Studies on the Chemistry of Thienoannelated *O,N*- and *S,N*-Containing Heterocycles. 17 [1]. Preparation of 1*H*-Thieno[2,3-b][1,4]thiazine-1-carboxamides as Smooth Muscle Relaxants

Maria E. Schreder and Thomas Erker*

Institute of Pharmaceutical Chemistry, University of Vienna, A-1090 Vienna, Althanstraße 14, Austria

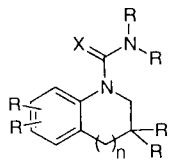
Received July 26, 1999

A new series of substituted thieno[1,4]thiazines with an urea moiety has been designed. The synthesis and results of replacement of the quinoline and indoline moieties of lead structure **1** are described. The key step in preparation was the substitution with 4-nitrophenyl chloroformate to obtain the required reactivity for substitution with diamines. Structural modifications of the amino side chain with the aim of finding tissue specific compounds were carried out. Pharmacological testings explored the presumed calcium-channel-antagonistic and potassium-channel-opening activities.

J. Heterocyclic Chem., **37**, 349 (2000).

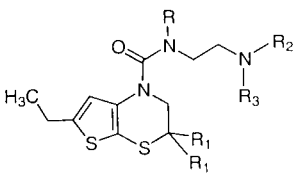
Many drugs act by modulating the functioning of ion channels in various tissues. For example, quinoline and indoline derivatives of the general formula **1** have potassium channel activating activity and are useful as antiischemic and antiarrhythmic agents [2]. In the course of our studies on new substances with cardiovascular activity, we considered to replace the quinoline or indoline moiety by substituted thieno[2,3-*b*][1,4]thiazines. This modification of the ring structure combined with a variation of the side chain by substitution with a series of diamino moieties could cause tissue selectivity or differentiated activity. The general formula of the target compounds **2** is shown in Scheme 1.

Scheme 1



1

R = aryl, alkyl, arylalkyl, heterocyclo
X = O, S, NCN
n = 0, 1

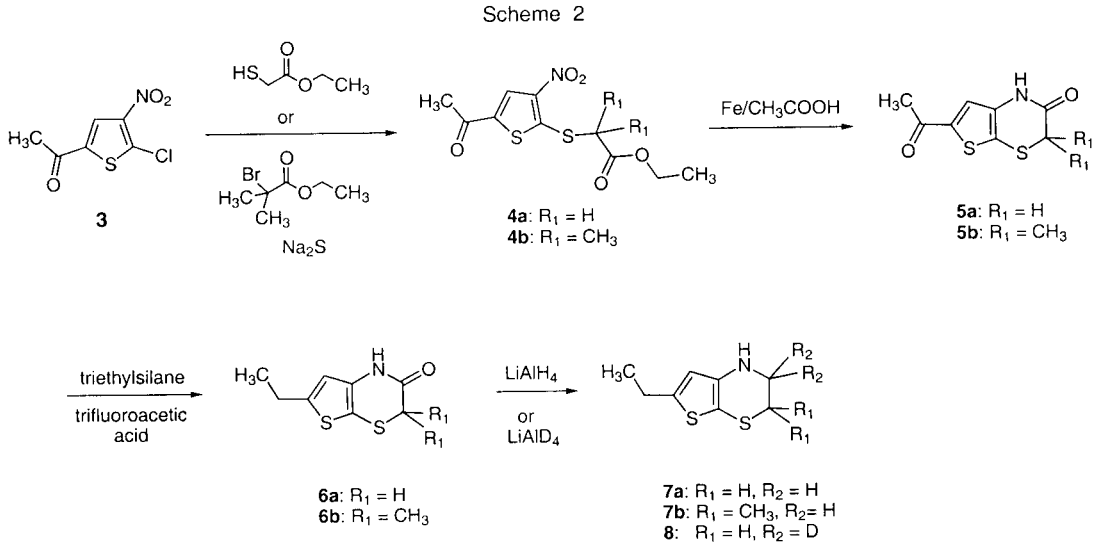


2

R_1 = H, CH_3
R_2, R_3 = alkyl, aryl
R = H, alkyl

The intermediates **7a** and **7b** were prepared as shown in Scheme 2. Treatment of 5-acetyl-2-chloro-3-nitrothiophene (**3**) [3] with ethyl 2-mercaptoacetate in the presence of potassium carbonate gave compound **4a** [4]. Derivative **4b** was prepared by an alternative synthetic route using ethyl 2-bromoisobutyrate and sodium sulphide nonahydrate. Ring closure was accomplished by reduction with iron powder in glacial acetic acid with traces of water and methanol to give 6-acetyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazinones (**5a** [4] and **5b**) *via* reductive cyclisation. It is known that drugs containing a thiophene ring can show increased biological activity if an alkyl group is proximate to the sulfur atom of the aromatic moiety [5]. Thus, reduction of the acetyl group in **5a** and **5b** with triethylsilane in trifluoroacetic acid afforded the desired derivatives **6a** [6] and **6b**. Treatment of the lactams **6a** and **6b** with an excess of lithium aluminium hydride gave the corresponding amines **7a** and **7b**.

