Quinolone Antibacterials. 1. 7-(2-Substituted-4-thiazolyl and thiazolidinyl)quinolones

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A series of 7-(2-substituted-4-thiazolyl and thiazolidinyl)-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids and their 6-fluoro analogues were synthesized. The Hantzsch method was used for the preparation of the thiazolylquinolones. The thiazolidinylquinolones were synthesized by quaternization of the corresponding thiazolyl analogues, followed by reduction of the obtained thiazolium salts with sodium borohydride in aqueous solution. Antibacterial activity was tested *in vitro*. Most of the compounds were inactive against Gram-negative bacteria but some of them showed however good activity against Gram-positive bacteria and mycobacteria. This activity pattern is rarely found among the quinolone antibacterials.

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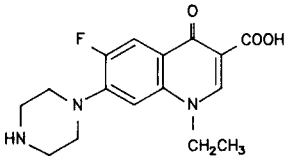
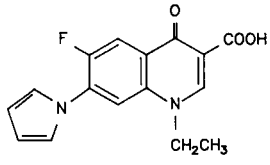
4-Quinolone-3-carboxylic acids have been a subject of interest since Lesher *et al.* reported in 1962 that nalidixic acid exhibited antibacterial activity against Gram-negative bacteria [1]. The recent discovery of fluorinated quinolones with much more potent antibacterial activities promoted the synthesis of a large number of analogues. Structure-activity relationship studies showed that quinolones having a five or six-membered heterocyclic ring at the C-7 position show good antibacterial activities [2-4], *e.g.*, piperazinyl in norfloxacin (**1**) and pyrrolyl in irloxacin (**2**). A fluorine atom at the C-6 position is also necessary for the excellent antibacterial potency of the compounds [5]. As part of our research programme to prepare sulfur-containing congeners of quinolone antibacterials, we synthesized a series of 7-(2-substituted-4-thiazolyl)quinolones and 7-(2-substituted-3-methyl-4-thiazolidinyl)quinolones which can be represented by the general formula **3** and **4**, respectively, where R is alkyl, aryl or amino and X is hydrogen or fluorine.



1.



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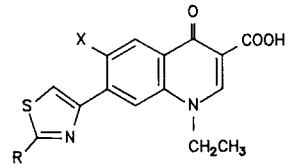

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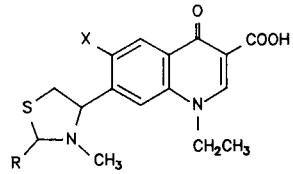


4.

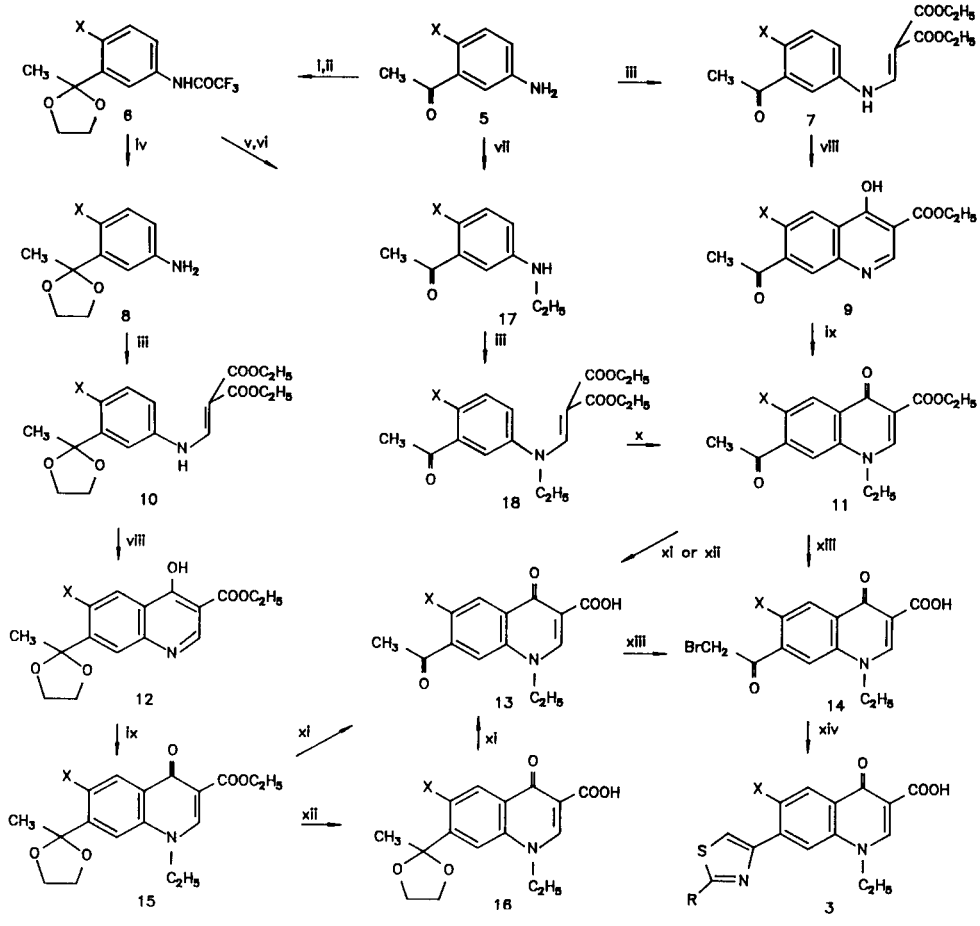
Some of the thiazolyl compounds have already been reported in the literature [6]. The different synthetic strategy and the preparation of the thiazolidinyl derivatives prompted us to report our results.

Chemistry.

Thiazole derivatives can be synthesized by several methods according to the components from which the skeleton of the ring is built up. The most frequently used method is the Hantzsch synthesis [7] which involves the reaction between a thioamide and an α-halocarbonyl compound. A general method for the synthesis of 4-quinolone-3-carboxylic acids is the Gould-Jacobs synthesis [2] which includes the condensation of a substituted aniline with diethyl ethoxymethylenemalonate (EMME) and a thermal cyclization in diphenyl ether at 250°. Both methods were used for the synthesis of our target compounds. Thus, the appropriate starting material for the synthesis of **3** is 3-aminoacetophenone (**5**, X = H) or 2-fluoro-5-aminoacetophenone (**5**, X = F). The latter compound was prepared by nitration of 2-fluoroacetophenone with nitric acid/sulfuric acid, followed by reduction of the nitro compound with iron powder/hydrochloric acid in a total yield of 70%. This method appeared easier to handle and give higher yield than the method reported in the literature [8].

Both the condensation of the aniline **5** with EMME in toluene at refluxing temperature and the subsequent thermal cyclization of anilinomethylenemalonate **7** in diphenyl ether at about 250° gave good yields. The ethylation of the obtained ethyl 7-acetyl-4-hydroxyquinoline-3-carboxylate or its 6-fluoro analogue **9** gave only poor results under various ethylating conditions such as: ethyl iodide/sodium hydride in *N*,*N*-dimethylformamide; ethyl iodide/potassium carbonate in *N*,*N*-dimethylformamide; triethyl phosphate/potassium carbonate; ethyl iodide/thallium ethoxide

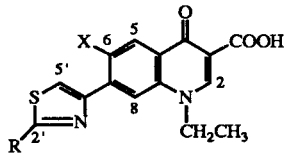
Scheme 1



in ethanol *etc.* The difficulty of this ethylation is probably due to the acidic properties of the 7-acetyl group. This can be overcome by converting the acetyl group into a ketal. Compound **12** was thus ethylated very easily with ethyl iodide/potassium carbonate in *N,N*-dimethylformamide in nearly quantitative yield. This protection of the carbonyl group also avoided the formation of a 5-acetyl quinoline isomer during the thermal ring closure in diphenyl ether. Our observations are in contrast with the findings of Cooper *et al.* where in a same reaction 50% of both isomers are formed [9]. The ketal **6** was obtained by reacting the as trifluoroacetamide protected **5** with ethylene glycol and *p*-toluenesulfonic acid in toluene. After hydrolysis in alkaline medium, the dioxolanyl substituted aniline **10** was converted into quinolones **12** and **15** in the same way as described above for the ketone, the yield of ethylation being 96%. The free ketone **13** was obtained by hydrolysis of **15** either in acidic medium or in basic medium. Quinolone acid **16** was obtained and further hydrolyzed with hydrochloric acid to **13**.

