins, cephalosporins, aminoglycosides, sulphonamides and tetracyclins.

These valuable properties make their use as chemotherapeutic active substances in medicine possible and also as substances for the preservation of inorganic and organic materials, particularly of organic materials of all types, for example polymers, lubricants, dyes, fibres, leather, paper and wood, food and water.

The compounds according to the invention are active against a very wide spectrum of microorganisms. They can be used to combat Gram-negative and Gram-positive bacteria and bacteria-like microorganisms and also to prevent, improve and/or cure diseases produced by these initiators.

The compounds according to the invention are particularly active against bacteria and bacteria-like microorganisms. They are therefore particularly well suited for the prophylaxis and chemotherapy of local and systemic infections, produced by these initiators, in human and veterinary medicine.

For example, local and/or systemic diseases which are caused by the following initiators or by mixtures of the following initiators can be treated and/or prevented: Micrococcaceae, such as Staphylococci, e.g. Staphylococcus aureus, Staph. Epidermidis, (Staph. = Staphylococcus); Lactobacteriaceae, such as Streptococci, e.g. Streptococcus pyogenes, α- or β-haemolytic Streptococci, non (γ-)haemolytic Streptocci, Enterococci and Diplococcus pneumoniae (Pneumococci); Enterobacteriaceae, such as Escherichia bacteria of the coli group: Escherichia bacteria, e.g. Escherichia coli, Enterobacter bacteria, e.g. E. aerogenes, E. Cloacae, Klebsiella bacteria, e.g. K. pneumoniae, Serratia, e.g. Serratia marcescens (E. = Enterobacter) (K. = Klebsiella), Proteae bacteria of the Proteus group: Proteus, e.g. Proteus vulgaris, Pr. morganii, Pr. rettgeri, Pr. mirabilis (Pr. = Proteus);

Pseudomonadaceae, such as Pseudomonas bacteria, e.g. Pseudomonas aeruginosa

Bacteroidaceae, such as Bacteroides bacteria, e.g. Bacteroides fragilis (B. = Bacteroides); Mycoplasma, e.g. Mycoplasma pneumoniae.

The above list of initiators is only by way of example and is in no way intended to be limiting.

As examples of diseases which may be prevented, improved and/or cured by the compounds according to the invention there may be mentioned:

Diseases of the airways and of the pharynx:

otitis; pharyngitis; pneumonia; peritonitis; pyelonephritis; cystitis; endocarditis; systemic infections; bronchitis; arthritis; local infections, septic diseases.

The invention includes pharmaceutical preparations which contain one or more compounds according to the invention in addition to non-toxic, inert pharmaceutically suitable carriers or which consist of one or more active substances according to the invention, and also processes for the production of these preparations.

The invention also includes pharmaceutical preparations in dosage units. This denotes that the preparations exist in the form of individual parts, e.g. tablets, dragees, capsules, pills, suppositories and ampoules, whose content of active substance corresponds to a fraction or a multiple of a single dose. The dosage units can, for example, contain 1, 2, 3 or 4 single doses or 1/2, 1/3 or 1/4 of a single dose. A single dose preferably contains the amount of active substance which is administered in an application and which usually corresponds to a whole, a half, a third, or a quarter of a daily dose.

Solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of any type are understood by non-toxic, inert pharmaceutically suitable carriers.

Preferred pharmaceutical preparations which may be mentioned include tablets, dragees, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays.

Tablets, dragees, capsules, pills and granules can contain the active substance or substances in addition to

the usual carriers, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, (c) moisture-retaining agents, for example glycerol, (d) disintegrating agents, for example agar agar, calcium carbonate and sodium carbonate, (e) solution-retarding agents, for example paraffin and (f) absorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorption agents, for example kaolin and bentonite and (i) lubricants, for example talc, calcium stearate and magnesium stearate and solid polyethylene glycols or mixtures of the substances listed under (a) to (i).

The tablets, dragees, capsules, pills and granules can be provided with the usual coatings and casings, which may optionally contain opacifying agents, and may also be so formulated that they optionally retard the release of the active substance or substances only or preferably in a determined part of the intestinal tract, for which purpose for example polymer substances and waxes can be used as embedding compounds.

The active substance or substances can optionally also exist in a microencapsulated form with one or more of the abovementioned carriers.

Suppositories can contain the usual water-soluble or water-insoluble carriers in addition to the active substance or substances, for example polyethylene glycols, fats, for example cocoa fat and higher esters (for example C_{14}-alcohol with C_{16}-fatty acid) or mixtures of these substances.

Ointments, pastes, creams and gels can contain the usual carriers in addition to the active substance or substances, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

Powders and sprays can contain the usual carriers in addition to the active substance or substances, for

example lactose, talc, silicic acid, aluminium hydroxide, calcium silicate and polyamide powder or mixtures of these substances. Sprays can additionally contain the usual propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain the usual carriers in addition to the active substance or substances, such as solvents, solubilizers and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, maize oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures of these substances.

For parenteral administration the solutions and emulsions can also exist in sterile and isotonic form.

Suspensions can contain the usual carriers in addition to the active substance or substances, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitol esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar agar and tragacanth or mixtures of these substances.

The types of formulations mentioned can also contain colorants, preservatives and also odour- and taste-improving additives, for example peppermint oil and eucalyptus oil and sweeteners, for example saccharin.

The therapeutically active compounds should be present in the pharmaceutical preparations exemplified above, preferably in a concentration of about 0.1 to 99.5, preferably of about 0.5 to 95, % by weight of the total mixture.

The pharmaceutical preparations exemplified above can also contain further pharmaceutical active substances in addition to the compounds according to the invention.

The production of the pharmaceutical preparations exemplified above takes place in a customary manner according to known methods, for example by mixing of the active

substance or substances with the carrier or carriers.

The active substances or the pharmaceutical preparations can be administered by local, oral, parenteral, intraperitoneal and/or rectal means, preferably by oral or parenteral as well as intravenous or intramuscular means.

In general, it has been shown to be advantageous both in human and in veterinary medicine to administer the active substance or substances according to the invention in total amounts of about 0.5 to about 500, preferably 5 to 100, mg/kg body weight every 24 hours, if appropriate in the form of several single doses, in order to attain the desired results. A single dose contains the active substance or substances according to the invention, preferably in amounts of about 1 to about 250, in particular 3 to 60, mg/kg body weight. It can, however, be necessary to depart from the mentioned dosages, depending on the type and the body weight of the subject to be treated, the type and the intensity of the disease, the type of the composition and the administration of the drug and also the period or interval within which the administration takes place.

