The Synthesis and Biological Activity of New 7-[2-(Cyanomethyl)piperazinyl]- and 7-[3-(Cyanomethyl)piperazinyl]quinolone Antibacterials

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Some novel 7-[2- or 3-(cyanomethyl)piperazinyl]quinolones have been prepared. Most notable, 2-cyanomethyl-piperazine **5** and 1-methyl-2-cyanomethylpiperazine **8** at the quinolone C-7 position produce products with good *in vitro* antibacterial activity. The key step in the synthesis of these products involves the regioselective deprotection of the benzyl group in function of the time reaction.

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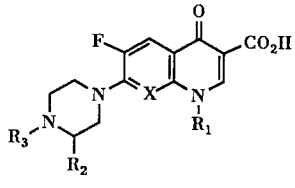
The therapeutic interest of the quinolone antibacterials is well known. In recent years, the emergence of compounds such as norfloxacin [1], enoxacin [2] and ciprofloxacin [3] is a clear example of their importance.



	R_1	R_2	R_3	X
Norfloxacin	Et	H	H	CH
Enoxacin	Et	H	H	N
Ciprofloxacin	c-C_3H_5	H	H	CH
Lomefloxacin	Et	CH_3	H	CH

Figure 1

Among the hosts of quinolone N-1 substituents synthesized since norfloxacin, the ethyl and cyclopropyl moieties are certainly the best in terms of antibacterial efficacy. At C-7, the piperazinyl and amino substituted pyrrolidinyl groups have been utilized with optimal results. As this field evolves, active compounds in the quinolone-3-carboxylic acid class are reported with novel C-5 [4], C-8 [5], and C-2 [6] substitution. We are particularly interested in preparing quinolone C-7 structural analogues [7], and the emergence of lomefloxacin [8] and the biological studies carried out by other authors over 7-[3-(fluoromethyl)piperazinyl)quinolone antibacterials [9] have suggested to us, as a logical extention of these findings, the study of the structure-activity relationship (SAR) of other 7-(2- or 3-substituted-piperazinyl)quinolone analogues.

In this paper, we describe our work on the synthesis and biological activity of some of these 1,4-dihydro-4-oxoquinoline-3-carboxylic acids **12-18**.

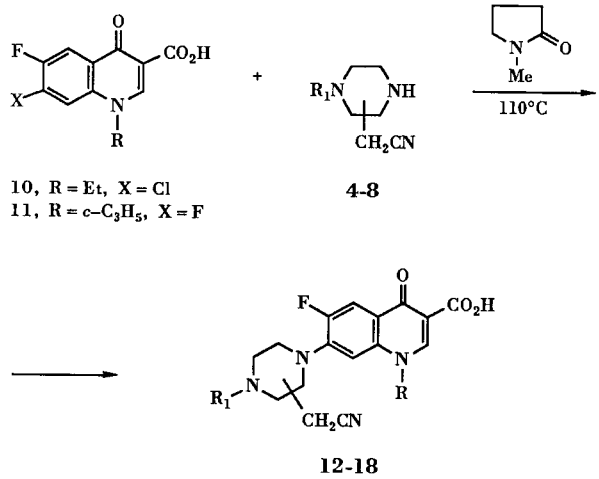
The synthesis of the cyanomethylpiperazines used in this study is outlined in Scheme 1.

Reflux-temperature treatment of 1,4-dibenzyl-2-(hydroxymethyl)piperazine **1** with thionyl chloride-carbon tetrachloride gave the chlorosubstitution product **2**, which is treated with sodium cyanide [10] to give the cyanomethyl derivative **3**. The deprotection of the piperazine ring system **3** is carried out with 1-chloroethyl chloroformate at reflux temperature and a final addition of methanol to the intermediate reaction product [11].

The reaction time is, at this point, an important factor, insomuch as a reaction time of 2 hours gives only the product **4** in good yield and purity, whereas the product **5** is obtained when the reaction time is longer (48 hours). The products **6** and **7** are prepared from **5** by a nucleophilic substitution process, and the same reaction process is used to obtain **9** using **7** as starting material. The obtention of the *N*-methylpiperazine **8** is carried out in the same form as the piperazine deprotection step (**3**→**4**).

