2093018

(12)

"Quinoline Carboxylic Acid Derivatives and their Preparation"

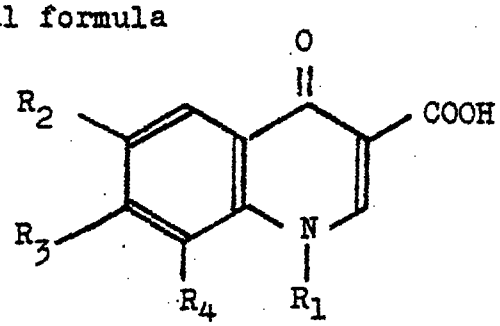
This invention relates to certain quinoline carboxylic acid derivatives, which are new and useful, having potent antibacterial activities, as well as their preparation.

Antibacterial agents such as nalidixic acid, piromidic acid and pipemidic acid have proved highly effective in the treatment of infections due to gram-negative bacteria, but such antibacterial agents suffer from the serious disadvantage of having only weak activities against most gram-positive bacteria and Pseudomonas aeruginosa.

Accordingly, attempts have been made to produce anti-bacterial agents having a wider spectrum of activity, and indeed the present Applicants themselves, in their earlier copending Application for Letters Patent No. 80-27372 (to be published as Specification Serial No. 2,057,440 A) have disclosed that certain 1,6,7,8-tetrasubstituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acids have still greater activity against gram-negative bacteria, including Pseudomonas aeruginosa, than the above-mentioned compounds, whilst still having potent anti-bacterial activity against gram-positive bacteria and other micro-organisms.

The 1,6,7,8-tetrasubstituted-1,4-dihydro-4-oxo-quinoline-3-carboxylic acids disclosed and claimed in our

Application No. 80-27372 aforesaid were the compounds of the general formula

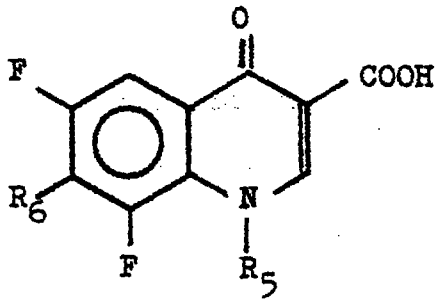


(I)

(wherein R_2 is a halogen atom; R_3 is a 1-piperazinyl radical which may optionally be substituted at the 4-position by an alkyl radical of from 1 to 5 carbon atoms; and <u>either</u> R_1 is an alkyl radical of from 1 to 5 carbon atoms and R_4 is a halogen atom or an alkyl radical of from 1 to 5 carbon atoms, <u>or</u> R_1 and R_4 each represent an alkylene radical and together with the intervening nitrogen atom and carbon atoms form a 5 or 6 membered ring which may optionally be substituted by an alkyl radical of from 1 to 5 carbon atoms) and the hydrates and salts thereof.

We have now found further 1,6,7,8-tetrasubstituted-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives which are particularly useful in that they possess potent antibacterial activity against both Gram-positive and Gram-negative bacteria, including <u>Pseudomonas aeruginosa</u>.

According to one aspect of the present invention there are now provided the 1,7-disubstituted-6,8-difluoro 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids of the general formula:



(II)

(wherein R_5 is an alkyl radical having from 1 to 5 carbon atoms and R_6 is a 1-piperazinyl radical, optionally substituted at the 4-position by an alkyl group, provided that when R_5 is an ethyl group then R_6 is not a 1-piperazinyl or 4-methyl-1-piperazinyl radical) and the hydrates and salts thereof.

Preferred quinoline carboxylic acid derivatives of general formula II above are those wherein R_5 is an alkyl radical having from 1 to 3 carbon atoms. Especially preferred derivatives are those wherein R_5 is a methyl or n-propyl radical and R_6 is a 1-piperazinyl radical, or those wherein R_5 is an ethyl radical and R_6 is a 4-ethyl-1-piperazinyl radical, as well as their hydrates and salts. A more restricted and preferred group of quinoline carboxylic acid derivatives of general formula II above are those wherein R_5 is an alkyl radical having either 1 or 3 carbon atoms and R_6 is a 1-piperazinyl radical, optionally substituted at the 4-position by an alkyl group.

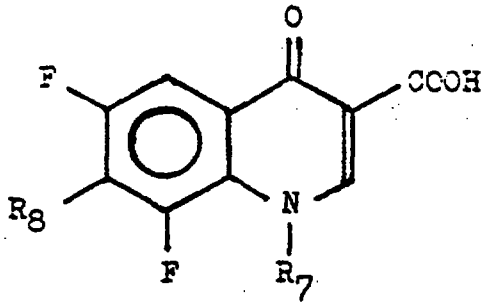
Specific preferred 1,7-disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives of general formula II above are:

- 6,8-difluoro-1,4-dihydro-1-methyl-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts;

- 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-n-propylquinoline-3-carboxylic acid, and its hydrates and salts; and

- 1-ethyl-7-(4-ethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

According to another aspect of the present invention there are also now provided the 1,7-disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acids of general formula:



