1,4-Benzothiazine-2-carboxylic Acid 1-Oxides as Analogues of Antibacterial Quinolones [1]

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The synthesis of 1,4-benzothiazine-2-carboxylic acid 1-oxides as agents which mimic quinolone antibacterial, are described. The key step includes intramolecular cyclization of phenylsulfinyl acrylates **17** and **18** which are prepared in six steps from **11**. None of new target compounds showed interesting antibacterial activity *in vitro* against the tested strains.

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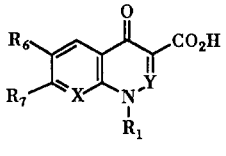
Introduction.

The class of quinolone antibacterial agents is fundamentally typified by a quinoline or 1,8-naphthyridine nucleus in which the 1-substituted-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety is the common structural feature (cinoxacin excluted).

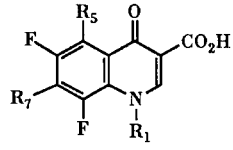
The quinolone structure-activity relationship (SAR) story is mainly focused on C-6, C-7 and N-1 substituents. These positional modifications of the parent structure showed that higher potency as well as broader bacterial coverage occured with a fluorine at C-6 and the concomitant presence of an heterocyclic base of optimal size, preferentially a piperazine or a pyrrolidine moiety, at C-7. Nevertheless, recent reports showed that heterocyclic nitrogen, linked at C-7, could be advantageously replaced by sp^2 carbon; these derivatives showed equal or greater antimicrobial activity than their nitrogen-bonded counterparts [2]. In general, optimum activity requires a substituent at the N-1 position such as ethyl or its bioisosters, such as fluoroethyl (fleroxacin [3]), methylamino (amifloxacin [4]) and methoxy (miloxacin [5]), but today the cyclopropyl group is recognized as one of the most effective substituents [6] even if other potent quinolones have a *tert*-butyl (BMY 40062 [7]) or a fluorophenyl group (difloxacin [8], temafloxacin [9], tosufloxacin [10]) (Figure 1).

Although the substitutions at C-5 are generally considered unfruitful [11], the 5-amino derivative (such as sparfloxacin [12d]) recently resulted in significantly more potent products than their non-amino analogues [12]. Substitution at C-8 with halogen, fluorine being better, provided potent quinolones (lomefloxacin [13], fleroxacin [3], CI-934 [14], PD-117596 [15], BMY 40062 [7]) (Figure 2). Annelation of a third ring between the N-1 and C-8 positions gave equally potent tricyclic compounds (ofloxacin [16], ibafloxacin [17], OPC-7241 [18], rufloxacin [19], QA-241 [20]) (Figure 3).



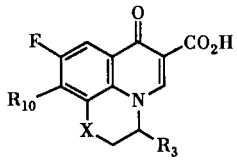
	R_1	Y	R_6	R_7	X
Norfloxacin	C_2H_5	CH	F	1-piperazinyl	CH
Enoxacin	C_2H_5	CH	F	1-piperazinyl	N
Cinoxacin	C_2H_5	N	OCH_2O		CH
Fleroxacin	$(CH_2)_2F$	CH	F	4-CH_3-1-piperazinyl	CF
Amifloxacin	$NHCH_3$	CH	F	4-CH_3-1-piperazinyl	CH
Miloxacin	OCH_3	CH	OCH_2O		CH
Ciprofloxacin	c-C_3H_5	CH	F	1-piperazinyl	CH
BMY 40062	t-C_4H_9	CH	F	2,5-diazabicyclo-[3.1.1]-2-heptyl	CF
Difloxacin	4-FC_6H_4	CH	F	4-CH_3-1-piperazinyl	CH
Temafloxacin	2,4-$F_2C_6H_3$	CH	F	3-CH_3-1-piperazinyl	CH
Tosufloxacin	2,4-$F_2C_6H_3$	CH	F	3-NH_2-1-pirrolidinyl	CH

Figure 1



	R_1	R_5	R_7
Sparfloxacin	c-C_3H_5	NH_2	3,5-$(CH_3)_2$-1-piperazinyl
Lomefloxacin	C_2H_5	H	3-CH_3-1-piperazinyl
CI-934	C_2H_5	H	3-$C_2H_5NHCH_2$-1-pirrolidinyl
PD-117596	c-C_3H_5	H	3-NH_2-1-pirrolidinyl

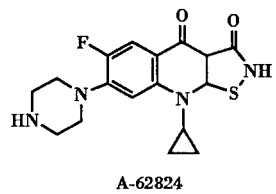
Figure 2



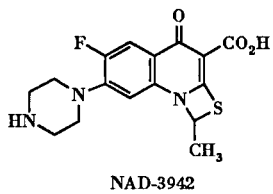
	R_3	X	R_{10}
Ofloxacin	CH_3	O	4-CH_3-1-piperazinyl
Ibafloxacin	CH_3	CH_2	CH_3
OPC-7241	CH_3	CH_2	4-CH_3-1-piperazinyl
Rufloxacin	H	S	4-CH_3-1-piperazinyl
QA-241	CH_3	CO	4-CH_3-1-piperazinyl

Figure 3

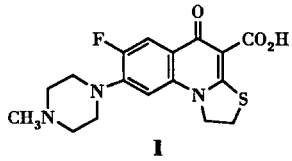
The alterations of the 1,4-dihydro-4-oxopyridine-3-carboxylic acid, a fundamental structure in a putative mechanism of action, such as carboxyl replacement by methylsulfinyl and methylsulfonyl groups [21], sulfonic [22], phosphoric [23] and hydroxamic acid [24] or formyl [25] and tetrazolyl groups [26] always led to inactive products. In contrast the modification of the carboxylic acid moiety by a thiohydroxamic acid chain to form an isothiazole ring at C-2 and C-3 furnished a series of extremely potent antibacterials (such as A-62824 [27]). Modifications at C-2 were generally considered as unfavourable [28], however this is not the case for cinoxacin [29]. Moreover, thio-substituted derivatives annelated between N-1 and C-2, recently developed, were reported to be extremely active *in vitro* (such as NAD-3942 [30], thiazoline[3,2-*a*]quinolone **1** [31] and benzothiazolo[3,2-*a*]quinolone derivatives **2** [32]) (Figure 4). Other substantial modifications, such as nitrogen replacement at the 1-position by carbon [33] or oxygen [34], always gave inactive compounds. Few derivatives with a 4-thioxo group have been described; no data on the biological activity of these compounds are available [35].