All the 7-substituted-quinolones, which are the object of this study, were prepared from the corresponding 2- or 3-piperazine derivatives in a straightforward fashion. Regiospecific nucleophilic aromatic substitution of the corresponding 1-substituted 6-fluoro-7-haloquinolone **10**

Equation 1

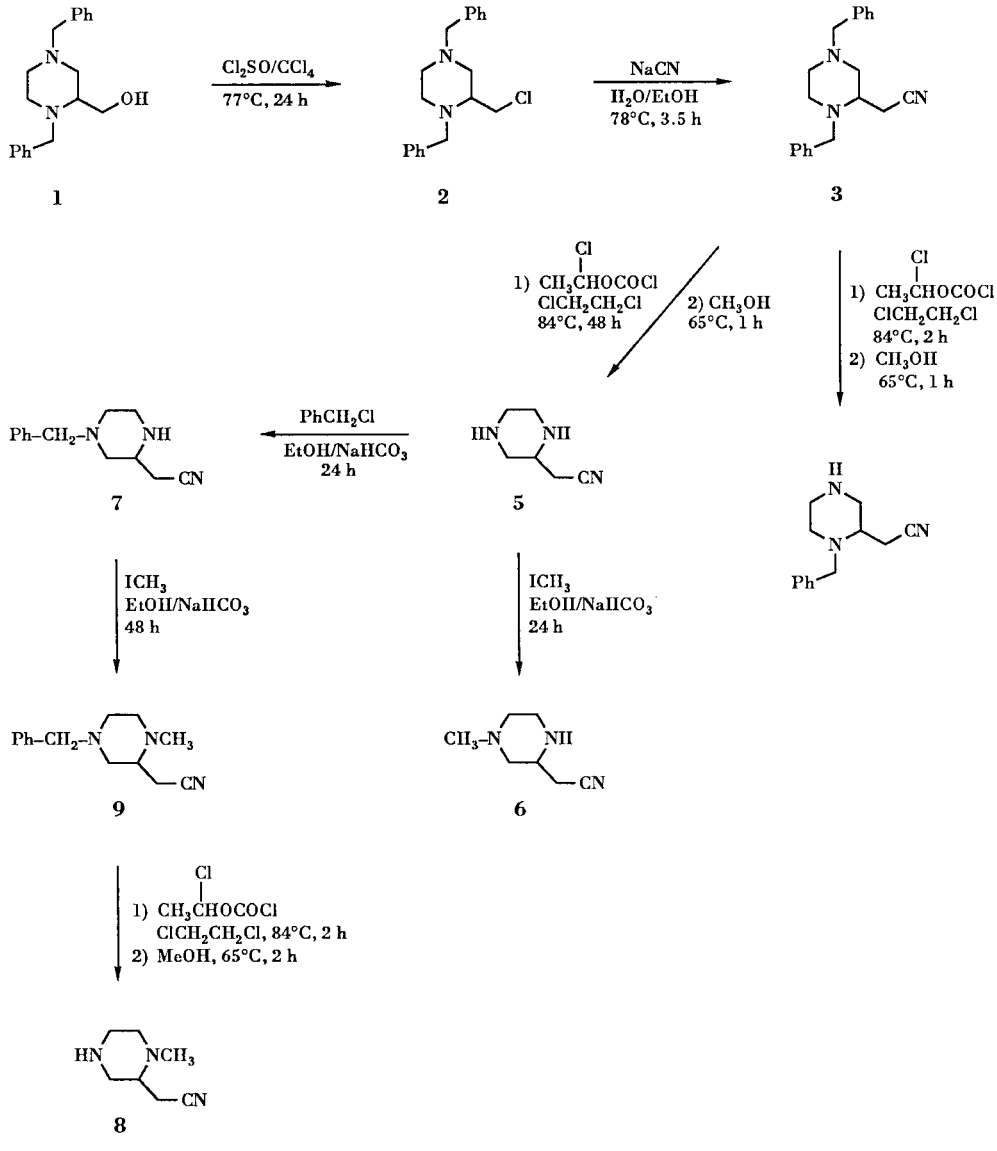


10, R = Et, X = Cl
11, R = c-C_3H_5, X = F

4-8

12-18

Scheme 1



or **11** with the appropriate secondary amine proceeded smoothly at temperature between 100-110° as shown in Equation 1.

