Synthesis and Antibacterial Activity of 6-Difluoromethoxy-7-piperazinyl-3-quinolinecarboxylic Acid Derivatives

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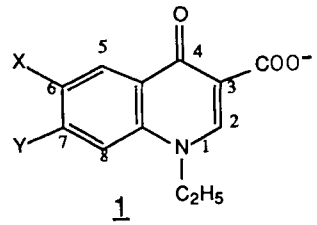
Abstract □ A series of novel 3-quinolinecarboxylic acid derivatives has been prepared and their antibacterial activity evaluated. These derivatives were characterized by a difluoromethoxy group attached to the 6-position and substituted piperazinyl groups attached to the 7-position.

Many *N*-substituted-4-quinolone-3-carboxylic acids have been reported recently and a majority of these have an interesting antibacterial profile. The newer third generation quinolones, as characterized in **1**, have a fluorine in the 6-position and a piperazine in the 7-position (X = F, Y = piperazine). Recent reviews document this development[1,2] and offer insight into the unique properties of the 6-F and the 7-nitrogen base (piperazine). Structure–activity relationships have also been published.[3,4] Mechanistically, the quinolones act as inhibitors of DNA gyrase by binding metals, and it is reasonable to assume a potential correlation between the amount of negative charge on the C-4 carbonyl and biological activity. A review of the few studies[5,6] available on a 6-fluorine replacement was made. Table I compares the relative minimum inhibitory concentration (MIC) values for quinolones containing a F, Cl, or Br moiety in the 6-position against three organisms, and the superiority of the fluorine over other analogues is clear from the data.

We were interested in replacing the 6-F by a CHF_2O moiety and investigating its effect on antibacterial activity. A series of compounds with substituents at the C-6 and C-7 positions in the aromatic ring systems were prepared and the antibacterial spectrum was determined.

Results and Discussion

A comparison of the antibacterial activity of **9a** and **9b** with that of **1a–f** shows them to be essentially inactive (Table I). Moderate activity was observed for **9c** against two gram-negative bacteria strains (*Escherichia coli* CLL0311 and *Pseudomonas aeruginosa* LLO1244), and for **9f–h** and **9l** against several staph organisms (Table II). The lack of antibacterial activity indicates that the presence of fluorine is probably essential for antibacterial activity and that the replacement of fluorine by CHF_2O leads to a loss in activity.



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Experimental Section

All melting points were taken on a Mel-Temp apparatus and are uncorrected. Where analyses are reported by symbols of the elements, results were within 0.4% of the calculated values. The IR, NMR, and MS data were determined for all numbered compounds in this section and were evaluated as consistent with the indicated structures. These data are presented only where required for structural assignment (other data available upon request). The IR spectra were obtained using a Perkin-Elmer 1310 IR spectrophotometer. The NMR spectra were determined with a Varian model FT-80 with Me_4Si as an internal standard. Mass spectra were obtained on Finnegan MAT model CH7 mass spectrometer.

Chemistry—2-Chloro-4-nitrophenol (**2**) served as the starting material for the synthesis of **6** and **8** (Scheme I). Treatment of **2** with chlorodifluoromethane in tetrahydrofuran (THF) in the presence of NaOH gave 2-chloro-1-(difluoromethoxy)-4-nitrobenzene (**3**) which, on reduction with hydrogen on palladium charcoal in the presence of HCl, gave the amine hydrochloride (**4**). Attempts to isolate the free base led to oxidation of the amine and hence the hydrochloride was utilized for further reaction without purification.

Treatment of **4** with diethyl ethoxymethylenemalonate in the presence of excess triethylamine gave the enamine (**5**) which was cyclized in 88% yield to the 7-chloro-6-(difluoromethoxy)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid ethyl ester (**6**) with diphenyl

Table I—Antibacterial Activity of Selected Quinolones[a]

Compound	X	Y	MIC[b]		
			S. aureus	*E. coli*	*P. aeruginosa*
1a	Cl	Piperazinyl	1.56	0.20	3.13
1b	Cl	4-Methylpiperazinyl	1.56	0.78	25
1c	Br	Piperazinyl	3.13	0.39	12.5
1d	Br	4-Methylpiperazinyl	1.56	0.39	100
1e	F	Piperazinyl (norfloxacin)	0.39	0.05	0.39
1f	F	4-Methylpiperazinyl (pefloxacin)	0.39	0.10	1.56
9a	CHF_2O	4-Methylpiperazinyl	>128	64	>128
9b	CHF_2O	Piperazinyl	>128	>128	>128

[a] Data reported in ref 7. [b] Minimum inhibitory concentration in μg/mL.

