Synthesis and Antibacterial Activities of Novel Dihydrooxazine and Dihydrothiazine Ring-Fused Tricyclic Quinolonecarboxylic Acids: 9-Fluoro-3-methylene-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid and Its 1-Thia Congener

Tetsuo Okada*, Teruji Tsuji, Tadahiko Tsushima,
Tadashi Yoshida, and Shinzo Matsuura

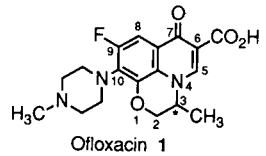
Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka 553, Japan

Received January 7, 1991

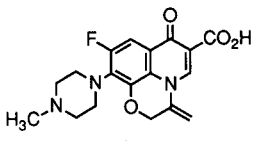
A new synthetic method was developed to obtain two novel tricyclic quinolonecarboxylic acids, 9-fluoro-3-methylene-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (**2**) and its 1-thia congener **3**. The method involves the key intermediate of an oxetane derivative and its cleavage with acids. Evaluation of the antibacterial activities showed that **2** and **3** are excellent against both Gram-positive and Gram-negative organisms *in vitro*, being comparable to or only slightly less effective than Ofloxacin. In experimental systemic infections in mice, compound **2** showed distinctly higher activity than Ofloxacin, especially against infection caused by *Escherichia coli*.

J. Heterocyclic Chem., **28**, 1061 (1991).

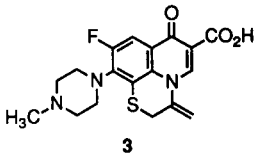
Ofloxacin (**1**), which is clinically one of the most widely used quinolone antibacterial agents, shows not only a well-balanced spectrum for diverse types of gram-positive and gram-negative bacteria but also excellent pharmacodynamic and toxicological characteristics [1-3]. Structurally, it has a rather unique tricyclic skeleton involving the 2,3-dihydro[1,4]oxazine ring fused with a quinolone moiety at the N-1 and C-8 positions and also an asymmetric center at the C-3 position of the dihydrooxazine ring. Consequently, much attention has been directed to the chemical modification of Ofloxacin to better understand its structure-activity relationships [4-6]. We thought that partial chemical modification of the [2,3]-dihydrooxazine ring would improve antibacterial activity of Ofloxacin while keeping its good pharmacodynamic characteristics which are very difficult to obtain. Furthermore, we hoped from a practical view point that removal of the asymmetric center from the dihydrooxazine ring would give rise to some additional synthetic and pharmacological advantages. To test our hypothesis, we first introduced a double bond into the ring in order to examine both the electronic and steric effects of the increased molecular planarity produced by the displacement of the sp^3 asymmetric carbon with the sp^2 one on the antibacterial activity. Second, we examined the effects of substitution of the ring oxygen with sulfur. In connection to our study, we found a literature precedent [4] on the synthesis of the 3-methyleneoxazine derivatives **2**. However, the method of that study required several steps to obtain the desired product only in a very poor yield. Also, no details were given concerning biological activities, particularly the *in vivo* activities. Our work led to the discovery of a new synthetic method and two unique compounds, 9-fluoro-3-methylene-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-[1,4]-benzoxazine-6-carboxylic acid (**2**) (see also [4]) and the corresponding 1-thia congener **3** having a 2,3-dihydrothiazine ring, with substantially improved antibacterial activities. These two derivatives commonly possess an exo-cyclic double bond at the C-3 positions of the dihydrooxazine and the dihydrothiazine ring. Our accompanying report also describes a relevant study on the corresponding compounds with an endo-cyclic double bond.