The final products **12-18** obtained at this point, are listed in Table I. The products **10** and **11** were obtained by the usual methods [12] [13].

Biology.

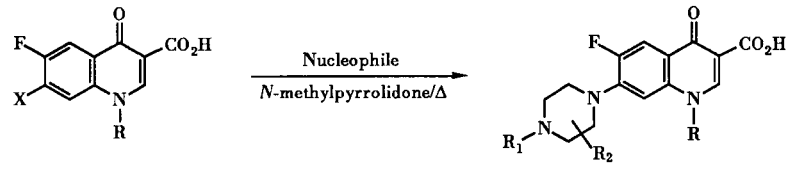
Drug susceptibility was tested by the twofold serial agar dilution method [14] in Mueller-Hinton agar. The test organisms (4 gram-positive and 17 gram-negative) were cultured overnight in Mueller-Hinton broth, and were diluted with saline to achieve a final inoculum of 10^5 colony-forming units (CFU) per spot. The MIC was determined after an overnight incubation at 37°.

Table I contains a summary of the *in vitro* antibacterial data for 7-substituted-4-quinolone-3-carboxylic acids **12** to **18** against four gram-positive organisms and seventeen gram-negative organisms. Testing data for norfloxacin is included for comparison. The best results are obtained when the substituent cyanomethyl group is at 3-position of the piperazine ring although they are less effective than the standard norfloxacin, especially for gram-negative organisms.

The other substituent, methyl or benzyl, at 4-position of the piperazine ring produces worse overall activity, especially for the benzyl group. As it is known, the best results are obtained when the cyclopropyl is used at the N-1 substitution.

Table I

7-substituted-4-quinolone-3-carboxylic Acids *in vitro* Antibacterial Activity Expressed as MIC (μg. ml^{-1})
(geometrical mean of the number of strains tested)



No.	R	R_1	R_2	X		Organism Sa [a]	Ec [b]	Kb [c]	Pa [d]	Pv [e]	Et [f]	E, NOR^R [g]	Pa, NOR^R [h]
					No. of strains	4	5	3	2	1	4	1	1
12	Et	$PhCH_2$	3-CH_2CN	Cl		2	R [i]	R	R	R	R	R	R
13	Et	H	3-CH_2CN	Cl		3.1	1.74	12.7	32	1	8	R	R
14	*c*-C_3H_5	H	3-CH_2CN	F		0.84	0.4	3.2	8	0.5	1.2	R	R
15	*c*-C_3H_5	H	2-CH_2CN	F		6.7	0.76	8	64	1	2	R	R
16	*c*-C_3H_5	Me	3-CH_2CN	F		0.84	0.75	8	45	2	3.4	R	R
17	*c*-C_3H_5	Me	2-CH_2CN	F		2	2.23	20	64	8	5.6	R	R
18	*c*-C_3H_5	$PhCH_2$	2-CH_2CN	F		0.5	2.64	32	R	32	19	R	R
Norfloxacin	Et	H	H	Cl		0.84	0.05	0.39	1	0.06	0.09	R	R

[a] *Staphylococcus aureus*. [b] *Escherichia coli*. [c] *Klebsiella pneumoniae*. [d] *Pseudomonas*. [e] *Proteus*. [f] *Enterobacter*. [g] *Escherichia coli* norfloxacin-resistant. [h] *Pseudomonas* norfloxacin-resistant. [i] MIC > 128 μg.ml^{-1}.

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers. *N,N'*-Dibenzylethylenediamine, ethyl 2,3-dibromopropionate, 1-chloroethyl chloroformate were purchased from Aldrich Chemical Co. Sodium cyanide and thionyl chloride were purchased from Merck Chemical Co. Solvents used were of spectroscopy grade quality with no special drying procedure observed. Merck silica gel F254 plates (0.25 mm) was used for thin layer chromatography. Silica gel (230-400 mesh) Merck kiesegel 60 was employed for flash column chromatography. Melting points were determined in open capillary tubes on a Büchi apparatus (Flawil, Switzerland) and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1710 spectrophotometer (Norwalk, USA). The ^{1}H-nmr (80 MHz) spectra were measured on a Bruker WP80DW spectrophotometer (Karlsruhe, Germany) using tetramethylsilane as an internal standard. Microanalyses were obtained using a Perkin-Elmer P.E. 2400 analyser. Chlorine was determined by Schöniger's method [15]. Acid and basic groups were determined by a potentiometric method in non-aqueous medium. The ir and nmr data of all compounds were consistent with assigned structures.

