Synthesis of 4*H*-1,4-Benzothiazine 1-Oxide and 1,1-Dioxide. Analogs of Quinolone Antibacterial Agents

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4-Cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic acid 1-oxide (**2c**) and 4-cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxide (**2d**) were prepared and assayed for antibacterial activity and inhibition of DNA gyrase.

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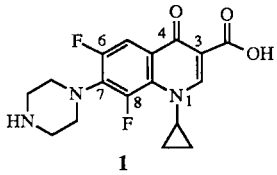
Quinolone antibacterial agents have evolved from compounds of modest activity to those with broad spectrum potency [1]. Structure-activity relationships developed through systematic modifications at various ring positions have identified certain optimum substitution patterns. Especially active were analogs with a cyclopropyl group at C-1, fluorines at C-6 and C-8 and a cyclic amine at C-7 [1]. For example, compound **1** was very active against gram-positive and gram-negative bacteria (MIC >1 μg/ml) and inhibited DNA gyrase at 0.5 μg/ml [2].

Although other quinolone ring positions have also been modified with varying degrees of success, very few modifications have been carried out at C-4. One attempt has been to replace the 4-carbonyl group of oxolinic acid with a sulfone to give **2a** [3] but it was reported to have no antibacterial activity. The corresponding sulfoxide isostere was not described. However, the tetrachloro analog **2b** in the sulfoxide case has been reported to have very weak activity. In order to better assess the possibility for a sulfoxide or a sulfone as a bioisostere at the quinolone C-4 position, we decided to investigate analogs which were more closely related to recently discovered highly active quinolones and selected 4*H*-1,4-benzothiazine 1-oxide **2c** and the 1,1-dioxide **2d** as suitable examples.



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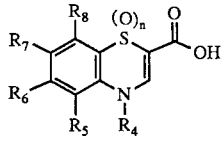

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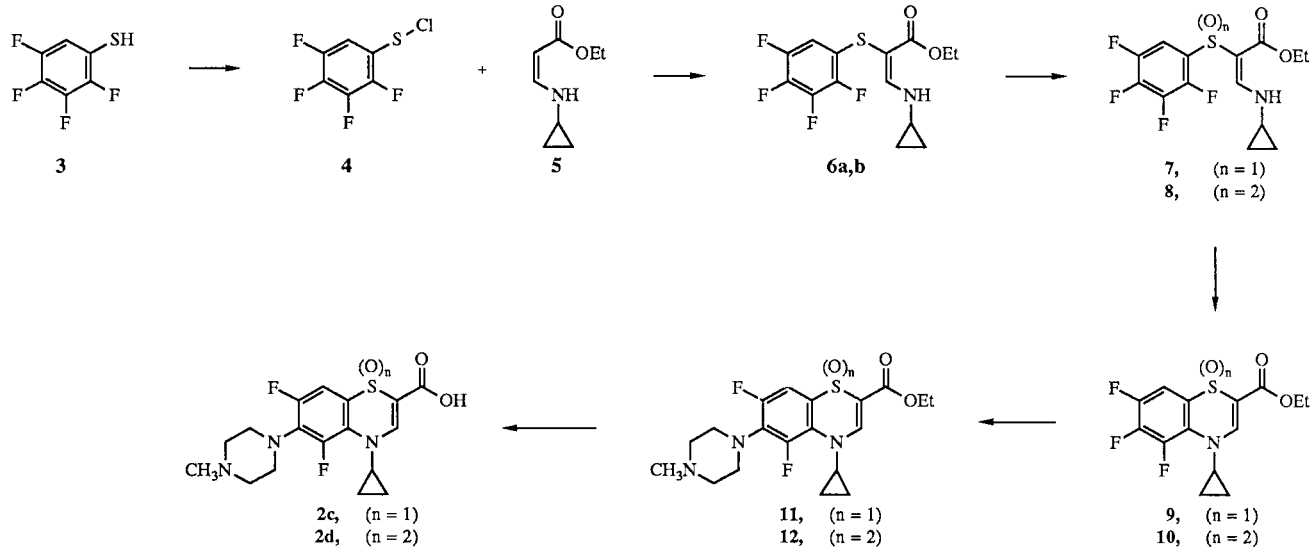
	R_4	R_5	R_6	R_7	R_8	n
a	Et	H	O–CH_2–O		H	2
b	Et	Cl	Cl	Cl	Cl	1
c		F	*N*-methyl-piperazinyl	F	H	1
d		F	"	F	H	2

The required intermediates, 4-cyclopropyl-5,6,7-trifluoro-4*H*-1,4-benzothiazine-2-carboxylic acid 1-oxide and 1,1-dioxide ethyl esters **9** and **10**, were synthesized by a procedure similar to that described for **2b** [4] (Scheme I).