Thus, in some cases it is sufficient to manage with less than the abovementioned amount of active substance, whereas in other cases the abovementioned amount of active substance must be exceeded. The selection of the necessary optimal dosage and type of administration of the active substances is in each case easily decided by any expert on the basis of his specialist knowledge.

The new compounds can be given in the usual concentrations and preparations together with food or food preparations or with drinking water. In this way an infection by gram-negative or gram-positive bacteria can be prevented, improved and/or cured and promotion of growth and improvement of the utilization of food can be achieved.

The MHC values of some of the compounds according to the invention are given in the table below.

Table

Strain	MIC mg/ml Ex. 13	Ex. 3	Ex. 5	Ex. 4	Ex. 12	Ex. 8	Ex. 28	Ex. 1	Ex. 2	Ex. 11
E.coli Neumann	0,015	0,015	0,015	0,015	0,06	0,015	0,015	0,015	0,015	0,06
E.coli 455/7	4	8	8	8	16	8	8	4	1	128
Klebsiella 63	0,03	0,015	0,015	0,06	0,125	0,125	0,015	0,015	0,015	0,5
Klebsiella 8085	0,015	0,015	0,015	0,015	0,03	0,015	0,015	0,015	0,015	0,125
Proteus mir. 8223	4	4	4	8	16	4	4	2	2	8
Proteus vulg. 1017	0,06	0,03	0,06	0,06	0,5	0,06	0,015	0,015	0,03	1
Proteus morg. 932	0,015	0,015	0,015	0,015	0,06	0,03	0,015	0,015	0,015	0,5
Staph.aur. 133	0,25	0,125	0,125	0,125	0,25	0,015	0,25	0,125	0,125	0,03
Streptococc. faec. 9790	1	0,5	0,5	0,5	2	0,125	0,5	0,25	0,5	0,5
Pseudom. W.	0,5	0,5	1	1	8	1	0,25	0,06	0,125	4

Agar dilution test

Isosensitest medium

Denley multipoint inoculator

Table (continuation)

	MIC mg/ml				
Strain	Example 15	Example 14	Example 6	Example 7	Example 10
E.coli Neumann	0,03	0,015	0,015	0,015	0,125
E.coli 455/7	16	16	8	16	32
Klebsiella 63	0,125	0,03	0,03	0,06	0,5
Klebsiella 8085	0,03	0,015	0,015	0,03	0,25
Proteus mir. 8223	8	16	4	8	8
Proteus vulg. 1017	0,5	0,25	0,06	0,25	1
Proteus morg. 932	0,06	0,03	0,015	0,06	1
Staph. aur. 133	0,25	0,125	0,06	0,03	0,015
Streptococc.faecal. 9790	2	1	0,5	0,5	0,25
Pseudomonas W.	8	4	1	1	4

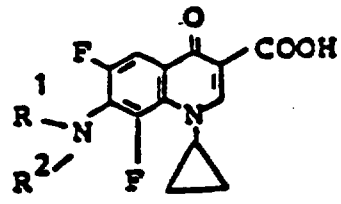
Agar dilution test

Isosensitest medium

Denley multipoint inoculator

Patent claims:

1. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the general formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5 -or 6-membered heterocyclic ring which can additionally contain as ring members the atoms or groups -O-, -S-, -SO-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 - 3 carbon atoms, amino, methylamino or ethylamino, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 6 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms for an alkyl radical, the cyano group, or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms

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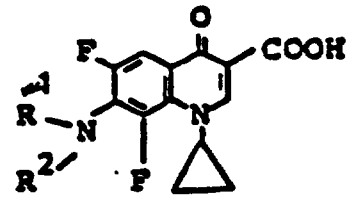
a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 is hydrogen, straight-chain or branched alkyl with 1 to 4 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 is straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl,

and their pharmaceutically acceptable salts.

2. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_3-alkyl radical optionally substituted by a hydroxyl or amino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain as ring members the atoms or groups -O-, -S-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono- or disubstituted on the carbon atoms by C_1-C_3-alkyl, hydroxyl, amino or methylamino, wherein each carbon atom can only

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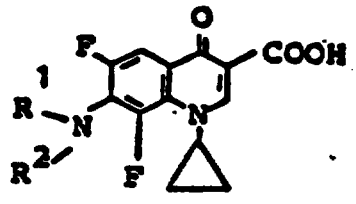
carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 4 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy or alkylmercapto group with 1 to 2 carbon atoms for an alkyl radical, the cyano group, or the alkoxycarbonyl group with 1 to 3 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group with up to 2 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenacyl radical, an oxoalkyl radical with up to 5 carbon atoms and also a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 2 carbon atoms in the acyclic part, furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 denotes hydrogen, straight-chain or branched alkyl with 1 to 3 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, methoxycarbonyl, carboxyl, alkoxy with 1 to 2 carbon atoms or trifluoromethylthio, phenyl optionally substituted by chlorine or hydroxyl, alkoxy or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 2 C atoms in the alkyl part or carboxyl, and

R^5 denotes methyl, ethyl, phenyl or methylphenyl.

3. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_2-alkyl radical optionally substituted by

a hydroxyl group and furthermore, together with the nitrogen atom to which they are bonded, can form a 6-membered heterocyclic ring which can additionally contain the group $>N-R^3$ as a ring member and which can optionally be mono- or disubstituted on the carbon atoms by C_1-C_2-alkyl or hydroxyl, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 3 carbon atoms which can optionally be substituted by a hydroxyl group or the alkoxycarbonyl group with 1 to 2 carbon atoms in the alcohol part, a benzyl group optionally substituted in the phenyl radical by amino, a phenacyl radical, an oxoalkyl radical with up to 4 carbon atoms and also a cyclopropylmethyl radical, furthermore denotes a radical COR^4 or SO_2R^5, wherein

R^4 denotes hydrogen, alkyl with 1 to 2 C atoms which is optionally substituted by a substituent from the series comprising amino or carbonyl, alkoxy with 1 to 2 C atoms or benzyloxy and

R^5 denotes methyl.