Starting aniline **5** can also be ethylated directly with ethyl iodide by heating in a sealed flask at 50° for 24 hours

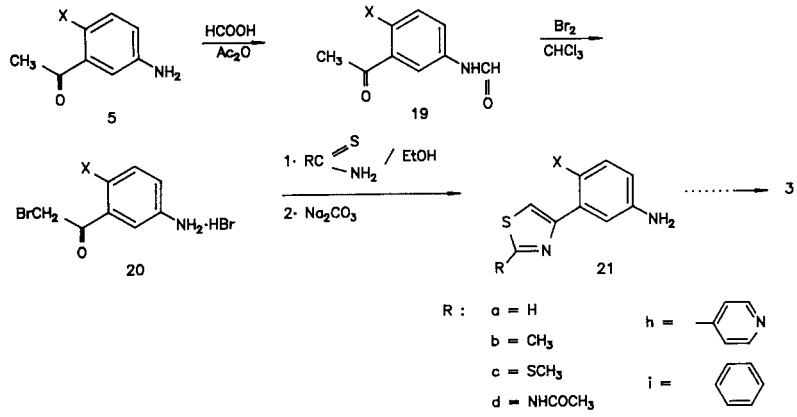
Table 1
Characteristics of Compounds 3



Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR (KBr) ν max	PMR (deuteriotrifluoroacetic acid) δ ppm
3(I)a	263 EtOH	91	$C_{15}H_{12}N_2O_3S$	59.99 60.01	4.02 4.04	9.33 9.35	10.68 10.72	1725 (C=O)	1.95 [a], 5.20 [b], 8.60 (d, 1H, J = 2, $C_{5'}$-H), 8.75 (d, 1H, J = 2, $C_{2'}$-H), 9.10 (m, 3H, $C_{5,6,8}$-H), 9.85 (s, 1H, C_2-H)
3(I)b	230 EtOH	82	$C_{16}H_{14}N_2O_3S$	61.13 61.18	4.48 4.50	8.91 8.89	10.20 10.17	1720 (C=O)	1.85 [a], 3.30 (s, 3H, CH_3), 5.10 [b], 8.05 (s, 1H, $C_{5'}$-H), 8.55 (d, 1H, J = 8, C_6-H), 8.80 (s, 1H, C_8-H), 9.05 (d, 1H, J = 8, C_5-H), 9.70 (s, 1H, C_2-H)
3(I)c	232 EtOH	86	$C_{16}H_{14}N_2O_3S_2$	55.47 55.34	4.07 4.08	8.09 8.05	18.51 18.48	1700 (C=O)	1.87 [a], 3.12 (s, 3H, SCH_3), 5.10 [b], 8.38 (s, 1H, $C_{5'}$-H), 8.48 (d, 1H, J = 8, C_6-H), 8.80 (s, 1H, C_5-H), 9.08 (d, 1H, J = 10, C_5-H), 9.68 (s, 1H, C_2-H)
3(I)d	>300 DMF	88	$C_{17}H_{15}N_3O_4S$	57.13 56.98	4.23 4.21	11.76 11.77	8.97 9.01	3260 (NH) 1720 (C=O)	1.92 [a], 2.66 (s, 3H, $COCH_3$), 5.26 [b], 8.25 (s, 1H, $C_{5'}$-H), 8.58 (d, 1H, J = 9, C_6-H), 9.03 (s, 1H, C_8-H), 9.13 (d, 1H, J = 9, C_5-H), 9.73 (s, C_2-H)
3(I)e	>300 DMF	89	$C_{15}H_{13}N_3O_3S$	57.13 57.01	4.15 4.14	13.33 13.23	10.17 10.20	3415 (NH) 3210 (NH) 1720 (C=O)	1.87 [a], 5.10 [b], 8.20 (s, 1H, $C_{5'}$-H), 8.50 (d, 1H, J = 9, C_6-H), 8.95 (s, 1H, C_8-H), 9.12 (d, 1H, J = 9, C_5-H), 9.62 (s, 1H, C_2-H)
3(I)f	268 DMF	83	$C_{17}H_{17}N_3O_3S$	59.46 59.47	4.99 5.01	12.24 12.29	9.34 9.31	1710 (C=O)	1.87 [a], 3.60 (s, 6H, $N(CH_3)_2$), 5.10 [b], 7.57 (s, 1H, $C_{5'}$-H), 8.40 (d, 1H, J = 9, C_6-H), 8.67 (s, 1H, C_8-H), 9.08 (d, 1H, J = 9, C_5-H), 9.73 (s, C_2-H)
3(I)g	283 DMF	72	$C_{20}H_{21}N_3O_3S$	62.64 62.59	5.51 5.50	10.96 10.90	8.36 8.38	1720 (C=O)	1.87 [a], 1.98 (s, 6H, broad, $-(CH_3)_3-$), 3.90 (s, 4H, broad, $-CH_2NCH_2-$), 5.10 [b], 7.52 (s, 1H, $C_{5'}$-H), 8.38 (d, 1H, J = 9, C_6-H), 8.65 (s, 1H, C_8-H), 9.08 (d, 1H, J = 9, C_5-H), 9.70 (s, 1H, C_2-H)
3(I)h	>300 DMF	80	$C_{20}H_{15}N_3O_3S$	63.65 63.69	4.00 4.02	11.13 11.12	8.50 8.53	1725 (C=O)	1.84 [a], 5.10 [b], 8.75-9.23 (m, 8H, aromatic H), 9.78 (s, 1H, C_2-H)
3(I)i	262 DMF	90	$C_{21}H_{16}N_2O_3S$	67.01 67.01	4.28 4.26	7.44 7.47	8.52 8.50	1720 (C=O)	1.84 [a], 5.10 [b], 7.90 (s, 5H, phenyl H), 8.10 (s, 1H, $C_{5'}$-H), 8.43 (d, 1H, J = 9, C_6-H), 8.87 (s, 1H, C_8-H), 9.10 (d, 1H, J = 9, C_5-H), 9.65 (s, 1H, C_2-H)
3(II)a	272 DMF	83	$C_{15}H_{11}FN_2O_3S$	56.60 56.55	3.48 3.43	8.80 8.84	10.07 10.09	1725 (C=O)	1.85 [a], 5.15 [b], 8.65-9.03 (m, 4H, aromatic H), 9.65 (s, 1H, C_2-H)
3(II)b	275 EtOH	84	$C_{16}H_{13}FN_2O_3S$	57.82 57.86	3.94 3.92	8.43 8.39	9.65 9.62	1725 (C=O)	1.85 [a], 3.30 (s, 3H, CH_3), 5.10 [b], 8.60 (s, 1H, $C_{5'}$-H), 8.75 (d, 1H, J = 3, C_8-H), 8.90 (d, 1H, J = 6, C_5-H), 9.60 (s, 1H, C_2-H)
3(II)e	>300 DMF	85	$C_{15}H_{12}FN_3O_3S$	54.05 54.01	3.63 3.64	12.61 12.64	9.62 9.60	3340 (NH) 3415 (NH) 1720 (C=O)	1.88 [a], 5.22 [b], 8.32 (s, 1H, $C_{5'}$-H), 8.55 (d, 1H, J = 10, C_5-H), 9.10 (d, 1H, J = 5, C_8-H), 9.62 (s, 1H, C_2-H)
3(II)f	>300 DMF	85	$C_{17}H_{16}FN_3O_3S$	56.50 56.47	4.46 4.44	11.63 11.60	8.87 8.83	1720 (C=O)	1.85 [a], 3.55 (s, 6H, $N(CH_3)_3$), 5.05 [b], 7.55 (s, 1H, $C_{5'}$-H), 8.55 (d, 1H, J = 9, C_5-H), 8.68 (d, 1H, J = 3, C_8-H), 9.60 (s, 1H, C_2-H)
3(II)g	287 DMF	52	$C_{20}H_{20}FN_3O_3S$	59.84 59.88	5.02 5.04	10.47 10.42	7.99 7.96	1725 (C=O)	1.85 [a], 1.95 (s, 6H, broad, $-(CH_2)_3-$), 3.85 (s, 4H, broad, $-CH_2NCH_2-$), 5.05 [b], 7.53 (s, 1H, $C_{5'}$-H), 8.53 (d, 1H, J = 9, C_5-H), 8.67 (d, 1H, J = 3, C_8-H), 9.58 (s, 1H, C_2-H)
3(II)i	275 DMF	69	$C_{21}H_{15}FN_2O_3S$	63.95 64.15	3.83 3.81	7.10 7.08	8.13 9.15	1725 (C=O)	1.85 [a], 5.08 [b], 7.72 (s, 5H, phenyl H), 8.38 (s, 1H, $C_{5'}$-H), 8.75 (d, 1H, J = 9, C_5-H), 9.25 (d, 1H, J = 5, C_8-H), 9.60 (s, 1H, C_2-H)

[a] t, 3H, J = 7 Hz, CH_2CH_3. [b] q, 2H, J = 7 Hz, CH_2CH_3.

