Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 7, pp 1339–1344, 1997

PII: S0968-0896(97)00084-9
0968-0896/97 $17.00 + 0.00

Synthesis and Antibacterial Evaluation of [1,3]Benzothiazino[3,2-*a*]quinoline- and [3,1]Benzothiazino[1,2-*a*]quinoline-6-carboxylic Acid Derivatives

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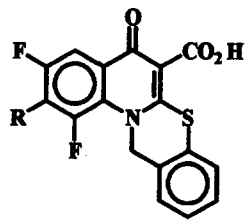
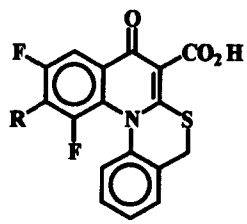
Abstract—A series of [1,3]benzothiazino[3,2-*a*]quinoline- (**5**) and [3,1]benzothiazino[1,2-*a*]quinoline-6-carboxylic acids (**10**) were synthesized and evaluated for their in vitro antibacterial activity. The activity is discussed in terms of their structural features revealed by molecular orbital correlation. © 1997 Elsevier Science Ltd.

Introduction

In earlier papers[1–3] we reported the synthesis and antibacterial activity of various series of pyridobenzothiazine carboxylic acids characterized by a 1,4-thiazine ring variously anelled to a quinoline nucleus. Good antibacterial activity and excellent pharmacokinetic properties were found for 9-fluoro-10-substituted-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzothiazine-6-carboxylic acid derivatives. Rufloxacin was developed from these as a once-daily marketed quinolone agent.[4]



5a-d



10a-d

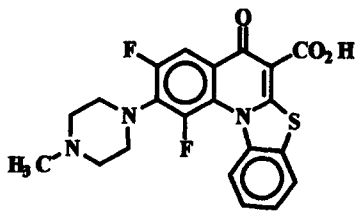


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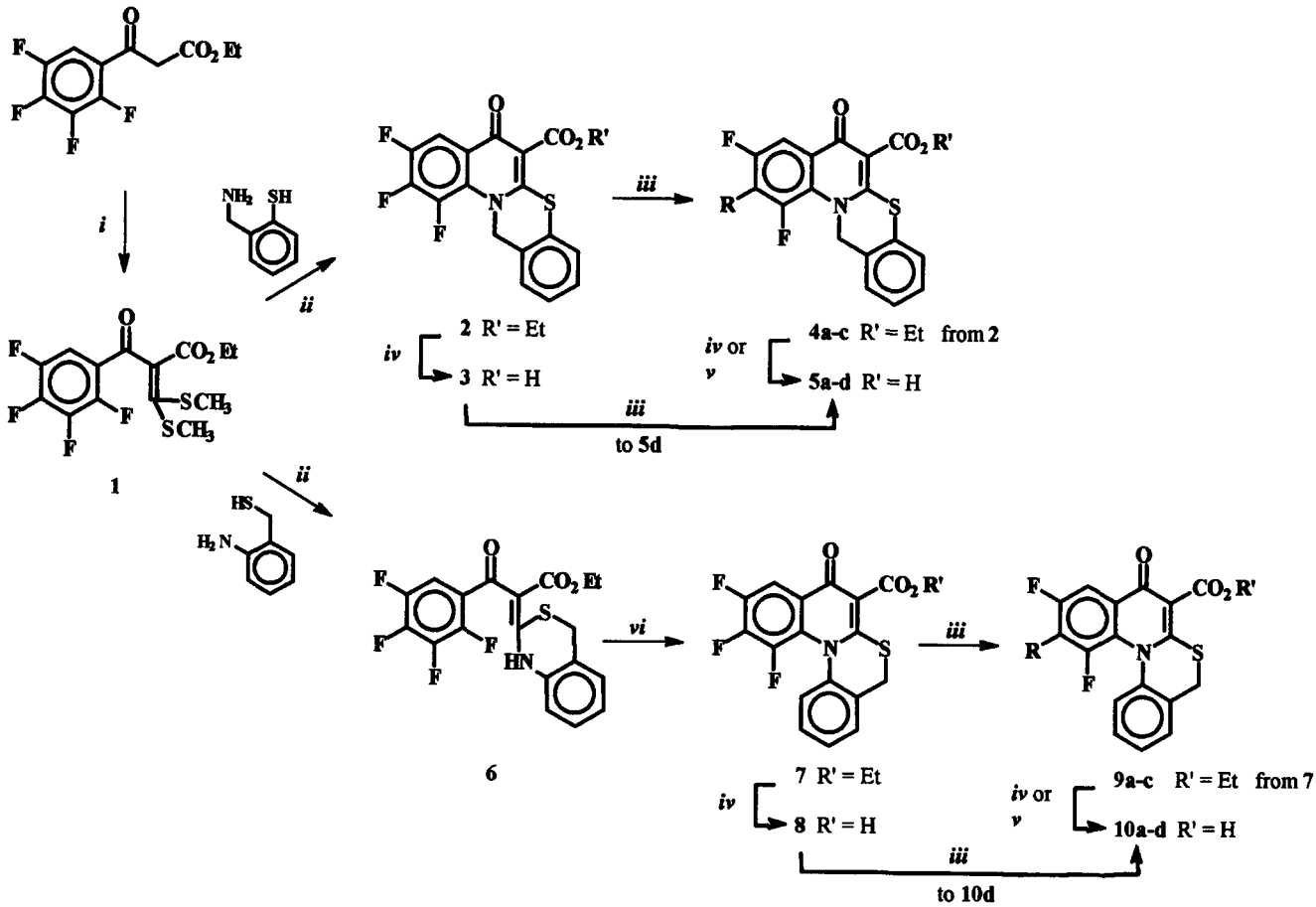
Figure 1.