Ofloxacin **1**



2



3

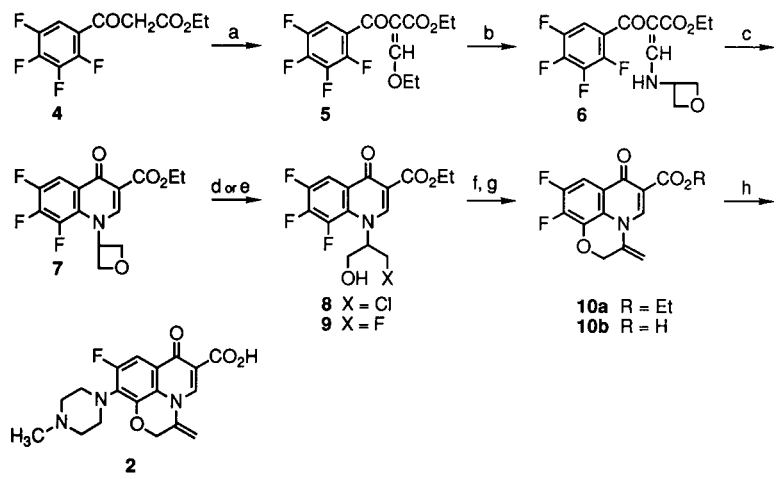
Results and Discussion.

Chemistry.

To synthesize the target compound **2**, the earlier work [4] employed a rare starting material, 2-nitro-5,6-difluorophenol, and a tedious cyclization procedure involving, in sequence, the formation of the benzoxazine, cyclization to build the quinolonecarboxylic acid skeleton, and the introduction of an *N*-methylpiperazine moiety at the C-10 position. The total yield was less than 1%.

We decided to take a completely different synthetic strategy as shown by Scheme I. We used a very common and commercially available starting material 2,3,4,5-tetrafluorobenzoic acid (TFBA) and converted it to the key in-

Scheme I



a) $(C_2H_5O)_3CH$, Ac_2O b) 3-Aminooxetane c) NaH / DMF d) 20% HCl / EtOH
e) HF / pyridine f) KF / DMF g) Dil. HCl (reflux) h) N-Methylpiperazine / DMSO

termediate **7** bearing the oxetane ring which was then directly cleaved with acids to produce a precursor of the oxazine derivative **10**, γ-chlorohydrin **8**. Finally, an *N*-methylpiperazine moiety was introduced to obtain the desired product **2**.

Table I

In Vitro Antibacterial Activity: MIC μg/ml[a]

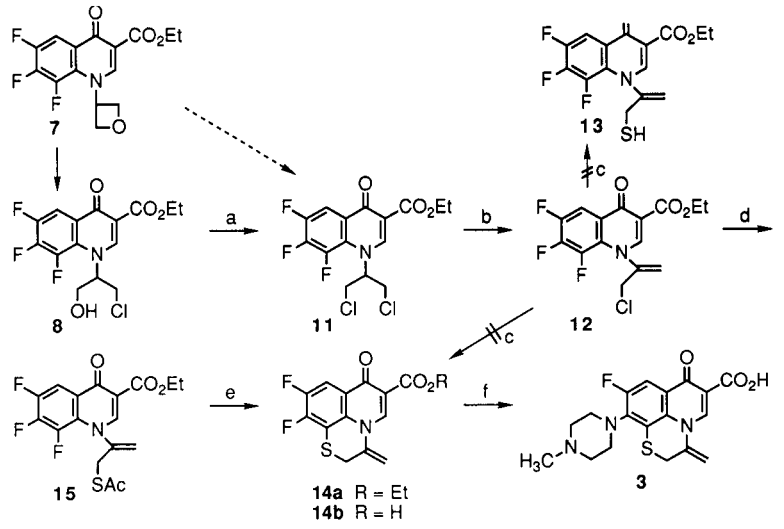
Compound	Organism									
	Sa(S)[b]	Sa(R)[c]	Sp[d]	Sn[e]	Ec(S)[f]	Ec(R)[g]	Kp[h]	Pv[i]	Ecl[j]	Pa[k]
Ofloxacin 1	0.4	0.4	1.6	1.6	0.1	0.8	0.1	0.1	0.2	1.6
2	0.8	0.8	3.1	3.1	0.1	0.8	0.1	0.1	0.1	1.6
3	0.4	0.4	3.1	1.6	0.2	3.1	0.4	0.2	0.4	3.1

[a] MIC (minimum inhibitory concentrations) were determined by the agar dilution method. Inoculation was performed with one loopful 10^6 cells per ml. [b] *Staphylococcus aureus* Smith. [c] *Staphylococcus aureus* C-14. [d] *Streptococcus pyogenes* C-203. [e] *Streptococcus pneumoniae* Type 1. [f] *Escherichia coli* EC-14. [g] *Escherichia coli* SR73. [h] *Klebsiella pneumoniae* SR1. [i] *Proteus vulgaris* CN-329. [j] *Enterobacter cloacae* SR233. [k] *Pseudomonas aeruginosa* SR24.

