Synthesis and Antibacterial Activity of Novel 7-Substituted-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid Derivatives

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A series of 7-substituted-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives (2a—l) was prepared and evaluated for antibacterial activity. These compounds were obtained by deacylation of 4-benzoyloxy-2-(1-chloro-2-fluoroethyl)thio-6,7-difluoroquinoline-3-carboxylate (10) and subsequent intramolecular cyclization followed by substitution with cyclic amines and then hydrolysis.

The intramolecular cyclization reaction of 18, one of the diastereomers (17, 18) revealed that the cyclization reaction proceeded through an inversion to afford (−)-11a in good chemical and optical yield. The enantiomers of 2a were prepared from the enantiomers of 11a, which were obtained by the optical resolution of the racemate using high-performance liquid chromatography (HPLC).

Compounds 2a,b showed excellent *in vitro* and *in vivo* antibacterial activity against both gram-negative and gram-positive bacteria including quinolone and Methicillin-resistant *Staphylococcus aureus*.

Key words antibacterial agent; fluoroquinolone; optically active isomer; 1-fluoromethyl derivative; optical resolution; 4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid

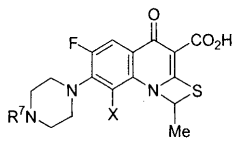
Quinolone antibacterial agents are one of the most attractive drugs in the antiinfective chemotherapy field, and a great number of compounds have been synthesized. In our research on new quinolone antibacterial agents, we have been studying tricyclic compounds characterized by a sulfur-bridge between C-2 and the substituent at N-1 of the quinolones.[1] Among these derivatives, 6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**1a**, NM394) showed excellent *in vitro* antibacterial activity.

Within a relatively short period after the introduction of the quinolones into clinical practice, rising levels of resistance to these antibacterial agents were noted in some bacteria, particularly in Methicillin-resistant *Staphylococcus aureus* (MRSA). The need for a useful agent for the treatment of infectious diseases caused by the bacteria such as quinolone-resistant MRSA has become extremely important.

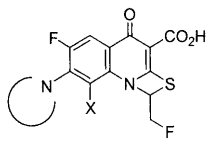
In recent years, quinolone antibacterial agents possessing a fluorine atom at the N-1 substituent have been developed. Namely, DU-6859 a (**3**) was reported to show broad activity against both gram-negative and gram-positive bacteria including resistant bacteria such as quinolone-resistant MRSA,[2] and fleroxacin (**4**) was reported to show good oral efficacy against systemic infections due to good bioavailability.[3]

These reports suggested that the introduction of a fluorine at the C-1 methyl group in the thiazetoquinolone should enhance the *in vitro* and *in vivo* antibacterial activity against various bacteria including quinolone-resistant MRSA and also improve its bioavailability. Therefore we synthesized a series of 1-fluoromethylthiazetoquinolone derivatives and examined the antibacterial activity.

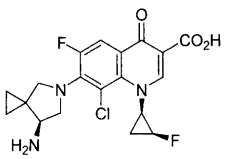
In this paper we report the synthesis and the antibacterial activity of the 1-fluoromethylthiazetoquinolone derivatives **2**. We also examined the mechanism of the intramolecular cyclization reaction forming the thiazetoquinolone ring system.



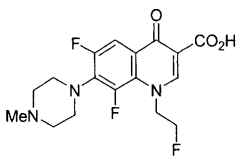
1a:R^7=H, X=H (NM394)
b:R^7=Me, X=H
c:R^7=Me, X=OMe



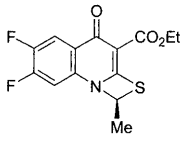
2:X=H,OMe,F



3 (DU-6859a)



4 (fleroxacin)



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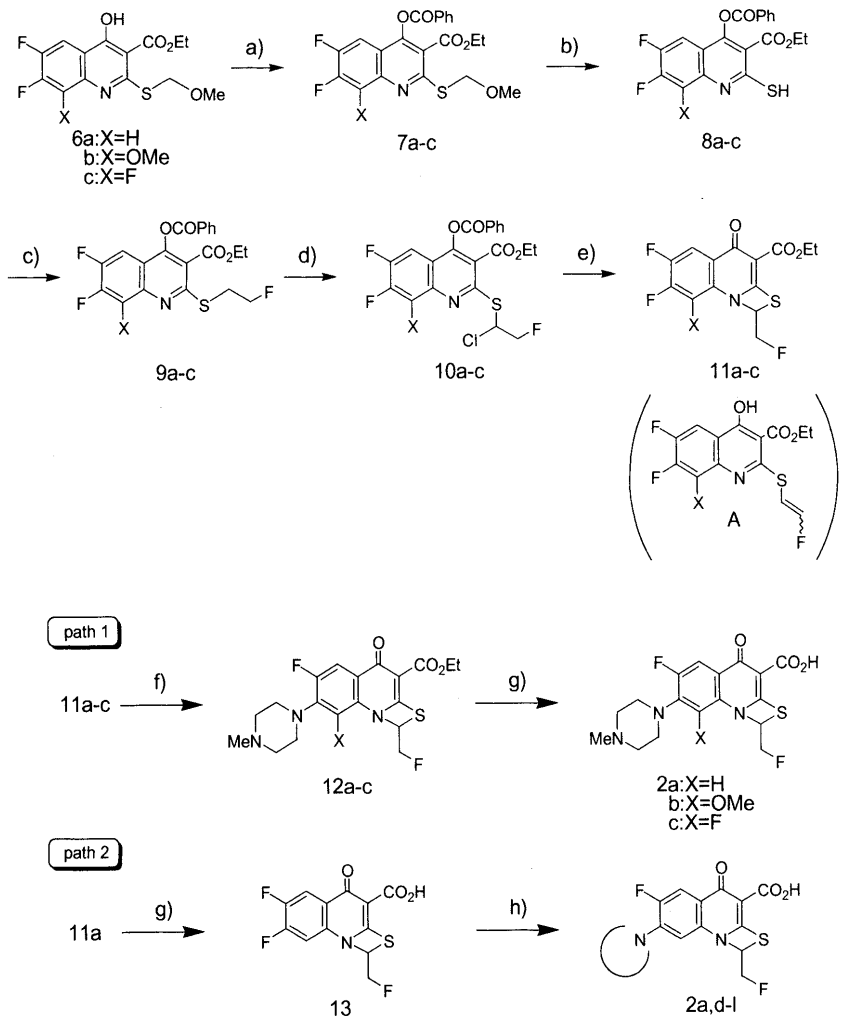


a)benzoyl chloride,pyridine b)c.HCl,EtOH c)$BrCH_2CH_2F$,$NaHCO_3$,DMF d)SO_2Cl_2,*n*-hexane e)Et_3N,H_2O,THF f)*N*-methylpiperazine,DMF g)H_2SO_4,H_2O h)cyclic amine,DMF

Chart 1

Chemistry

The 1-fluoromethyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives (**2**) were synthesized as illustrated in Chart 1. Compounds (**6a**—**c**)[1] were treated with benzoyl chloride to give the 4-benzoyloxy compounds (**7a**—**c**). Treatment of **7a**—**c** with hydrochloric acid in ethanol yielded the 2-mercapto compounds (**8a**—**c**), which were converted to the 2-(2-fluoroethyl)thio compounds (**9a**—**c**) by treatment with 1-bromo-2-fluoroethane in the presence of sodium hydrogencarbonate. Chlorination of **9a**—**c** with sulfuryl chloride gave the 2-(1-chloro-2-fluoroethyl)thio compounds (**10a**—**c**). When **10a**—**c** were treated with triethylamine in the presence of water, the hydrolysis of the benzoate and the intramolecular cyclization reaction occurred successively to afford the key intermediates (**11a**—**c**).[4] Compounds **11a**—**c** were treated with 1-methylpiperazine in *N*,*N*-dimethylformamide (DMF) to provide the ethyl esters (**12a**—**c**), which were converted to the carboxylic acids (**2a**—**c**) (path 1). Compound **2a** was also obtained *via* an alternative pathway (path 2); hydrolysis of **11a** with sulfuric acid gave the carboxylic acid (**13**), which was treated with 1-methylpiperazine to afford **2a**. This procedure was used to synthesize the other 8-unsubstituted analogs (**2d**—**l**).

