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Synthesis of 7-Thio-substituted 4-Oxoquinoline-3-carboxylic Acids with Antibacterial Activity[1)]

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A series of C-7 thio-substituted 1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids were prepared and tested for their antibacterial activity. Structure–activity relationships associated with the C-5 and C-7 substituents were discussed. Among the C-7 substituents including alkylthio, arylthio, heteroarylthio, and cyclic aminothio groups, a 2-aminoethylthio group was the best for enhancing *in vitro* antibacterial activity. The C-5 variants increased activity in the order OH < F < H < NH_2. Of compounds prepared in this work, 5-amino-7-(2-aminoethyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (18) was the most active.

Keywords quinolone; synthesis; antibacterial activity; structure–activity relationship

A class of antibacterials having a 1-substituted 1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety, collectively known as "quinolones," has aroused much interest because of their excellent potency and broad antibacterial spectrum. Importance of a C-7 amino substituent on the quinolones for improvement of activity was first reported in our papers,[2)] as exemplified by piromidic acid[2a)] and pipemidic acid,[2b)] which consist of a pyrido(2,3-*d*)pyrimidine ring and its C-2 position corresponds to C-7 on the quinolone ring. The synthetic study of quinolones has since been focused on compounds appended with various C-7 amino substituents, particularly a C-7 piperazinyl substituent.[3)] We recently reported the synthesis of a C-7 amino-substituted quinolone antibacterial agent, 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (AT-4140, sparfloxacin as a generic name),[4)] which has a potent broad-spectrum activity with an oral efficacy and is presently under clinical evaluation. In our synthetic study of quinolone antibacterials, the C-7 thio-substituted compounds such as the methylthio,[2b)] ethylthio,[5)] and tolylthio[6)] derivatives with a weak activity served as key intermediates for their C-7 amino-substituted analogues. However, a C-7 thio-substituent has recieved little attention in this field, because of a weak antibacterial activity of the thio-quinolones reported thus far. It became of interest for us to know whether a modified thio-substituent would be efficient for improving activity of this class of quinolones. The present study was undertaken to get further insight into structure–activity relationships of modified C-7 thio-substituents on some different quinolone derivatives. After our work was completed,[7)] the synthesis of several quinolones with the heterocyclic C-7 thio-substituents but a limited variant was reported.[8)] Therefore we wish to describe the synthesis and antibacterial activity of a new series of quinolones with various thio-substituents at C-7; of these quinolones, a compound showing an excellent activity comparable to that of AT-4140 was found.

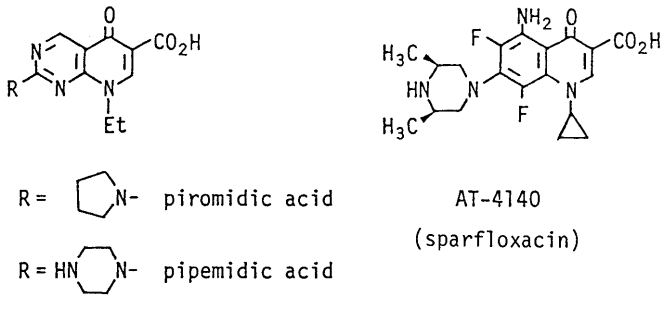


Chart 1

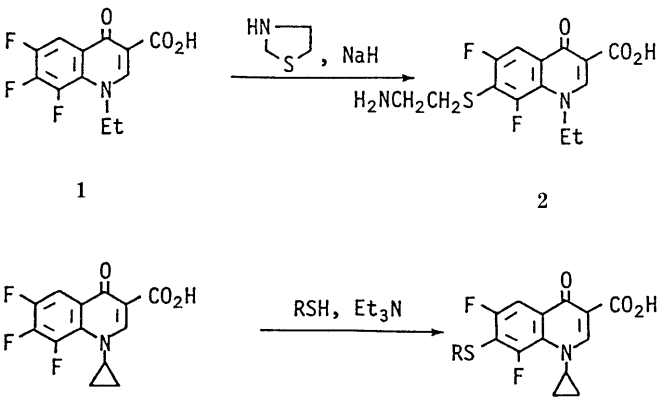
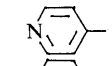
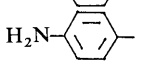
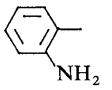
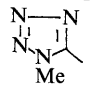
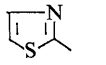
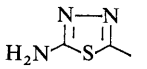
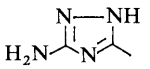
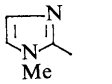
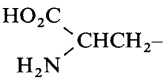


Chart 2

Chemistry Domagala *et al.*[9)] reported that the reaction of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**1**) with thiazolidine in the presence of sodium hydride gave incidentally 7-(2-aminoethyl)thio-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**2**) with a weak antibacterial activity. This reaction, however, is lacking in generality as a synthetic method for C-7 thio-substituted quinolones. We began by examining the reaction of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**3**)[10)] with several thiols in order to introduce a variety of thio-substituents into the C-7 position (Chart 2). Treatment of **3** with thiols gave the desired C-7 thio-substituted derivatives (**4a—o**) shown in Table I. Compound **4a** was identified with an authentic sample derived from **3** with thiazolidine according to the Domagala's method. This fact, along with the spectral data for **4a**, showed that the sulfur atom of aminoethanethiol rather than its nitrogen atom attacked the C-7 position of **3**. The structures of **4b—o** were confirmed by their mass and ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra.

