Synthesis and *In Vitro* Biological Activity of Some 7-[Hydrazino], -[Hydrazonyl] and -[Pyrazolyl]quinolone-3-carboxylic Acids

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1-Ethyl-6-fluoro-7-hydrazino-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**8**) has been prepared and served as a versatile intermediate from which a number of hydrazone, pyrazole and dihydropyridazine derivatives were synthesized. The *in vitro* biological activity of some of these derivatives is reported.

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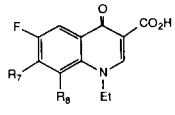
The quinolone-3-carboxylic acid group of orally active antibiotics has received an enormous amount of synthetic effort and their biological mode of action has been intensely studied [1]. One intriguing aspect of these compounds is that a wide range of fuctional group substitution at position C-7 is tolerated while good antibacterial efficacy is maintained [2]. From structure activity relationship (SAR) studies the best C-7 substituent usually is a medium-sized heterocycle possessing two nitrogens, one of which is bonded to C-7. Piperazines and amino-substituted pyrrolidines have formed the basis for such a criteria since potent antibacterials Pefloxacin (**1**) and CI-934 (**2**) are cogent examples [3,4].

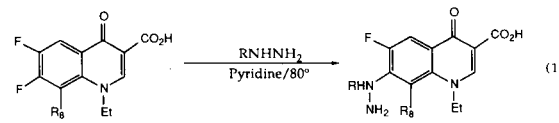


1 R_7 = piperazine, R_8 = H
2 R_7 = 3-(N-ethylaminomethyl)-1-pyrrolidinyl, R_8 = F
3 R_7 = $HNNH_2$, R_8 = H or F
4 R_7 = RR'C=NNH, R_8 = H or F
5 R_7 = substituted pyrazolyl, R_8 = H

In our search for potent quinolone analogues we have explored the SAR of various C-7 substituents. One group that interested us particularly were the 7-(hydrazino)quinolone-3-carboxylic acids **3** and their derivatives. Present in the C-7 substituent is a ready handle which allows synthetic manipulation. Thus, hydrazones **4** and pyrazoles **5** could be prepared from **3**. Herein we report the synthesis and *in vitro* biological activity of these analogues [5].

Chemistry.

Regioselective nucleophilic aromatic substitution with hydrazine proceded readily with either the 6,7-difluoro **6** [7] or the trifluoro quinolone **7** [6,8]. Similarly, methylhydrazine was an effective nucleophile as evidenced by **10** (equation 1). The 7-hydrazino moiety, in turn, served as a versatile building block for the preparation of various derivatives.



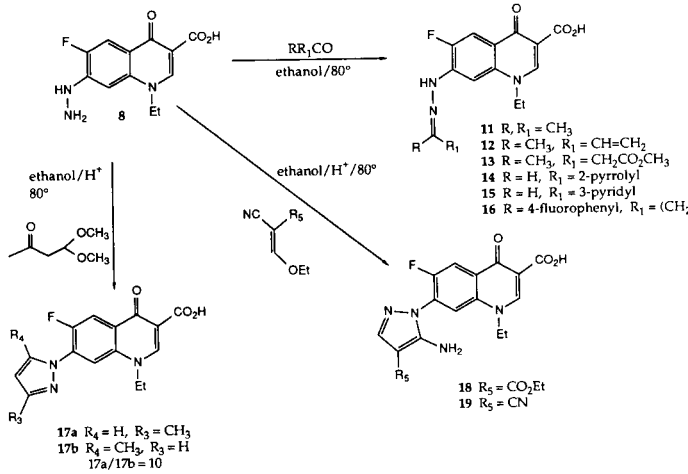
(1)

6 R_8 = H
7 R_8 = F

8 R_8 = H, R = H
9 R_8 = F, R = H
10 R_8 = H, R = CH_3

In Scheme 1 hydrazone derivatives **11-16** were prepared from **8** and the appropriate carbonyl compound in refluxing ethanol. Quinolone **8** was then converted to substituted pyrazolo derivatives **17-19**. Both possible isomers **17a** and **17b** were isolated in a 10:1 ratio on treatment of **8** with acetylacetaldehyde dimethyl acetal. Single isomers **18** and **19** resulted from the addition-elimination-cyclization sequence with ethyl (ethoxymethylene) cyanoacetate and ethoxymethylenemalononitrile, respectively. Is it worth noting that attempted substitution of 6,7-difluoroquinolone **6** with pyrazole in refluxing pyridine solvent was unsuccessful, attributable no doubt to the weak nucleophilic nature of pyrazone itself.