1,4-Dibenzyl-2-(chloromethyl)piperazine (**2**).

A solution of 1,4-dibenzyl-2-(hydroxymethyl)piperazine **1** [16] (19.5 g, 0.066 mole) in dry carbon tetrachloride (150 ml) was added dropwise over one hour to a solution of thionyl chloride (19.57 g, 0.16 mole) in dry carbon tetrachloride (150 ml). The mixture was heated at 77° and was stirred for 2 hours. The reaction solution was cooled to room temperature and water (200 ml) was added dropwise. The organic phase was separated and the aqueous phase was adjusted to *p*H 12 with 6*M* sodium hydroxide and extracted repeatedly with chloroform. The combined organic phases were washed with water, dried over magnesium sulfate, and evaporated to give the product **2** as an oil, which was purified by flash column chromatography giving 19.8 g (95%) of colorless oil.

A sample was recrystallized from methanol to give a white solid, mp 51-53°; two basic groups 97.25%; ir (potassium bromide): 2800, 1460, 1160, 750, 700 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.35-2.80 (m, 7H piperazinyl), 3.50 (s, 4H, two CH_2Ph), 3.80 (m, 2H, CH_2Cl), 7.30 (s, 10H arom).

Anal. Calcd. for $C_{19}H_{23}ClN_2$: C, 72.48; H, 7.36; N, 8.90; Cl, 11.26. Found: C, 72.46; H, 7.47; N, 9.01; Cl, 11.33.

1,4-Dibenzyl-2-(cyanomethyl)piperazine (**3**).

To a solution of chloromethyl derivative **2** (19.75 g, 0.063 mole) in ethanol (400 ml) was added a solution of sodium cyanide (4 g, 0.081 mole) in water (130 ml). The mixture was refluxed for 4 hours, then was allowed to slowly reach room temperature. The ethanol was removed and the resulting aqueous suspension was extracted with chloroform (2 x 100 ml). The combined organic phases were washed with water (2 x 100 ml), dried over magnesium sulfate and evaporated to an oil. The crude product **3** was purified by recrystallization in ethanol giving 15.4 g (80%) of a white solid, mp 74-75°; two basic groups 98.67%; ^{1}H-nmr (deuteriochloroform): δ 2.35-2.95 (m, 9H, -CH_2CN and piperazinyl), 3.45 (s, 4H, two -CH_2Ph), 7.25 (s, 10H arom); ir (potassium bromide): 2805, 2240, 1460, 1180, 750, 695 cm^{-1}.

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.65; H, 7.64; N, 13.43.

1-Benzyl-2-(cyanomethyl)piperazine (**4**).

1,4-Dibenzyl-2-(cyanomethyl)piperazine **3** (15.3 g, 0.05 mole)

was dissolved in dry 1,2-dichloroethane (150 ml) and cooled in an ice-salt bath at 0°. A solution of 1-chloroethyl chloroformate (21.5 g, 0.15 mole) in dry 1,2-dichloroethane (100 ml) was then added dropwise [11] over 30 minutes and stirring was continued at 0° for 15 minutes then the mixture was heated under reflux for 1 hour. After cooling to rt the solvents were removed under reduced pressure. The crude oil was dissolved in methanol (100 ml) and heated under reflux for 1 hour. The solvent was evaporated again and the crude product was dissolved in water (200 ml), washed with diethyl ether (2 x 50 ml), then sodium hydroxide 3*M* was added to the aqueous layer (*p*H solution strongly basic) which was extracted with chloroform (2 x 100 ml). The organic layer was dried (magnesium sulfate) and evaporated to give the product **4** as an oil, yield 8.7 g (81%). The product was recrystallized from diethyl ether to give 6.7 g (77%) of a yellow solid, mp 91-96°; two basic groups 97.2%; ^{1}H-nmr (deuteriochloroform): δ 1.45 (s, 1H, >NH), 2.25-2.95 (m, 9H, -C*H*$_2$CN and piperazinyl), 3.57 (dd, 2H, C*H*$_2$Ph, J = 12 Hz), 7.30 (s, 5H arom); ir (potassium bromide): 3200, 2805, 2250, 1460, 1160, 1140, 650 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.53. Found: C, 72.3; H, 7.98; N, 19.41.