This synthetic method is convenient for the C-7 thio-substituted quinolines when the requisite thiols are readily available. However the cyclic aminothiols, for example, 3-pyrrolidinethiol and 4-piperidinethiol are not always easy to prepare. Hence, we examined another

TABLE I. 7-Thio-substituted 6,8-Difluoroquinolones **4a—o**

Compd.	R	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
					C	H	F	N	S
4a	$H_2NCH_2CH_2$–	270—274[a,b]	83	$C_{15}H_{14}F_2N_2O_3S \cdot 1/4H_2O$	52.24	4.24	11.02	8.12	9.30
					(52.18	4.02	11.02	7.88	9.53)
4b	$Me_2NCH_2CH_2$–	99—100 (EtOH)	85	$C_{17}H_{18}F_2N_2O_3S \cdot 1/4H_2O$	54.76	5.00	10.19	7.51	8.60
					(54.65	4.75	9.99	7.48	8.30)
4c	Me	198—199 ($CHCl_3$)	91	$C_{14}H_{11}F_2NO_3S$	54.02	3.56	12.21	4.50	10.30
					(54.04	3.52	12.50	4.33	10.25)
4d	Et	149—150 (MeCN)	88	$C_{15}H_{13}F_2NO_3S$	55.38	4.03	11.68	4.31	9.86
					(55.15	3.92	11.46	4.16	10.03)
4e	$PhCH_2$–	162—163 (MeCN)	85	$C_{20}H_{15}F_2NO_3S$	62.01	3.90	9.82	3.62	8.28
					(61.86	3.89	9.52	3.50	8.56)
4f	$HOCH_2CH_2$–	154—155 (EtOH)	95	$C_{15}H_{13}F_2NO_3S$	52.78	3.84	11.13	4.10	9.39
					(53.05	3.89	11.08	4.13	9.63)
4g		274—278 ($CHCl_3$–EtOH)	70	$C_{18}H_{12}F_2N_2O_3S$	57.75	3.23	10.15	7.48	8.57
					(57.60	3.37	10.10	7.18	8.70)
4h		223—225 ($CHCl_3$–EtOH)	18	$C_{19}H_{14}F_2N_2O_3S$	58.76	3.63	9.78	7.21	8.26
					(58.59	3.49	9.67	7.17	8.50)
4i		177—179 ($CHCl_3$–EtOH)	63	$C_{19}H_{14}F_2N_2O_3S$	58.76	3.63	9.78	7.21	8.26
					(58.51	3.50	9.48	7.17	8.47)
4j		216—218 (EtOH)	17	$C_{15}H_{11}F_2N_5O_3S$	47.49	2.92	10.02	18.46	8.45
					(47.35	2.96	9.86	18.19	8.67)
4k		219—220 (EtOH)	30	$C_{16}H_{12}F_2N_2O_3S_2$	50.25	3.16	9.94	7.33	16.77
					(50.32	3.15	9.90	7.12	16.96)
4l		241—243[a] ($CHCl_3$–EtOH)	36	$C_{15}H_{11}F_2N_4O_3S_2$	45.34	2.79	9.56	14.10	16.14
					(45.12	2.55	9.39	13.94	16.18)
4m		290—292[b]	77	$C_{15}H_{11}F_2N_5O_3S$	47.49	2.92	10.02	18.46	8.45
					(47.72	2.64	9.90	18.21	8.70)
4n		186—187 (AcOEt)	38	$C_{17}H_{13}F_2N_3O_3S$	54.11	3.47	10.07	11.14	8.50
					(54.14	3.57	9.79	10.95	8.80)
4o		266—268[b]	66	$C_{16}H_{14}F_2N_2O_5S$	50.00	3.67	9.89	7.29	8.34
					(49.91	3.62	9.81	7.30	8.45)

a) Decomposition. *b*) The product was purified by reprecipitation with acid- and subsequent base-treatment or *vice versa*.

synthetic route involving the nucleophilic displacement of 7-fluoroquinolones with sodium hydrogensulfide followed by *S*-alkylation of the resulting 7-thioquinolones in order to prepare the cyclic aminothio compounds **10a—d** (Chart 3). Ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**5**)[10] was treated with 70% sodium hydrogensulfide in ethanol to give ethyl 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-mercapto-4-oxoquinoline-3-carboxylate (**6**). Hydrolysis of **6** under acidic conditions afforded the carboxylic acid **7**. Treatment of compound **7** with *N*-trityl-3-azetidinyl, -3-pyrrolidinyl, and -4-piperidinyl methanesulfonates (**8a—c**) gave compounds **9a—c**, respectively. The *N*-protecting groups in **9a—c** were removed by hydrolysis under acidic conditions, giving the corresponding C-7 thio-substituted derivatives **10a—c**. A similar treatment of **7** with 2-chloromethylmorpholine (**8d**) gave **10d**. Reductive methylation of **10a** and **10d** with formaldehyde–formic acid afforded the *N*-methyl derivatives **11a** and **11b**, respectively. The methanesulfonates **8a—c** were derived in two steps from 3-hydroxyazetidine, 3-hydroxypyrrolidine, and 4-hydroxypiperidine, respectively.