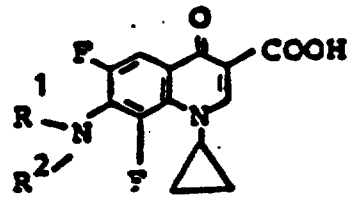
4. 1-Cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

5. 1-Cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

6. 1-Cyclopropyl-6,8-difluoro-7-(1-pyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

7. 1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

8. Process for the preparation of 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)



(I)

in which

* C L M S *

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain as ring members the atoms or groups -O-, -S-, -SO-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 - 3 carbon atoms, amino, methylamino or ethylamino, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 6 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms for an alkyl radical, the cyano group, or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and also a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, and furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 is hydrogen, straight-chain or branched alkyl with 1 to 4 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl optionally substi-

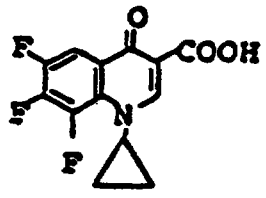
* C L M S *

tuted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 is straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl,

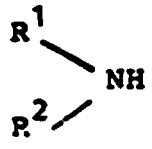
and their pharmaceutically acceptable salts, characterized in that either

a) trifluoroquinolinecarboxylic acid of the formula (II)



(II)

is reacted with amines of the formula (III)



(III)

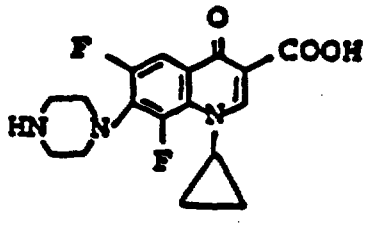
in which

R^1 and R^2 have the abovementioned meanings,

if appropriate in the presence of acid binders,

or

b) a 7-piperazinylquinolonecarboxylic acid of the formula (IV)



(IV)

in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent,

is reacted with compounds of the formula (V)

$$R^3X \qquad (V)$$

in which

R^3 has the abovementioned meaning, but cannot be

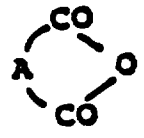
hydrogen, and

X denotes fluorine, chlorine, bromine, iodine, acyloxy, ethoxy, phenoxy, 4-nitrophenoxy,

in the presence of acid binders,

or

c) a piperazinyl-quinolonecarboxylic acid of the formula (IV) in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent, is reacted with anhydrides of the formula (VI)

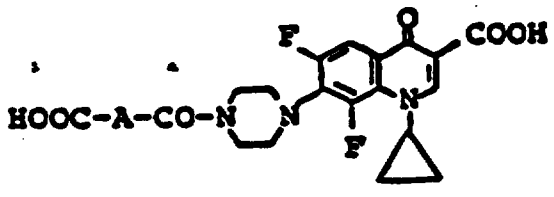


(VI)

in which

A denotes an optionally substituted alkylene chain with 2 or 3 carbon atoms or an arylene radical,

to give the compounds of the formula (Ia)



(Ia)

in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent,

or

d) a piperazinyl-quinolonecarboxylic acid of the formula IV in which the piperazinyl radical can be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, wherein each carbon atom can only carry one substituent, is reacted with Michael acceptors of the formula (VII)

$$B\text{-}CH{=}CH_2 \qquad \text{(VII)}$$

in which

B represents CN, CO-R^6 or $COOR^7$,

wherein

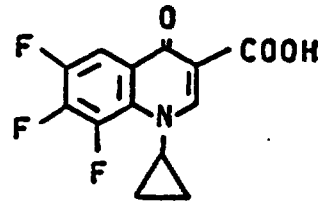
R^6 represents methyl or ethyl and

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R^7 represents methyl, ethyl, n- or i-propyl or benzyl.

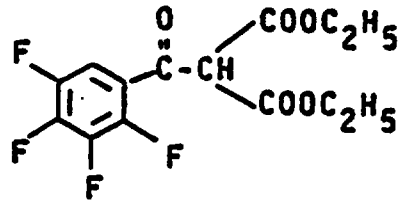
9. Medicament which contains at least one 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid according to Claim 1.

10. Process for the preparation of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (II)



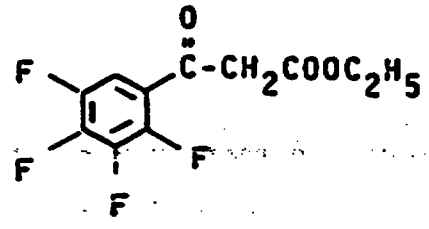
(II)

characterized in that diethyl malonate is acylated with 2,3,4,5-tetrafluorobenzoyl chloride in the presence of magnesium ethylate to give the aroyl malonic ester of the formula (3)



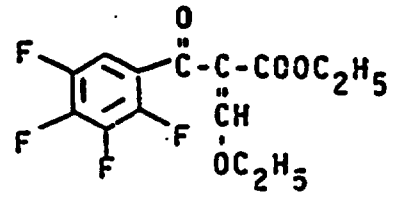
(3)

the aroyl malonic ester (3) is partially saponified in aqueous medium with catalytic amounts of sulphuric acid or p-toluenesulphonic acid and decarboxylated to give ethyl aroylacrylate of the formula (4)



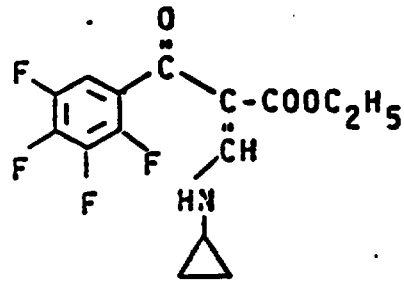
(4)

which is converted with triethyl orthoformate/acetic anhydride into ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate (5)



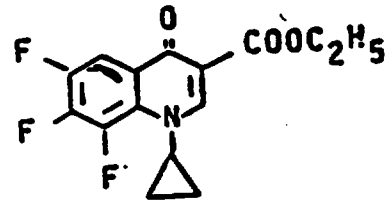
(5)

the compound of the formula (5) is converted with cyclopropylamine in a solvent such as methylene chloride, alcohol, chloroform, cyclohexane or toluene into a compound of the formula (6)



(6)

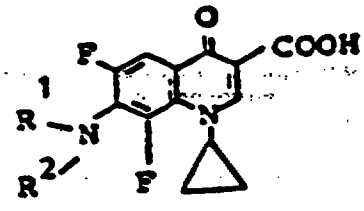
the compound of the formula (6) is cyclized at temperatures of about 60°C to 300°C in dioxane, dimethyl sulphoxide, N-methylpyrrolidone, sulpholane, hexamethylphosphoric triamide or dimethylformamide in the presence of an acid binder to give the compound of the formula (7)



(7)

and, if appropriate, the compound of the formula (7) is hydrolysed under acidic or basic conditions to give 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (II).

