4*H*-1-Benzothiopyran-4-one-3-carboxylic Acids and 3,4-Dihydro-2*H*-isothiazolo[5,4-*b*][1]benzothiopyran-3,4-diones as Quinolone Antibacterial Analogs

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The endocyclic replacement of a nitrogen atom at the 1-position of quinolone antibacterial nucleus with a sulfur atom was investigated. A series of 1-benzothiopyran-4-one-3-carboxylic acids **14-16** and isothiazolo-[5,4-*b*][1]benzothiopyran-3,4-diones **22-24**, suitably functionalized with a fluorine atom at C-6 and heterocyclic base at C-7, were prepared. The antibacterial evaluation of the target compounds showed an activity comparable to that of nalidixic acid for compounds **14-16**, while an increased activity against gram-positive bacteria was observed for compounds **22-24**.

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Introduction.

The fluoroquinolone carboxylic acids, generically represented by Figure 1, are a class of highly potent and broad spectrum antibacterial agents. All positions on the quinolone ring have been systematically investigated and optimized by SAR study. Nevertheless endocyclic substitution at the 1 position has received little attention; it has been limited to only two examples, dimethylcarba [1] and oxygen [2] analogues. These modifications indicated that bioisosteric replacement of nitrogen atom led to inactive compounds (MICs >250 μg/ml).

As a part of our research program to prepare sulfur-containing congeners of quinolone antibacterial agents [3], we explored and gathered additional data on the effect of endocyclic modifications at the 1-position by nitrogen replacement with a sulfur atom synthesizing benzothiopyran-4-one-3-carboxylic acids, suitably functionalized at C-6 and C-7, crucial positions on the quinolone nucleus for antibacterial activity.

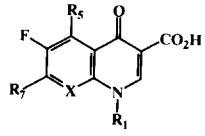
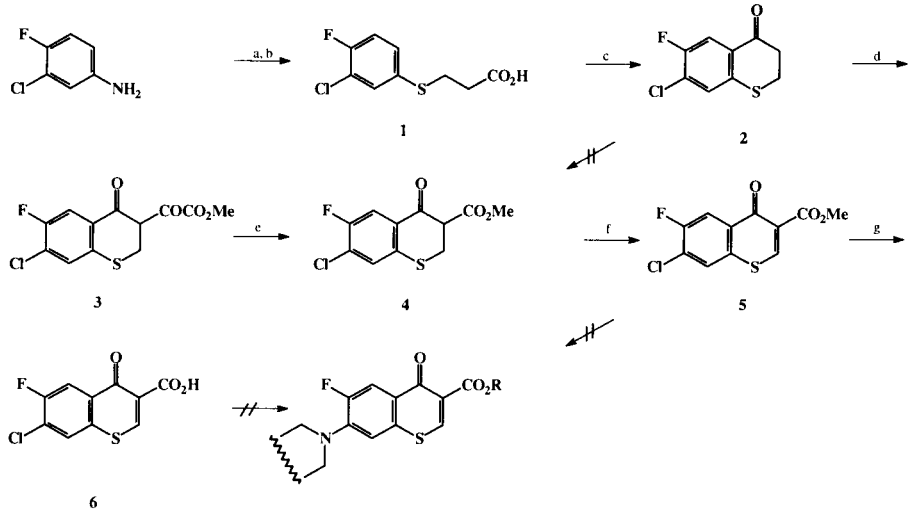


Figure 1

Chemistry.

Scheme I

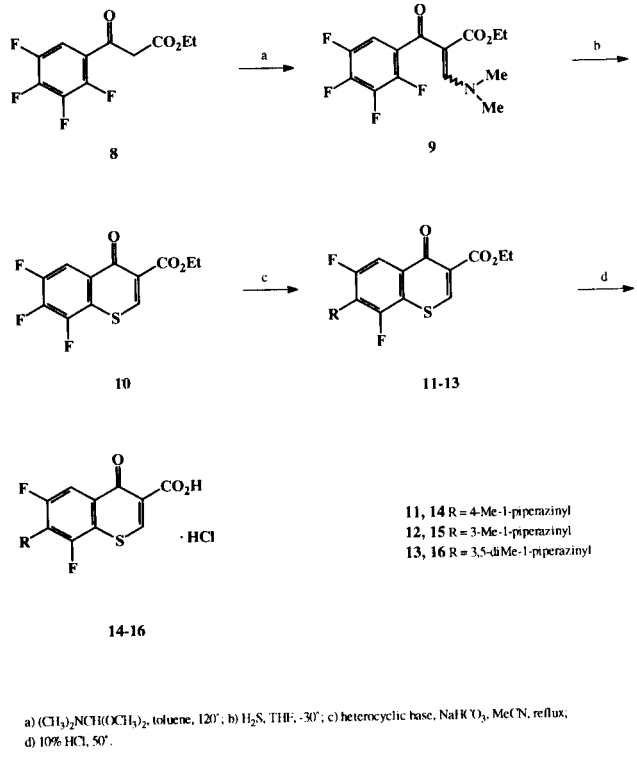


(a) $NaNO_2$, HCl; (b) $HS(CH_2)_2CO_2H$, 60°; (c) 96% H_2SO_4; (d) $(CO_2Me)_2$, MeONa, benzene; (e) glass powed, 140°; (f) Chloranil, dioxane, 60°; (g) 48% HBr, reflux.