Scheme 2



Scheme 3

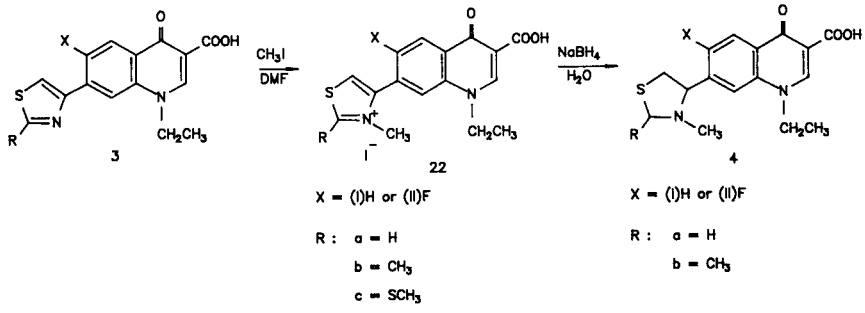
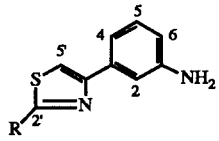


Table 2
Characteristics of Compounds **21**



Compound No.	R	Mp °C	Yield %	IR (KBr) ν max	PMR(deuteriochloroform) δ ppm
21a	H	oil	84	3460 (NH), 3370 (NH), 3220 (NH), 1625 (C=C)	3.95 (s, 2H, br, NH_2), 6.90 (m, 1H, C_5-H), 7.45-7.60 (m, 3H, $C_{2,4,6}$-H), 7.75 (d, 1H, J = 2, C_5-H), 9.20 (d, 1H, J = 2, C_2-H)
21b	CH_3	88-90	91	3420 (NH), 3320 (NH), 1625 (C=C), 1600 (C=C)	2.75 (s, 3H, CH_3), 5.20 (s, 2H, br, NH_2), 6.70 (m, 1H, C_5-H), 7.15-7.30 (m, 3H, $C_{2,4,6}$-H), 7.75 (s, 1H, C_5-H)
21c	SCH_3	78-81	90	3420 (NH), 3320 (NH), 1625 (C=C), 1610 (C=C)	2.80 (s, 3H, SCH_3), 5.45 (s, 2H, br, NH_2), 7.50-8.00 (m, 4H, phenyl H), 8.20 (s, 1H, C_5-H)
21d	$NHCOCH_3$	85-87	76	3410 (NH), 3300 (NH), 1715 (C=O), 1630 (C=C), 1600 (C=C)	2.25 (s, 3H, $COCH_3$), 4.35 (s, 2H, br, NH_2), 7.40 (m, 1H, C_5-H), 7.72 (s, 1H, C_5-H), 7.80-7.98 (m, 3H, $C_{2,4,6}$-H), 9.50 (s, 1H, br, NHCO)
21h	C_5H_4N	105-108	73	3380 (NH), 3200 (NH), 1630 (C=C), 1600 (C=C)	4.60 (s, 2H, br, NH_2), 6.90 (m, 1H, C_5-H), 7.25-7.52 (m, 3H, $C_{2,4,6}$-H), 7.88 (s, 1H, C_5-H), 8.00 (d, 2H, J = 6, pyridyl-H), 8.83 (d, 2H, J = 6, pyridyl-H)
21i	C_6H_5	94-98	89	3400 (NH), 3320 (NH), 1620 (C=C), 1600 (C=C)	4.85 (s, 2H, br, NH_2), 7.30-8.00 (m, 10H, aromatic H)

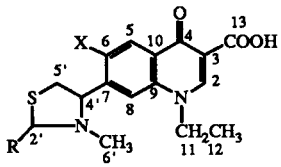
or by ethylating its trifluoroacetamide followed by hydrolysis to give the ethylated aniline **17**. This reacted with EMME to afford compound **18** which was cyclized in polyphosphoric acids (PPA) to the desired 7-acetyl-1-ethylquinolone (**11**). However, the purification of the products from every reaction step with silica gel column and the low total yield limited the utilization of this synthetic route.

Quinolone **11** or its acid **13** was further brominated with pyridinium bromide perbromide to afford the bromo-

Table 3
Characteristics of Compounds 22

Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max	Mass Spectrum (FAB)	MW
22(I)a	248-250	86	$C_{16}H_{15}IN_2O_3S$	43.45	3.42	6.33	7.25	1730 (C=O)	316 M^++1	442.3
				43.41	3.44	6.32	7.28			
22(I)b	286-288	92	$C_{17}H_{17}IN_2O_3S$	44.75	3.75	6.14	7.03	1735 (C=O)	330 M^++1	456.3
				44.73	3.78	6.17	7.07			
22(I)c	280-282	80	$C_{17}H_{17}IN_2O_3S_2$	41.81	3.51	5.74	13.13	1730 (C=O)	362 M^++1	488.4
				41.96	3.49	5.82	13.09			
22(II)a	236-238	81	$C_{16}H_{14}FIN_2O_3S$	41.75	3.06	6.09	6.97	1705 (C=O)	334 M^++1	460.3
				41.68	3.08	6.02	6.94			
22(II)b	265-266	84	$C_{17}H_{16}FIN_2O_3S$	43.05	3.40	5.91	6.76	1725 (C=O)	348 M^++1	474.3
				43.18	3.41	5.90	6.78			

Table 4
Characteristics of Compounds 4



Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max	Mass Spectrum (EI)	MW
4(I)a	220-221 dec	30	$C_{16}H_{18}N_2O_3S$	60.36	5.69	8.80	10.07	1725 (C=O)	318 M^+, 217 (100%)	318.4
				60.47	5.68	8.71	10.02		M^+-Thiazol	
4(I)b	170-181	42	$C_{17}H_{20}N_2O_3S$	61.42	6.06	8.43	9.65	1735 (C=O)	332 M^+, 317 (100%)	332.4
				61.39	6.08	8.45	9.63		M^+-CH_3	
4(II)a	238-240 dec	38	$C_{16}H_{17}FN_2O_3S$	57.13	5.09	8.33	9.53	1720 (C=O)	336 M^+ (100%)	336.4
				57.20	5.07	8.30	9.57	1705 (C=O)		
4(II)b	182-183 dec	40	$C_{17}H_{19}FN_2O_3S$	58.27	5.46	7.99	9.15	1720 (C=O)	350 M^+, 217 (100%)	350.4
				58.24	5.44	7.97	9.12		M^+-Thiazol.-F	

ketone **14**. The ester was cleaved in the same reaction. Bromoketone **14** reacted with a thioamide or thiourea to give **3** (Table 1).

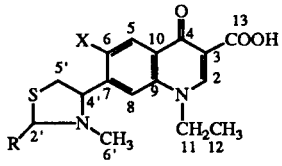
Quinolone acids **3** can also be synthesized by the Hantzsch synthesis of a thiazole followed by formation of a quinoline ring as shown in Scheme 2. Thus, the protected aminoacetophenone **19** was brominated with bromine in chloroform and the bromoketone **20** was reacted with a thioamide to form thiazole **21** which was then converted into **3** in similar way as described in Scheme 1. The formation of isomers during the quinoline ring closure was prevented due to the steric hinderance of thiazole. The major drawback of this method however is the time-consuming procedure for the synthesis of a series of analogues.

7-(2-Substituted-3-methyl-4-thiazolidinyl)quinolones **4** were synthesized by quaternization of the corresponding thiazole analogues with methyl iodide in a sealed reaction tube at 130°, followed by reduction of the thiazolium salts with aqueous sodium borohydride [10,11].

The attempt to quaternize 7-(2-phenyl-4-thiazolyl)quinolone **(3i)** with methyl iodide under the above condition failed to yield the thiazolium salt probably due to the high steric hinderance, whilst the reduction of the 3-methyl-2-methylthiothiazolium iodide **(22c)** with sodium borohydride did not give the desired thiazolidinyl analogue owing to hydrolysis in alkaline solution [10].