2-(Cyanomethyl)piperazine (**5**).

1,4-Dibenzyl-2-(cyanomethyl)piperazine **3** (15.3 g, 0.05 mole) was dissolved in dry 1,2-dichloroethane (150 ml) and cooled in an ice-salt bath at 0°. A solution of 1-chloroethyl chloroformate (21.5 g, 0.15 mole) in dry 1,2-dichloroethane (100 ml) was then added dropwise [11] over 30 minutes and stirring was continued at 0° for 15 minutes then the mixture was heated under reflux for 44 hours. After cooling to rt the solvent was removed under reduced pressure. The crude resin was dissolved in methanol (200 ml) and heated under reflux for 1 hour. The crystalline solid was collected, washed with methanol (2 x 50 ml) and dried giving 39.2 g of a hygroscopic solid as the dihydrochloride salt of the desired compound **5**, mp 176-180°. The dihydrochloride of **5** was converted to free base **5** by passing an aqueous solution of the salt (39.2 g, 0.2 mole) in water (50 ml) through a DOWEX 1-X8 (OH form) column. The free base eluted with water. The collected eluent fractions were evaporated *in vacuo* to leave a white solid, which was used in further reaction without purification, yield 19.7 g (50%), mp 89-92°; two basic groups 97.4%; ^{1}H-nmr (DMSO-d$_6$): δ 2.20 (s, 2H, -C*H*$_2$CN), 2.37-2.90 (m, 7H piperazinyl); ir (potassium bromide): 3220, 2840, 2240, 1330, 1150, 840 cm^{-1}.

Anal. Calcd. for $C_6H_{11}N_3$: C, 57.57; H, 8.86; N, 33.57. Found: C, 57.56; H, 8.90; C, 33.49.

1-Methyl-3-(cyanomethyl)piperazine (**6**).

A solution of 2-(cyanomethyl)piperazine **5** (4.7 g, 0.038 mole) in ethanol (100 ml) was treated at rt with sodium bicarbonate (3.8 g, 0.045 mole) and iodomethane (5.4 g, 0.038 mole). The mixture was stirred at rt for 18 hours, filtered and the ethanol was removed. The resin obtained was dissolved in water (25 ml) and extracted with chloroform (3 x 100 ml). The combined organic phases were washed with water (2 x 50 ml), dried over magnesium sulfate and evaporated to give the product **6** as a clear oil, yield 3.0 g (58%). An analytical sample was obtained by flash column chromatography (silica gel, chloroform-methanol) followed by distillation (6 mm Hg, 110°); two basic groups 97.35%; ^{1}H-nmr (deuteriochloroform): δ 1.7 (s, 1H, -NH), 1.9 (d, 2H, -C*H*$_2$CN), 2.25 (s, 3H, N-CH$_3$), 2.38-2.75 (m, 4H piperazinyl), 2.80-3.2 (m, 3H piperazinyl). Addition of Europium salts to the ^{1}H-nmr sample showed a shift modification of the piperazine signals which was consistent with the desired structure (1-methyl-3-cyanomethyl)-piperazine); ir (liquid film): 3300, 2805, 2240, 1460, 1160, 810 cm^{-1}.

Anal. Calcd. for $C_7H_{13}N_3$: C, 60.40; H, 9.41; N, 30.19. Found: C, 60.60; H, 9.45; N, 30.06.

1-Benzyl-3-(cyanomethyl)piperazine (**7**).