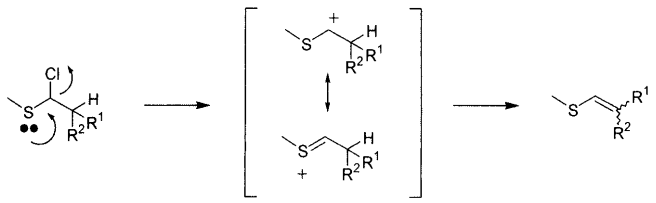


Fig. 1

In the course of the intramolecular cyclization reaction of **10a**—**c**, α-alkenylsulfide (A), a predicted β-eliminated by-product, was not obtained at all, although α-chlorosulfides bearing a β-proton are well known to be converted to the α-alkenylsulfides as shown in Fig. 1.[5] There have been only a few studies on the intramolecular cyclization reaction of compounds which have an α-chlorosulfenyl moiety as an electrophile.[6] In those cases, the conformation of the α-chlorosulfenyl group is fixed such that the β-elimination reaction cannot occur, that is, the lone pair of electrons on the sulfur atom are not placed in an *anti* position to the chlorine on the α-carbon atom.

On the other hand, the β-chlorosulfenyl moiety in **10a**—**c** does not have any conformational restriction to inhibit the β-

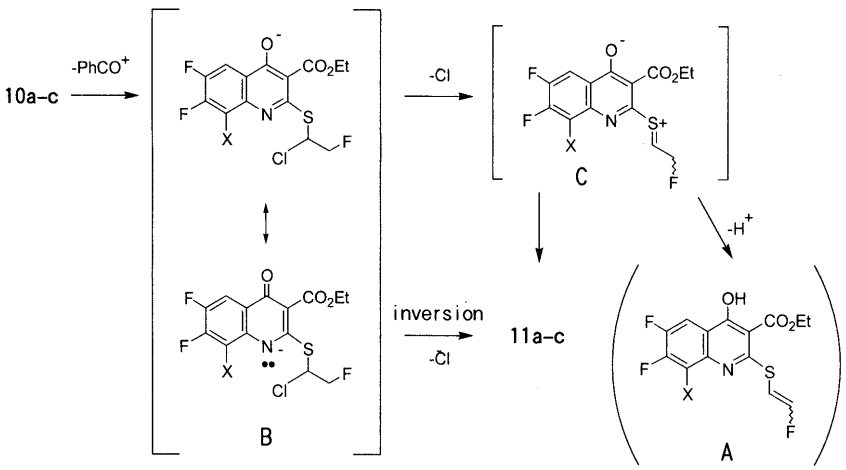
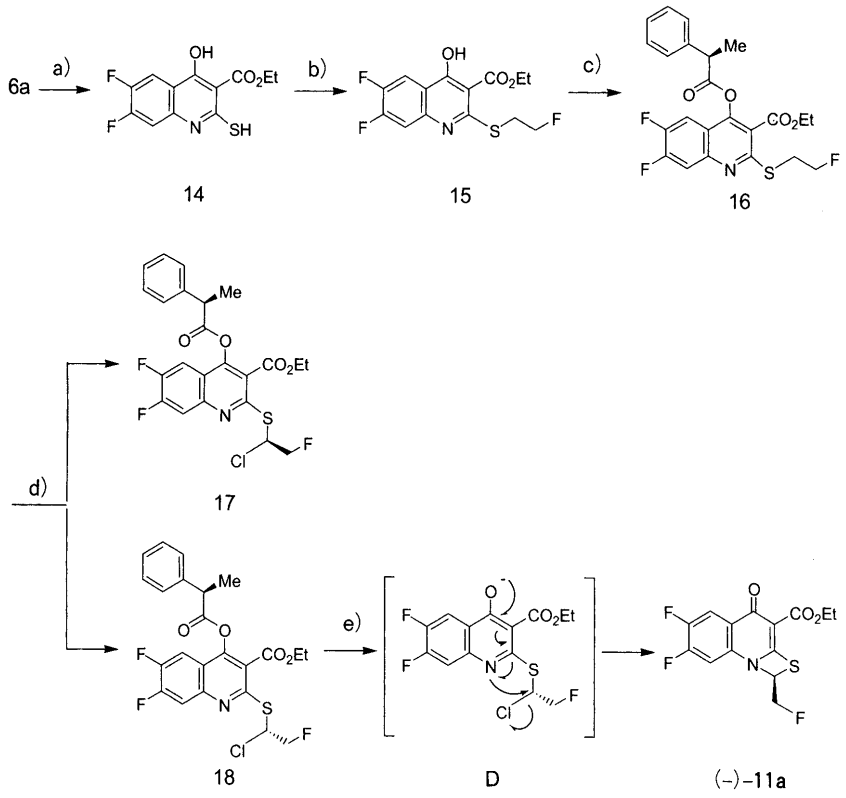


Fig. 2



a)H_2SO_4,EtOH b)$BrCH_2CH_2F$,$NaHCO_3$,DMF c)(*R*)-(-)-2-phenylpropionyl chloride,Et_3N,$CHCl_3$
d)SO_2Cl_2,*n*-hexane,recrystallization e) Et_3N,H_2O,THF

Chart 2

elimination reaction. We think the reason for the inhibition of the β-elimination reaction is that the lone pair of electrons on the sulfur atom of the anion (B) delocalizes to the quinolone ring and does not attack the α-carbon atom. Therefore B is not converted to the sulfenium cation (C) from which both A and **11a**—**c** could be obtained (Fig. 2).

In order to clarify the cyclization process more precisely, we examined the reaction of **18**, one of the diastereomers (**17**, **18**), which was obtained from **16** as illustrated in Chart 2. Compound **16** was synthesized from **6a** by using optically active (2*R*)-2-phenylpropionyl group as the hydoxy-protecting group at the C-4 position. In the same manner as for the synthesis of **10a**—**c**, **16** was converted to the diastereo mixture of ethyl 2-[(1*S*) or (1*R*)-1-chloro-2-fluoroethyl]thio-6,7-difluoro-4-[(2*R*)-2-phenylpropionyloxy]quinoline-3-carboxylate, **17** and **18**. Compound **18** was obtained by repeated fractional recrystallization of the mixture from isopropyl ether. The deacylation and the subsequent cyclization reaction of **18** afforded (−)-**11a** in good chemical and optical yield. This finding proves that the intramolecular cyclization reaction of **18** proceeds through an inversion mechanism *via* D (Chart 2), and the possibility of the pathway *via* C shown in Fig. 2 is excluded.

For the synthesis of the optical isomers (+)-**2a** and (−)-**2a** used for the antibacterial test, we used the optically pure intermediates (+)-**11a** and (−)-**11a**, which were obtained as il-

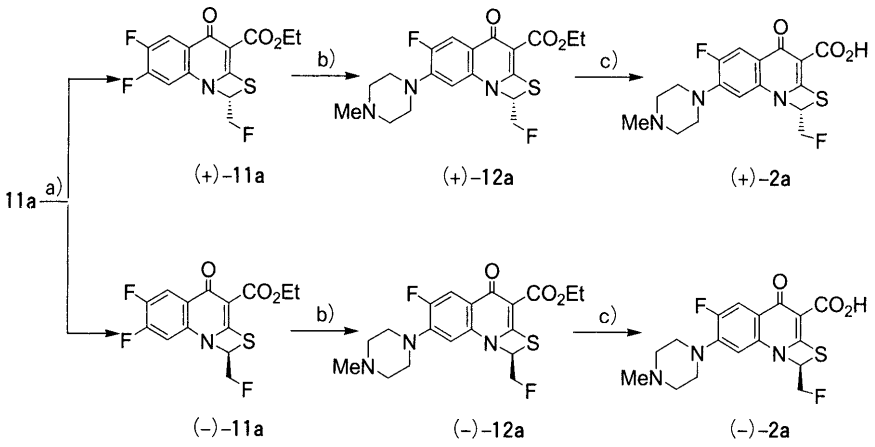


Chart 3

lustrated in Chart 3. The optical resolution of **11a** was achieved by using HPLC on a chiral stationary phase (Daicel Chiralcel OD) to yield the optically pure ethyl esters (+)-**11a** and (−)-**11a**, which were converted to the corresponding 7-(4-methyl-1-piperazinyl) analogs (+)-**2a** and (−)-**2a** *via* (+)-**12a** and (−)-**12a** respectively in the same manner as for the synthesis of the racemate **2a**.

The absolute configuration of (−)-**11a** was determined by comparing its circular dichroism (CD) spectrum with that of (*S*)-(−)-**5**[7] whose absolute configuration was determined by a single crystal X-ray analysis.[8] The CD spectra of (−)-**11a**, (+)-**11a**, and (*S*)-(−)-**5** are shown in Fig. 3. They showed typical split Cotton curves at four-wavelength maximum. While (−)-**11a** displayed negative Cotton effects in the 225, 250, and 308 nm region and a positive transition in the 270 nm region, (+)-**11a** gave a CD spectrum which was the mirror image of the other enantiomer. The CD spectra of (−)-**11a** and (*S*)-(−)-**5** were almost identical, which suggested that the absolute configuration at the C-1 position of (−)-**11a** is *S*.

