# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL 7-SUBSTITUTED 6-FLUORO-1-METHYLENE-4-OXO-4*H*-[1,3]-THIAZETO[3,2-*a*]QUINOLINE-3-CARBOXYLIC ACID DERIVATIVES

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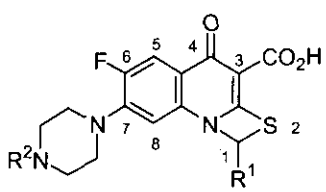
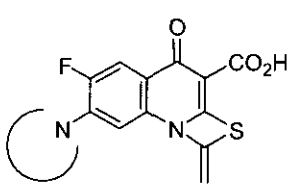
**Abstract** - A series of 7-substituted 6-fluoro-1-methylene-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives (**2**) and (**3**) was prepared and evaluated for antibacterial activity. These compounds were obtained by the treatment of the 1-methanesulfonyloxymethyl or 1-fluoromethyl thiazetoquinolone-3-carboxylates (**12**, **14** and **20**) with potassium hydroxide. Compounds (**2**) and (**3**) showed excellent *in vitro* antibacterial activity against both gram-negative and gram-positive bacteria including quinolone and Methicillin-resistant *Staphylococcus aureus*.

## Introduction



1a: $R^1$=$R^2$=Me
b: $R^1$=Me, $R^2$=H (NM394)
c: $R^1$=H, $R^2$=Me



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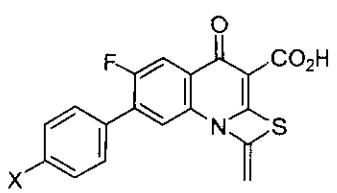


3a: X=H
b: X=$NH_2$

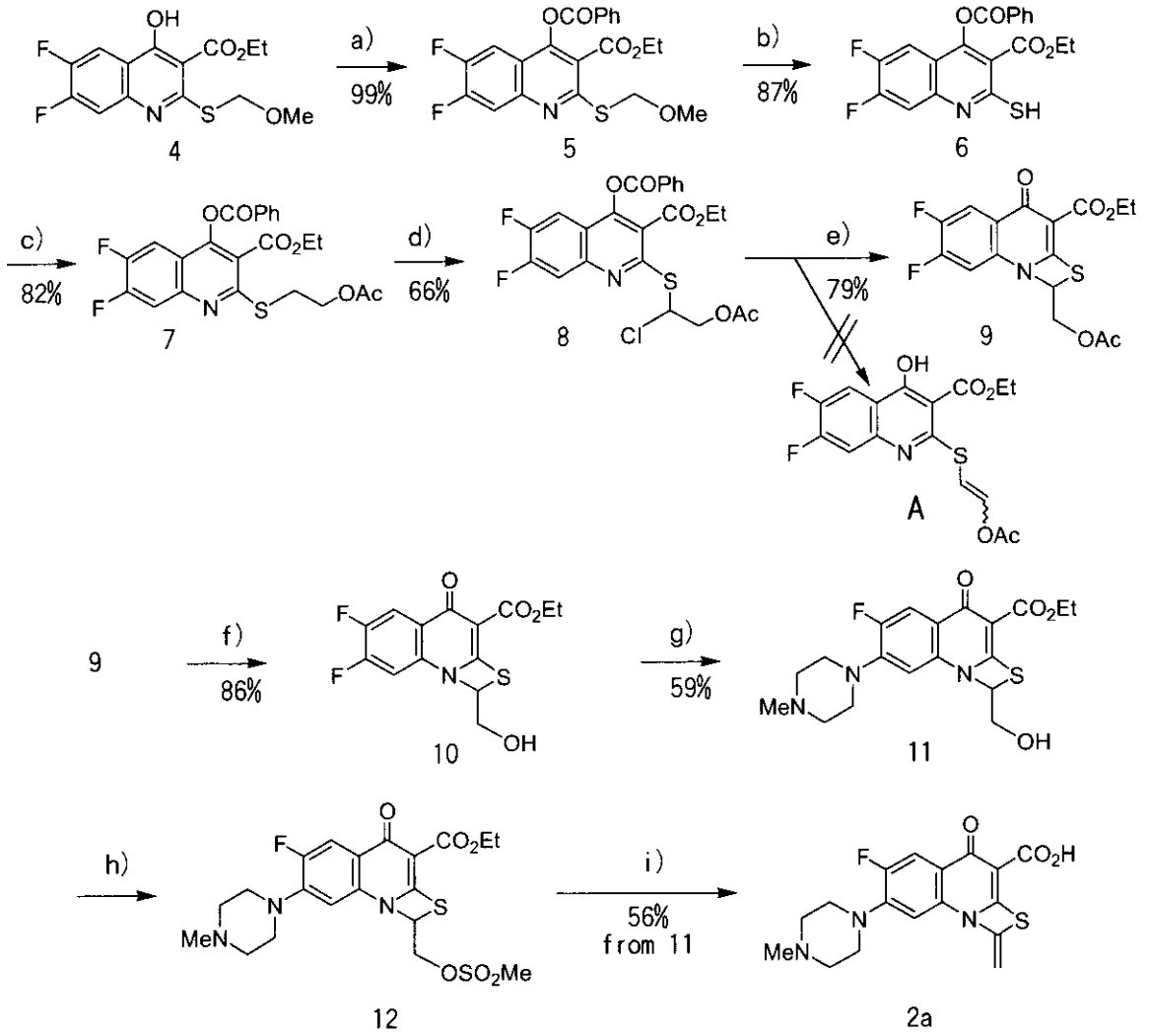
In our research on new, potent quinolones, we have been studying tricyclic compounds characterized by an *S*-bridge between the C-2 and the substituent at the N-1 of quinolones. Among these derivatives, compound (**1b**) (NM394) [1] showed excellent *in vitro* antibacterial activity. Compound (**1b**) has a methyl

group at the C-1 position in the thiazetoquinolone ring, producing an asymmetric center at this position. From the viewpoints of synthetic and pharmacological advantage, we planed to synthesize the thiazetoquinolone derivatives which have no chiral center at the C-1 position and possess potent antibacterial activity against both gram-negative and gram-positive bacteria including quinolone and Methicillin-resistant *Staphylococcus aureus* [quinolone-resistant MRSA]. Firstly, we prepared the 1-unsubstituted derivative (**1c**). [1] However, the antibacterial activity of **1c** was less potent than that of the 1-methyl derivative (**1a**). Next, we planed the synthesis of the 1-methylene derivatives. We considered that the thiazetoquinolone derivatives with a leaving group on C-1 methyl group should be subject to the $\beta$-elimination under the basic conditions to afford the corresponding 1-methylene derivatives, because the acidity of the proton at the C-1 position of the 1-alkylthiazetoquinolones is high ($^1$H-NMR spectra showed the signal at $\delta$ 6.0-7.0 ppm for the proton at C-1). [1] The synthetic route developed recently for the thiazetoquinolone derivatives *via* the 4-acetoxy-2-[(1-chloroethyl)thio]quinoline derivative [2] was thought to be applied to the synthesis of the 1-substituted methyl analogs which are the precursors of the 1-methylenethiazetoquinolone derivatives (**2** and **3**). In this paper, we report the synthesis and the antibacterial activity of **2** and **3**.