When 1,2-dichloroethane was used as a solvent, instead of ethanol, in the reaction of the ester **5** with 70% sodium hydrogensulfide, the 7-(2-chloroethyl)thio derivative **12** was exclusively produced without formation of the 7-mercapto derivative **6** (Chart 4). Separate treatment of **12** with piperazine and *N*-methylpiperazine, followed by acidic hydrolysis of the resulting esters, gave the 7-[2-(1-piperazinyl)ethyl]thio (**13a**) and 7-[2-(4-methyl-1-piperazinyl)ethyl]thio derivatives (**13b**), respectively.

Among the C-7 thio-substituted 6,8-difluoroquinolones (**4a—o**, **10a—d**, **11a,b**, and **13a,b**) thus prepared, the 7-(2-aminoethyl)thio derivative **4a** had the most potent antibacterial activity as discussed later. The 2-aminoethylthio group was hence introduced into the C-7 positions of the 5-amino-6,7,8-trifluoro-, 5-hydroxy-6,7,8-trifluoro-, and 5,6,7,8-tetrafluoroquinoline and 7-chloro-6-fluoro-1,8-naphthyridine derivatives (**14—17**) (Chart 5), because the C-7 amino-substituted derivatives of **14—17** had been found to possess a potent antibacterial activity.[4,11] Among compounds **18—21**, the 5-aminoquinoline derivative **18** was the most active. Then further modification of

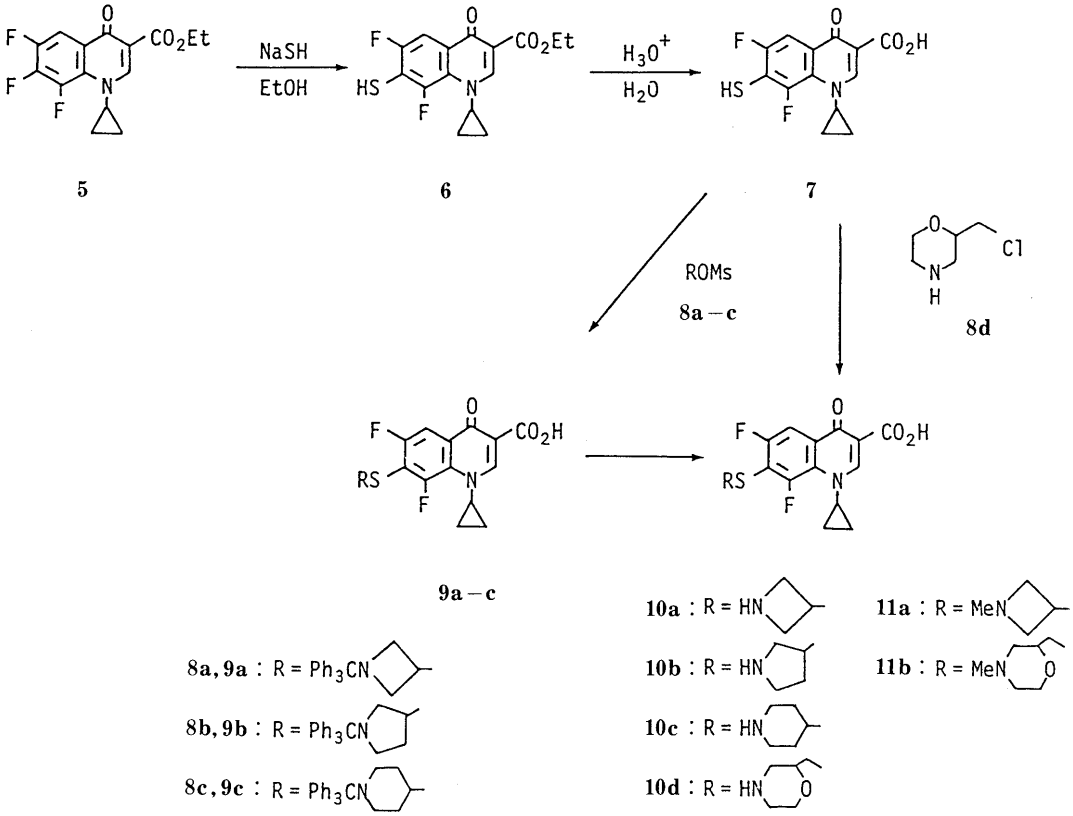


Chart 3

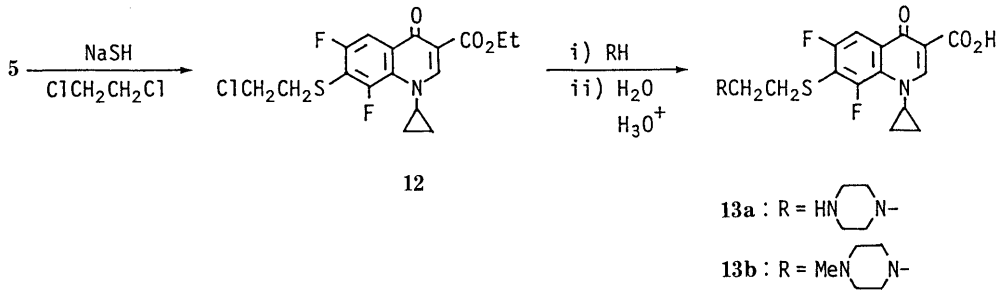
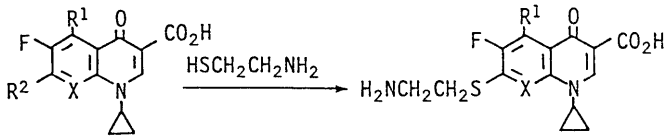