Continuing our research program on thiazine-containing congeners of fluoroquinolones, we have now synthesized and evaluated the antibacterial activity of some 1,3-difluoro-2-substituted-5-oxo-5,12-dihydro[1,3]-benzothiazino[3,2-*a*]quinoline-6-carboxylic acids (**5a–d**) and 1,3-difluoro-2-substituted-5-oxo-5,8-dihydro[3,1]-benzothiazino[1,2-*a*]quinoline-6-carboxylic acids (**10a–d**) in order to examine the effect of the 1,2-anellation with the six-ringed [1,3]- or [3,1]-benzothiazine nucleus on antibacterial activity (Fig. 1). The literature also reports that anellation with four or five rings such as thiazeto, thiazole or benzothiazole at the N-1/C-2 position of a quinolone or naphthyridone moiety, gives compounds with significant antibacterial activity.[5–9]

In order to make a proper comparison, we also synthesized and assayed the 1,3-difluoro-2-(4-methyl-1-piperazinyl)-5-oxo-5*H*-benzothiazolo[3,2-*a*]quinoline-6-carboxylic acid (**11**) as an example of a difluorobenzothiazole derivative (Fig. 1). The structure–activity relationships of these compounds are also discussed in terms of their structural features revealed by molecular orbital correlation.

Chemistry

Our synthetic pathway to the target compounds **5** and **10** was designed as in Scheme 1. Starting from the common dithioacetal intermediate **1**, treatment with 2-mercaptobenzylamine in the presence of Et_3N directly gives ester **2**, while treatment with 2-aminobenzylmercaptane affords intermediate acrylate **6**, which then needs to be cyclized to ester **7** by using DBU as an HF scavenger.



Scheme 1. Reagents: (i) $DMSO/H_2O$, KOH, CS_2 CH_3I; (ii) Et_3N, toluene, reflux; (iii) RH, Et_3N, CH_3CN, reflux; (iv) 18% HCl, EtOH, reflux; (v) 4% NaOH, EtOH, reflux; (vi) DBU, toluene, reflux.

The tetracyclic benzothiazinoquinoline esters **2** and **7**, so obtained, were subjected to a coupling reaction with selected heterocyclic bases (see Table 1) to give, after acidic or basic hydrolysis, the target acid derivatives **5a–c** and **10a–c**. When thiomopholine was used as the nucleophile, it was necessary to carry out the hydrolysis step before the coupling reaction in order to obtain the target acids **5d** and **10d**.