**Chemistry**

As shown in Scheme 1, 7-(4-methyl-1-piperazinyl) derivative (**2a**) was synthesized from ethyl 6,7-difluoro-4-hydroxy-2-(methoxymethylthio)quinoline-3-carboxylate [1] (**4**) (path 1). To protect the 4-hydroxy group, **4** was treated with benzoyl chloride to give the 4-benzoyloxy compound (**5**). Treatment of **5** with hydrochloric acid in ethanol yielded the 2-mercapto compound (**6**), which was converted to the 2-(2-acetoxyethyl)thio compound (**7**) by treatment with 2-bromoethyl acetate in the presence of sodium hydrogen carbonate. Chlorination of **7** with sulfuryl chloride gave the 2-(2-acetoxy-1-chloroethyl)thio compound (**8**). When **8** was treated with triethylamine in the presence of water, the hydrolysis of the benzoate and the cyclization reaction proceeded successively to afford the 1-acetoxymethylthiazeto-quinolone ester (**9**) as a sole product. In this reaction, the $\beta$-elimination product (**A**) was not obtained. [3]

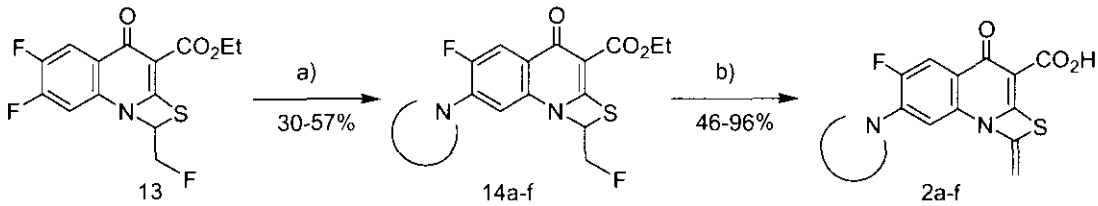
The acetoxyl group on C-1 methyl of **9** was converted to the methanesulfonyloxy group to enhance the $\beta$-elimination reaction. Thus, hydrolysis of the acetate on C-1 methyl substituent under acidic conditions in ethanol gave 1-hydroxymethyl analog (**10**) which was treated with 1-methylpiperazine in DMF to afford 7-(4-methyl-1-piperazinyl) compound (**11**). The reaction of **11** with methanesulfonyl chloride in the presence of triethylamine afforded **12** which was treated with aqueous potassium hydroxide to give the aimed compound (**2a**).




Scheme 1 (path 1)

On the other hand, during the study of the 7-cyclic amino-6-fluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]-thiazeto[3,2-*a*]quinoline-3-carboxylate (**14**) [3], the fluorine at C-1 methyl group in the thiazetoquinolone ring was found to be a good leaving group for the $\beta$-elimination reaction under the basic conditions. As shown in Scheme 2, we applied this method to an alternative synthetic route for **2** (path 2). Thus, ethyl 6,7-difluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**13**) was treated with cyclic amines in DMF to provide the 7-substituted compounds (**14a-f**), which were converted to the 1-

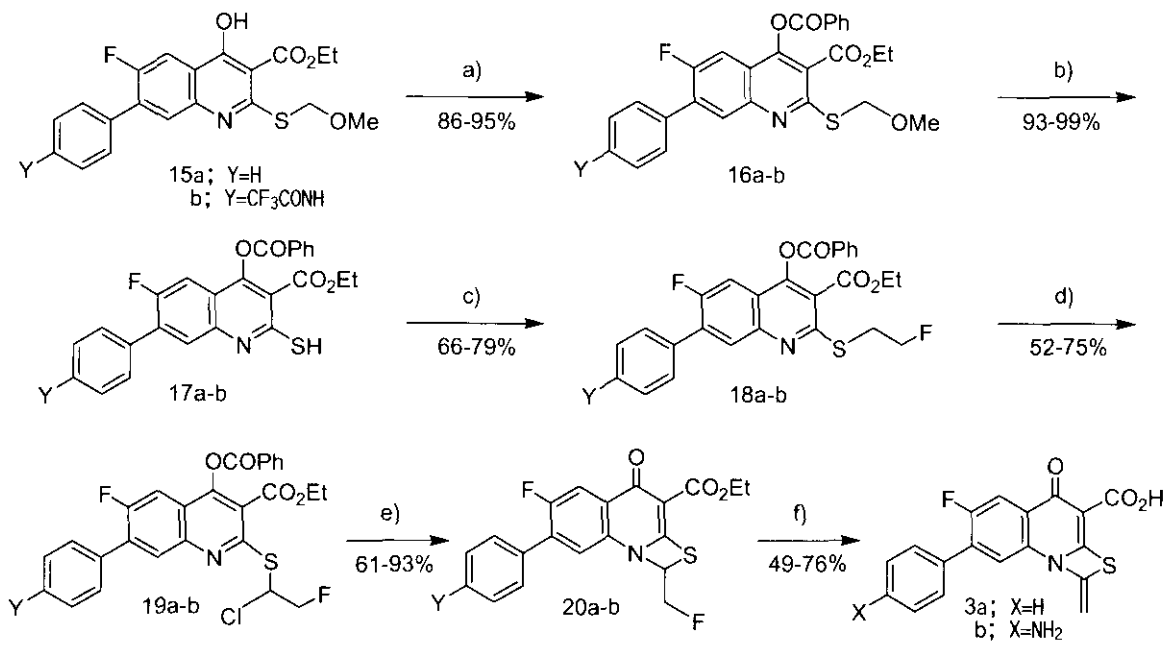
methylene-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acids (**2a-f**) in the same manner for the synthesis of **2a** from **12** as shown in Scheme 1.




a) cyclic amine, DMF b) 1% KOH in *t*-BuOH and $H_2O$

Scheme 2 (path 2)

The 7-aryl derivatives (**3a,b**) were synthesized from the ethyl 7-arylquinoline-3-carboxylates (**15a,b**) [4] *via* 1-fluoromethyl derivatives (**20a,b**) as shown in Scheme 3. Compounds (**15a,b**) were converted to the 2-mercapto compounds (**17a,b**) *via* **16a,b** by using the same method for the synthesis of **6** from **4** as shown in Scheme 1. Compounds (**17a,b**) were treated with 1-bromo-2-fluoroethane in the presence of sodium hydrogen carbonate to give the 2-(2-fluoroethyl)thio compounds (**18a,b**). Compound (**18a,b**) were converted to **20a,b** by using the same method for the synthesis of **9** from **7** as shown in Scheme 1. Compound (**20a,b**) were treated with aqueous potassium hydroxide to provide **3a,b**.




