Studies on Pyridonecarboxylic Acids. III.[1a] Synthesis and Antibacterial Activity Evaluation of 1,8-Disubstituted 6-Fluoro-4-oxo-7-piperazinyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid Derivatives

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A series of 1,8-disubstituted 6-fluoro-4-oxo-7-piperazinyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives was prepared and evaluated for antibacterial activity. In the 7-piperazinyl series, addition of a fluorine at C-8, which increased the *in vitro* activity for the 1-hydrogen and 1-methyl analogues and decreased it for the 1-phenyl analogue, improved the *in vivo* activity of all the analogues. Introduction of a methoxy group at C-8 of the 1-methyl-7-piperazinyl analogue also improved its *in vivo* antibacterial activity. The effect of 8-substituents on the *in vitro* and *in vivo* antibacterial activity of the 1-methyl-7-(4-methyl-1-piperazinyl) series is also discussed.

Keywords antibacterial agent; fluoroquinolone; 4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid; piperazine derivative; structure–activity relationship; synthesis

In our search for new quinolone antibacterial agents,[1] we have been studying tricyclic compounds characterized by an S-bridge between C-2 and the substituent at N-1 of quinolones (Fig. 1). We reported previously[1a] that NM394 (**1b**), an 8-unsubstituted thiazetoquinolone, has good *in vitro* antibacterial activity.

There are many reports on the effect of a substituent at C-8 of bicyclic quinolones on antibacterial activity. Some of these reports have shown that the effect of a fluorine at C-8 on the activity is greatly influenced by the choice of the substituent at N-1.[2-5] Namely, the introduction of a fluorine at C-8 of the 7-piperazinylquinolones has been reported to increase the *in vitro* antibacterial activity against gram-positive bacteria for the 1-cyclopropyl[2] analogues but to decrease the activity against both gram-positive and -negative bacteria for the 1-ethyl,[2c,d,3] 1-*tert*-butyl,[4] and 1-(4-fluorophenyl)[5] analogues. These reports led us to prepare several 1-substituted 8-fluorothiazetoquinolones in order to examine how the antibacterial activity of the 8-fluoro analogues is affected by a substituent at C-1. We also studied the effect of other substituents at C-8 on the antibacterial activity of the 1-methylthiazetoquinolone series. We report here the synthesis and antibacterial activity of 1,8-disubstituted 6-fluoro-4-oxo-7-piperazinyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives (Fig. 3).

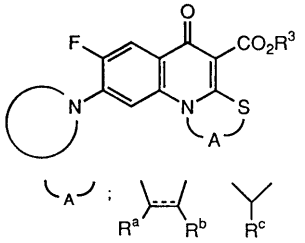
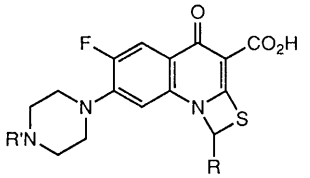


Fig. 1



1a: R = R' = H
1b: R = Me, R' = H (NM394)
1c: R = Ph, R' = H
1d: R = 4-F-Ph, R' = H
1g: R = R' = Me

Fig. 2

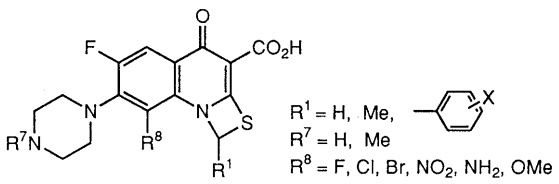
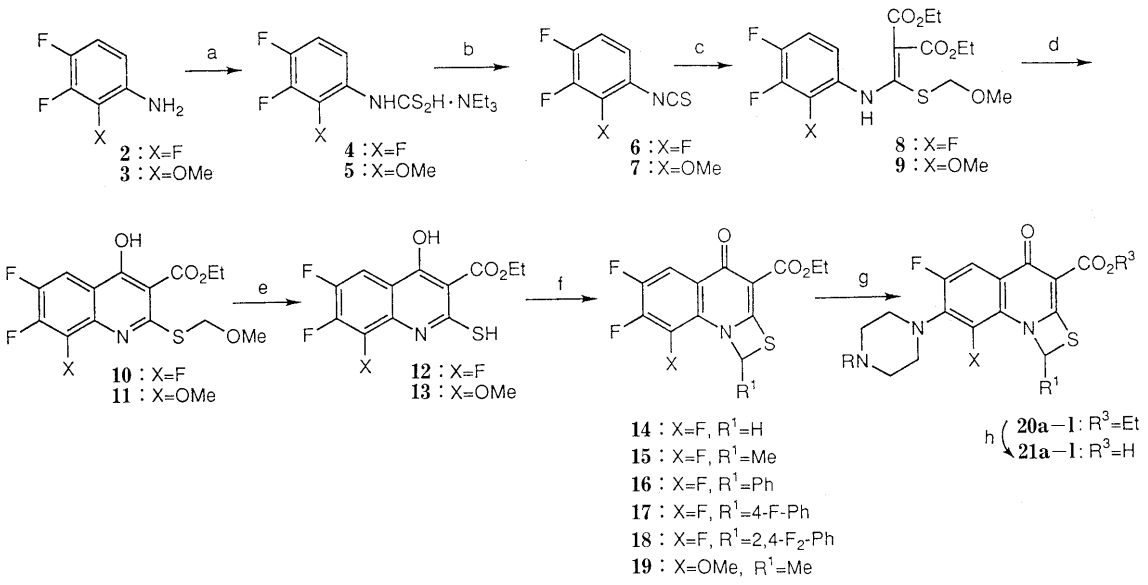


Fig. 3

Chemistry

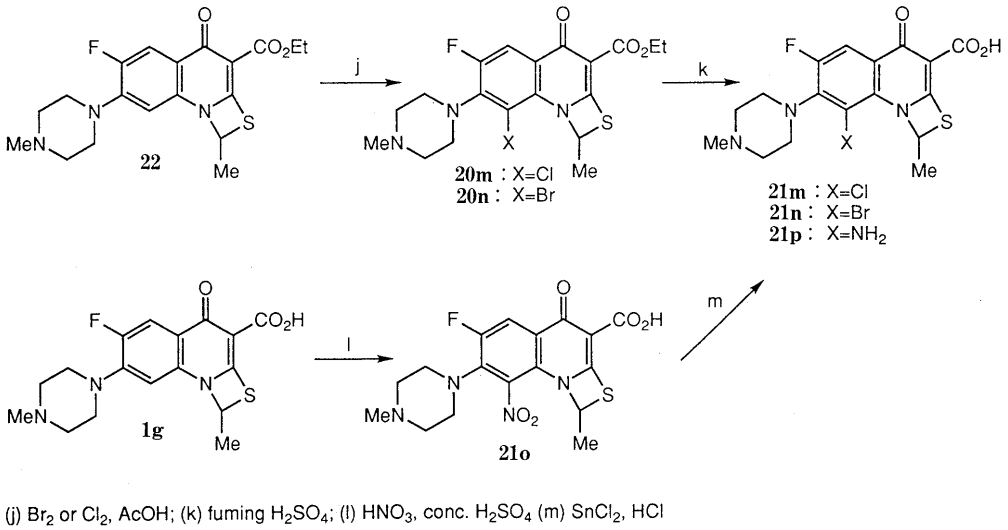
1,8-Disubstituted 4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acids were prepared as shown in Charts 1 and 2. The preparations of the 8-fluoro (**21a—j**) and 8-methoxy (**21k—l**) derivatives are illustrated in Chart 1. The thiazetoquinolone ring formation from the corresponding aniline is well documented[1a] and is unimpeded by the presence of the latent 8-substituent. Compounds **14—18** and **19** were prepared beginning with 2,3,4-trifluoroaniline (**2**) and 3,4-difluoro-2-methoxyaniline (**3**),[6] respectively. Treatment of **14—19** with piperazine derivatives gave 7-piperazinyl-3-carboxylates (**20a—l**). Hydrolysis of these carboxylates gave the corresponding 3-carboxylic acids (**21a—l**).

