Synthesis and Antibacterial Activity of 1-(Substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids and their 6,8-Difluoro Analogs

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Alkylation of 6,7-difluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester with substituted-benzyl chlorides gave 1-(substituted-benzyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl esters. Their treatment with piperazine or *N*-methylpiperazine in pyridine yielded 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid ethyl esters which were hydrolyzed with aqueous sodium hydroxide and then acidified with hydrochloric acid afforded the desired 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acids. The 6,8-difluoro analogs were prepared similarly using 6,7,8-trifluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester as a starting material. Some of these quinolones demonstrated fairly good antibacterial activities. Among them, 6-fluoro-1-(4-fluorophenylmethyl)-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (**7d**) and 6,8-difluoro-1-(3-fluorophenylmethyl)-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (**8c**) are two of the best.

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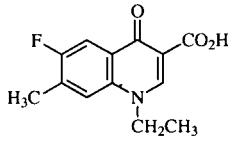
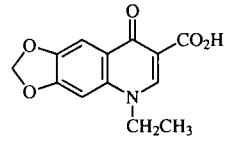
Introduction.

Since the discovery of nalidixic acid by Lesher in 1962 [1], a number of highly potent broad-spectrum antibacterial agents have been uncovered. Nalidixic acid has moderate activity against Gram-negative bacteria and is used for the treatment of urinary tract infections. Its congeners such as oxolinic acid [2] and rosoxacin [3] have been developed which possessed an enhanced antibacterial effect as well as some Gram-positive *in vitro* activity. The next series of quinolones emerged with a broad-spectrum antibacterial activity are norfloxacin [4], pefloxacin [5], enoxacin [6], ofloxacin [7], and ciprofloxacin [8]. These agents were shown to be specific inhibitors of the bacterial DNA gyrase [9-11], an enzyme which is responsible for negatively supercoiling covalently closed circular DNA and also in catenation and decatenation reactions [12].

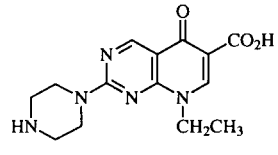
The antibacterial activity of quinolones depends not only on the bicyclic heteroaromatic system but also on the nature of the peripheral substituents and their spatial relationship. These substituents exert their influence on antibacterial activity by providing additional affinity for the bacterial enzymes, enhancing the cell penetration or altering the pharmacokinetics. Early structure-activity relationship (SAR) studies on quinolone antibacterial agents indicated that N-1 ethyl substituent is generally more active than analogs with smaller or larger alkyl substituents. Although compounds with the N-1 ethyl and its bioisosteres are potent antibacterial agents, ciprofloxacin, having a cyclopropyl group at N-1, is the marketed quinolone with the highest *in vitro* activity [8]. The high potency of ciprofloxacin may be due to the presence of hyperconjugation or enhancement of self-association properties introduced by the cyclopropyl ring. It became apparent that the



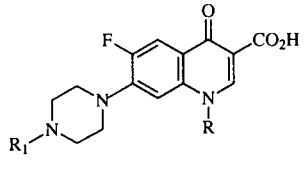
Nalidixic acid



Oxolinic acid



Rosoxacin



Norfloxacin	R = CH_2CH_3, R_1 = H
Ciprofloxacin	R = *c*-C_3H_7, R_1 = H
Difloxacin	R = *p*-F-C_6H_4, R_1 = CH_3

bulk factor at N-1 cannot alone account for optimal biological activity, other factors such as electron π donation and ideal spatial effects may also have a great influence on biological activity [13-15]. Other examples such as difloxacin [16] and temafloxacin [17], with the N-1 aryl group, compared favourably with norfloxacin in *in vitro* tests and were more effective than norfloxacin against various bacterial infections in experimental animals. Although the reason for the enhancement of activity by these aryl substitutions is not known, it is speculated that π stacking between N-1 aryl rings that allows self-association may account for the good antibacterial activity. In general, for potential quinolone derivatives, substituents in the lower portion of the molecule (*i.e.* N-1 and C-8) should be lipophilic to enhance self-association. Although the synthesis of norfloxacin analog in which the N-1 ethyl group was replaced by a benzyl moiety has been previously reported [4], a systemic study of the N-1 substituted-benzyl derivatives which possess an improved lipophilicity, with respect to the optimal antibacterial activity has not been established. Herein, several 1-(substituted-benzyl)-6-fluoro- and 6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acids were prepared and tested against both Gram-positive and negative bacteria.

Chemistry.

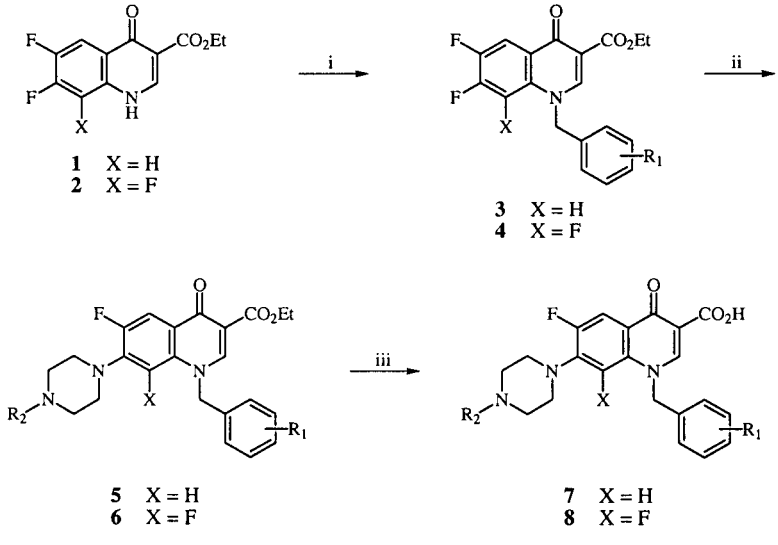
Preparations of 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acids **7a-p** and their 6,8-difluoro analogs **8a-j** are described in Scheme 1. The requisite 6,7-difluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester **1** and its 6,7,8-trifluoro analog **2** were synthesized according to the Gould-Jacobs cyclization route which included the condensation of 3,4-difluoroaniline or 2,3,4-trifluoroaniline with diethyl ethoxymethylenemalonate followed by a thermal cyclization in diphenyl ether at 250° [3]. Alkylation of the ester **1** or **2** with substituted-benzyl chlorides and anhydrous potassium carbonate in dry *N,N*-dimethylformamide at 80-90° gave 1-(substituted-benzyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid ethyl esters **3a-j** or their 6,7,8-trifluoro analogs **4a-j** respectively (Table 1). Treatment of **3a-j** or **4a-j** with piperazine or *N*-methylpiperazine in pyridine yielded 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid ethyl esters **5a-p** or their 6,8-difluoro analogs **6a-j** respectively (Table 2). The ethyl esters **5a-p** or **6a-j** were hydrolyzed with aqueous sodium hydroxide and then acidified with hydrochloric acid to give the desired 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acids **7a-p** or their 6,8-difluoro analogs **8a-j** respectively (Table 3).

Results and Discussion.