A-62824



NAD-3942



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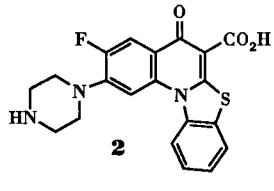

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Figure 4

In order to shed new light on quinolone SAR and as a continuation of our research on thiazinoquinolones [19,36], we herein report the synthesis and antibacterial evaluation of 1,4-benzothiazine-2-carboxylic acid 1-oxides in which the quinolone keto group was replaced by a sulfoxide group, with the hypothesis that the β-sulfoxide carboxylated moiety could equally satisfy the electronic requirements in the putative mechanism of action. Today, few examples of 1,4-benzothiazine-2-carboxylic acid, 1-oxide and 1,1-dioxide derivatives as antibacterial agents are reported [37-39] with poor or no activity, but neither of which were suitably functionalized at the benzene moiety, with the exception of the 1,1-dioxide oxolinic analogue [39] which was also inactive.

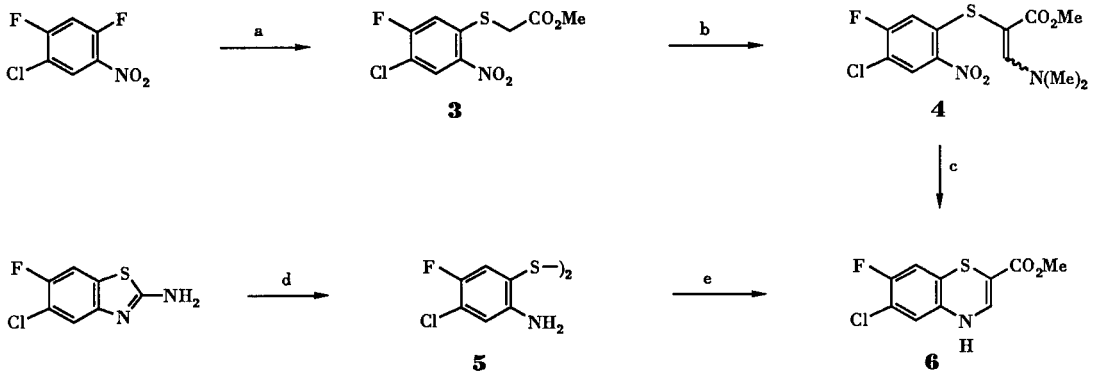
Chemistry.

Our strategy for the synthesis of 1,4-benzothiazine-2-carboxylic acid 1-oxides involved the initial preparation of methyl 6-chloro-7-fluoro-4*H*-1,4-benzothiazine-2-carboxylate (**6**) which was obtained by two different synthetic routes as shown in Scheme I. One route provided the preparation of **3** starting from 5-chloro-2,4-difluoronitrobenzene by regiospecific substitution of fluorine at C-2 with mercaptoacetate in benzene in the presence of triethylamine followed by conversion of **3** to the dimethyl acrylate derivative **4** by treatment with *N,N*-dimethylformamide dimethyl acetal and, finally, reductive cyclization with hydrogen on Raney-nickel in acetic acid to give **6**. The other route involved the hydrolytic cleavage of 5-chloro-6-fluoro-2-aminobenzothiazole under basic conditions and the reaction of the obtained disulfide **5** with methyl propiolate.

Afterwards, **6** was suitably functionalized, as outlined in Scheme II, by sulfoxidation with *m*-chloroperbenzoic acid (MCPBA) and by ethylation with ethyl iodide and potassium carbonate, or *vice versa*, to give the key intermediate **9** which, by displacement with different heterocyclic bases, should have produced many target compounds. Unfortunately, all attempts to carry out the nucleophilic substitution of chlorine at C-6 failed, using several of the usual conditions; employing acid **9a**, however, only the undesired decarboxylated derivative **10** was obtained.