Scheme I



Reaction of the lithium anion of 1,2,3,4-tetrafluorobenzene with sublimed sulfur afforded 2,3,4,5-tetrafluorothiophenol (**3**) [5]. Chlorination of **3** and reaction of the resulting sulfenyl chloride **4** with ethyl 3-(cyclopropylamino)-2-propenoate **5** afforded the enamine **6** as a *cis-trans* mixture. Separation by silica gel chromatography provided a major isomer **6a**, mp 98-99° and a minor isomer **6b**, mp 57-58°. Oxidation of **6a** with 1.3 equivalents of *m*-chloroperoxybenzoic acid gave the sulfoxide **7** while 3.1 equivalents of oxidant provided the sulfone **8**. Ring closures of **7** and **8** were carried out in THF solution with sodium hydride at room temperature to give the benzothiazine oxide **9** and dioxide **10**, respectively. Cyclization of **6a** was likewise attempted but only starting material was isolated even after several hours at reflux. The fluorine at C-6 of benzothiazines **9** and **10** was displaced by *N*-methylpiperazine in refluxing acetonitrile to afford esters **11** and **12**, respectively, with dioxide **10** being the more reactive. Base hydrolysis of **11** and **12** resulted in the desired acids **2c** and **2d**.

Compounds **2c** and **2d** were assayed against a series of gram-positive and gram-negative bacteria as well as DNA gyrase as was previously described for quinolones [6]. Both **2c** and **2d** were found to have no antibacterial activity and did not inhibit gyrase at <20 μg/ml. These results indicate that a sulfoxide or sulfone is not a bioisostere for the 4-carbonyl group of quinolones.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Bruker AM-250 spectrometer with shifts (δ) given in ppm downfield from tetramethylsilane, and coupling constants (J) are in Hz. Mass spectra were recorded on a VG analytical 7070/HF mass spectrometer. Thin layer chromatography (tlc) was carried out on E. Merck Kieselgel-60 plates and column chromatography with Kieselgel-60 230-400 mesh. Solutions were dried with anhydrous magnesium sulfate.

2,3,4,5-Tetrafluorophenylsulfenyl Chloride (**4**) [7].

While chlorine gas was passed into 50 ml of carbon tetrachloride cooled to −10° there was added dropwise over 1 hour a solution of 9.40 g (51.6 mmoles) of 2,3,4,5-tetrafluorothiophenol **3** [5] in 25 ml of carbon tetrachloride. The addition of chlorine was continued for an additional 0.5 hour and the mixture was then evaporated and distilled by Kugelrohr (air bath 50-70°, 0.1 mm) to afford 9.78 g (89%) of **4** as an orange liquid; ms: m/z 216 (M^+), 181 (-Cl).

Ethyl 3-(Cyclopropylamino)-2-propenoate (**5**).

To 0.73 g (12.8 mmoles) of cyclopropylamine in 30 ml of dichloromethane was added 0.98 g (10 mmoles) of ethyl propiolate dropwise. The mixture was refluxed 16 hours, evaporated, and distilled by Kugelrohr (air bath 60-70°, 0.1 mm) to give 1.05 g of liquid **5**; ^{1}H nmr (deuteriochloroform): δ 0.50-0.77 (complex m, 4H), 1.25 (m, 3H), 2.41 (m, 0.5H), 2.67 (m, 0.5H), 4.13 (m, 2H), 4.49 (d, 0.5H, J = 8), 4.73 (br s, 0.5H), 5.06 (d, 0.5H, J = 13), 6.75 (d, d, 0.5H, J = 8, 13), 7.44 (d, d, 0.5H, J = 7, 13), 7.89 (br s, 0.5H); ms: m/z 155 (M^+).

Anal. Calcd. for $C_5H_{13}NO_2 \cdot 0.1H_2O$: C, 61.20; H, 8.47; N, 8.92. Found: C, 61.25; H, 8.67; N, 8.73.

Ethyl 3-(Cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)thio]-2-propenoates **6a,b**.