11. Use of compounds of the general formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain as ring members the atoms or groups -O-, -S-, -SO-, $-SO_2-$ or $>N-R^3$ and which can optionally be mono-, di- or trisubstituted on the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 - 3 carbon atoms, amino, methylamino or ethylamino, wherein each carbon atom can only carry one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkynyl group with 1 to 6 carbon atoms, which can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms for an alkyl radical, the cyano group, or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and which is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and also a cycloalkylalkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 is hydrogen, straight-chain or branched alkyl with 1 to 4 C atoms which is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or

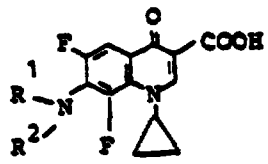
* C L M S *

trifluoromethylthio, phenyl optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino or alkylamino with 1 to 5 C atoms which is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 is straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl,

and their pharmaceutically acceptable salts, for the preparation of medicaments.

1. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecxylic acids of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical which is optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain, as a ring member, the atoms or groups —O—, —S—, —SO—, —SO_2— or >N—R^3 and which can optionally be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 to 3 carbon atoms, amino, methylamino or ethylamino, and each carbon atom concerned can carry only one substituent, wherein

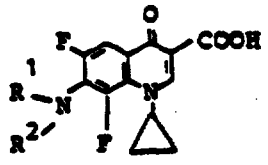
R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkinyl group which has 1 to 6 carbon atoms and can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms per alkyl radical, the cyano group or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical which is optionally mono- or di-

substituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical which is optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and a cycloalkyl-alkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, and also denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 represents hydrogen, straight-chain or branched alkyl which has 1 to 4 C atoms and is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl which is optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino, or alkylamino which has 1 to 5 C atoms and is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 represents straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl, and their pharmaceutically usable salts.

2. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_3-alkyl radical which is optionally substituted by a hydroxyl or amino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain, as a ring member, the atoms or groups —O—, —S—, —SO_2— or >N—R^3 and which can optionally be mono- to disubstituted at the carbon atoms by C_1-C_3-alkyl, hydroxyl, amino or methylamino, and each carbon atom concerned can carry only one substituent,

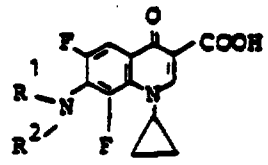
R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkinyl group which has 1 to 4 carbon atoms and can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy or alkylmercapto group with 1 to 2 carbon atoms per alkyl radical, the cyano group or the alkoxycarbonyl group with 1 to 3 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 2 carbon atoms in the aliphatic part and is optionally substituted in the phenyl radical by nitro or amino, a phenacyl radical, an oxoalkyl radical with up to 5 carbon atoms and a cycloalkyl-alkyl radical which has up to 6 carbon atoms in the cyclic part and up to 2 carbon atoms in the acyclic part, and furthermore denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 denotes hydrogen, straight-chain or branched alkyl which has 1 to 3 C atoms and is optionally substituted by 1 or 2 substituents from the series comprising amino, methoxycarbonyl, carbonyl, alkoxy with 1 to 2 carbon atoms or trifluoromethylthio, phenyl which is optionally substituted by chlorine or hydroxyl, alkoxy, or alkylamino which has 1 to 5 C atoms and is optionally substituted by alkoxycarbonyl with 1 to 2 C atoms in the alkyl part or carboxyl, and

R^5 denotes methyl, ethyl, phenyl or methylphenyl.

3. 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)

* C L M S *



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_2-alkyl radical which is optionally substituted by a hydroxyl group and furthermore, together with the nitrogen atom to which they are bonded, can form a 6-membered heterocyclic ring which can additionally contain the group $>N-R^3$ as a ring member and which can optionally be mono- to disubstituted at the carbon atoms by C_1-C_2-alkyl or hydroxyl, and each carbon atom concerned can carry only one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkinyl group which has 1 to 3 carbon atoms and can optionally be substituted by a hydroxyl group or the alkoxycarbonyl group with 1 to 2 carbon atoms in the alcohol part, a benzyl group which is optionally substituted in the phenyl radical by amino, a phenacyl radical, an oxoalkyl radical with up to 4 carbon atoms and a cyclopropylmethyl radical, and furthermore denotes a radical COR^4 or SO_2R^5, wherein

R^4 denotes hydrogen, alkyl which has 1 to 2 C atoms and is optionally substituted by a substituent from the series comprising amino or carboxyl, alkoxy with 1 to 2 C atoms or benzyloxy and

R^5 denotes methyl.

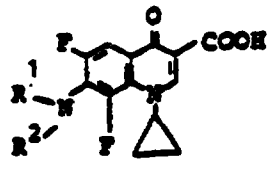
4. 1-Cyclopropyl-6,8-difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

5. 1-Cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

6. 1-Cyclopropyl-6,8-difluoro-7-(1-pyrrolidinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

7. 1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid.

8. Process for the preparation of 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinolinecarboxylic acids of the formula (I)



(I)

in which

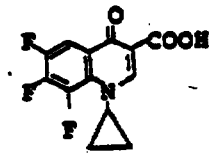
R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical which is optionally substituted by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain, as a ring member, the atoms or groups —O—, —S—, —SO—, —SO_2— or $>N-R^3$ and which can optionally be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 to 3 carbon atoms, amino, methylamino or ethylamino, and each carbon atom concerned can carry only one substituent, wherein

R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkinyl group which has 1 to 6 carbon atoms and can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms per alkyl radical, the cyano group or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical which is optionally mono- or di-substituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical which is optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and a cycloalkyl-alkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, and also denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 represents hydrogen, straight-chain or branched alkyl which has 1 to 4 C atoms and is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl which is optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino, or alkylamino which has 1 to 5 C atoms and is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 represents straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl, and their pharmaceutically usable salts, characterised in that either

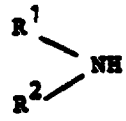
a) trifluoro-quinolinecarboxylic acid of the formula (II)



(II)

* C L M S *

is reacted with amines of the formula (III)



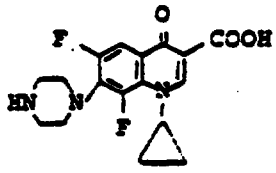
(III)

in which

R^1 and R^2 have the abovementioned meaning, if appropriate in the presence of acid-binding agents.

or

b) a 7-piperazinylquinolonecarboxylic acid of the formula (IV)