(III)

(wherein R_7 is an alkyl, hydroxy-alkyl, halogeno-alkyl, or alkenyl (in particular allyl or vinyl) radical and R_8 is a 1-piperazinyl radical (which may optionally be substituted at the 4-position by an alkyl, hydroxy-alkyl, or alkenyl (in particular allyl) radical), a 1-piperidinyl radical (which may optionally be substituted at the 3- and/or 4-positions by a hydroxy or a dimethyl-amino radical), a 1-pyrrolidinyl radical or a 4-morpholinyl radical, provided that when R_7 is an alkyl group having from 1 to 5 carbon atoms then R_8 is neither an unsubstituted

1-piperazinyl radical nor a 1-piperazinyl radical substituted at the 4 position by an alkyl radical) and their hydrates and salts.

Preferred quinoline carboxylic acid derivatives of general formula III above are those wherein the alkyl, hydroxy-alkyl, halogeno-alkyl or alkenyl radicals have no more than 5 carbon atoms, and advantageously not more than 3 carbon atoms. Specifically preferred compounds are those wherein R_7 is a 2-hydroxy-ethyl or 2-fluoroethyl or vinyl radical, and/or those wherein R_8 is a 4-methyl-, 4-ethyl-, 4-(2-hydroxy-ethyl)- or 4-allyl-1-piperazinyl radical or is a 3-hydroxy- or 4-hydroxy- or 4-dimethylamino-1-piperidinyl radical.

Preferred quinoline carboxylic acid derivatives of general formula III are those wherein <u>either</u> R_7 is an allyl, 2-fluoroethyl, 2-hydroxyethyl or vinyl radical and R_8 is a 1-piperazinyl radical <u>or</u> R_7 is an ethyl radical and R_8 is a 1-pyrrolidinyl, 4-morpholinyl, 3-hydroxy-, 4-hydroxy- or 4-dimethylamino-1-piperidinyl or a 4-allyl- or 4-(2-hydroxy-ethyl)-1-piperazinyl radical, <u>or</u> R_7 is a 2-fluoroethyl radical and R_8 is a 4-methyl-1-piperazinyl radical, as well as the hydrates and salts thereof.

A more restricted and preferred group of quinoline carboxylic acid derivatives of general formula III are those wherein either R_7 is an allyl or 2-hydroxyethyl radical and R_8 is a 1-piperazinyl radical, <u>or</u> R_7 is an

ethyl radical and R_8 is a 4-hydroxy, 3-hydroxy- or 4-dimethylamino-1-piperidinyl, 4-morpholinyl or 1-pyrrolidinyl radical, as well as the hydrates and salts thereof.

Specific preferred 1,7-disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives of general formula III above are:

- 1-allyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts;

- 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts;

- 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 7-(4-allyl-1-piperazinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-7-[4-(2-hydroxyethyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)quinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-morpholinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

- 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-dimethylamino-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts;

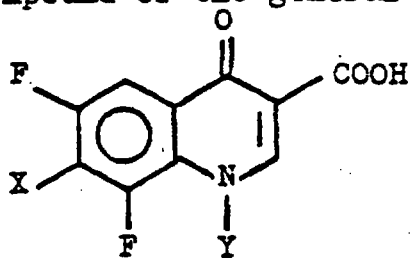
- 6,8-difluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts; and

- 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-vinylquinoline-3-carboxylic acid, and its hydrates and salts.

The salts of the acids of general formulae II and III above may be those formed with any non-toxic cations, such as calcium, magnesium, aluminium, ceric, chromic, cobaltic, cupric, ferric, silver and zinc cations, as well as the cations of organic bases and non-toxic anions such as hydrochlorides, sulphates, phosphates, acetates, lactates, and methanesulphonates or the like. They can of course be obtained in the usual manner.

According to another aspect of this invention there is provided a process for the preparation of the 1,7-di-substituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3--carboxylic acids of general formulae II or III above, and their hydrates and salts, in

which a compound of the general formula



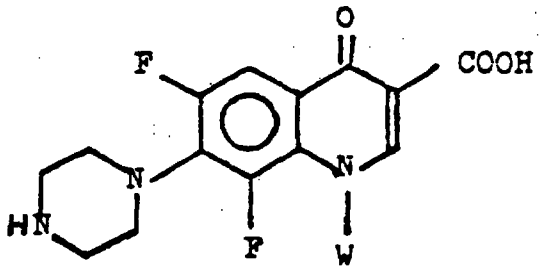
(IV)

(in which X is a halogen atom and Y is either R_5 or R_7 as hereinbefore defined) or an hydrate or salt thereof is reacted with a compound of general formula

Z-H (V)

wherein Z is either R_6 or R_8 as hereinbefore defined, to form the desired corresponding acid of general formula II or III or hydrate or salt thereof.

According to another aspect of this invention there is provided a process for the preparation of the 1,7-di-substituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3--carboxylic acids of general formulae II or III above, and their hydrates and salts, in which a compound of the general formula



(VI)

(wherein W is either R_5 or R_7 as hereinbefore defined) or its hydrate or salt is reacted with a halide of general formula

Q.X (VII)

(wherein X is a halogen atom and



is either R_6 or R_8 as hereinbefore defined) to form the desired corresponding 7-substituted-piperazinyl derivative of general formula II or III or its hydrate or salt.

