Synthesis and *In Vitro* Biological Activity of Some 7-(5-Aminomethyl-2-isoxazolidinyl)quinolone-3-carboxylic Acids

Carl B. Ziegler, Jr.*, Nydia A. Kuck, Timothy W. Strohmeyer and Yang-i Lin

American Cyanamid Company, Medical Research Division, Lederle Laboratories,
Pearl River, New York 10965

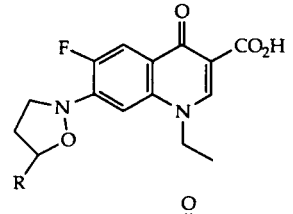
Received May 17, 1990

The synthesis of the title compounds *via* nitrone cycloaddition is described. The *in vitro* antibacterial activity of these compounds is compared against 1-ethyl-6,8-difluoro-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (CI-934).

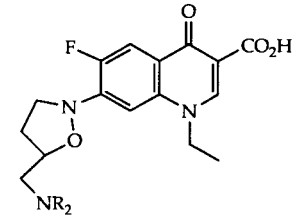
J. Heterocyclic Chem., **27**, 2077 (1990).

Previously we reported a novel synthetic method to prepare some 7-substituted quinolone carboxylic acids *via* nitrone cycloaddition [1]. The procedure provided an easy access to 7-(4-substituted-3-isoxazolidinyl)-1,4-dihydro-4-quinoline-3-carboxylic acids such as **1**. Our interest in this

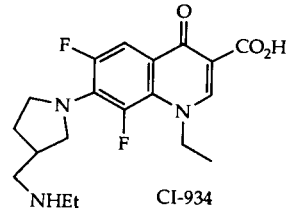
1



2



3



CI-934

functional substitution originates from the desire to develop new quinolone carboxylic acids possessing broad spectrum antibacterial activity. Certain heterocyclic groups employed as substituents at the quinolone 7-position contribute significantly to their antibacterial efficacy [2]. The ever increasing number of examples has become most apparent in the past 5 years [3]. To date, the antibacterial profile attributable to the isooxazolidinyl moiety as a new quinolone 7-substituent is limited [4]. In this paper we extend our quinolone synthetic method *via* nitrone dipolar cycloaddition to the preparation of 7-(4-aminomethyl-3-