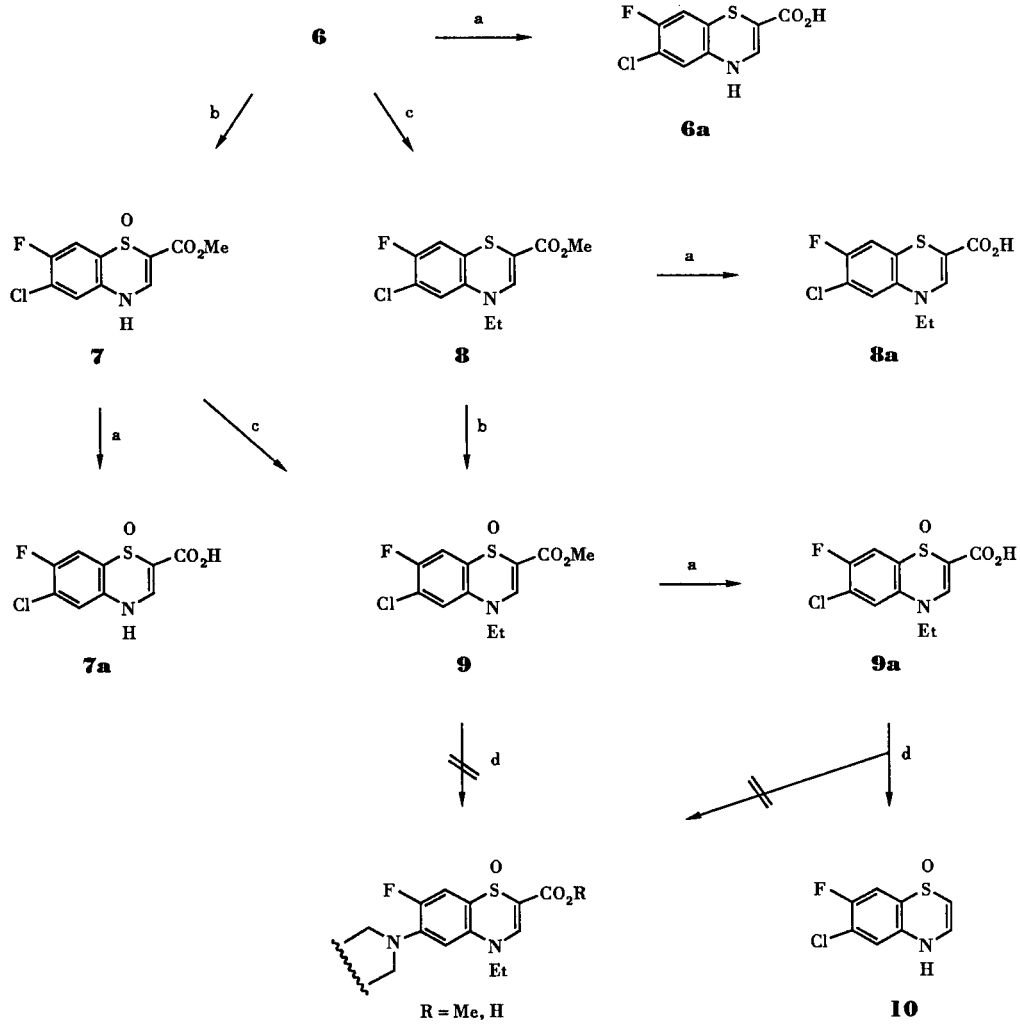
Therefore, an alternative synthesis for the preparation of the target compounds was planned as outlined in Schemes III and IV. This synthesis has a limitation because the heterocyclic base is introduced at an early stage of the synthesis, thus making it difficult to vary other substituents at this position. Indeed, *N*-methylpiperazine was at first easily introduced into 5-chloro-4-fluoro-2-nitroacetanilide to give, after hydrolysis, 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**11**). By diazotation and treatment with cuprous chloride, **11** was converted to the

Scheme I



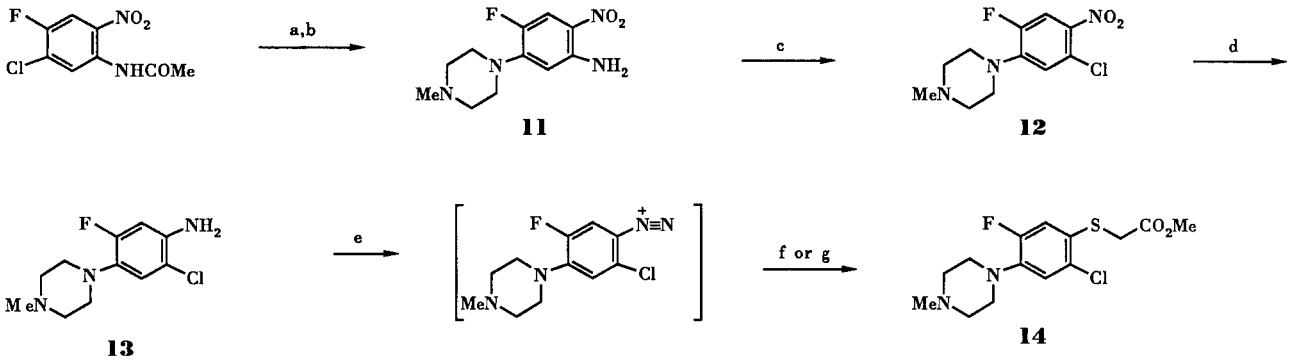
a) $HSCH_2CO_2Me$, Et_3N, benzene, 40°C. b) $(Me)_2NCH(OEt)_2$, benzene, 70°C. c) H_2/Ni-Raney, AcOH. d) 5% NaOH, reflux. e) $HC{\equiv}CCO_2Me$, EtOH, 120°C.

Scheme II



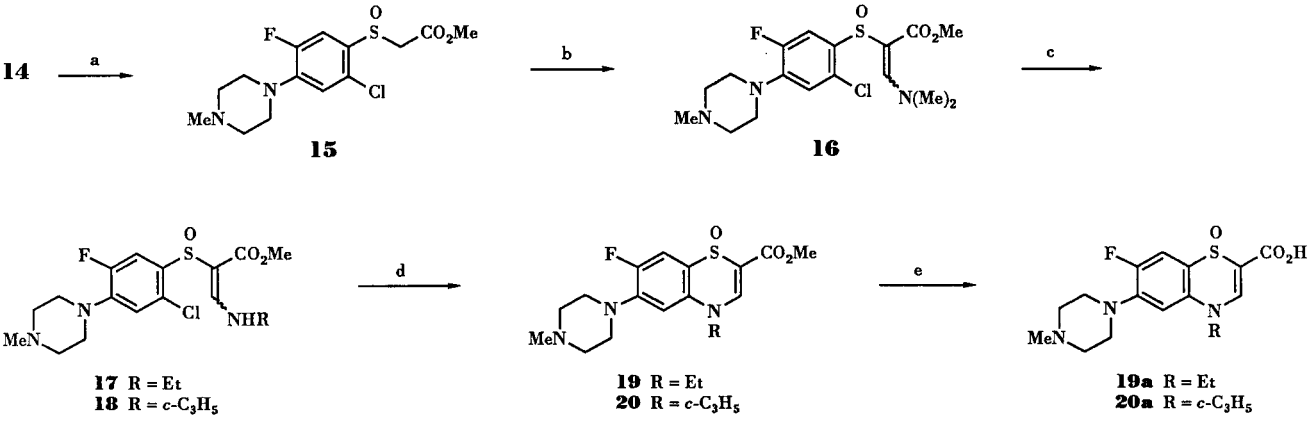
a) 5% NaOH, reflux. b) MCPBA, EtOH. c) EtI, K_2CO_3, 70°C. d) *N*-Methylpiperazine, DMF, 110°C.