It will of course be understood that the preferred processes of this invention are those wherein the starting materials are such as to yield the preferred classes and specific preferred compounds hereinbefore identified.

According to a still further aspect of this invention there is also provided a process for producing 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-vinyl-quinoline-3-carboxylic acid, or its hydrates or salts, in which 7-(4-acetyl-1-piperazinyl)-1-(2-chloro-ethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester is subjected to treatment with alkali.

The invention of course extends also to the 1,7-di-substituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, and their hydrates and salts, whenever prepared in or by any of the processes herein described.

(21)

In order that the invention may be well understood it will now be described in further detail, but by way of illustration only, with reference to the following Examples:-

Example 1 — 6,8-Difluoro-1,4-dihydro-1-methyl-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride

A mixture of 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxo-quinoline-3-carboxylic acid (0.22 g), piperazine (0.37 g), and pyridine (3 ml) was refluxed for 4 hours. The reaction mixture was evaporated to dryness. The residue was acidified by the addition of hot aqueous acetic acid solution and the insoluble materials were removed by filtration. The filtrate was acidified to pH 1 with concentrated hydrochloric acid and cooled. The resulting precipitate was filtered off and recrystallized from water to give 6,8-difluoro-1,4-dihydro-1-methyl-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride (0.13 g), mp 286-288°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{15}H_{15}F_2N_3O_3$ HCl :	50.08	4.48	11.68
Found :	49.98	4.38	11.58

The starting material, 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylic acid, was obtained by the following method.

A mixture of 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (0.3 g), anhydrous potassium carbonate (0.8 g), methyl iodide (1.6 g), and N,N-dimethyl-formamide (DMF)(10 ml) was heated with stirring at 90-100°C for 10 hours. The mixture was evaporated to dryness. The residue was treated with water and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated. The residue was added to a mixture of 18 % hydrochloric acid (5 ml) and ethanol (2.5 ml) and the mixture was refluxed for 2.5 hours. After water (5 ml) and ethanol (5 ml) had been added and the mixture cooled, the resulting precipitate was filtered off and recrystallized from a mixture of DMF and ethanol to give 0.22g of 6,7,8-trifluoro-1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylic acid, mp 255-258°C.

Example 2 — 6,8-Difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-n-propylquinoline-3-carboxylic acid hydrochloride

A mixture of 6,7,8-trifluoro-1,4-dihydro-4-oxo-1-n-propyl-quinoline-3-carboxylic acid (0.22 g), piperazine (0.34 g), and pyridine (3 ml) was refluxed for 6 hours. The mixture was evaporated to dryness, adjusted to pH 1 with

aqueous hydrochloric acid solution, and cooled. The solid was filtered off and recrystallized from water to afford 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-n-propylquinoline-3-carboxylic acid hydrochloride (0.11 g), mp 279-282°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{17}H_{19}F_2N_3O_3$ HCl :	52.65	5.20	10.83
Found :	52.46	5.16	10.63

The preparation of the starting material, 6,7,8-trifluoro-1,4-dihydro-4-oxo-1-n-propylquinoline-3-carboxylic acid (mp 202-205°C), was accomplished by the same method as that described for the starting material in Example 1, but using n-propyl-bromide in place of methyl iodide.

Example 3 — 1-Allyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride

A mixture of 1-allyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.24 g), piperazine (0.37 g), and pyridine (3 ml) was refluxed for 6 hours. The mixture was evaporated to dryness, and the residue adjusted to pH 1 with diluted hydrochloric acid and cooled. The solid was filtered off and recrystallized from water to give 1-allyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl) quinoline-3-carboxylic acid hydrochloride (0.12 g), mp 278-281°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{17}H_{17}F_2N_3O_3$ HCl :	52.93	4.70	10.39
Found :	52.65	4.68	10.82

The starting material, 1-allyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (mp 194-197°C), was obtained by the same method as mentioned for the starting material in Example 1 by using allyl bromide instead of methyl iodide.

Example 4 — 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride

To a mixture of 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.2 g) and piperazine (0.3 g) was added pyridine (5 ml), and the mixture was refluxed for 6 hours. The solvent was evaporated and the residue was strongly acidified with aqueous hydrochloric acid solution. After cooling, the solid was filtered off and recrystallized from water to give 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid hydrochloride (0.09 g), mp 291-294°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{16}H_{16}F_3N_3O_3$ HCl :	49.05	4.37	10.73
Found :	49.04	4.36	10.68

The starting material, 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, was prepared by the method described below.