As shown in Chart 2, the 8-chloro and 8-bromo derivatives (**21m, n**) were prepared by halogenation of **22**[1a] in acetic acid followed by acidic hydrolysis. The 8-nitro derivative (**21o**), obtained by nitration of **1g**,[1a] was converted to the 8-amino analogue (**21p**) by reduction with stannous chloride in hydrochloric acid.



(a) CS_2, NEt_3; (b) $ClCO_2Et$,$CHCl_3$; (c) $CH_2(CO_2Et)_2$, KOH, $ClCH_2OMe$, dioxane; (d) heat, Ph_2O; (e) H^+,EtOH;
(f) 1,1-dihaloalkane, K_2CO_3, DMF; (g) piperazine derivatives, K_2CO_3, DMF; (h) KOH, H_2O, *tert*-BuOH or fuming H_2SO_4

Chart 1



(j) Br_2 or Cl_2, AcOH; (k) fuming H_2SO_4; (l) HNO_3, conc. H_2SO_4 (m) $SnCl_2$, HCl

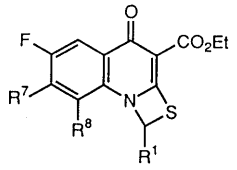
Chart 2

Biology

The *in vitro* antibacterial activity of the 1,8-disubstituted 7-piperazinylthiazetoquinolones (**21a—p**) against gram-positive bacteria (*Staphylococcus aureus*, *Micrococcus luteus* and *Bacillus subtilis*) and gram-negative bacteria (*Escherichia coli*, *Serratia marcescens*, *Shigella flexneri* and *Pseudomonas aeruginosa*) is shown in Table V. Data for ciprofloxacin (CPFX), ofloxacin (OFLX), and the 8-unsubstituted thiazetoquinolones (**1a—d, g**)[1a] are included for comparison.

In the 7-piperazinylthiazetoquinolone series (**21a—e**), the 8-fluoro analogue with 1-hydrogen (**21a**) was 2—4 times more potent than the corresponding 8-unsubstituted analogue (**1a**) against both gram-positive and -negative bacteria. The 8-fluoro analogue with the 1-methyl group (**21b**) was 1—2 times more potent than **1b**, while the 8-fluoro analogues with the 1-phenyl (**21c**) or 1-(4-fluorophenyl) group (**21d**) were 2—4 times less potent than **1c** and **1d**. This result is considered to indicate that the steric bulk at C-1 is an important factor influencing the effect of the fluorine at C-8 on *in vitro* activity. Similar results have been reported in bicyclic quinolones. Namely, the 1-cyclopropyl-8-fluoro analogue[2] had increased *in vitro* activity and the 1-*tert*-butyl-8-fluoro[4] and 1-(4-fluorophenyl)-8-fluoro[5] analogues had decreased activity when compared with the corresponding 8-unsubstituted analogues. However, the 1-ethyl-8-fluoro analogue[2c,d,3] has also been reported to show decreased activity as compared with the corresponding 8-unsubstituted analogue although an ethyl group has similar steric parameters to a cyclopropyl group.[7] Accordingly, the steric interaction between the substituent at C-1 and the fluo-

TABLE I. Synthesis of the Ethyl Thiazetoquinolone-3-carboxylates and Physical Data



Compd. No.	R^1	R^7	R^8	Yield (%)[a]	Appearance mp (°C)	Formula	Analysis (%)[b] Calcd (Found)		
							C	H	N
14	H	F	F	92	Colorless powder 272—274 (dec.)	$C_{13}H_8F_3NO_3S$		315.0177[c] (315.0162)	
15	Me	F	F	47	Colorless powder 208—209 (dec.)	$C_{14}H_{10}F_3NO_3S$		329.0330[c] (329.0283)	
16	Ph	F	F	42	Colorless powder 175—178	$C_{19}H_{12}F_3NO_3S \cdot 1/5H_2O$	57.78 (57.61	3.16 3.16	3.55 3.70)
17	4-F-Ph	F	F	41	Pale yellow powder 222—224	$C_{19}H_{11}F_4NO_3S$	55.26 (55.10	2.78 2.66	3.39 3.44)
18	2,4-F_2-Ph	F	F	58	Colorless powder 232—234 (dec.)	$C_{19}H_{10}F_5NO_3S$		427.0302[c] (427.0323)	
19	Me	F	OMe	46	Colorless needles 226—227	$C_{15}H_{13}F_2NO_4S$	52.78 (52.61	3.84 3.54	4.10 4.32)
20a	H	P[d]	F	83	Colorless powder 220—230 (dec.)	$C_{17}H_{17}F_2N_3O_3S \cdot 1/2H_2O$	52.30 (52.40	4.65 4.59	10.76 10.68)
20b	Me	P	F	67	Pale yellow crystals 195—198	$C_{18}H_{19}F_2N_3O_3S \cdot 1/4H_2O$	54.06 (54.19	4.91 5.09	10.51 10.49)
20c	Ph	P	F	35	Pale yellow crystals 236—239 (dec.)	$C_{22}H_{21}F_2N_3O_3S \cdot 1/4H_2O$	59.80 (59.79	4.69 4.75	9.10 9.05)
20d	4-F-Ph	P	F	37	Pale yellow crystals 159—163 (dec.)	$C_{23}H_{20}F_3N_3O_3S \cdot 1/10H_2O$	57.88 (57.83	4.26 4.31	8.80 8.66)
20e	2,4-F_2-Ph	P	F	56	Colorless powder 285 (dec.)	$C_{23}H_{19}F_4N_3O_3 \cdot 1/2H_2O$	54.98 (54.94	4.01 3.87	8.36 8.39)
20f	H	4-Me-P	F	30	Colorless powder 227—230 (dec.)	$C_{18}H_{19}F_2N_3O_3S$	54.67 (54.54	4.84 4.97	10.63 10.59)
20g	Me	4-Me-P	F	60	Pale yellow crystals 183—185	$C_{19}H_{21}F_2N_3O_3S \cdot 1/4H_2O$	55.13 (54.99	5.23 5.29	10.15 10.21)
20h	Ph	4-Me-P	F	44	Colorless powder 216—218 (dec.)	$C_{24}H_{23}F_2N_3S \cdot 1/4H_2O$	60.56 (60.77	4.98 5.12	8.83 8.71)
20i	4-F-Ph	4-Me-P	F	51	Colorless powder 165—167	$C_{24}H_{22}F_3N_3O_3S$	58.89 (58.69	4.53 4.59	8.58 8.57)
20j	2,4-F_2-Ph	4-Me-P	F	47	Colorless powder 185—187	$C_{24}H_{21}F_4N_3O_3S$	61.13 (60.98	4.92 5.15	8.91 8.66)
20k	Me	P	OMe	14	Colorless powder 185—187	$C_{19}H_{22}FN_3O_4S$	56.01 (55.78	5.44 5.59	10.31 10.03)
20l	Me	4-Me-P	OMe	93	Colorless powder 215—216 (dec.)	$C_{20}H_{24}FN_3O_4S$	56.99 (56.95	5.74 5.76	9.97 9.95)
20m	Me	4-Me-P	Cl	33	Colorless powder 201—202	$C_{19}H_{21}ClFN_3O_3S$	53.58 (53.54	4.97 5.06	9.87 9.70)
20n	Me	4-Me-P	Br	44	Pale tan powder 205—206	$C_{19}H_{21}BrFN_3O_3S$	44.35 (44.50	4.16 3.88	9.13 8.94)