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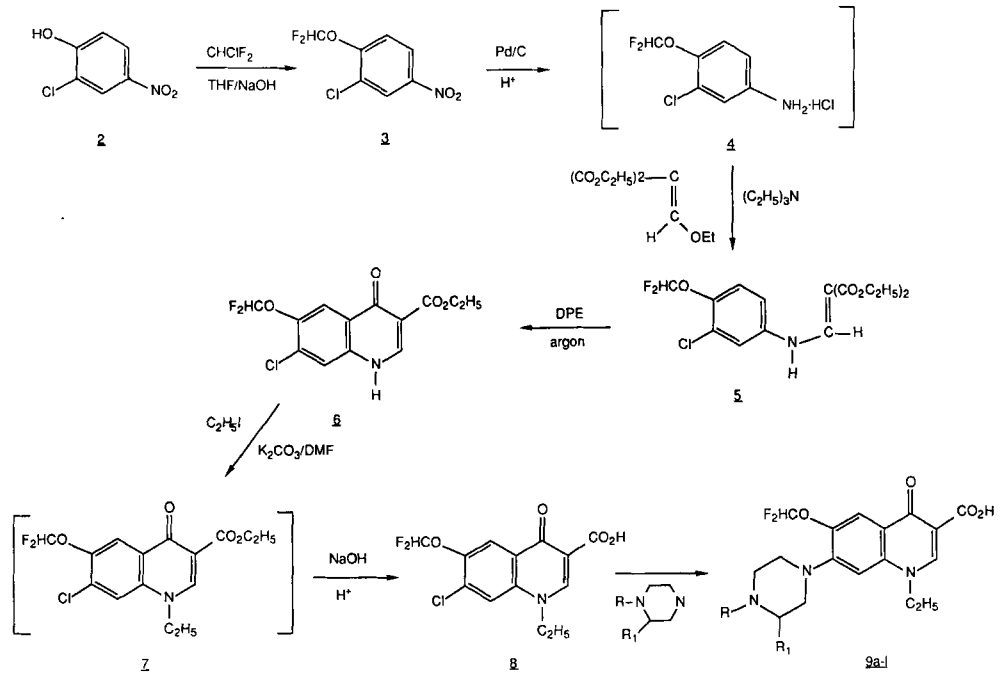
Table II—Minimum Inhibitory Concentration[a]

Compound	*E. coli* #311	*S. marc* K84-18	*P. aerug.* 12-4-4	*S. aereus* VGH 84-45	*S. aureus* Smith	*S. faecalis* VGH 84-65	*S. aureus* ATCC 29215
9a	64	64	128	128	128	128	128
9b	128	64	>128	>128	>128	>128	>128
9c	8	8	>128	>128	>128	>128	>128
9d	>128	>128	>128	>128	>128	>128	>128
9e	>128	>128	>128	>128	>128	>128	>128
9f	>128	>128	>128	16	8	8	8
9g	>128	>128	>128	32	32	16	8
9h	>128	>128	>128	64	64	64	32
9i	>128	>128	>128	>128	>128	>128	>128
9j[b]	>128	>128	>128	>128	>128	>128	>128
9k	>128	>128	>128	>128	>128	>128	>128
9l	>128	>128	>128	16	16	16	8
10	>128	>128	>128	>128	>128	>128	>128
Ciprofloxacin	—	0.03	0.12	2	0.25	1	0.5
Pefloxacin	—	0.03	0.12	2	0.25	4	0.25

[a] Expressed in μg/ml. [b] Anal. for fluorine: calcd. 7.58; found 8.17.



Scheme I

ether in the presence of argon. When the cyclization was attempted in the absence of argon, appreciable decomposition occurred and (6) was obtained in <30% yield.

Ethylation of 6 with C_2H_5I:K_2CO_3:dimethylformamide (DMF) at 90–95 °C gave 7 which, on alkaline hydrolysis followed by acidification, afforded 8. Compound 8 was converted to **9a–10** by reaction with excess piperazines and morpholine, respectively.

2-Chloro-1-(difluoromethoxy)-4-nitrobenzene (3)—Chlorodifluoromethane (15 g, 0.173 mol) was passed into THF (40 mL) at 5–10 °C. Into this solution, a suspension of 2-chloro-4-nitrophenol (5 g, 0.028 mol) in 28% sodium hydroxide solution (40 mL) was added over a 60-min period of time. After this addition, the cooling bath was removed and the temperatures of the solution gradually rose to 36–38 °C. When the exotherm was over, the mixture was heated to 40–45 °C for 18 h.