A solution of 6.89 g (44.4 mmoles) of ethyl 3-(cyclopropylamino)-2-propenoate (**5**) in 30 ml of pyridine was treated dropwise over 10 minutes with 9.60 g (44.4 mmoles) of 2,3,4,5-tetrafluorobenzenesulfenyl chloride (**4**). The exothermic reaction which warmed to 50° was then heated at 60° for 15 minutes in an oil bath. After evaporation of the pyridine *in vacuo* the residue was dissolved in dichloromethane, washed with water, dried, and evaporated to give 13.89 g of solid which showed two spots by tlc (dichloromethane), Rf 0.40 and 0.70. Crystallization from hexanes afforded 7.55 g (51%) of yellow crystals of **6a** (Rf 0.40) mp 98-99°; ^{1}H nmr (deuteriochloroform): δ 0.70 (m, 2H), 0.80 (m, 2H), 1.26 (t, 3H, J = 7), 2.81 (m, 1H), 4.19 (q, 4H, J = 7), 6.04 (d, 1H, J = 14), 6.73 (m, 1H), 8.16 (d, 1H, J = 14); ms: m/z 335 (M^+) and 336 (M + 1).

Anal. Calcd. for $C_{14}H_{13}F_4NO_2S$: C, 50.14; H, 3.91; N, 4.18; S, 9.56. Found: C, 50.27; H, 3.91; N, 4.08; S, 9.52.

Chromatography of the filtrate with dichloromethane-hexanes (1:1) afforded 0.46 g of **6b** (Rf 0.70) mp 57-58°; ^{1}H nmr (deuteriochloroform): δ 0.72 (m, 2H), 0.80 (m, 2H), 1.19 (t, 3H, J = 7), 2.82 (m, 1H), 4.14 (q, 2H, J = 7), 6.69 (m, 1H), 7.42 (d, 1H, J = 13.5), 8.75 (br d, 1H, J = 13.1); ms: m/z 336 (M + 1).

Ethyl 3-(Cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)sulfinyl]-2-propenoate (**7**).

A solution of 0.34 g (1 mmole) of ethyl 3-(cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)thio]-2-propenoate **6a** in 10 ml of dichloromethane was treated with 0.22 g (1.29 mmoles) of 80% *m*-chloroperoxybenzoic acid in small portions over 0.5 hours. The mixture was stirred overnight, extracted with sodium bicarbonate solution, dried, and evaporated to give 0.37 g of a syrup. Chromatography with dichloromethane-ethyl acetate (9:1) and crystallization of the desired product from hexanes afforded 0.20 g (57%) of **7**, mp 88-89°; ^{1}H nmr (deuteriochloroform): δ 0.74 (m, 2H), 0.83 (m, 2H), 1.12 (t, 3H, J = 7), 2.89 (m, 1H), 4.08 (m, 2H), 7.51 (m, 1H), 7.62 (d, 1H, J = 13.7), 8.70 (br d, 1H); ms: m/z 352 (M + 1).

Anal. Calcd. for $C_{14}H_{13}F_4NO_3S$: C, 47.86; H, 3.73; N, 3.99; S, 9.13. Found: C, 47.91; H, 3.75; N, 3.87; S, 9.21.

Ethyl 3-(Cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)sulfonyl]-2-propenoate (**8**).

A solution of 1.82 g (5.43 mmoles) of sulfide **6a** in 50 ml of dichloromethane stirred at 0° was treated portionwise with 2.90 g (16.9 mmoles) of 80% *m*-chloroperoxybenzoic acid, let warm to room temperature and stirred 36 hours. The mixture was diluted with 50 ml of dichloromethane, extracted with sodium bicarbonate solution, dried, evaporation, and the residue chromatographed (dichloromethane-ethyl acetate, 20:1) to afford 0.91 g (46%) of **8** as a thick yellow syrup; ^{1}H nmr (deuteriochloroform): δ 0.80 (m, 2H), 0.90 (m, 2H), 1.14 (t, 3H, J = 7), 2.96 (m, 1H), 4.09 (q, 2H, J = 7), 7.69 (m, 1H), 8.18 (d, 1H, J = 14), 9.08 (bd, 1H); ms: m/z 367 (M^+).

4-Cyclopropyl-5,6,7-trifluoro-4*H*-1,4-benzothiazine-2-carboxylic Acid 1-Oxide, Ethyl Ester (**9**).