Chart 4



14 : $R^1 = NH_2$, $R^2 = F$, X = CF
15 : $R^1 = OH$, $R^2 = F$, X = CF
16 : $R^1 = R^2 = F$, X = CF
17 : $R^1 = H$, $R^2 = Cl$, X = N
18 : $R^1 = NH_2$, X = CF
19 : $R^1 = OH$, X = CF
20 : $R^1 = F$, X = CF
21 : $R^1 = H$, X = N

Chart 5

the 7-(2-aminoethyl)thio group was carried out in hopes of finding new thio-substituents contributing to an improved activity.

Treatment of ethyl 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**22**)[4] with 70% sodium hydrogensulfide in ethanol, followed by hydrolysis of the intermediate **23**, gave 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-mercapto-4-oxoquinoline-3-carboxylic acid (**24**). 1-Phthalimido-2-propyl, 2-phthalimido-1-propyl, and 2-phthalimido-2-methyl-1-propyl methanesulfonates (**26a—c**) were treated with **24** to give the corresponding 7-substituted derivatives **27a—c**. The phthalimido group of **27a—c** was deprotected with hydrazine, giving the desired 7-(1-amino-2-propyl)thio, 7-(2-amino-1-propyl)thio, and 7-(2-amino-2-methyl-1-propyl)thio derivatives (**28a—c**), respectively. The methanesulfonates **26a—c** thus used were prepared from the corresponding aminopropanols **25a—c** as shown in Chart 6.

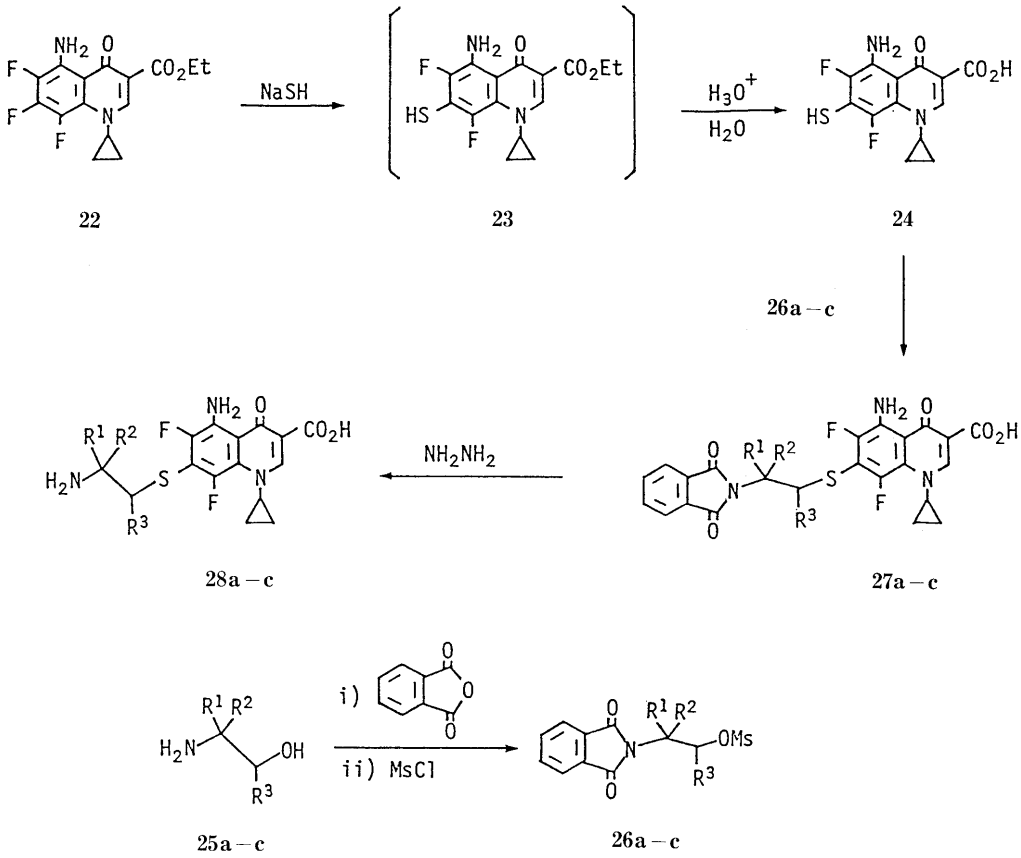
Antibacterial Activity The *in vitro* antibacterial activity of the C-7 thio derivatives was tested against representatives of gram-positive (*Staphylococcus aureus* 290P JC-1) and gram-negative (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* 12) bacteria. The screening results are summarized in Table III, in which the data for AT-4140 are included for comparison.