(IV)

in which the piperazinyl radical can be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, and each carbon atom concerned can carry only one substituent,

is reacted with compounds of the formula (V)

$$R^3X \qquad (V)$$

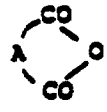
in which

R^3 has the abovementioned meaning, but cannot be hydrogen, and

X denotes fluorine, chlorine, bromine, iodine, acyloxy, ethoxy, phenoxy or 4-nitrophenoxy,

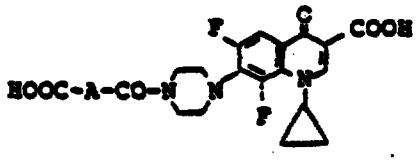
in the presence of acid-binding agents, or

c) a piperazinyl-quinolonecarboxylic acid of the formula (IV) in which the piperazinyl radical can be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, and each carbon atom concerned can carry only one substituent, is reacted with anhydrides of the formula (VI)



(VI)

in which A denotes an optionally substituted alkylene chain with 2 or 3 carbon atoms or an arylene radical, to give the compounds of the formula (Ia)



(Ia)

in which the piperazinyl radical can be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, and each carbon atom concerned can carry only one substituent, or

d) a piperazinyl-quinolonecarboxylic acid of the formula IV, in which the piperazinyl radical can be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, and each carbon atom concerned can carry only one substituent, is reacted with Michael acceptors of the formula (VII)

$$B\text{—}CH{=}CH_2 \qquad (VII)$$

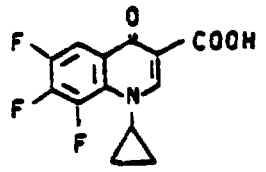
in which B represents CN, CO—R^6 or $COOR^7$, wherein

R^6 represents methyl or ethyl and

R^7 represents methyl, ethyl, n- or i-propyl or benzyl.

9. Medicaments, characterised by a content of at least one 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid according to Claim 1.

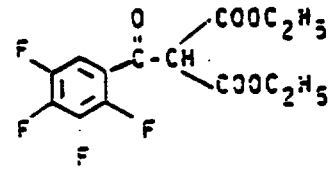
10. Process for the preparation of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (II)



(II)

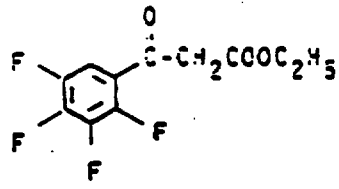
* C L M S *

characterised in that diethyl malonate is acylated in the presence of magnesium methylate with 2,3,4,5-tetrafluorobenzoyl chloride to give the aroylmalonic ester of the formula (3)



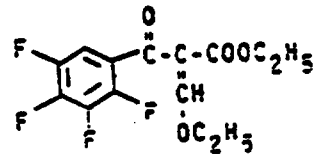
(3)

the aroylmalonic ester (3) is partially saponified and decarboxylated in an aqueous medium with catalytic quantitites of sulphuric acid or p-toluenesulphonic acid, to give ethyl aroylacetate of the formula (4)



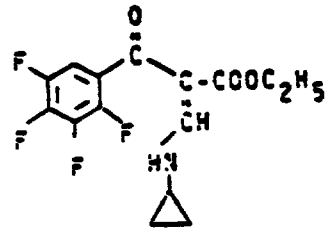
(4)

the latter is converted with triethyl o-formate/acetic anhydride into ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxy-acrylate (5),



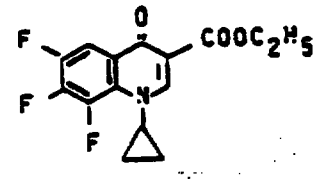
(5)

the compound of the formula (5) is converted with cyclopropylamine in a solvent such as methylene chloride, alcohol, chloroform, cyclohexane or toluene, into a compound of the formula (6)



(6)

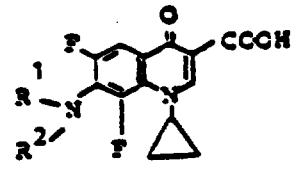
the compound of the formula (6) is cyclised, at temperatures of about 60 °C to 300 °C in dioxane, dimethyl sulphoxide, N-methyl-pyrrolidone, sulpholane, hexamethylphosphoric acid triamide or dimethyl formamide, in the presence of an acid-binding agent, to give the compound of the formula (7)



(7)

and, if desired, the compound of the formula (7) is hydrolysed, under acid or basic conditions to give 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (II).

11. Use of compounds of the general formula (I)



(I)

in which

R^1 and R^2 can be identical or different and represent a C_1-C_4-alkyl radical which is optionally substitued by a hydroxyl, amino, methylamino or dimethylamino group and furthermore, together with the nitrogen atom to which they are bonded, can form a 5- or 6-membered heterocyclic ring which can additionally contain, as a ring member, the atoms or groups —O—, —S—, —SO—, —SO_2— or $\geq N-R^3$ and which can optionally be mono- to trisubstituted at the carbon atoms by C_1-C_4-alkyl, hydroxyl, alkoxy with 1 to 3 carbon atoms, amino, methylamino or ethylamino, and each carbon atom concerned can carry only one substituent, wherein

* C L M S *

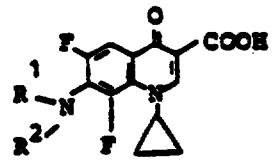
R^3 represents hydrogen, a branched or unbranched alkyl, alkenyl or alkinyl group which has 1 to 6 carbon atoms and can optionally be substituted by a hydroxyl, trifluoromethylmercapto, alkoxy, alkylmercapto, alkylamino or dialkylamino group with 1 to 3 carbon atoms per alkyl radical, the cyano group or the alkoxycarbonyl group with 1 to 4 carbon atoms in the alcohol part, the benzyloxycarbonyl group, a phenylalkyl group which has up to 4 carbon atoms in the aliphatic part and is optionally substituted in the phenyl radical by nitro or amino, a phenyl radical which is optionally mono- or di-substituted by hydroxyl, methoxy, chlorine and fluorine, a phenacyl radical which is optionally mono- or disubstituted by hydroxyl, methoxy, chlorine and fluorine, an oxoalkyl radical with up to 6 carbon atoms and a cycloalkyl-alkyl radical with up to 6 carbon atoms in the cyclic part and up to 3 carbon atoms in the acyclic part, and also denotes a radical COR^4, CN or SO_2R^5, wherein

R^4 represents hydrogen, straight-chain or branched alkyl which has 1 to 4 C atoms and is optionally substituted by 1 or 2 substituents from the series comprising amino, alkoxycarbonyl with 1 to 3 carbon atoms in the alkyl part, carboxyl, alkoxy with 1 to 3 carbon atoms or trifluoromethylthio, phenyl which is optionally substituted by chlorine, hydroxyl, amino or carboxyl, alkoxy with 1 to 4 C atoms, alkylthio with 1 to 2 C atoms, benzyloxy, amino, or alkylamino which has 1 to 5 C atoms and is optionally substituted by alkoxycarbonyl with 1 to 3 C atoms in the alkyl part or carboxyl, and

R^5 represents straight-chain or branched alkyl with 1 to 3 C atoms, phenyl or methylphenyl, and their pharmaceutically usable salts, for the preparation of medicaments.