A solution of 3.68 g (10.5 mmoles) of ethyl 3-(cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)sulfinyl]-2-propenoate **7** in 100 ml of THF was treated in smll protions with 0.60 g (15 mmoles) of 60% sodium hydride (oil suspension). There was vigorous evolution of hydrogen after each addition. After stirring for 1 hour the mixture was filtered through a pad of silica gel and the filtrate evaporated to dryness. The residue was crystallized from ether-hexanes to provide 2.86 (82%) of **9**, mp 103-105°; ^{1}H nmr (deuteriochloroform): δ 1.04-1.27 (m, 4H), 1.40 (t, 3H, J = 7), 3.91 (m, 1H), 4.39 (q, 2H, J = 7), 7.62 (d, t, 1H, J = 7.6, 2.4), 8.32 (s, 1H); ms: m/z 332 (M + 1).

Anal. Calcd. for $C_{14}H_{12}F_3NSO_3$: C, 50.74; H, 3.65; N, 4.23; S, 9.68. Found: C, 50.82; H, 3.69; N, 4.15; S, 9.90.

4-Cyclopropyl-5,6,7-trifluoro-4*H*-1,4-benzothiazine-2-carboxylic Acid 1,1-Dioxide, Ethyl Ester (**10**).

A solution of 1.10 g (3 mmoles) of ethyl 3-(cyclopropylamino)-2-[(2,3,4,5-tetrafluorophenyl)sulfonyl]-2-propenoate **8** in 20 ml of THF stirred in an ice bath was treated in small portions with 0.18 g (4.6 mmoles) of 60% sodium hydride (oil suspension). After stirring for 3 hours a few drops of ethanol were added and the solvent was evaporated. The residue was dissolved in 50 ml dichloromethane, washed with water, dried, and evaporated to give 0.64 g of a solid. Crystallization from toluene-hexanes afforded 0.37 g (37%) of **10**, mp 200-203°; ^{1}H nmr (deuteriochloroform): δ 1.03 (m, 2H), 1.20 (m, 2H), 1.40 (t, 3H, J = 7), 3.81 (m, 1H), 4.40 (q, 2H, J = 7), 7.78 (d, t, 1H, J = 7.4, 2.4), 8.07 (s, 1H).

Anal. Calcd. for $C_{14}H_{12}F_3NO_4S$: C, 48.41; H, 3.48; N, 4.03; S, 9.23. Found: C, 48.42; H, 3.42; N, 3.66; S, 8.85.

4-Cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic Acid 1-Oxide, Ethyl Ester (**11**).

A solution of 0.17 g (0.5 mmole) of 4-cyclopropyl-5,6,7-trifluoro-4*H*-1,4-benzothiazine-2-carboxylic acid 1-oxide, ethyl ester **9** and 0.20 g (2 mmoles) of 1-methylpiperazine in 7 ml of acetonitrile was refluxed for 2.5 days. The mixture was evaporated and the residue was suspended in water, made slightly basic with dilute sodium hydroxide and extracted with dichloromethane. The organic layer was dried, evaporated and the residue was triturated with ethyl ether to give 0.12 g (60%) of **11**, mp 184-187°; ^{1}H nmr (deuteriochloroform): δ 1.10 (m, 4H), 1.40 (t, 3H, J = 7), 2.40 (s, 3H), 2.56 (m, 4H), 3.33 (m, 4H), 3.91 (m, 1H), 4.37 (q, 2H, J = 7), 7.41 (d, d, 1H, J = 8.2, 2.1), 8.28 (s, 1H); ms: m/z 411 (M^+).

Anal. Calcd. for $C_{19}H_{23}F_2N_3O_3S$: C, 55.46; H, 5.34; N, 10.21. Found: C, 55.41; H, 5.70; N, 9.98.

4-Cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic Acid 1,1-Dioxide, Ethyl Ester (**12**).

A mixture of 0.32 g (0.92 mmole) of 4-cyclopropyl-5,6,7-trifluoro-4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxide, ethyl ester **10** and 0.40 g (4 mmoles) of 1-methylpiperazine in 10 ml of acetonitrile was refluxed for 22 hours. Evaporation of the mixture afforded a syrup which crystallized from ethyl ether to give 0.24 g (62%) of **12**, mp 139-141°; ^{1}H nmr (deuteriochloroform): δ 0.96 (m, 2H), 1.12 (m, 2H), 1.39 (t, 3H, J = 7.2), 2.36 (s, 3H), 2.54 (m, 4H), 3.33 (m, 4H), 3.80 (m, 1H), 4.38 (q, 2H, J = 7.2), 7.56 (d, d, 1H, J = 2.1, 8.6), 8.04 (s, 1H); ms: m/z 427 (M^+).