Among the 7-thio-substituted 6,8-difluoroquinolines (**4a—o**, **10a—d**, **11a,b**, and **13a,b**), the 7-(2-aminoethyl)thio

TABLE II. Physical Data for the Quinolones and Related Compounds

Compd.	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
				C	H	F	N	S
6	180—182[a]	77	$C_{15}H_{13}F_2NO_3S$	55.38	4.03	11.68	4.31	9.86
				(55.53	4.06	11.63	4.43	10.00)
7	231—231[a]	89	$C_{13}H_9F_2NO_3S \cdot 1/2H_2O$	50.98	3.29	12.41	4.59	10.47
				(51.03	3.01	12.31	4.48	10.66)
8a	131—134[a]	22	$C_{13}H_{23}NO_3S$	70.20	5.89		3.56	8.15
	(AcOEt–*n*-hexane)			(70.38	6.15		3.47	7.97)
8b	119—120	80	$C_{24}H_{25}NO_3S$	70.73	6.18		3.43	7.87
	(AcOEt)			(70.70	6.31		3.36	7.61)
8c	183—184	84	$C_{25}H_{27}NO_3S$	71.23	6.46		3.32	7.61
	(AcOEt)			(71.03	6.55		3.11	7.53)
9a	224–225	83	$C_{35}H_{28}F_2N_2O_3S \cdot 1/2H_2O$	69.64	4.84	6.29	4.64	5.31
	($CHCl_3$–EtOH)			(69.90	4.90	6.30	4.50	5.45)
9b	210—211	43	$C_{36}H_{30}F_2N_2O_3S \cdot 1/4H_2O$	70.51	5.01	6.20	4.57	5.22
	($CHCl_3$–EtOH)			(70.64	5.03	6.28	4.52	5.44)
9c	256—258	38	$C_{37}H_{32}F_2N_2O_3S \cdot 1/4H_2O$	69.35	5.34	5.93	4.37	5.00
	($CHCl_3$–EtOH)			(69.41	5.50	5.86	4.27	5.03)
10a	222—224[a]	96	$C_{16}H_{14}F_2N_2O_3S \cdot 2H_2O$	49.48	4.67	9.78	7.21	8.26
				(49.59	4.86	9.73	7.08	8.43)
10b	248—250	34	$C_{17}H_{16}F_2N_2O_2S \cdot HCl \cdot 1/4H_2O$[c]	50.15	4.33	9.29	6.88	7.87
	(H_2O–MeOH)			(50.36	4.18	9.18	6.99	7.59)
10c	277—279[a]	57	$C_{18}H_{18}F_2N_2O_3S$	56.83	4.77	9.99	7.36	8.43
				(56.56	5.05	10.07	7.26	8.61)
10d	268—272[a,b]	32	$C_{18}H_{18}F_2N_2O_4S \cdot 1/4H_2O$	53.93	4.65	9.48	6.99	8.00
				(53.85	4.36	9.29	7.03	8.27)
11a	190—191	53	$C_{17}H_{16}F_2N_2O_3S \cdot 1/4H_2O$	55.05	4.48	10.25	7.55	8.63
	($CHCl_3$–EtOH)			(55.31	4.43	9.98	7.34	8.78)
11b	48—50	63	$C_{19}H_{20}F_2N_2O_4S \cdot H_2O$	53.26	5.18	8.87	6.53	7.47
	(H_2O)			(52.99	4.93	8.74	6.35	7.66)
12	130—131	86	$C_{17}H_{16}ClF_2NO_3S$[d]	52.65	4.16	8.29	3.61	9.80
	(AcOEt)			(52.72	4.17	8.49	3.61	9.97)
13a	204—207[a,b]	50	$C_{19}H_{21}F_2N_3O_3S \cdot 2H_2O$	51.23	5.66	8.53	9.43	7.20
				(51.35	5.92	8.37	9.28	7.37)
13b	173—174	34	$C_{20}H_{23}F_2N_3O_3S$	56.72	5.47	8.97	9.92	7.57
	(EtOH)			(56.80	5.63	9.14	9.78	7.80)
18	215—219[a]	50	$C_{15}H_{15}F_2N_3O_3S \cdot 1/5H_2O$	50.18	4.26	8.93	11.70	10.59
				(49.88	4.38	9.21	11.43	10.41)
19	230—232[a]	70	$C_{15}H_{14}F_2N_2O_4S \cdot 1/4H_2O$	49.93	4.05	10.53	7.76	8.89
				(49.75	3.75	10.27	7.48	9.02)
20	205—209[a]	82	$C_{15}H_{13}F_3N_2O_3S \cdot 1/4H_2O$	49.65	3.75	15.71	7.72	8.84
				(49.85	3.76	15.87	7.56	9.05)
21	284—287[a]	82	$C_{14}H_{14}FN_3O_3S \cdot 7/4H_2O$	47.38	4.97	5.35	11.84	9.04
				(47.47	5.09	5.10	11.73	9.03)
24	>300	98	$C_{13}H_{10}F_2N_2O_3S \cdot 1/4H_2O$	49.28	3.26	12.00	8.84	10.10
	($CHCl_3$–EtOH)			(49.17	3.00	12.07	8.57	10.39)
26a	123—124	87	$C_{12}H_{13}NO_5S$	50.87	4.63		4.94	11.32
	(AcOEt)			(51.15	4.74		4.88	11.09)
26b	88—89	38	$C_{12}H_{13}NO_5S$	50.87	4.63		4.94	11.32
	(AcOEt)			(50.99	4.67		4.93	11.27)
26c	94—95	41	$C_{13}H_{15}NO_5S$	52.51	5.09		4.71	10.78
	(AcOEt)			(52.76	5.23		4.64	10.48)
27a	227—229	20	$C_{24}H_{19}F_2N_3O_5S$	57.71	3.83	7.61	8.41	6.42
	($CHCl_3$–EtOH)			(57.68	3.90	7.67	8.11	6.69)
27b	225—227	32	$C_{24}H_{19}F_2N_3O_5S$	57.71	3.83	7.61	8.41	6.42
	($CHCl_3$–EtOH)			(57.72	3.83	7.82	8.21	6.67)
27c	237—239	14	$C_{25}H_{21}F_2N_3O_5S$	58.47	4.12	7.40	8.18	6.24
	($CHCl_3$–EtOH)			(58.56	4.07	7.26	7.97	6.48)
28a	201—202[a]	58	$C_{16}H_{17}F_2N_3O_3S \cdot 3/4H_2O$	50.18	4.87	9.92	10.98	8.36
				(50.45	4.65	9.97	10.72	8.59)
28b	194—195[a]	57	$C_{16}H_{17}F_2N_3O_3S \cdot 3/4H_2O$	50.18	4.87	9.92	10.98	8.36
				(50.38	4.70	9.83	10.73	8.40)
28c	204—205[a]	25	$C_{17}H_{19}F_2N_3O_3S \cdot AcOH$	51.46	5.23	8.57	9.48	7.22
				(51.25	5.18	8.54	9.32	7.05)