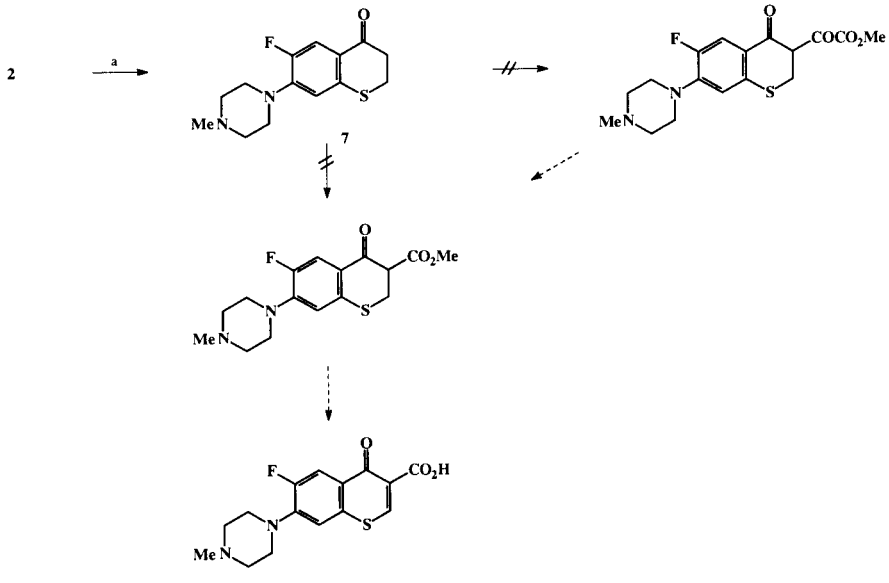
Our first approach to obtain the target compounds (Scheme I) involved the synthesis of the framework 7-chloro-6-fluoro-4*H*-1-benzothiopyran-4-one-3-carboxylic acid (**6**), which by nucleophilic substitution of chlorine at C-7 with suitable heterocyclic bases, should have produced many target derivatives which could be submitted to antibacterial evaluation. The synthetic route to **6** involved first, the preparation of **1** by reaction of diazo derivative of 3-chloro-4-fluoroaniline with 3-mercaptopropionic acid. Successive sulfuric acid cyclodehydration of **1** gave **2** as a single product. Since the direct carboxymethylation of **2** to give ester **4** failed, this was obtained indirectly by oxalylation with dimethyl oxalate and subsequent decarbonylation of the obtained glyoxylate **3**. Finally, **4** was dehydrogenated with chloranil to give ester **5** which, after hydrolysis with hydrobromic acid, gave acid **6**. All attempts to carry out the nucleophilic substitution of chlorine at C-7 of ester **5** or acid **6**, using several usual conditions as well as forced conditions (net or autoclavated reaction) failed. Therefore, an alternate route (Scheme II) was planned which first involved the introduced of a base at C-7. This route was also unfruitful because all successive carboxylation or oxalylation attempts at C-3 of **7** failed.

After this series of unsuccessful attempts, it seemed necessary to prepare a new intermediate 6,7,8-trifluoro-4*H*-1-benzothiopyran-4-one-3-carboxylic acid ethyl ester (**10**) in order to obtain the target compounds. In this new key intermediate **10** the halogen at C-7 was activated by an *ortho* fluorine atom at C-8. In this way (Scheme III), the starting material was the 2,3,4,5-tetrafluoro-β-oxobenzenepropanoic acid ethyl ester (**8**) [4] which, by reaction with *N,N*-dimethylformamide dimethyl acetal, gave the ethyl α-[(*N,N*-dimethylamino)methylene]-2,3,4,5-tetrafluoro-β-oxobenzene-propanoate (**9**) as a 1:4 or 4:1 mixture of (*E*)- and (*Z*)-isomers as shown by its ^{1}H-nmr spectra. Conversion of **9** to **10** was then obtained in good yield by treatment at -30° with hydrogen sulfide in tetrahydro-