The common ethyl 2,3,4,5-tetrafluorobenzoylacetate (**4**), frequently used in the preparation of quinolone carboxylic acid antibacterials, was prepared from TFBA by a known method [7] and heated with ethyl orthoformate in acetic anhydride to give the 2-benzo-3-ethoxyacrylate derivative **5**. This unstable intermediate was then treated, without any purification, with an equimolar amount of 3-aminooxetane and gave a good yield of the enamino ketoester **6** as a mixture of *E* and *Z* isomers in approximately equal amounts. 3-Aminooxetane used here was prepared from epichlorohydrin according to a known method [8]. The resulting **6** was then treated with sodium hydride in dimethylformamide (DMF), giving the quinolonecarboxylate derivative **7** in 83% yield. Then, to prepare γ-halohydrins by acid cleavage of the oxetane ring, we considered some methods reported in literature [9] but none seemed suitable for our purpose. Therefore, after a careful search for the optimal reaction conditions, we found that treatment of the oxetane derivative **7** with 10 to 20% hydrogen chloride-ethanol solution produced the desired chlorohydrin **8** in five minutes in an almost quantitative yield. The use of an alcoholic hydrochloric acid solution at this high concentration completely suppressed the formation of other solvolytic by-products such as diols, ethers, and polymers. Furthermore, the chlorohydrin formed was spontaneously precipitated out from the solution during the reaction, thus preventing its side reaction. The oxetane ring cleavage with 70% HF-pyridine, required more drastic conditions, *e.g.* heating and a much longer reaction time, to afford the desired fluorohydrin **9** in a much lower yield of 35%. Next, heating the chlorohydrin **8** thus obtained in the presence of potassium fluoride in DMF smoothly effected both cyclization into the dihydrooxazine ring and dehydrochlorination to give the tricyclic quinolonecarboxylate **10a** with an exo-methylene group at the C-3 position. Finally, conversion of **10b** into the dehydro-Ofloxacin (**2**) was achieved with 32% yield by a known method, namely heating **10** together with large excess of *N*-methylpiperazine in a polar aprotic solvent such as acetonitrile or dimethyl sulfoxide. The low yield may have been due to steric and/or electronic repulsion between the oxazine and *N*-methylpiperazine rings.

In order to prepare the 1-thia congener **3** as shown in Scheme II, the chlorohydrin **8** was converted into the dichloride **11** with a good yield by treatment with thionyl chloride. There was a known method for one-step conversion of the oxetane ring into dichlorides by treatment with phosphorus pentachloride [10] but its yield was low. Instead, we treated **11** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile and obtained the allyl chloride

Scheme II



12 in 89% yield. Next, we attempted to directly convert **11** and **12** into either the allyl thiol **13** or the dihydrothiazine derivative **14** by treatment with sodium hydrosulfide under various conditions but all our attempts failed. Therefore, we undertook an alternative method for converting the allyl chloride **12** into the thioacetate **15** by treatment with potassium thioacetate in acetone using a sonicator. We were able to obtain the desired product **15** in 51% yield after column chromatography. Cyclization of **15** into **14** was readily achieved by gentle heating in DMF in the presence of potassium carbonate. Hydrolysis of **14** under acidic conditions, followed by substitution of the C-10 fluorine with *N*-methylpiperazine afforded the final product **3** with a 3-methylenedihydrothiazine ring. The compounds **2** and **3** thus prepared were subjected to biological assay for *in vitro* and *in vivo* antibacterial activity.

Biological Results.

Table I summarizes the *in vitro* antibacterial activities of Ofloxacin (**1**) and its structural analogs **2** and **3** against four Gram-positive and six Gram-negative bacteria. In comparison with Ofloxacin, **2** and **3** showed almost the same or slightly lower activity against both Gram-positive and Gram-negative bacteria. For Gram-negative bacteria, **2** showed somewhat higher activity than **3**, whereas **3** was more effective against Gram-positive bacteria.