Scheme 1

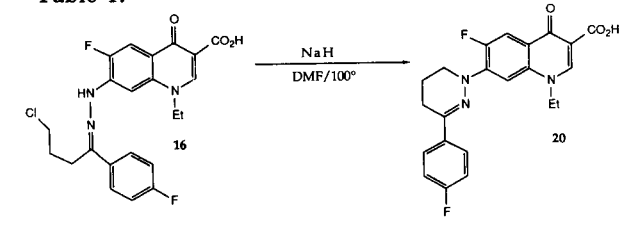


11 R, R_1 = CH_3
12 R = CH_3, R_1 = $CH{=}CH_2$
13 R = CH_3, R_1 = $CH_2CO_2CH_3$
14 R = H, R_1 = 2-pyrrolyl
15 R = H, R_1 = 3-pyridyl
16 R = 4-fluorophenyl, R_1 = $(CH_2)_3Cl$

17a R_4 = H, R_3 = CH_3
17b R_4 = CH_3, R_3 = H
17a/17b = 10

18 R_5 = CO_2Et
19 R_5 = CN

Another synthetic variation of the hydrazone derivatives is shown in equation 2. Cyclization of **16** to the tetrahydropyridazine **20** using sodium hydride in hot DMF occurred in 46% yield. This, as well as all other quinolone-3-carboxylic acid derivatives prepared, are listed in Table 1.



(2)

16

20

Table 1

Quinolone-3-carboxylic Acid Derivatives

Compound	mp	Yield (%) [a]	Recrystallization Solvent	Formula	Analysis % Calcd.(Found) C	H	N	F
8	255° dec	91%	pyridine	$C_{12}H_{12}FN_3O_3$	54.34 (54.16)	4.56 (4.38)	15.84 (15.97)	7.16 (7.16)
9	240-243° dec	66%	pyridine	$C_{12}H_{11}F_2N_3O_3$	50.89 (51.09)	3.92 (3.81)	14.83 (14.94)	13.42 (13.50)
10	244-247°	48%	pyridine	$C_{13}H_{14}FN_3O_3$	55.91 (55.58)	5.05 (4.98)	15.05 (15.33)	6.80 (6.91)
11	272-275° dec	95%	ethanol	$C_{15}H_{16}FN_3O_3$	59.01 (58.69)	5.28 (5.22)	13.76 (13.83)	6.22 (6.09)
12	215-217°	69%	DMF/water	$C_{16}H_{16}FN_3O_3$	60.56 (60.30)	5.08 (5.14)	13.24 (12.86)	5.99 (6.07)
13	181-184°	54%	ethanol	$C_{17}H_{16}FN_3O_5$	56.20 (56.12)	4.99 (4.86)	11.56 (11.42)	5.23 (5.13)
14	270° dec	93%	ethanol	$C_{17}H_{15}FN_4O_3$	59.65 (59.27)	4.41 (4.43)	16.36 (16.61)	5.55 (5.51)
15	275°dec	78%	ethanol	$C_{16}H_{15}FN_4O_3$	61.02 (60.82)	4.27 (4.17)	15.81 (16.07)	5.36 (5.11)
16	190° dec	47%	methanol/methylene chloride	$C_{22}H_{20}ClF_2N_3O_3$	59.00 (59.02) 7.92 (Cl) (7.56) (Cl)	4.50 (4.54)	9.38 (9.49)	8.49 (8.71)
17a/17b	290° dec	30%	methanol/water	$C_{16}H_{14}N_3FO_3$	60.95 (60.67)	4.48 (4.47)	13.32 (13.24)	6.03 (6.07)
18	280° dec	80%	ethanol	$C_{16}H_{17}FN_4O_5$	55.67 (55.39)	4.41 (4.35)	14.42 (14.32)	4.89 (5.04)
19	>300° dec	51%	ethanol	$C_{16}H_{12}FN_5O_3$	56.31 (55.94)	3.54 (3.75)	20.51 (20.16)	5.57 (5.35)
20	250-252° dec	46%	DMF	$C_{22}H_{19}F_2N_3O_3$	64.23 (64.24)	4.65 (4.55)	10.21 (10.05)	9.24 (9.45)

[a] Yields of hydrazones and pyrazoles are based on starting hydrazine.