a) Yields not optimized. *b*) C, H and N analyses were within ±0.4% of the theoretical values unless otherwise noted. *c*) Determined by high-resolution mass spectrometry (HR-MS). *d*) P stands for a piperazinyl group.

rine at C-8 might not be the sole factor influencing the *in vitro* activity in the 7-piperazinylthiazetoquinolone series. Among these derivatives, compound **21b** showed the best *in vitro* antibacterial activity.

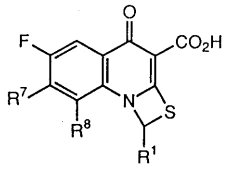
In the 1-methyl-7-(4-methyl-1-piperazinyl)thiazetoquinolone series, addition of a fluorine at C-8 slightly increased *in vitro* antibacterial activity against gram-positive bacteria and slightly decreased the activity against gram-negative bacteria (**21g** *vs.* **1g**). Compound **21g** showed less potent activity against gram-negative bacteria than the 1-methyl-7-piperazinyl analogue (**21b**). This result is similar to that in the case of the 8-unsubstituted 1-methyl analogues (**1b** *vs.* **1g**).

Introduction of a methoxy group at C-8 increased *in vitro* antibacterial activity against gram-positive bacteria for the 1-methyl-7-piperazinyl analogue (**21k** *vs.* **1b**), but decreased the activity against both gram-positive and -negative bacteria for the 1-methyl-7-(4-methyl-1-piperazinyl) analogue (**21l** *vs.* **1g**).

The efficacy of selected compounds against systemic infections in mice caused by *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* is shown in Table VI.

In the 7-piperazinylthiazetoquinolone series, the 8-

TABLE II. Synthesis of the Thiazetoquinolone-3-carboxylic Acids and Physical Data



Compd. No.	R^1	R^7	R^8	Yield (%)[a]	Appearance mp (°C)	Formula	Analysis (%)[b] Calcd (Found)		
							C	H	N
21a	H	P[c]	F	99	Pale yellow crystals >300	$C_{15}H_{13}F_2N_3O_3S \cdot H_2O$	48.51 (48.75	4.07 4.11	11.31 11.07)
21b	Me	P	F	93	Yellow crystals 260 (dec.)	$C_{16}H_{15}F_2N_3O_3S \cdot 3/4H_2O$	50.45 (50.29	4.37 4.54	11.03 10.97)
21c	Ph	P	F	82	Pale yellow crystals 260—264 (dec.)	$C_{21}H_{17}F_2N_3O_3S \cdot 1/4H_2O$	58.13 (58.00	4.06 4.03	9.68 9.95)
21d	4-F-Ph	P	F	89	Pale yellow crystals >300	$C_{21}H_{16}F_3N_3O_3S \cdot 1/2H_2O$	55.26 (55.19	3.75 3.56	9.21 9.38)
21e	2,4-F_2-Ph	P	F	99	Pale yellow crystals >300	$C_{21}H_{15}F_4N_3O_3S \cdot 1/2H_2O$	53.17 (53.19	3.40 3.32	8.86 8.76)
21f	H	4-Me-P	F	90	Pale yellow crystals 249—252	$C_{16}H_{15}F_2N_3O_3S \cdot 1/2H_2O$	51.06 (51.23	4.28 4.01	11.16 10.96)
21g	Me	4-Me-P	F	90	Pale brown crystals 238 (dec.)	$C_{17}H_{17}F_2N_3O_3S \cdot 1/4H_2O$	52.91 (52.93	4.57 4.64	10.89 10.95)
21h	Ph	4-Me-P	F	62	Pale yellow crystals 188—190	$C_{22}H_{19}F_2N_3O_3S \cdot 1/5H_2O$	59.11 (59.10	4.37 4.47	9.40 9.28)
21i	4-F-Ph	4-Me-P	F	63	Pale brown powder 268—271 (dec.)	$C_{22}H_{18}F_3N_3O_3 \cdot 11/10H_2O$	54.90 (54.98	4.23 4.03	8.73 8.85)
21j	2,4-F_2-Ph	4-Me-P	F	77	Colorless powder 204—206 (dec.)	$C_{22}H_{17}F_4N_3O_3 \cdot 1/4H_2O$	54.60 (54.64	3.64 3.58	8.68 8.65)
21k	Me	P	OMe	48	Pale yellow crystals 242—243 (dec.)	$C_{17}H_{18}FN_3O_4S \cdot HCl$	49.10 (49.34	4.60 4.79	10.10 10.01)
21k'	Me	P	OMe	64	Pale yellow powder 193 (dec.)	$C_{17}H_{18}FN_3O_4S \cdot 3/2H_2O$	50.24 (50.19	5.21 4.93	10.34 10.11)
21l	Me	4-Me-P	OMe	73	Gray needles 220—221 (dec.)	$C_{18}H_{20}FN_3O_4S$	54.95 (54.69	5.12 5.19	10.68 10.56)
21m	Me	4-Me-P	Cl	43	Colorless powder 189—191	$C_{17}H_{17}ClFN_3O_3S \cdot 1/2H_2O$	50.19 (50.47	4.46 4.20	10.32 10.33)
21n	Me	4-Me-P	Br	14	Cray powder 198—200 (dec.)	$C_{17}H_{17}BrFN_3O_3S \cdot H_2O$	44.35 (44.50	4.16 3.88	9.13 8.94)
21o	Me	4-Me-P	NO_2	63	Orange powder 200—201 (dec.)	$C_{17}H_{17}FN_4O_5S$	50.00 (50.08	4.20 4.18	13.72 13.90)
21p	Me	4-Me-P	NH_2	56	Yellow crystals 250 (dec.)	$C_{17}H_{19}FN_4O_3S \cdot H_2O$	51.50 (51.77	5.33 5.25	14.13 14.07)

a) See Table I footnote *a*). *b*) C, H and N analyses were within ±0.4% of the theoretical values. *c*) See Table I footnote *d*).

fluoro analogues with 1-hydrogen (**21a**), 1-methyl (**21b**) and 1-phenyl (**21c**) groups showed more potent *in vivo* activity than the corresponding 8-unsubstituted analogues (**1a—c**). This is interesting because, so far, the effect of fluorine at C-8 of bicyclic 7-piperazinylquinolones on the *in vivo* activity has not been clarified for various C-1 substituted analogues other than the 1-cyclopropyl analogue, which was reported to show increased *in vivo* efficacy against infections due to both gram-positive and -negative bacteria as compared with the corresponding 8-unsubstituted analogue.[2a,d]

In the 1-methyl-7-piperazinylthiazetoquinolone series, introduction of a methoxy group at C-8 improved the *in vivo* activity (**21k** *vs.* **1b**). This is also interesting, because the contribution of the methoxy group at C-8 of bicyclic quinolones to oral efficacy has not been clarified, although several 8-methoxy derivatives[8] are undergoing clinical testing.