Table II presents the *in vivo* antibacterial activity of compounds **1-3** in terms of the median effective dose (ED_{50}) by the oral route, which was determined for acute lethal infection in mice. The ED_{50} values of three compounds ranged between 5.73 and 8.68 mg/kg for the efficacy of each compound. Against *E. coli* infection, however, the ED_{50} of compound **2** was 0.39 mg/kg, making it about four times more effective than **1** (ED_{50}: 1.74 mg/kg) and **3** (ED_{50}: 1.38 mg/kg), respectively. The superiority of the *in vivo* activity of compound **2** may be due to its improved pharmacodynamic properties such as metabolic stability or oral absorption. Our present findings may lead to new quinolone carboxylic acid derivatives with these unique tricyclic skeletons and other substituents at the C-10 position. In the accompanying paper which deals with the endo-cyclic isomers of these compounds, we discuss the structural properties of these exo-cyclic as well as endo-cyclic molecules based on their molecular orbital calculations.

Table II

In vivo Antibacterial Activity: ED_{50} mg/kg [a]

	S. aureus Smith	*E. coli* EC-14
Ofloxacin 1	8.68 (0.4)[b]	1.74 (0.1)
2	5.73 (0.8)	0.39 (0.1)
3	5.73 (0.4)	1.38 (0.2)

[a] Median effective dose. Compounds were administered orally 1 hour after intraperitoneal infection in mice. [b] MIC from Table I.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot stage apparatus and were not corrected. Unless otherwise stated, the 90 MHz and 200 MHz ^1H nmr spectra were recorded for deuteriochloroform solutions on a Varian EM-390 and VXR-200, respectively, using TMS as an internal standard. In the case of spectra taken in deuterium oxide, external TMS was used. The assignment of proton signals were done only for significant protons. Column chromatography was performed on a Merck Silica gel 60

(230-400 mesh or 70-230 mesh). Medium-pressure liquid chromatography was performed on Merck 'Lobar' columns packed with Lichroprep® Si 60. Organic extracts of reaction products were dried over anhydrous magnesium sulfate, and solvents were evaporated under reduced pressure using a rotary evaporator.

Ethyl 2-[(Oxetan-3-yl)aminomethylene]-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (**6**).

A mixture of benzoylacetate **4** (5.20 g, 19.7 mmoles), triethyl orthoformate (5.0 ml), and acetic anhydride (5.7 ml) was refluxed for 2 hours and then all volatile substances were evaporated at 100° under a reduced pressure of 5 mm Hg. The residue was dissolved in ethanol (5 ml) and treated with 3-aminooxetane (1.30 g, 17.8 mmoles) dissolved in cold ethanol (5 ml). The reaction mixture was stirred at room temperature and then aged overnight at 0° to complete precipitation of the crystalline product. The resulting crystals were collected to give 3.87 g of **6**, mp 79-80°. A further 1.5 g of **6**, mp 80-81°, was obtained as a second crop from the mother liquid after its column chromatographic separation over silica gel. The total yield was 74%; 90 MHz ^{1}H nmr: δ 1.10 (t, 3H, J = 7 Hz, C*H*$_3$), 4.09 (q, 2H, J = 7 Hz, C*H*$_2$), 4.5-5.1 (m, 5H, oxetane part), 7.1 (m, 1H, aromatic *H*), 8.06 (s, 0.5H, vinyl *H*), 8.20 (s, 0.5H, vinyl *H*).

Ethyl 1-(Oxetan-3-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**7**).

To a DMF solution (200 ml) of the enamino ketoester **6** (7.80 g, 20.7 mmoles) was added with stirring 60% sodium hydride in oil dispersion (910 mg, 22.8 mmoles) over a period of 10 minutes with the reaction temperature kept below 40° using a cold water bath. After stirring at room temperature for 20 minutes, the reaction mixture was poured into water and the resulting precipitate was collected by filtration, washed with water, dissolved in dichloromethane and dried. After the solution had been appropriately concentrated and diluted with some ether, the product was crystallized, giving 6.10 g (83%) of **7**, mp 158-160°; 90 MHz ^{1}H nmr: δ 1.40 (t, 3H, J = 7 Hz), 4.38 (q, 2H, J = 7 Hz), 5.1 (m, 4H, oxetane ring C$_2$-*H* and C$_4$-*H*), 5.8 (m, 1H, oxetane ring C$_3$-*H*), 8.13 (m, 1H), 8.69 (s, 1H, C$_2$-*H*).