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) 1% KOH, *t*-BuOH, $H_2O$

Scheme 3

## Results and Discussion

Table 1 summarizes the *in vitro* antibacterial activity of the 1-methylenethiazetoquinolone derivatives against 5 gram-positive bacteria (*Staphylococcus aureus* 209P JC-1, *Staphylococcus aureus* Smith, *Enterococcus faecalis* ATCC 29212, Methicillin-resistant *Staphylococcus aureus* OWPH 1984 [quinolone-susceptible MRSA] and quinolone and Methicillin-resistant *Staphylococcus aureus* OWPH 2125 [quinolone-resistant MRSA]) and 5 gram-negative bacteria (*Escherichia coli* NIH JC-2, *Escherichia coli* KC-14, *Serratia marcescens* IFO3736, *Pseudomonas aeruginosa* IFO3445 and quinolone-resistant *Pseudomonas aeruginosa* SIR-5). The data for **1a**, **1b** and Ciprofloxacin (CPFX) are included for comparison.

In comparison with **1a**, **1b** and Ciprofloxacin, the 1-methylene derivatives (**2a-f**) and (**3a,b**) showed more potent *in vitro* antibacterial activity against gram-positive bacteria especially for MRSA although they showed almost the same or less potent activity against gram-negative bacteria. For those compounds with 7-cyclic amino group, the order of the *in vitro* activity of substitution at the C-7 position against gram-positive bacteria including quinolone-resistant MRSA was pyrrolidine (**2e**) > (3*S*)-3-aminopyrrolidine (**2f**) > morpholine (**2c**) and piperidine (**2d**) > 4-methylpiperazine (**2a**) > piperazine (**2b**).

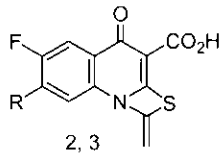
For the 7-(1-piperazinyl) and the 7-(4-methyhyl-1-piperazinyl) analogs, the substitution of a methyl group by a methylene group at the C-1 position of the thiazetoquinolone derivatives enhanced the *in vitro* antibacterial activity against quinolone-resistant MRSA and weakened the activity against gram-negative bacteria (**2a** *vs.* **1a**, **2b** *vs.* **1b**). Among the 7-cyclic amino analogs synthesized, **2e** had the most potent antibacterial activity against gram-positive bacteria including quinolone-resistant MRSA, and **2f** had the most potent antibacterial activity against gram-negative bacteria.

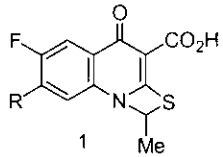
Introduction of an aryl group into 7-position of the 1-methylene-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid derivatives significantly improved the *in vitro* antibacterial activity against gram-positive bacteria. [5] Compound **3b** had the most potent antibacterial activity against gram-positive bacteria among all the compounds synthesized.

## Conclusion

In this paper, we have demonstrated the convenient synthetic procedure of the 1-methylenethiazeto-quinolone derivatives and the antibacterial activity of these compounds. Among the compounds synthesized, **2f** showed the most potent antibacterial activity against gram-negative bacteria, and **3b** showed the most potent activity against gram-positive bacteria including quinolone-resistant MRSA.

Table 1 *In vitro* Antibacterial Activity (MIC $\mu$ g/mL)




| | R | Gram-positive bacteria | | | | | Gram-negative bacteria | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Staphylococcus aureus* | | *Enterococcus faecalis* | Methicillin-resistant *Staphylococcus aureus* | | *Escherichia coli* | | *Serratia marcescens* | *Pseudomonas aeruginosa* | |
| | | P209 JC-1 | Smith | ATCC 29212 | OWPH 1984 | OWPH 2125* | NIHJ JC-2 | KC-14 | IFO 3736 | IFO 3445 | SIR-5* |
| 2a | 4-methylpiperazinyl | 0.05 | 0.05 | 0.2 | 0.1 | 0.39 | 0.05 | 0.12 | 0.39 | 0.39 | 6.25 |
| 2b | piperazinyl | 0.1 | 0.05 | 0.39 | 0.2 | 0.78 | 0.05 | 0.05 | 0.39 | 0.78 | 25 |
| 2c | morphorino | 0.025 | ≦0.006 | 0.2 | 0.025 | 0.05 | 0.2 | 0.1 | 0.78 | 0.39 | >100 |
| 2d | piperidino | 0.025 | 0.025 | 0.2 | 0.025 | 0.05 | 0.39 | 0.39 | 3.13 | 0.39 | >100 |
| 2e | pyrrolidinyl | 0.012 | ≦0.006 | 0.025 | ≦0.006 | 0.025 | 0.05 | 0.05 | 0.39 | 0.2 | >100 |
| 2f | (3*S*)-3-aminopyrrolidinyl | 0.012 | 0.0125 | 0.1 | 0.025 | 0.2 | 0.012 | 0.006 | 0.025 | 0.05 | 1.56 |
| 3a | phenyl | 0.012 | ≦0.006 | 0.1 | <0.006 | 0.025 | 0.39 | 0.2 | 0.78 | 0.2 | >100 |
| 3b | 4-aminophenyl | ≦0.006 | ≦0.006 | 0.025 | <0.006 | 0.012 | 0.05 | 0.025 | 0.39 | 0.1 | >100 |
| 1a | 4-methylpiperazinyl | 0.05 | 0.05 | 0.2 | 0.1 | 1.56 | 0.05 | 0.025 | 0.05 | 0.2 | 6.25 |
| 1b | piperazinyl | 0.05 | 0.1 | 0.39 | 0.39 | 6.25 | 0.012 | 0.012 | 0.05 | 0.05 | 12.5 |
| CPFX | | 0.1 | 0.1 | 0.39 | 0.78 | 12.5 | 0.012 | 0.012 | 0.1 | 0.05 | 25 |

*Quinolone-resistant

## 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 20h of incubation at 37℃.

### Chemistry

All melting points were determined in capillary tubes on a Büchi melting point apparatus and were 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 ( $\delta$ ). $^1$H-NMR spectra of all compounds obtained were consistent with assigned structures. IR spectra were recorded on a Shimadzu IR-453-U-03 spectrophotometer. HPLC analyses were carried out with Shimadzu LC-6A and LC-10A liquid chromatographs. 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-(methoxymethylthio)quinoline-3-carboxylate (5)**

Benzoyl chloride (46.95 g, 0.334 mol) was added dropwise to a stirred solution of ethyl 6,7-difluoro-4-hydroxy-2-(methoxymethylthio)quinoline-3-carboxylate **4** (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 were added to the reaction mixture. The resulting precipitate was collected by filtration, washed with water, and dissolved in chloroform. The solution was washed with 1N hydrochloric acid and water. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to give **5** (130 g, 99%) as a light yellow crystal. An analytical sample was preapared by recrystalization from ethyl acetate, mp 103℃. IR (KBr) cm$^{-1}$: 2950, 1740, 1605, 1525, 1270, 1205. $^1$H-NMR ($CDCl_3$) $\delta$ : 1.12 (3H, t, $J$=7.0 Hz), 3.47 (3H, s), 4.28 (2H, q, $J$=7.0 Hz), 5.56 (2H, s), 7.0-9.0 (7H, m). *Anal.* Calcd for $C_{21}H_{17}NO_5F_2S$: C, 58.19; H, 3.95; N, 3.23. Found: C, 58.55; H, 3.78; N, 3.44.