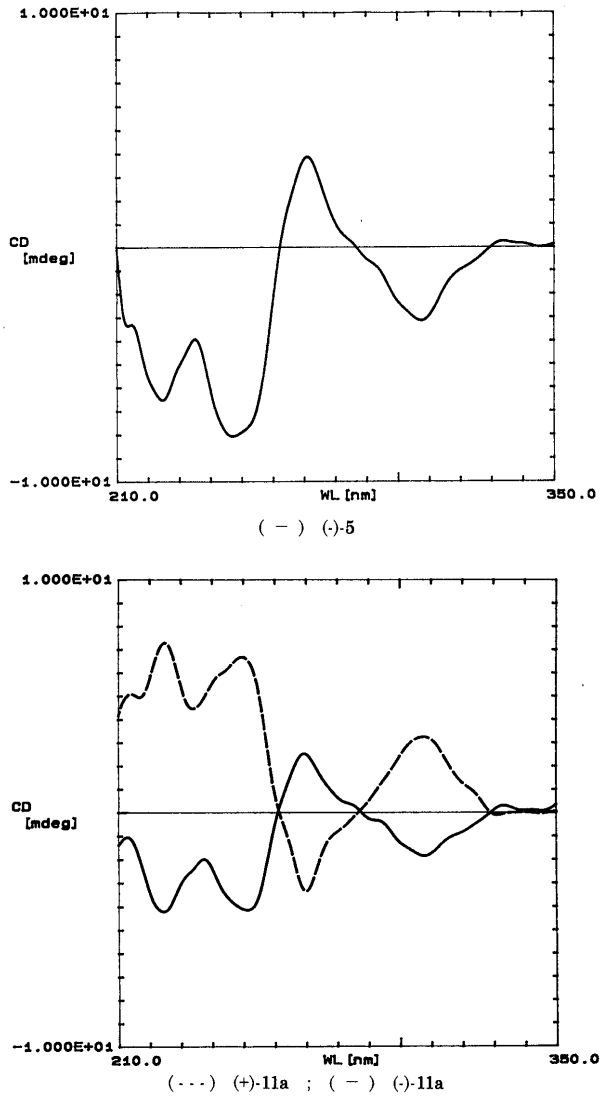


Fig. 3. Correlation of the Configuration of Enantiomerically Pure **5**, (+)-**11a**, and (+)-**11b** by Circular Dichroism CD

Solvent: MeOH; c=0.010 mg/ml.

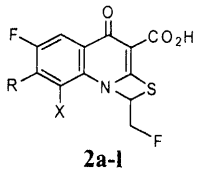
Results and Discussion

Table 1 summarizes the *in vitro* antibacterial activity of the 1-fluoromethylthiazetoquinolone derivatives against 5 gram-positive bacteria (*Staphylococcus aureus* 209-P JC-1, *Staphylococcus aureus* SMITH, *Enterococcus faecalis* ATCC 29212, MRSA OWPH 1984 [quinolone-susceptible MRSA], and MRSA KC-5879 [quinolone-resistant MRSA]) and 4 gram-negative bacteria (*Escherichia coli* NIH JC-2, *Escherichia coli* KC-14, *Serratia marcescens* IFO3736, and *Pseudomonas aeruginosa* IFO3445). The data for **1a**, **1b**, **1c**, ciprofloxacin (CPFX), and ofloxacin (OFLX) are included for comparison.

The order of the *in vitro* activity of substitution at the C-7 position against gram-positive bacteria including quinolone-susceptible MRSA was 3-hydroxyazetizine (**2l**)>morpholine (**2f**)>piperazine analogs (**2a**, **2d**, **2e**)>thiomorpholine (**2g**)>piperidine analogs (**2h**—**k**). Among the 8-unsubstituted-1-fluoromethylthiazetoquinolone derivatives, 7-(3-hydroxyazetizine) analog **2l** showed the most potent antibacterial activity against gram-positive bacteria including quinolone-susceptible MRSA. The 7-(4-methyl-1-piperazinyl) analog **2a** and 7-morpholino analog **2f** showed good antibacterial activity against quinolone-resistant MRSA, while other analogs including 7-(3-hydroxyazetizine) analog **2l** as well as **1a** and OFLX showed no significant activity.

Against gram-negative bacteria the order of *in vitro* activ-

Table 1. *In Vitro* Antibacterial Activity (MIC μg/ml)



2a-l

Comd. No.	R	X	Gram-positive bacteria					Gram-negative bacteria			
			Staphylococcus aureus		*Enterococcus faecalis*	MRSA		*Escherichia coli*		*Serratia marcescens*	*Pseudomonas aeruginosa*
			FDA 209P JC-1	SMITH	ATCC 29212	OWPH 1984	KC-5879[a]	NIH JC-2	KC-14	IFO 3736	IFO 3445
2a	4-Methylpiperazinyl	H	0.1	0.1	0.39	0.1	1.56	0.05	0.05	0.2	0.39
2b	4-Methylpiperazinyl	MeO	0.1	0.05	0.39	0.1	0.78	0.05	0.025	0.39	0.78
2c	4-Methylpiperazinyl	F	0.2	0.2	1.56	0.39	3.13	0.2	0.05	0.39	0.78
2d	Piperazinyl	H	0.05	0.1	0.78	0.39	6.25	0.025	0.025	0.1	0.39
2e	*cis*-3,5-Dimethylpiperazinyl	H	0.1	0.1	0.78	0.2	6.25	0.1	0.05	0.78	0.78
2f	Morpholino	H	0.1	0.05	0.78	0.05	3.13	0.39	0.2	1.56	1.56
2g	Thiomorpholino	H	0.2	0.1	1.56	0.2	12.5	3.13	0.78	12.5	6.25
2h	4-Hydroxypiperidino	H	0.2	0.05	0.78	0.39	12.5	0.2	0.2	0.78	0.78
2i	4-Aminopiperidino	H	0.1	0.2	1.56	0.78	12.5	0.2	0.2	0.78	1.56
2j	4-Hydroxymethylpiperidino	H	0.39	0.1	3.13	0.2	6.25	3.13	3.13	12.5	6.25
2k	4-Aminomethylpiperidino	H	0.2	0.78	3.13	0.78	25	3.13	1.56	25	12.5
2l	3-Hydroxyazetizino	H	0.0125	≦0.00625	0.78	0.025	6.25	0.39	0.05	1.56	1.56
(+)-**2a**	4-Methylpiperazinyl	H	0.39	0.2	3.13	0.39	50	0.2	0.1	0.78	0.78
(−)-**2a**	4-Methylpiperazinyl	H	0.025	0.05	0.2	0.1	0.78	0.025	0.0125	0.2	0.2
1a			0.05	0.1	0.39	0.39	6.25	0.0125	0.0125	0.05	0.05
1b			0.05	0.05	0.2	0.1	6.25	0.05	0.025	0.05	0.2
1c			0.2	0.1	0.39	0.1	1.56	0.2	0.1	0.39	0.78
CPFX			0.1	0.1	0.39	0.78	12.5	0.0125	0.0125	0.1	0.05
OFLX			0.2	0.1	1.56	0.2	6.25	0.1	0.025	0.39	0.78

a) Quinolone-resistant.

ity was different: *i.e.* **2a**, **2d**, **2e**>**2h**, **2i**>**2l**>**2f**>**2g**, **2j**, **2k**. Among the 8-unsubstituted-1-fluoromethylthiazetoquinolone derivatives, the 7-piperazinyl analogs (**2a**, **2d**, **2e**) showed the most balanced *in vitro* activity against both gram-negative and gram-positive bacteria including quinolone-resistant MRSA. This result is in agreement with the generally accepted structure–activity relationship (SAR) of the substitution at the C-7 position of the 1-methylthiazetoquinolone derivatives.[1a)]

The introduction of a fluorine at the C-1 methyl group of the thiazetoquinolone derivatives influenced their *in vitro* antibacterial activity. In the 8-unsubstituted-7-(4-methyl-1-piperazinyl) derivatives, the antibacterial activity of 1-fluoromethyl analog **2a** against quinolone-resistant MRSA was more potent than that of the 1-methyl analog (**2a** *vs.* **1b**), although the activity of **2a** against other bacteria was almost the same or less potent in comparison with that of **1b**. However, in the 7-(1-piperazinyl) derivatives, the antibacterial activity of 1-fluoromethyl analog **2d** was almost equal to that of 1-methyl analog **1a** against gram-positive bacteria including quinolone-resistant MRSA, but much less potent than that of **1a** against gram-negative bacteria. The introduction of a methoxy group at the C-8 position of **2a** slightly increased *in vitro* antibacterial activity against gram-positive bacteria including quinolone-resistant MRSA (**2b** *vs.* **2a**). The activity of **2b** was slightly more potent than that of the corresponding 1-methyl analog (**1c**).