Anhydrous potassium carbonate (2.2 g), 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (0.8 g), 1-bromo-2-fluoroethane (3.8 g), sodium iodide (4.5 g), and DMF (30 ml) were combined and heated with stirring at 90-100°C for 10 hours. After the solvent had evaporated and the residue cooled, water was added to the residue and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate, and evaporated. To the residual solid was added a mixture of 18 % hydrochloric acid (14 ml) and ethanol (7 ml) and the acidic mixture was then refluxed for 2.5 hours. Water (14 ml) and ethanol (14 ml) were added to the reaction mixture and the reaction mixture cooled. The precipitate was collected by filtration, and recrystallized from a mixture of DMF and ethanol to give 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.34 g), mp 209-210°C.

	C%	H%	N%
Anal. Calcd. for $C_{12}H_7F_4NO_3$:	49.84	2.44	4.84
Found :	49.86	2.37	5.01

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

A mixed solution of 1-methylpiperazine (0.34 g) and pyridine (3 ml) was added to 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.12 g) and refluxed for 6 hours. After the solvent had evaporated and the residue cooled, the residue was adjusted to pH 1 with aqueous hydrochloric acid. The cooled mixture was filtered

off and the solid was recrystallized from water to give 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid hydrochloride (0.08 g), mp 269-271°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{17}H_{18}F_3N_3O_3$ HCl :	50.32	4.72	10.36
Found :	50.12	4.97	10.24

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

A mixture of 1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride (0.13 g), triethylamine (0.12 g), allyl bromide (0.09 g), and DMF (3 ml) was heated with stirring at 90° for 3 hours and the solvent was evaporated. The residue was dissolved in 2N sodium hydroxide solution. The alkaline solution was adjusted to pH 7 with aqueous acetic acid and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated. The residue was recrystallized from a mixture of DMF and ethanol to give 7-(4-allyl-1-piperazinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.055 g), mp 227-230°C (decomp.).

	C%	H%	N%
Anal. Calcd. for $C_{19}H_{21}F_2N_3O_3$ $1/4H_2O$:	59.76	5.67	11.00
Found :	59.69	5.52	10.89

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

Triethylamine (0.2 g), 1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride (0.3 g), ethyl iodide (0.19 g), and DMF (5 ml) were mixed, heated with stirring at 90°C for 3 hours, and the solvent was evaporated. The residue was dissolved in 2N sodium hydroxide solution. The alkaline solution was neutralized with aqueous acetic acid and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over anhydrous sodium sulphate and evaporated. The residue was recrystallized from a mixture of DMF and ethanol to give 1-ethyl-7-(4-ethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.06 g), mp 236-239°C.

		C%	H%	N%
Anal. Calcd. for $C_{18}H_{21}F_2N_3O_3$ 1/4H_2O	:	58.45	5.86	11.36
Found	:	58.38	5.74	11.31

Example 8 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-[4-(2-hydroxyethyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic acid

A mixture of 1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid hydrochloride (0.3 g), triethylamine (0.2 g), 2-bromoethanol (0.15 g), and DMF (5 ml) was heated with stirring at 90°C for 3 hours. After the solvent was evaporated and the residue was dissolved in 2N sodium hydroxide solution, neutralized with

aqueous acetic acid, and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate, and evaporated. The solid was recrystallized from a mixture of DMF and ethanol to give 1-ethyl-6,8-difluoro-1,4-dihydro-7-[4-(2-hydroxyethyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic acid (0.08 g), mp 225-228°C.

		C%	H%	N%
Anal. Calcd. for	$C_{18}H_{21}F_2N_3O_4$:	56.69	5.55	11.02
Found	:	56.43	5.62	10.93

Example 9 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid

To a solution of pyridine (3 ml) and 4-hydroxy piperidine (1.6 g), 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.43 g) was added and the mixture was heated under reflux for 6 hours. After the solvent had evaporated off, the residue was treated with water, acidified with acetic acid and extracted with dichloro-methane. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated. The residue was recrystallized from a mixture of DMF and ethanol to afford 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl-4-oxoquinoline-3-carboxylic acid (0.42 g), mp 216-218°C.

		C%	H%	N%
Anal. Calcd. for	$C_{17}H_{18}F_2N_2O_4$ 1/4H_2O :	57.22	5.23	7.85
Found	:	57.41	5.01	8.03

Example 10 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.43 g), 3-hydroxypiperidine (1.6 g), and pyridine (3 ml) was refluxed for 6 hours. The mixture was evaporated to dryness, treated with water, acidified with acetic acid, and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over anhydrous sodium sulphate, and evaporated. The residue was recrystallized from a mixture of DMF and ethanol to give 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid (0.3 g), mp 232-234°C.

	C %	H %	N %
Anal. Calcd. for $C_{17}H_{18}F_2N_2O_4$ 1/4 H_2O :	57.22	5.23	7.85
Found :	57.18	5.13	7.97

Example 11 — 1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)quinoline-3-carboxylic acid

A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (0.43 g), pyrrolidine (1.2 g), and pyridine (3 ml) was refluxed for 6 hours. The solvent was evaporated off. The residue was treated with water, acidified with acetic acid, and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate, and evaporated. The solid was recrystallized from a mixture of DMF and ethanol and gave 1-ethyl-6,8-

difluoro-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)quinoline-3-carboxylic acid (0.34 g), mp 284-286°C (decomp.).