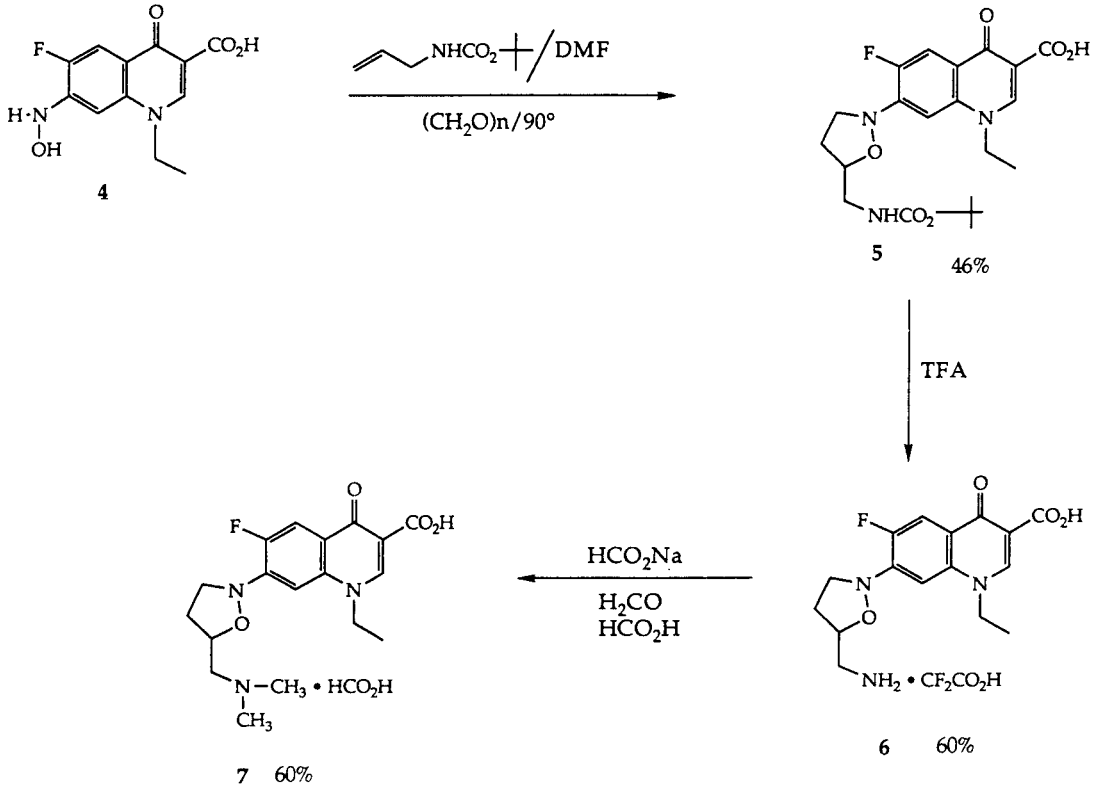
Table I

In Vitro Antibacterial Activity against CI-934

Compound	Organism MIC, μg/ml [a]							
	Sa (A) [b]	Sa (S) [c]	S (f) [d]	S (C) [e]	E (A) [f]	Sm [g]	E(C) VGH [h]	Pa VGH [i]
6	2	2	4	2	1	1	1	16
7	4	4	16	8	1	1	1	64
CI-934	0.12	0.12	0.25	0.12	0.12	0.25	0.25	16

[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] *Staphylococcus 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.

Scheme 1



isoxazolidinyl)-quinolones with general structure **2** shown. The antibacterial activity of these compounds **2** are compared to CI-934, **3**, a quinolone antibacterial whose potent *in vitro* activity has been demonstrated [5].

Chemistry.

The 7-hydroxylaminoquinolone **4** [1] underwent formaldehyde condensation to form the expected methylenenitrone. In the presence of excess *N-t*-BOC-allylamine, the nitrone, formed *in situ*, underwent dipolarcycloaddition to give **5** (46%) as the only detectable regioisomeric cycloadduct (Scheme 1). Removal of the *t*-BOC group with trifluoroacetic acid at 20° gave **6** (60%) as the trifluoroacetate salt. Reductive alkylation of **6** under Leuckart-Wallach reaction conditions gave **7** in 60% yield.

Biology.

Table I contains a summary of the *in vitro* antibacterial data for quinolones **6** and **7** against four Gram-positive and four Gram-negative organisms. For comparison, the activity of CI-934 is included. As can be seen, some enhancement of the broad spectrum activity is gained on going from **6** to **7**. However, neither compound compares favorably with CI-934.

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 ^1H (300 MHz) nmr spectra were recorded either on a Varian FT80 or a Nicolet NT-300 WB spectrometer. Analtech silica gel GF plates (250 μm) 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 open 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 structures.

Synthesis of 1-Ethyl-6-fluoro-7-[5-[[[(1,1-dimethylethoxy)carbonyl]-amino]methyl]-2-isoxazolidinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **5**.

To a solution containing allylamine (0.86 g, 15 mmoles) stirring in THF (5 ml) at 0° was slowly added di-*t*-butyl dicarbonate (3.1 g, 14.2 mmoles) dissolved in THF (2 ml). The resulting reaction mixture was allowed to warm to 20° and stir overnight. All volatiles were removed *in vacuo* leaving a solid.

To this solid (crude *t*-butoxycarbonylallylamine) was added quinolone **4** [1] (1.2 g, 4 mmoles), paraformaldehyde (2 g) and DMF (7 ml). The mixture was heated with stirring at 90° under an argon atmosphere for 15 hours. Thin layer chromatographic monitoring (solvent system: chloroform:methanol:water - 65:25:3) showed complete consumption of **4**. The reaction solvent was removed *in vacuo*. The residue remaining was recrystallized from acetone/water to give 0.8 g (46%) of **5**, mp 140° dec; ^{1}H nmr (deuteriochloroform): δ 1.47 (s, 9H, $3CH_3$), 1.6 (t, 3H, CH_3), 2.2 (m, 1H), 2.5 (m, 1H), 3.47 (m, 2H), 3.72 (m, 1H), 3.85 (m, 1H), 4.37 (m, 2H, N-CH_2), 4.5 (m, 1H), 4.96 (m, 1H), 7.4 (d, 1H, aromatic H_8, $J_{H\text{-}F}$ = 7 Hz), 8.08 (d, 1H, aromatic H_5, $J_{H\text{-}F}$ = 12 Hz), 8.7 (s, 1H, H_2); ir (potassium bromide): cm^{-1} 3580-2450, 1713, 1631, 1617, 1521, 1474; ms: (ci) m/e (relative intensity) 436 (M+H, 80), 364 (18), 307 (20), 251 (100).

Anal. Calcd. for $C_{21}H_{26}FN_3O_6$: C, 57.92; H, 5.99; N, 9.65; F, 4.36. Found: C, 58.30; H, 5.79; N, 9.62; F, 4.31.