The addition of a fluorine at the C-8 position decreased the *in vitro* antibacterial activity (**2c** *vs.* **2a**). This finding is different from what is observed with 1-methyl-7-(4-methyl-1-piperazinyl)thiazetoquinolone.[1a)]

Recently, various optically active tricyclic quinolones have been prepared.[9)] In those compounds, the (*S*)-isomer has been reported to be more potent than the (*R*)-isomer in *in vitro* antibacterial activity. In the previous paper, we also reported the synthesis and antibacterial activity of the optically active isomers of **1a**.[7)]

We prepared optically active (+)-**2a** and (−)-**2a** and examined the *in vitro* antibacterial activity. The activity of (−)-**2a** was 2 to 64 times more potent than that of (+)-**2a** and about twice as active as the racemate (±)-**2a** against both gram-positive and gram-negative bacteria tested. This result is in agreement with the generally accepted SAR for antibacterial activity and the stereochemistry of quinolone derivatives.[7,10)]

The efficacy of selected 1-fluoromethyl analogs against systemic infections in mice caused by *Staphylococcus aureus* SMITH, *Staphylococcus aureus* KC-5879 [quinolone-resistant MRSA], and *Escherichia coli* KC-14 is shown in Table 2. Data for **1a**, **1b**, **1c**, and OFLX are included for comparison.

In general, the *in vivo* antibacterial activity of 1-fluoromethyl-7-(4-methyl-1-piperazinyl)thiazetoquinolone derivatives against gram-positive bacteria was more potent than that of OFLX especially against quinolone-resistant MRSA. Compound **2a** had more potent *in vivo* efficacy than **1b** against infections due to both *Staphylococcus aureus* SMITH and *Escherichia coli* KC-14, although **2a** had less potent *in vitro* activity than **1b** against these bacteria. Furthermore, **2a** showed good *in vivo* efficacy against infection caused by quinolone-resistant MRSA while both **1a** and OFLX showed

Table 2. Oral Efficacy on Systemic Infections in Mice

Compd. No.	*Staphylococcus aureus* SMITH		*Staphylococcus aureus* KC-5879[a]		*Escherichia coli* KC-14	
	MIC (μg/ml)	ED50 (mg/kg)	MIC (μg/ml)	ED50 (mg/kg)	MIC (μg/ml)	ED50 (mg/kg)
2a	0.10	2.43	1.56	31.3	0.05	0.85
(−)-**2a**	0.05	1.00	0.78	25.9	0.025	0.66
2b	0.05	1.28	0.78	18.3	0.05	0.76
2d	0.10	>12.5	6.25	>100	0.025	—
1a	0.10	>40	6.25	>100	0.0125	>6.25
1b	0.05	3.19	6.25	>100	0.025	0.97
1c	0.10	7.92	1.56	—	0.10	1.28
OFLX	0.10	4.90	6.25	>200	0.025	1.20

a) Quinolone and Methicillin-resistant.

Table 3. Pharmacokinetics Properties in Mice

Compd. No.	PK after a 20 mg/kg single oral dose in mice		
	C_{max}[a] (μg/ml)	$t_{1/2\beta}$[b] (h)	$AUC_{0-\infty}$[c] (μg/ml·h)
2a	4.4	1.5	6.9
2b	3.2	1.2	3.5
1b	0.94	2.8	2.6
1c	0.84	4.9	2.7

a) Maximum concentration in plasma. *b*) Plasma half-time. *c*) Area under time–concentration curve.

no significant efficacy. Compound **2b** also had more potent *in vivo* efficacy than the corresponding 1-methyl analog **1c** against both gram-negative and gram-positive bacteria reflecting its superior *in vitro* activity to that of **1c**.

The *in vivo* antibacterial activity of (*S*)-(−)-**2a** was found to be more potent than that of the racemate. In the 7-(1-piperazinyl) derivatives, neither the 1-fluoromethyl analog **2d** nor the 1-methyl analog **1a** showed significant oral efficacy although they had potent *in vitro* activity.[1a)]

Some standard pharmacokinetics properties of selected compounds are displayed in Table 3. In mice, **2a** and **2b** showed a good pharmacokinetic profile after oral administration. The introduction of a fluorine at the C-1 methyl group of the 7-(4-methyl-1-piperazinyl) derivatives improved the pharmacokinetic profile and oral efficacy (**2a** *vs.* **1b**, **2b** *vs.* **1c**).

In conclusion, our study has revealed that the effect of a fluorine introduced at the C-1 methyl group of the 1-methylthiazetoquinolone derivatives on *in vitro* and *in vivo* antibacterial activity is influenced by the choice of the substituent at the C-7 and the C-8 positions, and that the introduction of a fluorine at the C-1 methyl group of the 7-(4-methyl-1-piperazinyl)thiazetoquinolone derivatives markedly improved *in vivo* antibacterial activity against gram-negative and gram-positive bacteria including quinolone-resistant MRSA

Experimental

***In Vitro* Antibacterial Activity** Minimum inhibitory concentrations (MICs) were determined by the agar dilution method recommended by the Japan Society of Chemotherapy. 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 (Slc : ddY, 20±2 g, Japan SLC Inc., Shizuoka, Japan) were used for each dose of drug. *Staphylococcus aureus* SMITH (2.5×10^5 cfu/mouse), *Staphylococcus aureus* KC-5879 (6.25×10^5 cfu/mouse), and *Escherichia coli* KC-14 (2.2×10^5 cfu/mouse) were suspended in 5% gastric mucin. A 0.5 ml volume of bacterial suspension was challenged intraperitoneally. Drugs were 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 the survival rates at 7 d after infection.

Pharmacokinetics Study in Mice Male mice (Slc : ddY, weight, 24 to 26 g, Japan SLC Inc., Shizuoka, Japan) were orally administered 20 mg of **2a**, **2b**, **1b**, and **1c** per kg of body weight. At 0.5, 1, 2, and 4 h after dosing, blood samples were collected from the orbital sinus of 3 to 5 mice in each group. Serum samples were assayed by the agar-well method, with *E. coli* Kp used as the assay organisms.

Chemistry All melting points were determined in capillary tubes on a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanaco CHN Corder MT-3 elemental analyzer. ^{1}H-NMR spectra were determined on a Varian XL-200 or a Hitachi R-24-B spectrometer with tetramethylsilane as an internal standard; chemical shifts are given in ppm (δ). ^{1}H-NMR spectra of all compounds obtained were consistent with assigned structures. IR spectra were recorded on a Shimadzu IR-453-U-03 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102 spectrometer at 70 eV ionization potential. Optical rotations were recorded on a Horiba SEPA-200 polarimeter. CD spectra were recorded on a JASCO J-720 spectropolarimeter. HPLC analyses were carried out with Shimadzu LC-8A and LC-10A liquid chromatograph equipped with a chiral stationary phase column (Daicel Chiralcel OD). Column chromatography separations were carried out on Wako Gel C-200 and C-300 instruments. Yields are of purified products and are not optimized.

Ethyl 4-Benzoyloxy-6,7-difluoro-2-(methoxymethyl)thioquinoline-3-carboxylate (7a) Benzoyl chloride (46.95 g, 0.334 mol) was added dropwise to a stirred solution of ethyl 6,7-difluoro-4-hydroxy-2-(methoxymethyl)thioquinoline-3-carboxylate **6a** (100 g, 0.303 mol) in 500 ml of pyridine with ice cooling. After stirring at the same temperature for 2 h, 1500 ml of water was added to the reaction mixture. The resulting precipitate was collected by filtration, washed with water, and dissolved in chloroform. The solution was washed with 1 N hydrochloric acid and water. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to give **7a** (132 g, 100%) as light yellow crystals, mp 103 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7 Hz), 3.47 (3H, s), 4.28 (2H, q, J=7 Hz), 5.56 (2H, s), 7.0—9.0 (7H, m). *Anal.* Calcd for $C_{21}H_{17}F_2NO_5S$: C, 58.19; H, 3.95; N, 3.23. Found: C, 57.89; H, 3.82; N, 3.36.

Ethyl 4-Benzoyloxy-6,7-difluoro-8-methoxy-2-(methoxymethyl)thioquinoline-3-carboxylate (7b) By using the same procedure as for **7a**, **7b** was prepared in 92% yield from **6b**, mp 97—98 °C. IR (KBr) cm^{-1}: 2900, 1742, 1727, 1603, 1500, 1246, 1080, 706. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz), 3.47 (3H, s), 4.1—4.5 (5H, m), 5.58 (2H, s), 7.1—7.8 (4H, m), 8.1—8.4 (2H, m). *Anal.* Calcd for $C_{22}H_{19}F_2NO_6S$: C, 57.01; H, 3.02; N, 4.13. Found: C, 57.01; H, 3.19; N, 4.38.