**Ethyl 4-benzoyloxy-6,7-difluoro-2-mercaptoquinoline-3-carboxylate (6)**

A suspension of ethyl 4-benzoyloxy-6,7-difluoro-2-(methoxymethylthio)quinoline-3-carboxylate **5** (132 g, 0.305 mol) and 38 mL of conc. hydrochloric acid in ethanol (1280 mL) was stirred for 22 h at rt. The resulting precipitate was collected by filtration, washed with ether, and air-dried at rt to give **6** (102.6 g,

87%). An analytical sample was preapared by recrystalization from ethanol, mp 165℃. IR (KBr) $cm^{-1}$: 2900, 1725, 1605, 1520, 1400, 1240, 1200. $^1$H-NMR ($CDCl_3$) δ : 1.18 (3H, t, *J*=7.0 Hz), 4.33 (2H, q, *J*=7.0 Hz), 7.0-8.0 (5H, m), 8.0-8.5 (2H, m), 10.5 (1H, br s). *Anal.* Calcd for $C_{19}H_{13}NO_4F_2S$: C, 58.61; H, 3.37; N, 3.60. Found: C, 58.60; H, 3.49; N, 3.63.

**Ethyl 2-(2-acetoxyethylthio)-4-benzoyloxy-6,7-difluoroquinoline-3-carboxylate (7)**

2-Bromoethyl acetate (51.5 g, 0.308 mol) was added dropwise to a stirred suspension of ethyl 4-benzoyloxy-6,7-difluoro-2-mercaptoquinoline-3-carboxylate (**6**) (120 g, 0.308 mol) and sodium hydrogen carbonate (25.9 g, 0.308 mol) in 1000 mL of DMF at rt for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was washed with *n*-hexane until the washings were no longer colored, then recrystallized from isopropyl ether to give **7** (120 g, 82%) as a pale yellow solid, mp 110℃. IR (KBr) $cm^{-1}$: 1755, 1740, 1725, 1655, 1590, 1510, 1430. $^1$H-NMR ($CDCl_3$) δ : 1.08 (3H, t, *J*=7.0 Hz), 2.08 (3H, s), 3.56 (2H, t, *J*=6.2 Hz), 4.26 (2H, q, *J*=7.0 Hz), 4.42 (2H, t, *J*=6.2 Hz), 7.68 (7H, m). *Anal.* Calcd for $C_{23}H_{19}NO_6F_2S$: C, 58.10; H, 4.03; N, 2.95. Found: C, 57.84; H, 3.77; N, 3.18.

**Ethyl 2-(2-acetoxy-1-chloroethylthio)-4-benzoyloxy-6,7-difluoroquinoline-3-carboxylate (8)**

A solution of sulfuryl chloride (52.4 g, 0.389 mol) in 150 mL of dichloromethane was added dropwise to a stirred suspension of ethyl 2-(2-acetoxyethylthio)-4-benzoyloxy-6,7-difluoroquinoline-3-carboxylate (**7**) (61.6 g, 0.130 mol) in 600 mL of dichloromethane over 0.5 h with ice-cooling and refluxed at 40℃ for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was washed with *n*-hexane, then recrystallized from isopropyl ether to give **8** (43.7 g, 66%), mp 110-111℃. IR (KBr) $cm^{-1}$: 1750, 1740, 1720, 1635, 1585, 1510, 1430. $^1$H-NMR ($CDCl_3$) δ : 1.06 (3H, t, *J*=7.2 Hz), 2.16 (3H, s), 4.26 (2H, q, *J*=7.2 Hz), 4.68 (2H, m), 6.53 (1H, t, *J*=5.3 Hz), 7.70 (7H, m).

*Anal.* Calcd for $C_{23}H_{18}NO_6ClF_2S$: C, 54.18; H, 3.56; N, 2.75. Found: C, 54.18; H, 3.60; N, 2.72.

**Ethyl 1-acetoxymethyl-6,7-difluoro-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (9)**

A solution of ethyl 2-(2-acetoxy-1-chloroethylthio)-4-benzoyloxy-6,7-difluoroquinoline-3-carboxylate (**8**) (27.6 g, 0.0542 mol), $H_2O$ (1.95 g, 0.108 mol) and triethylamine (16.45 g, 0.163 mol) in 300 mL of THF was refluxed at 80℃ for 24 h. The resulting precipitate was collected by filtration and washed with water, ethanol and ether, then dissolved in a mixture of chloroform and methanol, and washed with brine. The

organic layer was concentrated under reduced pressure and air-dried at 60℃ to give **9** (15.8 g, 79%). An analytical sample was preapared by recrystalization from ethyl acetate, mp 226-228 ℃. IR (KBr) $cm^{-1}$: 3045, 1745, 1715, 1610, 1560, 1495. $^1$H-NMR ($CDCl_3$) δ : 1.40 (3H, t, *J*=7.2 Hz), 2.20 (3H, s), 4.37 (2H, q, *J*=7.2 Hz), 4.84 (2H, m), 6.02 (1H, t, *J*=4.5 Hz), 7.20 (1H, m), 8.18 (1H, m). *Anal.* Calcd for $C_{16}H_{13}NO_5F_2S$: C, 52.03; H, 3.55; N, 3.79. Found: C, 52.15; N, 3.57; N, 3.75.