Table 4 summarizes the *in vitro* antibacterial activity of the 1-(substituted-benzyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acids **7a-p** and their 6,8-difluoro analogs **8a-j** against two Gram-postive bacteria *(Staphylococcus aureus* and *Staphylococcus epidermidies)* and seven Gram-negative bacteria *(Escherichia Coli, Enterbacter cloacae, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhimurium, Serratia marcescens, Pseudomonas aeruginosa).* The data for norfloxacin is included for comparison.

The biological data for the first ten entries indicated that 1-benzyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piper-

Scheme 1



1 X = H
2 X = F

3 X = H
4 X = F

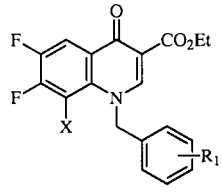
5 X = H
6 X = F

7 X = H
8 X = F

Reagents and conditions: i) substituted-benzyl chloride, K_2CO_3, *N,N*-dimethylformamide, 90-100°, 12 hours; ii) piperazine or 1-methylpiperazine, pyridine, 70-80°, 16 hours; iii) 1*N* NaOH, tetrahydrofuran, reflux, 2 hours.

Table 1

1-(Substituted-benzyl)-6,7-difluoro and 6,7,8-Trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Esters



Compound	R_1	X	Yield (%) [a]	mp (°C)	Formula	Analysis Calcd/Found C	H	N	PMR (deuteriochloroform) δ ppm
3a	H	H	85	208-209	$C_{19}H_{15}F_2NO_3$	66.47 66.54	4.40 4.49	4.08 4.08	1.39 (t, 3H, J = 7.1, CH_3), 4.38 (q, 2H, J = 7.1, OCH_2), 5.35 (s, 2H, NCH_2), 7.08-7.39 (m, 6H, Ar-H and 8-H), 8.26 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.57 (s, 1H, 2-H)
3b	2-F	H	81	203-204	$C_{19}H_{14}F_3NO_3$	63.16 62.99	3.90 3.98	3.88 3.91	1.42 (t, 3H, J = 7.1, CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.37 (s, 2H, NCH_2), 6.95-7.42 (m, 5H, Ar-H and 8-H), 8.30 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.62 (s, 1H, 2-H)
3c	3-F	H	72	223-224	$C_{19}H_{14}F_3NO_3$	63.16 63.00	3.90 3.96	3.88 3.93	1.42 (t, 3H, J = 7.1, CH_3), 4.41 (q, 2H, J = 7.19, OCH_2), 5.34 (s, 2H, NCH_2), 6.83-7.44 (m, 5H, Ar-H and 8-H), 8.30 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.57 (s, 1H, 2-H)
3d	4-F	H	78	206-208	$C_{19}H_{14}F_3NO_3$	63.16 62.85	3.90 3.96	3.88 3.90	1.40 (t, 3H, J = 7.1, CH_3), 4.39 (q, 2H, J = 7.1, OCH_2), 5.32 (s, 2H, NCH_2), 7.05-7.27 (m, 5H, Ar-H and 8-H), 8.27 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.56 (s, 1H, 2-H)
3e	2-Cl	H	68	198-199	$C_{19}H_{14}ClF_2NO_3$	60.41 60.45	3.74 3.80	3.71 3.76	1.40 (t, 3H, J = 7.1, CH_3), 4.39 (q, 2H, J = 7.1, OCH_2), 5.32 (s, 2H, NCH_2), 6.77-7.54 [g], 7.03 (dd, 1H, J = 11.0 and 6.2, 8-H), 8.32 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.56 (s, 1H, 2-H)
3f	3-Cl	H	57	185-186	$C_{19}H_{14}ClF_2NO_3$	60.41 60.21	3.74 3.82	3.71 3.77	1.42 (t, 3H, J = 7.1, CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.33 (s, 2H, NCH_2), 7.02-7.36 (m, 5H, Ar-H and 8-H), 8.30 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.58 (s, 1H, 2-H)
3g	4-Cl	H	84	229-230	$C_{19}H_{14}ClF_2NO_3$	60.41 60.28	3.74 3.80	3.71 3.65	1.42 (t, 3H, J = 7.1, CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.31 (s, 2H, NCH_2), 7.01-7.41 (m, 5H, Ar-H and 8-H), 8.29 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.57 (s, 1H, 2-H)
3h	4-Br	H	56	234-236	$C_{19}H_{14}BrF_2NO_3$	54.06 53.76	3.34 3.36	3.32 3.45	1.41 (t, 3H, J = 7.1, CH_3), 4.40 (q, 2H, J = 7.1, OCH_2), 5.29 (s, 2H, NCH_2), 7.01-7.54 (m, 5H, Ar-H and 8-H), 8.29 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.57 (s, 1H, 2-H)
3i	4-CH_3	H	91	198-200	$C_{20}H_{17}F_2NO_3$	67.22 67.08	4.79 4.81	3.92 4.00	1.42 (t, 3H, J = 7.1, CH_3), 2.35 (s, 3H, Ar-CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.29 (s, 2H, NCH_2), 7.03-7.2 (m, 5H, Ar-H and 8-H), 8.29 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.59 (s, 1H, 2-H)
3j	4-CF_3	H	62	255-257	$C_{20}H_{14}F_5NO_3$	58.40 58.17	3.43 3.43	3.40 3.38	1.43 (t, 3H, J = 7.1, CH_3), 4.43 (q, 2H, J = 7.1, OCH_2), 5.40 (s, 2H, NCH_2), 7.25-7.30 (m, 4H, Ar-H), 7.52 (dd, 1H, J = 11.3 and 6.4, 8-H), 8.33 (dd, 1H, J = 10.4 and 8.8, 5-H), 8.60 (s, 1H, 2-H)
4a	H	F	94	181-183	$C_{19}H_{14}F_3NO_3$	63.16 63.42	3.90 3.90	3.88 3.98	1.42 (t, 3H, J = 7.1, CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.52, 5.54 (two s, 2H, NCH_2), 7.11-7.40 (m, 5H, Ar-H), 8.17 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.54 (s, 1H, 2-H)
4b	2-F	F	86	227-229	$C_{19}H_{13}F_4NO_3$	60.16 60.10	3.45 3.50	3.69 3.50	1.41 (t, 3H, J = 7.1, CH_3), 4.40 (q, 2H, J = 7.1, OCH_2), 5.58, 5.59 (two s, 2H, NCH_2), 6.94-7.42 (m, 4H, Ar-H), 8.18 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.54 (s, 1H, 2-H)
4c	3-F	F	85	214-216	$C_{19}H_{13}F_4NO_3$	60.16 59.93	3.45 3.48	3.69 3.44	1.42 (t, 3H, J = 7.19, CH_3), 4.41 (q, 2H, J = 7.1, OCH_2), 5.50, 5.52 (two s, 2H, NCH_2), 6.82-7.40 (m, 4H, Ar-H), 8.18 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.51 (s, 1H, 2-H)
4d	4-F	F	89	207-209	$C_{19}H_{13}F_4NO_3$	60.16 60.08	3.45 3.48	3.69 3.34	1.42 (t, 3H, J = 7.1, CH_3), 4.42 (q, 2H, J = 7.1, OCH_2), 5.48, 5.50 (two s, 2H, NCH_2), 7.02-7.18 (m, 4H, Ar-H), 8.17 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.53 (s, 1H, 2-H)
4e	2-Cl	F	98	222-223	$C_{19}H_{13}ClF_3NO_3$	57.66 57.61	3.31 3.36	3.54 3.21	1.40 (t, 3H, J = 7.1, CH_3), 4.39 (q, 2H, J = 7.1, OCH_2), 5.61, 5.62 (two s, 2H, NCH_2), 6.75-7.52 (m, 4H, Ar-H), 8.20 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.46 (s, 1H, 2-H)
4f	3-Cl	F	80	190-191	$C_{19}H_{13}ClF_3NO_3$	57.66 57.36	3.31 3.33	3.54 3.18	1.42 (t, 3H, J = 7.1, CH_3), 4.42 (q, 2H, J = 7.1, OCH_2), 5.48, 5.50 (two s, 2H, NCH_2), 6.98-7.33 (m, 4H, Ar-H), 8.18 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.51 (s, 1H, 2-H)