The reaction was cooled to room temperature, added to water (150 mL), and extracted with CH_2Cl_2 (3 × 80 mL). The CH_2Cl_2 layer was washed with water, dried, and evaporated to yield an oil (3; 60%) which was used without further purification; ^{1}H NMR (DMSO-d_6): δ 6.7–7.9 (t, 1H, J_{H-F} = 23 Hz, $OCHF_2$), 7.1–7.3 (m, 2H), and 8.2–8.35 ppm (m, 1H); IR (KBr): 2980 and 1520 cm^{-1}; MS (70 ev): *m/z* = 223 (M^+).

Anal.—Calc. for $C_7H_4NO_3ClF_2$: C, H, N, Cl, F.

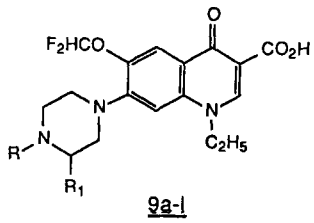
[[3-Chloro-4-(difluromethoxy)phenyl]amino]methylenepropanedioic Acid Diethyl Ester (5)—A slurry of 3 (6 g, 0.027 mol), 600 mg of 10% Pd/C in ethanol (20 mL), and conc. HCl (7 mL) was hydrogenated in a Parr apparatus at ~50 psi for 45 min. The catalyst was removed by filtration and the filtrate was concentrated to leave 5.8 g (95%) of 4.

To the above 4 was added diethyl ethoxymethylenemalonate (22 g, 0.10 mol) in an excess of triethylamine and the mixture was heated at 120–130 °C for 16 h. The reaction mixture was cooled and triturated with methanol, and the crude solid was recrystallized from EtOH to yield 5 (8 g, 87%), mp 95–97 °C; ^{1}H NMR (DMSO-d_6): δ 1.2–1.45 (6H, m, CH_3), 4.1–4.4 (4H, m, CH_2), 6.2–7.5 (1H, t, $OCHF_2$), 7.2–8.1 (3H, m, ArH); 8.33 (1H, d, J_{H-H} = 13 Hz, N—CH), and 10.99 ppm (1H, d, J_{H-H} = 13 Hz, NH); IR (KBr): 1685 cm^{-1} (ester); MS (70 ev): *m/z* = 363 (M^+).

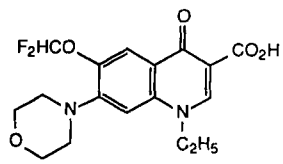
Anal.—Calc. for $C_{15}H_{16}NO_5ClF_2$: C, H, N, Cl, F.

7-Chloro-6-(difluoromethoxy)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid ethyl ester (6)—The above 5 (16.6 g, 0.0456 mol) was added to diphenylether (160 mL) under argon and refluxed for 45 min. The solution was cooled, and the resulting precipitate was filtered, washed with hexane, and dried. Recrystallization from DMF yielded 6 (70%), mp > 300 °C; ^{1}H NMR (CF_3COOD): δ 1.56 (3H, t, J_{H-H} = 7 Hz, CH_3), 4.72 (2H, q, J_{H-H} = 7 Hz, CH_2), 5.95–7.45 (1H,

Table III—Physical Data



9a-l



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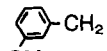
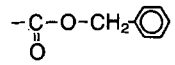
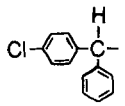
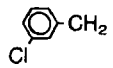
Compound	R	R_1	Method	Yield, %	Recrystallization Solvent	mp, °C	Formula
9a	CH_3	H	A	80	DMF	>300	$C_{18}H_{21}N_3O_4F_2$
9b	H	H	A	80	DMF	>300	$C_{17}H_{19}N_3O_4F_2$
9c	H	CH_3	A	75	DMF	>300	$C_{18}H_{21}N_3O_4F_2$
9d	$Me_2N(CH_2)_3$	H	B	66	Ethanol	>300	$C_{22}H_{30}N_4O_4F_2$
9e	CHO	H	B	86	DMF	>300	$C_{18}H_{19}N_3O_5F_2$
9f	C_6H_5	H	B	90	DMF	>300	$C_{23}H_{23}N_3O_4F_2$
9g	Ph—O—$(CH_2)_4$	H	B	86	DMF	>300	$C_{27}H_{31}N_3O_5F_2$
9h		H	B	88	DMF	>300	$C_{25}H_{27}N_3O_5F_2$
9i		H	B	92	DMF	>300	$C_{23}H_{22}N_3O_4F_3$
9j		H	B	75	EtOH:DMF (50:50)	>300	$C_{25}H_{25}N_3O_6F_2$
9k		H	B	92	DMF	>300	$C_{30}H_{28}N_3O_4ClF_2$
9l		H	B	80	DMF	>300	$C_{24}H_{24}N_3O_4F_2Cl$
10	—	—	B	80	DMF	>300	$C_{17}H_{18}N_2O_5F_2$