Revendications

1. Acides 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoléine-carboxyliques de formule I



(I)

dans laquelle

R^1 et R^2, qui peuvent avoir des significations identiques ou différentes, représentent chacun un groupe alkyle en C_1-C_4 éventuellement substitué par un groupe hydroxy, amino, méthylamino ou diméthylamino, ou bien forment ensemble et avec l'atome d'azote auquel ils sont reliés un noyau hétérocyclique à 5 ou 6 chaînons contenant en outre, en tant que chaînons cycliques, les atomes ou groupes —O—, —S—, —SO—, —SO_2— ou >N—R^3 et qui peut le cas échéant être mono- à trisubstitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, hydroxy, alcoxy en C_1-C_3, amino, méthylamino ou éthylamino, chaque atome de carbone ne pouvant porter qu'un seul substituant,

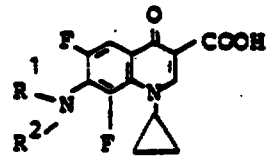
R^3 représente l'hydrogène ou un groupe alkyle, alcényle ou alcynyle droit ou ramifié en C_1-C_6 qui peut être le cas échéant substitué par un groupe hydroxy, trifluorométhylmercapto, alcoxy, alkylmercapto, alkylamino ou dialkylamino contenant 1 à 3 atomes de carbone par groupe alkyle, le groupe cyano, le groupe alcoxycarbonyle contenant 1 à 4 atomes de carbone dans la partie alcoolique, le groupe benzyloxycarbonyle, un groupe phénylalkyle contenant jusqu'à 4 atomes de carbone dans la partie aliphatique, éventuellement substitué dans la partie phényle par des groupes nitro ou amino, un groupe phényle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un groupe phénacyle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un groupe oxoalkyle contenant jusqu'à 6 atomes de carbone ou un groupe cycloalkyl-alkyle contenant jusqu'à 6 atomes de carbone dans la partie cyclique et jusqu'à 3 atomes de carbone dans la partie acyclique, ou un reste COR^4, CN ou SO_2R^5,

R^4 représente l'hydrogène, un groupe alkyle à chaîne droite ou ramifiée en C_1-C_4 portant éventuellement 1 ou 2 substituants choisis parmi les groupes amino, alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle, carboxy, alcoxy en C_1-C_3 ou trifluorométhylthio, un groupe phényle éventuellement substitué par le chlore, des groupes hydroxy, amino ou carboxy, un groupe alcoxy en C_1-C_4, alkylthio en C_1-C_2, benzyloxy, amino, alkylamino en C_1-C_5 éventuellement substitué par un groupe alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle ou par un groupe carboxy,

R^5 représente un groupe alkyle à chaîne droite ou ramifiée en C_1-C_3, phényle ou méthylphényle, et leurs sels acceptables pour l'usage pharmaceutique.

2. Acides 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoléine-carboxyliques de formule I

* C L M S *



(I)

dans laquelle

R^1 et R^2, qui peuvent avoir des significations identiques ou différentes, représentent chacun un groupe alkyle en C_1-C_3 éventuellement substitué par un groupe hydroxy ou amino ou forment ensemble et avec l'atome d'azote auquel ils sont reliés un noyau hétérocyclique à 5 ou 6 chaînons contenant en

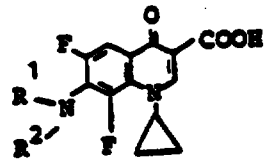
outre, en tant que chaînons cycliques, les atomes ou groupes —O—, —S—, —SO_2— ou $\geq$N—R^3 et qui peut le cas échéant être mono- ou di-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_3, hydroxy, amino ou méthylamino, chaque atome de carbone ne pouvant porter qu'un seul substituant,

R^3 représente l'hydrogène, un groupe alkyle, alcényle ou alcynyle à chaîne droite ou ramifiée en C_1-C_4, qui peut le cas échéant être substitué par un groupe hydroxy, trifluorométhylmercapto, alcoxy ou alkylmercapto contenant 1 ou 2 atomes de carbone par groupe alkyle, le groupe cyano, le groupe alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alcoolique, le groupe benzyloxycarbonyle, un groupe phénylalkyle contenant jusqu'à 2 atomes de carbone dans la partie aliphatique, éventuellement substitué dans la partie phényle par des groupes nitro ou amino, un radical phénacyle, un groupe oxoalkyle contenant jusqu'à 5 atomes de carbone ou un groupe cycloalkyl-alkyle contenant jusqu'à 6 atomes de carbone dans la partie cyclique et jusqu'à 2 atomes de carbone dans la partie acyclique, ou encore un reste COR_4, CN ou SO_2R^5,

R^4 représente l'hydrogène, un groupe alkyle à chaîne droite ou ramifiée en C_1-C_3 portant éventuellement 1 ou 2 substituants choisis parmi les groupes amino, méthoxycarbonyle, carboxy, alcoxy en C_1-C_2 ou trifluorométhylthio, un groupe phényle éventuellement substitué par le chlore ou un groupe hydroxy, un groupe alcoxy, un groupe alkylamino en C_1-C_3 éventuellement substitué par un groupe alcoxycarbonyle contenant 1 à 2 atomes de carbone dans la partie alkyle ou par un groupe carboxy, et

R^5 représente un groupe méthyle, éthyle, phényle ou méthylphényle.