Ethyl 4-Benzoyloxy-6,7,8-trifluoro-2-(methoxymethyl)thioquinoline-3-carboxylate (7c) By using the same procedure as for **7a**, **7c** was prepared in 89% yield from **6c**, mp 112 °C. IR (KBr) cm^{-1}: 2950, 2850, 1740, 1710, 1500, 1460, 1250, 1060, 700. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7 Hz), 3.49 (3H, s,), 4.59 (2H, q, J=7 Hz), 5.65 (2H, s,), 7.5—8.0 (4H, m), 8.10—8.40 (2H, m). *Anal.* Calcd for $C_{21}H_{16}F_3NO_5S$: C, 55.87; H, 3.57; N, 3.10. Found: C, 55.65; H, 3.82; N, 2.92.

Ethyl 4-Benzoyloxy-6,7-difluoro-2-mercaptoquinoline-3-carboxylate (8a) A suspension of **7a** (132 g, 0.305 mol) and conc. hydrochloric acid (38 ml) in 1280 ml of ethanol was stirred for 22 h at room temperature. The resulting precipitate was collected by filtration, washed with ether, and air-dried at room temperature to give **8a** (103 g, 87%), mp 165 °C. IR (KBr) cm^{-1}: 2900, 1725, 1605, 1520, 1400, 1240, 1200. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7 Hz), 4.33 (2H, q, J=7 Hz), 7.0—8.0 (5H, m), 8.0—8.5 (2H, m), 10.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{13}F_2NO_4S$: C, 58.61; H, 3.37; N, 3.60. Found: C, 58.60; H, 3.49; N, 3.63.

Ethyl 4-Benzoyloxy-6,7-difluoro-2-mercapto-8-methoxyquinoline-3-carboxylate (8b) By using the same procedure as for **8a**, **8b** was prepared in 94% yield from **7b**, mp 165 °C. IR (KBr) cm^{-1}: 1750, 1730, 1620, 1595, 1510, 1470, 1415. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz), 4.1—4.5 (5H, m), 6.9—8.2 (6H, m), 10.70 (1H, br s). *Anal.* Calcd for $C_{20}H_{15}F_2NO_5S$: C, 57.28; H, 3.60; N, 3.34. Found: C, 57.16; H, 3.81; N, 3.44.

Ethyl 4-Benzoyloxy-6,7,8-trifluoro-2-mercaptoquinoline-3-carboxylate (8c) By using the same procedure as for **8a**, **8c** was prepared in 72% yield from **7c**, mp 149 °C. IR (KBr) cm^{-1}: 2900, 1730, 1610, 1525, 1260, 1050. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7 Hz), 1.56 (1H, br s), 4.28 (2H, q, J=7 Hz), 7.19 (1H, m), 7.56 (2H, dd, J=8, 7 Hz), 7.6—7.8 (1H, m), 8.17 (2H, dd, J=7, 1 Hz), 10.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{12}F_3NO_4S$: C, 56.02; H, 2.97; N, 3.44. Found: C, 56.23; H, 3.08; N, 3.37.

Ethyl 4-Benzoyloxy-6,7-difluoro-2-(2-fluoroethyl)thioquinoline-3-carboxylate (9a) 1-Bromo-2-fluoroethane (17.5 g, 0.138 mol) was added dropwise to a stirred suspension of **8a** (53.8 g, 0.138 mol) and sodium hydrogencarbonate (11.6 g, 0.138) in 500 ml of DMF at room temperature. After stirring for 17 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform and washed with water. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was washed with diethyl ether until the washings were no longer colored to give **9a** (34.2 g, 57%) as a pale yellow solid, mp 125 °C. IR (KBr) cm^{-1}: 2980, 1745, 1715, 1590, 1500, 1420, 1315, 1235, 1040, 1020, 700. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7 Hz), 3.64 (2H, dt, J=18, 6.4 Hz), 4.27 (2H, q, J=7 Hz), 4.72 (2H, dt, J=47, 6.4 Hz), 5.11 (1H, t, J=6.4 Hz), 7.2—8.0 (5H, m), 8.0—8.4 (2H, m). *Anal.* Calcd for $C_{21}H_{16}FS_3NO_4S$: C, 57.93; H, 3.70; N, 3.22. Found: C, 57.83; H, 3.70; N, 3.37.

Ethyl 4-Benzoyloxy-6,7-difluoro-2-(2-fluoroethyl)-8-methoxythioquinoline-3-carboxylate (9b) By using the same procedure as for **9a**, **9b** was prepared in 84% yield from **8b**, mp 128—129 °C. IR (KBr) cm^{-1}: 1755, 1715, 1625, 1590, 1570, 1495, 1465, 1425. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7 Hz), 3.68 (2H, dt, J=18, 6.4 Hz), 4.23 (3H, s), 4.33 (2H, q, J=7 Hz), 4.77 (2H, dt, J=48, 6.4 Hz), 7.0—8.0 (4H, m), 8.0—8.5 (2H, m). *Anal.* Calcd for $C_{22}H_{18}F_3NO_5S$: C, 56.77; H, 3.90; N, 3.01. Found: C, 56.92; H, 3.91; N, 3.04.

Ethyl 4-Benzoyloxy-6,7,8-trifluoro-2-(2-fluoroethyl)thioquinoline-3-carboxylate (9c) By using the same procedure as for **9a**, **9c** was prepared in 90% yield from **8c**, mp 135 °C. IR (KBr) cm^{-1}: 3000, 1750, 1715, 1680, 1500, 1460, 1320, 1260, 1050, 860, 700. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 3.68 (2H, dt, J=20, 6.4 Hz), 4.0—4.8 (3H, m), 5.18 (1H, t, J=6.4 Hz), 7.0—8.0 (4H, m), 8.0—8.6 (2H, m). *Anal.* Calcd for $C_{21}H_{15}F_4NO_4S$: C, 55.63; H, 3.33; N, 3.09. Found: C, 55.06; H, 3.33; N, 3.32.

Ethyl 4-Benzoyloxy-2-(1-chloro-2-fluoroethyl)thio-6,7-difluoroquinoline-3-carboxylate (10a) A solution of sulfuryl chloride (27.3 g, 0.202 mol) in 100 ml of *n*-hexane was added dropwise to a stirred suspension of **9a** (34.2 g, 0.0785 mol) in 350 ml of *n*-hexane over 0.5 h under reflux and stirred for 19 h at the same temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel with chloroform to give **10a** (22.0 g, 56%) as a pale yellow solid, mp 105 °C. IR (KBr) cm^{-1}: 1760, 1710, 1510, 1430, 1330, 1050. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7 Hz), 4.0—4.6 (3H, m), 5.0—5.6 (1H, m), 6.2—6.8 (1H, m), 7.4—8.0 (5H, m), 8.1—8.4 (2H, m). *Anal.* Calcd for $C_{21}H_{15}ClF_3NO_4S \cdot 1/4H_2O$: C, 53.17; H, 3.29; N, 2.95. Found: C, 53.11; H, 3.17; N, 3.09.

Ethyl 4-Benzoyloxy-2-(1-chloro-2-fluoroethyl)thio-6,7-difluoro-8-methoxyquinoline-3-carboxylate (10b) By using the same procedure as for **10a**, **10b** was prepared in 86% yield from **9b**, mp 107—108 °C. IR (KBr) cm^{-1}: 1760, 1715, 1625, 1590, 1750, 1495, 1470, 1430. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7 Hz), 4.10—4.60 (6H, m), 5.31 (1H, m), 6.3—6.8 (1H, m), 7.2—7.9 (4H, m), 8.1—8.5 (2H, m). *Anal.* Calcd for $C_{22}H_{17}ClF_3NO_5S$: C, 52.86; H, 3.43; N, 2.80. Found: C, 53.38; H, 3.12; N, 2.85.

Ethyl 4-Benzoyloxy-2-(1-chloro-2-fluoroethyl)thio-6,7,8-trifluoroquinoline-3-carboxylate (10c) By using the same procedure as for **10a**, **10c** was prepared in 86% yield from **9c**, mp 130 °C. IR (KBr) cm^{-1}: 1755, 1715, 1505, 1470, 1260, 1235, 1050. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 4.28 (2H, q, J=7 Hz), 4.4—4.8 (1H, m), 5.2—5.6 (1H, m), 6.57 (1H, dt, J=16, 5.2 Hz), 7.2—8.0 (4H, m), 8.0—8.5 (2H, m). *Anal.* Calcd for $C_{21}H_{14}ClF_4NO_4S \cdot 1/2H_2O$: C, 50.76; H, 3.04; N, 2.82. Found: C, 50.88; H, 2.96; N, 3.02.