The reference, benzothiazoloquinoline acid **11**, was obtained by the same procedure used to prepare the type **5** derivatives, except 2-aminothiophenol was used instead of 2-mercaptobenzylamine.

Results and Discussion

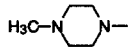
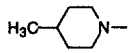
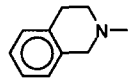
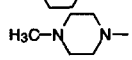
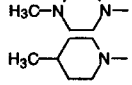
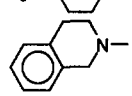
All benzothiazinoquinoline target acids **5a–d** and **10a–d**, as well as benzothiazoloquinoline acid **11**, were tested in vitro against an assortment of five Gram-positive and eight Gram-negative organisms by conventional agar dilution procedure.[3]

The MIC values, reported in Table 2, show a total inactivity of [1,3]benzothiazino[3,2-*a*]quinoline derivatives **5**, while a modest antibacterial activity against Gram-positive bacteria was found in the [3,1]benzothiazino[1,2-*a*]quinoline derivatives **10**; 4-methylpiperazinyl derivative **10a** also displays a moderate potency against some Gram-negative bacteria. The reference benzothiazole derivative **11** is the most active compound, even though its antibacterial activity is definitely less than that reported in the literature for its 1-desfluoro counterpart.[7]

In an attempt to explain the lack of antibacterial activity of benzothiazinoquinoline derivatives **5** and **10**, compared with the benzothiazoloquinoline analogue **11**, we evaluated the strength of the interaction between the quinolone molecules, keeping in mind the drug–drug association in the cooperative binding model for quinolone's gyrase inhibition proposed by Shen.[10]

Different factors can affect the molecular association: electrostatic and hydrophobic forces, steric hindrances and π–π stacking between the quinolone rings. Each of these factors is dependent upon the distance between the interacting molecules. For polycyclic quinolones, it can be expected that the greater the coplanarity between the added fused rings and the flat quinolone ring, the shorter the distance will be between the two interacting molecules. Therefore, the increased interaction strength will be mainly due to π–π forces. In our

Table 1. Physical properties of target acids used in this study

Compd	R[a]	Coupling reaction[b] Purification method[c]	Yield (%)	Hydrolysis reaction Method[d]	Yield (%)	Mp (°C)	Formula[e]
5a		C	54	B	45	265–267	$C_{22}H_{19}F_2N_3SO_3$
5b		D	80	A	90	255–257	$C_{23}H_{20}F_2N_2SO_3$
5c		D	95	B	50	248–251	$C_{26}H_{18}F_2N_2SO_3$
5d		E	42	—	—	286–287	$C_{21}H_{16}F_2N_2S_2O_3$
10a		C	40	A	63	285–288	$C_{22}H_{19}F_2N_3SO_3 \cdot HCl \cdot$
10b		D	65	A	92	141–143	$C_{23}H_{20}F_2N_2SO_3$
10c		G	72	B	55	220–225	$C_{26}H_{18}F_2N_2SO_3$
10d		F	25	—	—	240–242	$C_{21}H_{16}F_2N_2S_2O_3$

[a]See Figure 1.
[b]For compounds **5a–c** and **10a–c**, the purification method and yield refer to the corresponding intermediate esters **4a–c** and **9a–c**, respectively. For compounds **5d** and **10d** the purification method and yield refer to the target acids.
[c]The solvents used for silica gel column chromatography or for purification are as follows: (C) elution with 5% MeOH/$CHCl_3$; (D) treatment with water acidified with HCl followed by extraction with CH_2Cl_2; (E) washing with H_2O, then with EtOH; (F) elution with $CHCl_3$; (G) elution with 12% EtOAc/cycloexane.
[d]See Experimental.
[e]All compounds had elemental analyses within ±0.4% of theoretical value.

case, the computer-aided graphical analysis of tetracyclic quinolones **5a**, **10a** and **11**, performed by the SYBYL program package, shows different levels of coplanarity of the benzothiazine or benzothiazole ring with the quinolone moiety; the degree coplanarity decreases in the order **11>10a>5a** (Fig. 2).