a) The product was purified by reprecipitation with acid- and subsequent base-treatment or *vice versa*. *b*) Decomposition. *c*) Calcd for Cl: 8.71, Found: 8.70. *d*) Calcd for Cl: 9.14, Found: 8.91.



a : $R^1 = R^2 = H$, $R^3 = Me$
b : $R^1 = Me$, $R^2 = R^3 = H$
c : $R^1 = R^2 = Me$, $R^3 = H$

Chart 6

derivative **4a** is the most active against gram-negative bacteria and has a well balanced potency *versus* all the bacteria tested. Against gram-positive *S. aureus*, the 7-methylthio (**4c**) and 7-(4-aminophenyl)thio derivatives (**4h**) are slightly more active than **4a**, but less active against gram-negative bacteria. In general, the heteroarylthio derivatives (**4j**—**n**) display obviously a decreased activity. The heterocyclic (alkyl)thio groups (**10a**—**d**, **11a**,**b**, and **13a**,**b**) cause a significant overall decrease in activity. Introduction of a carboxyl group to the aminoethylthio substituent, giving **4o**, is deleterious to activity.

A comparison of the activities of the 7-(2-aminoethyl)thio derivatives (**4a** and **18**—**20**) shows that contribution of their C-5 variants to activity are in increasing order OH (**19**) < F (**20**) < H (**4a**) < NH_2 (**18**). Thus compound **18** is notably the most potent against the bacteria tested, being essentially as active as AT-4140. The 1,8-naphthyridine derivative (**21**) is interestingly much less active than its quinolone counterpart (**4a**) against *S. aureus*, of all bacteria tested. Insertion of one or two additional methyl groups into the aminoethylthio side chain of **18**, giving **28a**—**c**, results in a strikingly unfavorable influence on activity. Thus **28a**—**c** are 60 times less active against *S. aureus* and 2—16 times less active against *E. coli* and *P. aeruginosa* than 18.

In conclusion, a series of the C-7 thio-substituted quinolones were synthesized by efficient synthetic routes. Compound **18** with the C-7 2-aminoethylthio and C-5 amino groups was found to possess a potent *in vitro* antibacterial activity which compared favorably with that of AT-4140.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 spectrometer. The ^{1}H-NMR spectra were taken at 60 MHz with a Varian EM-360A or at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS D-300 or on a Hitachi RMU-6L spectrometer.

7-(2-Aminoethyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (4a) According to Domagala's method, a mixture containing thiazolidine (1.56 g, 17.5 mmol), 60% sodium hydride (in mineral oil, 1.0 g, 17.5 mmol), and *N*,*N*-dimethylformamide (DMF) (15 ml) was stirred for 1 h at room temperature. 1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**3**)[10] (1.0 g, 3.5 mmol) was added to the mixture. The resulting mixture was stirred for 1 h at the same temperature and then concentrated to dryness *in vacuo*. The residue was taken up in 10% AcOH. The mixture was filtered to remove the insoluble material. The filtrate was neutralized with 10% NaOH and the precipitate was collected by filtration to give **4a** (335 mg, 28%). IR (KBr) cm^{-1}: 3400, 3080, 1620. ^{1}H-NMR (80 MHz, NaOD) δ: 0.95—1.36 (4H, m), 2.55—2.85, 2.85—3.18 (each 2H, m), 3.75—4.25 (1H, m), 7.75 (1H, dd, J = 10, 2 Hz), 8.55 (1H, s). MS *m*/*z*: 328 (M^+), 281.