Scheme III



a) *N*-Methylpiperazine, DMF, 110-120°C. b) 30% KOH, reflux. c) $NaNO_2$, H_2SO_4 conc 70°C; CuCl, HCl, 80°C. d) $SnCl_2 \cdot H_2O$, HCl conc, reflux, NaOH. e) $NaNO_2$, HCl conc, 0°. f) $HSCH_2CO_2Me$, K_2CO_3, MeOH/H_2O. g) K-Ethylxantate, 45°C; KOH, MeOH; reflux; $ClCH_2CO_2Me$.

Scheme IV



a) H_2O_2, AcOH. b) DMF-DMA, toluene, 80°C. c) $EtNH_2$ or H_2N-*c*-C_3H_5, *t*-BuOH. d) NaH, toluene, 110°C. e) 5% NaOH, reflux.

chloro derivative **12** and after reduction to the amino derivative **13**. The diazonium salt of **13** was converted to **14** by two procedures: directly by reaction with methyl thioglycolate and sodium carbonate, or by reaction with potassium ethyl xanthate followed by treatment with methyl chloroacetate and potassium hydroxide. The successive steps, reported in Scheme IV, involved: sulfoxidation of **14** with hydrogen peroxide in acetic acid, treatment of obtained sulfoxide **15** with *N,N*-dimethylformamide dimethyl acetal to give dimethyl acrylate **16**, reaction of this with ethylamine or cyclopropylamine, and intramolecular cyclization by sodium hydride of the corresponding acrylates **17** and **18** and, finally, basic hydrolysis of esters **19** and **20** to yield the target acids **19a** and **20a**. Careful acidification after hydrolysis was necessary to avoid decarboxylation, a reaction which we observed at *p*H <5.

Microbiology.

The acids **6a-9a**, **19a** and **20a** were tested *in vitro* against representative gram-negative and gram-positive bacteria (clinical isolates). These compounds were virtually inactive showing MIC 128 μg/ml.

This failure of the 4-carbonyl derivatives to exhibit activity could be due either to the non-fruitful replacement with the sulfoxide group or, more likely, to the instability of the acids. Indeed the latter decarboxylate very easily, losing the β-sulfoxide acid functionality that should have mimicked the β-ketoacid which is the fundamental moiety for the proposed mechanism of action.

EXPERIMENTAL

Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. All compounds were analyzed for C, H, and N, and the analytical values are within ±0.4% of the theoretical values. The ^1H nmr spectra were recorded on a 90-MHz Varian EM 390 spectrometer using TMS as the internal standard, and chemical shifts are given in ppm (δ). The ^1H nmr spectra of all compounds obtained were consistent

with assigned structures. Reagents and solvents were purchased from common commercial suppliers and were used as received. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70-230). Organic solutions were dried over anhydrous sodium sulfate and concentrated on a Büchi rotary evaporator at low pressure. Yields were not optimized.

Methyl 4-Chloro-5-fluoro-2-nitrophenylthioacetate (**3**).

A stirred mixture of 5-chloro-2,4-difluoronitrobenzene [40] (2 g, 10.3 mmoles), methyl mercaptoacetate (1.09 g, 10.3 mmoles) and a catalytic amount of triethylamine in benzene (50 ml) was heated at 40° for 40 hours. The reaction mixture was then concentrated to dryness and the residue chromatographed on silica gel column eluting with hexane to give 1 g of unreacted starting nitrobenzene derivative and 0.78 g (27%) of **3**, crystallized from hexane, mp 95-97°; ^{1}H nmr (deuteriochloroform): δ 3.80 (3 H, s, OCH_3), 3.85 (2 H, s, SCH_2), 7.20 (1 H, d, J = 12 Hz, H-6), 8.05 (1 H, d, J = 7.5 Hz, H-3).

Anal. Calcd. for $C_9H_7ClFNO_4S$: C, 38.86; H, 2.52; N, 5.01. Found: C, 38.91; H, 2.43; N, 4.96.

Methyl 2-(4-Chloro-5-fluoro-2-nitrophenylthio)-3-dimethylaminoacrylate (**4**).

A stirred mixture of **3** (0.5 g, 1.8 mmoles) and *N,N*-dimethylformamide dimethyl acetal (2.1 g, 17.6 mmoles) in dry benzene (20 ml) was heated at 70° for 1 hour. The solution was concentrated to dryness and the residue was crystallized from ethanol to give 0.35 g (58%) of **4** as an orange solid, mp 168-171°; ^{1}H nmr (DMSO-d_6): δ 3.15 [6 H, s, $N(CH_3)_2$], 3.55 (3 H, s, OCH_3), 7.20 (1 H, d, J = 12 Hz, H-6), 8.15 (1 H, s, vinyl H), 8.45 (1 H, d, J = 7.5 Hz, H-3).

Anal. Calcd. for $C_{12}H_{12}ClFN_2O_4S$: C, 43.06; H, 3.61; N, 8.37. Found: C, 43.28; H, 3.43; N, 8.51.

2-Amino-4-chloro-5-fluorophenyl Disulfide (**5**).

A solution of 2-amino-5-chloro-6-fluorobenzothiazole [19] (10 g, 49 mmoles) in aqueous solution of 50% sodium hydroxide (100 ml) was refluxed for 18 hours until the evolution of ammonia ceased. After cooling, the reaction mixture was filtered on charcoal and the resulting clear solution acidified with acetic acid. The precipitate was collected by filtration, washed with water and dried to give 12.8 g (74%) of **5** which was sufficiently pure to use in the next step without further purification, mp 198-200°; ^{1}H nmr (DMSO-d_6): δ 5.60 (2 H, br s, NH_2), 6.80 (1 H, d, J = 9 Hz, H-3), 6.95 (1 H, d, J = 12 Hz, H-6).

Methyl 6-Chloro-7-fluoro-4*H*-1,4-benzothiazine-2-carboxylate (**6**).

From **4**.

