Studies on Pyridonecarboxylic Acids. V. A Practical Synthesis of Ethyl 6,7-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate, a Key Intermediate for the New Tricyclic Quinolone, Prulifloxacin (NM441) and Versatile New Syntheses of the 2-Thioquinoline Skeleton

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A practical synthesis of ethyl 6,7-difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (**9**), the key intermediate for 6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-1-piperazinyl]-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**2**), NM441, was developed. The crucial points of this synthetic route are the chlorination of ethyl 4-acetoxy-2-(ethylthio)-6,7-difluoroquinoline-3-carboxylate (**12**) and the subsequent deacetylation of the resulting 2-(1-chloroethyl)thio compound **13** followed by the intramolecular cyclization reaction. Versatile new syntheses of 2-thioquinoline skeleton were also developed. The first route includes the intramolecular cyclization of the *N,S*-acetal **22** which was prepared from 2,4,5-trifluorobenzoic acid in three steps. The second one contains the regioselective attack of lithium enolate of ethyl acetate to the novel 2-(methylthio)-4*H*-[3,1]benzothiazine-4-one **29** at the 4-position followed by the intramolecular cyclization of the resulting β-ketoester **30**.

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In our search for new, potent quinolones, we have been studying tricyclic compounds characterized by a sulfur-bridge between the 2-position and the substituent at the 1-position of quinolones. Among these derivatives, 6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]-thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**1**), NM394, showed excellent *in vitro* antibacterial activity, and 6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-1-piperazinyl]-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (**2**), a prodrug of **1**, was found to possess good oral efficacy in clinical testing [1] (Figure 1).

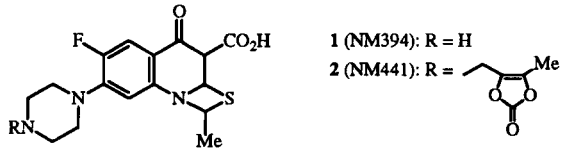
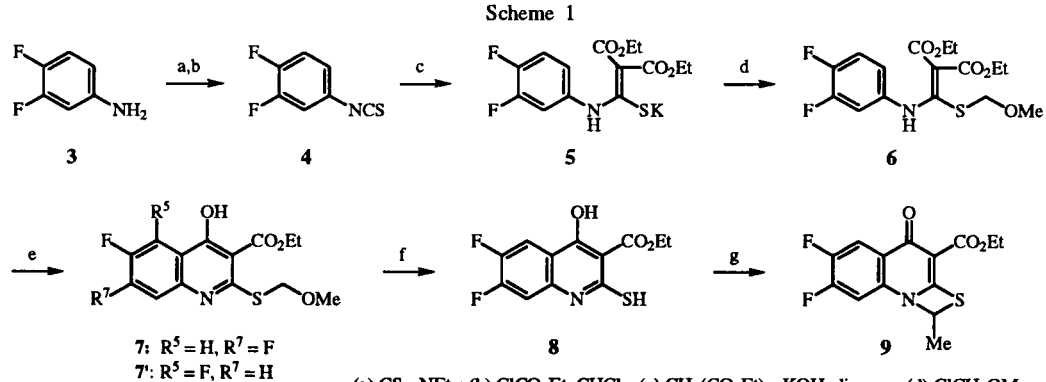


Figure 1

In the previous paper, we reported the synthesis of ethyl 6,7-difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto-[3,2-*a*]quinoline-3-carboxylate **9**, the key intermediate for **2**. The synthetic route contains the Gould-Jacobs cyclization [2] of a *N,S*-acetal **6** which is derived from the mercapto compound **5** by using chloromethyl methyl ether. The required quinoline **7** was obtained in fairly good yield along with an amount of the regio-isomer **7'**. Compound **7** is then deprotected by acid to give the mercapto compound **8**, which is converted to the tricyclic compound **9** by using 1,1-dibromoethane [1a] (Scheme 1). In order to retrieve the lack of the regiospecificity in quinoline ring formation and the use of harmful chloromethyl methyl ether and expensive 1,1-dibromoethane, we examined several different synthetic routes and found a practical route for **9** and two versatile new routes to the 2-thioquinoline skeleton. In this paper, we report these synthetic approaches in detail.

Scheme 1



(a) CS_2, NEt_3; (b) $ClCO_2Et$, $CHCl_3$; (c) $CH_2(CO_2Et)_2$, KOH, dioxane; (d) $ClCH_2OMe$, NEt_3, toluene; (e) Ph_2O, heat; (f) H^+, EtOH; (g) $MeCHBr_2$, K_2CO_3, DMF.

Results and Discussion.

The drawback of the reported method for synthesizing **9** lies in the circuitous protection and deprotection steps and the use of harmful chloromethyl methyl ether and expensive 1,1-dibromoethane. In order to avoid these disadvantages, we considered the retrosynthesis to **9** (Figure 2) and examined the route which involves the synthesis of the 2-(1-chloroethyl)thio compound **I** and the cyclization reaction of **I** to the required compound **9**.