Table II

In Vitro Antibacterial Activity of 7-Substituted Quinolone Derivatives

Compound	Organism MIC, μg/ml [a] Sa (A) [b]	Sa (S) [c]	S (f) [d]	S (C) [e]	E (A) [f]	Sm [g]	Et (C) VGH [h]	Pa VGH [i]
8	16	16	256	32	4	4	256	256
10	4	4	128	8	1	32	256	128
11	32	>128	>128	128	16	4	128	>128
14	128	>128	128	>128	128	64	>128	>128
17	256	64	>256	128	64	64	128	>256
19	>256	>256	>256	>256	64	256	256	>256
20	>128	>128	>128	>128	>128	>128	>128	>128
Pefloxacin	0.25	0.25	4.0	0.25	0.06	2.0	0.12	1

[a] Minimum inhibitory concentration (MIC) is the lowest concentration of the quinolone that inhibits visible growth of the organism after 48 hours at 37°. [b] *Staphylcoccus aureus* VGH 84-47. [c] *Staphylococcus aureus* Smith. [d] *Streptococcus faecalis* VGH 84-65. [e] *Staphylococcus aureus* ATCC 29213. [f] *Escherichia coli* ATCC 25922. [g] *Serratia marcescens* MOR 84-41. [h] *Enterobacter cloacae* VGH 84-39. [i] *Pseudomonas aeruginosa* VGH 84-4.

Biology.

Table II contains a summary of the *in vitro* antibacterial data for a sampling of those quinolones prepared against four Gram-positive and four Gram-negative organisms. For comparison, the activity of Pefloxacin (**1**) is shown. Enhancement of the Gram-negative activity is seen for the *N*-methylhydrazine derivative **10** relative to the 7-hydrazino **8**. Hydrazone derivatives **11** and **14** show little activity as do the cyclized analogues **17**, **19** and **20**.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The following were used for spectral characterizations: mass spectra, Varian CH-7 spectrometer, ir spectra, FT Nicolet 7199 spectrometer. The ^1H (80 MHz) and ^{13}C (75 MHz) nmr spectra were recorded either on a Varian FT80 or a Nicolet NT-300 WB spectrometer. Analtech silica gel GF plates (250 mm) were used for thin layer chromatography. Silica gel (300-400 mesh) Merck Kieselgel 60 was employed for flash column chromatography. Solvents used were from freshly opened bottles of spectroscopy grade quality with no special drying procedure observed.

The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublet of doublets. The ir, nmr and ms data of all compounds were consistent with assigned structure.

General Procedure for the Preparation of Hydrazines **8**, **9** and **10**: 1-Ethyl-6,8-difluoro-7-hydrazino-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**9**).

A suspension containing **7** (1.0 g, 3.7 mmoles), pyridine (8 ml) and hydrazine monohydrate (2.9 g, 58 mmoles, 3 ml) was stirred at 80° in a capped bottle for 1 hour. On cooling, water (30 ml) was added and the *p*H of the solution was adjusted to 5 with acetic acid. The precipitated product was collected by filtration then washed sequentially with water, methanol, ether and finally dried *in vacuo* to give 690 mg (66%) **9** as a yellow solid, mp 240° dec; ^1H nmr (trifluoroacetic acid): δ 1.8 (t, 3H, CH_3), 5.1 (q, 2H, CH_2), 8.4 (dd, 1H, J = 11 Hz, J = 1.5 Hz), 9.45 (s, 1H, H_2); ir (potassium bromide): 3350, 3240, 3160, 2980, 2940, 1720, 1620, 1550, 1480, cm^{-1}; ms: (ci), m/e (relative intensity) 283 (M^+, 40), 239 (M^+-CO_2, 100), 224 (54), 209 (50), 195 (34).

The preparation of **8** (from **6** and hydrazine hydrate) and **10** (from **6** and methylhydrazine) was similar. See Table 1 for the physical data of these compounds.

General Procedure for the Preparation of Hydrazones **11-16**: 1-Ethyl-6-fluoro-7-[1*H*-pyrrol-2-ylmethylene)hydrazono]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**14**).

A suspension containing **8** (1 g, 3.8 mmoles), pyrrole-2-carboxaldehyde (1.5 g, 15.8 mmoles) and ethanol (25 ml) was refluxed 36 hours. Tlc analysis (silica gel plates 65:25:4 chloroform-methanol-water) showed the complete consumption of **8**. The reaction was cooled, filtered and the collected product was washed with ethanol then ether and finally dried *in vacuo* to give 1.2 g (93%) of **14**, mp 270° dec; ^1H nmr (DMSO-d_6): δ 1.45 (t, 3H, CH_3), 3.4 (s, H_2O), 4.2 (q, 2H, CH_2), 6.2 (m, 1H), 6.5 (m, 1H), 7.1 (m, 1H), 7.7 (d, 1H, J = 7 Hz), 7.95 (d, 1H, J = 12 Hz), 8.25 (s, 1H), 8.9 (s, 1H, H_2), 10.85 (bs, 1H), 11.46 (bs, 1H), 13.2 (s, 1H); ir (potassium bromide): 3600-3080, 3040, 2980, 1705, 1630, 1525, 1470 cm^{-1}; ms: (ei), m/e (relative intensity) 342 (M^+, 78), 298 (M^+-CO_2, 100), 206 (30), 176 (27), 149 (33).