Table 1 (continued)

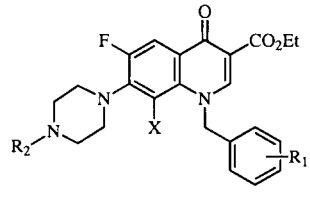
Compound	R_1	X	Yield (%) [a]	mp (°C)	Formula	Analysis Calcd/Found C	H	N	PMR (deuteriochloroform) δ ppm
4g	4-Cl	F	87	214-216	$C_{19}H_{13}ClF_3NO_3$	57.66 57.66	3.31 3.39	3.54 3.11	1.42 (t, 3H, J = 7.1, CH_3), 4.42 (q, 2H, J = 7.1, OCH_2), 5.48, 5.49 (two s, 2H, NCH_2), 7.06-7.37 (m, 4H, Ar-H), 8.17 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.52 (s, 1H, 2-H)
4h	4-Br	F	91	181-184	$C_{19}H_{13}BrF_3NO_3$	51.84 51.60	2.98 3.04	3.18 2.74	1.42 (t, 3H, J = 7.1, CH_3), 4.42 (q, 2H, J = 7.1, OCH_2), 5.45, 5.47 (two s, 2H, NCH_2), 6.99-7.52 (m, 4H, Ar-H), 8.17 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.52 (s, 1H, 2-H)
4i	4-CH_3	F	84	204-206	$C_{20}H_{16}F_3NO_3$	64.00 63.77	4.30 4.33	3.73 3.45	1.42 (t, 3H, J = 7.1, CH_3), 2.33 (s, 3H, Ar-CH_3), 4.45 (q, 2H, J = 7. 1, OCH_2), 5.47, 5.49 (two s, 2H, NCH_2), 7.01-7.19 (m, 4H, Ar-H), 8.17 (m, 1H, J = 10.5, 8.2 and 2.4, 5-H), 8.53 (s, 1H, 2-H)
4j	4-CF_3	F	66	247-249	$C_{20}H_{13}F_6NO_3$	55.95 55.37	3.05 3.15	3.26 2.96	1.42 (t, 3H, J = 7.1, CH_3), 4.42 (q, 2H, J = 7.1, OCH_2), 5.57, 5.58 (two s, 2H, NCH_2), 7.23-7.66 (m, 4H, Ar-H), 8.18 (m, 1H, J = 10. 5, 8.2 and 2.4, 5-H), 8.53 (s, 1H, 2-H)

[a] Yields calculated from the 6,7-difluoro- or 6,7,8-trifluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester.

azinyl)quinoline-3-carboxylic acid (**7a**) and its N-1 substituted benzyl derivatives **7b-j** are less potent than norfloxacin against most of the bacteria tested. Among them, compound **7d** which has a fluorine substituted at the 4'-position, is the most potent compound in this series. Replacement of fluorine with chlorine (**7g**), bromine (**7h**), methyl (**7i**), or trifluoromethyl (**7j**) resulted in a decrease of antibacterial activity. For those analogs having 4-methylpiperazine at the 7-position, potencies are sharply decreased compared to their piperazinyl counterparts (**7k** *vs* **7a**; **7l** *vs* **7d**; **7m** *vs* **7g**). In order to relate the lipophilicity to antibacterial activity, a fluorine was introduced at the 8-position of **7a-j**. Although these two series, **7a-j** and **8a-j,** of compounds possess comparable potency, compound **8c** which has a fluorine substituted at the 3'-position, exhibits a fairly good antibacterial activity.

Table 2

1-(Substituted-benzyl)-6-fluoro- and 6,8-Difluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Esters



Compound	R_1	R_2	X	Yield (%) [a]	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (deuteriochloroform) δ ppm
5a	H	H	H	97	192-193	$C_{23}H_{24}FN_3O_3$	67.47 67.04	5.91 5.95	10.26 10.40	1.40 (t, 3H, J = 7.1, CH_3), 2.97 (m, 8H, piperazinyl-H), 4.39 (q, 2H, J = 7.1, OCH_2), 5.33 (s, 2H, NCH_2), 6.59 (d, 1H, J = 7.0, 8-H), 7.14-7.37 (m, 5H, Ar-H), 8.03 (d, 1H, J = 13.4, 5-H), 8.54 (s, 1H, 2-H)
5b	2-F	H	H	98	179-180	$C_{23}H_{23}F_2N_3O_3$	64.63 64.57	5.42 5.40	9.83 9.94	1.42 (t, 3H, J = 7.1, CH_3), 3.04 (m, 8H, piperazinyl-H), 4.41 (q, 2H, J = 7.1, OCH_2), 5.36 (s, 2H, NCH_2), 6.67 (d, 1H, J = 7.0, 8-H), 7.01-7.41 (m, 4H, Ar-H), 8.05 (d, 1H, J = 13.4, 5-H), 8.59 (s, 1H, 2-H)
5c	3-F	H	H	96	185-187	$C_{23}H_{23}F_2N_3O_3$	64.63 64.42	5.42 5.39	9.83 9.76	1.42 (t, 3H, J = 7. 1, CH_3), 2.99 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.33 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 6.86-7.14 (m, 4H, Ar-H), 8.02 (d, 1H, J = 13.4, 5-H), 8.50 (s, 1H, 2-H)
5d	4-F	H	H	98	196-197	$C_{23}H_{23}F_2N_3O_3$	64.63 64.38	5.42 5.39	9.83 9.89	1.46 (t, 3H, J = 7.1, CH_3), 3.03 (m, 8H, piperazinyl-H), 4.39 (q, 2H, J = 7.1, OCH_2), 5.13 (s, 2H, NCH_2), 6.57 (d, 1H, J = 7.0, 8-H), 7.03-7.21 (m, 4H, Ar-H), 8.04 (d, 1H, J = 13.4, 5-H), 8.52 (s, 1H, 2-H)

Table 2 (continued)