A solution of **4** (0.5 g, 1.5 mmoles) in acetic acid (15 ml) was hydrogenated over 0.1 g of Raney-nickel at room temperature and atmospheric pressure for 30 minutes. The mixture was filtered and the filtrate was concentrated to half of the initial volume and diluted with water. The resulting yellow solid was filtered off and crystallized from aqueous ethanol to give 0.26 g (67%) of **6**, mp 237-240°; ^{1}H nmr (DMSO-d_6): δ 3.60 (3 H, s, OCH_3), 6.55 (1 H, d, J = 7.5 Hz, H-5), 6.80 (1 H, d, J = 12 Hz, H-8), 7.00 (1 H, d, J = 6 Hz, vinyl H), 8.75 (1 H, d, J = 6 Hz, NH).

Anal. Calcd. for $C_{10}H_7ClFNO_2S$: C, 46.25; H, 2.72; N, 5.39. Found: C, 46.33; H, 2.91; N, 5.23.

From **5**.

A mixture containing **5** (5.1 g, 14.5 mmoles) and methyl propiolate (2.4 g, 28.5 mmoles) in ethanol (120 ml) was allowed to react in an autoclave at 120° for 8 hours. The reaction mixture was evaporated to dryness and the solid residue, after crystallization, gave 3.27 g (82%) of **6**.

Methyl 6-Chloro-7-fluoro-4*H*-1,4-benzothiazin-2-carboxylate 1-Oxide (**7**).

A solution of 55% MCPBA (0.67 g, 2.13 mmoles) in absolute ethanol (7 ml) was added portionwise to a stirred solution of **6** (0.5 g, 1.92 mmoles) in absolute ethanol (50 ml). The resulting mixture was stirred at room temperature for 15 minutes. The separated white solid was filtered off and dried to give 0.44 g (83%) of pure **7**, mp 209-210°; ^{1}H nmr (DMSO-d_6): δ 3.85 (3 H, s, OCH_3), 7.75 (1 H, d, J = 6 Hz, H-5), 8.15 (1 H, d, J = 9.75 Hz, H-8), 8.30 (1 H, s, H-3), 12.00 (1 H, br s, OH).

Anal. Calcd. for $C_{10}H_7ClFNO_3S$: C, 43.57; H, 2.56; N, 5.08. Found: C, 43.80; H, 2.63; N, 4.87.

Methyl 6-Chloro-4-ethyl-7-fluoro-1,4-benzothiazine-2-carboxylate (**8**).

To a solution of **6** (0.519 g, 2 mmoles) in DMF (5 ml) potassium carbonate (0.69 g, 5 mmoles) and ethyl iodide (0.8 ml, 10 mmoles) were added. The mixture was stirred vigorously at 70° for 12 hours and then poured into ice-water. The precipitated solid was filtered off, dried and purified by column chromatography eluting with cyclohexane-ethyl acetate 95/5 yielding 0.25 g of unreacted **6** and 0.14 g (24%) of **8** as a dark red solid, mp 128-131°; ^{1}H nmr (deuteriochloroform): δ 1.30 (3 H, t, J = 7 Hz, CH_2CH_3), 3.40 (2 H, q, J = 7 Hz, CH_2CH_3), 3.75 (3 H, s, OCH_3), 6.40 (1 H, d, J = 7.5 Hz, H-5), 6.55 (1 H, d, J = 11.3 Hz, H-8), 7.00 (1 H, s, H-3).

Anal. Calcd. for $C_{12}H_{11}ClFNO_2S$: C, 50.09; H, 3.85; N, 4.87. Found: C, 50.20; H, 3.94; N, 4.79.

Methyl 6-Chloro-4-ethyl-7-fluoro-1,4-benzothiazine-2-carboxylate 1-Oxide (**9**).

From **7**.

Compound **9** was prepared in 65% yield by following the procedure described for the conversion of **6** to **8** except for the reaction time which was 30 minutes; it was crystallized from ethanol, mp 196-198°; ^{1}H nmr (deuteriochloroform): δ 1.55 (3 H, t, J = 7 Hz, CH_2CH_3), 3.90 (3 H, s, OCH_3), 4.15 (2 H, q, J = 7 Hz, CH_2CH_3), 7.50 (1 H, d, J = 7 Hz, H-5), 7.75 (1 H, d, J = 12 Hz, H-8), 8.10 (1 H, s, H-3).

Anal. Calcd. for $C_{12}H_{11}ClFNO_3S$: C, 47.46; H, 3.65; N, 4.61. Found: C, 47.13; H, 3.66; N, 4.55.

From **8**.

Compound **9** was prepared in 90% yield as described for the conversion of **6** to **7**.

6-Chloro-4-ethyl-7-fluoro-1,4-benzothiazine-2-carboxylic Acid 1-Oxide (**9a**).

A stirred suspension of **9** (0.15 g) in 5% of sodium hydroxide (3 ml) was refluxed for 30 minutes. The cooled mixture was acidified to *p*H 5-6 with dilute hydrochloric acid and the white precipitate was filtered off, washed with water and dried to give 0.08 g (56%) of **9a**, mp 237-240°; ^{1}H nmr (DMSO-d_6): δ 1.30 (3 H, t, J = 6.5 Hz, CH_2CH_3), 4.30 (2 H, q, J = 6.5 Hz, CH_2CH_3), 8.10 (1 H, d, J = 5.8 Hz, H-5), 8.20 (1 H, d, J = 8.2 Hz, H-8), 8.40 (1 H, s, H-3).

Anal. Calcd. for $C_{11}H_9ClFNO_3S$: C, 45.61; H, 3.13; N, 4.84. Found: C, 45.66; H, 3.27; N, 5.01.

By using a similar procedure the following acids were prepared:

6-Chloro-7-fluoro-4*H*-1,4-benzothiazin-2-carboxylic Acid (**6a**).

This compound was obtained in 60% yield and was crystallized from ethanol, mp 183-185°; ^{1}H nmr (DMSO-d_6): δ 6.55 (1 H, d, J = 7 Hz, H-5), 6.85 (1 H, d, J = 10.5 Hz, H-8), 6.95 (1 H, d, J = 7 Hz, H-3), 8.55 (1 H, d, J = 7 Hz, NH).