Ethyl 6,7-Difluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (11a) A solution of **10a** (22.0 g, 46.8 mmol), triethylamine (12.2 g, 121 mmol) and H_2O (1.26 g, 70.2 mmol) in 350 ml of tetrahydrofuran (THF) was stirred for 22 h at room temperature. The resulting precipitate was collected by filtration, washed with ether, and air-dried at room temperature to give **11a** (15.0 g, 98%) as a pale gray solid, mp 225 °C. IR (KBr) cm^{-1}: 3400, 3000, 1715, 1610, 1550, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.63 (1H, dd, J=9.4, 2.9 Hz), 5.3—5.8 (1H, m), 6.0—6.6 (1H, m), 7.33 (1H, dd, J=9.5, 6.5 Hz), 8.23 (1H, dd, J=10, 8 Hz). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.06; H, 3.06; N, 4.25. Found: C, 51.09; H, 3.12; N, 4.25.

Ethyl 6,7-Difluoro-1-fluoromethyl-8-methoxy-4-oxo-4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylate (11b) By using the same procedure as for **11a**, **11b** was prepared in 75% yield from **10b**, mp 231—233 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 4.21 (3H, d, J=3.5 Hz), 4.42 (2H, q, J=7 Hz), 5.12 (2H, dd, J=46, 4 Hz), 6.09 (1H, dt, J=12, 4 Hz), 7.83 (1H, dd, J=11, 8 Hz). *Anal.* Calcd for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; N, 3.90. Found: C, 50.05; H, 3.19; N, 3.93.

Ethyl 6,7,8-Trifluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (11c) By using the same procedure as for **11a**, **11c** was prepared in 93% yield from **10c**, mp 227 °C. IR (KBr) cm^{-1}: 3000, 1720, 1600, 1520, 1490, 1180, 800. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.6—4.8 (1H, m), 5.3—5.6 (1H, m), 5.8—6.4 (1H, m), 8.10 (1H, m). *Anal.* Calcd for $C_{14}H_9F_4NO_3S \cdot 1/2H_2O$: C, 47.19; H, 2.83; N, 3.93. Found: C, 47.09; H, 2.85; N, 4.17.

Path 1. Ethyl 6-Fluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (12a) A suspension of **11a** (4.08 g, 12.4 mmol) and 1-methylpiperazine (2.48 g, 24.8 mmol) in 40 ml of DMF was stirred at 60 °C for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate and washed with water. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to give **12a** (1.70 g, 34%), mp 251 °C. IR (KBr) cm^{-1}: 3400, 1720, 1630, 1600, 1500. ^{1}H-NMR (DMSO-d_6) δ:1.39 (3H, t, J=7 Hz), 2.35 (3H, s), 2.2—2.9 (4H, m), 3.0—3.6 (4H, m), 4.37 (2H, q, J=7 Hz), 4.60 (1H, d, J=6.4 Hz), 5.40 (1H, d, J=5.2 Hz), 5.5—6.5 (1H, m), 6.66 (1H, d, J=7 Hz), 7.94 (1H, d, J=14 Hz). *Anal.* Calcd for $C_{19}H_{21}F_2N_3O_3S$: C, 55.73; H, 5.17; N, 10.26. Found: C, 55.62; H, 5.28. N, 10.10.

Ethyl 6-Fluoro-1-fluoromethyl-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylate (12b) By using the same procedure as for **12a**, **12b** was prepared in 13% yield from **11b**, mp 212—213 °C (dec.). IR (KBr) cm^{-1}: 2940, 1730, 1605, 1475, 1375, 1330, 1295, 1205. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.37 (3H, s), 2.4—3.8 (8H, m), 3.98 (3H, s), 4.33 (2H, q, J=7 Hz), 4.7—4.9 (1H, m), 5.4—5.7 (1H, m), 5.8—6.3 (1H, m), 7.70 (1H, d, J=13 Hz). *Anal.* Calcd for $C_{20}H_{23}F_2N_3O_4S$: C, 54.66; H, 5.27; N, 9.56. Found: C, 54.82; H, 4.87; N, 9.66.

Ethyl 6,8-Difluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (12c) By using the same procedure as for **12a**, **12c** was prepared in 38% yield from **11c**, mp 151 °C. IR (KBr) cm^{-1}: 3150, 2800, 1720, 1600, 1580, 1540, 1480, 1380. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.39 (3H, s), 2.0—3.0 (4H, m), 3.0—4.0 (4H, m), 4.40 (2H, q, J=7 Hz), 4.8—6.4 (2H, m), 7.88 (1H, dd, J=13, 2 Hz). *Anal.* Calcd for $C_{19}H_{19}F_2N_3O_3S$: C, 56.01; H, 4.70; N, 10.32. Found: C, 55.75; H, 5.02; N, 10.54.

Path 1. 6-Fluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylic Acid (2a) A suspension of **12a** (2.05 g, 5.0 mmol) in 100 ml of 1% sulfuric acid was heated under reflux for 5 h. Then the solution was cooled and neutralized with sodium hydrogen carbonate, and treated with 20% methanol in $CHCl_3$. The organic layer obtained was dried and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to give **2a** (1.37 g, 72%), mp 220 °C. IR (KBr) cm^{-1}: 1710, 1630, 1600, 1500, 1380. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s), 2.0—3.5 (8H, m), 4.7—5.7 (2H, m), 6.70 (1H, m), 7.01 (1H, d, J=7 Hz), 7.82 (1H, d, J=12 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{17}H_{17}F_2N_3O_3S \cdot 1/2H_2O$: C, 52.30; H, 4.65; N, 10.76. Found: C, 52.32; H, 4.17. N, 10.50.

6-Fluoro-1-fluoromethyl-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylic Acid (2b) By using the same procedure as for **2a**, **2b** was prepared in 40% yield from **12b**, mp 200—201 °C (dec.). IR (KBr) cm^{-1}: 3400, 1710, 1620, 1510. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.4—2.7 (4H, m), 3.2—3.4 (2H, m), 3.4—3.7 (2H, m), 3.93 (3H, s), 5.0—5.1 (1H, m), 5.2—5.3 (1H, m), 6.1—6.2 (1H, m), 7.76 (1H, d, J=13 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{19}F_2N_3O_4S$: C, 52.55; H, 4.65; N, 10.21. Found: C, 52.32; H, 4.34; N, 10.21.

6,8-Difluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2c) By using the same procedure as for **2a**, **2c** was prepared in 21% yield from **12c**, mp 226 °C. IR (KBr) cm^{-1}: 3700, 2650, 1710, 1640, 1540, 1390. ^{1}H-NMR (CF_3CO_2D) δ: 3.16 (3H, s), 3.3—4.3 (8H, m), 4.9—5.9 (2H, m), 6.94 (1H, br d, J=24 Hz), 8.08 (1H, d, J=12 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}F_3N_3O_3S$: C, 51.12; H, 4.04; N, 10.52. Found: C, 50.87; H, 3.77; N, 10.33.

Path 2. 6,7-Difluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (13) A suspension of **11a** (10.0 g, 30.4 mmol) in 100 ml of 1% sulfuric acid was heated under reflux for 5 h. Then the solution was cooled and neutralized with sodium hydrogen carbonate, and treated with 20% methanol in $CHCl_3$. The organic layer obtained was dried and concentrated under reduced pressure to give **13** (9.2 g, 100%), mp 292 °C. IR (KBr) cm^{-1}: 1700, 1610, 1550, 1490, 1360, 1300, 1250, 900. ^{1}H-NMR (DMSO-d_6) δ: 4.5—5.0 (1H, m), 5.2—5.8 (1H, m), 6.50 (1H, m), 7.51 (1H, dd, J=10, 7 Hz), 8.17 (1H, dd, J=10, 8 Hz), 13.5 (1H, br s). *Anal.* Calcd for $C_{12}H_6F_3NO_3S$: C, 46.46; H, 2.27; N, 4.51. Found: C, 46.05; H, 2.04; N, 4.31.

Path 2. 6-Fluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2a) A suspension of **13** (1.51, 5 mmol) and 1-methylpiperazine (1.11 g, 11 mmol) in 40 ml of DMF was stirred at 60 °C for 3 h. The resultant mixture was concentrated under reduced pressure, and the residue was washed with water and purified by recrystallization from ethanol to give **2a** (0.62 g, 33%), mp 232 °C. IR (KBr) cm^{-1}: 1710, 1630, 1600, 1500, 1380. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s), 3.0—3.5 (8H, m), 4.7—5.7 (2H, m), 6.70 (1H, m), 7.01 (1H, d, J=7 Hz), 7.82 (1H, d, J=12 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{17}H_{17}F_2N_3O_3S$: C, 53.54; H, 4.49; N, 11.02. Found: C, 53.31; H, 4.13. N, 10.73.