Anal. Calcd. for $C_{19}H_{23}F_2N_3O_4S$: C, 53.38; H, 5.42; N, 9.83. Found: C, 53.19; H, 5.46; N, 9.51.

4-Cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic Acid 1-Oxide (**2c**).

A solution of 0.80 g (1.95 mmoles) of 4-cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic acid 1-oxide, ethyl ester **11** in 25 ml of ethanol was treated with 1.2 ml of 2*N* sodium hydroxide and stirred at reflux for 0.5 hour. The mixture was filtered and evaporated to dryness. The residue was dissolved in 25 ml of water, adjusted to *p*H 5.7 by addition of 1 ml of 2*N* hydrochloric acid and the solution was lyophilized. The crude product was taken up in DMF, filtered, and evaporated. Trituration of residue with ethyl ether afforded 0.70 g (93%) of **2c**. A sample for analysis was obtained by crystallization from methanol, mp 233-234° dec; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 0.75-1.25 (complex m, 4H), 2.32 (s, 3H), 2.57 (m, 4H), 2.30 (m, 4H), 3.97 (m, 1H), 7.77 (d, 1H, J = 9.1), 8.19 (s, 1H); ms: m/z 384 (M + 1), 368 (-O), 340 (-CO_2).

Anal. Calcd. for $C_{17}H_{19}F_2N_3O_3S \cdot H_2O$: C, 50.86; H, 5.27; N, 10.47; S, 7.98. Found: C, 50.79; H, 5.39; N, 10.24; S, 8.04.

4-Cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic Acid 1,1-Dioxide (**2d**).

A solution of 0.22 g (0.51 mmole) of 4-cyclopropyl-5,7-difluoro-6-(4-methyl-1-piperazinyl)-4*H*-1,4-benzothiazine-2-carboxylic acid 1,1-dioxide, ethyl ester **12** in 6 ml of ethanol and 0.3 ml of 2*N* sodium hydroxide was stirred at room temperature for 22 hours and filtered. The filtrate was evaporated to dryness, dissolved in 6 ml water, and adjusted to *p*H 7 with 1*N* hydrochloric acid. The precipitate was filtered, washed with water and dried to afford 0.16 g of **2d**, mp 178-179°; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 1.02 (br s, 2H), 1.05 (m, 2H), 2.34 (s, 3H), 2.61 (m, 4H), 3.30 (m, 4H), 3.83 (m, 1H), 7.57 (d, 1H, J = 10.2), 7.94 (s, 1H); ms: m/z 399 (M^+).

Anal. Calcd. for $C_{17}H_{19}F_2N_3O_4S \cdot 1.1H_2O$: C, 48.65; H, 5.09; N, 10.01. Found: C, 48.65; H, 5.01; N, 10.00.

REFERENCES AND NOTES

[1a] P. B. Fernandes, Quinolones, Proceedings of an International Telesymposium, May 1989, Published by J. R. Prous Science Publishers, Barcelona, Spain; [b] D. R. White and L. C. Davenport, Annual Reports in Medicinal Chemistry, Vol **25**, p 109.

[2] J. P. Sanchez, J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols and A. K. Trehan, *J. Med. Chem.*, **31**, 983 (1988).

[3] H. Tacha, M. Lavergne and M. Pesson, *C. R. Acad. Sci. Paris*, **282**, 975 (1976).

[4] G. Fengler, D. Arlt, K. Grobe, H. Zieler and G. Metzger, United States Patent 4,548,934 (1985); *Chem. Abstr.*, **100**, 209385 (1984).

[5] H. Bock and P. Rittmeyer, *Phosphorus Sulfur*, **35**, 291 (1988).

[6a] M. A. Cohen, T. J. Griffin, P. A. Bien, C. L. Heifetz and J. M. Domagala, *Antimicrob. Agents Chemother.*, **28**, 766 (1985); [b] J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez and M. Solomon, *J. Med. Chem.*, **29**, 394 (1986).

[7] For the preparation of pentafluorobenzenesulfenyl chloride see: P. Satori and A. Galloch, *Chem. Ber.*, **103**, 3936 (1970).