		C%	H%	N%
Anal.	Calcd. for $C_{16}H_{16}F_2N_2O_3$ 1/4H_2O :	58.80	5.09	8.57
	Found :	58.54	4.87	8.62

Example 12 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-morpholinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.43 g), morpholine (1.4 g), and pyridine (3 ml) was refluxed for 6 hours. After the mixture had evaporated to dryness, the residue was acidified with aqueous acetic acid and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated. The solid was recrystallized from a mixture of DMF and ethanol and gave 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-morpholinyl)-4-oxoquinoline-3-carboxylic acid (0.28 g), mp 268-271°C (decomp.).

		C%	H%	N%
Anal.	Calcd. for $C_{16}H_{16}F_2N_2O_4$ 1/4 H_2O :	56.06	4.85	8.17
	Found :	56.27	4.65	8.32

Example 13 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-dimethylamino-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid

A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (0.43 g), 4-dimethylaminopiperidine (2.1 g), and pyridine (3 ml) was refluxed for 6 hours. The mixture was evaporated to dryness. The residue

was treated with water and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated. The solid was recrystallized from ethyl acetate and gave 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-dimethylamino-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid (0.22 g), mp 210-211°C.

		C%	H%	N%
Anal. Calcd. for $C_{19}H_{23}F_2N_3O_3$ $1/4H_2O$	:	59.44	6.17	10.95
Found	:	59.44	6.01	10.77

Example 14 — 6,8-Difluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid hydrochloride

A mixture of 6,7,8-trifluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxoquinoline-3-carboxylic acid (0.14 g), piperazine (0.22 g), and pyridine (3 ml) was refluxed for 6 hours. After the mixture had evaporated to dryness, the residue was strongly acidified with aqueous hydrochloric acid and cooled. The solid was filtered off and recrystallized from water to give 6,8-difluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-7-(1-piperazinyl) quinoline-3-carboxylic acid hydrochloride (0.05 g), mp 298-300°C (decomp.).

		C %	H %	N%
Anal. Calcd. for $C_{16}H_{17}F_2N_3O_4$ HCl	:	49.30	4.65	10.78
Found	:	48.94	4.50	10.76

The starting material, 6,7,8-trifluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxoquinoline-3-carboxylic acid, was prepared as described for the starting material in Example 1 by using 2-bromoethanol instead of methyl iodide.

Example 15 — 6,8-Difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-vinylquinoline-3-carboxylic acid hydrochloride

To a solution of sodium hydroxide (0.2 g), water (2.5 ml), and ethanol (2.5 ml), 7-(4-acetyl-1-piperazinyl)-1-(2-chloroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (0.2 g) was added and the mixture was heated with stirring at 80-90°C for 3 hours. After cooling, the reaction mixture was strongly acidified with concentrated hydrochloric acid.

The precipitate was filtered off and recrystallized from water to give 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-vinylquinoline-3-carboxylic acid hydrochloride, mp 267-270°C (decomp.); mass spectrum, m/e 335 (M^+-HCl).

The starting material, 7-(4-acetyl-1-piperazinyl)-1-(2-chloroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester, was prepared by the following method.

A mixture of 6 7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester (4.1 g), anhydrous potassium carbonate (5.2 g), 2-bromoethanol (9.5 g), and DMF (90 ml) was stirred at 100°C for 10 hours. After the mixture had evaporated to dryness, the residue was treated with water, extracted with dichloromethane, washed with water, dried, and evaporated.

The solid was recrystallized from ethanol to give 6,7,8-trifluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxoquinoline-3-carboxylic acid ethyl ester (mp 175-177°C).

A mixture of the above 1-(2-hydroxyethyl)quinoline ester (1.2 g), piperazine (1.7 g), and pyridine (10 ml) was refluxed for 4 hours. After the mixture evaporated to dryness, the residue was treated with water, made basic with potassium carbonate, and extracted with dichloromethane The organic layer was washed with water, dried, and evaporated to give 6,8-difluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid ethyl ester.

To a solution of the above 7-(1-piperazinyl) quinoline ester (1.1 g) and acetic acid (6.5 ml), acetic anhydride (0.4 g) was added and the mixture was stirred at 80°C for 1 hour. After the solvent was evaporated, the residue was treated with water and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated to give 7-(4-acetyl-1-piperazinyl)-6,8-difluoro-1,4-dinydro-1-(2-hydroxyethyl)-4-oxoquinoline-3-carboxylic acid ethyl ester.

To an ice-cooled solution of the above 7-(4-acetyl-1-piperazinyl)quinoline ester (1.0 g), pyridine (0.27 g), and cnloroform (30 ml), a solution of thionylchloride (3.2 g) and chloroform (13 ml) was added dropwise. The mixture was stirred at room temperature for 15 hours. The solvent was evaporated.

The residue was made weakly basic with aqueous potassium carbonate, extracted with chloroform, washed with

water, dried, and evaporated. The residue was purified by chromatography on alumina with chloroform as the eluting agent to give 7-(4-acetyl-1-piperazinyl)-1-(2-chloroethyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester.