The 4-hydoxy-2-(ethylthio) compound **11** was synthesized by using a similar method for the synthesis of ethyl 6,7-difluoro-4-hydroxy-2-(methoxymethyl)thioquinoline-3-carboxylate (**7**) [1a]. Ethylation of **5** with diethyl sulfate or ethyl bromide gave the *N,S*-acetal **10**, which was heated in diphenyl ether to afford the 6,7-difluoroquinoline **11** along with a considerable amount of the regioisomer **11'**. Further examination showed that the yield and regioselectivity were highest when **10** was heated in xylene under refluxing. The halogenation of 2-(ethylthio) compounds **11** and **12** was attempted to obtain compound **I** by using a Pummerer like halogenation reaction [3]. First the 4-hydroxy-2-(ethylthio) compound **11** was treated with *N*-chlorosuccinimide (NCS) in methylene chloride to give the *N*-chloro compound **14** instead of the required 2-(1-chloroethyl)thio compound **15**. The structure of **14** was speculated from the nmr and ir data. To suppress the side reaction in the chlorination, **11** was converted to the 4-acetoxy-2-(ethylthio) compound **12** by treatment with acetyl chloride or acetic anhydride. The chlorination of **12** was attained by using the Maslankiewicz method [4]: **12** was treated with *N*-chlorosuccinimide in carbon tetrachloride by irradiation with a 500 watt lamp to afford the required 2-(1-chloroethyl)thio compound **13** in 70% yield. The structure of **13** was confirmed by nmr and elemental analyses. The methyl protons resonated as a doublet at δ 2.02 (J = 7 Hz) and the methine proton as a quartet at δ 6.41 (J = 7 Hz). Further examination showed that the chlorination of **12** with sulfuryl chloride also gave **13** in fairly good yield. As **13** was found to be unstable under acidic condition, the chlorination was attempted under reflux by removing hydrogen chloride generated in the reaction vessel along with the solvent as soon as possible to give the best results. The deacetylation of **13** and the subsequent cyclization reaction was examined under anhydrous condition because **13** was unstable in water. Thus, **13** was treated with sodium acetate in tetrahydrofuran to afford **9** in good yield (Scheme 2).

An alternative method of synthesizing **10** in which expensive 3,4-difluoroaniline was used in the later step was examined. Treatment of diethyl malonate with carbon disulfide and ethyl iodide successively in the presence of sodium hydride in dry tetrahydrofuran afforded the ketene dithioacetal **16** quantitatively [5]. As the substitution reaction of **16** with 3,4-difluoroaniline **3** did not proceed [6], **16** was oxidized to the monosulfoxide **17** with

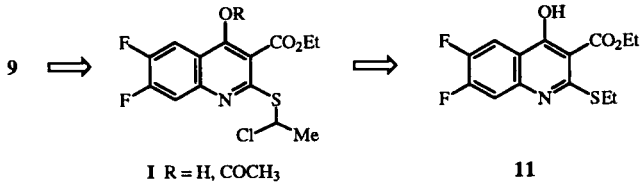
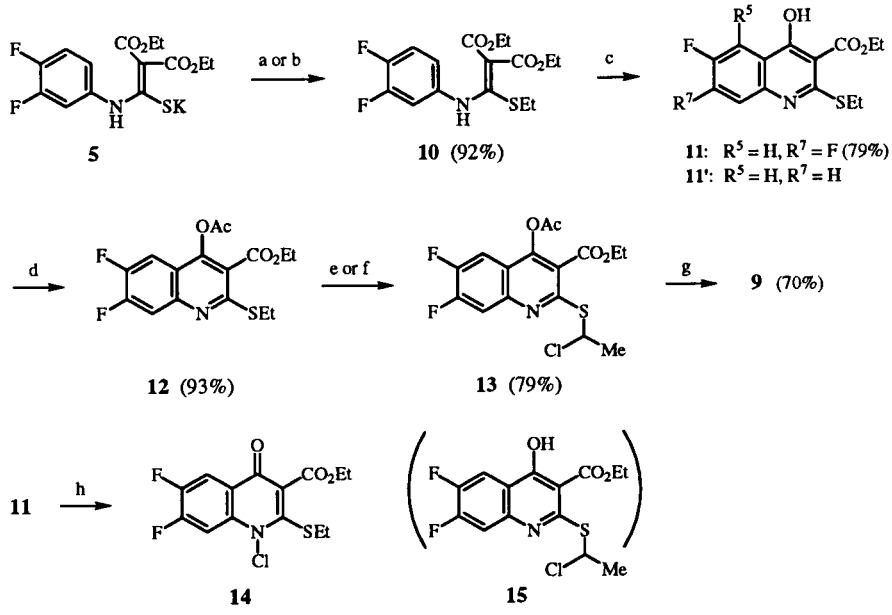