3. Acides 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoléine-carboxyliques de formule I



(I)

dans laquelle

R^1 et R^2, qui peuvent avoir des significations identiques ou différentes, représentent chacun un groupe alkyle en C_1-C_2 éventuellement substitué par un groupe hydroxy ou forment ensemble et avec l'atome d'azote auquel ils sont reliés un noyau hétérocyclique à 6 chaînons qui peut contenir en outre en tant que chaînon cyclique le groupe $\geq$N—R^3 et qui peut le cas échéant être mono- ou di-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_2 ou hydroxy, chaque atome de carbone ne pouvant porter qu'un seul substituant,

R^3 représente l'hydrogène, un groupe alkyle, alcényle ou alcynyle à chaîne droite ou ramifiée en C_1-C_3 qui peut le cas échéant être substitué par un groupe hydroxy, le groupe alcoxycarbonyle contenant 1 à 2 atomes de carbone dans la partie alcoolique, un groupe benzyle éventuellement substitué dans la partie phényle par un groupe amino, un radical phénacyle, un groupe oxoalkyle contenant jusqu'à 4 atomes de carbone ou un groupe cyclopropylméthyle, ou encore un reste COR^4 ou SO_2R^5,

R^4 représente l'hydrogène, un groupe alkyle en C_1-C_2, alcoxy en C_1-C_2 ou benzyloxy portant éventuellement un substituant choisi parmi les groupes amino ou carboxy, et

R^5 représente un groupe méthyle.

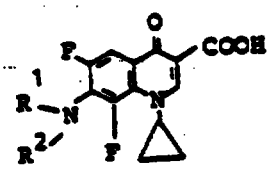
4. L'acide 1-cyclopropyl-6,8-difluoro-7-(1-pipérazynyl)-1,4-dihydro-4-oxo-3-quinoléine-carboxylique.

5. L'acide 1-cyclopropyl-6,8-difluoro-7-(4-méthyl-1-pipérazinyl)-1,4-dihydro-4-oxo-3-quinoléine-carboxylique.

6. L'acide 1-cyclopropyl-6,8-difluoro-7-(1-pyrrolidinyl)-1,4-dihydro-4-oxo-3-quinoléine-carboxylique.

7. L'acide 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinoléine-carboxylique.

8. Procédé de préparation des acides 7-amino-1-cyclo-propyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoléine-carboxyliques de formule I



(I)

dans laquelle

R^1 et R^2, qui peuvent avoir des significations identiques ou différentes, représentent chacun un groupe alkyle en C_1-C_4 éventuellement substitué par un groupe hydroxy, amino, méthylamino ou diméthylamino, ou bien forment ensemble et avec l'atome d'azote auquel ils sont reliés un noyau hétérocyclique à 5 ou 6 chaînons contenant en outre, en tant que chaînons cycliques, les atomes ou groupes —O—, —S—, —SO—, —SO_2— ou $\geq$N—R^3 et qui peut le cas échéant être mono- à trisubstitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, hydroxy, alcoxy en C_1-C_3, amino, méthylamino ou éthylamino, chaque atome de carbone ne pouvant porter qu'un seul substituant,

R^3 représente l'hydrogène ou un groupe alkyle, alcényle ou alcynyle droit ou ramifié en C_1-C_6 qui

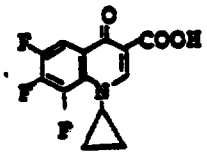
* C L M S *

peut être le cas échéant substitué par un groupe hydroxy, trifluorométhylmercapto, alcoxy, alkylmercapto, alkylamino ou dialkylamino contenant 1 à 3 atomes de carbone par groupe alkyle, le groupe cyano, le groupe alcoxycarbonyle contenant 1 à 4 atomes de carbone dans la partie alcoolique, le groupe benzyloxycarbonyle, un groupe phénylalkyle contenant jusqu'à 4 atomes de carbone dans la partie aliphatique, éventuellement substitué dans la partie phényle par des groupes nitro ou amino, un groupe phényle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un groupe phénacyle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un groupe oxoalkyle contenant jusqu'à 6 atomes de carbone ou un groupe cycloalkyl-alkyle contenant jusqu'à 6 atomes de carbone dans la partie cyclique et jusqu'à 3 atomes de carbone dans la partie acyclique ou un reste COR^4, CN ou SO_2R^5,

R^4 représente l'hydrogène, un groupe alkyle à chaîne droite ou ramifiée en C_1-C_4 portant éventuellement 1 à 2 substituants choisis parmi les groupes amino, alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle, carboxy, alcoxy en C_1-C_3 ou trifluorométhylthio, un groupe phényle éventuellement substitué par le chlore, des groupes hydroxy, amino ou carboxy, un groupe alcoxy en C_1-C_4, alkylthio en C_1-C_2, benzyloxy, amino, alkylamino en C_1-C_3 éventuellement substitué par un groupe alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle ou par un groupe carboxy,

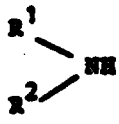
R^5 représente un groupe alkyle à chaîne droite ou ramifiée en C_1-C_3, phényle ou méthylphényle, et de leurs sels acceptables pour l'usage pharmaceutique, caractérisé en ce que :

a) ou bien on fait réagir l'acide trifluoro-quinoléine-carboxylique de formule II



(II)

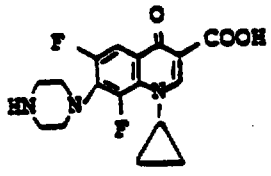
avec des amines de formule III



(III)

dans laquelle R^1 et R^2 ont les significations indiquées ci-dessus, éventuellement en présence d'accepteurs d'acides,

b) ou bien on fait réagir un acide 7-pipérazinyl-quinolone-carboxylique de formule IV



(IV)

dans laquelle le groupe pipérazinyle peut être mono à tri-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, chaque atome de carbone ne pouvant porter qu'un seul substituant, avec des composés de formule V

$$R^3X \qquad (V)$$

dans laquelle

R^3 a les significations indiquées ci-dessus à l'exception de l'hydrogène, et

X représente le fluor, le chlore, le brome, l'iode, un groupe alcoxy, éthoxy, phénoxy, 4-nitrophénoxy, en présence d'accepteurs d'acides,

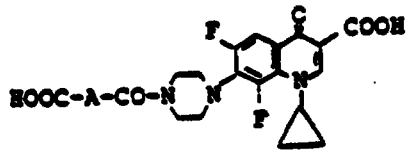
c) ou bien on fait réagir un acide pipérazinyl-quinolone-carboxylique de formule IV dans lequel le groupe pipérazinyle peut être mono- à tri-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, chaque atome de carbone ne pouvant porter qu'un seul substituant, avec des anhydrides de formule VI



(VI)

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dans laquelle A représente une chaine alkylène en C_2 ou C_3 éventuellement substituée ou un radical arylène, ce qui donne les composés de formule Ia



(Ia)

dans lesquels le groupe pipérazinyle peut être mono- à tri-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, chaque atome de carbone ne pouvant porter qu'un seul substituant,

d) ou bien on fait réagir un acide pipérazinyl-quinolone-carboxylique de formule IV dans lequel le groupe pipérazinyle peut être mono- à tri-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, chaque atome de carbone ne pouvant porter qu'un seul substituant, avec des accepteurs de Michael de formule VII

$$B—CH=CH_2 \qquad \text{(VII)}$$

dans laquelle

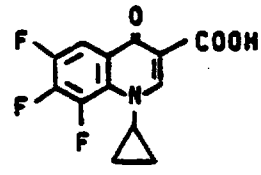
B représente CN, CO—R^6 ou $COOR^7$,

R^6 représente un groupe méthyle ou éthyle, et

R^7 représente un groupe méthyle, éthyle, n- ou iso-propyle ou benzyle.