A solution of 2-(cyanomethyl)piperazine **5** (2 g, 0.016 mole) in ethanol (40 ml) was treated at rt with sodium bicarbonate (1.61 g, 0.019 mole) and benzyl chloride (2.02 g, 0.016 mole), then the mixture was stirred at rt for 22 hours, filtered and the solvent was removed under reduced pressure in a rotatory evaporator. The crude product was dissolved in water (50 ml) and strongly basified with sodium hydroxide 3*M*, then it was extracted with chloroform (2 x 50 ml). The combined organic phases were washed with water (2 x 50 ml), dried over magnesium sulfate and evaporated to give the product **7** as a clear oil. The oil was purified by flash column chromatography (silica gel, acetonitrile-ethanol) giving 2.25 g (66%) of a colorless oil; two basic groups 98.4%; ^{1}H-nmr (deuteriochloroform): δ 1.7 (s, 1H, -NH), 1.9 (d, 2H, -C*H*$_2$CN), 2.25-3.1 (m, 7H piperazinyl), 3.5 (s, 2H, PhC*H*$_2$), 7.3 (s, 5H arom); ir (liquid film): 3300, 2940, 2805, 2240, 1450, 1140, 750 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.81; H, 8.01; N, 19.44.

1-Methyl-2-(cyanomethyl)piperazine (**8**).

To a solution of 1-benzyl-3-(cyanomethyl)piperazine **7** (9.4 g, 0.0437 mole) in ethanol (200 ml) was slowly added iodomethane (6.2 g, 0.0437 mole) and sodium bicarbonate (5.5 g, 0.0656 mole) and the resulting reaction mixture was stirred overnight at 20°, filtered and the ethanol was evaporated. The product **9** was isolated via flash column chromatography (silica gel, chloroform-methanol) to give 4.6 g (46%) of a crystalline solid, mp 95-98°; two basic groups 99.5%.

Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.21; H, 8.49; C, 18.29.

A solution of this 1-methyl-2-(cyanomethyl)-4-benzylpiperazine **9** (3.4 g, 0.0148 mole) in dry 1,2-dichloroethane (100 ml) was cooled in an ice-bath at 0°. A solution of 1-chloroethyl chloroformate (2.33 g, 0.0163 mole) in dry 1,2-dichloroethane (50 ml) was then added dropwise over 30 minutes. The mixture was heated under reflux for 1 hour and after cooling to rt the solvents were removed. The crude oil was dissolved in methanol (75 ml) and heated under reflux 1 hour. The solvent was evaporated again and the crude product was dissolved in water (100 ml), washed with diethyl ether (2 x 25 ml), then sodium hydroxide 3*M* was added to the aqueous layer and once the solution was strongly basic, was extracted with chloroform (3 x 50 ml). The organic layer was dried (magnesium sulfate) and evaporated to give the product **8** as an oil, yield 1.2 g (58%); two basic group 96.4%; ^{1}H-nmr (DMSO-d$_6$): δ 2.25 (s, 3H, N-CH$_3$), 2.52 (d, 2H, -C*H*$_2$CN), 2.70-3.1 (m, 7H piperazinyl + NH); ir (liquid film): 3300, 2230, 1460, 1170, 800 cm^{-1}.

General Procedure for the Reaction of Cyanomethylpiperazines **4-8** with Quinolonecarboxylic Acids **10-11** (Table I).

All of these reactions were carried out under a nitrogen atmosphere.

To a stirred and warmed (110°) solution of quinolonecarboxylic acid **10** or **11** in *N*-methyl-2-pyrrolidone was added the corresponding cyanomethylpiperazine (2.5 equivalents) in the same solvent, and the reaction mixture was stirred at this temperature for 24 hours. The *N*-methyl-2-pyrrolidone was removed under reduced pressure on a rotary evaporator to give the crude products **12-18** (Equation I). The crude residue were suspended in ethanol, carried to reflux and then cooled and filtered to give a pale yellow solid which was recrystallized in DMF giving the corresponding pure products.

1-Ethyl-6-fluoro-7-[3-(cyanomethyl)-4-benzyl-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**12**).