Scheme III



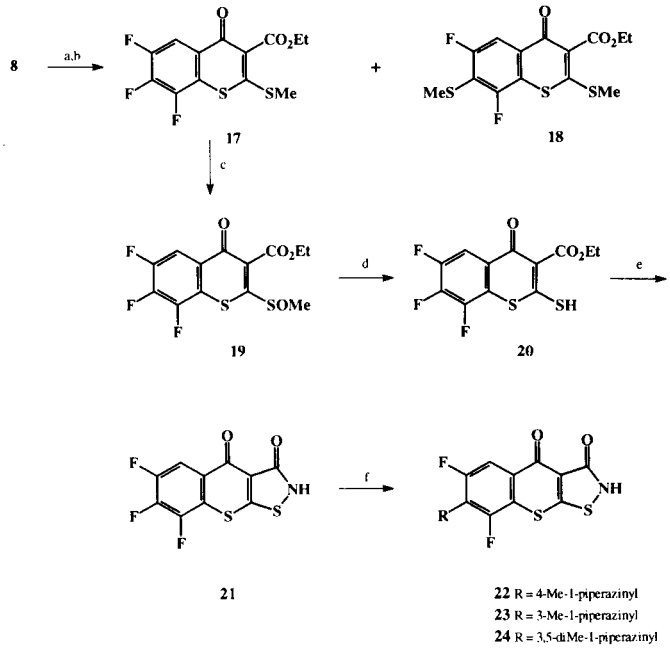
Scheme II



furan. Finally, the substituted esters **11-13** were obtained by nucleophilic substitution of **10** with heterocyclic bases (*N*-methylpiperazine, 2-methylpiperazine and 2,6-dimethylpiparazine). The regiospecific replacement of fluorine at C-7 was confirmed by ^{1}H-nmr spectra which showed two doublets of doublets with an *ortho* coupling of 12 Hz and a *para* coupling of 2 Hz for H-5. Hydrolysis of esters **11-13** in hydrochloric acid yielded the target acids **14-16**, respectively.

Stimulated by the high antibacterial potency discovered in a series of 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-diones [5,6], in which the acidity of isothiazolo moiety mimics the carboxylic functionality, we wanted to verify if an isothiazolo ring bridged at the 2,3-positions of benzothiopyrano moiety would increase the activity. To anellate an isothiazol-3(2*H*)-one to benzothiopyrano moiety, ethyl 2-methylthio-6,7,8-trifluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**17**) was utilized as key intermediate. Intermediate **17** was obtained from **8** by reaction with carbon disulfide followed by treatment with dimethyl sulfate (Scheme IV). From this reaction a 20% yield of side product **18** was formed from simultaneous displacement of the C-7 fluorine atom by thiolate anion. The sulfoxide **19**, obtained by *m*-chloroperbenzoic acid (MCPBA) oxidation of **17**, was then submitted to regiospecific displacement of sulfinyl group by treatment with sodium hydrosulfide to give **20**, in accord with the literature [6]. Successive reaction of **20** with hydroxylamine-*O*-sulfonic acid directly gave 6,7,8-trifluoro-3,4-dihydro-2*H*-isothiazolo[3,2-*b*][1]-benzothiopyran-3,4-dione (**21**) which, by a last treatment with bases such as *N*-methylpiperazine, 2-methylpiperazine and 2,6-dimethylpiparazine, gave target compounds **22**, **23** and **24**, respectively.

Scheme IV



a) KOH, DMSO, CS_2, 10°; b) $(CH_3)_2SO_4$; c) MCPBA, CH_2Cl_2; d) NaHS, THF; e) H_2NOSO_3H, THF; f) heterocyclic base, DMF, 100°

Microbiology.

The series of benzothiopyran-4-one-3-carboxylic acids **14-16** and isothiazolo[5,4-*b*][1]benzothiopyran-3,4-diones **22-24** were tested against representative gram-positive and gram-negative bacteria. The activities were determined by conventional agar dilution procedure; the results of these assays are summarized in Table I. The data for nalidixic acid and lomefloxacin are included for comparison. The *in vitro* antibacterial assay strengthens the thesis that a nitrogen at quinolone 1-position is a fundamental requisite for potent antibacterial activity. Indeed the activity of benzothiopyrano acids **14-16** fell sharply when compared with the analog quinolone derivative lomefloxacin. Nevertheless the N-1 endocyclic substitution with a sulfur atom in quinolone moiety for **14-16** gave an activity comparable to nalidixic acid for all assayed organisms while the carba- and oxa-quinolone analogues were inactive [1,2]. The MICs of isothiazole derivatives **22-24** indicated that the presence of isothiazole ring increases the activity against gram-positive bacteria when compared to acids **14-16** and nalidixic acid although it is less effective than the lomefloxacin.

Table I. In Vitro Antibacterial Activities[a]

organism	MIC, μg/mL							
	14	**15**	**16**	**22**	**23**	**24**	NAL[b]	LOM[c]
Staphylococcus aureus ATCC 6538	32	32	128	2	2	32	64	0.25
Streptococcus faecalis LEP Br.	128	128	64	32	64	128	128	0.5
Escherichia coli ISF 432	2	2	4	1	0.5	16	1	0.03
Enterobacter cloacae OMNFI 174	16	8	64	4	4	64	4	0.06
Proteus vulgaris CNUR 6	128	128	128	32	128	128	128	4
Klebsiella pneumoniae ATCC 10031	2	2	8	2	2	16	1	0.03
Shighella enteritidis	16	8	64	4	8	128	16	0.06
Pseudomonas aeruginosa ATCC 9027	128	128	128	4	128	128	128	0.5

[a] Structures are shown in Schemes III and IV. [b] NAL = nalidixic acid. [c] LOM = lomefloxacin.