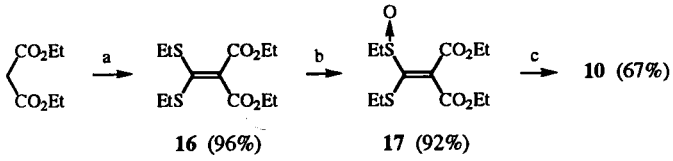
Figure 2

Scheme 2



(a) $(EtO)_2SO_2$, EtOH; (b) EtBr, acetone; (c) xylene, heat; (d) AcCl, NEt_3, $CHCl_3$; (e) *N*-Chlorosuccinimide, CCl_4 (70%); (f) SO_2Cl_2, *n*-hexane (79%); (g) NaOAc, THF; (h) *N*-Chlorosuccinimide, CH_2Cl_2

Scheme 3



(a) NaH, CS_2, EtI, THF; (b) *m*-Chloroperbenzoic acid, CH_2Cl_2; (c) 3,4-Difluoroaniline

m-chloroperbenzoic acid to increase the electrophilicity. Substitution reaction of **17** with **3** afforded the required compound **10** in fairly good yield. However, the yield of the last step should yet be improved (Scheme 3).

Although the synthetic route free from circuitous protection and deprotection steps and using of harmful chloromethyl methyl ether and expensive 1,1-dibromoethane was developed as described above, the challenge to increase the regioselectivity in the quinoline ring formation step was not accomplished. In order to solve this problem, we investigated the retrosythesis to **11** (Figure 3), and examined firstly the route A.

The β-ketoester **19** was synthesized from 2,4,5-trifluorobenzoic acid **18** by the reported method [7]. Compound **19** was treated with carbon disulfide in the presence of anhydrous potassium carbonate followed by ethylation with ethyl iodide under ice cooling to give the dithioacetal **20** [8]. When this reaction was conducted at room temperature, the benzothiopyran derivative **21** was obtained. Amination of **20** with 10% ammonia in ethyl alcohol in sealed tube at 80° afforded the *N,S*-acetal **22** along with a considerable amount of diamino compound **23** and the starting material **20**. Compound **22** was then treated with potassium hydrogen carbonate in dimethylformamide at 80° for 24 hours to yield **11**. Although **11** was synthesized regiospecifically by this method, the yield of **22** and **11** could not be improved (Scheme 4).

Route B, in which **8** was expected to be obtained easily by intramolecular cyclization of the 2-isothiocyanato or 2-dithiocarbamoyl benzoate derivative **V** [9], was examined (Figure 3).

As 4,5-difluoroanthranilic acid **24** was treated with carbon disulfide and ethyl chloroformate in the presence of triethylamine to afford no isothiocyanate compound **25**, **24** was treated with carbon disulfide in the presence of triethylamine followed by methylation with methyl iodide to give the alternative reactive dithiocarbamate **27**. The carboxyl group of **27** was activated by treating with *N*-hydroxysuccimide in

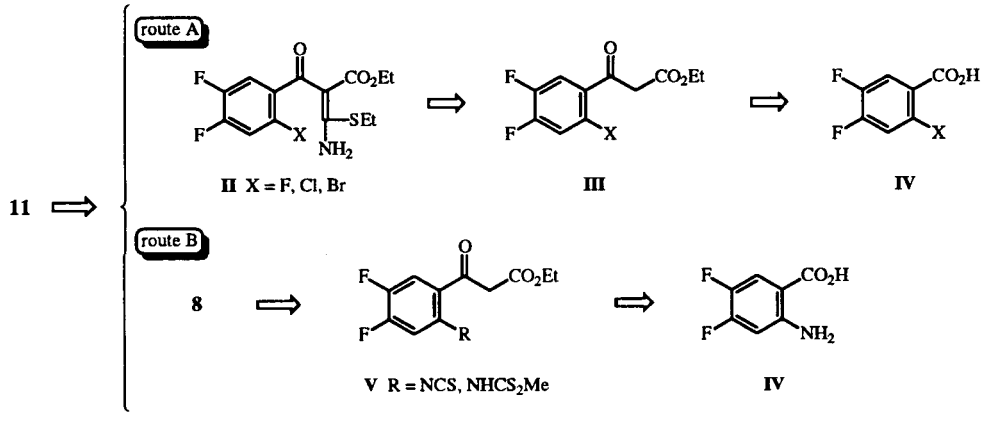
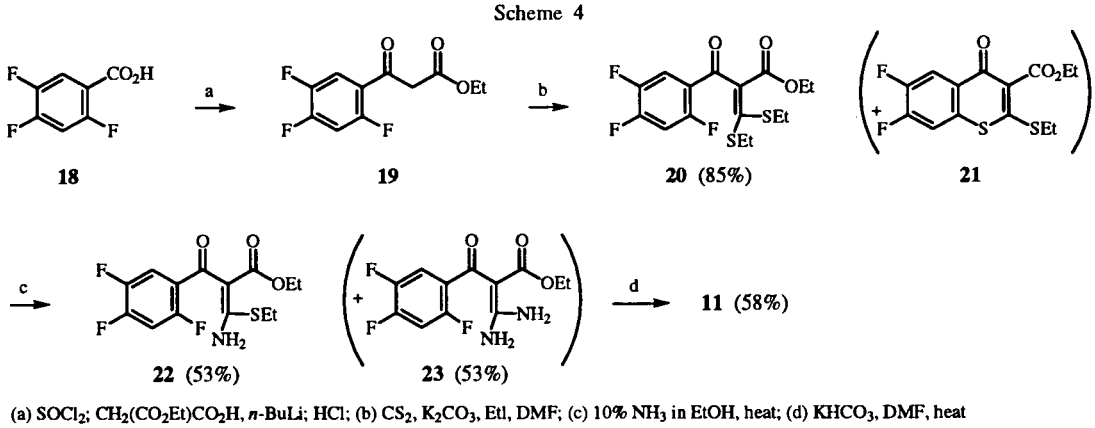