As expected, the observation of two sets of resonances in the pmr and cmr spectra of compounds **4** suggested that these compounds consisted of two diastereoisomers. The ratio of diastereoisomers is approximately from 10:1 to 2:1. This result is in agreement with the observations of

Table 5
NMR Spectral Data of Compounds **4a** [a]



No.	X	R	PMR [b], [c]	CMR [b]
4(I)a	H	H	1.56 (t, 3H, J = 7.8, CH_2CH_3), 2.40 and 2.50 (two s, 3H, NCH_3), 2.91 (q, 1H, J = 8.1, $C_{5'}$-H), 3.48 (q, 1H, J = 8.1, $C_{5'}$-H), 3.80-4.25 (m, 3H, $C_{2'}$, $_{4'}$-H), 4.44 (q, 2H, J = 7.8, CH_2CH_3), 7.58-7.75 (m, 2H, C_5,C_6-H), 8.56 (d, 1H, J = 7.6, C_8-H) 8.80 (s, 1H, C_2-H)	14.57 (C_{12}), 35.84 ($C_{5'}$), 37.50 and 38.33 ($C_{6'}$), 49.02 (C_{11}), 58.74 ($C_{2'}$), 67.88 ($C_{4'}$), 107.59 (C_7), 113.84 (C_6), 123.89 (C_8), 125.99 (C_5), 137.87 (C_9), 139.13 (C_3), 149.11 (C_2), 154.55 (C_{10}), 166.17 (C_{13}), 177.50 (C_4)
4(I)b	H	CH_3	1.52 (d, 3H, J = 5.4, $CHCH_3$), 1.61 (t, 3H, J = 7.3, CH_2CH_3), 2.19 and 2.33 (two s, 3H, NCH_3), 2.95 (q, 1H, J = 5.8, $C_{5'}$-H), 3.20 (q, 1H, J = 5.8, $C_{5'}$-H), 3.80 (q, 1H, J = 10.25, $C_{4'}$-H), 3.97 (q, 1H, J = 5.8, $CHCH_3$), 4.42 (q, 2H, J = 7.3, CH_2CH_3), 7.26-7.69 (m, 2H, $C_{5,6}$-H), 8.54 (d, 1H, J = 7.8, C_8-H), 8.80 (s, 1H, C_2-H)	14.72 (C_{12}), 21.02 (NCH_3), 37.49 ($C_{5'}$), 36.44 and 37.90 ($C_{6'}$) 49.70 (C_{11}), 67.51 ($C_{4'}$), 74.52 ($C_{2'}$), 109.03 (C_7), 114.75 (C_6), 125.73 (C_8), 128.01 (C_5), 138.25 (C_9), 139.57 (C_3), 147.98 (C_2), 148.62 (C_{10}), 167.02 (C_{13}), 178.17 (C_4)
4(II)a	F	H	1.61 (t, 3H, J = 7.1, CH_2CH_3), 2.48 (s, 3H, NCH_3), 3.01 (q, 1H, J = 10.7, $C_{5'}$-H), 3.51 (q, 1H, J = 10.7, $C_{5'}$-H), 3.80 (d, 1H, J = 8.5, $C_{2'}$-H), 4.31 (d, 1H, J = 8.5, $C_{2'}$-H), 4.40-4.49 (m, 3H, CH_2CH_3 and $C_{4'}$-H), 7.93 (d, 1H, J = 5.86, C_8-H), 8.16 (d, 1H, J = 9.76, C_5-H), 8.78 (s, 1H, C_2-H)	14.71 (C_{12}), 36.38 ($C_{5'}$), 38.66 ($C_{6'}$), 50.06 (C_{11}), 59.68 ($C_{2'}$), 65.99 ($C_{4'}$), 108.56 (C_7), 112.71 (C_5), 116.04 (C_8), 127.60 (C_6), 135.89 (C_9), 136.42 (C_3), 147.75 (C_2), 155.92 (C_{10}), 166.73 (C_{13}), 177.41 (C_4)
4(II)b	F	CH_3	1.56 (d, 3H, J = 5.86, $CHCH_3$), 1.61 (t, 3H, J = 7.32, CH_2CH_3), 2.30 and 2.41 (two s, 3H, NCH_3), 2.87 (q, 1H, J = 10.25, $C_{5'}$-H), 3.36 (q, 1H, J = 10.25, $C_{5'}$-H), 4.01 (q, 1H, J = 5.85, $C_{2'}$-H), 4.20 (q, 1H, J = 7.57, $C_{4'}$-H), 4.43 (q, 2H, J = 6.83, CH_2CH_3), 7.97 (d, 1H, J = 5.37, C_8-H), 8.19 (d, 1H, J = 9.77, C_5-H), 8.79 (s, 1H, C_2-H)	14.69 (C_{12}), 21.04 (NCH_3), 37.26 ($C_{5'}$), 37.52 and 37.83 ($C_{6'}$), 49.85 (C_{11}), 63.54 ($C_{2'}$), 67.41 ($C_{4'}$), 109.29 (C_7), 117.53 (C_5), 118.74 (C_8), 125.57 (C_6), 136.68 (C_9), 139.42 (C_3), 148.04 (C_2), 149.77 (C_{10}), 167.13 (C_{13}), 178.06 (C_4)

[a] δ from internal TMS in ppm. [b] Deuteriochloroform solution. [c] Coupling constants are in Hz.

Clarke and Sykes [10,11]. No attempts were made to separate the diastereoisomers.

EXPERIMENTAL

All compounds were checked for their structures with ir spectrophotometry, pmr, mass spectrometry and elemental analysis. The thiazolidinyl quinolones **4** were also checked with cmr spectrometry. The ir spectra were obtained with a Beckman Acculab-4 spectrophotometer. The ν max are given in cm^{-1}. All compounds were examined as potassium bromide pellets. The pmr spectra of most compounds were recorded on a Varian EM 360A spectrometer, whilst the pmr and cmr spectra of the thiazolidinylquinolone compounds were recorded on a JEOL FX 200 spectrometer with Spin-Echo Fourier Transform (SEFT) technique for the cmr. Chemical shifts are given in ppm (δ) relative to tetramethylsilane and coupling constants are in Hz. Mass spectral data were registered on a VG 70 SEQ mass spectrometer with fast atom bombardment (FAB) ionization method for the thiazolium salts and electron impact (EI) ionization method for the other compounds. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected.

5'-Amino-2'-fluoroacetophenone (**5(II)**).

To 100 ml of concentrated sulfuric acid cooled $<0°$ was added 20.7 g (0.15 mole) of pure 2'-fluoroacetophenone at such a speed that the temperature of the reaction mixture was maintained $<5°$. After addition, the mixture was cooled to -20° and a nitrating mixture of 15 ml of nitric acid and 22.5 ml of sulfuric acid was added as fast as possible while the temperature was kept at $<-15°$. Stirring was then continued for 15 minutes and the mixture was poured onto cracked ice. The white precipitate was collected by filtration and washed well with cold water to afford 2'-fluoro-5'-nitroacetophenone, yield 86%, mp 51-52°; ir (potassium bromide): ν max 1690 (C=O), 1530 (NO_2), 1260 (NO_2); pmr (deuteriochloroform): δ 2.65 (d, 3H, J = 5, CO-CH_3), 7.50 (dd, 1H, J = 9, C_3-H), 8.45-8.85 (m, 2H, C_4- and C_6-H).