For the 1-methyl-8-fluoro and 1-methyl-8-methoxy analogues, the 7-(4-methyl-1-piperazinyl) analogues (**21g** and **21l**) had almost the same or more potent *in vivo* activity than the 7-piperazinyl analogues (**21b** and **21k**), although **21g** and **21l** have less potent *in vitro* activity than **21b** and **21k**, respectively.

In conclusion, our study has shown that the effect of a fluorine at C-8 of the 7-piperazinylthiazetoquinolones on *in vitro* antibacterial activity is greatly influenced by the choice of the substituent at C-1, and the introduction of a fluorine or methoxy group at C-8 of the 7-piperazinylthiazetoquinolones markedly improved *in vivo* antibacterial activity.

Experimental

Chemistry Melting points were determined on a Büchi melting point apparatus without correction. Elemental analyses were done with a Yanaco CHN Corder MT-3 element analyzer. ^{1}H-NMR spectra were recorded on a 200-MHz Varian XL-200 or a 60-MHz Hitachi R-24-B

TABLE III. IR and ^{1}H-NMR Data for the Ethyl Thiazetoquinolone-3-carboxylates

Compd. No.	IR (KBr) cm^{-1} (C=O)	^{1}H-NMR	
		Solvent	δ (J=Hz)
14	1715	CF_3CO_2D	1.54 (3H, t, J=7, CH_2CH_3), 4.68 (2H, q, J=7, CH_2CH_3), 6.34 (2H, d, J=3, 1-H), 8.14 (1H, ddd, J=2, 7, 10, 5-H)
15	1720	CF_3CO_2D	1.56 (3H, t, J=7, CH_2CH_3), 2.40 (3H, dd, J=7, 3, 1-CH_3), 4.65 (2H, δ, J=7, CH_2CH_3), 6.68 (1H, dq, J=1, 7, 1-H), 8.18 (1H, ddd, J=2, 7, 10, 5-H)
16	1725	$CDCl_3$+ CD_3OD	1.35 (3H, t, J=7, CH_2CH_3), 4.30 (2H, q, J=7, CH_2CH_3), 6.79 (1H, d, J=2, 1-H), 7.39 (5H, br s, 1-phenyl), 7.7—8.2 (1H, m, 5-H)
17	1720	$CDCl_3$	1.48 (3H, t, J=7, CH_2CH_3), 4.35 (2H, q, J=7, CH_2CH_3), 6.92 (1H, d, J=2, 1-H), 7.0—7.7 (4H, m, 5-H, aromatic), 7.95 (1H, ddd, J=1, 6, 11, 5-H)
18	1730	$CDCl_3$+ CD_3OD	1.34 (3H, t, J=7, CH_2CH_3), 4.25 (2H, q, J=7, CH_2CH_3), 6.7—7.7 (3H, m, aromatic), 6.90 (1H, d, J=2, 1-H), 7.89 (1H, ddd, J=1, 6, 11, 5-H)
19	1720	$CDCl_3$	1.48 (3H, t, J=7.5, CH_2CH_3), 2.12 (3H, d, J=7, 1-CH_3), 4.18 (3H, d, J=3.5, OCH_3), 4.35 (2H, q, J=7.5, CH_2CH_3), 6.01 (1H, q, J=7, 1-H), 7.31 (1H, dd, J=8, 10, 5-H)
20a	1715	CF_3CO_2D	1.53 (3H, t, J=7, CH_2CH_3), 3.5—4.2 (8H, m, piperazine), 4.65 (2H, q, J=7, CH_2CH_3), 6.26 (2H, d, J=3, 1-H), 7.98 (1H, dd, J=2, 12, 5-H)
20b	1720	$CDCl_3$	1.40 (3H, t, J=7, CH_2CH_3), 2.15 (3H, dd, J=3, 7, 1-CH_3), 2.17 (1H, s, NH), 2.8—3.5 (8H, m, piperazine), 4.70 (2H, q, J=7, CH_2CH_3), 6.00 (1H, dq, J=3, 7, 1-H), 7.72 (1H, dd, J=2, 12, 5-H)
20c	1720	CF_3CO_2D	1.35 (3H, t, J=7, CH_2CH_3), 2.6—3.5 (8H, m, piperazine), 4.30 (2H, q, J=7, CH_2CH_3), 6.85 (1H, d, J=3, 1-H), 7.40 (5H, s, 1-phenyl), 7.69 (1H, dd, J=2, 14, 5-H)
20d	1720	$CDCl_3$	1.36 (3H, t, J=7.5, CH_2CH_3), 2.00 (1H, s, NH), 2.7—3.3 (8H, m, piperazine), 4.32 (2H, q, J=7.5, CH_2CH_3), 6.75 (1H, d, J=3, 1-H), 6.9—7.5 (4H, m, aromatic), 7.65 (1H, dd, J=2, 12, 5-H)
20e	1720	$CDCl_3$	1.38 (3H, t, J=7, CH_2CH_3), 2.23 (1H, s, NH), 2.2—3.3 (8H, m, piperazine), 4.32 (2H, q, J=7, CH_2CH_3), 6.7—7.5 (3H, m, aromatic), 7.03 (1H, d, J=2, 1-H), 7.67 (1H, dd, J=2, 12, 5-H)
20f	1710	CF_3CO_2D	1.32 (3H, t, J=7, CH_2CH_3), 2.30 (3H, s, NCH_3), 2.4—2.7 (4H, m, piperazine), 3.2—3.5 (4H, m, piperazine), 4.25 (2H, q, J=7, CH_2CH_3), 5.60 (2H, d, J=3, 1-H), 7.52 (1H, dd, J=2, 12, 5-H)
20g	1720	$CDCl_3$	1.40 (3H, t, J=7, CH_2CH_3), 2.15 (3H, dd, J=3, 7, 1-CH_3), 2.37 (3H, s, NCH_3), 2.4—2.7 (4H, m, piperazine), 3.2—3.5 (4H, m, piperazine), 4.35 (2H, q, J=7, CH_2CH_3), 6.00 (1H, dd, J=3, 7, 1-H), 7.70 (1H, dd, J=2, 12, 5-H)
20h	1720	CF_3CO_2D	1.38 (3H, t, J=7, CH_2CH_3), 2.30 (3H, s, NCH_3), 2.2—2.7 (4H, m, piperazine), 3.0—3.5 (4H, m, piperazine), 4.33 (2H, q, J=7, CH_2CH_3), 6.93 (1H, d, J=3, 1-H), 7.42 (5H, s, 1-phenyl), 7.67 (1H, dd, J=2, 12, 5-H)
20i	1725	$CDCl_3$	1.37 (3H, t, J=7.5, CH_2CH_3), 2.27 (3H, s, NCH_3), 2.1—2.6 (4H, m, piperazine), 2.9—3.4 (4H, m, piperazine), 4.32 (2H, q, J=7.5, CH_2CH_3), 6.74 (1H, d, J=2, 1-H), 6.9—7.5 (4H, m, aromatic), 7.67 (1H, dd, J=2, 12, 5-H)
20j	1725	$CDCl_3$	1.36 (3H, t, J=7, CH_2CH_3), 2.27 (3H, s, NCH_3), 2.1—2.6 (4H, m, piperazine), 2.9—3.4 (4H, m, piperazine), 4.31 (2H, q, J=7, CH_2CH_3), 6.7—7.5 (3H, m, aromatic), 7.02 (1H, d, J=2, 1-H), 7.67 (1H, dd, J=2, 12, 5-H)
20k	1720	$CDCl_3$	1.40 (3H, t, J=7, CH_2CH_3), 1.81 (1H, s, NH), 2.12 (3H, d, J=7, 1-CH_3), 2.9—3.5 (8H, m, piperazine), 3.95 (3H, s, OCH_3), 4.37 (2H, q, J=7, CH_2CH_3), 5.93 (1H, q, J=7, 1-H), 7.78 (1H, d, J=13, 5-H)
20l	1720	$CDCl_3$	1.40 (3H, t, J=7, CH_2CH_3), 2.39 (3H, d, J=7, 1-CH_3), 2.5—2.7 (4H, m, piperazine), 3.2—3.3 (2H, m, piperazine), 3.4—3.6 (2H, m, piperazine), 3.91 (3H, s, OCH_3), 4.37 (2H, q, J=7, CH_2CH_3), 5.92 (1H, q, J=7, 1-H), 7.78 (1H, d, J=13, 5-H)
20m	1720	$CDCl_3$	1.41 (3H, t, J=8, CH_2CH_3), 2.23 (3H, d, J=7, 1-CH_3), 2.5—2.9 (4H, m, piperazine), 3.2—3.5 (4H, m, piperazine), 4.38 (2H, q, J=8, CH_2CH_3), 6.35 (1H, q, J=7, 1-H), 8.03 (1H, d, J=13, 5-H)
20n	1720	$CDCl_3$	1.40 (3H, t, J=8, CH_2CH_3), 2.23 (3H, d, J=6, 1-CH_3), 2.5—2.7 (4H, m, piperazine), 3.1—3.5 (4H, m, piperazine), 4.38 (2H, q, J=8, CH_2CH_3), 6.50 (1H, q, J=6, 1-H), 8.10 (1H, d, J=12, 5-H)