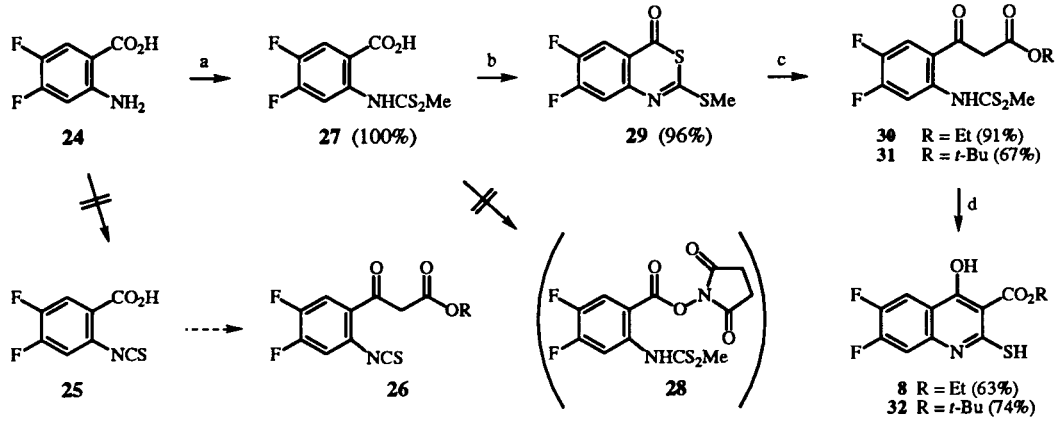
Figure 3

Scheme 4



(a) $SOCl_2$; $CH_2(CO_2Et)CO_2H$, *n*-BuLi; HCl; (b) CS_2, K_2CO_3, EtI, DMF; (c) 10% NH_3 in EtOH, heat; (d) $KHCO_3$, DMF, heat

Scheme 5



the presence of 1,3-dicyclohexylcarbodiimide to afford the 4*H*-[3,1]benzothiazine-4-one derivative **29** instead of the expected compound **28**. Compound **29** was also obtained quantitatively by treating **27** with acetic anhydride (Scheme 5).

Only a few studies on the reactivity of the 4*H*-[3,1]benzothiazin-4-one to nucleophiles have been reported. Thus, 2-phenyl derivative **33** was reacted with ammonia at the 2-position to give amidine derivative **34** [10a], and with primary amines at the 4-position to give thioamide **35** [10b] (Figure 4). There was no report on the 2-(alkylthio)-4*H*-[3,1]benzothiazin-4-ones, and on the regioselectivity of the reaction of the carbanion to the 2-substituted-4*H*-[3,1]benzothiazin-4-ones. We considered that the desired β-ketoester **30** should have been obtained in good yield if the anion of ethyl acetate attacked **29** at the 4-position regioselectively.

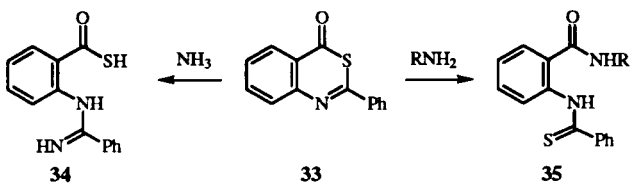


Figure 4

Thus, **29** was treated with the lithium enolate of ethyl acetate. As expected, the regiospecific attack of the enolate occurred at the 4-position of **29** to afford the β-ketoester **30** in 91% yield. Compound **30** was then treated with sodium ethoxide in ethyl alcohol to yield the 2-mercaptoquinoline derivatives **8**. When **29** was treated with the lithium enolate of *tert*-butyl acetate followed by an intramolecular cyclization reaction with sodium ethoxide to give the corresponding compound **32** (Scheme 5).