The energy interaction values of the two quinolone molecules (self-associated in antiparallel fashion [Fig. 3] as predicted by Shen's cooperative model) calculated using the DOCK method implemented in SYBYL, can be considered to be an estimate of the relative stability of the drug–drug interaction complex. A comparison of the obtained energy values shows a good correlation between the antibacterial activity (MIC) and the total energy interaction values (E_{tot}). Indeed, the benzothiazole derivative **11**, having the highest antibacterial activity, shows the most negative total energy value (E_{tot} = −20.36 kcal/mol); the [3,1]benzothiazino[1,2-*a*]-quinoline derivative **10a**, with a modest antibacterial activity shows an intermediate total energy value (E_{tot} = −14.23 kcal/mol), while the inactive [1,3]benzothiazino-

Table 2. In vitro antibacterial activity (MICs, μg/mL)

	Compound								
	5a	**5b**	**5c**	**5d**	**10a**	**10b**	**10c**	**10d**	**11**
Gram-positive organisms									
S. aureus MPR5	>128	4	>128	>128	8	8	4	2	1
S. aureus ATCC 6538	>128	4	>128	>128	8	8	4	2	4
S. epidermidis HCF Berset C	>128	4	>128	>128	16	8	8	4	16
S. epidermidis CPHL A2	>128	8	>128	>128	16	8	8	2	64
S. faecalis LEP Br	>128	>128	>128	>128	128	32	64	16	4
Gram-negative organisms									
E. coli ATCC 8739	>128	>128	>128	>128	2	8	16	4	64
E. coli ISF 432	>128	>128	>128	>128	1	4	8	4	0.5
E. cloacae OMNFI 174	>128	>128	>128	>128	32	>128	>128	>128	16
P. vulgaris CNUR 5	>128	>128	>128	>128	>128	>128	>128	>128	8
P. stuardii CNUR5	>128	>128	>128	>128	32	>128	128	32	8
K. pneumoniae ATCC 10031	>128	>128	>128	>128	1	4	8	4	16
S. enteritidis	>128	>128	>128	>128	32	>128	>128	>128	8
P. aeruginosa ATCC 9027	>128	>128	>128	>128	128	>128	>128	>128	32