Example 16 — 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid silver salt

To a stirred solution of 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid (235 mg), sodium hydroxide (26.7 mg), and water (3 ml), a solution of silver nitrate (113 mg) and water (2 ml) was added. The precipitate was filtered off, washed with water, and dried to give 1-ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid silver salt (284 mg), mp 181-184°C (decomp.).

Experiment 1 Antibacterial Activity

The antibacterial activities of the compounds of the present invention were assayed by the standard agar dilution streak method against Gram-positive and Gram-negative bacteria [Chemotherapy, 22, 1126 (1974)]. The results are shown in Table 1.

Table 1 Antibacterial Activity

Organisms	Minimum inhibitory concentration (μg/ml)														
	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 16
Bacillus subtilis PCI 219	0.39	0.20	0.39	0.39	0.10	0.10	0.10	0.10	≦0.05	≦0.05	≦0.05	≦0.05	0.10	3.13	≦0.05
Staphylococcus aureus 209 p	3.13	1.56	3.13	3.13	0.78	0.78	0.78	0.78	0.20	0.20	0.10	0.20	0.39	12.5	0.20
S.aureus Terajima	3.13	3.13	3.13	3.13	0.78	0.78	0.78	0.78	0.20	0.39	0.10	0.39	0.39	25	0.39
S.epidermidis IID 866	3.13	3.13	3.13	1.56	0.78	0.78	0.78	0.78	0.39	0.78	0.20	0.39	0.39	12.5	0.39
Escherichia coli NIHJ JC-2	≦0.05	≦0.05	0.10	≦0.05	≦0.05	0.10	≦0.05	≦0.05	0.20	0.39	0.20	0.20	≦0.05	0.39	0.78
E. coli ATCC 10536	0.10	0.20	0.39	0.10	0.10	0.39	0.10	0.20	0.20	0.78	0.20	0.39	0.20	0.39	0.78
Proteus vulgaris 3167	0.10	≦0.05	0.10	≦0.05	≦0.05	0.20	≦0.05	0.10	≦0.05	0.10	≦0.05	≦0.05	0.10	0.39	0.10
P. mirabilis IID 994	0.10	0.10	0.20	≦0.05	≦0.05	0.39	0.20	0.20		0.39	0.10	0.20	0.39	1.56	0.39
P. morganii IID 602	0.20	0.39	0.39	0.20	0.10	0.78	0.39	0.78	0.78	1.56	0.39	0.78	1.56	1.56	1.56
Klebsiella pneumoniae IFO 3512	≦0.05	0.10	0.10	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	0110	≦0.05	≦0.05	≦0.05	0.39	0.10
Enterobacter cloacae IID 977	0.10	0.78	0.78	≦0.05	0.10	1.56	0.39	0.39	1.56	6.25	1.56	1.56	3.13	0.39	3.13
Citrobacter freundii IID 976	≦0.05	0.20	0.20	≦0.05	≦0.05	0.78	0.20	0.39	0.78	1.56	0.39	0.78	0.39	0.20	1.56
Serratia marcescens IID 618	0.10	0.39	0.39	0.39	0.10	1.56	0.39	0.78	1.56	3.13	1.56	1.56	0.78	6.25	3.13
Shigella sonnei IID 969	≦0.05	0.10	0.10	≦0.05	≦0.05	0.20	0.10	0.10	0.20	0.78	0.20	0.20	0.10	0.20	0.39
Salmonella enteritidis IID 604	0.10	0.20	0.20	0.05	0.10	1.56	0.39	0.78	1.56	6.25	1.56	1.56	0.78	0.39	1.56
Yersinia enterocolitica IID 981	0.10	0.39	0.39	0.05	0.10	0.78	0.20	0.39	0.78	1.56	0.39	0.39	0.78	0.39	1.56

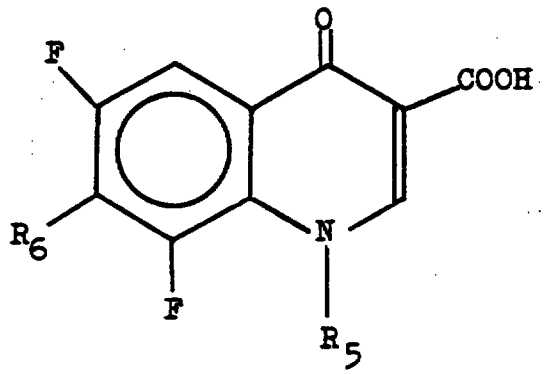
... to be cont'd

Table 1 Antibacterial Activity (cont'd)

Organisms	Minimum inhibitory concentration (g/ml)														
	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 16
Pseudomonas aeruginosa V-1	3.13	12.5	12.5	6.25	3.13	12.5	6.25	12.5	6.25	25	6.25	12.5	12.5	1.56	3.13
P. aeruginosa IFO 12639	1.56	6.25	6.25	1.56	3.13	25	6.25	12.5	12.5	25	6.25	12.5	25	12.5	25
Acinetobacter anitratus IID 876	1.56	1.56	3.13	3.13	0.39	0.78	0.39	1.56	1.56	1.56	0.39	1.56	0.78	25	1.56
Alcaligenes faecalis 0104002	6.25	1.56	3.13	3.13	0.78	3.13	1.56	1.56	1.56	3.13	0.39	1.56	6.25	100	3.13

CLAIMS

1. The 1,7-disubstituted-6,8-difluoro-1,4-dihydro-4-oxo--quinoline-3-carboxylic acids of the general formula:



(II)

(wherein R_5 is an alkyl radical having from 1 to 5 carbon atoms and R_6 is a 1-piperazinyl radical, optionally substituted at the 4-position by an alkyl group, provided that when R_5 is an ethyl group then R_6 is not a 1-piperazinyl or 4-methyl-1-piperazinyl radical) and their hydrates and salts.