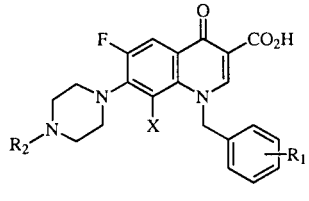
Compound	R_1	R_2	X	Yield (%) [a]	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (deuteriochloroform) δ ppm
5e	2-Cl	H	H	96	183-184	$C_{23}H_{23}ClFN_3O_3$	62.23 62.07	5.22 5.30	9.47 9.39	1.42 (t, 3H, J = 7.1, CH_3), 3.01 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.44 (s, 2H, NCH_2), 6.48 (d, 1H, J = 7.0, 8-H), 6.88-7.52 (m, 4H, Ar-H), 8.06 (d, 1H, J = 13.4, 5-H), 8.55 (s, 1H, 2-H)
5f	3-Cl	H	H	94	163-165	$C_{23}H_{23}ClFN_3O_3$	62.23 62.03	5.22 5.30	9.47 9.28	1.42 (t, 3H, J = 7.1, CH_3), 3.00 (m, 8H, piperazinyl-H), 4.41 (q, 2H, J = 7.1, OCH_2), 5.31 (s, 2H, NCH_2), 6.53 (d, 1H, J = 7.0, 8-H), 7.03-7.35 (m, 4H, Ar-H), 8.02 (d, 1H, J = 13.4, 5-H), 8.51 (s, 1H, 2-H)
5g	4-Cl	H	H	87	212-213	$C_{23}H_{23}ClFN_3O_3$	62.23 62.00	5.22 5.28	9.47 9.35	1.41 (t, 3H, J = 7.1, CH_3), 3.00 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.30 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 7.10-7.37 (m, 4H, Ar-H), 8.02 (d, 1H, J = 13.4, 5-H), 8.50 (s, 1H, 2-H)
5h	4-Br	H	H	89	215-216	$C_{23}H_{23}BrFN_3O_3$	56.57 56.13	4.75 4.74	8.60 8.51	1.42 (t, 3H, J = 7.1, CH_3), 3.01 (m, 8H, piperazinyl-H), 4.41 (q, 2H, J = 7.1, OCH_2), 5.28 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 7.04-7.53 (m, 4H, Ar-H), 8.05 (d, 1H, J = 13.4, 5-H), 8.52 (s, 1H, 2-H)
5i	4-CH_3	H	H	91	202-203	$C_{24}H_{26}FN_3O_3$	68.07 67.78	6.19 6.18	9.92 9.80	1.42 (t, 3H, J = 7.1, CH_3), 2.34 (s, 3H, Ar-CH_3), 3.01 (m, 8H, piperazinyl-H), 4.41 (q, 2H, J = 7.1, OCH_2), 5.29 (s, 2H, NCH_2), 6.64 (d, 1H, J = 7.0, 8-H), 7.05-7.19 (m, 4H, Ar-H), 8.05 (d, 1H, J = 13.4, 5-H), 8.55 (s, 1H, 2-H)
5j	4-CF_3	H	H	96	220-221	$C_{24}H_{23}F_4N_3O_3$	60.37 60.18	4.86 4.85	8.80 8.74	1.41 (t, 3H, J = 7.1, CH_3), 2.99 (m, 8H, piperazinyl-H), 4.39 (q, 2H, J = 7.1, OCH_2), 5.41 (s, 2H, NCH_2), 6.47 (d, 1H, J = 7.0, 8-H), 7.28-7.67 (m, 4H, Ar-H), 8.02 (d, 1H, J = 13.4, 5-H), 8.51 (s, 1H, 2-H)
5k	H	CH_3	H	88	178-179	$C_{24}H_{26}FN_3O_3$ $0.5H_2O$	66.65 66.73	6.29 6.31	9.72 9.58	1.41 (t, 3H, J = 7.1, CH_3), 2.34 (s, 3H, NCH_3), 2.52 and 3.03 (m, 8H, piperazinyl-H), 4.41 (q, 2H, J = 7.1, OCH_2), 5.27 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 7.12-7.41 (m, 5H, Ar-H), 8.06 (d, 1H, J = 13.4, 5-H), 8.48 (s, 1H, 2-H)
5l	4-F	CH_3	H	95	123-124	$C_{24}H_{25}F_2N_3O_3$ H_2O	62.74 62.83	5.92 5.91	9.14 9.06	1.42 (t, 3H, J = 7.1, CH_3), 2.33 (s, 3H, NCH_3), 2.54 and 3.07 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.31 (s, 2H, NCH_2), 6.56 (d, 1H, J = 7.0, 8-H), 7.07-7.21 (m, 4H, Ar-H), 8.04 (d, 1H, J = 13.4, 5-H), 8.52 (s, 1H, 2-H).
5m	4-Cl	CH_3	H	84	166-167	$C_{24}H_{25}ClFN_3O_3$ $0.25H_2O$	62.34 62.11	5.45 5.47	9.09 8.98	1.41 (t, 3H, J = 7.1, CH_3), 2.33 (s, 3H, NCH_3), 2.53 and 3.07 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.30 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 7.09-7.37 (m, 4H, Ar-H), 8.02 (d, 1H, J = 13.4, 5-H), 8.50 (s, 1H, 2-H)
5n	4-Br	CH_3	H	96	166-168	$C_{24}H_{25}BrFN_3O_3$ $0.5H_2O$	56.37 56.58	4.93 5.00	8.22 8.24	1.42 (t, 3H, J = 7.1, CH_3), 2.36 (s, 3H, NCH_3), 2.53 and 3.08 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.28 (s, 2H, NCH_2), 6.52 (d, 1H, J = 7.0, 8-H), 7.03-7.52 (m, 4H, Ar-H), 8.03 (d, 1H, J = 13.4, 5-H), 8.51 (s, 1H, 2-H)
5o	4-CH_3	CH_3	H	87	145-147	$C_{25}H_{28}FN_3O_3$ $0.5H_2O$	67.25 67.52	6.32 6.53	9.41 9.45	1.42 (t, 3H, J = 7.1, CH_3), 2.33 (br s, 6H, NCH_3 and Ar-CH_3), 2.53 and 3.08 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.28 (s, 2H, NCH_2), 6.64 (d, 1H, J = 7.0, 8-H), 7.04-7.19 (m, 4H, Ar-H), 8.05 (d, 1H, J = 13.4, 5-H), 8.55 (s, 1H, 2-H)
5p	4-CF_3	CH_3	H	96	106-108	$C_{25}H_{25}F_4N_3O_3$ $0.5H_2O$	60.00 60.22	5.03 5.23	8.40 8.44	1.41 (t, 3H, J = 7.1, CH_3), 2.32 (s, 3H, NCH_3), 2.52 and 3.06 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.40 (s, 2H, NCH_2), 6.48 (d, 1H, J = 7.0, 8-H), 7.28-7.66 (m, 4H, Ar-H), 8.03 (d, 1H, J = 13.4, 5-H), 8.52 (s, 1H, 2-H)
6a	H	H	F	86	142-143	$C_{23}H_{23}F_2N_3O_3$ $0.25H_2O$	63.95 63.81	5.48 5.38	9.73 9.63	1.40 (t, 3H, J = 7.1, CH_3), 2.95 and 3.16 (m, 8H, piperazinyl-H), 4.39 (q, 2H, J = 7.1, OCH_2), 5.50 (s, 2H, NCH_2), 7.12-7.35 (br s, 5H, Ar-H), 7.94 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.47 (s, 1H, 2-H)
6b	2-F	H	F	91	112-114	$C_{23}H_{22}F_3N_3O_3$ $0.5H_2O$	60.79 60.82	5.10 5.11	9.25 9.08	1.40 (t, 3H, J = 7.1, CH_3), 2.94 and 3.18 (m, 8H, piperazinyl-H), 4.59 (q, 2H, J = 7.1, OCH_2), 5.55 (s, 2H,