In conclusion, the practical synthetic route for **9** was accomplished in high yield by the chlorination of the 2-(ethylthio) compound **12** followed by the deacetylation of the resulting 4-acetyl-2-(1-chloroethyl)thio compound **13** and the subsequent intramolecular cyclization reaction. As the later two steps are carried out in one pot, the number of the reaction steps is equal to that of the previous method. This new procedure has advantages over the previous one, avoiding the circuitous protection and deprotection steps, and as a result, not using harmful chloromethyl methyl ether and expensive 1,1-dibromoethane. In addition, two new versatile methods for preparing the 2-thioquinoline skeleton were developed. These two procedures have an advantage over the previous ones in regioselective formation of the quinoline skeleton.

EXPERIMENTAL

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. The ^{1}H nmr spectra were determined on a Varian XL-200 or an Hitachi R-24-B spectrometer with tetramethylsilane as an internal standard; chemical shifts are given in ppm (δ). The ^{1}H nmr spectra of all compounds obtained were consistent with assigned structures. The ir spectra were recorded on a Shimadzu IR-453-U-03 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102 spectrometer at 70eV ionization potential. Hplc analyses were carried out with a Shimadzu LC-6A liquid chromatograph. Column chromatography separations were carried out on a Wako Gel C-200 and C-300. Yields are of purified products and are not optimized.

Ethyl 2-(Ethylthio)-6,7-difluoro-4-hydroxyquinoline-3-carboxylate (**11**). (The First Method).

Diethyl sulfate (1.54 g, 0.01 mole) in 45 ml of ethyl alcohol was added dropwise to a stirred suspension of potassium salt of diethyl [(3,4-difluorophenyl)amino]mercaptomethylenemalonate (**5**) [1a] (4.64 g, 0.01 mole) with ice cooling. After stirring at room temperature for 4 hours, the reaction mixture was stirred at 50° for 1 hour and

concentrated to dryness under reduced pressure. The residue was taken up in water and extracted with *n*-hexane (50 ml). The organic layer was washed with water, dried with magnesium sulfate, and concentrated to dryness under reduced pressure to give 3.30 g (92%) of diethyl [(3,4-difluorophenyl)amino](ethylthio)methylenemalonate (**10**) as an oil. Without purification, **10** (1.00 g, 2.79 m moles) was dissolved in 5 ml of xylene and heated under reflux for 3 hours. After cooling, the reaction mixture was diluted with 5 ml of *n*-hexane. The resulting crystalline product was collected by filtration to give 0.69 g (79%) of **11**, mp 127-128°; ir (potassium bromide): 1645 (C=O), 1500, 1430, 1310, 1230, 1205 cm^{-1}; ^1H nmr (deuteriochloroform):δ 1.2-1.8 (m, 6H, SCH_2CH_3 and OCH_2CH_3), 3.2 (q, J = 7 Hz, 2H, SCH_2CH_3), 4.55 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 7.2-8.2 (m, 2H, 5-H and 8-H), 13.22 (s, 1H, OH).

Anal. Calcd. for $C_{14}H_{13}F_2NO_3S$: C, 53.67; H, 4.18; N, 4.47. Found: C, 53.88; H, 4.10; N, 4.28.

Ethyl 4-Acetoxy-6,7-difluoro-2-(ethylthio)quinoline-3-carboxylate (**12**).

Triethylamine (15.2 g, 0.15 mole) was added to a stirred suspension of **11** (31.3 g, 0.10 mole) in 150 ml of chloroform, and then acetyl chloride (8.2 g, 0.11 mole) was added dropwise with ice cooling. After stirring at the same temperature for 1 hour, 100 ml of 1*N* hydrochloric acid was added to the reaction mixture. The organic layer was washed with water, dried with magnesium sulfate, and concentrated to dryness under reduced pressure. The residue was treated in *n*-hexane and the resulting precipitate was collected by filtration to afford 33.1 g (93%) of **12** as light brown crystals, mp 64-67°; ir (potassium bromide): 1785 (C=O), 1715 (C=O), 1510, 1320, 1010, 965 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (t, J = 7 Hz, 6H, SCH_2CH_3, $COOCH_2CH_3$), 2.43 (s, 3H, $OCOCH_3$), 3.28 (q, J = 7 Hz, 2H, SCH_2CH_3), 4.44 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 7.2-8 (m, 2H, 5-H and 8-H).

Anal. Calcd. for $C_{16}H_{15}F_2NO_4S$: C, 54.08; H, 4.25; N, 3.94. Found: C, 54.23; H, 4.29; N, 3.88.

Ethyl 4-Acetoxy-2-(1-chloroethyl)thio-6,7-difluoroquinoline-3-carboxylate (**13**).