This compound was obtained as a colorless crystalline solid, yield 86%, mp 219-223°; two basic groups 97.1%; ^{1}H-nmr (DMSO-d_6): δ 1.40 (t, 3H, -CH_2CH_3), 2.4-3.7 (m, 10H, $PhCH_2$-, -CH_2CN, piperazinyl), 4.0 (m, 1H piperazinyl), 4.55 (q, 2H, CH_2CH_3), 7.20 (d, 1H arom, J_{H-F} *meta* = 7 Hz), 7.35 (s, 5H, $PhCH_2$-), 7.85 (d, 1H arom, J_{H-F} *ortho* = 13 Hz), 8.9 (s, 1H, NCH); ir (potassium bromide): 2820, 2245, 1720, 1630, 1470, 760, 705 cm^{-1}.

Anal. Calcd. for $C_{25}H_{25}FN_4O_3$: C, 66.95; H, 5.62; N, 12.49. Found: C, 66.65; H, 5.67; N, 12.41.

1-Ethyl-6-fluoro-7-[3-(cyanomethyl)-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**13**).

This compound was obtained as a white crystalline solid, yield 75%, mp 215-218° dec; two basic groups 97.7%; ^{1}H-nmr (DMSO-d_6): δ 1.4 (t, 3H, -CH_2CH_3), 2.73 (d, 2H, -CH_2CN), 2.80-3.70 (broad m, 7H piperazinyl), 4.57 (q, 2H, -CH_2CH_3), 7.15 (d, 1H arom,' J_{H-F} *meta* = 7.4 Hz), 7.9 (d, 1H arom, J_{H-F} *ortho* = 13.4 Hz), 8.95 (s, 1H, NC*H*); ir (potassium bromide): 3320, 2805, 2240, 1715, 1630, 1250 cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}FN_4O_3$: C, 60.33; H, 5.34, N, 15.63. Found: C, 60.41; H, 5.25; N, 15.75.

1-Cyclopropyl-6-fluoro-7-[3-(cyanomethyl)-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**14**).

This compound was obtained in pure form by two-fold crystallization in DMF, yield 54%, mp 223-224°; one basic group 100.13%; one acid group 100.30%; ^{1}H-nmr (DMSO-d_6): δ 1.05-1.5 (broad m, 4H, -CH_2CH_2), 3.15 (d, 2H, -CH_2CN), 3.30-3.80 (m, 8H piperazinyl), 3.95 (m, 1H, NC*H*-), 7.6 (d, 1H arom, J_{H-F} *meta* = 7 Hz), 7.85 (d, 1H arom, J_{J-F} *ortho* = 13 Hz), 8.65 (s, 1H, NCH-); ir (potassium bromide): 3400, 2805, 2240, 1720, 1630, 1450, 1420 cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}FN_4O_3$: C, 61.61; H, 5.17; N, 15.13. Found: C, 61.28; H, 5.04; N, 14.90.

1-Cyclopropyl-6-fluoro-7-[3-(cyanomethyl)-4-methyl-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**16**).

This compound was obtained as colorless needles, yield 75%, mp 235-239° dec; one basic group 100.2%; one acid group 99.9%; ^{1}H-nmr (DMSO-d_6 + TFA): δ 1.10-1.45 (broad m, 4H, -CH_2CH_2-), 3.1 (d, 2H, -CH_2CN), 3.20-3.70 (m, 7H piperazinyl), 3.75 (s, 3H, $NHCH_3$), 3.95 (m, 1H, N-C*H*-), 7.5 (d, 1H arom, J_{H-F} *meta* = 7 Hz), 7.80 (d, 1H arom, J_{H-F} ortho = 13 Hz), 8.45 (s, 1H, N-C*H*); ir (potassium bromide): 3450, 2810, 2240, 1720, 1630, 1460, 1270 cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}FN_4O_3$: C, 62.49; H, 5.51; N, 14.58. Found: C, 62.08; H, 5.43; N, 14.41.

1-Cyclopropyl-6-fluoro-7-[2-(cyanomethyl)-4-methyl-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**17**).

This compound was obtained as a white solid, yield 25%, mp 201-205°; one basic group 97.3%; one acid group 100.3%; ^{1}H-nmr (DMSO-d_6): δ 1.15-1.40 (broad m, 4H, -CH_2CH_2), 2.25 (s, 3H, NCH_3), 3.0 (d, 2H, -CH_2CN), 3.15-3.85 (m, 7H piperazinyl), 4.27 (m, 1H, -NCH-), 7.60 (d, 1H arom, J_{H-F} *meta* = 7.5 Hz), 7.85 (d, 1H arom, J_{H-F} *ortho* = 13.5 Hz), 8.65 (s, 1H, NC*H*-); ir (potassium bromide): 3440, 2805, 2240, 1730, 1630, 1480, 1280, cm^{-1}.