Table 2 (continued)

Compound	R_1	R_2	X	Yield (%) [a]	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (deuteriochloroform) δ ppm
										NCH_2), 6.90-7.38 (m, 4H, Ar-H), 7.96 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.46 (s, 1H, 2-H)
6c	3-F	H	F	90	129-130	$C_{23}H_{22}F_3N_3O_3$	62.02 61.98	4.98 4.92	9.43 9.50	1.42 (t, 3H, J = 7.1, CH_3), 2.94 and 3.16 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.48 (s, 2H, NCH_2), 6.80-7.38 (m, 4H, Ar-H), 7.96 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.44 (s, 1H, 2-H)
6d	4-F	H	F	86	106-108	$C_{23}H_{22}F_3N_3O_3$ $0.25H_2O$	61.40 61.22	5.04 4.98	9.34 9.36	1.41 (t, 3H, J = 7.1, CH_3), 2.95 and 3.16 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.46 (s, 2H, NCH_2), 7.00-7.16 (m, 4H, Ar-H), 7.95 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.47 (s, 1H, 2-H)
6e	2-Cl	H	F	82	176-180	$C_{23}H_{22}ClF_2N_3O_3$	59.81 59.76	4.80 4.92	9.10 9.15	1.39 (t, 3H, J = 7.1, CH_3), 2.93 and 3.15 (m, 8H, piperazinyl-H), 4.38 (q, 2H, J =7.1, OCH_2), 5.57 (s, 2H, NCH_2), 6.75-7.50 (m, 4H, Ar-H), 8.00 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.37 (s, 1H, 2-H)
6f	3-Cl	H	F	95	–	$C_{23}H_{22}ClF_2N_3O_3$ $0.5H_2O$	58.66 58.48	4.92 4.76	8.92 8.98	1.42 (t, 3H, J = 7.1, CH_3), 2.95 and 3.17 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.46 (s, 2H, NCH_2), 6.96-7.30 (m, 4H, Ar-H), 7.95 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.44 (s, 1H, 2-H)
6g	4-Cl	H	F	92	108-109	$C_{23}H_{22}ClF_2N_3O_3$ $0.5H_2O$	58.66 58.53	4.92 4.87	8.92 8.99	1.41 (t, 3H, J = 7.1, CH_3), 2.95 and 3.17 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.45 (s, 2H, NCH_2), 7.04-7.34 (m, 4H, Ar-H), 7.95 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.44 (s, 1H, 2-H)
6h	4-Br	H	F	91	161-163	$C_{23}H_{22}BrF_2N_3O_3$ $0.25H_2O$	54.01 53.92	4.43 4.37	8.22 8.35	1.41 (t, 3H, J = 7.1, CH_3), 2.95 and 3.16 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J =7. 1, OCH_2), 5.43 (s, 2H, NCH_2), 6.98-7.50 (m, 4H, Ar-H), 7.96 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.44 (s, 1H, 2-H)
6i	4-CH_3	H	F	86	109-111	$C_{24}H_{25}F_2N_3O_3$	65.30 65.13	5.71 5.60	9.52 9.67	1.41 (t, 3H, J = 7.1, CH_3), 2.33 (s, 3H, Ar-H), 2.96 and 3.17 (m, 8H, piperazinyl-H), 4.39 (q, 2H, J = 7.1, OCH_2), 5.45 (s, 2H, NCH_2), 6.99-7.16 (m, 4H, Ar-H), 7.95 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.46 (s, 1H, 2-H)
6j	4-CF_3	H	F	88	169-171	$C_{24}H_{22}F_5N_3O_3$ H_2O	56.14 56.03	4.71 4.71	8.18 8.21	1.41 (t, 3H, J = 7.1, CH_3), 2.95 and 3.16 (m, 8H, piperazinyl-H), 4.40 (q, 2H, J = 7.1, OCH_2), 5.56 (s, 2H, NCH_2),7.27-7.64 (m, 4H, Ar-H), 7.96 (dd, 1H, J = 12.2 and 2.0, 5-H), 8.46 (s, 1H, 2-H)

Table 3

1-(Substituted-benzyl)-6-fluoro- and 6,8-difluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic acids



Compound	R_1	R_2	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (dimethyl sulfoxide-d_6) δ ppm
7a	H	H	H	89	249-252	$C_{21}H_{20}FN_3O_3$	66.13 65.78	5.28 5.28	11.02 11.01	2.78 and 3.03 (two m, each 4H, piperazinyl-H), 5.85 (s, 2H, NCH2), 7.30-7.39 (m, 5H, Ar-H), 7.03 (d, 1H, J = 7.3, 8-H), 7.88 (d, 1H, J = 13.2, 5-H), 9.21 (s, 1H, 2-H), 15.02 (br s, 1H , COOH)
7b	2-F	H	H	84	292-294 (dec)	$C_{21}H_{19}F_2N_3O_3$ HCl	57.87 57.50	4.62 4.67	9.64 9.48	3.24 and 3.42 (two m, each 4H, piperazinyl-H), 5.96 (s, 2H, NCH_2), 7.20-7.43 (m, 5H, Ar-H and 8-H), 7.94 (d, 1H, J = 13.2, 5-H), 9.17 (s, 1H, 2-H), 9.50 (br s, 1.2 H, HCl and H_2O), 15.13 (br s, 1H, COOH)
7c	3-F	H	H	68	>300	$C_{21}H_{19}F_2N_3O_3$ HCl $0.25H_2O$	57.28 57.29	4.69 4.72	9.54 9.65	3.24 and 3.35 (two m, each 4H, piperazinyl-H), 5.96 (s, 2H, NCH_2), 7.10-7.45 (m, 5H, Ar-H and 8-H), 7.97 (d, 1H, J = 13.2, 5-H), 9.06 (br s, 1.4H, HCl and H_2O), 9.21 (s, 1H, 2-H), 15.17 (br s, 1H, COOH)

Table 3 (continued)