2. Quinoline carboxylic acids, hydrates and salts as claimed in claim 1, wherein R_5 is an alkyl radical having from 1 to 3 carbon atoms.

3. Quinoline carboxylic acids, hydrates and salts as claimed in claim 1 or claim 2, wherein R_5 is a methyl or n-propyl radical and R_6 is a 1-piperazinyl radical, or wherein R_5 is an ethyl radical and R_6 is a 4-ethyl--1-piperazinyl radical.

4. Quinoline carboxylic acids, hydrates and salts as claimed in any of claims 1 to 3, wherein R_5 is an alkyl

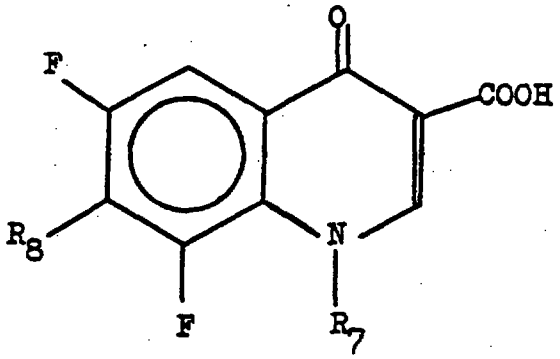
radical having either 1 or 3 carbon atoms and R_6 is a 1-piperazinyl radical, optionally substituted at the 4-position by an alkyl group.

5. 6,8-Difluoro-1,4-dihydro-1-methyl-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts.

6. 6,8-Difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-n-propylquinoline-3-carboxylic acid, and its hydrates and salts.

7. 1-Ethyl-7-(4-ethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

8. The 1,7-disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acids of general formula:



(III)

(wherein R_7 is an alkyl, hydroxy-alkyl, halogeno-alkyl, or alkenyl radical; and R_8 is a 1-piperazinyl radical [which may optionally be substituted at the 4-position by an alkyl, hydroxy-alkyl, or alkenyl radical], a 1-piperidinyl radical [which may

optionally be substituted at the 3- and/or 4-positions by a hydroxy or a dimethyl-amino radical], a 1-pyrrolidinyl radical or a 4-morpholinyl radical; provided that when R_7 is an alkyl group having from 1 to 5 carbon atoms then R_8 is neither an unsubstituted 1-piperazinyl radical nor a 1-piperazinyl radical substituted at the 4-position by an alkyl radical) and their hydrates and salts.

9. Quinoline carboxylic acids, hydrates and salts as claimed in claim 8, wherein the alkyl, hydroxy-alkyl, halogeno-alkyl or alkenyl radicals have no more than 5 carbon atoms.

10. Quinoline carboxylic acids, hydrates and salts as claimed in claim 8 or claim 9, wherein the alkyl, hydroxy--alkyl, halogeno-alkyl or alkenyl radicals have no more than 3 carbon atoms.

11. Quinoline carboxylic acids, hydrates and salts as claimed in any of claims 8 to 10, wherein R_7 is a 2-hydroxy-ethyl or 2-fluoro-ethyl or vinyl radical, and/or wherein R_8 is a 4-methyl-, 4-ethyl-, 4-(2-hydroxy--ethyl)- or 4-allyl-1-piperazinyl radical or is a 3-hydroxy-, 4-hydroxy- or 4-dimethylamino-1-piperidinyl radical.

12. Quinoline carboxylic acids, hydrates and salts as claimed in any of claims 8 to 11, wherein <u>either</u> R_7 is an allyl, 2-fluoroethyl, 2-hydroxyethyl or vinyl radical and R_8 is a 1-piperazinyl radical <u>or</u> R_7 is an ethyl

radical and R_8 is a 1-pyrrolidinyl, 4-morpholinyl, 3-hydroxy-, 4-hydroxy- or 4-dimethylamino-1-piperidinyl radical or a 4-allyl- or 4-(2-hydroxy-ethyl)-1--piperazinyl radical, or R_7 is a 2-fluoroethyl radical and R_8 is a 4-methyl-1-piperazinyl radical.

13. Quinoline carboxylic acids, hydrates and salts as claimed in any of claims 8 to 12, wherein either R_7 is an allyl or 2-hydroxy-ethyl radical and R_8 is a 1-piperazinyl radical, or R_7 is an ethyl radical and R_8 is a 4-hydroxy-, 3-hydroxy- or 4-dimethylamino-1--piperidinyl, 4-morpholinyl or 1-pyrrolidinyl radical.