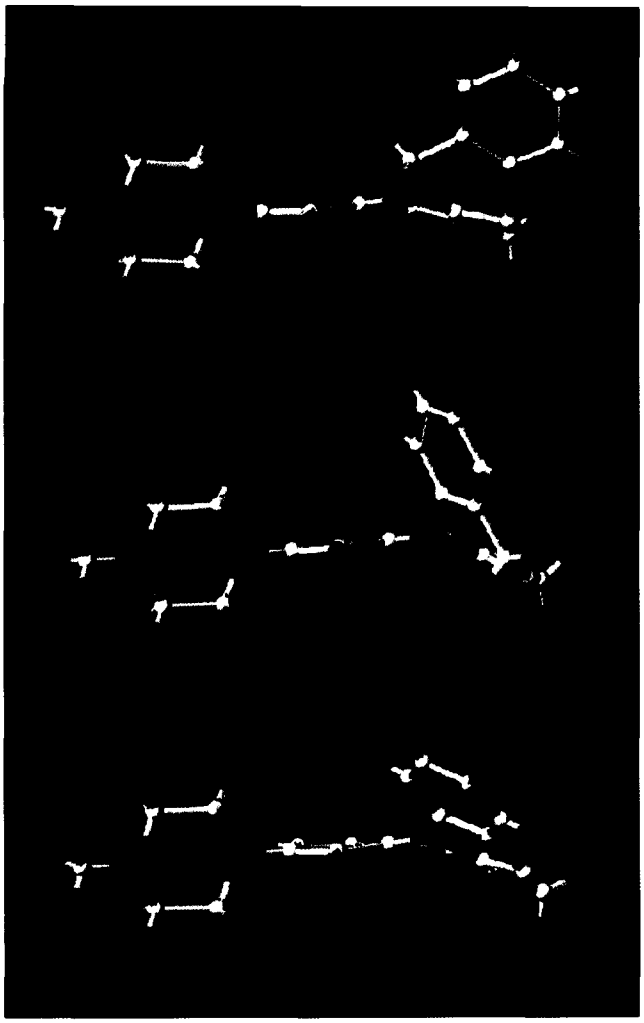


Figure 2. Modelled structures of tetracyclic quinolones **5a**, **10a** and **11** viewed from the N-1 to 4-keto direction.

[3,2-*a*]quinoline derivative **5a** shows the most positive total energy value (E_{tot} = −7.29 kcal/mol).

These different total energy values of the drug–drug interaction complex are proportional to the degree of coplanarity of the tetracyclic quinolones and could justify the lack of, or the decreased antibacterial activity of the [1,3]benzothiazino[3,2-*a*]quinoline derivatives **5** and [3,1]benzothiazino[1,2-*a*]quinoline derivatives **10**, compared with the benzothiazole derivative **11**.

Experimental

Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H and N are within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded at 200 MHz (Bruker AC-200 spectrometer) with Me_4Si as the internal standard. Chemical shifts are given in ppm (δ) and the spectral data are consistent with the assigned structures. Reagents and solvents were purchased from common

Figure 3. Two molecules of compound **10a**, self-associated in antiparallel fashion. The stacked molecular pair is viewed from the N-1 to 4-keto direction. The figure shows that the molecular surfaces of the two stacked molecules are complementary.

commercial suppliers and used as received. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70–230) and flash chromatography on Merck silica gel 60 (mesh 230–400). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure. Yields are of purified product and were not optimized. All starting materials were commercially available unless otherwise indicated. The physical properties of the target acid derivatives are summarized in Table 1.

Ethyl-3,3-dimethylthio-2-(2,3,4,5-tetrafluorobenzoyl)-acrylate (1). A solution of KOH (5.4 g, 96.4 mmol) in H_2O (55 mL) was added to a mixture of ethyl-2,3,4,5-tetrafluorobenzoylacetate[11] (11 g, 41.6 mmol) in DMSO (110 mL) and H_2O (25 mL) maintained below 15 °C. After stirring for 20 min at the same temperature, a mixture of CS_2 (8 mL, 133 mmol) and CH_3I (10 mL, 160 mmol) was added. The resulting mixture was stirred for 6 h at room temperature, then poured into water and extracted with EtOAc. The combined organic layers were dried and evaporated to dryness. The resulting residue was purified by column chromatography eluting with 1% EtOAc in cyclohexane to give **1** (7.36 g, 48%) as a yellow semisolid. ^{1}H NMR ($CDCl_3$): δ 1.19 (3 H, t, J = 7.1 Hz, $CH_2\underline{CH_3}$), 2.40 (6 H, s, CH_3), 4.20 (2 H, q, J = 7.1 Hz, $\underline{CH_2}CH_3$), 7.50–7.68 (1 H, m, aromatic H).

Ethyl-1,2,3-trifluoro-5-oxo-5,12-dihydro[1,3]benzothiazino[3,2-*a*]quinoline-6-carboxylate (2). A mixture of **1** (3.36 g, 9.1 mmol), 2-mercaptobenzylamine[12] (2.5 g, 18 mmol) and Et_3N (3.6 g, 36 mmol) in toluene (30 mL) was refluxed for 6 h. The solvent was then evaporated to dryness and the residue was poured into ice–water and extracted with $CHCl_3$. The combined organic layers were dried and evaporated to dryness giving a residue which was purified by column chromatography eluting with cyclohexane:EtOAc 80:20 to give **2** (2.3 g, 64%),

mp 168–175 °C. ^{1}H NMR ($CDCl_3$): δ 1.45 (3 H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 4.50 (2 H, q, J = 7.2 Hz, $\underline{CH_2}CH_3$), 5.17 (2 H, s, $\underline{CH_2}$), 7.40–7.65 (4 H, m, aromatic H), 8.00 (1 H, ddd, J = 10.2, 8.3 and 2.2 Hz, H-4). Anal. ($C_{19}H_{12}F_3NO_3S$) C, H, N.