t, J_{H-F} = 23 Hz, $OCHF_2$), 8.3 (1H, s, ArH), 8.41 (1H, s, ArH), and 9.32 ppm (1H, s, C_2H); IR (KBr): 1690 cm^{-1} (ester); MS (70 ev): *m/z* = 317 (M^+).

Anal.—Calc. for $C_{13}H_{10}NO_4ClF_2$: C, H, N, Cl, F.

7-Chloro-6-(difluoromethoxy)-1,4-dihydro-1-ethyl-4-oxo-3-quinolinecarboxylic acid (8)—A mixture of 6 (2.9 g, 0.00913 mol), K_2CO_3 (2.51 g, 0.0018 mol), C_2H_5I (3 mL, 0.0371 mol) and DMF (30 mL) was heated at 90–95 °C with stirring. After 24 h, the mixture was evaporated to dryness. The crude ester was used in the successive reaction without further purification.

To the above crude 7 was added 5% NaOH (29 mL), and the mixture was refluxed with stirring. After 4 h, the mixture was filtered and the filtrate was acidified with 15% HCl. The resulting precipitate was filtered, washed with water, and dried. The solid was recrystallized from DMF to yield 8 (2.5 g, 86%), mp > 300 °C; ^1H NMR (CF_3 COOD): δ 1.81 (3H, t, J_{H-H} = 7 Hz, CH_3), 4.91 (2H, q, J_{H-H} = 7 Hz, CH_2), 6.2–7.7 (1H, t, J_{H-F} = 23 Hz, $OCHF_2$), 8.5 (1H, s, ArH), 8.6 (1H, s, ArH), and 9.5 ppm (1H, s, C_2H); IR (KBr): 1715 (COOH) and 1610 (C=O) cm^{-1}; MS (70 ev): *m/z* = 317 (M^+).

Anal.—Calc. for $C_{13}H_{10}NO_4ClF_2$: C, H, N, Cl, F.

General Method for the Preparation of 6-(Difluoromethoxy)-1,4-dihydro-1-ethyl-4-oxo-7-(piperazinyl)-3-quinolinecarboxylic acid derivatives (9a–l)—A mixture of 8 (3.18 g, 0.01 mol) and the appropriate piperazine (0.05 mol) was heated at 130–140 °C with stirring. After 3 h, the reaction was worked up by one of two methods. In method A, the mixture was evaporated to dryness, the residue was extracted repeatedly with ether, and the etheral layer was discarded. The solid obtained was recrystallized from a suitable solvent. In method B, the mixture was cooled, extracted with hot ethanol, and filtered. The solid was recrystallized from a suitable solvent. The yield and mp data are shown in Table III.

6-(Difluoromethoxy)-1-ethyl-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (9a)—General method A was used to prepare 9a in 80% yield, mp > 300 °C; ^1H NMR (CF_3 COOD): δ 1.48 (3H, t, J_{H-H} = 7 Hz, CH_3), 2.2 (3H, s, NCH_3), 3.2–3.7 (8H, m, piperazine CH_2), 4.5 (2H, q, J_{H-H} = 7 Hz, CH_2), 6.5–7.7 (1H, t, J_{H-F} = 23 Hz, $OCHF_2$), 7.9 (1H, s, ArH), 8.1 (1H, s, ArH), and 8.7 ppm (1H, 2, C_2H); IR (KBr): 1730 (COOH), and 1620 (C=O) cm^{-1}; MS (70 ev): *m/z* = 381 (M^+).

Anal.—Calc. for $C_{18}H_{21}N_3O_4F_2$: C, H, N, F.

In Vitro Antibacterial Activity—The MIC (μg/mL) of compounds was determined by means of a standard two-fold serial dilution method using agar media.[7]

References and Notes

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