Ethyl 1-(3-Chloro-1-hydroxy-propan-2-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**8**).

A solution of **7** (1.00 g, 3.06 mmoles) in 20% hydrogen chloride-ethanol (5 ml) was stirred at room temperature for 5 minutes. During this time, a crystalline product precipitated. The crystals were collected by filtration and recrystallized from dichloromethane, giving 1.08 g (97%) of **8**, mp 183-184°; 200 MHz ^{1}H nmr (DMSO-d$_6$): δ 1.28 (t, 3H, J = 7 Hz), 3.94 (m, 2H, C*H*$_2$OH), 4.23 (d, 2H, J = 5 Hz, C*H*$_2$Cl), 4.25 (q, 2H, J = 7 Hz), 5.25 (m, 1H, C*H*CH$_2$OH), 5.48 (t, 1H, J = 5 Hz, O*H*), 8.04 (m, 1H), 8.73 (s, 1H).

Anal. Calcd. for $C_{15}H_{13}NO_4F_3Cl$: C, 49.53; H, 3.60; N, 3.85; F, 15.67; Cl, 9.75. Found: C, 49.15; H, 3.63; N, 3.79; F, 15.58; Cl, 10.13.

Ethyl 1-[(3-Fluoro-1-hydroxy)-propan-2-yl]-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**9**).

A solution of **7** (500 mg, 1.53 mmoles) in 70% hydrogen fluoride in pyridine (2.0 ml) was heated in a sealed tube at 90° for 5 hours. The reaction mixture was poured into water and the resulting precipitates were collected by filtration and recrystallized from dichloromethane, giving 189 mg (35%) of **9**, mp 184-185°; 90 MHz ^{1}H nmr: δ 1.38 (t, 3H, J = 7 Hz), 4.83 (q, 2H, J = 7 Hz), 4.9-5.3 (m, 4H, C*H*$_2$F and C*H*$_2$OH), 5.8 (m, 1H, C*H*CH$_2$OH), 8.05 (m, 1H), 8.66 (s, 1H).

Anal. Calcd. for $C_{15}H_{13}NO_4F_4$: C, 51.88; H, 3.77; N, 4.03; F, 21.88. Found: C, 51.46; H, 3.87; N, 4.02; F, 20.78.

Ethyl 9,10-Difluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*][1,4]benzooxazine-6-carboxylate (**10a**).

A suspension of chlorohydrin **8** (985 mg, 2.98 mmoles) and potassium fluoride (500 mg) in DMF (10 ml) was heated at 120° for 3 hours under stirring. The reaction mixture was poured into water and the precipitates were collected and recrystallized from dichloromethane, giving 550 mg (66%) of **10a**, mp 264-265°; 90 MHz ^{1}H nmr (deuteriochloroform-tetradeuteriomethanol): δ 1.42 (t, 3H, J = 7 Hz), 4.38 (q, 2H, J = 7 Hz), 4.90 (s, 2H, C$_2$-*H*), 5.30 (d, 1H, J = 4 Hz, methylene-*H*), 5.61 (d, 1H, J = 4 Hz, methylene-*H*), 7.78 (dd, 1H, J = 11, 8 Hz), 8.73 (s, 1H).

Anal. Calcd. for $C_{15}H_{11}NO_4F_2$: C, 58.64; H, 3.61; N, 4.56; F, 12.37. Found: C, 58.43; H, 3.67; N, 4.54; F, 12.33.

A suspension of fluorohydrin **9** (50 mg) and potassium fluoride (50 mg) in DMF (0.5 ml) was allowed to react at 120° for 4 hours under stirring. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated. The residue was purified by silica-gel column chromatography, giving 18 mg of **10a**, mp 265-266°.

9,10-Difluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-[1,4]benzoxazine-6-carboxylic Acid (**10b**).

A suspension of ester **10a** (500 mg, 1.63 mmoles) in 6 *N* hydrochloric acid (2 ml) and ethanol (2 ml) was refluxed for 1 hour. The resulting crystals gave 415 mg (91%) of **10b**, mp 275-277°; 90 MHz ^{1}H nmr (DMSO-d$_6$): δ 5.12 (s, 2H), 5.63 (d, 1H, J = 4 Hz), 6.10 (d, 1H, J = 4 Hz), 7.87 (dd, 1H, J = 11, 8 Hz), 9.04 (s, 1H).