EXPERIMENTAL

Melting points were determined in capillary tubes (Gallenkamp melting point apparatus) and are uncorrected. The ^{1}H-nmr spectra were recorded on a Bruker AC 200 spectrometer with tetramethylsilane, at 0.0 ppm, as internal standard. Chemical shifts are given in ppm (δ). Elemental analyses were performed on a Carlo Erba elemental analyzer, model 1106, and the data for C, H, N are within ±0.4% of the theoretical values. Gl-ms analyses were carried out with a Hewlett-Packard HP 5890 apparatus, with a 15.5-m dimethylsilicone capillary column. Column flash chromatographic separations were carried out on Merck silica gel 60 (mesh 230-400). Organic solutions were dried over anhydrous sodium sulfate and concentrated with a Büchi rotary evaporator at low pressure. Yields are of purified products and are not optimized.

S-(3-Chloro-4-fluorophenyl)thiopropanoic Acid (**1**).

Diazotised 3-chloro-4-fluoroaniline (from 6.0 g, 42 mmoles) in 0.2 *N* hydrochloric acid (150 ml) was added to the solution of 3-mercaptopropionic acid (4.2 g, 42 mmoles) in aqueous sodium hydroxide (3.6 g, 84 mmoles; in 20 ml of water) over a 30 minute period with stirring at 0°, and the mixture was then kept at 0° for 30 minutes. The collected precipitate was poured into water (90 ml) and the suspension was heated at 60° until the evolution of nitrogen ceased. The pitch solid was extracted with ethyl acetate, dried and then evaporated to give **1** which was recrystallized from water (5.1 g, 92%), mp 70-72°; ^{1}H-nmr (deuterochloroform): δ 2.50-2.70 (2H, m, SCH_2), 2.90-3.20 (2H, m, CH_2CO), 6.85-7.30 (2H, m, H-5 and H-6), 7.30 (1H, dd, J = 3 and 6 Hz, H-2), 10.70 (1H, s, OH).

Anal. Calcd. for $C_9H_8ClFO_2S$: C, 46.07; H, 3.44. Found: C, 45.85; H, 3.51.

7-Chloro-6-fluoro-2,3-dihydro-4*H*-1-benzothiopyran-4-one (**2**).

The acid **1** (5.1 g, 21.6 mmoles) was added to 96% sulfuric acid (15 ml) and the mixture allowed to stand at room temperature overnight. The resulting red solution was poured into crushed ice and the separated solid was filtered, washed with 10% aqueous sodium carbonate and then with water, dried and recrystallized from cyclohexane to give **2** (4.2 g, 92%), mp 84-86°; ^{1}H-nmr (deuterochloroform): δ 2.90-3.15 (2H, m, SCH_2), 3.20-3.40 (2H, m, CH_2CO), 7.25 (1H, d, J = 6.5 Hz, H-8), 7.70 (1H, d, J = 9.5 Hz, H-5).

Anal. Calcd. for C_9H_6ClFOS: C, 49.90; H, 2.79. Found: C, 50.05; H, 2.83.

7-Chloro-6-fluoro-3-carbomethoxycarbonyl-2,3-dihydro-4*H*-1-benzothiopyran-4-one (**3**).

A solution of **2** (3.0 g, 13.3 mmoles) in anhydrous benzene (20 ml) was slowly added under nitrogen to a mixture of sodium methoxide (1.5 g, 26 mmoles) and dimethyloxalate in anhydrous benzene (30 ml). As the reaction proceeded, a reddish-brown solid gradually precipitated. The reaction mixture was stirred for 2 hours at room temperature, the precipitate filtered, dissolved in water (20 ml) and acidified with 2*N* hydrochloric acid. The yellowish precipitate was collected and recrystallized from methanol to give **3** (2 g, 49%), mp 134-136°; ^{1}H-nmr (deuterochloroform): δ 3.95 (3H, s, CH_3), 4.15 (2H, s, SCH_2), 7.40 (1H, d, J = 6.5 Hz, H-8), 7.80 (1H, d, J = 9.5 Hz, H-5).

Anal. Calcd. for $C_{12}H_8ClFO_4S$: C, 47.62; H, 2.66. Found: C, 47.51; H, 2.58.

Methyl 7-Chloro-6-fluoro-2,3-dihydro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**4**).

A powdered mixture of **3** (2 g) and soft glass powder were heated to about 140° until the evolution of carbon monoxide ceased. The mixture was cooled, extracted with acetone, filtered, evaporated to dryness and recrystallized from ethanol to give **4** (1.5 g, 85%), mp 135-138°; ^{1}H-nmr (deuterochloroform): δ 3.80 (2H, s, SCH_2), 3.90 (3H, s, CH_3), 7.40 (1H, d, J = 6.5 Hz, H-8), 7.65 (1H, d, J = 9.5 Hz, H-5), 12.65 (1H, s, OH).