Ethyl-2-(2,3,4,5-tetrafluorobenzoyl)-3-(2H-1,4-dihydro-3,1-benzothiazin-2-yl)acrylate (6). A mixture of **1** (0.88 g, 2.4 mmol), 2-aminobenzylmercaptano[13] (0.337 g, 2.4 mmol) and Et_3N (1 g, 99 mmol) in toluene (5 mL) was refluxed for 24 h. The solvent was evaporated to dryness and the residue was purified by flash chromatography eluting with a gradient of cyclohexane to 3% EtOAc: cyclohexane to give **6** (0.5 g, 51%) in an approximate 1:1 mixture of *E*:*Z* isomers. ^{1}H NMR ($CDCl_3$): δ 0.95 and 0.97 (3 H, each t, J = 7.1 Hz $CH_2\underline{CH_3}$), 3.80 and 3.90 (2 H, each s, CH_2), 4.07 and 4.10 (2 H, each q, J = 7.1 Hz, $\underline{CH_2}CH_3$), 7.05–7.45 (5 H, m, aromatic H), 13.20 and 14.90 (1 H, each bs, NH). Anal. ($C_{19}H_{13}F_4NO_3S$) C, H, N.

Ethyl-1,2,3-trifluoro-5-oxo-5,8-dihydro[3,1]benzothiazino-[1,2-*a*]quinoline-6-carboxylate (7). The mixture of **6** (0.25 g, 0.608 mmol) and DBU (0.185 g, 1.21 mmol) in toluene (5 mL) was refluxed for 1 h. After cooling, the solution was diluted with toluene (5 mL) and washed with acidified water. The organic layer was dried and evaporated to dryness to give **7** (0.2 g, 84%) as a pale-yellow solid, mp 154–160 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (3 H, t, J = 7.1 Hz, $CH_2\underline{CH_3}$), 3.75 and 4.07 (each 1 H, d, J = 13.5 Hz, CH_2), 4.45 (2 H, q, J = 7.1 Hz, $\underline{CH_2}CH_3$), 6.95–7.05 (1 H, m, aromatic H), 7.30–7.45 (3 H, m, aromatic H), 8.00 (1 H, ddd, J = 10.0, 7.9 and 2.3 Hz, H-4). Anal. ($C_{19}H_{12}F_3NO_3S$) C, H, N.

General procedure for the coupling reaction

Preparation of ethyl 1,3-difluoro-2-(4-methyl-1-piperazinyl)-5-oxo-5,12-dihydro[1,3]benzothiazino[3,2-*a*]-quinoline-6-carboxylate (4a). A mixture of ester **2** (0.3 g, 0.767 mmol), *N*-methypiperazine (0.5 g, 5 mmol) and Et_3N (0.3 g, 3 mmol) in CH_3CN (3 mL) was refluxed for 10 h. The solvent was removed and the residue was treated with water and extracted with CH_2Cl_2. The combined organic layers were dried and evaporated to dryness. The resulting residue was purified by column chromatography eluting with 5% MeOH/$CHCl_3$ to give **4a** (0.195 g, 54%), mp 135–139 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (3 H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 2.32 (3 H, s, NCH_3), 2.50–2.65 and 3.25–3.50 (each 4 H, m, piperazine CH_2), 4.50 (2 H, q, J = 7.2 Hz, $\underline{CH_2}CH_3$), 5.05 (2 H, s, CH_2), 7.35–7.65 (4 H, m, aromatic H), 7.80 (1 H, dd, J = 11.9 and 1.45 Hz, H-4). Anal. ($C_{24}H_{23}F_2N_3O_3S$) C, H, N.