**Ethyl 6,7-difluoro-1-hydroxymethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (10)**

A suspension of ethyl 1-acetoxymethyl-6,7-difluoro-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**9**) (12.25 g, 33.2 mmol) and 2.5 g of sulfuric acid in 250 mL of ethanol was refluxed at 80℃ for 5 h. The reaction mixture was concentrated under reduced pressure, and the residue was washed with aqueous ethanol to give **10** (9.35 g, 86%). An analytical sample was preapared by recrystalization from ethanol, mp 288-290℃. IR (KBr) $cm^{-1}$: 3390, 1720, 1610, 1555, 1495. $^1$H-NMR (DMSO-$d_6$) δ : 1.26 (3H, t, *J*=7.0 Hz), 4.10 (2H, q, *J*=7.0 Hz), 4.11 (2H, ddd, *J*=26.0 Hz, 12.0 Hz, 4.0 Hz), 5.69 (1H, t, *J*=6.0 Hz), 6.18 (1H, t, *J*=4.0 Hz), 7.77 (1H, dd, *J*=12.0 Hz, 8.0 Hz), 8.80 (1H, dd, *J*=11.0 Hz, 9.0 Hz). *Anal.* Calcd for $C_{14}H_{11}NO_4F_2S$: C, 51.37; H, 3.39; N, 4.28. Found: C, 51.57;N, 3.14; N, 4.31.

**Ethyl 6-fluoro-1-hydroxymethyl-4-oxo-7-(4-methyl-1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (11)**

A suspension of ethyl 6,7-difluoro-1-hydroxymethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**10**) (2.00 g, 6.11 mmol) and 1-methylpiperazine (1.84 g, 18.33 mmol) in 40 mL of DMF was stirred at 60℃ for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was treated by 40 mL of water, then extracted with a mixture of chloroform and methanol (4:1). The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a pale yellow solid, which was purified by recrystallization from acetonitrile to give **11** (1.45 g, 59%), mp 263-265℃ (decomp). IR (KBr) $cm^{-1}$: 3300, 2800, 1720, 1630, 1600, 1495, 1395, 1330. $^1$H-NMR ($CDCl_3$) δ : 1.50 (3H, t, *J*=7.0 Hz), 3.11 (3H, s), 3.3-5.2 (11H, m), 4.63 (2H, q, *J*=7.0 Hz), 6.4-6.6 (1H, m), 7.43 (1H, d, *J*=6.0 Hz), 8.16 (1H, d, *J*=12.0 Hz). *Anal.* Calcd for $C_{19}H_{22}N_3O_4FS$: C, 56.01; H, 5.44; N, 10.31. Found: C, 55.97; H, 5.25; N, 10.14.

**6-Fluoro-1-methylene-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2a) (path 1)**

A solution of methanesulfonyl chloride (0.562 g, 4.91 mmol) in 5 mL of DMF was added dropwise to a

stirred suspension of ethyl 6-fluoro-1-hydroxymethyl-4-oxo-7-(4-methyl-1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**11**) (1.00 g, 2.45 mmol) and triethylamine (0.497 g, 4.91 mmol) in 10 mL of DMF with ice cooling. After stirring at rt for 12 h, the reaction mixture was washed with 5% sodium hydrogen carbonate aqueous solution, dried over magnesium sulfate and concentrated under reduced pressure to give **12** (1.07 g). Without further purification, **12** was dissolved in the solution of potassium hydroxide (0.1 g, 1.78 mmol) in *tert*-butyl alcohol (5 mL) and $H_2O$ (5 mL), and stirred at 60℃ for 24 h. After removal of insoluble material by filtration, the filtrate was acidified with acetic acid. The resulting precipitate was collected by filtration and purefied by recrystalization from acetonitrile to give **2a** (0.493 g, 56%), mp 244℃. IR (KBr) $cm^{-1}$: 3300, 1720, 1630, 1500. $^1$H-NMR (DMSO-$d_6$) δ :2.26 (3H, s), 3.0-3.6 (8H, m), 5.68 (1H, d, *J*=7.0 Hz), 6.30 (1H, d, *J*=7.0 Hz), 7.02 (1H, d, *J*=8.0 Hz), 7.88 (1H, d, *J*=14.0 Hz), 9.0 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_3O_3FS\cdot H_2O$: C, 53.82; H, 4.78; N, 11.08. Found: C, 54.16; H, 4.56; N, 10.80.

**Ethyl 6-fluoro-1-fluoromethy-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (14a)**

A suspension of ethyl 6,7-difluoro-1-fluoromethyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**13**) (8.2 g, 24.9 mmol), 1-methylpiperazine (4.99 g, 49.8 mmol) and potassium carbonate (6.88 g, 49.8 mmol) in 80 mL of DMF was stirred at 60℃ for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was poured into 40 mL of water and extracted with a mixture of chloroform and methanol (4:1). The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a pale yellow solid, which was purified by recrystallization from ethanol to give **14a** (3.06 g, 30%), mp 251℃. IR (KBr) $cm^{-1}$: 3400, 1720, 1630, 1600, 1500. $^1$H-NMR ($CDCl_3$) δ : 1.39 (3H, t, *J*=7.0 Hz), 2.35 (3H, s), 2.2-2.9 (4H, m), 3.0-3.6 (4H, m), 4.37 (2H, q, *J*=7.0 Hz), 4.99 (2H, dd, *J*=48.0 Hz, 6.0 Hz), 5.5-6.5 (1H, m), 6.66 (1H, d, *J*=7.0 Hz), 7.94 (1H, d, *J*=14.0 Hz). *Anal.* Calcd for $C_{19}H_{21}N_3O_3F_2S$: C, 55.73; H, 5.17; N, 10.26. Found: C, 55.62; H, 5.28; N, 10.10.

**Ethyl 6-fluoro-1-fluoromethy-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (14b)**

By using the same procedure with **14a**, compound (**14b**) was prepared in 30% yield from **13** and piperazine, mp 187℃. IR (KBr) $cm^{-1}$: 3300, 1730, 1630, 1610, 1500. $^1$H-NMR ($CDCl_3$) δ : 1.39 (3H, t, *J*=7.0 Hz), 3.14 (8H, br s), 4.38 (2H, q, *J*=7.0 Hz), 5.09 (2H, dd, *J*=46.0 Hz, 6.0 Hz), 5.7-6.0 (1H, m), 6.65 (1H, d, *J*=7.0 Hz), 7.30 (1H, br s), 7.92 (1H, d, *J*=12.0 Hz). *Anal.* Calcd for $C_{18}H_{19}N_3O_3F_2S\cdot 1/2H_2O$:

C, 53.46; H, 4.98; N, 10.39. Found: C, 53.55; H, 4.94; N, 10.45.

**Ethyl 6-fluoro-1-fluoromethy-7-morpholino-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (14c)**

By using the same procedure with **14a**, compound (**14c**) was prepared in 33% yield from **13** and morpholine, mp 273-274℃. IR (KBr) $cm^{-1}$: 2900, 1710, 1630, 1600, 1500, 1380. $^1$H-NMR ($CDCl_3$) δ : 1.40 (3H, t, *J*=7.0 Hz), 3.1-3.4 (4H, m), 3.8-4.0 (4H, m), 4.38 (2H, q, *J*=7.0 Hz), 5.09 (2H, dd, *J*=49.0 Hz, 6.0 Hz), 6.04 (1H, m), 6.67 (1H, d, *J*=7.0 Hz), 7.96 (1H, d, *J*=14.0 Hz). *Anal.* Calcd for $C_{18}H_{18}N_2O_4F_2S$: C, 54.54; H, 4.58; N, 7.07. Found: C, 54.77; H, 4.86; N, 6.93.