The Hydrochloride of 9-Fluoro-3-methylene-10-[(4-methyl)-piperazin-1-yl]-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (**2**).

To a solution of the carboxylic acid **10b** (200 mg) in DMSO (3 ml) was added *N*-methylpiperazine (0.160 ml) and the mixture was heated at 80° for 1 hour under stirring. The mixture was concentrated, dissolved in 1 *N* hydrochloric acid (3 ml), and again concentrated. The resulting residue was recrystallized from methanol to give 90 mg (32%) of the hydrochloride of **2**, mp 272-274°, as yellow crystals; 90 MHz ^{1}H nmr (deuterium oxide): δ 3.48 (s, 3H, NC*H*$_3$), 3.6-4.2 (m, 8H, piperazine part), 5.37 (s, 2H), 5.97 (d, 1H, J = 4 Hz), 6.15 (d, 1H, J = 4 Hz), 7.67 (d, 1H, J = 12 Hz), 9.14 (s, 1H).

Anal. Calcd. for $C_{18}H_{19}N_3O_4FCl\cdot0.5H_2O$: C, 53.41; H, 4.98; N, 10.38; F, 4.98; Cl, 8.76. Found: C, 53.33; H, 5.01; N, 10.33; F, 4.99; Cl, 8.78.

Ethyl 1-(1,3-Dichloropropan-2-yl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (**11**).

To a suspension of chlorohydrin **8** (2.90 g, 7.97 mmoles) in dichloromethane (20 ml) was added thionyl chloride (4.0 ml) at room temperature. After stirring at the same temperature for 4.0 hours, the reaction mixture was concentrated to an oily residue which was chromatographed on a Lobar column (size B). The fractions eluted with toluene-ethyl acetate (2:1) were collected,

concentrated, and recrystallized from dichloromethane-ether, giving 2.60 g (85%) of **11**, mp 133-134°; 200 MHz ^{1}H nmr (DMSO-d_6): δ 1.29 (t, 3H, J = 7 Hz), 4.26 (q, 2H, J = 7 Hz), 4.28 (d, 4H, J = 7 Hz, CH_2Cl), 5.52 (quint, 1H, J = 7 Hz, CHCH$_2$Cl), 8.05 (ddd, 1H, J = 10, 9, 2 Hz), 8.70 (s, 1H).

Anal. Calcd. for $C_{15}H_{12}NO_3F_3Cl_2$: C, 47.14; H, 3.16; N, 3.67; F, 14.91; Cl, 18.55. Found: C, 46.89; H, 3.20; N, 3.75; F, 14.73; Cl, 18.75.

Ethyl 1-[1-(1-Chloromethyl)vinyl]-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-4-carboxylate (**12**).

A solution of the dichloride **11** (500 mg, 1.31 mmoles) and DBU (0.400 ml) in acetonitrile (3 ml) was stirred at room temperature for 1.0 hour. The resulting crystals yielded 402 mg (89%) of **12**, mp 236-237°; 200 MHz ^{1}H nmr (DMSO-d_6): δ 1.27 (t, 3H, J = 7 Hz), 4.24 (q, 2H, J = 7 Hz), 4.76 (br d, 2H, J = 13 Hz, CH_2Cl), 5.92 (s, 1H, vinyl-*H*), 6.00 (s, 1H, vinyl-*H*), 8.00 (ddd, 1H, J = 10, 9, 2 Hz), 8.33 (s, 1H).

Anal. Calcd. for $C_{15}H_{11}NO_3F_3Cl$: C, 52.12; H, 3.21; N, 4.06; F, 16.46; Cl, 10.26. Found: C, 52.16; H, 3.25; N, 4.18; F, 16.67; Cl, 10.28.

Ethyl 1-[1-(1-Acetylthiomethyl)vinyl]-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15**).