14. 1-Allyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1--piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts.

15. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo--7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts.

16. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7--(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

17. 7-(4-Allyl-1-piperazinyl)-1-ethyl-6,8-difluoro--1,4-dihydro-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

18. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-[4-(2-hydroxy--ethyl)-1-piperazinyl]-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

19. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-hydroxy-1-

-piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

20. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1--piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

21. 1-Ethyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1--pyrrolidinyl)quinoline-3-carboxylic acid, and its hydrates and salts.

22. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-morpholinyl)--4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

23. 1-Ethyl-6,8-difluoro-1,4-dihydro-7-(4-dimethylamino-1-piperidinyl)-4-oxoquinoline-3-carboxylic acid, and its hydrates and salts.

24. 6,8-Difluoro-1,4-dihydro-1-(2-hydroxyethyl)-4--oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid, and its hydrates and salts.

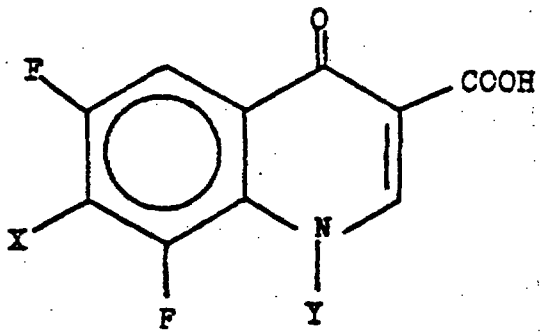
25. 6,8-Difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)--1-vinylquinoline-3-carboxylic acid, and its hydrates and salts.

26. Quinoline carboxylic acid salts as claimed in any of the preceding claims, wherein the non-toxic cation forming said salt is a calcium, magnesium, aluminium, ceric, chromic, cobaltic, cupric, ferric, silver or zinc cation or the cation of an organic base.

27. Quinoline carboxylic acid salts as claimed in any of the preceding claims, wherein the non-toxic anion

forming said salt is a hydrochloride, sulphate, phosphate, acetate, lactate or methanesulphonate anion.

28. A process for the preparation of the 1,7--disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline--3-carboxylic acids, hydrates and salts claimed in any of the preceding claims, in which a compound of the general formula:



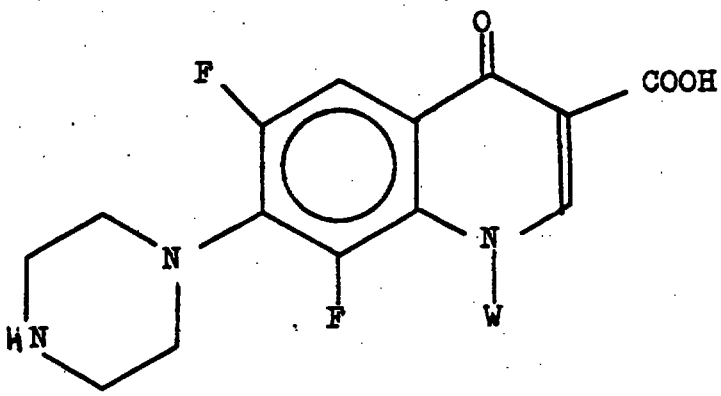
(IV)

(in which X is a halogen atom and Y is either R_5 or R_7 as defined in the relevant claim to which this one is appendant or an hydrate or salt thereof is reacted with a compound of general formula:

Z-H (V)

wherein Z is either R_6 or R_8 as defined in the relevant claim to which this one is appendant) so as to form the desired corresponding acid of general formula II or III as claimed in claims 1 to 25 or hydrate or salt thereof.

29. A process for the preparation of the 1,7--disubstituted-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3--carboxylic acids, hydrates and salts claimed in any of claims 1 to 27, in which a compound of the general formula:

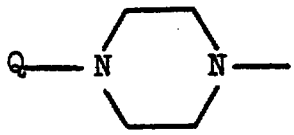


(VI)

(wherein W is either R_5 or R_7 as defined in the relevant claim to which this one is appendant) or its hydrate or salt is reacted with a halide of general formula:

Q.X (VII)

(wherein X is a halogen atom and



is either R_6 or R_8 as defined in the relevant claim to which this one is appendant) so as to form the desired corresponding 7-substituted-piperazinyl derivative of general formula II or III or its hydrate or salt.

30. A process for producing 6,8-difluoro-1,4-dihydro--4-oxo-7-(1-piperazinyl)-1-vinyl-quinoline-3-carboxylic acid, or its hydrates or salts, in which 7-(4-acetyl-1--piperazinyl)-1-(2-chloro-ethyl)-6,8-difluoro-1,4--dihydro-4-oxoquinoline-3-carboxylic acid ethyl ester

* C L M S *

is subjected to treatment with alkali.

31. 1,7-Di-substituted-6,8-difluoro-1,4-dihydro-4--oxo-quinoline-3-carboxylic acids, hydrates and salts, whenever prepared in or by the processes claimed in any of claims 28 to 30.