Compound	R_1	R_2	X	yield (%)	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (dimethyl sulfoxide-d_6) δ ppm
7d	4-F	H	H	75	266-268 (dec)	$C_{21}H_{19}F_2N_3O_3$	63.15 63.14	4.79 4.75	10.52 10.43	3.23 and 3.42 (two m, each 4H, piperazinyl-H), 5.89 (s, 2H, NCH_2), 7.16-7.46 (m, 5H, Ar-H and 8-H), 7.92 (d, 1H, J = 13.2, 5-H), 9.21 (s, 1H, 2-H), 9.53 (br s, 1.1H, HCl and H_2O), 15.19 (br s, 1H, COOH)
7e	2-Cl	H	H	82	292-294 (dec)	$C_{21}H_{19}ClFN_3O_3$ HCl 0.25H_2O	55.22 55.12	4.52 4.48	9.20 9.32	3.23 and 3.37 (two m, each 4H, piperazinyl-H), 5.93 (s, 2H, NCH_2), 7.10-7.61 (m, 4H, Ar-H), 7.01 (d, 1H, J = 7.3, 8-H), 7.98 (d, 1H, J = 13.2, 5-H), 9.08 (s, 1H, 2-H), 9.43 (br s, 1.3H, HCl and H_2O), 15.09 (br s, 1H, COOH)
7f	3-Cl	H	H	86	295-298 (dec)	$C_{21}H_{19}ClFN_3O_3$ HCl 0.5H_2O	54.68 54.35	4.59 4.72	9.11 9.08	3.22 and 3.37 (two m, each 4H, piperazinyl-H), 5.90 (s, 2H, NCH_2), 7.28-7.49 (m, 4H, Ar-H), 7.15 (d, 1H, J = 7.3, 8-H), 7.95 (d, 1H, J = 13.2, 5-H), 9.21 (s, 1H, 2-H), 9.40 (br s, 1.5H, HCl and H_2O), 15.17 (br s, 1H, COOH)
7g	4-Cl	H	H	92	283-285 (dec)	$C_{21}H_{19}ClFN_3O_3$ HCl	55.76 55.42	4.46 4.49	9.29 9.28	3.24 and 3.40 (two m, each 4H, piperazinyl-H), 5.90 (s, 2H, NCH_2), 7.35-7.47 (m, 4H, Ar-H), 7.17 (d, 1H, J = 7.3, 8-H), 7.94 (d, 1H, J = 13.2, 5-H), 9.22 (s, 1H, 2H), 9.47 (br s, 1.1H, HCl and H_2O), 15.17 (br s, 1H, COOH)
7h	4-Br	H	H	94	245-248 (dec)	$C_{21}H_{19}BrFN_3O_3$ HCl 0.25H_2O	50.32 50.08	4.12 4.15	8.38 8.36	3.26 and 3.39 (two m, each 4H, piperazinyl-H), 5.87 (s, 2H, NCH_2), 7.28-7.59 (m, 4H, Ar-H), 7.16 (d, 1H, J = 7.3, 8-H), 7.96 (d, 1H, J = 13.2, 5-H), 9.22 (s, 1H, 2-H), 9.31 (br s, 1.3H, HCl and H_2O), 15.17 (br s, 1H, COOH)
7i	4-CH_3	H	H	72	276-278 (dec)	C22H22FN303 HCl	61.18 60.88	5.37 5.40	9.73 9.93	2.26 (s, 3H, Ar-CH3), 3.23 and 3.39 (two m, each 4H, piperazinyl-H), 5.83 (s, 2H, NCH_2), 7.15-7.26 (m, 5H, Ar-H and 8-H), 7.91 (d, 1H, J = 13.2, 5-H), 9.17 (s, 1H, 2-H), 9.50 (br s, 1.1H, HCl and H_2O), 15.20 (br s, 1H, COOH)
7j	4-CH_3	H	H	92	252-254 (dec)	$C_{22}H_{19}F_4N_3O_3$ HCl H_2O	52.44 52.62	4.40 4.60	8.34 8.38	3.22 and 3.37 (two m, each 4H, piperazinyl-H), 6.02 (s, 2H, NCH_2), 7.53-7.76 (m, 4H, Ar-H), 7.15 (d, 1H, J = 7.3, 8-H), 7.94 (d, 1H, J = 13.2, 5-H), 9.25 (s, 1H, 2-H), 9.49 (br s, 2.1H, HCl and H_2O), 15.15 (br s, 1H, COOH)
7k	H	CH_3	H	73	232-234	$C_{22}H_{22}FN_3O_3$ 0.25H_2O	66.07 66.00	5.67 5.57	10.51 10.16	2.19 (s, 3H, piperazinyl-CH_3), 2.38 and 3.11 (two m, each 4H, piperazinyl-H), 5.85 (s, 2H, NCH_2), 7.30-7.38 (m, 5H, Ar-H), 7.06 (d, 1H, J = 7.3, 8-H), 7.88 (d, 1H, J = 13.2, 5-H), 9.21 (s, 1H, 2-H), 15.25 (br s, 1H, COOH)
7l	4-F	CH_3	H	90	223-226	$C_{22}H_{21}F_2N_3O_3$	63.92 63.73	5.12 5.14	10.16 10.12	2.19 (s, 3H, piperazinyl-CH_3), 2.40 and 3.13 (two m, each 4H, piperazinyl-H), 5.83 (s, 2H, NCH_2), 7.17-7.44 (m, 4H, Ar-H), 7.05 (d, 1H, J = 7.3, 8-H), 7.88 (d, 1H, J = 13.2, 5-H), 9.20 (s, 1H, 2-H), 15.18 (br s, 1H, COOH)
7m	4-Cl	CH_3	H	84	242-244	$C_{22}H_{21}ClFN_3O_3$	61.47 61.18	4.92 4.96	9.77 9.77	2.19 (s, 3H, piperazinyl-CH_3), 2.38 and 3.15 (two m, each 4H, piperazinyl-H), 5.83 (s, 2H, NCH_2), 7.32-7.47 (m, 4H, Ar-H), 7.00 (d, 1H, J = 7.3, 8-H), 7.88 (d, 1H, J = 13.2, 5-H), 9.17 (s, 1H, 2-H)
7n	4-Br	CH_3	H	83	196-198 (dec)	$C_{22}H_{21}BrFN_3O_3$ 0.25H_2O	55.18 55.29	4.52 4.53	8.78 8.70	2.19 (s, 3H, piperazinyl-CH_3), 2.38 and 3.15 (two m, each 4H, piperazinyl-H), 5.83 (s, 2H, NCH_2), 7.27-7.60 (m, 4H, Ar-H), 7.01 (d, 1H, J = 7.3, 8-H), 7.89 (d, 1H, J = 13.2, 5-H), 9.21 (s, 1H, 2-H)
7o	4-CH_3	CH_3	H	90	247-249 (dec)	$C_{23}H_{24}FN_3O_3$ HCl 0.5H_2O	60.72 60.78	5.76 5.75	9.24 9.28	2.27 (s, 3H, Ar-CH_3), 2.79 (s, 3H, piperazinyl-CH_3), 3.15-3.65 (two m, each 4H, piperazinyl-H), 5.83 (s, 2H, NCH_2), 7.16-7.27 (m, 5H, Ar-H and 8-H), 7.95 (d, 1H, J = 13.2, 5-H), 9.17 (s, 1H, 2-H), 11.22 (br s, 1.6H, HCl and H_2O), 15.18 (br s, 1H, COOH)
7p	4-CF_3	CH_3	H	88	202-204 (dec)	$C_{23}H_{21}F_4N_3O_3$ HCl 0.25H_2O	54.77 54.63	4.50 4.67	8.33 8.41	2.77 (s, 3H, piperazinyl-CH_3), 3.15-3.63 (two m, each 4H, piperazinyl-H), 6.02 (s, 2H, NCH_2), 7.53-7.77 (m, 4H, Ar-H), 7.17 (d, 1H, J = 7.3, 8-H), 7.96 (d, 1H, J = 13.2, 5-H), 9.24 (s, 1H, 2-H), 11.33 (br s, 1.3H, HCl and H_2O), 15.25 (br s, 1H , COOH)

Table 3 (continued)