A suspension of 18.3 g (0.1 mole) of 2'-fluoro-5'-nitroacetophenone and 16.8 g (0.3 mole) of fine iron powder in 200 ml of 50% ethanol was refluxed with vigorous stirring. To this mixture was added dropwise a solution of 0.5 ml of concentrated

Table 6

Antibacterial Activity of 7-(4-Thiazoly)quinolones and 7-(4-Thiazolidinyl)quinolones

Compound	X	R'	MICs (μg/ml) Gram-positive Str. [1]	St. [2]	B. [3]	My. [4]	Gram-negative E. [5]	K. [6]	P. [7]	Sa. [8]	En. [9]	Ps. [10]
3(I)a	H	H	3.12	25	0.8	3.12	12.5	6.25	6.25	12.5	6.25	>100
3(I)b	H	CH_3	6.25	25	1.6	6.25	50	12.5	50	50	50	>100
3(I)c	H	SCH_3	6.25	6.25	1.6	3.12	>100	>100	>100	>100	>100	>100
3(I)d	H	$NHCOCH_3$	12.5	25	3.12	6.25	>100	>100	>100	>100	>100	>100
3(I)e	H	NH_2	12.5	50	6.25	1.6	>100	>100	>100	>100	>100	>100
3(I)f	H	$N(CH_3)_2$	6.25	25	12.5	12.5	>100	>100	>100	>100	>100	>100
3(I)g	H	1-piperidyl	6.25	12.5	3.12	3.12	>100	>100	>100	>100	>100	>100
3(I)h	H	4-pyridyl	1.6	3.12	0.25	1.6	>100	>100	>100	>100	>100	>100
3(I)i	H	Ph	0.8	0.25	0.25	1.6	>100	>100	>100	>100	>100	>100
3(II)a	F	H	6.25	6.25	0.12	25	6.25	6.25	12.5	3.12	6.25	50
3(II)b	F	CH_3	12.5	12.5	0.5	25	50	25	50	50	50	>100
3(II)e	F	NH_2	12.5	3.12	0.4	3.12	12.5	3.12	6.25	12.5	6.25	50
3(II)f	F	$N(CH_3)_2$	6.25	6.25	1.6	12.5	>100	25	>100	>100	>100	>100
3(II)g	F	1-piperidyl	3.12	3.12	0.8	3.12	>100	>100	>100	>100	>100	>100
3(II)i	F	Ph	1.6	1.6	0.8	3.12	>100	>100	>100	>100	>100	>100
4(I)a	H	H	50	0.4	0.4	>100	>100	>100	>100	>100	>100	>100
4(I)b	H	CH_3	50	12.5	0.4	>100	>100	>100	>100	>100	>100	>100
4(II)a	F	H	50	12.5	12.5	>100	>100	>100	>100	>100	>100	>100
4(II)b	F	CH_3	50	50	6.25	>100	>100	>100	>100	>100	>100	>100

[1] *Streptococcus pyogenes*, [2] *Staphylococcus aureus*, [3] *Bacillus cereus*, [4] *Mycobacterium fortuitum*, [5] *Escherichia coli*, [6] *Klebsiella*, [7] *Proteus vulgarius*, [8] *Salmonella*, [9] *Enterobacter*, [10] *Pseudomonas aeruginosa*.

hydrochloric acid in 2 ml of 50% ethanol. After addition, stirring was continued for 2 hours. After cooling, the mixture was treated with 10% aqueous sodium hydroxide solution to *p*H 14 and filtered. The iron cake was washed well with acetone and the combined filtrate was evaporated to dryness. The slightly yellow solid residue was washed with water and filtered to give **5(II)**, yield 82%, mp 71-72° [lit [9,10] mp 68-70°]; ir (potassium bromide): ν max 3440 (NH), 3360 (NH), 1725 (C=O); pmr (deuteriochloroform): δ 2.60 (d, 3H, J = 5, $COCH_3$), 3.80 (br s, 2H, NH_2), 6.90 (m, 2H, C_4- and C_6-H), 7.20 (m, 1H, C_3-H).

2-(2-Fluoro-5-trifluoroacetylamino)phenyl-2-methyl-1,3-dioxolane (**6(II)**).

To a solution of 15.3 g (0.1 mole) of **5(II)** in 50 ml of trifluoroacetic acid was added 31.5 g (0.15 mole) of trifluoroacetic anhydride. After refluxing for 4 hours, the solution was poured into ice-water and the white precipitate was collected by filtration to afford 2'-fluoro-5'-trifluoroacetylaminoacetophenone which, after drying, was added to a mixture of 15.5 g (0.25 mole) of ethylene glycol and 0.5 g (2.6 mmoles) of *p*-toluenesulfonic acid monohydrate in 500 ml of toluene. The reaction mixture was refluxed with a Dean-Stark trap overnight. After removing the insoluble material on the bottom of the flask, the toluene solution was evaporated to dryness, the brown oily residue was triturated with water and extracted with chloroform. The chloroform extract, after drying over sodium sulfate, was evaporated to dryness to give compound **6(II)** as a brown oil which was used without further purification, yield 91%; ir (potassium bromide): ν max 3350 (NH), 1750 (C=O); pmr (deuteriochloroform): δ 1.80 (s, 3H, CH_3), 3.90 (m, 4H, CH_2CH_2), 6.85-7.70 (m, 3H, aromatic H), 9.00 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}F_4NO_3$: C, 49.16; H, 3.78. Found: C, 48.89; H, 3.79.

2-Methyl-2-(3-trifluoroacetylamino)phenyl-1,3-dioxolane (**6(I)**).

Compound **6(I)** was prepared as a white crystalline powder from compound **5(I)** in the similar way as compound **6(II)**, yield 82%, mp 69-71°; ir (potassium bromide): 3300 (NH), 1740 (C=O); pmr (deuteriochloroform): δ 1.65 (s, 3H, CH_3), 3.85 (m, 4H, CH_2CH_2), 7.45-7.70 (m, 4H, aromatic H), 8.75 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39. Found: C, 52.42; H, 4.37.

2-(5-Amino-2-fluoro)phenyl-2-methyl-1,3-dioxolane (**8(II)**).

Compound **6(II)** (23.4 g, 0.08 mole) was dissolved in 50 ml of ethanol. To this solution was added 60 ml of 10% aqueous sodium hydroxide solution and the mixture was refluxed for three hours. After cooling, the mixture was diluted with water and extracted with chloroform. After drying with sodium sulfate, the chloroform extracts were evaporated to dryness to afford **8(II)** as a brown oil which was used without further purification, yield 76%; pmr (deuteriochloroform): δ 1.75 (s, 3H, CH_3), 3.60 (br s, 2H, NH_2), 4.00 (m, 4H, CH_2CH_2), 6.40-7.10 (m, 3H, aromatic H).

Anal. Calcd. for $C_{10}H_{12}FNO_2$: C, 60.90; H, 6.13. Found: C, 61.08; H, 6.11.

2-(3-Amino)phenyl-2-methyl-1,3-dioxolane (**8(I)**).

Compound **8(I)** was prepared as a slightly yellow crystalline powder from compound **6(I)** in the similar way as compound **8(II)**, yield 72%, mp 80-81°; ir (potassium bromide): ν max 3340 (NH), 1610 (C=C); pmr (deuteriochloroform): δ 1.65 (s, 3H, CH_3), 3.60 (br s, 2H, NH_2), 3.90 (m, 4H, CH_2CH_2), 6.60-7.30 (m, 4H,

aromatic H).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.30. Found: C, 66.89; H, 7.33.

Diethyl 4-Fluoro-3-(2-methyl-1,3-dioxolan-2-yl)anilino methylenemalonate (**10(II)**).

A solution of 10.8 g (0.055 mole) of compound **8(II)** and 12 g (0.056 mole) of EMME in 50 ml of toluene was refluxed with stirring for four hours. After removing the solvent, compound **10(II)** was obtained as a brown oil which was used without further purification, yield 99% pmr (deuteriochloroform): δ 1.30 and 1.35 (each t, 3H, J = 7, CH_2CH_3), 1.80 (s, 3H, CH_3), 4.00 (m, 4H, CH_2CH_2), 4.30 and 4.40 (each q, 2H, J = 7, CH_2CH_3), 7.10-7.45 (m, 3H, aromatic H), 8.55 (d, 1H, J = 13, NH-CH=C), 11.10 (br d, 1H, J = 13, NH-CH=C).

Anal. Calcd. for $C_{18}H_{22}FNO_6$: C, 58.85; H, 6.03. Found: C, 58.91; H, 6.01.

Diethyl 3-(2-Methyl-1,3-dioxolan-2-yl)anilinomethylenemalonate (**10(I)**).

Compound **10(I)** was prepared from compound **8(I)** as an oil in the similar way as compound **10(II)**, yield 100%; pmr (deuteriochloroform): δ 1.35 and 1.40 (each t, 3H, J = 7, CH_2CH_3), 1.70 (s, 3H, CH_3), 4.00 (m, 4H, CH_2CH_2), 4.30 and 4.40 (each q, 2H, J = 7, CH_2CH_3), 7.10-7.75 (m, 4H, aromatic H), 8.72 (d, 1H, J = 14, NH-CH=C), 11.20 (br d, 1H, J = 14, NH-CH=C).

Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.63. Found: C, 61.76; H, 6.61.

Ethyl 6-Fluoro-4-hydroxy-7-(2-methyl-1,3-dioxolan-2-yl)quinoline-3-carboxylate (**12(II)**).