By using a similar procedure, compounds **4b**, **4c** and **9a–c** were prepared starting from esters **2** or **7** by reaction with the appropriate amine. The crude reaction products were purified as reported in Table 1. By using a similar procedure the target acids **5d** and **10d** were also obtained starting from acids **3** and **8**, respectively. The physical properties of compounds **5d** and **10d** are reported in Table 1, while their spectral data are enumerated below:

5d: ^{1}H NMR (DMSO-d_6) δ 2.70–2.85 and 3.50–3.65 (each 4 H, m, thiomorpholine CH_2), 5.20 (2 H, bs, CH_2), 7.45–7.80 (5 H, m, aromatic H).

10d: ^{1}H NMR ($CDCl_3$) δ 2.55–2.80 and 3.30–3.60 (each 2 H, m, thiomorpholine CH_2), 3.75 and 3.90 (each 1 H, d, J = 13.4 Hz, CH_2), 6.90–7.40 (4 H, m, aromatic H), 7.85 (1 H, d, J = 10.3 Hz, H-4), 15.20 (1 H, bs, CO_2H).

General procedures for hydrolysis reaction

Method A. Preparation of 1,2,3-trifluoro-5-oxo-5,12-dihydro[1,3]benzothiazino[3,2-*a*]quinoline-6-carboxylic acid (3). The solution of ester **2** (0.6 g, 1.5 mmol) in EtOH and 18% HCl (15 mL) was refluxed for 1 h. After cooling, the precipitate was filtered, washed with water, Et_2O and dried to give **3** (0.44 g, 81%), mp 258–262 °C. ^{1}H NMR (DMSO-d_6) δ 5.25 (2 H, s, CH_2), 7.20–7.35 and 7.50–7.60 (each 2 H, m, aromatic H), 8.10 (1 H, ddd, J = 10.1, 8.3 and 2.2 Hz, H-4). Anal. ($C_{17}H_8F_3NO_3S$) C, H, N.

In the same manner, acid **8** was obtained starting from the ester **7**, as well as the target acid derivatives **5b**, **10a** and **10b** starting from the corresponding esters **4b**, **9a** and **9b**. The physical properties of the target acids **5b**, **10a** and **10b** are reported in Table 1, while their spectral data are enumerated below:

5b: ^{1}H NMR (DMSO-d_6) δ 1.00 (3 H, d, J = 6.05 Hz, CH_3), 1.15–1.40 and 1.55–1.80 (each 2 H, m, piperidine CH_2), 3.10–3.65 (5 H, m, piperidine CH_2 and CH), 5.20 (2 H, s, CH_2), 7.50–7.70 (5 H, m, aromatic H), 18.85 (1 H, s, CO_2H).

10a: ^{1}H NMR (DMSO-d_6) δ 2.75 (3 H, d, J = 4.2 Hz, $NH^+C\underline{H_3}$), 3.00–3.25 and 3.35–3.60 (each 4 H, m, piperazine CH_2), 4.00 and 4.20 (each 1 H, d, J = 13.2 Hz, CH_2), 7.20–7.70 (4 H, m, aromatic H), 7.90 (1 H, d, J = 10 Hz, H-4), 11.15 (1 H, bs, $N\underline{H}^+CH_3$), 15.35 (1 H, bs, CO_2H).

10b: ^{1}H NMR (DMSO-d_6) δ 1.20 (3 H, d, J = 6 Hz, CH_3), 1.15–1.40 and 1.50–1.75 (each 2 H, m, piperidine CH_2), 3.10–3.65 (5 H, m, piperidine CH_2 and CH), 3.80 and 4.05 (each 1 H, d, J = 13.4 Hz, CH_2), 6.90–7.40 (4 H, m, aromatic H), 7.85 (1 H, d, J = 10.3 Hz, H-4), 15.25 (1 H, bs, CO_2H).