6-Fluoro-1-fluoromethyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid Hydrochloride (2d) By using the same procedure as for **2a**, **2d** was prepared in 30% yield from **13** and piperazine, mp 270—272 °C (dec.). IR (KBr) cm^{-1}: 3350, 2470, 1715, 1630, 1605, 1500, 1260. ^{1}H-NMR (DMSO-d_6) δ: 3.2—3.9 (9H, m), 5.0—5.8 (2H, m), 6.6—6.8 (1H, m), 7.16 (1H, d, J=8 Hz), 7.88 (1H, d, J=12 Hz), 12.0 (1H, br s). *Anal.* Calcd for $C_{16}H_{15}F_2N_3O_3S \cdot HCl$: C, 47.59; H, 3.99; N, 10.41. Found: C, 47.70; H, 3.95; N, 10.34.

7-(*cis*-3,5-Dimethyl-1-piperazinyl)-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2e) By using the same procedure as for **2a**, **2e** was prepared in 21% yield from **13** and *cis*-2,6-dimethylpiperazine, mp 220 °C (dec.). IR (KBr) cm^{-1}: 3300, 1620, 1540, 1360. ^{1}H-NMR (CF_3CO_2D) δ: 1.58 (6H, d, J=6 Hz), 3.0—4.5 (7H, m), 4.9—5.7 (2H, m), 6.82 (1H, m), 7.30 (1H, d, J=6 Hz), 8.20 (1H, d, J=14 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{19}F_2N_3O_3S$: C, 52.29; H, 5.12; N, 10.16. Found: C, 52.44; H, 5.48; N, 10.38.

6-Fluoro-1-fluoromethyl-7-morpholino-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2f) By using the same procedure as for **2a**, **2f** was prepared in 22% yield from **13** and morpholine, mp 239 °C. IR (KBr) cm^{-1}: 1700, 1630, 1500, 1450, 1370. ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 3.2—3.5 (4H, m), 4.8—5.0 (4H, m), 5.0—5.4 (2H, m), 6.30 (1H, m), 6.80 (1H, d, J=8 Hz), 7.95 (1H, d, J=12 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}F_2N_2O_4S$: C, 52.17; H, 3.83; N, 7.60. Found: C, 52.61; H, 3.73; N, 7.51.

6-Fluoro-1-fluoromethyl-4-oxo-7-thiomorpholino-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2g) By using the same procedure as for **2a**, **2g** was prepared in 55% yield from **13** and thiomorpholine, mp 231—234 °C. IR (KBr) cm^{-1}: 3500, 2900, 2360, 1710, 1625, 1600, 1500. ^{1}H-NMR (DMSO-d_6) δ; 2.7—2.9 (4H, m), 3.5—3.7 (4H, m), 4.9—5.7 (2H, m), 6.69 (1H, br d, J=20 Hz), 7.04 (1H, d, J=8 Hz), 7.82 (1H, d, J=14 Hz), 14.4 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}F_2N_2O_3S_2$: C, 49.99; H, 3.67; N, 7.29. Found: C, 50.11; H, 4.05; N, 7.38.

6-Fluoro-1-fluoromethyl-7-(4-hydroxypiperizino)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2h) By using the same procedure as for **2a**, **2h** was prepared in 65% yield from **13** and 4-hydroxypiperizine, mp 245—248 °C (dec.). IR (KBr) cm^{-1}: 3300, 2850, 1700, 1630, 1510. ^{1}H-NMR (DMSO-d_6) δ: 1.4—1.7 (2H, m), 1.7—2.0 (2H, m), 2.9—3.2 (2H, m), 3.4—3.7 (2H, m), 3.7—3.9 (1H, m), 4.77 (1H, d, J=4 Hz), 4.9—6.7 (2H, m), 6.70 (1H, br d, J=14 Hz), 7.01 (1H, d, J=7 Hz), 7.79 (1H, d, J=14 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}F_2N_2O_4S$: C, 53.04; H, 4.22; N, 7.33. Found: C, 53.58; H, 4.00; N, 7.60.

7-(4-Aminopiperizino)-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid Hydrochloride (2i) By using the same procedure as for **2a**, **2i** was prepared in 25% yield from **13** and 4-aminopiperizine, mp >300 °C. IR (KBr) cm^{-1}: 2950, 1700, 1630, 1600, 1500, 1385. ^{1}H-NMR (DMSO-d_6) δ: 1.6—1.9 (2H, m), 2.0—2.2 (2H, m), 2.9—3.1 (2H, m), 3.2—3.4 (1H, m), 3.32 (1H, br s), 3.6—3.9 (2H, m), 5.0—5.7 (2H, m), 6.69 (1H, br d, J=20 Hz), 7.05 (1H, d, J=7 Hz), 7.85 (1H, d, J=14 Hz), 8.15 (2H, br s), 14.50 (1H, br s). *Anal.* Calcd for $C_{17}H_{18}F_2N_3O_3S \cdot HCl \cdot H_2O$: C, 46.84; H, 4.62; N, 9.64. Found: C, 47.02; H, 4.56; N, 9.46.

6-Fluoro-1-fluoromethyl-7-(4-hydroxymethylpiperizino)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2j) By using the same procedure as for **2a**, **2j** was prepared in 36% yield from **13** and 4-hydroxymethylpiperizine, mp 234—236 °C (dec.). IR (KBr) cm^{-1}: 3400, 2900, 1710, 1625, 1600, 1505. ^{1}H-NMR (DMSO-d_6) δ: 1.2—1.5 (2H, m), 1.5—1.7 (1H, m), 1.7—1.9 (2H, m), 2.8—3.0 (2H, m), 3.32 (2H, d, J=7 Hz), 3.6—3.8 (2H, m), 4.52 (1H, t, J=5 Hz), 5.0—5.7 (2H, m), 6.70 (1H, br d, J=20 Hz), 7.0 (1H, d, J=7 Hz), 7.9 (1H, d, J=15 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{18}F_2N_2O_4S$: C, 54.54; H, 4.58; N, 7.07. Found: C, 54.53; H, 4.81; N, 7.16.

7-(4-Aminomethylpiperizino)-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid Hydrochloride (2k) By using the same procedure as for **2a**, **2k** was prepared in 63% yield from **13** and 4-aminomethylpiperizine, mp 253—257 °C (dec.). IR (KBr) cm^{-1}: 3400, 2900, 1700, 1630, 1600, 1500, 1260. ^{1}H-NMR (DMSO-d_6) δ: 1.2—1.6 (2H, m), 1.8—2.0 (3H, m), 2.7—3.0 (2H, m), 2.80 (2H, d, J=7 Hz), 3.6—3.8 (2H, m), 5.0—5.7 (2H, m), 6.73 (1H, br d, J=14 Hz), 7.05 (1H, d, J=7 Hz), 7.81 (1H, d, J=14 Hz), 8.18 (2H, br s), 14.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{19}F_2N_3O_3S$: C, 50.06; H, 4.67; N, 9.73. Found: C, 50.34; H, 4.68; N, 9.58.

6-Fluoro-1-fluoromethyl-7-(3-hydroxyazetidino)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (2l) By using the same procedure as for **2a**, **2l** was prepared in 31% yield from **13** and 3-hydroxyazetidine, mp >300 °C (dec.). IR (KBr) cm^{-1}: 3300, 1700, 1630, 1600, 1540, 1515, 1460, 1390. ^{1}H-NMR (DMSO-d_6) δ: 3.8—4.0 (2H, m), 4.3—4.5 (2H, m), 4.5—4.7 (1H, m), 4.9—5.7 (2H, m), 5.82 (1H, d, J= Hz), 6.4 (1H, d, J=8 Hz), 6.60 (1H, br s, J=14 Hz), 7.70 (1H, d, J=14 Hz), 14.50 (1H, br s). *Anal.* Calcd for $C_{15}H_{12}F_2N_2O_4S$: C, 50.85; H, 3.41; N, 7.91. Found: C, 50.66; H, 3.77; N, 7.74.

Ethyl 6,7-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (14) A suspension of **6** (12.0 g, 36.5 mmol) and sulfuric acid (36 g) in 180 ml of ethanol was refluxed with stirring for 1 h, then cooled to 0—5 °C in an ice-bath. The resulting precipitate was collected by filtration, washed with ether, and air-dried at room temperature to give **14** (9.97 g, 96%), mp 208 °C. IR (KBr) cm^{-1}: 3000, 1640, 1590, 1515. ^{1}H-NMR (CF_3CO_2D) δ: 1.56 (1H, br s), 1.62 (3H, t, J=7 Hz), 4.74 (2H, q, J=7 Hz), 7.68 (1H, dd, J=7, 9 Hz), 8.20 (1H, dd, J=8, 9 Hz), 13.30 (1H, br s). *Anal.* Calcd for $C_{12}H_9F_2NO_4S$: C, 50.53; H, 3.18; N, 4.91. Found: C, 50.56; H, 3.08; N, 4.70.