Compound	R_1	R_2	X	yield (%)	mp (°C)	Formula	Analysis (%) Calcd/Found C	H	N	PMR (dimethyl sulfoxide-d_6) δ ppm
8a	H	H	F	81	168-171 (dec)	$C_{21}H_{19}F_2N_3O_3$ HCl $0.5H_2O$	56.70 56.49	4.87 4.99	9.44 9.46	3.16 and 3.41 (two m, each 4H, piperazinyl-H), 5.86 and 5.87 (two s, 2H, NCH_2), 7.15-7.40 (m, 5H, Ar-H), 7.92 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.11 (s, 1H, 2-H), 9.34 (br s, 1.5H, HCl and H_2O), 14.72 (br s, 1H, COOH)
8b	2-F	H	F	78	254-257 (dec)	$C_{21}H_{18}F_3N_3O_3$ HCl	55.57 55.48	4.22 4.23	9.26 9.18	3.14 and 3.35 (two m, each 4H, piperazinyl-H), 5.92 and 5.94 (two s, 2H, NCH_2), 7.00-7.41 (m, 4H, Ar-H), 7.93 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.11 (s, 1H, 2-H), 9.31 (br s, 1.1H, HCl and H_2O), 14.67 (br s, 1H, COOH)
8c	3-F	H	F	83	256-258 (dec)	$C_{21}H_{18}F_3N_3O_3$ HCl $0.25H_2O$	55.03 54.96	4.29 4.32	9.17 9.08	3.15 and 3.38 (two m, each 4H, piperazinyl-H), 5.87 and 5.88 (two s, 2H, NCH_2), 6.97-7.46 (m, 4H, Ar-H), 7.90 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.08 (s, 1H, 2-H), 9.50 (br s, 1.3H, HCl and H_2O), 14.70 (br s, 1H, COOH)
8d	4-F	H	F	85	251-254 (dec)	$C_{21}H_{18}F_3N_3O_3$ HCl	55.57 55.48	4.22 4.22	9.26 9.04	3.15 and 3.43 (two m, each 4H, piperazinyl-H), 5.83 and 5.84 (two s, 2H, NCH_2), 7.14-7.29 (m, 4H, Ar-H), 7.91 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.10 (s, 1H, 2-H), 9.39 (br s, 1.2H, HCl and H_2O), 14.70 (br s, 1H , COOH)
8e	2-Cl	H	F	82	248-250 (dec)	$C_{21}H_{18}ClF_2N_3O_3$ HCl $0.5H_2O$	52.62 52.64	4.21 4.29	8.77 8.74	3.14 and 3.36 (two m, each 4H, piperazinyl-H), 5.91 and 5.93 (two s, 2H, NCH_2), 6.83-7.60 (m, 4H, Ar-H), 7.96 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.07 (s, 1H, 2-H), 9.19 (br s, 1.7H, HCl and H_2O), 14.68 (br s, 1H , COOH)
8f	3-Cl	H	F	78	243-245 (dec)	$C_{21}H_{18}ClF_2N_3O_3$ HCl $0.25H_2O$	53.12 52.98	4.14 4.24	8.85 8.83	3.15 and 3.41 (two m, each 4H, piperazinyl-H), 5.85 and 5.87 (two s, 2H, NCH_2), 7.08-7.40 (m, 4H, Ar-H), 7.92 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.09 (s, 1H, 2-H), 9.35 (br s, 1.3H, HCl and H_2O), 14.70 (br s, 1H , COOH)
8g	4-Cl	H	F	81	223-224 (dec)	$C_{21}H_{18}ClF_2N_3O_3$ HCl $0.5H_2O$	52.62 52.63	4.21 4.31	8.77 8.68	3.14 and 3.36 (two m, each 4H, piperazinyl-H), 5.84 and 5.85 (two s, 2H, NCH_2), 7.19-7.44 (m, 4H, Ar-H), 7.93 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.12 (s, 1H, 2-H), 9.22 (br s, 1.7H, HCl and H_2O), 14.70 (br s, 1H , COOH)
8h	4-Br	H	F	81	220-221 (dec)	$C_{21}H_{18}BrF_2N_3O_3$ HCl H_2O	47.34 47.33	3.97 3.86	7.89 7.86	3.16 and 3.44 (two m, each 4H, piperazinyl-H), 5.83 and 5.84 (two s, 2H, NCH_2), 7.14-7.58 (m, 4H, Ar-H), 7.92 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.12 (s, 1H, 2-H), 9.44 (br s, 2.2H, HCl and H_2O), 14.72 (br s, 1H , COOH)
8i	4-CH_3	H	F	72	240-242 (dec)	$C_{22}H_{21}F_2N_3O_3$ HCl $0.5H_2O$	57.58 57.42	5.02 5.06	9.16 9.14	2.27 (s, 3H, Ar-CH_3), 3.16 and 3.45 (two m, each 4H, piperazinyl-H), 5.81 and 5.82 (two s, 2H, NCH_2), 7.04-7.19 (m, 4H, Ar-H), 7.91 [(dd, 1H, J = 11.8 and 1.8, 5-H), 9.09 (s, 1H, 2-H), 9.47 (br s, 1.7H, HCl and H_2O), 14.73 (br s, 1H, COOH)
8j	4-CF_3	H	F	82	234-236 (dec)	$C_{22}H_{18}F_5N_3O_3$ HCl $0.5H_2O$	51.52 51.47	3.93 3.98	8.19 8.14	3.15 and 3.42 (two m, each 4H, piperazinyl-H), 5.97 (br s, 2H, NCH_2), 7.44-7.76 (m, 4H, Ar-H), 7.94 (dd, 1H, J = 11.8 and 1.8, 5-H), 9.16 (s, 1H, 2-H), 9.37 (br s, 1.6H, HCl and H_2O), 14.68 (br s, 1H, COOH)

Table 4

In Vitro Antibacterial Activity of 1-(Substituted-benzyl)-6-fluoro and 6,8-Difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids

	minimal inhibitory concentration (MIC) [a], μg/ml								
Compound	Sa	Se	Ec	EcI	Kp	Pv	St	Sm	Pa
7a	25	1.56	1.56	1.56	0.78	0.78	1.56	1.56	3.2
7b	12.5	25	12.5	>50	3.2	25	50	12.5	50
7c	6.25	50	6.25	6.25	0.78	50	25	6.25	6.25
7d	25	6.25	0.39	0.78	0.39	3.125	0.78	1.56	6.25
7e	1.56	1.56	1.56	12.5	1.56	12.5	3.125	6.25	25
7f	>50	25	>50	>50	6.25	25	25	25	25
7g	>50	25	1.56	3.2	0.78	12.5	1.56	6.25	25
7h	>50	25	3.2	12.5	6.25	25	6.25	12.5	>50
7i	>50	>50	>50	>50	12.5	>>50	>50	>50	>>50
7j	>50	>50	>>50	>>50	>>50	>>50	>>50	>>50	>>50
7k	3.2	50	6.25	3.2	3.2	50	50	50	50
7l	>50	50	>50	>50	50	>50	>50	50	50
7m	>50	>50	12.5	>50	12.5	50	>50	>50	>50

Table 4 (continued)