A solution of sulfuryl chloride (5.94 g, 0.044 mole) in 6 ml of *n*-hexane was added dropwise to a stirred suspension of **12** (7.11 g, 0.020 mole) in 35 ml of *n*-hexane over 1.5 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (3:1), then subsequent recrystallization from *n*-hexane to give 6.17 g (79%) of **13**, mp 71-73°; ir (potassium bromide): 2980, 1785 (C=O), 1710 (C=O), 1505, 1425, 1320, 1170 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (t, J = 7 Hz, 3H, $COOCH_2CH_3$), 2.02 (d, J = 7 Hz, 3H, $SCHClCH_3$), 2.46 (s, 3H, $OCOCH_3$), 4.44 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 6.41 (1H, q, J = 7 Hz, $SCHClCH_3$), 7.2-8 (2H, m, 5-H and 8-H).

Anal. Calcd. for $C_{16}H_{14}ClF_2NO_4S$: C, 49.30; H, 3.62; N, 3.59. Found: C, 49.35; H, 3.59; N, 3.58.

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

A mixture of **13** (1.95 g, 5.0 mmoles) and sodium acetate (2.46 g, 30 mmoles) in 25 ml of tetrahydrofuran was heated under reflux for 4 hours. After cooling, water was added to the reaction mixture and the resulting precipitate was collected by filtration to give 1.08 g (69%) of **9** as light brown crystals, which was identified with the authentic sample [1a].

Diethyl (Ethylsulfinyl)(ethylthio)methylenemalonate (**17**).

A solution of diethyl malonate (35.2 g, 0.22 mole) in dry tetrahydrofuran (35 ml) was added dropwise to a stirred suspension of 60% sodium hydride (16.8 g, 0.42 mole) in dry tetrahydrofuran (170 ml) over 30 minutes under ice cooling. The mixture was allowed to warm to room temperature and was stirred for 30 minutes. A solution of carbon disulfide (15.2 g, 0.20 mole) in dry tetrahydrofuran (30 ml) was added dropwise to the mixture over 30 minutes, and the mixture was stirred for 30 minutes. A solution of ethyl iodide (65.5 g, 0.42 mole) in dry tetrahydrofuran (60 ml) was added dropwise to the reaction mixture over 1 hour and the mixture was stirred for 2 hours. The reaction mixture was taken up in ice water and extracted with ethyl ether in the presence of sodium chloride. The organic layer was washed with brine, dried with magnesium sulfate and concentrated to dryness under reduced pressure. The resulting oil was distilled under reduced pressure to give 56.1 g (96%) of diethyl bis(ethylthio)methylenemalonate (**16**) as a yellow oil, bp 153-160°/2 mm Hg (lit bp 128-134°/0.5 mm Hg).

m-Chloroperbenzoic acid (39.7 g, 0.23 mole) was added to a solution of **16** (56.1 g, 0.192 mole) in methylene chloride (300 ml) over 90 minutes under ice cooling. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. After removing the precipitated *m*-chlorobenzoic acid by filtration, the reaction mixture was washed with aqueous sodium hydrogen carbonate solution, dried with magnesium sulfate and concentrated to dryness under reduced pressure. The residue was purified by chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (5:1-2:1) to give 54.2 g (92%) of **17** as a yellow oil; ir (chloroform): 1720 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.31 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.44 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.88-3.20 (m, 4H, SCH_2CH_3), 4.26 (q, J = 7.2 Hz, 2H, $COOCH_2CH_3$), 4.34 (q, J = 7.2 Hz, 2H, $COOCH_2CH_3$).

Anal. Calcd. for $C_{12}H_{20}O_5S_2 \cdot 1/5H_2O$: C, 46.19; H, 6.58. Found: C, 46.08; H, 6.53.

Ethyl 2-(Ethylthio)-6,7-difluoro-4-hydroxyquinoline-3-carboxylate (**11**). (The Second Method).

A mixture of 3,4-difluoroaniline (1.29 g, 10 mmoles) and **17** (3.40 g, 11 mmoles) was stirred at 70° for 48 hours. After cooling, the reaction mixture was purified by chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (20:1) to afford 2.42 g (67%) of **10**, which was converted to **11** by the same procedure used in the first method. Compound **10** and **11** were identified with the authentic samples prepared by the first method.

Ethyl 3,3-Bis(ethylthio)-2-(2,4,5-trifluorobenzoyl)acrylate (**20**).