Anal. Calcd. for $C_{11}H_8ClFO_3S$: C, 48.10; H, 2.94. Found: C, 48.25; H, 3.05.

Methyl 7-Chloro-6-fluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**5**).

Chloranil (4.4 g, 18 mmoles) was added to a solution of **4** (5.0 g, 18 mmoles) in dioxane (40 ml) and the mixture was stirred at 60° for 1 hour. After evaporation, the solid residue was treated with chloroform, filtered and the solution washed with 2*N* sodium carbonate and then with water. Evaporation to dryness gave a residue which was recrystallized from carbon tetrachloride to give **5** (3.2 g, 64%), mp 157-159°; ^{1}H-nmr (deuterochloroform): δ 3.95 (3H, s, CH_3), 7.80 (1H, d, J = 6.5 Hz, H-8), 8.30 (1H, d, J = 9.5 Hz, H-5), 8.70 (1H, s, H-2).

Anal. Calcd. for $C_{11}H_6ClFO_3S$: C, 48.46; H, 2.22. Found: C, 48.30; H, 2.31.

7-Chloro-6-fluoro-4*H*-1-benzothiopyran-4-one-3-carboxylic Acid (**6**).

Hydrobromic acid (48%) (10 ml) was added to a solution of **5** (1 g, 3.7 mmoles) in methanol (15 ml) and the mixture was refluxed for 15 minutes. After concentrating under reduced pressure, the resulting precipitate was collected and recrystallized from ethyl acetate-ethanol to give **6** (0.8 g, 87%), mp 235-237°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.32 (1H, d, J = 9.5 Hz, H-5), 8.58 (1H, d, J = 6 Hz, H-8), 9.55 (1H, s, H-2).

Anal. Calcd. for $C_{10}H_4ClFO_3S$: C, 46.44; H, 1.56. Found: C, 46.34; H, 1.61.

6-Fluoro-7-(4-methyl-1-piperazinyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-one (**7**).

A mixture of **2** (1 g, 4.3 mmoles) and *N*-methylpiperazine (2.5 ml, 22.5 mmoles) was stirred at 120° for 24 hours. The mixture was then poured into ice-water and extracted with chloroform. The organic phase was dried, evaporated and the residue recrystallized from ligroin to give **7** (0.3 g, 23%), mp 116-118°; ^{1}H-nmr (deuterochloroform): δ 2.35 (3H, s, CH_3), 2.50-2.70 (4H, m, $CH_2N(CH_3)CH_2$), 2.75-3.00 (2H, m, SCH_2), 3.12-3.42 (6H, m, CH_2CO and CH_2NH_2), 6.62 (1H, d, J = 7.5 Hz, H-8), 7.70 (1H, d, J = 15 Hz, H-5).

Anal. Calcd. for $C_{14}H_{17}FN_2OS$: C, 59.98; H, 6.11; N, 9.99. Found: C, 60.11; H, 6.22; N, 9.81.

Ethyl α-[(*N*,*N*-Dimethylamino)methylene]-2,3,4,5-tetrafluoro-β-oxobenzenepropanoate (**9**).

N,*N*-Dimethylformamide dimethyl acetal (1.25 ml, 9.4 mmoles) was added to a solution of ketoester **8** [4] (1 g, 3.7 mmoles) in 20 ml of dry toluene. The mixture was heated at 115-120° for 1 hour and then evaporated to dryness and purified by flash chromatography eluting with hexane-chloroform 2:1 to give **9** (1.1 g, 91%) as a thick oil (a 1:4 or 4:1 mixture of (*E*)- and (*Z*)-isomers); ^{1}H-nmr (deuterochloroform): δ 1.10 (2.4H, t, J = 7.5 Hz, CH_2CH_3), 1.30 (0.6H, t, J = 7 Hz, CH_2CH_3), 2.90-3.40 [6H, br s, $N(CH_3)_2$], 4.05 (0.4H, q, J = 7.5 Hz, CH_2CH_3), 4.10 (1.6H, q, J = 7.5 Hz, CH_2CH_3), 4.10 (1.6H, q, J = 7.5 Hz, CH_2CH_3), 7.00-7.30 (1H, m, aromatic H), 7.50 (0.2H, s, vinyl H), 7.80 (0.8H, s, vinyl H).

Anal. Calcd. for $C_{14}H_{13}F_4NO_3$: C, 52.67; H, 4.10; N, 4.39. Found: C, 52.71; H, 3.90; N, 4.44.

Ethyl 6,7,8-Trifluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**10**).

Hydrogen sulfide was bubbled into a solution of **9** (1 g) in tetrahydrofuran (60 ml) at -30° for 4 hours. The mixture was concentrated and the syrup obtained was purified by flash chromatography eluting with cyclohexane-ethyl acetate 2:1 to give **10** which was recrystallized from hexane (0.7 g, 77%), mp 133-136°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 6.5 Hz, CH_2CH_3), 4.40 (2H, q, J = 6.5 Hz, CH_2CH_3), 8.15-8.30 (1H, m, H-5), 8.75

(1H, s, H-2).