**Ethyl 6-fluoro-1-fluoromethy-4-oxo-7-piperidino-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (14d)**

By using the same procedure with **14a**, compound (**14d**) was prepared in 38% yield from **13** and piperidine, mp 244-245℃. IR (KBr) $cm^{-1}$: 3400, 2940, 1715, 1625, 1600, 1500. $^1$H-NMR ($CDCl_3$) δ : 1.40 (3H, t, *J*=7.0 Hz), 1.5-1.9 (6H, m), 3.1-3.3 (4H, m), 4.37 (2H, q, *J*=7.0 Hz), 5.02 (2H, dd, *J*=48.0 Hz, 6.0 Hz), 6.0 (1H, m), 6.64 (1H, d, *J*=8.0 Hz), 7.94 (1H, d, *J*=14.0 Hz). *Anal.* Calcd for $C_{19}H_{20}N_2O_3F_2S$: C, 57.86; H, 5.11; N, 7.10. Found: C, 57.86; H, 5.13; N, 7.02.

**Ethyl 6-fluoro-1-fluoromethy-4-oxo-7-(1-pyrrolidinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (14e)**

By using the same procedure with **14a**, compound (**14e**) was prepared in 38% yield from **13** and pyrrolidine, mp 274℃. IR (KBr) $cm^{-1}$: 3500, 2980, 1710, 1630, 1590, 1510, 1380, 1100. $^1$H-NMR ($CDCl_3$) δ : 1.32 (3H, t, *J*=7.0 Hz), 2.10 (4H, br s), 3.50 (4H, br s), 4.36 (2H, q, *J*=7.0 Hz), 4.98 (2H, dd, *J*=47.0 Hz, 6.0 Hz), 5.7-6.2 (1H, m), 6.21 (1H, d, *J*=7.0 Hz), 7.88 (1H, d, *J*=15.0 Hz). *Anal.* Calcd for $C_{18}H_{18}N_2O_3F_2S$: C, 56.83; H, 4.77; N, 7.36. Found: C, 56.60; H, 4.72; N, 7.05.

**Ethyl 7-[(3*R*)-3-amino-1-pyrrolidinyl]-6-fluoro-1-fluoromethy-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (14f)**

By using the same procedure with **14a**, compound (**14f**) was prepared in 57% yield from **13** and (3*R*)-3-amino-1-pyrrolidine, mp >300℃ (decomp). $^1$H-NMR ($CDCl_3$+DMSO-$d_6$) δ : 1.23 (3H, t, *J*=7.0 Hz), 3.46 (9H, br s), 3.70 (2H, q, *J*=7.0 Hz), 4.98 (2H, dd, *J*=48.0 Hz, 6.0 Hz), 5.2-5.8 (1H, m), 6.0-6.5 (1H, d), 7.90 (1H, d). *Anal.* Calcd for $C_{18}H_{19}N_3O_3F_2S$: C, 54.67; H, 4.84; N, 10.63. Found: C, 54.82; H, 4.69; N, 10.35.

**6-Fluoro-1-methylene-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2a) (path 2)**

A mixture of ethyl 6-fluoro-1-fluoromethyl-4-oxo-7-(4-methyl-1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**14a**) (1.97 g, 4.8 mmol) and potassium hydroxide (1 g, 17.8 mmnol) in of *tert*-butyl alcohol (50 mL) and $H_2O$ (50 mL) was stirred at 50℃ for 12 h. After removal of insoluble material by filtration, the filtrate was acidified with acetic acid. The resulting precipitate was collected by filtration, washed with ethanol and ether, then air-dried at rt to give **2a** (1.67 g, 96%). An analytical sample was preapared by recrystalization from ethanol, mp 244℃. IR (KBr) $cm^{-1}$: 3300, 1720, 1630, 1500. $^1$H-NMR (DMSO-$d_6$) δ : 2.26 (3H, s), 3.0-3.6 (8H, m), 5.68 (1H, d, *J*=7.0 Hz), 6.30 (1H, d, *J*=7.0 Hz), 7.02 (1H, d, *J*=8.0 Hz), 7.88 (1H, d, *J*=14.0 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_3O_3FS\cdot H_2O$: C, 53.82; H, 4.78; N, 11.08. Found: C, 54.06; H, 4.65; N, 10.96.

**6-Fluoro-1-methylene-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2b)**

By using the same procedure with **2a**, compound (**2b**) was prepared in 94% yield from **14b**, mp >300℃ (decomp). IR (KBr) $cm^{-1}$: 3400, 3000, 1720, 1610, 1495, 1360, 1250, 1220, 1100, 820, 790. $^1$H-NMR (DMSO-$d_6$) δ : 3.0-3.9 (9H, m), 5.70 (1H, d, *J*=7.0 Hz), 6.30 (1H, d, *J*=7.0 Hz), 7.00 (1H, d, *J*=8.0 Hz), 7.88 (1H, d, *J*=12.0 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}N_3O_3FS\cdot H_2O$: C, 52.60; H, 4.41; N, 11.50. Found: C, 52.33; H, 4.23; N, 11.39.

**6-Fluoro-1-methylene-7-morpholino-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2c)**

By using the same procedure with **2a**, compound (**2c**) was prepared in 46% yield from **14c**, mp 276-277℃. IR (KBr) $cm^{-1}$: 1715, 1632, 1610, 1500. $^1$H-NMR ($CF_3CO_2D$) δ : 3.6-4.0 (4H, m), 4.1-4.4 (4H, m), 5.88 (1H, d, *J*=8.0 Hz), 6.46 (1H, d, *J*=8.0 Hz), 7.22 (1H, d, *J*=7.0 Hz), 8.17 (1H, d, *J*=14.0 Hz). *Anal.* Calcd for $C_{16}H_{13}N_2O_4FS\cdot H_2O$: C, 52.45; H, 4.13; N, 7.65. Found: C, 52.64; H, 3.98; N, 7.66.

**6-Fluoro-1-methylene-4-oxo-7-piperidino-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2d)**

By using the same procedure with **2a**, compound (**2d**) was prepared in 85% yield from **14d**, mp 246-247℃. IR (KBr) $cm^{-1}$: 2900, 1710, 1630, 1600, 1500, 1470, 1390. $^1$H-NMR ($CDCl_3$) δ : 1.6-1.9 (6H, m), 3.2-3.4 (4H, m), 5.20 (1H, d, *J*=6.0 Hz), 5.72 (1H, d, *J*=6.0 Hz), 6.77 (1H, d, *J*=6.0 Hz), 7.92 (1H, d, *J*=14.0 Hz), 13.9 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}N_2O_3FS\cdot H_2O$: C, 56.03; H, 4.70; N, 7.69. Found: C,

56.37; H, 4.51; N, 7.58.