Anal. Calcd. for $C_9H_5ClFNO_2S$: C, 44.01; H, 2.05; N, 5.70. Found: C, 44.12; H, 2.08; N, 5.55.

6-Chloro-7-fluoro-4*H*-1,4-benzothiazin-2-carboxylic Acid 1-Oxide (**7a**).

This compound was obtained in 90% yield and was crystallized from ethanol, mp 275°; ^{1}H nmr (DMSO-d_6): δ 7.70 (1 H, d, J = 5.8 Hz, H-5), 8.15 (1 H, d, J = 9 Hz, H-8), 8.20-8.30 (1 H, m, H-3), 11.80-11.90 (1 H, m, NH).

Anal. Calcd. for $C_9H_5ClFNO_3S$: C, 41.32; H, 1.93; N, 5.35. Found: C, 41.48; H, 2.05; N, 5.25.

6-Chloro-4-ethyl-7-fluoro-4*H*-1,4-benzothiazin-2-carboxylic Acid (**8a**).

This compound was obtained in 70% yield and was crystallized from ethanol, mp 215-218°; ^{1}H nmr (DMSO-d_6): δ 1.25 (3 H, t, J = 6.5 Hz, CH_2CH_3), 4.25 (2 H, q, J = 6.5 Hz, CH_2CH_3), 6.50 (1 H, d, J = 10.5 Hz, H-8), 6.95 (1 H, s, H-3).

Anal. Calcd. for $C_{11}H_9ClFNO_2S$: C, 48.27; H, 3.31; N, 5.12. Found: C, 48.35; H, 3.28; N, 5.16.

Attempted Reaction of **9a** with *N*-Methylpiperazine.

N-Methylpiperazine (0.1 ml, 0.86 mmole) was added to a suspension of **9a** (0.05 g, 0.17 mmole) in dry DMF (3 ml) and the mixture was heated at 110°. After a few minutes the reaction was analyzed by tlc showing the loss of starting compound **9a**. Therefore, the mixture was cooled, poured into ice-water and extracted with chloroform. The organic phases were combined, washed with water and dried. The solvent was evaporated to dryness to give 0.03 g (71%) of solid residue which, by ^{1}H nmr, was the undesired decarboxylated product, 6-chloro-7-fluoro-4-ethyl-4*H*-1,4-benzothiazine 1-oxide (**10**), mp 135-138°; ^{1}H nmr (DMSO-d_6): δ 1.10 (3 H, t, J = 6.5 Hz, CH_2CH_3), 4.05 (2 H, q, J = 6.5 Hz, CH_2CH_3), 5.40 (1 H, d, J = 7.5 Hz, H-2), 7.10 (1 H, d, J = 7.5 Hz, H-3), 7.50 (1 H, d, J = 7.5 Hz, H-5), 7.55 (1 H, d, J = 10.5 Hz, H-8).

Anal. Calcd. for $C_{10}H_9ClFNOS$: C, 48.89; H, 3.69; N, 5.70. Found: C, 49.12; H, 3.55; N, 5.75.

4-Fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**11**).

A stirred mixture of 5-chloro-4-fluoro-2-nitroacetanilide [41] (2 g, 8.6 mmoles) and *N*-methylpiperazine (2.85 ml, 25.8 mmoles) in DMF (10 ml) was heated at 110-120° for 1 hour. The reaction mixture was poured into ice-water and the resulting yellow precipitate was collected by filtration and suspended in a hydroalcoholic solution of 30% potassium hydroxide (25 ml). The resulting mixture was refluxed for 1 hour and then concentrated to half its volume. After cooling, the precipitated yellow solid was filtered off, washed with water to give 1.85 g (85%) of **11** as a pure solid, mp 154-155°; ^{1}H nmr (DMSO-d_6): δ 2.10 (3 H, s, CH_3), 2.35-2.60 and 3.10-3.35 (each 4 H, m, piperazine CH_2), 6.40 (1 H, d, J = 7.5 Hz, H-2), 7.30 (2 H, br s, NH_2), 7.60 (1 H, d, J = 13.5 Hz, H-5).

Anal. Calcd. for $C_{11}H_{15}FN_4O_2$: C, 51.96; H, 5.95; N, 22.04. Found: C, 52.06; H, 5.79; N, 22.32.

2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)nitrobenzene (**12**).

Sodium nitrite (1.7 g, 24.6 mmoles) was added portionwise into concentrated sulfuric acid (22 ml) keeping the temperature below 15°. Successively the mixture was heated at 70° until all the sodium nitrite was dissolved, then cooled to 15°, and a solution of **11** (5 g, 19.7 mmoles) in glacial acetic acid (55 ml) was added at such a rate that the temperature remained below 15°. After the addition was completed, the solution was stirred at 40° for 30 minutes and then poured into a cooled solution of cuprous chloride (4.8 g, 48.5 mmoles) in concentrated hydrochloric acid (50 ml). The resulting mixture was heated at 80° until the effervescence ceased, then cooled in an ice-bath and basified with 30% sodium hydroxide. The obtained precipitate was filtered off, washed with water, dried and extracted several times with boiling methanol. The methanolic extracts were clarified with charcoal and reduced giving, after filtration, 3.3 g (60%) of yellow solid **12** which was sufficiently pure for the next step, mp 105-107°; ^{1}H nmr (deuteriochloroform): δ 2.35 (3 H, s, CH_3), 2.50-2.65 and 3.20-3.40 (each 4 H, m, piperazine CH_2), 6.90 (1 H, d, J = 7.2 Hz, H-3), 7.80 (1 H, d, J = 13.5 Hz, H-6).

2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)aniline (**13**).

A solution of stannous chloride dihydrate (1.23 g, 5.5 mmoles) in concentrated hydrochloric acid (5 ml) was added to a suspension of **12** (0.5 g, 1.83 mmoles) in dilute hydrochloric acid (60 ml) and the stirring mixture was refluxed for 1 hour. After cooling the solution was alkalinized with 10% sodium hydroxide and extracted with chloroform. The organic phases were combined, washed with water, dried and evaporated to dryness. The oil residue was triturated with cyclohexane and filtered to give 0.40 g (91%) of **13** as a crystalline white solid, mp 84-86°; ^{1}H nmr (deuteriochloroform): δ 2.35 (3 H, s, CH_3), 2.50-2.65 and 2.90-3.10 (each 4 H, m, piperazine CH_2), 3.80 (1 H, br s, NH_2), 6.50 (1 H, d, J = 13.5 Hz, H-6), 6.85 (1 H, d, J = 7.5 Hz, H-3).