Anal. Calcd. for $C_{12}H_7F_3O_3S$: C, 50.01; H, 2.45. Found: C, 50.09; H, 2.57.

General Procedure for the Preparation of Esters **11-13**.

The mixture of fluoro derivative **10** (1 mmole), appropriate base (1.1 mmoles) and sodium bicarbonate (1 mmole) in acetonitrile was refluxed for 3 hours. The resulting mixture was diluted with water, extracted with chloroform and the organic layer was dried, evaporated and the residue recrystallized from cyclohexane-ethyl acetate. The products and data are described below.

Ethyl 6,8-Difluoro-7-(4-methyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylate (**11**).

This compound was obtained in 68% yield using *N*-methylpiperazine as base, mp 124-126°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.50 (3H, s, NCH_3), 2.65-2.90 and 3.45-3.60 (each 4H, m, piperazine H), 4.40 (2H, q, J = 7 Hz, CH_2CH_3), 8.05 (1H, dd, J = 12 and 2 Hz, H-5), 8.60 (1H, s, H-2).

Anal. Calcd. for $C_{17}H_{18}F_2N_2O_3S$: C, 55.43; H, 4.92; N, 7.60. Found: C, 55.48; H, 5.01; N, 7.58.

Ethyl 6,8-Difluoro-7-(3-methyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylate (**12**).

This compound was obtained in 40% yield using 2-methylpiperazine as base, mp 115-118°; ^{1}H-nmr (deuterochloroform): δ 1.25 (3H, d, J = 6 Hz, $CHCH_3$), 1.50 (3H, t, J = 7 Hz, CH_2CH_3), 2.50 (1H, br s, NH), 2.90-3.60 (7H, m, piperazine H), 4.45 (2H, q, J = 7 Hz, CH_2CH_3), 8.00 (1H, dd, J = 12 and 2 Hz, H-5), 8.60 (1H, s, H-2).

Anal. Calcd. for $C_{17}H_{18}F_2N_2O_3S$: C, 55.43; H, 4.92; N, 7.60. Found: C, 55.09; H, 5.09; N, 7.61.

Ethyl 6,8-Difluoro-7-(3,5-dimethyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylate (**13**).

This compound was obtained in 20% yield using 2,6-dimethylpiperazine as base, mp 97-100°; ^{1}H-nmr (deuterochloroform): δ 1.15 (6H, d, J = 6 Hz, piperazine CH_3), 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.30 (1H, br s, NH), 2.75-3.45 (7H, m, piperazine H), 4.40 (2H, q, J = 7 Hz, CH_2CH_3), 7.90 (1H, dd, J = 12 and 2 Hz, H-5), 8.55 (1H, s, H-2).

Anal. Calcd. for $C_{18}H_{20}F_2N_2O_3S$: C, 56.54; H, 5.27; N, 7.33. Found: C, 56.50; H, 5.30; N, 7.27.

General Procedure for the Preparation of Acids **14-16**.

A suspension of esters (0.2 g) in 10% hydrochloric acid (3 ml) was heated at 50° for 3 hours. The precipitated solid was collected and crystallized from methanol. The products and data are described below.

6,8-Difluoro-7-(4-methyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylic Acid Hydrochloride (**14**).

This compound was obtained in 78% yield, mp 240-242°; ^{1}H-nmr (trifluoroacetic acid): δ 3.20 (3H, d, J = 4.5 Hz, piperazine CH_3), 3.30-4.20 (8H, m, piperazine H), 8.20 (1H, dd, J = 12 and 1.5 Hz, H-5), 8.65 (1H, s, H-2).

Anal. Calcd. for $C_{15}H_{14}F_2N_2O_3S{\cdot}HCl$: C, 47.82; H, 4.01; N, 7.43. Found: C, 47.80; H, 4.05; N, 7.50.

6,8-Difluoro-7-(3-methyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylic Acid Hydrochloride (**15**).

This compound was obtained in 73% yield, mp 252-254°; ^{1}H-nmr (trifluoroacetic acid): δ 1.60 (3H, d, J = 6 Hz, piperazine CH_3), 3.50-4.20 (7H, m, piperazine H), 8.40 (1H, dd, J = 12 and 1.3 Hz, H-5), 9.97 (1H, s, H-2).

Anal. Calcd. for $C_{15}H_{14}F_2N_2O_3S{\cdot}HCl$: C, 47.82; H, 4.01; N, 7.43. Found: C, 47.88; H, 4.09; N, 7.39.

6,8-Difluoro-7-(2,3-dimethyl-1-piperazinyl)-4*H*-1-benzothiopyran-4-one-3-carboxylic Acid Hydrochloride (**16**).