Ethyl 6,7-Difluoro-2-(2-fluoroethyl)thio-4-hydroxyquinoline-3-carboxylate (15) 1-Bromo-2-fluoroethane (26.7 g, 0.210 mol) was added dropwise to a stirred suspension of **14** (50.0 g, 0.175 mol) and triethylamine (17.7 g, 0.175 mol) in 250 ml of DMF at room temperature. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform and washed with water. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was washed with diethyl ether until the washings were no longer colored to give **15** (47.8 g, 82%), mp 120—122 °C. IR (KBr) cm^{-1}: 1651, 1595, 1570, 1516, 1431. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, t, J=7.0 Hz), 3.55 (2H, dt, J=18.8, 6.5 Hz), 4.56 (2H, q, J=7.0 Hz), 4.85 (2H, dt, J=46.8, 6.6 Hz), 7.50 (1H, dd, J=11.1, 7.6 Hz), 7.91 (1H, dd, J=10.6, 8.8 Hz), 13.26 (1H, s). *Anal.* Calcd for $C_{14}H_{12}F_3NO_3S$: C, 50.75; H, 3.65; N, 4.23. Found: C, 51.00; H, 3.61; N, 4.33.

Ethyl 6,7-Difluoro-2-(2-fluoroethyl)thio-4-[(2*R*)-2-phenylpropionyl]-oxyquinoline-3-carboxylate (16) (*R*)-(−)-2-Phenylpropionyl chloride (1.70 g, 10.1 mmol) was added dropwise to a stirred solution of **15** (2.40 g, 8.4 mmol) and triethylamine (1.02 g, 10.1 mmol) in 25 ml of chloroform with ice cooling. After stirring at room temperature for 3 h, 25 ml of water was added to the reaction mixture. The organic layer was washed with 1% hydrochloric acid, then 2% sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with chloroform to give **16** (2.0 g, 80%), mp 71—73 °C. $[\alpha]_D^{20}$ −64.16° (c=1.066, $CDCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.39

(3H, t, J=7.2 Hz), 1.69 (3H, d, J=6.9 Hz), 3.59 (2H, dt, J=18.0, 6.0 Hz), 4.11 (1H, q, J=6.9 Hz), 4.35 (2H, q, J=7.2 Hz), 4.67 (2H, dt, J=46.8, 6.6 Hz), 6.70 (1H, dd, J=10.5, 8.1 Hz), 7.4—7.5 (5H, m), 7.68 (1H, dd, J=10.8, 7.2 Hz). *Anal.* Calcd for $C_{23}H_{20}F_3NO_4S$: C, 59.60; H, 4.35; N, 3.02. Found: C, 59.66; H, 4.43; N, 3.04.

Ethyl 2-(1-Chloro-2-fluoroethyl)thio-6,7-difluoro-4-[(2*R*)-2-phenylpropionyl]oxyquinoline-3-carboxylate (18) A solution of sulfuryl chloride (1.42 g, 10.2 mmol) in 15 ml of dichloromethane was added dropwise to a stirred suspension of **16** (2.35 g, 5.1 mmol) in 50 ml of dichloromethane over 0.5 h under reflux and stirred for 2 h at the same temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel with chloroform to give a mixture of ethyl 2-(1-chloro-2-fluoroethyl)thio-6,7-difluoro-4-[(2*R*)-2-phenylpropionyl]-oxyquinoline-3-carboxylate (**17**, **18**) (2.10 g, 83%).

The diastereomeric mixture (**17**, **18**) was recrystallized from isopropyl ether (three times) to give ethyl 2-(1-chloro-2-fluoroethyl)thio-6,7-difluoro-4-[(2*R*)-2-phenylpropionyl]oxyquinoline-3-carboxylate **18** (0.31 g, 15%), mp 108—109 °C. $[\alpha]_D^{20}$ +87.14° (c=0.778, $CHCl_3$) and d.e.=96.3% (HPLC). IR (KBr) cm^{-1}: 1765, 1715, 1595, 1508, 1429. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.2 Hz), 1.68 (3H, d, J=6.9 Hz), 4.12 (1H, q, J=6.9 Hz), 4.38 (2H, m,) 4.81 (2H, m), 6.46 (1H, m), 6.69 (1H, dd, J=10.2, 8.4 Hz), 7.4—7.5 (5H, m), 7.68 (1H, dd, J=10.8, 7.2 Hz). *Anal.* Calcd for $C_{23}H_{19}ClF_3NO_4S$: C, 55.48; H, 3.85; N, 2.81. Found: C, 55.72; H, 3.52; N, 2.74.

(*S*)-(−)-Ethyl 6,7-Difluoro-1-fluoromethyl-4-oxo-4*H*[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (11a) By using the same procedure as for racemic **11a**, (*S*)-(−)-**11a** was prepared in 84% yield from **18**, mp 209—210 °C. $[\alpha]_D^{20}$ −103.68° (c=0.824, DMF) and e.e.=95.1% (chiral HPLC). IR (KBr) cm^{-1}: 3400, 3000, 1715, 1610, 1550, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.63 (1H, dd, J=9.4, 2.9 Hz), 5.3—5.8 (1H, m), 6.0—6.6 (1H, m), 7.33 (1H, dd, J=9.5, 6.5 Hz), 8.23 (1H, dd, J=10, 8 Hz). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.06; H, 3.06; N, 4.25. Found: C, 50.85; H, 3.15; N, 4.39.

Optical Resolution of (±)-Ethyl 6,7-Difluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (±)-11a Compound (±)-**11a** (1.0 g, 3 mmol) was dissolved in 1000 ml of isopropanol and the solution was subject to HPLC with *n*-hexane–isopropanol (3 : 1) mixture at a flow of 7.6 ml/min and detection at 254 nm to give the optically pure isomer (+)-**11a** (0.364 g) and (−)-**11a** (0.377 g). HPLC: Chiralcel OD column (250×20 mm i.d.)-(Daicel Chemical Industries, Ltd.).

The first fraction at 59 min retention time afforded (*R*)-(+)-**11a**, mp 225 °C. $[\alpha]_D^{20}$ +94.52° (c=0.493, DMF). IR (KBr) cm^{-1}: 3400, 3000, 1715, 1610, 1550, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.63 (1H, dd, J=9.4, 2.9 Hz), 5.3—5.8 (1H, m), 6.0—6.6 (1H, m), 7.33 (1H, dd, J=9.5, 6.5 Hz), 8.23 (1H, dd, J=10, 8 Hz). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.06; H, 3.06; N, 4.25. Found: C, 50.86; H, 3.42; N, 4.38.

The second fraction at 74 min retention time gave (*S*)-(−)-**11a**, mp 225 °C. $[\alpha]_D^{20}$ −105.82° (c=0.429, DMF). IR (KBr) cm^{-1}: 3400, 3000, 1715, 1610, 1550, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.63 (1H, dd, J=9.4, 2.9 Hz), 5.3—5.8 (1H, m), 6.0—6.6 (1H, m), 7.33 (1H, dd, J=9.5, 6.5 Hz), 8.23 (1H, dd, J=10, 8 Hz). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.06; H, 3.06; N, 4.25. Found: C, 50.84; H, 3.22; N, 4.30.

(1*R*)-(+)-6-Fluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylic Acid (+)-2a By using the same procedure as for racemic **2a** from **11a**, (*R*)-(+)-**2a** was prepared in 43% yield from (*R*)-(+)-**11a**, mp 262 °C. $[\alpha]_D^{20}$ +89.02° (c=0.793, DMSO). IR (KBr) cm^{-1}: 1703, 1630, 1605, 1504. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s), 2.4—2.6 (4H, m), 3.2—3.4 (4H, m), 5.0—5.6 (2H, m), 6.69 (1H, br d, J=14 Hz), 7.01 (1H, d, J=7 Hz), 7.81 (1H, d, J=12 Hz), 14.60 (1H, br s). *Anal.* Calcd for $C_{17}H_{17}F_2N_3O_3S \cdot 1/2H_2O$: C, 52.30; H, 4.65; N, 10.76. Found: C, 52.06; H, 4.58. N, 10.50.

(1*S*)-(−)-6-Fluoro-1-fluoromethyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylic Acid (−)-2a By using the same procedure as for racemic **2a** from **11a**, (*S*)-(−)-**2a** was prepared in 39% yield from (*S*)-(−)-**11a**, mp 262—264 °C. $[\alpha]_D^{20}$ −85.62° (c=0.633, DMSO). IR (KBr) cm^{-1}: 1700, 1630, 1605, 1500. ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s), 2.4—2.6 (4H, m), 3.2—3.4 (4H, m), 5.0—5.6 (2H, m), 6.69 (1H, br d, J=14 Hz), 7.01 (1H, d, J=7 Hz), 7.81 (1H, d, J=12 Hz), 14.6 (1H, br s). *Anal.* Calcd for $C_{17}H_{17}F_2N_3O_3S \cdot 3/4H_2O$: C, 51.70; H, 4.72; N, 10.64. Found: C, 51.66; H, 4.64. N, 10.56.

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