Anal. Calcd. for $C_{20}H_{21}FN_4O_3$: C, 62.49; H, 5.51; N, 14.57. Found: C, 62.45; H, 5.46; N, 14.56.

1-Cyclopropyl-6-fluoro-7-[2-(cyanomethyl)-4-benzyl-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**18**).

This compound was obtained as a colorless crystalline solid, yield 60%, mp 178-181°; one basic group 101.1% ^{1}H-nmr (DMSO-d_6 + TFA): δ 1.05-1.45 (broad m, 4H, -CH_2CH_2-), 3.10 (d, 2H, -CH_2CN), 3.25-3.90 (m, 7H piperazinyl), 4.40 (m, 1H, NC*H*-), 4.52 (s, 2H, -$CH_2C_6H_5$), 7.52 (s, 5H, C_6H_5), 7.8 (d, 1H arom, J_{H-F} *meta* = 7 Hz), 7.95 (d, 1H arom, J_{H-F} *ortho* = 12 Hz), 8.70 (s, 1H, NC*H*-); ir (potassium bromide): 3440, 2810, 2240, 1720, 1630, 1490, 1460 cm^{-1}.

Anal. Calcd. for $C_{26}H_{25}FN_4O_3$: C, 67.81; H, 5.47; N, 12.17. Found: C, 67.70; H, 5.58; N, 11.99.

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REFERENCES AND NOTES

[1] H. Koga, A. Itoh, S. Muruyama, S. Suzue and T. J. Irkura, *J. Med. Chem.*, **23**, 1358 (1980).

[2] J. Matsumoto, T. Miyamoto, A. Minamida, Y. Nishimura, H. Egawa and H. Nihimura, *J. Med. Chem.*, **27**, 292, (1984).

[3] R. Wise, J. M. Andrews and I. Edward, *J. Antimicrob. Agents Chemother.*, **23**, 559 (1983).

[4] D. B. Moran, C. B. Ziegler Jr., T. S. Dunne, N. A. Kuck and Y.-i Lin, *J. Med. Chem.*, **32**, 1312 (1989).

[5] J. P. Sanchez, J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols and A. K. Trehan, *J. Med. Chem.*, **31**, 983 (1988).

[6] D. T. W. Chu, P. B. Fernandes and A. G. Pernet, *J. Med. Chem.*, **29**, 1531 (1986).

[7] S. Gubert, C. Braojos, A. Sacristan and J. A. Ortiz, *Synthesis*, 318 (1991).

[8] H. Kato, N. Ogawa, E. Koshinata and N. Yagi, European Patent 140,116 (1985); *Chem. Abstr.*, **103**, 123517b (1985).

[9] C. B. Ziegler Jr., P. Bitha, N. A. Kuck, T. J. Fenton, P. J. Petersen and Y.-i Lin, *J. Med. Chem.*, **33**, 142 (1990).

[10] Y. Khandelwal and Padam. C. Jain, *Indian J. Chem.*, **16B**, 1012 (1978).

[11] R. A. Olofson, J. T. Martz, J. P. Senet, M. Piteau and T. J. Malfroot, *J. Org. Chem.*, **49**, 2081 (1984).

[12] T. Irikura, S. Suzue, A. Ho and H. Koga, Japanese Patent (Kokai) 55-47658 (1980); *Chem. Abstr.*, **93**, 26295v (1980).

[13] K. Grohe, H. Ziegler and K. Metzger, European Patent 078362 (1983); *Chem. Abstr.*, **99**, 53709h (1983).

[14] J. A. Washington, Susceptibility Test; Agar Dilution in Manual of Clinical Microbiology, Americal Society for Microbiology, Washington DC, (1985), pp 967-971.

[15] W. Schöniger, *Mikrochim. Acta*, 123 (1954).

[16] E. Jucker and E. Rissi, *Helv. Chim. Acta*, **45**, 2383 (1962).