7-Thio-substituted 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (4a—o) General Procedure: A mixture containing

TABLE III. *In Vitro* Antibacterial Activity[a)]

Compd.	Minimum inhibitory concentrations (μg/ml)		
	S. aureus 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
4a	0.39	0.1	0.78
4b	3.13	0.39	6.25
4c	0.2	0.2	1.56
4d	0.78	0.78	3.13
4e	0.78	3.13	>100
4f	0.78	0.39	3.13
4g	0.78	3.13	12.5
4h	0.2	1.56	6.25
4i	0.39	1.56	6.25
4j	12.5	6.25	100
4k	0.39	0.78	6.25
4l	6.25	12.5	100
4m	6.25	25	>100
4n	6.25	6.25	100
4o	50	50	>100
10a	0.78	0.39	0.78
10b	0.78	3.13	1.56
10c	0.39	0.78	3.13
10d	0.78	0.78	3.13
11a	1.56	0.39	1.56
11b	1.56	3.13	12.5
13a	1.56	3.13	25
13b	1.56	1.56	12.5
18	0.05	0.025	0.1
19	1.56	1.56	6.25
20	3.13	0.78	3.13
21	6.25	0.1	0.39
28a	3.13	0.1	0.78
28b	3.13	0.05	0.78
28c	3.13	0.1	1.56
AT-4140	0.05	0.025	0.2

a) See the experimental section.

3 (3.7 mmol), an appropriate thiol (4.5 mmol), Et_3N (7.4 mmol), and MeCN (20 ml) was heated to reflux for 2 h and then allowed to cool. The resulting solid was collected by filtration and dissolved in 10% NaOH. The mixture was filtered to remove the insoluble material. The filtrate was neutralized with 10% AcOH. The precipitate was recrystallized from the solvent given in Table I to yield the corresponding 7-thio-substituted derivatives **4a**—**o** (Table I).

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-mercapto-4-oxoquinoline-3-carboxylate (6) A mixture containing ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**5**)[10] (1.6 g, 5 mmol), 70% sodium hydrogensulfide (600 mg, 7.5 mmol), and EtOH (20 ml) was heated to reflux for 10 min, and then allowed to cool. The resulting solid was collected by filtration and dissolved in 10% NaOH. The mixture was filtered to remove the insoluble material. The filtrate was neutralized with 10% AcOH to give **6** (1.25 g, 77%). IR (KBr) cm^{-1}: 3420, 1720, 1695, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.00—1.35 (4H, m), 1.40 (3H, t, J=6 Hz), 3.60—4.05 (1H, m), 4.36 (2H, q, J=6 Hz), 7.97 (1H, dd, J=9, 2 Hz), 8.53 (1H, s).

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-mercapto-4-oxoquinoline-3-carboxylic Acid (7) A mixture containing **6** (3.1 g, 10 mmol), AcOH (16 ml), water (12 ml), and H_2SO_4 (2 ml) was heated to reflux for 1 h and then the reaction mixture was poured into ice-water. The resulting solid was collected by filtration and recrystallized from $CHCl_3$–EtOH to give **7** (2.65 g, 89%). IR (KBr) cm^{-1}: 3080, 1720, 1610. ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 1.00—1.35 (4H, m), 4.05—4.20 (1H, m), 8.05 (1H, dd, J=7.5, 2 Hz), 8.77 (1H, s), 14.28 (1H, br s).

***N*-Trityl-3-azetidinyl, -3-pyrrolidinyl and -4-piperidinyl Methanesulfonates (8a—c)** General Procedure: A solution containing 3-hydroxyazetidine, 3-hydroxypyrrolidine or 4-hydroxypiperidine (10 mmol), and Et_3N (15 mmol) in $CHCl_3$ (20 ml) was stirred while ice-cooled. Tritylchloride (10 mmol) was added to the mixture. The reaction mixture was stirred for 1 h at the same temperature and then poured into water. The organic layer was separated and concentrated to dryness *in vacuo*. The residue was dissolved in toluene (20 ml). Et_3N (20 mmol) and methanesulfonyl chloride (10 mmol) were added to the toluene solution while ice-cooled. The resulting mixture was stirred for 1 h at room temperature and filtered to remove the insoluble material. The filtrate was concentrated to dryness *in vacuo*, and the residue was recrystallized from the solvent given in Table II to yield the corresponding methanesulfonates **8a**—**c**.

7-(*N*-Trityl-3-azetidinyl, -3-pyrrolidinyl, and -4-piperidinyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (9a—c) General Procedure: A mixture containing **7** (8 mmol), the mesylate **8a**—**c**, Et_3N (24 mmol) and MeCN (60 ml) was heated to reflux for 6 h. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in a mixture of water and $CHCl_3$. The organic layer was concentrated to dryness *in vacuo* and the residue was recrystallized from the solvent given in Table II to yield the corresponding compounds **9a**—**c**.

7-(3-Azetidinyl, 3-Pyrrolidinyl, and 4-Piperidinyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (10a—c) General Procedure: A mixture containing **9a**—**c** (1 mmol) and 10% HCl (10 ml) was heated for 0.5 h at 80 °C and then allowed to cool. The resulting solid was collected by filtration and dissolved in water. The mixture was filtered to remove the insoluble material and the filtrate was neutralized with 10% NaOH to give the corresponding compounds **10a**—**c**.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(2-morpholinylmethyl)thio-4-oxoquinoline-3-carboxylic Acid (10d) Compound **10d** was prepared from **7** and 2-chloromethylmorpholine according to the same procedure for **9a**—**c**.