Anal. Calcd. for $C_{11}H_{15}ClFN_3$: C, 54.21; H, 6.20; N, 17.24. Found: C, 54.50; H, 6.32; N, 16.96.

Methyl 2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)phenylthioacetate (**14**).

A solution of **13** (3 g, 12.3 mmoles) in 6*N* hydrochloric acid (6 ml) was cooled to 0° and treated dropwise with a solution of sodium nitrite (1.3 g, 18.8 mmoles) in water (2 ml) keeping the temperature at 0°. The mixture was then stirred at 0-5° for 20 minutes and a little urea was added to quenche the excess nitrous acid.

Method A.

The above solution was slowly added to a solution of methyl mercaptoacetate (1.4 g, 13.2 mmoles) and anhydrous potassium carbonate (0.8 g, 7.8 mmoles) in 7:3 aqueous methanol (10 ml) maintained at 0°. When the addition was completed, the mixture was stirred and allowed to come to room temperature over 30 minutes. The precipitated solid was filtered off to give 1.4 g (34%) of **14** as a yellow solid which was crystallized from ethyl acetate-methanol, mp 141-142°; ^{1}H nmr (deuteriochloroform): δ 2.40 (3 H, s, NCH_3), 2.50-2.65 and 3.05-3.25 (each 4 H, m, piperazine CH_2), 3.60 (2 H, s, SCH_2), 3.70 (3 H, s, OCH_3), 6.90 (1 H, d, J = 7.5 Hz, H-3), 7.20 (1 H, d, J = 13.5 Hz, H-6).

Anal. Calcd. for $C_{14}H_{18}ClFN_2O_2S$: C, 50.53; H, 5.45; N, 8.42. Found: C, 50.82; H, 5.52; N, 8.69.

Method B.

To a solution of potassium ethyl xanthate (7.9 g, 49 mmoles) in water (10 ml), kept at 40°, the cold diazonium salt solution was added dropwise under stirring at such a rate that the temperature did not exceed 45°. The mixture was stirred for 30 minutes at the same temperature then cooled and extracted several times with chloroform. The combined extracts were washed with 10% sodium carbonate solution, then with water and finally dried. The solvent was evaporated to give an oil which was mixed with a hot solution of potassium hydroxide (1.54 g, 27.6 mmoles) in methanol (80 ml). The resulting mixture was refluxed for 1 hour then cooled at 40° and methyl chloroacetate (2.6 g, 24 mmoles) was then added. After standing for 1 hour at room temperature the solution was diluted with water and extracted with chloroform. The extracts were washed with water, dried and evaporated. The crude residue was chromatographed on a silica gel column using 8:2 chloroform-methanol giving 2.5 g (63%) of **14**.

Methyl 2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)phenylsulfinylacetate (**15**).

To a solution of **14** (2 g, 6.02 mmoles) in acetic acid (7.2 ml), 35% hydrogen peroxide (0.6 ml) was added portionwise. The mixture was stirred at room temperature for 48 hours, then basified with a saturated solution of sodium carbonate and finally extracted with ethyl acetate. The organic layers were combined, dried and evaporated to dryness to give 1.25 g (60%) of pure **15** as yellow solid, mp 154-155°; ^{1}H nmr (deuteriochloroform): δ 2.35 (3 H, s, NCH_3), 2.50-2.70 and 3.00-3.40 (each 4H, m, piperazine CH_2), 3.65 and 3.95 (each 1 H, d, J = 13.5 Hz, $SOCH_2$), 3.75 (3 H, s, OCH_3), 6.85 (1 H, d, J = 7.5 Hz, H-3), 7.50 (1 H, d, J = 13.5 Hz, H-6).

Anal. Calcd. for $C_{14}H_{18}ClFN_2O_3S$: C, 48.21; H, 5.20; N, 8.03. Found: C, 48.22; H, 5.20; N, 8.00.

Methyl 2-[2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)phenylsulfinyl]-3-dimethylaminoacrylate (**16**).

A stirred mixture of **15** (1.2 g, 3.43 mmoles) and *N,N*-dimethylformamide dimethyl acetal (2.4 ml, 18.1 mmoles) in dry toluene (25 ml) was heated at 80° for 2 hours. After cooling, the separated solid was filtered off and recrystallized from cycloexane to give 0.9 g (66%) of white solid **16** as an approximate 1:2 or 2:1 mixture of (*E*)- and (*S*)-isomers, mp 150-152°; ^{1}H nmr (deuteriochloroform): δ 2.35 (3 H, s, NCH_3), 2.50-2.65 (4 H, m, piperazine CH_2), 3.30-3.45 (7 H, m, CH_3NCH_3 and piperazine CH_2), 3.40 (3 H, br s, CH_3NCH_3), 3.50 and 3.58 (3 H, each s, OCH_3), 6.75 and 6.85 (1 H, each d, J = 6.5 Hz, H-3), 7.40 and 7.90 (1 H, each s, vinyl H), 7.50 and 7.70 (1 H, each d, J = 10.7 Hz, H-6).

Anal. Calcd. for $C_{17}H_{23}ClFN_3O_3S$: C, 50.56; H, 5.74; N, 10.40. Found: C, 50.67; H, 5.66; N, 10.68.

Methyl 2-[2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)phenylsulfinyl]-3-ethylaminoacrylate (**17**).