spectrometer with Me_4Si as the internal standard. The chemical shifts are given in δ (ppm). IR spectra were recorded on a Shimadzu IR-453-U-03 spectrometer. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-SX102 spectrometer at the ionization potential of 70 eV. HPLC analyses were done with a Shimadzu LC-6A liquid chromatograph. Column chromatographic separation was conducted on Wako Gel C-200. Yields are for the purified products, and were not optimized. The characteristics of the synthesized compounds are given in Tables I—IV.

***In Vitro* Antibacterial Activity** Minimum inhibitory concentrations (MICs) were determined by the agar dilution method recommended by the Japan Society of Chemotherapy.[9] The bacterial inoculum contained approximately 10^6 colony-forming units/ml, and bacterial growth was monitored after 20 h of incubation at 37 °C.

***In Vivo* Efficacy on Systemic Infection** Seven male mice (ddY, 20±2 g, Japan SLC Inc., Shizuoka, Japan) were used for each drug dose. *Escherichia* coli KC-14 (2.5×10^5 cfu/ml), *Staphylococcus aureus* Smith (2.5×10^6 cfu/ml) and *Pseudomonas aeruginosa* E-2 (2.5×10^5) were suspended in 5% gastric mucin. A 0.5-ml volume of the bacterial suspension was administered intraperitoneally. The test drug was suspended in 0.5% HPC-SL (hydroxypropylcellulose type SL) and administered orally 1 h after the challenge. The 50% effective doses were calculated by the Probit method from survival rates 7 d after infection.

2,3,4-Trifluorophenyl Isothiocyanate (6) CS_2 (262 g, 3.44 mol) and NEt_3 (790 g, 7.80 mol) were added dropwise to a mixture of **2** (230 g, 1.56 mol) under ice cooling. The reaction mixture was gradually warmed to room temperature and stirred for 6 d. The resulting precipitate was collected by filtration, washed with ether, and dried to give triethylammonium (2,3,4-trifluorophenyl)dithiocarbamate (**4**) (451 g, 89%) as a pale brown powder, which, without further purification, was suspended in $CHCl_3$ (1.5 l) and NEt_3 (125 g, 1.23 mol). Ethyl chloroformate (134 g, 1.23 mol) in $CHCl_3$ (400 ml) was added dropwise to this suspension under ice cooling over 2 h. The reaction mixture was stirred at room temperature for 1 h, poured into ice-water, neutralized with aqueous HCl solution and treated with $CHCl_3$. The organic layer was dried and concentrated under reduced pressure, affording a crude oil, which was chromatographed on silica gel with *n*-hexane to give **6** (185 g, 75% from **3**), bp 61—62 °C (4 mmHg) [lit.,[7] 96—97 °C (17 mmHg)]. IR: 2050, 1615, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.7—7.3 (2H, m, aromatic). MS *m/z*: 189 (M^+); HPLC: 99.9%.