Compound **10(II)** (20 g, 0.054 mole) was added to 250 ml of diphenyl ether and the mixture was refluxed for 0.5 hour. After cooling, the solution was diluted with 1l of petroleum ether and filtered. The precipitate was washed well with petroleum ether and diethyl ether to afford **12(II)** as a slightly yellow crystalline compound, yield 65%, mp 272-273°; ir (potassium bromide): ν max 1710 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 2.10 (s, 3H, CH_3), 4.35 (m, 4H, CH_2CH_2), 4.80 (q, 2H, J = 7, CH_2CH_3), 8.50 (d, 1H, J = 9, C_5-H), 8.65 (d, 1H, J = 5, C_8-H), 9.52 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{16}FNO_5$: C, 59.81; H, 5.01. Found: C, 59.75; H, 5.00.

Ethyl 4-Hydroxy-7-(2-methyl-1,3-dioxolan-2-yl)quinoline-3-carboxylate (**12(I)**).

Compound **12(I)** was prepared from compound **10(I)** as a crystalline compound in the similar way as compound **12(II)**, yield 60%, mp 206-207°; ir (potassium bromide): ν max 1710 (C=O), 1615 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.55 (t, 3H, J = 7, CH_2CH_3), 2.10 (s, 3H, CH_3), 4.10 (m, 4H, CH_2CH_2), 4.70 (q, 2H, J = 7, CH_2CH_3), 8.10-8.45 (m, 1H, C_6-H), 8.70 (d, 1H, J = 6, C_8-H), 8.85 (d, 1H, J = 10, C_5-H), 9.55 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.64. Found: C, 63.42; H, 5.62.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-4-oxoquinoline-3-carboxylate (**15(II)**).

To a stirred suspension of 8.6 g (0.062 mole) of potassium carbonate in 100 ml of dry *N,N*-dimethylformamide, was added 10 g (0.031 mole) of **12(II)**. The mixture was heated at 80° and 9.72 g (0.062 mole) of ethyl iodide was added. The mixture was then stirred at about 100° overnight. After evaporation of the solvent *in vacuo*, the residue was taken up in chloroform, washed with water and dried over sodium sulfate. The chloroform was distilled off *in vacuo* to yield compound **15(II)** as colourless crystals, yield 96%, mp 122-123°; ir (potassium bromide): ν max 1730 (C=O), 1630 (C=C); pmr (deuteriochloroform): δ 1.55 (m, 6H, CH_2CH_3), 1.80 (s, 3H, CH_3), 4.05 (m, 4H, CH_2CH_2), 4.35 (m, 4H, CH_2CH_3), 7.75 (d, 1H, J = 6, C_8-H), 8.20 (d, 1H, J = 10, C_5-H), 8.60 (s, 1H, C_2-H).

Anal. Calcd. for $C_{18}H_{20}FNO_5$: C, 61.88; H, 5.76. Found: C, 61.93; H, 5.74.

Ethyl 1-Ethyl-1,4-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-4-oxoquinoline-3-carboxylate (**15(I)**).

Compound **15(I)** was prepared from compound **12(I)** as a solid compound in the similar way as compound **15(II)**, yield 94%, mp 132-133°; ir (potassium bromide): ν max 1720 (C=O), 1710 (C=O), 1610 (C=C); pmr (deuteriochloroform): δ 1.45 (m, 6H, CH_2CH_3), 1.75 (s, 3H, CH_3), 4.05 (m, 4H, CH_2CH_2), 4.45 (m, 4H, CH_2CH_3), 7.70 (m, 2H, C_6- and C_8-H), 8.70 (m, 2H, C_2- and C_5-H).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.22; H, 6.38. Found: C, 65.07; H, 6.35.

1-Ethyl-6-fluoro-1,4-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-4-oxoquinoline-3-carboxylic Acid (**16(II)**).

Compound **15(II)** (2 g, 0.006 mole) was added to 50 ml of 1*N* aqueous sodium hydroxide solution and refluxed for 5 minutes. After cooling, the mixture was filtered to remove the insoluble material and the clear filtrate was neutralized with concentrated hydrochloric acid. The white precipitate was collected by filtration, washed with water and dried at 50° to afford compound **16(II)** as colourless solid, yield 92%, mp 226-229°; ir (potassium bromide): ν max 1735 (C=O), 1620 (C=C); pmr (deuteriotrifluoroacetic acid): δ 2.00 (t, 3H, J = 7, CH_2CH_3), 2.20 (s, 3H, CH_3), 4.30 (m, 4H, CH_2CH_2), 5.05 (q, 2H, J = 7, CH_2CH_3), 8.38 (d, 1H, J = 9, C_5-H), 8.52 (d, 1H, J = 6, C_8-H), 9.52 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{16}FNO_5$: C, 59.81; H, 5.01. Found: C, 59.99; H, 5.03.

1-Ethyl-1,4-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-4-oxoquinoline-3-carboxylic Acid (**16(I)**).

Compound **16(I)** was prepared from compound **15(I)** as a colourless solid compound in a similar way as compound **16(II)**, yield 87%, mp 225-226°; ir (potassium bromide): ν max 1735 (C=O), 1625 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.90 (t, 3H, J = 7, CH_2CH_3), 2.03 (s, 3H, CH_3), 4.33 (m, 4H, CH_2CH_2), 5.15 (q, 2H, J = 7, CH_2CH_3), 8.30-9.10 (m, 3H, C_5-, C_6- and C_8-H), 9.67 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.64. Found: C, 63.29; H, 5.61.

7-Acetyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**13(II)**).

Method A.

Compound **16(II)** (1.5 g, 0.005 mole) was dissolved in 50 ml of a mixture of 1*N* hydrochloric acid/90% acetic acid and refluxed for 3 hours. The solution obtained was cooled and diluted with water. The precipitated acid was collected and washed with water, ethanol and diethyl ether, yield 81%, mp 248-251°; ir (potassium bromide): ν max 1720 (C=O), 1695 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.85 (t, 3H, J = 7, CH_2CH_3), 3.02 (d, 3H, J = 5, CH_3), 5.10 (q, 2H, J = 7, CH_2CH_3),

8.60 (d, 1H, J = 9, C_5-H), 8.90 (d, 1H, J = 5, C_8-H), 9.60 (s, 1H, C_2-H).

Anal. Calcd. for $C_{14}H_{12}FNO_4$: C, 60.65; H, 4.36. Found: C, 60.59; H, 4.38.

Method B.

Compound **15(II)** (8.38 g, 0.024 mole) was added to 50 ml of concentrated hydrochloric acid and the mixture was refluxed with stirring for 1.5 hours. After cooling, the mixture was diluted with water and filtered to give compound **13(II)** which was identical to the material prepared by method A, yield 92%.

Method C.

Compound **13(II)** was also prepared from compound **11(II)**. In this case, 1.52 g (0.005 mole) of compound **11(II)** was hydrolyzed either in basic medium (as described under **16(II)**) or in the acidic medium (as described under above method A and B) to give compound **13(II)** in 89% and 95% yield, respectively. The product was purified by recrystallization from *N,N*-dimethylformamide and was identical to the material prepared by method A and B.

7-Acetyl-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**13(I)**).

Compound **13(I)** was prepared by similar methods as described for compound **13(II)** in yields of 85%, 96% and 80%, respectively, mp 268-270°; ir (potassium bromide): ν max 1720 (C=O), 1690 (C=O), 1615 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.90 (t, 3H, J = 7, CH_2CH_3), 3.10 (s, 3H, CH_3), 5.18 (q, 2H, J = 7, CH_2CH_3), 8.68-9.20 (m, 3H, C_5-, C_6- and C_8-H), 9.75 (s, 1H, C_2-H).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.91; H, 5.01.

7-(Bromoacetyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**14(II)**).

To a suspension of 12 g (0.043 mole) of quinolone acid **13(II)** in 70 ml of glacial acetic acid was added 17.28 g (0.054 mole) of pyridinium bromide perbromide. The mixture was gently refluxed with stirring for 2 hours. After cooling, the solution was poured into ice-water and the colourless precipitate was collected by filtration and washed well with water, ethanol and diethyl ether to give compound **14(II)** which was pure enough for analysis, yield 91%, mp 217-219° dec; ir (potassium bromide): ν max 1725 (C=O), 1620 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.90 (t, 3H, J = 7, CH_2CH_3), 4.90 (d, 2H, J = 1, $BrCH_2C$), 5.15 (q, 2H, J = 7, CH_2CH_3), 8.65 (d, 1H, J = 9, C_5-H), 8.90 (d, 1H, J = 5, C_8-H), 9.70 (s, 1H, C_2-H).