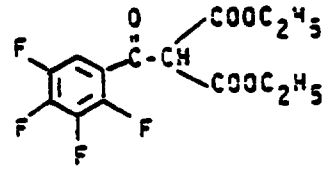
9. Médicament caractérisé en ce qu'il contient au moins un acide 7-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinoléine-carboxylique selon la revendication 1.

10. Procédé de préparation de l'acide 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinoléine-carboxylique de formule II



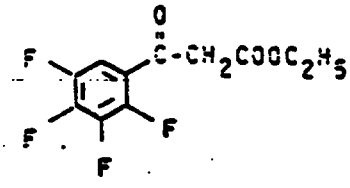
(II)

caractérisé en ce que l'on acyle le malonate de diéthyle en présence d'éthylate de magnésium à l'aide du chlorure de 2,3,4,5-tétrafluorobenzoyle, ce qui donne l'ester aroylmalonique de formule (3)



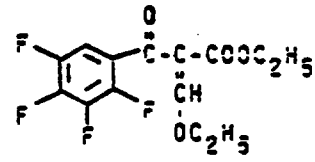
(3)

qu'on soumet à saponification partielle et décarboxylation en milieu aqueux à l'aide de quantités catalytiques d'acide sulfurique ou d'acide p-toluène-sulfonique, ce qui donne l'aroylacétate d'éthyle de formule (4)



(4)

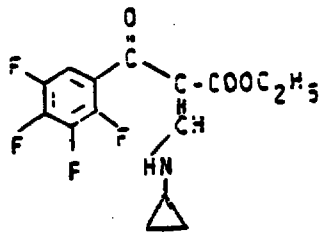
qu'on convertit à l'aide de l'orthoformiate de triéthyle/anhydride acétique en le 2-(2,3,4,5-tétrafluorobenzoyl)-3-éthoxy-acrylate d'éthyle (5).



(5)

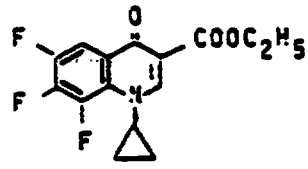
qu'on convertit à l'aide de la cyclopropylamine dans un solvant tel que le chlorure de méthylène, l'alcool, le chloroforme, le cyclohexane ou le toluène en un composé de formule (6)

* C L M S *



(6)

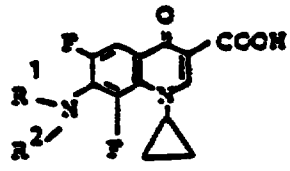
qu'on cyclise à des températures de 60 à 300 °C environ dans le dioxanne, le diméthylsulfoxyde, la N-méthylpyrrolidone, le sulfolan, l'hexaméthylphosphorotriamide ou le diméthylformamide en présence d'un accepteur d'acide, en un composé de formule VII



(7)

qu'on hydrolyse le cas échéant en milieu acide ou basique, en l'acide 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinoléine-carboxylique II.

11. Utilisation des composés de formule générale I



(I)

dans laquelle

R^1 et R^2, qui peuvent avoir des significations identiques ou différentes, représentent chacun un groupe alkyle en C_1-C_4 éventuellement substitué par un groupe hydroxy, amino, méthylamino ou diméthylamino ou forment ensemble et avec l'atome d'azote auquel ils sont reliés un hétérocycle à 5 ou 6 chaînons qui peut contenir en outre en tant que chaînons cycliques les atomes ou groupes —O—, —S—, —SO—, $—SO_2—$ ou $>N—R^3$ et qui peut le cas échéant être mono- à tri-substitué sur les atomes de carbone par des groupes alkyle en C_1-C_4, hydroxy, alcoxy en C_1-C_3, amino, méthylamino ou éthylamino, chaque atome de carbone ne pouvant porter qu'un seul substituant,

R^3 représente l'hydrogène, un groupe alkyle, alcényle ou alcynyle droit ou ramifié en C_1-C_6, qui peut le cas échéant être substitué par un groupe hydroxy, trifluorométhylmercapto, alcoxy, alkylmercapto, alkylamino ou dialkylamino contenant 1 à 3 atomes de carbone dans chaque groupe alkyle, le groupe cyano, un groupe alcoxycarbonyle contenant 1 à 4 atomes de carbone dans la partie alcoolique, le groupe benzyloxycarbonyle, un groupe phénylalkyle contenant jusqu'à 4 atomes de carbone dans la partie aliphatique et éventuellement substitué dans le noyau phényle par des groupes nitro ou amino, un groupe phényle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un radical phénacyle éventuellement mono- ou di-substitué par des groupes hydroxy, méthoxy, le chlore et le fluor, un groupe oxoalkyle contenant jusqu'à 6 atomes de carbone ou un groupe cycloalkyl-alkyle contenant jusqu'à 6 atomes de carbone dans la partie cyclique et jusqu'à 3 atomes de carbone dans la partie acyclique, ou un reste COR^4, CN ou SO_2R^5,

R^4 représente l'hydrogène, un groupe alkyle à chaîne droite ou ramifiée en C_1-C_4 portant le cas échéant 1 ou 2 substituants choisis parmi les groupes amino, alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle, carboxy, alcoxy en C_1-C_3 ou trifluorométhylthio, un groupe phényle éventuellement substitué par le chlore, des groupes hydroxy, amino ou carboxy, un groupe alcoxy en C_1-C_4, alkylthio en C_1-C_2, benzyloxy, amino, alkylamino en C_1-C_3 éventuellement substitué par un groupe alcoxycarbonyle contenant 1 à 3 atomes de carbone dans la partie alkyle ou par un groupe carboxy.

R^5 représente un groupe alkyle à chaîne droite ou ramifiée en C_1-C_3, phényle ou méthylphényle, et de leurs sels acceptables pour l'usage pharmaceutique, pour la préparation de médicaments.

* C L M S *