TABLE IV. IR and ^{1}H-NMR Data for the Thiazetoquinolone-3-carboxylic Acids

Compd. No.	IR (KBr) cm^{-1} (C=O)	^{1}H-NMR	
		Solvent	δ (J=Hz)
21a	1700	CF_3CO_2D	3.4—4.3 (8H, m, piperazine), 6.30 (2H, d, J=2, 1-H), 8.01 (1H, dd, J=2, 12, 5-H)
21b	1700	CF_3CO_2D	2.40 (3H, dd, J=3, 6, 1-CH_3), 3.4—4.3 (8H, m, piperazine), 6.62 (1H, dq, J=3, 6, 1-H), 8.07 (1H, dd, J=2, 12, 5-H)
21c	1700	CF_3CO_2D	3.3—4.3 (8H, m, piperazine), 7.0—7.7 (6H, m, 1-H, 1-phenyl), 8.01 (1H, dd, J=2, 12, 5-H)
21d	1700	CF_3CO_2D	3.4—4.2 (8H, m, piperazine), 7.0—7.8 (5H, m, 1-H, aromatic), 8.03 (1H, dd, J=2, 12, 5-H)
21e	1700	CF_3CO_2D	3.3—4.2 (8H, m, piperazine), 6.7—7.7 (4H, m, 1-H, aromatic), 8.04 (1H, dd, J=2, 12, 5-H)
21f	1700	CF_3CO_2D	3.20 (3H, s, NCH_3), 3.1—4.3 (8H, m, piperazine), 6.28 (2H, d, J=3, 1-H), 8.01 (1H, dd, J=2, 12, 5-H)
21g	1700	CF_3CO_2D	2.34 (3H, dd, J=3, 6, 1-CH_3), 3.14 (3H, s, NCH_3), 3.2—3.5 (8H, m, piperazine), 6.54 (1H, dq, J=3, 6, 1-H), 7.97 (1H, dd, J=2, 12, 5-H)
21h	1700	CF_3CO_2D	2.31 (3H, s, NCH_3), 2.3—2.7 (4H, m, piperazine), 2.9—3.6 (4H, m, piperazine), 7.10 (1H, d, J=3, 1-H), 7.4—7.7 (5H, m, 1-phenyl), 7.68 (1H, dd, J=2, 12, 5-H)
21i	1700	$CDCl_3$ + CD_3OD	2.42 (3H, s, NCH_3), 2.4—2.9 (4H, m, piperazine), 3.0—3.6 (4H, m, piperazine), 6.9—7.5 (5H, m, 1-H, aromatic), 7.69 (1H, dd, J=2, 12, 5-H)
21j	1700	$CDCl_3$ + CD_3OD	2.35 (3H, s, NCH_3), 2.2—2.7 (4H, m, piperazine), 3.0—3.5 (4H, m, piperazine), 6.7—7.4 (3H, m, aromatic), 7.28 (1H, d, J=2, 1-H), 7.70 (1H, dd, J=2, 12, 5-H)
21k	1700	CF_3CO_2D	2.39 (3H, d, J=7, 1-CH_3), 3.6—4.3 (8H, m, piperazine), 4.08 (3H, s, OCH_3), 6.60 (1H, q, J=7, 1-H), 8.05 (1H, d, J=13, 5-H)
21l	1710	$CDCl_3$	2.18 (3H, d, J=7, 1-CH_3), 2.41 (3H, s, NCH_3), 2.5—2.8 (4H, m, piperazine), 3.1—3.4 (2H, m, piperazine), 3.5—3.7 (2H, m, piperazine), 3.91 (3H, s, OCH_3), 6.49 (1H, q, J=7, 1-H), 7.74 (1H, d, J=13, 5-H), 14.10 (1H, s, CO_2H)
21m	1700	$CDCl_3$	2.28 (3H, d, J=7, 1-CH_3), 2.39 (3H, s, NCH_3), 2.5—2.8 (4H, m, piperazine), 3.2—3.8 (4H, m, piperazine), 6.50 (1H, q, J=7, 1-H), 7.98 (1H, d, J=12, 5-H), 14.0 (1H, s, CO_2H)
21n	1700	$CDCl_3$	2.29 (3H, d, J=6, 1-CH_3), 2.40 (3H, s, NCH_3), 2.5—2.8 (4H, m, piperazine), 3.1—3.6 (4H, m, piperazine), 6.68 (1H, q, J=6, 1-H), 8.07 (1H, J=12, 5-H), 11.0 (1H, s, CO_2H)
21o	1710	CF_3CO_2D	2.12 (3H, d, J=6, 1-CH_3), 3.18 (3H, s, NCH_3), 3.0—4.2 (8H, m, piperazine), 6.51 (1H, q, J=6, 1-H), 8.40 (1H, d, J=12, 5-H)
21p	1700	DMSO-d_6	2.18 (3H, d, J=6, 1-CH_3), 2.30 (3H, s, NCH_3), 2.6—3.1 (8H, m, piperazine), 5.40 (2H, s, NH_2), 6.82 (1H, q, J=6, 1-H), 7.20 (1H, d, J=12, 5-H)

TABLE V. *In Vitro* Antibacterial Activity[a] (MIC μg/ml)

Compd. No.	Gram-positive organisms				Gram-negative organisms				
	Staphylococcus aureus		*Micrococcus luteus*	*Bacillus subtilis*	*Escherichia coli*		*Serratia marcescens*	*Shigella flexneri*	*Pseudomonas aeruginosa*
	209P JC-1	Smith	ATCC 9341	ATCC 6633	NIHJ JC-2	KC-14	IFO 3736	2a EW-10	E-2
21a	0.10	0.10	3.13	0.10	0.025	0.025	0.05	0.012	0.39
21b	0.05	0.05	0.39	0.05	0.012	≦0.006	0.05	≦0.006	0.20
21c	0.20	0.10	6.25	0.10	0.10	0.10	1.56	0.05	0.78
21d	0.20	0.20	6.25		0.10	0.025	1.56	0.05	0.78
21e	1.56	0.39	6.25		0.20	0.20	6.25	0.20	3.13
21f	0.20	0.10	6.25	0.05	0.05	0.025	0.10	0.025	0.78
21g	0.10	0.05	0.78	0.025	0.025	0.025	0.10	0.025	0.39
21h	0.39	0.39	12.5	0.20	0.78	0.39	12.5	0.78	3.13
21i	0.78	0.39	12.5		0.78	0.39	12.5	0.39	3.13
21j	1.56	0.78	6.25		1.56	0.78	50	1.56	12.5
21k	0.05	0.05	0.20	0.025	0.012	0.012	0.20	≦0.006	0.39
21l	0.20	0.10	0.78	0.10	0.20	0.10	0.78	0.10	1.56
21m	0.20	0.39	12.5	0.20	0.10	0.10	0.39	0.05	0.78
21n	0.20	0.10	0.78	0.10	0.20	0.10	0.78	0.10	1.56
21o	0.39	0.10	3.13	0.10	0.78	0.39	6.25		6.25
21p	0.39	0.20	50	0.20	0.10	0.05	0.39	0.05	1.56
1a	0.20	0.20	12.5	0.20	0.10	0.05	0.10	0.025	1.56
1b	0.05	0.10	0.78	0.05	0.012	0.012	0.05	≦0.006	0.20
1c	0.20	0.05	3.13		0.025	0.012	0.05	0.025	0.20
1d	0.20		1.56		0.025		0.39	0.025	0.39
1g	0.10	0.05	1.56	0.05	0.025	0.025	0.05	0.012	0.39
OFLX[b]	0.39	0.20	3.13		0.10	0.05	0.39	0.10	1.56
CPFX[c]	0.10	0.05	1.56		0.012	0.012	0.10	≦0.006	0.20

a) See Experimental. *b*) Ofloxacin. *c*) Ciprofloxacin.

3,4-Difluoro-2-methoxyphenyl Isothiocyanate (**7**) was similarly prepared from 3,4-difluoro-2-methoxyaniline (**3**)[3] in 63% yield. Compound **7**: bp 94—95 °C (4 mmHg). IR: 2930, 2000, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.05 (3H, d, J=2 Hz, OCH_3),6.6—7.0 (2H, m, aromatic). HR-MS m/z: 201.0049 (M^+, Calcd for $C_8H_5F_2NOS$: 201.0060). HPLC: 99.5%

TABLE VI. Oral Efficacy on Systemic Infections in Mice[a)]

Compd. No.	*Staphylococcus aureus* Smith		*Escherichia coli* KC-14		*Pseudomonas aeruginosa* E-2	
	MIC [μg/ml]	ED_{50} [mg/kg]	MIC [μg/ml]	ED_{50} [mg/kg]	MIC [μg/ml]	ED_{50} [mg/kg]
21a	0.10	21.32 (14.62—31.40)[b)]	0.025	5.63 (3.86—24.39)	0.39	NT[c)]
21b	0.05	8.40 (6.07—10.60)	≦0.006	0.50 (0.32—0.76)	0.20	15.45 (3.90—24.28)
21c	0.10	NT	0.10	5.83 (3.84—8.46)	0.78	NT
21g	0.05	4.87 (3.39—7.03)	0.025	0.55 (0.38—0.81)	0.39	17.64 (10.51—27.45)
21k	0.05	11.65 (7.98—17.15)	0.012	1.21 (0.77—2.10)	0.39	39.85 (23.61—72.34)
21l	0.10	7.92 (4.60—15.29)	0.10	1.28 (0.76—7.55)	1.56	23.30 (14.99—34.85)
1a	0.20	>40	0.05	>6.25	1.56	NT
1b	0.10	>40	0.012	>6.25	0.20	>40
1c	0.05	>40	0.012	>6.25	0.20	20.94 (13.81—58.05)
1g	0.05	3.19 (2.17—4.65)	0.025	0.97 (0.62—1.47)	0.39	8.84 (6.19—12.63)
CPFX[d)]	0.05	8.40 (6.76—11.44)	0.012	0.45 (0.35—0.60)	0.20	9.01 (6.93—10.96)

a) See Experimental. *b*) 95% confidence limits. *c*) Not tested. *d*) Ciprofloxacin.