Potassium carbonate (6.22 g, 0.045 mole) and carbon disulfide (1.71 g, 0.023 mole) were added to a solution of ethyl (2,4,5-trifluorobenzoyl)acetate (**19**) [7] (3.69 g, 0.015 mole) in anhydrous dimethylformamide (30 ml) under ice cooling. After stirring for 5 minutes, ethyl iodide (7.02 g, 0.045 mole) was added dropwise to the mixture. After stirring at the same temperature for 3 hours, the reaction mixture was poured into 150 ml of ice water and extracted with ethyl acetate. The organic layer was washed with water, dried with magnesium sulfate and concentrated to dryness under reduced pressure. The resulting solid was recrystallized from *n*-hexane to give 4.85 g (85%) of **20** as pale yellow crystals, mp 54-56°; ir (potassium bromide): 1705 (C=O), 1675 (C=O), 1615, 1510, 1430, 1150, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.04-1.35 (m,

9H, SCH_2CH_3 and $COOCH_2CH_3$), 2.92 (q, 4H, J = 7 Hz, SCH_2CH_3), 4.20 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 6.68-7.18 (m, 1H, 3-H), 7.58-8.00 (m, 1H, 6-H).

Anal. Calcd. for $C_{16}H_{17}F_3O_3S_2$: C, 50.78; H, 4.53. Found: C, 50.78; H, 4.40.

Ethyl 3-Amino-3-(ethylthio)-2-(2,4,5-trifluorobenzoyl)acrylate (**22**).

A mixture of **20** (3.41 g, 9.0 mmoles) and ammonia (0.23 g, 13.5 mmoles) in 90 ml anhydrous ethyl alcohol was heated in a sealed tube at 80° for 18 hours. The reaction mixture was concentrated to dryness under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was washed with water, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with a mixture of chloroform and methyl alcohol (50:1). The obtained solid was recrystallized from *n*-hexane to afford 1.60 g (53%) of **22** as pale yellow crystals, mp 87-91°; ir (potassium bromide): 3400 (NH_2), 1545, 1505, 1430, 1345, 1145 m^{-1}; ^1H nmr (deuteriochloroform): δ 0.88 (t, J = 7 Hz, 3H, $COOCH_2CH_3$), 1.42 (t, J = 7 Hz, 3H, SCH_2CH_3), 2.87 (q, J = 7 Hz, 2H, SCH_2CH_3), 3.96 (q, J = 7 Hz, 2H, $COOCH_2CH_3$), 6.66-7.42 (m, 2H, 3-H and 6-H).

Anal. Calcd. for $C_{14}H_{14}F_3NO_3S$: C, 50.45; H, 4.23; N, 4.20. Found: C, 50.80; H, 4.09; N, 4.18.

Ethyl 2-(Ethylthio)-6,7-difluro-4-hydroxyquinoline-3-carboxylate (**11**). (The Third Method).

A mixture of **22** (0.33 g, 1.0 mmole), potassium hydrogen carbonate (0.20 g, 2.0 mmoles) and anhydrous dimethylformamide (10 ml) was heated at 80° for 24 hours. After cooling, the reaction mixture was poured into ice water (50 ml) and acidified with dilute hydrochloric acid. The precipitates were collected by filtration, washed with water and dissolved in ethyl acetate. The organic layer was dried with magnesium sulfate and concentrated to dryness under reduced pressure. The residue was purified by chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (40:1) to give a solid, which was recrystallized from *n*-hexane to afford 0.18 g (58%) of **11** as colorless crystals. This compound was identified with that prepared by the first method.

4,5-Difluoro-2-[(methylthio)thiocarbonylamino]benzoic Acid (**27**).

Triethylamine (14.0 g, 0.139 mole) was added dropwise to a solution of 4,5-difluoroanthranilic acid (10.0 g, 0.058 mole) and carbon disulfide (8.8 g, 0.116 mole) in 100 ml of dioxane with ice cooling. After stirring for 5.5 hours at the same temperature, methyl iodide (9.0 g, 0.063 mole) was added dropwise to the reaction mixture and stirred for 1.5 hours. The reaction mixture was allowed to warm to room temperature and stirred for 21 hours. The resultant mixture was poured into 1% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure to afford the crude **27** as a yellow solid, which was recrystallized from chloroform to give 15.2 g (100%) of **27**, mp 165-166°; ir (potassium bromide): 3050, 1670 (C=O), 1610, 1540, 1400, 1240, 1220 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.69 (s, 3H, SCH_3), 7.96 (dd, J = 9 and 11 Hz, 1H, 5-H), 9.42 (dd, J = 8 and 14 Hz, 1H, 2-H).

Anal. Calcd. for $C_9H_7F_2NO_2S_2$: C, 41.06; H, 2.68; N, 5.32. Found: C, 41.16; H, 2.54; N, 5.18.

6,7-Difluoro-2-(methylthio)-4H-[3,1]benzothiazin-4-one (**29**).