Anal. Calcd. for $C_{14}H_{11}BrFNO_4$: C, 47.21; H, 3.11. Found: C, 47.14; H, 3.10.

Bromoacetylquinolone **14(II)** was also directly prepared by bromination of quinolone ester **11(II)**. Thus, 3.05 g (0.01 mole) of ester **11(II)** was dissolved in 50 ml glacial acetic acid. To this solution was added at room temperature 4.0 g (0.0125 mole) of pyridinium bromide perbromide. The reaction mixture was refluxed for 2 hours. The same work up as described under method A gave colourless crystalline compound **14(II)** which was identical to the material prepared by method A, yield 94%.

7-(Bromoacetyl)-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**14(I)**).

Quinolone acid **14(I)** was prepared respectively from compound **13(I)** and **11(I)** in a similar way as compound **14(II)**, yield 95% (from acid) and 89% (from ester), mp 199-201° dec; ir (potassium bromide): ν max 1720 (C=O), 1615 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.95 (t, 3H, J = 7, CH_2CH_3), 4.88 (s, 2H, $BrCH_2C$), 5.25 (q, 2H, J = 7, CH_2CH_3), 8.90 (dd, 1H, J = 8, C_6-H), 9.20 (d, 1H, J = 3, C_8-H), 9.30 (d, 1H, J = 10, C_5-H), 9.85 (s, 1H, C_2-H).

Anal. Calcd. for $C_{14}H_{12}BrNO_4$: C, 49.73; H, 3.57. Found: C, 49.80; H, 3.58.

General Procedure for the Preparation of 7-(2-Substituted-4-thiazolyl)quinolone Acids **3**.

Bromoacetylquinolone **14(II)** or **14(I)** (1.5 mmoles) was dissolved in *N,N*-dimethylformamide. To this solution was added 1.7 mmoles of the corresponding thioamide or thiourea. The mixture was heated at about 100° with stirring overnight. After cooling, the mixture was poured into water and the precipitate was collected by filtration, washed with water, ethanol and diethyl ether to give quinolone acids **3** which were purified by recrystallization from the appropriate solvent; see Table 1 for product data.

Diethyl 3-Acetyl-4-fluoroanilinomethylenemalonate (**7(II)**).

Compound **5(II)** (6.12 g, 0.04 mole) and EMME (8.64 g, 0.04 mole) in anhydrous ethanol was refluxed with stirring for 3 hours. After evaporating to dryness, the oily residue was crystallized by adding cold diethyl ether. The white crystalline compound was collected by filtration and dried to afford **7(II)**, yield 83%, mp 68-69° (lit [6] mp 70-72°); ir (potassium bromide): ν max 1690 (C=O), 1605 (C=C); pmr (deuteriochloroform): δ 1.35 and 1.40 (each t, 3H, J = 7, CH_2CH_3), 2.70 (d, 3H, J = 5, $COCH_3$), 4.28 and 4.40 (each q, 2H, J = 7, CH_2CH_3), 7.22-7.80 (m, 3H, aromatic H), 8.55 (d, 1H, J = 13, NH-CH=C), 11.15 (br d, 1H, J = 13, NH-CH=C).

Diethyl 3-Acetylanilinomethylenemalonate (**7(I)**).

Compound **7(I)** was prepared fro **5(I)** in a similar way as compound **7(II)**, yield 75%, mp 83-84° (lit [12] mp 85-86°); ir (potassium bromide): ν max 1700 (C=O), 1660 (C=O), 1610 (C=C); pmr (deuteriochloroform): δ 1.30 and 1.50 (each t, 3H, J = 7, CH_2CH_3), 2.65 (s, 3H, $COCH_3$), 4.20 and 4.50 (each q, 2H, J = 7, CH_2CH_3), 7.50-7.80 (m, 4H, aromatic H), 8.68 (d, 1H, J = 13, NH-CH=C), 11.20 (br d, 1H, J = 13, NH-CH=C).

Ethyl 7-Acetyl-6-fluoro-4-hydroxyquinoline-3-carboxylate (**9(II)**).

Compound **7(II)** (21 g, 0.065 mole) was added portionwise to 500 ml of preheated diphenyl ether at 250° with stirring. After addition, the stirring was continued for 0.5 hour. After cooling to room temperature, the white precipitate was collected by filtration and washed with hexane to give **9(II)**, yield 61%, mp >300°; ir (potassium bromide): ν max 1710 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 2.98 (d, 3H, J = 4, $COCH_3$), 4.80 (q, 2H, J = 7, CH_2CH_3), 8.55 (d, 1H, J = 10, C_5-H), 8.90 (d, 1H, J = 5, C_8-H), 9.55 (s, 1H, C_2-H).

Ethyl 7-Acetyl-4-hydroxyquinoline-3-carboxylate (**9(I)**).

Compound **9(I)** was prepared from compound **7(I)** in a similar way as compound **9(II)**, yield 58%, mp >300° (lit [12] mp 302-303°); ir (potassium bromide): ν max 1700 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 2.85 (s, 3H, $COCH_3$), 4.80 (q, 2H, J = 7, CH_2CH_3), 8.00-8.80 (m, 3H, C_5, C_6- and C_8-H), 9.55 (s, 1H, C_2-H).

Ethyl 7-Acetyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**11(II)**).

Compound **9(II)** (5.54 g, 0.02 mole), ethyl iodide (6.24 g, 0.04 mole), potassium carbonate (5.52 g, 0.04 mole) and 100 ml of dry *N,N*-dimethylformamide were mixed and heated with stirring at 80° overnight. After evaporation of the solvent, the residue was taken up in chloroform, washed with water, dried over sodium sulfate and the chloroform distilled off *in vacuo*. The resulting solid was recrystallized from methanol to afford a white crystalline product **11(II)**, yield 37%, mp 191-194° (lit [6] mp 120-121°); ir (potassium bromide): ν max 1730 (C=O), 1710 (C=O), 1625 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.55 and 1.80 (each t, 3H, J = 7, CH_2CH_3), 2.95 (s, 3H, $COCH_3$), 4.80 and 5.05 (each q, 2H, J = 7, CH_2CH_3), 8.20 (d, 1H, J = 8, C_5-H), 8.40 (d, 1H, J = 4, C_8-H), 9.50 (s, 1H, C_2-H).

Ethyl 7-Acetyl-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**11(I)**).

Compound **11(I)** was prepared in the following ways:

(1). From compound **9(I)** as described under **11(II)**, the yield was 32%, mp 176-178° (lit [6] mp 184-187°); ir (potassium bromide): ν max 1700 (C=O), 1615 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 and 1.90 (each t, 3H, J = 7, CH_2CH_3), 3.10 (s, 3H, $COCH_3$), 4.82 and 5.20 (each q, 2H, J = 7, CH_2CH_3), 8.65 (dd, 1H, J = 7, C_6-H), 8.85 (s, 1H, C_8-H), 9.22 (d, 1H, J = 9, C_5-H), 9.75 (s, 1H, C_2-H).

(2). Compound **18(I)** (3.0 g, 9.0 mmoles) was added to 10 g of polyphosphoric acid. The mixture was heated in an oil-bath at 130° for 30 minutes. After cooling, the reaction mixture was poured into ice-water and neutralized with sodium hydroxide solution. The precipitate was collected by filtration and washed with water to yield slightly brown crystalline **11(I)** which was purified by recrystallization from ethanol, yield 72%. The product was identical to the material prepared by method (1).

3'-Ethylamino-acetophenone (**17(I)**).

Method A.

3'-Aminoacetophenone (6.75 g, 0.05 mole) was powdered and mixed wth 7.8 g (0.05 mole) of ethyl iodide. The bottle was sealed and heated at 50° for 24 hours. The dark mixture was then treated with 40 ml of 10% aqueous sodium hydroxide solution and extracted with chloroform. After removal of the solvent, the residue was put on a silica gel column and eluated with diethyl ether/hexane 1:1 giving compound **17(I)** as a slightly brown oil, yield 33%; ir (potassium bromide): ν max 3300 (NH), 1690 (C=O); pmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7, CH_2CH_3), 2.55 (s, 3H, $COCH_3$), 3.30 (q, 2H, J = 7, CH_2CH_3), 3.75 (br s, 1H, NH), 6.95 (m, 1H, C_5-H), 7.35 (d, 3H, J = 5, other aromatic H).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.02. Found: C, 73.66; H, 8.00.

Method B.