**6-Fluoro-1-methylene-4-oxo-7-(1-pyrrolidinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2e)**

By using the same procedure with **2a**, compound (**2e**) was prepared in 66% yield from **14e**, mp 285-286℃. IR (KBr) $cm^{-1}$: 1720, 1630, 1600, 1500. $^1$H-NMR ($CF_3CO_2D$) δ : 2.25 (4H, br s), 3.90 (4H, br s), 5.82 (1H, d, *J*=8.0 Hz), 6.30 (1H, d, *J*=8.0 Hz), 6.71 (1H, d, *J*=6.0 Hz), 8.01 (1H, d, *J*=12.0 Hz). *Anal.* Calcd for $C_{16}H_{13}N_2O_3FS \cdot 3/2H_2O$: C, 53.47; H, 4.49; N, 7.79. Found: C, 53.41; H, 4.04; N, 7.54.

**7-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-fluoro-1-methylene-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (2f)**

By using the same procedure with **2a**, compound (**2f**) was prepared in 48% yield from **14f**, mp >300℃ (decomp). IR (KBr) $cm^{-1}$: 3400, 2900, 1630, 1510, 1360, 1230, 790. $^1$H-NMR ($CF_3CO_2D$) δ : 2.4-2.9 (3H, m), 3.6-4.6 (6H, m), 5.87 (1H, d, *J*=8.0 Hz), 6.38 (1H, d, *J*=8.0 Hz), 6.79 (1H, d, *J*=6.0 Hz), 8.10 (1H, d, *J*=14.0 Hz). *Anal.* Calcd for $C_{16}H_{14}N_3O_3FS \cdot H_2O$: C, 52.60; H, 4.41; N, 11.50. Found: C, 52.42; H, 4.43; N, 10.86.

**Ethyl 4-benzoyloxy-6-fluoro-2-(methoxymethylthio)-7-phenylquinoline-3-carboxylate (16a)**

By using the same procedure with **5**, compound (**16a**) was prepared in 95% yield from **15a**, mp 110-111℃. IR (KBr) $cm^{-1}$: 2980, 1745, 1730, 1630, 1595, 1540, 1505, 1485, 1450, 1430, 1405. $^1$H-NMR ($CDCl_3$) δ : 1.13 (3H, t, *J*=7.0 Hz), 3.47 (3H, s), 4.30 (2H, q, *J*=7.0 Hz), 5.59 (2H, s), 7.4-8.3 (12H, m). *Anal.* Calcd for $C_{27}H_{22}NO_5FS$: C, 65.98; H, 4.51; N, 2.85. Found: C, 66.05; H, 4.29; N, 2.84.

**Ethyl 4-benzoyloxy-6-fluoro-2-mercapto-7-phenylquinoline-3-carboxylate (17a)**

By using the same procedure with **6**, compound (**17a**) was prepared in 93% yield from **16a**, mp 203-204℃. IR (KBr) $cm^{-1}$: 2365, 1745, 1735, 1640, 1615, 1510, 1485, 1450, 1425. $^1$H-NMR ($CDCl_3$) δ : 1.17 (3H, t, *J*=7.0 Hz), 4.34 (2H, q, *J*=7.0 Hz), 7.4-8.3 (12H, m), 12.00 (1H, br s). *Anal.* Calcd for $C_{25}H_{18}NO_4FS$: C, 67.10; H, 4.05; N, 3.13. Found: C, 67.13; H, 3.76; N, 3.02.

**Ethyl 4-benzoyloxy-6-fluoro-2-(2-fluoroethylthio)-7-phenylquinoline-3-carboxylate (18a)**

By using the same procedure with **7**, compound (**18a**) was prepared in 79% yield from **17a** and 2-bromo-1-fluoroethane, mp 147-148℃. IR (KBr) $cm^{-1}$: 3855, 2365, 1760, 1725, 1595, 1560, 1540, 1505, 1480,

1450, 1430, 1405. $^1$H-NMR ($CDCl_3$+$CF_3CO_2D$) δ : 1.11 (3H, t, *J*=7.0 Hz), 3.52 (1H, t, *J*=6.4 Hz), 3.82 (1H, t, *J*=4.0 Hz), 4.1-4.5 (3H, m), 5.14 (1H, t, *J*=4.0 Hz), 7.4-8.3 (12H, m). *Anal.* Calcd for $C_{27}H_{21}NO_4F_2S$: C, 65.71; H, 4.29; N, 2.84. Found: C, 65.99; H, 4.31; N, 2.91.

**Ethyl 4-benzoyloxy-2-[(1-chloro-2-fluoroethyl)thio]-6-fluoro-7-phenylquinoline-3-carboxylate (19a)**

By using the same procedure with **8**, compound (**19a**) was prepared in 75% yield from **18a**, mp 145℃. IR (KBr) cm$^{-1}$: 1740, 1710, 1585, 1545, 1505, 1480, 1450, 1430, 1410. $^1$H-NMR ($CDCl_3$) δ : 1.07 (3H, t, *J*=7.0 Hz), 4.1-4.6 (3H, m), 5.2-5.3 (1H, m), 6.5-6.8 (1H, m), 7.4-8.4 (12H, m). *Anal.* Calcd for $C_{27}H_{20}NO_4ClF_2S$: C, 61.42; H, 3.82; N, 2.65. Found: C, 61.46; H, 4.20; N, 2.70.

**Ethyl 6-fluoro-1-fluoromethyl-4-oxo-7-phenyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (20a)**

By using the same procedure with **9**, compound (**20a**) was prepared in 61% yield from **19a**, mp 241-242℃. IR (KBr) cm$^{-1}$: 3400, 1730, 1665, 1615, 1485, 1445, 1340. $^1$H-NMR ($CDCl_3$) δ : 1.27 (3H, t, *J*=7.0 Hz), 4.20 (2H, q, *J*=7.0 Hz), 4.6-5.0 (1H, m), 5.5-5.8 (1H, m), 6.2-6.5 (1H, m), 7.70 (6H, m), 7.88 (1H, d, *J*=11.0 Hz). *Anal.* Calcd for $C_{20}H_{15}NO_3F_2S$: C, 62.01; H, 3.90; N, 3.62. Found: C, 61.70; H, 3.87; N, 3.65.