The preparation of **11** (from **8** and acetone), **12** (from **8** and methyl vinylketone), **13** (from **8** and methyl acetylacetate), **15** (from **8** and pyridine-3-carboxaldehyde) and **16** (from **8** and 4-chloro-4'-fluorobutyrophenone) was similar. Table 1 contains the physical data for these products.

1-Ethyl-6-fluoro-7-(3-methyl-1*H*-pyrazol-1-yl)- and 1-Ethyl-6-fluoro-7-(5-methyl-1*H*-pyrazol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Isomers (**17a**) and (**17b**).

A mixture containing **8** (0.5 g, 1.9 mmoles), acetylacetaldehyde dimethyl acetal (0.26 g, 2 mmoles), methanol (20 ml) and a few drops of 37% hydrochloric acid were heated under reflux for 0.75 hour. On cooling, the precipitated solid was collected and washed with cold methanol. Tlc analysis showed a mixture of two components less polar than **8** (tlc - 65:25:4 chloroform-methanol-water); ^1H nmr (trifluoroacetic acid): isomeric mixture, δ 1.8 (t, 3H, CH_3), 2.6 (s, 5-methyl) and 2.75 (s, 3-methyl) ratio of 5-methyl/3-methyl = 10, 5.0 (q, 2H, CH_2), 7.0 (d, 1H, J = 2 Hz, pyrazole H), 8.5 (d, 1H, J = 2 Hz, pyrazole H), 8.75 (d, 1H, J = 9 Hz), 8.9 (d, 1H, J = 5 Hz), 9.65 (s, 1H, H_2); ir (potassium bromide): 3600-2500 (CO_2H), 3070, 3050, 2980, 1710, 1615, 1545, 1500 cm^{-1}; ms: (ei), m/e (relative intensity) 315 (M^+, 15), 271 (M^+-CO_2, 100), 243 (25).

Similarly, **8** was used to form the following compounds; **11** (from acetone) **12** (from methyl vinyl ketone) **13** (from methyl acetoacetate) **15** (from 3-pyridylcarboxaldehyde) and **16** (from 4-chloro-4'-fluorobutyrophenone. The yields and physical data of these compounds are presented in Table 1.

1-Ethyl-6-fluoro-7-(5-amino-4-cyano-1*H*-pyrazol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**19**).

A mixture containing **8** (1 g, 3.77 mmoles), ethoxymethylenemalononitrile (0.92 g, 7.5 mmoles) and 10 ml of ethanol saturated with anhydrous hydrogen chloride was refluxed for 1 hour. On cooling, the product was filtered and washed with cold ethanol then air dried to give 0.66 g (51%) of **19**;^1H nmr (trifluoroacetic acid): δ 1.85 (t, 3H, CH_3), 5.05 (q, 2H, CH_2), 8.5 (s, 1H), 8.65 (d, 1H, J = 2 Hz), 8.75 (s, 1H), 9.1 (s, 1H); ir (potassium bromide): 3370, 3330, 3240, 2940, 2920, 2220, 1710, 1650, 1620, 1580, 1530, 1490 cm^{-1}; ms: (ei) m/e (relative intensity) 341 (M^+, 15), 324 (M^+-NH_2, 10), 297 (M^+-CO_2, 100), 282 (35), 269 (28).

1-Ethyl-6-fluoro-7-[5-amino-4-(ethoxycarbonyl)-1*H*-pyrazol-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**18**).

This was prepared similarly to **19** from **8** and ethyl (ethoxymethylene) cyanoacetate. See Table 1 for the physical data of this compound.

1-Ethyl-6-fluoro-7-[3-(4-fluorophenyl)-5,6-dihydro-1(4*H*)pyridazinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**20**).

A suspension containing hydrazone **16** (1 g, 2.2 mmoles), sodium hydride (0.2 g, 4.5 mmoles, hexane washed) and DMF (10 ml) was heated at 100° for 3 hours. The reaction was cooled and the DMF was removed *in vacuo*. Water was then added and the *p*H of the solution was adjusted to **6** with acetic acid. The yellow solid was collected by filtration and recrystallized from hot DMF to give 0.42 g (46%) **20**; ^1H nmr (DMSO-d_6): δ 1.45 (t, 3H, CH_3), 2.05 (m, 2H, CH_2), 2.45 (DMSO), 2.65 (m, 2H, CH_2), 3.3 (water), 3.8 (m, 2H, allylic CH_2), 4.55 (q, 2H, CH_2), 7.25 (t, 2H), 7.75 (m, 5H), 8.95 (s, 1H); ir (potassium bromide): 3140, 3060, 2960, 2920, 1730, 1650 cm^{-1}; ms: (ei) m/e (relative intensity) 411 (M^+, 45), 367 (M^+-CO_2, 100).

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