Compound **6(I)** (2.75 g, 0.01 mole), ethyl iodide (3.12 g, 0.02 mole), potassium carbonate (2.76 g, 0.02 mole) in 50 ml of dry acetone was refluxed with stirring overnight. After removing the solvent, the residue was treated with water and extracted with chloroform. The chloroform extracts were then evaporated to dryness giving 2-[3-(*N*-ethyl)trifluoroacetylamino]phenyl-2-methyl-1,3-dioxolane as a slightly brown oil. This oil was dissolved in 20 ml of ethanol and 20 ml of 20% hydrochloric acid. The reaction mixture was refluxed for 2 hours. After cooling, the solution was neutralized with 20% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform extracts, after drying with sodium carbonate, were evaporated to dryness giving compound **17(I)** which was used without further purification, yield 100%. The structural characteristics of this product were identical to the material prepared by method A.

Diethyl *N*-Ethyl-3-acetyl-anilinomethylenemalonate (**18(I)**).

Compound **17(I)** (2 g, 0.012 mole), EMME (2.66 g, 0.012 mole) and 10 ml of anhydrous ethanol were mixed and refluxed overnight. After removing the ethanol, the oily residue was put on a silica gel column and eluated with diethyl ether/hexane 2:1. Compound **18(I)** was obtained as a slightly yellow thick oil, yield 56%; ir (potassium bromide): ν max 1720 (C=O), 1690 (C=O); pmr (deuteriochloroform): δ 1.25 (m, 9H, CH_2CH_3), 2.62 (s, 3H, $COCH_3$), 3.80 and 3.88 (each q, 2H, J = 7, OCH_2CH_3), 4.30 (q, 2H, J = 7, NCH_2CH_3), 7.50-7.90 (m, 5H, N-CH=C and aromatic H).

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95. Found: C, 64.78; H, 6.92.

3'-Formylaminoacetophenone (**19(I)**).

To 8.6 ml of 99% formic acid was added 20.4 ml of acetic anhydride, the mixture was stirred at 50-60° for 2 hours. After cooling to room temperature, 13.5 g, (0.01 mole) of **5(I)** was added portionwise below 39°. Stirring was continued at room temperature for 48 hours. After evaporation, the residue was crystallized by adding diethyl ether and the white crystalline product was collected by filtration and dried to give **19(I)**, yield 90%, mp 93-94°; ir (potassium bromide): ν max 3260 (NH), 1700 (C=O), 1680 (C=O), 1600 (C=C); pmr (deuteriochloroform): δ 2.64 (s, 3H, $COCH_3$), 7.45-8.20 (m, 4H, aromatic H), 8.50 (s, 1H, CHO), 8.85 (s, 1H, NHCO).

3'-Amino-2-bromoacetophenone Hydrobromide (**20(I)**).

To a solution of 16.3 g (0.1 mole) of compound **19(I)** in 100 ml alcohol-free chloroform was added slowly 16.0 g (0.1 mole) of bromine in 50 ml of alcohol-free chloroform. The mixture was refluxed for 30 minutes. After cooling, the slightly orange precipitate was collected by filtration and recrystallized from ethyl acetate to give the white crystalline **20(I)**, yield 80%, mp 102-104°; ir (potassium bromide): ν max 3060 (NH), 1690 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 4.95 (s, 2H, $BrCH_2C$), 7.80-8.10 (m, 4H, aromatic H).

General Procedure for the preparation of 2-Substituted-4-(3-amino)phenylthiazoles **21(I)a-21d**, **21h** and **21i**.

2-Bromoacetophenone **20(I)** was reacted with equivalents of the thioamides or thiourea in ethanol at 50° with stirring for 2 hours. After removing the solvent, the residue was dissolved in water and treated with 30% aqueous sodium hydroxide solution to alkaline. The product was obtained by filtration or extraction with chloroform; see Table 2 for product data.

1-Ethyl-1,4-dihydro-4-oxo-7-(2-phenyl-4-thiazolyl)quinoline-3-carboxylic Acid (**3(I)i**). General Procedure for the Synthetic Scheme 2.

Compound **21(I)i** (2.52 g, 0.01 mole) and EMME (2.16 g, 0.01 mole) was heated at 110° on an oil-bath with stirring for 1 hour. After cooling, the solid was washed with methanol and dried *in vacuo*. This malonate was then added to 20 ml of preheated diphenyl ether at 250°. Stirring was continued at this temperature for 30 minutes. After cooling, the mixture was diluted with 100 ml of petroleum ether, filtered and washed with

petroleum ether to give the quinoline compound. After drying, the compound (2 g, 5.4 mmoles) was added together with 0.24 g (6 mmoles) 60% sodium hydride to 50 ml of dry *N,N*-dimethylformamide. The mixture was heated with stirring to about 80° and 2.12 g (13.6 mmoles) of ethyl iodide was added. Stirring was continued at this temperature for 4 hours. After evaporating to dryness, the residue was taken up in chloroform to remove inorganic salts. After evaporating chloroform, the residue was washed with diethyl ether to give a colourless solid product. This solid product was then dissolved in a mixture of concentrated hydrochloric acid and acetic acid (50/50). The obtained solution was refluxed for 3 hours. After cooling, the mixture was diluted with water and the precipitate was collected by filtration, washed with water, ethanol and diethyl ether to give **3(I)i**, total yield 58%; see Table 1 for product data.

Compounds **3(I)a-3(I)d** and **3(I)h** were prepared from **21(I)a-21(I)d** and **21(I)h** in the same way as described for compound **3(I)i**.

General Procedure for the Preparation of 3-Methyl-4-(4-oxoquinolinyl)thiazolium Iodides **22(I)a-22(I)c**, **22(II)a-22(II)b**.

A solution of 3 mmoles of thiazolylquinolone **3** and 15 mmoles of methyl iodide in 20 ml of dry *N,N*-dimethylformamide was added to a reaction tube. The sealed tube was heated at 130° for 5 hours. After cooling to room temperature, the precipitate was collected by filtration, washed with dry diethyl ether and dried at 50°. The products were purified by recrystallization from *N,N*-dimethylformamide; see Table 3 for product data.

General Procedure for the Preparation of 7-(4-Thiazolidinyl)-quinolone Acids **4(I)a-4(I)b** and **4(II)a-4(II)b**.

To a solution of 2 mmoles of thiazolium iodide **22** in 50 ml of water was added portionwise 6 mmoles of sodium borohydride at 5-10°. After addition, the reaction mixture was stirred at room temperature for 4 hours. The mixture was then carefully adjusted to *p*H 4 with 10% hydrochloric acid and extracted with chloroform. After drying over sodium sulfate, the combined chloroform extracts were evaporated to dryness. Quinolone acid **4** was filtered out with diethyl ether as a slightly yellow crystalline powder which was further purified by recrystallization from ethanol; see Table 4 and 5 for product data.

Microbiology.

Compounds **13**, **16**, **3** and **4** were tested *in vitro* for their antibacterial activity against a series of Gram-negative strains (Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Enterobacter agglomerans, Salmonella group B and Pseudomonas aeruginosa) and Gram-positive strains (Bacillus cereus, Streptococcus pyogenes, Staphylococcus aureus, and Mycobacterium fortuitum). *In vitro* bacterial susceptibility (minimum inhibitory concentration) was determined with the agar dilution method on T.S.A. agar. For mycobacteria Middlebrook 7H9 agar supplemented with 10% oleic acid, albumin, dextrose solution was used; the results are summarized in Table 6.

From this table we can conclude that low activity of the 4-thiazolylquinolones against Gram-negative organisms in comparison with the activity against Gram-positive ones is the most interesting observation. Only the fluorinated amino compound **3(II)e** shows some activity against Gram-negative bacteria. The most interesting compounds against Gram-positive bacteria are the phenyl- and pyridyl-substituted thiazolylquinolones **3(I)h**, **3(I)i** and **3(II)i**. These activities were confirmed by testing the latter compounds against a series of ten clinical isolates of S. aureus, S. aureus (methicillin resistant) and Mycobacterium tuberculosis. Compound **3(II)i** appears the most interesting compound: being inactive against Gram-negative bacteria, this quinolone shows MIC values of 0.5 μg/ml against each S. aureus and M. tuberculosis strain tested. The activities against these organisms are comparable with these of lead compounds as ciprofloxacin and ofloxacin. This separation between Gram-positive and Gram-negative activities have rarely been reported in the quinolone literature.

The thiazolidinylquinolones were less active than their thiazolyl parent compounds.

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