**6-Fluoro-1-methylene-4-oxo-7-phenyl-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (3a)**

By using the same procedure with **2a**, compound (**3a**) was prepared in 49% yield from **20a**, mp 265-266℃ (decomp). $^1$H-NMR (DMSO-$d_6$) δ : 5.66 (1H, d, *J*=7.0 Hz), 6.54 (1H, d, *J*=7.0 Hz), 7.59 (5H, br s), 7.96 (1H, d, *J*=5.0 Hz), 8.01 (1H, d, *J*=12.0 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{18}H_{10}NO_3FS$: C, 63.71; H, 2.97; N, 4.13. Found: C, 63.40; H, 3.14; N, 4.03.

**Ethyl 4-benzoyloxy-6-fluoro-2-(methoxymethylthio)-7-(4-trifluoroacetylaminophenyl)quinoline-3-carboxylate (16b)**

By using the same procedure with **5**, compound (**16b**) was prepared in 86% yield from **15b**, which was used directly without further purification. $^1$H-NMR ($CDCl_3$) δ : 1.13 (3H, t, *J*=7.0 Hz), 3.48 (3H, s), 4.31 (2H, q, *J*=7.0 Hz), 5.58 (2H, s), 7.4-8.4 (12H, m).

**Ethyl 4-benzoyloxy-6-fluoro-2-mercapto-7-(4-trifluoroacetylaminophenyl)quinoline-3-carboxylate (17b)**

By using the same procedure with **6**, compound (**17b**) was prepared in 99% yield from **16b**, mp 257℃. IR (KBr) cm$^{-1}$: 3300, 1730, 1610, 1250, 1190, 1050. $^1$H-NMR ($CDCl_3$) δ : 1.18 (3H, t, *J*=7.0 Hz), 4.37

(2H, q, *J*=7.0 Hz), 7.3-8.5 (12H, m), 12.00 (1H, br s). *Anal.* Calcd for $C_{27}H_{18}N_2O_5F_4S \cdot 1/2H_2O$: C, 57.14; H, 3.37; N, 4.94. Found: C, 57.33; H, 3.46; N, 5.13.

**Ethyl 4-benzoyloxy-6-fluoro-2-(2-fluoroethylthio)-7-[4-(trifluoroacetylamino)phenyl]quinoline-3-carboxylate (18b)**

By using the same procedure with **7**, compound (**18b**) was prepared in 66% yield from **17b** and 2-bromo-1-fluoroethane, mp 170℃. IR (KBr) $cm^{-1}$: 3310, 1760, 1730, 1700, 1600, 1545, 1250, 1190, 1150, 1045, 1022. $^1$H-NMR ($CDCl_3$) δ : 1.10 (3H, t, *J*=7.0 Hz), 3.2-4.0 (2H, m), 4.29 (2H, q, *J*=7.0 Hz), 4.0-5.4 (2H, m), 7.5-8.4 (11H, m), 8.76 (1H, br s). *Anal.* Calcd for $C_{29}H_{21}N_2O_5F_5S$: C, 57.62; H, 3.50; N, 4.63. Found: C, 58.02; H, 3.54; N, 4.72.

**Ethyl 4-benzoyloxy-2-(1-chloro-2-fluoroethylthio)-6-fluoro-7-[4-(trifluoroacetylamino)phenyl]-quinoline-3-carboxylate (19b)**

By using the same procedure with **8**, compound (**19b**) was prepared in 52% yield from **18b**, which was used directly without further purification. $^1$H-NMR ($CDCl_3$) δ : 1.07 (3H, t, *J*=7.0 Hz), 4.28 (2H, q, *J*=7.0 Hz), 4.3-4.7 (1H, m), 5.0-5.5 (1H, m), 6.3-6.8 (1H, m), 7.4-8.6 (12H, m).

**Ethyl 6-fluoro-1-fluoromethyl-4-oxo-7-(4-trifluoroacetylaminophenyl)-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (20b)**

A solution of ethyl 4-benzoyloxy-2-[(1-chloro-2-fluoroethyl)thio]-6-fluoro-7-(4-trifluoroacetylamino-phenyl)quinoline-3-carboxylate (**19b**) (4.0 g, 6.26 mmol), $H_2O$ (0.23 g, 12.52 mmol) and triethylamine (3.17 g, 31.3 mmol) in 40 mL of *n*-hexane was refluxed at 80℃ for 3 days. The resulting precipitate was collected by filtration and washed with water, ethanol and ether, then dissolved in a mixture of chloroform and methanol, then washed with brine. The organic layer was concentrated under reduced pressure and purified by chromatography on silica gel with chloroform to give **20b** (2.9 g, 93%). An analytical sample was preapared by recrystalization from acetonitrile, mp 259℃. IR (KBr) $cm^{-1}$: 3260, 1725, 1595, 1540, 1480, 1160. $^1$H-NMR (DMSO-$d_6$) δ : 1.28 (3H, t, *J*=7.0 Hz), 4.22 (2H, q, *J*=7.0 Hz), 4.9-5.7 (2H, m), 6.52 (1H, br d, *J*=22.0 Hz), 7.4-8.0 (6H, m), 10.42 (1H, br s). *Anal.* Calcd for $C_{22}H_{15}N_2O_4F_5S$: C, 53.01; H, 3.03; N, 5.62. Found: C, 53.40; H, 3.37; N, 5.73.

**7-(4-Aminophenyl)-6-fluoro-1-methylene-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (3b)**

A mixture of ethyl 6-fluoro-1-fluoromethyl-4-oxo-7-(4-trifluoroacetylaminophenyl)-4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylate (**20b**) (0.50 g, 1 mmol), potassium hydroxide (0.25 g, 4.5 mmol) in *tert*-

butyl alcohol (12.5 mL) and $H_2O$ (12.5 mL) was stirred at 50℃ for 2 h. After removal of insoluble material by filtration, the filtrate was acidified with acetic acid. The resulting precipitate was collected by filtration, then dissolved in the mixture of chloroform and methanol. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give **3b** (0.27 g, 76%). An analytical sample was preapared by recrystalization from acetonitrile, mp >300℃ (decomp). IR (KBr) $cm^{-1}$: 3450, 3350, 1920, 1630, 1490, 1360, 1290, 1190. $^1$H-NMR (DMSO-$d_6$) δ : 5.60 (2H, br s), 5.70 (1H, d, *J*=7.0 Hz), 6.52 (1H, d, *J*=7.0 Hz), 6.72 (2H, d, *J*=9.0 Hz), 7.47 (2H, dd, *J*=8.0 Hz, 3.0 Hz), 7.83 (1H, d, *J*=6.0 Hz), 7.97 (1H, d, *J*=10.0 Hz), 13.9 (1H, br s). *Anal.* Calcd for $C_{18}H_{11}N_2O_3FS \cdot 3/4H_2O$: C, 58.77; H, 3.42; N, 7.61. Found: C, 58.67; H, 3.43; N, 7.26.

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