A mixture of **16** (0.5 g, 1.23 mmoles) and ethylamine (0.4 ml, 6.15 mmoles) in *tert*-butyl alcohol (20 ml) was heated in an autoclave at 55-60° for 2.5 hours and then evaporated to dryness to give 0.44 g (89%) of pure **17** as a semisolid which was used as such in the next step; ^{1}H nmr (deuteriochloroform): δ 1.25 (3 H, t, J = 6 Hz, CH_2CH_3), 2.40 (3 H, s, NCH_3), 2.50-2.65 (4 H, m, piperazine CH_2), 3.10-3.50 (6 H, m, CH_2CH_3 and piperazine CH_2), 3.65 (3 H, s, OCH_3), 6.80 (1 H, d, J = 7.5 Hz, H-3), 7.35 (1 H, d, J = 15 Hz, vinyl H), 7.60 (1 H, d, J = 12 Hz, H-6), 8.32-8.65 (1 H, m, NH).

Methyl 2-[2-Chloro-5-fluoro-4-(4-methyl-1-piperazinyl)phenylsulfinyl]-3-cyclopropylaminoacrylate (**18**).

A stirred mixture of **16** (0.42 g, 1.04 mmoles) and cyclopropylamine (0.1 ml, 1.56 mmoles) in *tert*-butyl alcohol was heated at 45° for 2 hours. The solution was evaporated to dryness to give 0.4 g (95%) of pure **18** as a semisolid which was used in the next step without further purification; ^{1}H nmr (deuteriochloroform): δ 0.35-0.85 (4 H, m, cyclopropyl CH_2), 2.32 (1 H, s, NCH_3), 2.35-2.65 (4 H, m, piperazine CH_2), 2.70-2.90 (1 H, m, cyclopropyl CH), 2.95-3.25 (4 H, m, piperazine CH_2), 3.60 (1 H, s, OCH_3), 6.75 (1 H, d, J = 7.5 Hz, H-3), 7.45 (1 H, d, J = 13.5 Hz, vinyl H), 7.55 (1 H, d, J = 13.5 Hz, H-6), 8.55 (1 H, d, J = 13.5 Hz, NH).

Methyl 4-Ethyl-7-fluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylate 1-Oxide (**19**).

A 60% sodium hydride-in-oil suspension (0.037 g, 0.92 mmole) was slowly added to a cold solution of **17** (0.25 g, 0.62 mmole) in dry toluene (20 ml). The mixture was heated at 110° for 2 hours under nitrogen atmosphere, then poured into ice-water and extracted with ethyl acetate. The organic layers were combined, washed with water, dried, and evaporated to dryness giving 0.1 g (44%) of crude solid **19** which was used as such in the next step. An analytical sample of **19** was obtained by silica gel column chromatography eluting with 97:3 chloroform-methanol, mp 95-96°; ^{1}H nmr (deuteriochloroform): δ 1.50 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.42 (3 H, s, NCH_3), 2.55-2.75 and 3.10-3.25 (each 4 H, m, piperazine CH_2), 3.95 (3 H, s, OCH_3), 4.15 (2 H, q, J = 7.5 Hz, CH_2CH_3), 7.15 (1 H, d, J = 13.5 Hz, H-8), 7.55 (1 H, d, J = 9 Hz, H-5), 8.10 (1 H, s, H-3).

Anal. Calcd. for $C_{17}H_{22}FN_3O_3S$: C, 55.57; H, 6.03; N, 11.44. Found: C, 55.28; H, 6.23; N, 11.27.

Methyl 4-Cyclopropyl-7-fluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylate 1-Oxide (**20**).

By using this procedure **20** was prepared from **18** in 19% yield, mp 95-100°; ^{1}H nmr (deuteriochloroform/perdeuteriomethanol): δ 1.05-1.40 (4 H, m, cyclopropyl CH_2), 2.35 (3 H, s, NCH_3), 2.50-2.75 and 3.10-3.35 (each 4 H, m, piperazine CH_2), 3.90 (3 H, s, OCH_3), 7.50 (1 H, d, J = 9 Hz, H-5), 7.80 (1 H, d, J = 15 Hz, H-8), 8.30 (1 H, s, H-3).

Anal. Calcd. for $C_{18}H_{22}FN_3O_3S$: C, 56.98; H, 5.84; N, 11.07. Found: C, 56.81; H, 5.76; N, 11.04.

4-Ethyl-7-fluoro-6-(4-methyl-1-piperazinyl)-1,4-benzothiazine-2-carboxylic Acid 1-Oxide (**19a**).

A stirred suspension of **19** (0.3 g, 0.82 mmole) in 5% sodium hydroxide (3 ml) was refluxed for 45 minutes. The cooled mixture was acidified to *p*H 5-6 by dilute hydrochloric acid, evaporated to dryness *in vacuo* and the solid residue extracted several times with boiling chloroform. The hot chloroform solution was filtered through Celite and then concentrated (20 ml final volume) to leave a crude product which was recrystallized from chloroform to give 0.2 g (70%) of **19a**, mp 220-223°; ^{1}H nmr (perdeuteriomethanol): δ 1.45 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.90 (3 H, s, NCH_3), 3.15-3.60 (8 H, m, piperazine CH_2), 4.20 (2 H, q, J = 7.5 Hz, CH_2CH_3), 7.50 (1 H, d, J = 15 Hz, H-8), 7.72 (1 H, d, J = 9 Hz, H-5), 8.20 (1 H, s, H-3).

Anal. Calcd. for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.70; N, 11.89. Found: C, 54.39; H, 5.48; N, 11.74.

4-Cyclopropyl-7-fluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic Acid 1-Oxide (**20a**).

By using this procedure compound **20a** was prepared in 63% yield from **20**, mp 210-215°; ^{1}H nmr (perdeuteriomethanol): δ 1.10-1.40 (4 H, m, cyclopropyl CH_2), 2.95 (3 H, s, NCH_3), 3.20-3.70 (9 H, m, cyclopropyl CH and piperazine CH_2), 7.70 (1 H, d, J = 7 Hz, H-5), 7.75 (1 H, d, J = 15 Hz, H-8), 8.30 (1 H, s, H-3).

Anal. Calcd. for $C_{17}H_{20}FN_3O_3S$: C, 55.88; H, 5.52; N, 11.50. Found: C, 55.73; H, 5.32; N, 11.25.

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