Method B. Preparation of 1,3-difluoro-2-(4-methyl-1-piperazinyl)-5-oxo-5,12-dihydro[1,3]benzothiazino[3,2-*a*]-quinoline-6-carboxylic acid (5a). The suspension of **4a** (0.094 g, 0.199 mmol) in 4% NaOH (2 mL) and EtOH (2 mL) was refluxed for 4 h. After cooling at room temperature, the solution was neutralized with diluted AcOH. The resulting precipitate was filtered, washed with water and EtOH to give **5a** (0.040 g, 45%), mp 265–267 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (3 H, s,

NCH_3), 2.40–2.60 and 3.15–3.60 (each 4 H, m, piperazine CH_2), 5.20 (2 H, s, CH_2), 7.45–7.81 (5 H, m, aromatic H). Anal. ($C_{22}H_{19}F_2N_3O_3S$) C, H, N.

In the same manner, acid derivatives **5c** and **10c** were obtained starting from esters **4c** and **9c**, respectively. Their physical properties are reported in Table 1, while their spectral data are enumerated below:

5c: ^{1}H NMR ($CDCl_3$) δ 3.10 and 3.70 (each 2 H, t, J = 5.5 Hz, isoquinoline CH_2), 4.65 (2 H, bs, isoquinoline CH_2), 5.10 (2 H, s, CH_2), 7.05–7.30 and 7.45–7.68 (each 4 H, m, aromatic H), 7.90 (1 H, dd, J = 11.8 and 1.5 Hz, H-4), 15.70 (1 H, bs, CO_2H).

10c: ^{1}H NMR ($CDCl_3$) δ 2.80–3.05 and 3.40–3.70 (each 2 H, m, isoquinoline CH_2), 3.75 and 3.90 (each 1 H, d, J = 13.4 Hz, CH_2), 4.40 and 4.60 (each 1 H, d, J = 15.7 Hz, isoquinoline CH_2), 6.90–7.45 (4 H, m, aromatic H), 7.80 (1 H, d, J = 10.8 Hz, H-4), 15.30 (1 H, bs, CO_2H).

1,3-Difluoro-2-(4-methyl-1-piperazinyl)-5-oxo-5*H*-benzothiazolo[3,2-*a*]quinoline-6-carboxylic acid hydrochloride (11). This compound was synthesized by a procedure similar to the preparation of **5b**, starting from dithioacetal **1** and employing 2-aminothiophenol instead of 2-mercaptobenzylamine. mp 258–262 °C; ^{1}H NMR (DMSO-d_6) δ 2.90 (3 H, d, J = 3.8 Hz, $NH^+C\underline{H}_3$), 3.20–3.90 (4 H, m, piperazine CH_2), 6.50–8.30 (5 H, m, aromatic H), 11.00 (1 H, bs, NH^+CH_3), 15.30 (1 H, bs, CO_2H). Anal. ($C_{21}H_{17}F_2N_3O_3S$) C, H, N.

Molecular modelling

The molecular models were performed using the SYBYL program package.[14] The initial structures were built starting from the quinoline skeleton stored in the SYBYL fragment library and then changing the substituents in the different positions to obtain the required molecular structures. Energy minimization of the molecular conformations were performed by using the MAXIMIN II molecular mechanic procedure implemented in SYBYL. The geometry optimization of the molecular models was obtained by molecular orbital calculations carried out using the MNDO program of the MOPAC package.[15]

Simulation of molecular interaction was carried out using the DOCK command[16,17] provided by the SYBYL package, which permits a real-time approximation of the total intermolecular energy of all possible non-bonded interactions between pairs of molecules. More precisely, the total interaction energy is given by: $E_{tot} = \sum(E_Q + E_{LJ})$ where E_Q is the electrostatic contribution to the interaction energy of each atom i of one molecule interacting with all the j atoms of the other molecule, and where E_{LJ} are the steric attractive and repulsive contributions of each atom i of one molecule interacting with all the j atoms of the other molecule. The analytical dissection of E_Q and E_{LJ} into parameters and mathematical formulas are not within the scope of this work and may be found elsewhere.[16,17] Positive energies highlight repulsive interactions, while negative energies along with their locations delineate regions of attraction between the two interacting molecules.

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(*Received in U.S.A.* 2 *December* 1996; *accepted* 21 *February* 1997)