Synthesis of 1-Ethyl-6-fluoro-7-[5-(aminomethyl)-2-isoxazolidinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid, Trifluoroacetate **6**.

A solution containing quinolone **5** (0.5 g, 1.1 mmoles), methylene chloride (15 ml) and trifluoroacetic acid (1.5 ml) was stirred at 20° for 36 hours. All volatiles were removed *in vacuo* leaving an oil that solidified on repeated trituration with ethanol. The solid was recrystallized from ethanol to yield 0.3 g of **6** as the trifluoroacetate salt (60%), mp 222° dec; ^{1}H nmr (DMSO-d_6): δ 1.42 (t, 3H, CH_3), 2.2 (m, 1H), 2.5 (DMSO), 3.2 (m, 2H, CH_2NH_2), 3.36 (water in DMSO), 3.8 (m, 2H), 4.63 (m, 3H, N-CH_2CH_3, CH-O), 7.6 (d, 1H, aromatic H_8, $J_{H\text{-}F}$ = 7 Hz), 8.0 (d, 1H, aromatic H_5, $J_{H\text{-}F}$ = 11.3 Hz), 8.3 (bs, 3H, NH_3^+), 9.0 (s, 1H, H_2); ir (potassium bromide): cm^{-1}: 3600-2400, 1694, 1631, 1526, 1476; ms: (ci) m/e (relative intensity) 336 (M+H, 100).

Anal. Calcd. for $C_{18}H_{19}F_4N_3O_6$: C, 48.11; H, 4.26; F, 16.91; N, 9.35. Found: C, 47.89; H, 4.03; F, 17.00; N, 9.03.

Synthesis of 1-Ethyl-6-fluoro-7-[5-[(dimethylamino)methyl]-2-isoxazolidinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid, Formate **7**.

A solution containing quinolone **6** (1 g, 2.2 mmoles), sodium formate (0.5 g, 8.9 mmoles), 37% aqueous formaldehyde (22 ml) and 90% aqueous formic acid (22 ml) was refluxed for 4 hours. The solvent was then removed *in vacuo*. The residue was triturated several times with hot chloroform. The collected triturates were reduced to dryness leaving the crude product as a solid. Recrystallization from ethanol-ether gave 0.54 g (60%) of **7** as the formate salt, mp 194-196° (dec); ^{1}H nmr (deuteriochloroform): δ 1.58 (t, 3H, CH_3), 2.17 (m, 1H), 2.6 (bs, 6H, $2CH_3$), 2.8 (m, 2H), 3.73 (m, 1H), 3.87 (m, 1H), 4.38 (q, 2H, CH_2-N), 4.63 (m, 1H, CH-O), 7.5 (d, 1H, aromatic H_8, $J_{H\text{-}F}$ = 6.5 Hz), 8.1 (d, 1H, aromatic H_5, $J_{H\text{-}F}$ = 12 Hz), 8.7 (s, 1H, H_2); ir (potassium bromide): cm^{-1} 3600-2400, 1721, 1631, 1523, 1474; ms: (ci) m/e (relative intensity) 364 (M+H, 100).

Anal. Calcd. for $C_{19}H_{24}FN_3O_6$: C, 55.74; H, 5.91; N, 10.26. Found: C, 56.10; H, 5.54; N, 10.55.

Acknowledgments.

The authors wish to thank Drs. J. Ashraf and T. Dunne for spectral analysis, Dr. R. Ryall and group for microanalysis and Mr. T. Fenton for *in vitro* biological testing.

We are particularly grateful to Dr. John Domagala and Parke-Davis Pharmaceutical Research Division for their generous gift of CI-934.

REFERENCES AND NOTES

[1] C. B. Ziegler, Jr., P. Bitha and Y.-i. Lin, *J. Heterocyclic Chem.*, **25**, 719 (1988).

[2] For a review of the older literature, see R. Albrecht, *Prog. Drug Res.*, **21**, 9 (1977).

[3a] M. P. Wentland and J. B. Cornett, *Annu. Rep. Med. Chem.*, **20**, 145 (1985); [b] P. Fernandes and D. T. W. Chu, *ibid.*, **22**, 117 (1987); [c] P. Fernandes and D. T. W. Chu, *ibid.*, **23**, 133 (1988); [d] J. V. Heck, *ibid.*, **24**, 101 (1989).

[4] Recently, the synthesis of aminoisoxazolidine-substituted quinolone-3-carboxylic acids has been reported with only a mention that they are biologically active, no data is presented: K. S. Kim, *Heterocycles*, **31**, 87 (1990).

[5] J. M. Domagala, C. L. Heifetz, T. F. Mich and J. B. Nichols, *J. Med. Chem.*, **29**, 446 (1986).