Ethyl 6,7,8-Trifluoro-4-hydroxy-2-[(methoxymethyl)thio]quinoline-3-carboxylate (10) Diethyl malonate (172 g, 1.07 mol) was added dropwise to a stirred suspension of powdered KOH (96%) (63 g, 1,07 mol) in toluene (2 l). The mixture was stirred at room temperature for 3 h, then **6** (203 g, 1.07 mol) was added gradually at 25 °C, and the whole was stirred for 7 h. The reaction mixture was kept in a refrigerator (4° C) for 15 h, and the resulting precipitate was collected by filtration and washed with dioxane to give the potassium salt of the diethyl [[(2,3,4-trifluorophenyl)amino](mercapto)methylene]malonate (403 g, 97%). Chloromethyl methyl ether (40.3 g, 0.50 mol) was added dropwise to a solution of NEt_3 (30.4 g, 0.30 mol) in toluene (1 l) under ice cooling. The reaction mixture was stirred at 0 °C for 0.5 h, then warmed gradually to room temperature. The potassium salt (194 g, 0.50 mol) was added in portions, and the whole was stirred for 3 h. The reaction mixture was poured into ice-water. The organic layer was washed with 1% aqueous HCl solution, then with saturated aqueous $KHCO_3$ solution, and lastly with water, after which it was dried and concentrated under reduced pressure, affording diethyl[(2,3,4-trifluorophenyl)amino][(methoxymethyl)thio]methylene]malonate (**8**) (179 g, 91%) as a pale yellow oil, which, without further purification, was dissolved in 535 g of Ph_2O. This solution was stirred at 150 °C for 6 h. After cooling, the reaction mixture was chromatographed on silica gel with $CHCl_3$ to give **10** (99.5 g, 56% from **6**), mp 93—95 °C. IR: 3000, 1650, 1580, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, t, J=7 Hz, CH_2CH_3), 3.47 (3H, s, OCH_3), 4.54 (2H, q, J=7 Hz, CH_2CH_3), 5.45 (2H, s, SCH_2O), 7.65 (1H, ddd, J=2, 8, 11 Hz, 5-H), 13.30 (1H, s, OH). *Anal.* Calcd for $C_{14}H_{12}F_3NO_4S$: C, 48.42; H, 3.48; N, 4.03. Found: C, 48.47; H, 3.60; N, 3.97.

Ethyl 6,7-Difluoro-4-hydroxy-8-methoxy-2-[(methoxymethyl)thio]-quinoline-3-carboxylate (**11**) was prepared from **7** in 53% yield by the same procedure. Compound **11**: mp 129—130 °C. IR: 2990, 1670, 1600, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=8 Hz, CH_2CH_3), 3.49 (3H, s, CH_2OCH_3), 4.17 (3H, d, J=1.5 Hz, 8-OCH_3), 4.45 (2H, q, J=8 Hz, CH_2CH_3), 5.30 (2H, s, SCH_2O), 7.61 (1H, dd, J=8, 11 Hz, 5-H). *Anal.* Calcd for $C_{15}H_{15}F_2NO_5S$: C, 50.14; H, 4.21; N, 3.90. Found: C, 50.12; H, 4.24; N, 3.91.

Ethyl 6,7,8-Trifluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (12) Sulfuric acid (11 g, 0.11 mol) was added dropwise to a suspension of **10** (292 g, 0.84 mol) in EtOH (1.5 l), and the whole was stirred at 80 °C for 2 h. After cooling, the precipitate was collected and washed with ether to give **12** (243 g, 95%), mp 190—192 °C [lit.,[10)] 190]. IR: 3000, 1590, 1510, 1470 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 1.62 (3H, t, J=7 Hz, CH_2CH_3), 4.76 (2H, q, J=7 Hz, CH_2CH_3), 8.10 (1H, ddd, J=2, 8, 10 Hz, 5-H). MS m/z: 303 (M^+).

Ethyl 6,7-Difluoro-4-hydroxy-2-mercapto-8-methoxyquinoline-3-carboxylate (**13**) was prepared from **11** in 97% yield by the same procedure. Compound **13**: mp 181—185 °C (dec.). IR: 3140, 1635, 1570, 1495 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7.5 Hz, CH_2CH_3), 4.03 (3H, d, J=1.5 Hz, OCH_3), 4.23 (2H, q, J=7.5 Hz, CH_2CH_3), 6.25 (2H, br s, OH, SH), 7.64 (1H, dd, J=11, 8 Hz, 5-H). *Anal.* Calcd for $C_{13}H_{11}F_2NO_4S$: C, 49.52; H, 3.52; N, 4.44. Found: C, 49.34; H, 3.48; N, 4.53.

Ethyl 6,7,8-Trifluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (15) A typical example is given to illustrate the general procedure. A solution of **12** (6.1 g, 0.02 mol) in *N*,*N*-dimethylformamide (DMF) (60 ml) was added dropwise to a mixture of 1,1-diiodoethane (12.0 g, 0.04 mol) and K_2CO_3 (8.3 g, 0.06 mol) in DMF (85 ml) at 100—105 °C, and the whole was stirred vigorously for 1.5 h. After being stirred at the same temperature for a further 0.5 h, the reaction mixture was concentrated under reduced pressure. The residue was treated with $CHCl_3$–MeOH, then washed with water, dried, and concentrated under reduced pressure to give a crude solid, which was recrystallized from EtOAc to give **15** (3.4 g, 53%). The other compounds, **14** and **16**—**19**, were similarly prepared. See Tables I and III for physical constants and spectral data.

Ethyl 6,8-Difluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylate (20b) A typical example is given to illustrate the general procedure. A mixture of **15** (0.33 g, 1.0 mmol), K_2CO_3 (0.14 g, 1.0 mmol), and piperazine (0.13 g, 1.5 mmol) in DMF (10 ml) was stirred at 60 °C for 2 h. After removal of the solvent, the residue was diluted with water then treated with $CHCl_3$. The organic layer obtained was dried and concentrated under reduced pressure, affording a solid, which was chromatographed on silica gel with 20% MeOH in $CHCl_3$, giving **20b** (0.29 g, 67%). All other compounds (**20a, c**—**j**) were prepared similarly. See Tables I and III for physical constants and spectral data.