A solution of **27** (5.00 g, 0.019 mole) in acetic anhydride (25 g, 0.245 mole) was heated under reflux for 30 minutes and concentrated to dryness under reduced pressure. Resulting solid was recrystallized from ethyl alcohol to afford 4.46 g (96%) of **29**, mp 86-87°; ir (potassium bromide): 3050, 1765 (C=O), 1665, 1615, 1580, 1545 1490 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.70 (s, 3H, SCH_3), 7.47 (dd, J = 7 and 11 Hz, 1H, 8-H), 7.94 (dd, J = 9 and 10 Hz, 1H, 5-H).

Anal. Calcd. for $C_9H_5F_2NOS_2 \cdot H_2O$: C, 41.06; H, 2.68; N, 5.32. Found: C, 40.73; H, 2.47; N, 5.41.

Ethyl 3-[4,5-Difluoro-2-[(methylthio)thiocarbonylamino]-phenyl]-3-oxopropanoate (**30**).

A solution of 3.91 ml (6.26 mmoles) *n*-butyllithium in *n*-hexane (1.6 *M* solution) was added dropwise to a solution of diisopropylamine (0.683 g, 6.75 mmoles) in 10 ml of tetrahydrofuran at -78° under argon atmosphere. The mixture was allowed to warm to -15° and stirred for 30 minutes and then cooled to -78° again. Ethyl acetate (0.551 g, 6.25 mmoles) was added dropwise to the mixture at the same temperature and stirred for 1 hour. A solution of **29** (0.613 g, 2.50 mmoles) in 10 ml of tetrahydrofuran was added dropwise to the mixture and the resulting reaction mixture was stirred for further 2 hours at the same temperature. After addition of a solution of ammonium chloride (1 g) in 3 ml of water, the reaction mixture was allowed to warm to room temperature and extracted with ethyl acetate. The organic layer was washed with brine, dried with magnesium sulfate and concentrated to dryness under reduced pressure. The residue was purified by chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (4:1) to give 0.758 g (91%) of **30**, mp 96°; ir (potassium bromide): 2960 (NH), 1730 (C=O), 1655 (C=O), 1540, 1340, 1135 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7 Hz, 3H, CH_2CH_3), 2.67 (s, 3H, SCH_3), 3.98 (s, 2H, $COCH_2COO$), 4.25 (q, J = 7 Hz, 2H, CH_2CH_3), 7.68 (dd, J = 9 and 11 Hz, 1H, 5-H), 9.48 (dd, J = 8 and 13 Hz, 1H, 2-H), 12.6 (bs, 1H, NH).

Anal. Calcd. for $C_{13}H_{13}F_2NO_3S_2$: C, 46.84; H, 3.93; N, 4.20. Found: C, 46.77; H, 3.98; N, 4.17.

Compound **31** was prepared by the same method.

tert-Butyl 3-[4,5-Difluoro-2-[(methylthio)thioxoamino]phenyl]-3-oxopropanoate (**31**).

Pale yellow crystals were obtained in a yield of 67%, mp 122-124°; ir (potassium bromide): 2950 (NH), 1712 (C=O), 1658 (C=O), 1618, 1535, 1422, 1345, 1132 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 9H, *t*-Bu), 2.69 (s, 3H, SCH_3), 3.88 (s, 2H, $COCH_2COO$), 7.75 (dd, J = 9 and 11 Hz, 1H, 5-H), 9.55 (dd, J = 8 and 13 Hz, 1H, 2-H), 11.65-13.12 (bs, 1H, NH)

Anal. Calcd. for $C_{15}H_{17}F_2NO_3S_2$: C, 49.85; H, 4.74; N, 3.88. Found: C, 49.88; H, 4.73; N, 4.02.

Ethyl 6,7-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxyalte (**8**).

Compound **30** (0.118 g, 0.35 mmole) was added to a solution of sodium (0.024 g, 1.06 mmoles) in absolute ethyl alcohol (2 ml) with ice cooling. The reaction mixture was stirred for 3 hours and concentrated to dryness under reduced pressure. The residue was dissolved in water and the precipitate was removed by filtration. The filtrate was neutralized with dilute hydrochloric acid and the precipitates were collected by filtration to give 0.064 g (63%) of 8, mp 200-202° dec, which was identified with an authentic sample [1a].

Compound **32** was prepared by the same procedure.

tert-Butyl 6,7-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxyalte (**32**).

Compound **32** was obtained as yellow crystals, yield 74%, mp 145°; ir (potassium bromide): 2920, 1632 (C=O), 1580, 1512,

1432, 1415, 1312, 1142, 1008, 892, 840 cm^{-1}; ^1H nmr (deuteriochloroform+DMSO-d_6):δ 1.61 (s, 9H, *t*-Bu), 7.35 (dd, 1H, J = 7 and 9 Hz, 8-H), 7.80 (dd, 1H, J = 10 and 12 Hz, 5-H).

Anal. Calcd. for $C_{14}H_{13}F_2NO_3S$: C, 53.67; H, 4.18; N, 4.47. Found: C, 54.29; H, 4.74; N, 4.67.

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