Compound	minimal inhibitory concentration (MIC) [a], μg/ml								
	Sa	Se	Ec	EcI	Kp	Pv	St	Sm	Pa
7n	>50	>50	50	>50	12.5	>50	>50	>50	>50
7o	>50	50	>50	>50	>50	>>50	>>50	>>50	>>50
7p	>50	>50	>>50	>>50	>>50	>>50	>>50	>>50	>>50
8a	6.25	6.25	3.2	6.25	1.56	12.5	1.56	3.2	6.25
8b	50	50	12.5	50	6.25	50	50	25	50
8c	6.25	6.25	0.2	0.8	0.8	1.56	0.8	6.25	6.25
8d	12.5	6.25	0.8	0.8	1.56	6.25	6.25	6.25	6.25
8e	50	12.5	6.25	12.5	6.25	50	12.5	>50	50
8f	50	6.25	3.2	6.25	6.25	25	25	25	50
8g	12.5	6.25	6.25	6.25	6.25	50	12.5	50	50
8h	50	25	12.5	25	25	>>50	25	>>50	>>50
8i	>50	>50	>>50	>>50	>>50	>>50	>>50	>>50	>>50
8j	>>50	>>50	>>50	>>50	>>50	>>50	>>50	>>50	>>50
Nor [b]	12.5	6.25	0.1	0.1	0.2	0.8	0.8	3.2	3.2

[a] Organisms selected for inclusion in the table are Sa, *Staphylococcus aureus;* Se, *Staphylococcus epidermidis;* Ec, *Escherichia coli;* Ecl, *Enterbacter cloacae;* Kp, *Klebsiella pneumoniae;* Pv, *Proteus vulgaris;* St, *Salmonella typhimurium;* Sm, *Serratia marcescens;* Pa, *Pseudomonas aeruginosa.* [b] Norfloxacin in dimethyl sulfoxide.

EXPERIMENTAL

Melting points were determined on a Fargo MP-ID melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co.. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University and National Chung-Hsing University using Heraeus CHN-O Rapid EA.

General Procedure for the Preparation of 1-Benzyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Esters **3a-j** and their 6,7,8-Trifluoro anlogs **4a-j**.

A mixture of 6,7-difluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester (**1**, 1.27 g, 5 mmoles), anhydrous potassium carbonate (1.73 g, 12.5 mmoles) and 7.5 mmoles of substituted-benzyl chloride in 20 ml of dry *N,N*-dimethylformamide was stirred at 90-100° for 12 hours. After removing the solvent, the residue was taken up by dichloromethane and the dichloromethane solution, after washed with water and dried with sodium sulfate, was evaporated to dryness. Crystallization of the solid residue from ethyl acetate afforded the desired **3a-j**.

Following the same procedures, compounds **4a-j** were prepared from 6,7,8-trifluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester (**2**) and the appropriate substituted-benzyl chloride.

The characteristics of compounds **3a-j** and **4a-j** are summarized in Table 1.

General Procedure for the Preparation of 1-Benzyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid Ethyl Esters **5a-p** and their 6,8-Difluoro Analogs **6a-j**.

A mixture of **3a-j** (4.4 mmoles), piperazine (1.13 g, 13.2 mmoles) and pyridine (30 ml) was stirred at 70-80° under nitrogen atmosphere. After 16 hours, the mixture was evaporated to dryness and water was added to the residue. The resulting solid was filtered off, washed with water, dried, and crystallized from ethyl acetate-ethanol to give **5a-j** respectively.

Following the same procedures, compounds **5k-p** were prepared from **3k-p** and *N*-methylpiperazine, compounds **6a-j** were prepared from **4a-j** and piperazine.

The characteristics of compounds **5a-p** and **6a-j** are summarized in Table 2.

General Procedure for the Preparation of 1-Benzyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic Acids **7a-p** and their 6,8-Difluoro Analogs **8a-j**.

To a suspension of **5a-p** (3.3 mmoles) in dry tetrahydrofuran (15 ml) was added a solution of 1.0 *N* sodium hydroxide (3.5 ml). The mixture was heated at reflux for 2 hours and then the solvent was evaporated under reduced pressure. The residue thus obtained was dissolved in water (20 ml) and the solution acidified with 1.0 *N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried to afford **7a-p**.

Following the same procedures, compounds **8a-j** were prepared from **6a-j** respectively.

The characteristics of compounds **7a-p** and **8a-j** are summarized in Table 3.

In Vitro Antibacterial Activity.

The antibacterial activity was determined by argar dilution assay using a multipoint inoculator. Mueller-Hinton agar (20 ml in a Petri dish) was used. The test compounds were dissolved and incorporated by the twofold dilution method in the agar medium. Bacterial inocula, coming from overnight broth and containing 10^5 colony-forming units per point, were inoculated by multipoint inoculator. Bacterial growth was observed after 18 hours of incubation at 37°. The lowest concentration of test compounds that completely inhibited growth was considered to be the minimal inhibitory concentration (MIC). The *in vitro* antibacterial data was summarized in Table 4.

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REFERENCES AND NOTES

[1] G. Y. Lesher, E. J. Froelich, M. D. Garnett, J. H. Bailey, and P. R. Brundage, *J. Med. Chem.*, **5**, 259 (1962).

[2] D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968).

[3] J. Matsumoto and S. Minami, *J. Med. Chem.*, **18**, 74 (1975).

[4] H. Koga, A. Itoh, S. Murayama, S. Suzue, and T. Irikura, *J. Med. Chem.*, **23**, 1358 (1980).

[5] Y. Goueffon, G. Montay, F. Roquet, and M. Pesson, *C. R. Acad. Sci., Ser. 3*, **292**, 37 (1981).

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

[7] I. Hayakawa, T. Hiramitsu, and Y. Tanaka, *Chem. Pharm. Bull.*, **32**, 4907 (1984).

[8] K. Grohe and H. Heitzer, *Liebigs Ann. Chem.*, 29 (1987).

[9] L. L. Shen and A. G. Pernet, *Proc. Natl. Acad. Sci.*, **82**, 307 (1985).

[10] L. L. Shen, *Biochem. Pharmacol.*, **38**, 2042 (1989).

[11] J. F. Barrett, J. A. Sutcliffe, and T. D. Gootz, *Antimicrob. Agents Chemother.*, **34**, 1 (1990).

[12] J. S. Wolfson and D. C. Hooper, *Clin. Microbiol. Rev.*, **2**, 378 (1989).

[13] D. T. W. Chu, P. B. Fernandes, A. K. Claiborne, E. Pihuleac, C. W. Nordeen, R. E. Maleczka, and A. G. Pernet, *J. Med. Chem.*, **28**, 1558 (1985).

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

[15] J. M. Domagala, C. L. Heifetz, M. P. Huff, T. F. Mich, J. B. Nichols, M. Solomon, and D. F. Worth, *J. Med. Chem.*, **31**, 991 (1988).

[16] D. T. W. Chu, P. B. Fernandes, and G. R. Grenneman, *Drug. Future*, **10**, 543 (1985).

[17] D. J. Hardy, R. N. Swanson, D. M. Hensey, N. R. Ramer, R. R. Bower, C. W. Hanson, D. T. W. Chu, and P. B. Fernandes, *Antimicrob. Agents Chemother.*, **31**, 1768 (1987).