A suspension of potassium thioacetate (600 mg, 5.25 mmoles) and allyl chloride **12** (900 mg, 2.60 mmoles) in acetone (10 ml) was subjected to sonication for 5 minutes to facilitate the reaction and then was mechanically stirred for 10 minutes. After addition of toluene, the reaction mixture was concentrated to dryness to completely remove acetone. The residue was chromatographed on a Lobar column (size B) and the fractions eluted with toluene-ethyl acetate (5:1) were collected and concentrated to a solid residue. Recrystallization from toluene gave 510 mg (51%) of **15**, mp 155-156°; 200 MHz ^{1}H nmr: δ 1.42 (t, 3H, J = 7 Hz), 2.29 (s, 3H, SCOCH_3), 3.92 (s, 2H, CH_2S), 4.40 (q, 2H, J = 7 Hz), 5.50 (s, 1H), 5.67 (s, 1H), 8.13 (ddd, 1H, J = 10, 9, 2 Hz), 8.28 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}NO_4F_3S$: C, 52.99; H, 3.66; N, 3.63; F, 14.79; S, 8.32. Found: C, 53.04; H, 3.70; N, 3.77; F, 14.65; S, 8.34.

Ethyl 9,10-Difluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*][1,4]benzothiazine-6-carboxylate (**14a**).

A suspension of the thioacetate **15** (500 mg, 1.30 mmoles) and finely powdered potassium carbonate (500 mg, 3.62 mmoles) in DMF (5 ml) was vigorously stirred at room temperature for 30 minutes to complete the reaction. The reaction mixture was poured into 1 *N* hydrochloric acid and the products were extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel and the fractions eluted with dichloromethane-methanol (100:1) were collected and concentrated to crystals. Recrystallization from dichloromethane gave 254 mg (61%) of **14a**, mp 270-271°; 200 MHz ^{1}H nmr: δ 1.42 (t, 3H, J = 7 Hz), 3.74 (s, 2H, CH_2S), 4.42 (q, 2H, J = 7 Hz), 5.23 (d, 1H, J = 2 Hz, vinyl-*H*), 5.37 (d, 1H, J = 2 Hz, vinyl-*H*), 8.09 (dd, 1H, J = 7 Hz), 8.64 (s, 1H).

9,10-Difluoro-3-methylene-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzothiazine-6-carboxylic Acid (**14b**).

A suspension of **14a** (169 mg, 0.52 mmole) in a mixture of 6 *N* hydrochloric acid (2 ml) and ethanol (2 ml) was refluxed for 3 hours. The resulting crystals were collected to give 141 mg (91%) of **14b**, mp 291-293°; 200 MHz ^{1}H nmr (DMSO-d_6): δ 4.09 (s, 2H), 5.53 (d, 1H, J = 2 Hz), 5.72 (d, 1H, J = 2 Hz), 8.09 (dd, 1H, J = 10, 9 Hz), 8.80 (s, 1H).

Anal. Calcd. for $C_{13}H_7NO_3F_2S$: C, 52.88; H, 2.39; N, 4.74; F, 12.87; S, 10.86. Found: C, 52.54; H, 2.51; N, 5.01; F, 12.57; S, 11.11.

9-Fluoro-3-methylene-10-[4-methylpiperazin-1-yl]-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzothiazine-6-carboxylic Acid (**3**).

A well stirred solution of the acid **14b** (100 mg, 0.34 mmole) and *N*-methylpiperazine (0.200 ml, 1.65 mmoles) in acetonitrile (2.0 ml) was heated at 120° for 2 hours in a sealed tube. The reaction mixture was concentrated and the residue was crystallized from methanol, giving 31 mg (24%) of **3**, mp 260-261°; 200 MHz ^{1}H nmr (DMSO-d_6): δ 2.25 (s, 3H, NCH_3), 3.10 (br s, 4H, piperazine ring-*H*), 3.30 (br s, 4H, piperazine ring-H), 3.96 (s, 2H, CH_2S), 5.45 (d, 1H, J = 2 Hz, vinyl-*H*), 5.61 (d, 1H, J = 2 Hz, vinyl-*H*), 7.84 (d, 1H, J = 12 Hz), 8.75 (s, 1H).

Anal. Calcd. for $C_{18}H_{18}N_3O_3FS$: C, 57.59; H, 4.83; N, 11.19; F, 5.06; S, 8.54. Found: C, 57.23; H, 4.83; N, 11.03; F, 5.09; S, 8.55.

Acknowledgments.

We thank Dr. H. Miwa, Messrs. Y. Kameda, and K. Motokawa for the microbiological testing.

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