Ethyl 6-Fluoro-8-methoxy-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]-thiazeto[3,2-*a*]quinoline-3-carboxylate (20k) A mixture of **19** (1.00 g, 2.94 mmol), piperazine (0.51 g, 5.87 mmol), and K_2CO_3 (0.81 g, 5.87 mmol) in dimethyl sulfoxide (DMSO) (80 ml) was heated at 60 °C for 42 h, after which it was poured into ice-water and treated with EtOAc. The organic layer obtained was washed with 5% aqueous K_2CO_3 solution and treated with 2% aqueous HCl solution. The aqueous layer was neutralized with $NaHCO_3$ then treated with $CHCl_3$. The organic layer was washed with water, dried, and concentrated under reduced pressure. The residue obtained was purified on a silica gel column with 5% MeOH in $CHCl_3$ to afford **20k** (0.16 g, 14%). See Tables I and III for physical

constants and spectral data.

Ethyl 6-Fluoro-8-methoxy-1-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (20l) A mixture of **20k** (15.0 g, 0.037 mol), 24.4 g (0.530 mol) of formic acid (24.4 g, 0.530 mol) and 50 ml of formaldehyde (35 wt% solution in water) was heated under reflux for 0.5 h, then poured into aqueous $NaHCO_3$ solution and treated with $CHCl_3$. The organic layer obtained was washed with water, dried, and concentrated under reduced pressure to afford **20l** (14.5 g, 93%). See Tables I and III for physical constants and spectral data.

6,8-Difluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (21b) A mixture of **20b** (37.5 g, 9.50 mmol) and KOH (37.5 g, 6.68 mmol) in *tert*-BuOH (600 ml), and H_2O (200 ml) was heated at 60 °C for 1 h. After removal of the solvent, the residue was dissolved in H_2O. The resulting solution was washed with $CHCl_3$ then neutralized with AcOH. The precipitate formed was collected by filtration and washed with H_2O, MeOH, affording **21b** (32.5 g, 93%). The other compounds, **21a** and **21c—j**, were similarly prepared. See Tables II and IV for physical constants and spectral data.

6-Fluoro-8-methoxy-1-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (21l) Compound **20l** (23.4 g, 0.055 mol) was added in portions to 120 ml of fuming sulfuric acid under ice cooling, then the solution was heated at 55 °C for 2 h. After being cooled, the reaction mixture was poured into ice-water, neutralized with $NaHCO_3$, and treated with 20% MeOH in $CHCl_3$. The organic layer obtained was dried and concentrated under reduced pressure to give a crude solid, which was recrystallized from EtOH to afford **21l** (16.0 g, 73%). The other compounds, **21m** and **21n**, were similarly prepared. See Tables II and IV for physical constants and spectral data.

6-Fluoro-8-methoxy-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (21k′) and Its Hydrochloride (21k) A mixture of acetic anhydride (0.79 g, 7.74 mmol) and formic acid (88%) (0.44 g, 8.41 mmol) was heated at 60 °C for 1 h then cooled to room temperature. A solution of **20k** (2.04 g, 5.01 mmol) in $CHCl_3$ (10 ml) was added to this mixture and the whole was stirred at 45 °C for 4 h. After cooling, the mixture was poured into ice-water and treated with $CHCl_3$. The organic layer obtained was washed with water, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel with 2% MeOH in $CHCl_3$ to give 1.98 g (91%) of ethyl 6-fluoro-7-(4-formyl-1-piperazinyl)-8-methoxy-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate, mp 235 °C (dec.) IR: 3430, 2910, 1720, 1665, 1600, 1540, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz, CH_2CH_3), 2.08 (3H, d, J=6 Hz, 1-CH_3), 2.8—3.8 (8H, m, piperazine), 3.92 (3H, s, OCH_3), 4.31 (2H, q, J=7 Hz, CH_2CH_3), 5.91 (1H, q, J=6 Hz, 1-H), 7.67 (d, J=13 Hz, 5-H), 8.07 (1H, s, formyl). *Anal.* Calcd for $C_{20}H_{22}FN_3O_5S$: C, 55.16; H, 5.09; N, 9.65. Found: C, 54.82; H, 5.06; N, 9.56.

This compound was dissolved in fuming H_2SO_4 (20 ml) under ice cooling, and the solution was stirred for 1 h. Stirring was continued at room temperature for 4 h, then the resulting mixture was poured into ice-water and treated with $CHCl_3$. The organic layer obtained was washed with water, dried, and concentrated under reduced pressure to give the crude carboxylic acid, which, without further purification, was added to a mixture of EtOH (5 ml) and aqueous 35% hydrochloric acid solution (1 ml), and the whole was refluxed for 5 h. After removal of the solvent, the residue was recrystallized from EtOH to give **21k** (0.51 , 48% from **20k**). See Tables II and IV for physical constants and spectral data.

A solution of sodium acetate (76 mg 0.93 mmol) was added to a suspension of **21k** (402 mg 0.93 mmol) in 2 ml of H_2O, and the whole was stirred for 1 h. The resulting mixture was treated with 20% MeOH in $CHCl_3$. The organic layer obtained was washed with water, dried, and concentrated under reduced pressure to yield a crude product, which was recrystallized from EtOH to afford 255 mg (64%) of **21k′**. See Tables I and IV for physical constants and spectral data.

Ethyl 8-Bromo-6-fluoro-1-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (20n) A solution of Br_2 (0.08 g, 0.51 mmol) in AcOH (25 ml) was added dropwise to a solution of **22** (0.20 g, 0.51 mmol) in AcOH (10 ml), and the whole was stirred overnight. The reaction mixture was poured into H_2O, neutralized with $NaHCO_3$, then treated with EtOAc. The organic layer was washed with aqueous $Na_2S_2O_3$ solution, dried, and concentrated under reduced pressure, giving the crude product, which was recrystallized from EtOAc to afford **20n** (0.11 g, 44%). Compound **20m** was similarly prepared by using Cl_2. See Tables I and III for physical constants and spectral data.

6-Fluoro-1-methyl-7-(4-methyl-1-piperazinyl)-8-nitro-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (21o) Compound **1g** (1.00 g, 2.75 mmol) was added in portions to a stirred mixture of concentrated H_2SO_4 (3.35 g) and HNO_3 (70% 3.35 g) under ice cooling. The reaction mixture was stirred at room temperature for 5 h, then poured into ice-water and neutralized with $NaHCO_3$. The resulting mixture was treated with $CHCl_3$–MeOH, washed with H_2O, then dried and concentrated under reduced pressure to afford a crude solid, which was recrystallized from EtOAc to give **21o** (0.71 g, 63%). See Tables II and IV for physical constants and spectral data.

8-Amino-6-fluoro-1-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (21p) A solution of $SnCl_2 \cdot 2H_2O$ (21.3 g, 94.4 mmol) in concentrated HCl (93 ml) was added dropwise to a solution of **21o** (9.3 g 19.6 mmol) in concentrated HCl (93 ml) and the mixture was stirred for 3 h. The resulting precipitate was collected by filtration, washed with water, then dissolved in 2.5 N NaOH. This alkaline solution was neutralized with AcOH. The precipitate that formed was collected, washed with water, and purified on a silica gel column with 50% MeOH in $CHCl_3$ to give **21p** (4.2 g, 56%). See Tables II and IV for physical constants and spectral data.

The methods of preparation for compounds **1a—d, g** and **22** have been reported in the previous paper.[1a)]

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