This compound was obtained in 78% yield, mp 264-266°; ^{1}H-nmr (trifluoroacetic acid): δ 1.60 (6H, d, J = 3 Hz, piperazine CH_3), 3.40-4.20 (6H, m, piperazine H), 8.40 (1H, dd, J = 10.5 and 1.3 Hz, H-5), 9.95 (1H, s, H-2).

Anal. Calcd. for $C_{16}H_{16}F_2N_2O_3S{\cdot}HCl$: C, 49.17; H, 4.38; N, 7.17. Found: C, 49.30; H, 4.40; N, 7.20.

Ethyl 2-Methylthio-6,7,8-trifluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**17**).

A solution of potassium hydroxide (0.45 g, 8 mmoles) in water (5 ml) was added to a solution of **8** (1 g, 3.7 mmoles) in dimethyl sulfoxide (10 ml). To this mixture, cooled at 10°, carbon disulfide (0.86 g, 11 mmoles) was added over a 30 minute period and the red solution was stirred for 4 hours at room temperature. Dimethyl sulfate (0.95 g, 7.5 mmoles) was then added and the colorless mixture was stirred at room temperature for 1 hour, poured into water and then extracted with ethyl acetate. Solvent removal and recrystallization from hexane gave **17** (0.84 g, 78%), mp 130-132°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.70 (3H, s, SCH_3), 4.50 (2H, q, J = 7 Hz, CH_2CH_3), 7.90-8.20 (1H, m, H-5); m/z: 334 (34.1), 290 (100), 287 (75.66), 262 (38.76), 216 (38.03), 174 (37.02), 99 (52.19).

Anal. Calcd. for $C_{13}H_9F_3O_3S_2$: C, 46.71; H, 2.71. Found: C, 46.80; H, 2.74.

The mother liquor from **17** was evaporated and the residue was flash chromatographed eluting with gradient of hexane to 10% ethyl acetate/hexane to give ethyl 2,7-dimethylthio-6,8-difluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**18**) (0.27 g, 20%), mp 88-91°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.65 and 2.75 (each 3H, s, SCH_3), 4.45 (2H, q, J = 7 Hz, CH_2CH_3), 7.95 (1H, dd, J = 10 and 2 Hz, H-5); m/z: 362 (64.13), 3.17 (100), 316 (68.82), 290 (68.82), 288 (31.88), 244 (52.19), 218 (28.69), 175 (20.50), 99 (61.75).

Anal. Calcd. for $C_{14}H_{12}F_2O_3S_3$: C, 46.40; H, 3.34. Found: C, 46.50; H, 3.38.

Ethyl 2-Methylsulfinyl-6,7,8-trifluoro-4*H*-1-benzothiopyran-3-carboxylate (**19**).

MCPBA (55%) (0.47 g, 1.49 mmoles) was added to a solution of **17** (0.5 g, 1.49 mmoles) in methylene chloride (30 ml). After stirring at room temperature for 1 hour, the solution was filtered on neutral aluminum oxide, Brockmann III, and concentrated to give **19** which was recrystallized from hexane-ethyl acetate (0.37 g, 71%), mp 118-122°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 3.15 (3H, s, $SOCH_3$), 4.50 (2H, q, J = 7 Hz, CH_2CH_3), 8.00-8.30 (1H, m, H-5).

Anal. Calcd. for $C_{13}H_9F_3O_4S_2$: C, 44.57; H, 2.59. Found: C, 44.61; H, 2.50.

Ethyl 2-Mercapto-6,7,8-trifluoro-4*H*-1-benzothiopyran-4-one-3-carboxylate (**20**).

A solution of sodium hydrosulfide (0.25 g, 4.46 mmoles) in 2%

aqueous tetrahydrofuran (5 ml) was added to a solution of **19** (0.5 g, 1.42 mmoles) in tetrahydrofuran (20 ml). The mixture was stirred at room temperature for 2 hours then diluted with water, acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The organic phase was evaporated and the residue recrystallized from hexane to give **20** (0.38 g, 85%), mp 131-133°; ^{1}H-nmr (deuterochloroform): δ 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 4.50 (2H, q, J = 7 Hz, CH_2CH_3), 7.80-8.10 (1H, m, H-5).

Anal. Calcd. for $C_{12}H_7F_3O_3S_2$: C, 45.00; H, 2.20. Found: C, 45.15; H, 2.15.

6,7,8-Trifluoro-3,4-dihydro-2*H*-isothiazolo[5,4-*b*][1]benzothiopyran-3,4-dione (**21**).

A solution of sodium bicarbonate (1.16 g, 13.9 mmoles) in water (20 ml) was added to a solution of **20** (0.5 g, 1.56 mmoles) in tetrahydrofuran (20 ml), followed by the addition of hydroxylamine-*O*-sulfonic acid (0.61 g, 5.39 mmoles). The mixture was stirred at room temperature for 3 hours, diluted with water, acidified with 1*N* hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and concentrated to dryness to give **21** which was recrystallized from ethanol (0.4 g, 89%), mp 208-210°; ^{1}H-nmr (dimethyl sulfoxide-d_6/trifluoroacetic acid): δ 8.05-8.35 (1H, m, aromatic H).