7-(3-Methyl-1-azetidinyl and 4-Methyl-2-morpholinylmethyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (11a and 11b) General Procedure: A mixture containing **10a** or **10d** (5 mmol), formic acid (10 ml), and formaldehyde (10 ml) was heated to reflux for 16 h. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in water and the mixture was neutralized with NaOH. The resulting mixture was extracted with $CHCl_3$. The organic layer was concentrated to dryness *in vacuo* and the residue was recrystallized from the solvent given in Table II to yield **11a** or **11b**.

Ethyl 7-(2-Chloroethythio)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (12) A mixture containing **5** (5 g, 16 mmol), 70% sodium hydrogensulfide (2.6 g, 32 mmol), Et_3N (3.3 g, 32 mmol) and 1,2-dichloroethane (100 ml) was stirred for 1.5 h at room temperature. The resulting solid was collected by filtration and dissolved in a mixture of water and $CHCl_3$. The organic layer was concentrated to dryness *in vacuo* and the residue was recrystallized from AcOEt to give **12** (5.1 g, 86%). IR (KBr) cm^{-1}: 1720, 1610. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 1.05—1.20 (4H, m), 1.40 (3H, t, J=6.5 Hz), 3.15—3.75 (4H, m), 3.75—4.15 (1H, m), 4.40 (2H, q, J=6.5 Hz), 8.03 (1H, dd, J=8, 2 Hz), 8.59 (1H, s).

7-[2-(1-Piperazinyl)ethyl]thio- and 7-[2-(4-Methyl-1-piperazinyl)ethyl]-thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (13a and 13b) General Procedure: A mixture containing **12** (2.6 mmol), piperazine or *N*-methylpiperazine (11.6 mmol), and MeCN (30 ml) was heated to reflux for 3 h. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in a mixture of water and $CHCl_3$. The organic layer was concentrated to dryness *in vacuo*. The residue was suspended in 10% NaOH. The suspension was heated for 1 h at 90—100 °C and then neutralized with 10% AcOH. The precipitate was collected by filtration to give **13a** or **13b**.

5-Amino-, 5-Hydroxy-, and 5-Fluoro-7-(2-aminoethyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (18—20) and 7-(2-Aminoethyl)thio-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (21) General Procedure: A mixture containing 5-amino-, 5-hydroxy or 5-fluoro derivatives (**14**—**16**)[4] of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids, or 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**17**)[12] (6.7 mmol), aminoethanethiol (20 mmol), Et_3N (39.6 mmol), and MeCN (40 ml) was heated to reflux for 1 h. The resulting solid was collected by filtration and dissolved in 10% AcOH. The solution was neutralized with 10% NaOH to give the precipitate, which was collected by filtration, giving the corresponding 7-(2-aminoethyl)thio derivatives **18**—**21**.

5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-mercapto-4-oxoquinoline-3-carboxylic Acid (24) A mixture containing **22** (32.6 g, 0.1 mol), 70% sodium hydrogensulfide (17.6 g, 0.22 mol) and EtOH (500 ml) was heated to reflux for 1.5 h at 70—75 °C. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in a mixture of AcOH (240 ml), water (180 ml) and H_2SO_4 (30 ml). The resulting mixture was heated for 0.5 h at 90—100 °C and added to a mixture of water and ice. The resulting

solid was collected by filtration and recrystallized from $CHCl_3$–EtOH to give **24** (30.7 g, 98%). IR(KBr) cm^{-1}: 3450, 3330, 1710, 1630. ^1H-NMR (80 MHz, DMSO-d_6) δ: 0.85—1.25 (4H, m), 3.75—4.25 (1H, m), 8.50 (1H, s).

Phthalimidopropyl Methanesulfonates (26a—c) General Procedure: A mixture containing 1-amino-2-propanol (**25a**), 2-amino-1-propanol (**25b**) or 2-amino-2-methyl-1-propanol (**25c**) (6.7 mmol), phthalic anhydride (8 mmol), and toluene (50 ml) was heated to reflux for 5 h, during which period the water formed was removed by the Dean Stark apparatus. The mixture was diluted with water and made alkaline with 10% NaOH. The organic layer was concentrated to dryness *in vacuo* and the residue was recrystallized from AcOEt. Methanesulfonyl chloride (8 mmol) was added to a solution of the product and Et_3N (10 mmol) in toluene (100 ml) while ice-cooled. The mixture was stirred for 1.5 h at room temperature and then dissolved in a mixture of water and $CHCl_3$. The organic layer was concentrated to dryness *in vacuo* and the residue was recrystallized from the solvent given in Table II to yield the corresponding mesylates **26a—c**.

7-(Phthalimidopropyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (27a—c) General Procedure: A mixture containing **24** (10 mmol), the mesylate **26a—c** (12 mmol), Et_3N (15 mmol), and MeCN (50 ml) was heated to reflux for 4 h. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in a mixture of water and $CHCl_3$. The organic layer was concentrated to dryness *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give the corresponding 7-(phthalimidopropyl)thio derivatives **27a—c**.

7-(Aminopropyl)thio-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids (28a—c) General Procedure: A mixture containing **27a—c** (2 mmol), hydrazine hydrate (30 mmol), and MeOH (30 ml) was heated to reflux for 3 h. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in 10% AcOH. The solution was filtered to remove the insoluble material. The filtrate was neutralized with NH_4OH to give the corresponding 7-(aminopropyl)thio derivatives **28a—c**.

Biological Screenings The *in vitro* antibacterial activity was tested by the same method reported in the previous paper.[13]

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