Anal. Calcd. for $C_{10}H_2F_3NO_2S_2$: C, 41.53; H, 0.70; N, 4.84. Found: C, 41.23; H, 0.85; N, 4.70.

General Procedure for the Preparation of Isothiazole Derivatives **22-24**.

The mixture of fluoro derivative **21** (1 mmole) and appropriate base (1.15 mmoles) in *N*,*N*-dimethylformamide was stirred at 100° for 1 hour. The reaction mixture was cooled and filtered. The solid residue was washed with ethanol and then with cold water. The products and data are described below.

6,8-Difluoro-7-(4-methyl-1-piperazinyl)-3,4-dihydro-2*H*-isothiazolo[5,4-*b*][1]benzothiopyran-3,4-dione (**22**).

This compound was obtained in 63% yield using *N*-methylpiperazine as base, mp >300°; ^{1}H-nmr (trifluoroacetic acid): δ 3.20 (3H, s, CH_3), 3.70-4.20 (8H, m, piperazine H), 8.25 (1H, d, J = 12 Hz, H-5).

Anal. Calcd. for $C_{15}H_{13}F_2N_3O_2S_2 \cdot 2H_2O$: C, 44.44; H, 4.23; N, 10.36. Found: C, 44.59; H, 4.33; N, 10.05.

6,8-Difluoro-7-(3-methyl-1-piperazinyl)-3,4-dihydro-2*H*-isothiazolo[5,4-*b*][1]benzothiopyran-3,4-dione (**23**).

This compound was obtained in 67% yield using 2-methylpiperazine as base, mp >300°; ^{1}H-nmr (trifluoroacetic acid): δ 1.55 (3H, d, J = 6 Hz, CH_3), 3.70-4.10 (7H, m, piperazine H), 8.25 (1H, d, J = 12 Hz, H-5).

Anal. Calcd. for $C_{15}H_{13}F_2N_3O_2S_2 \cdot 2H_2O$: C, 44.44; H, 4.23; N, 10.36. Found: C, 44.48; H, 4.03; N, 10.29.

6,8-Difluoro-7-(3,5-dimethyl-1-piperazinyl)-3,4-dihydro-2*H*-isothiazolo[5,4-*b*][1]benzothiopyran-3,4-dione (**24**).

This compound was obtained in 75% yield using 2,6-dimethylpiperazine as base, mp >300°; ^{1}H-nmr (trifluoroacetic acid): δ 1.55 (6H, d, J = 6 Hz, piperazine CH_3), 3.50-4.10 (6H, m, piperazine H), 8.30 (1H, d, J = 12 Hz, H-5).

Anal. Calcd. for $C_{16}H_{15}F_2N_3O_2S_2 \cdot 2H_2O$: C, 45.82; H, 4.57; N, 10.02. Found: C, 45.76; H, 4.24; N, 10.07.

In Vitro Antibacterial Activity.

The *in vitro* antibacterial activity was determined by standard agar dilution procedure on T.S.A. agar. Suspensions of microorganisms, up to 10^7 colony-forming units (CFU), were stored at -80° and diluted in peptonated water before using. A twofold dilution method was used to incorporate the compounds into a melted medium of 50° just prior to pouring and using the plates. Bacterial inocula were applied to the agar surface with a multipoint inoculator. Minimum inhibitory concentrations (MICs) were defined as the lowest concentration of the compounds that prevented visible growth of bacteria after incubation at 35° for 24 hours.

REFERENCES AND NOTES

[1] T. Hogberg, I. Khanna, S. D. Drake, L. A. Mitscher and L. L. Shen, *J. Med. Chem.*, **27**, 306 (1984).

[2] T. Hogberg, M. Vora, S. D. Drake, L. A. Mitscher and D. T. W. Chu, *Acta Chem. Scand.*, **B38**, 359 (1984).

[3a] V. Cecchetti, S. Dominici, A. Fravolini and F. Schiaffella, *Eur. J. Med. Chem.*, **19**, 29 (1984); [b] V. Cecchetti, A. Fravolini, R. Fringuelli, G. Mascellani, P. Pagella, M. Palmioli, G. Segre and P. Terni, *J. Med. Chem.*, **30**, 465 (1987); [c] V. Cecchetti, A. Fravolini, F. Schiaffella, O. Tabarrini and W. Zhou, *J. Heterocyclic Chem.*, **29**, 375 (1992).

[4] J. M. Domagala, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. B. Nichols, M. Solomon and D. F. Worth, *J. Med. Chem.*, **31**, 991 (1988).

[5] D. T. W. Chu, P. B. Fernandes, A. K. Claiborne, L. Shen and A. G. Pernet, *Drugs Exptl. Clin. Res.*, **XIV**, 378 (1988).

[6] D. T. W. Chu, *J. Heterocyclic Chem.*, **27**, 839 (1990).