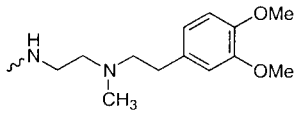
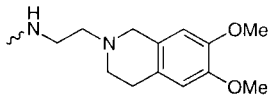
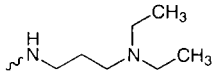
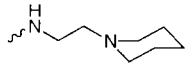
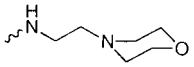
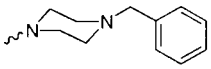
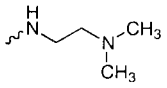
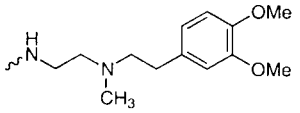
Scheme 2



Compound **6a** was also reacted with lithium aluminium deuteride to afford **8**, the deuterio-analog of **7a**. Thus, exact assignment of the nmr signals of the thiazine ring methylene groups was possible.

molecule could be observed. Heating to 40°C in chloroform gave a time-averaged spectrum. Finally, derivatisation of the resulting esters **11a** and **11b** with several diamines afforded at room temperature or heating the

Table 1

Compound	R_1	R_2	Reaction temperature (°C)	Reaction time (hours)	salt/melting point (°C)
12a	H, H		reflux	2	oxalate 146-149
12b	H, H		reflux	20	hydrochloride 135-137
12c	H, H		room temperature	24	oxalate 112-114
12d	H, H		room temperature	8	oxalate 153
12e	H, H		50	15	oxalate 155
12f	H, H		60	20	oxalate 191-194
12g	H, H		room temperature	1.5	oxalate 177-178
12h	CH_3, CH_3		reflux	20	—

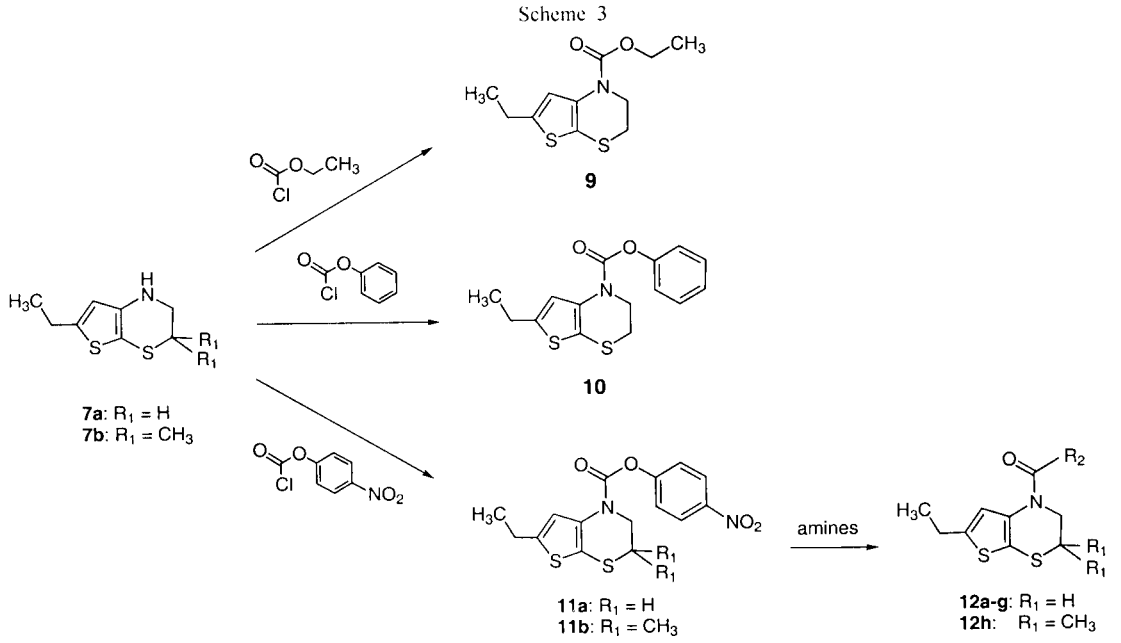
Reaction of carbamic acid esters with amines is generally used to synthesize ureas. Thus, the carbamic acid ester **9** was prepared from reaction of amine **7a** and ethyl chloroformate (Scheme 3). Attempts to replace the ethyl ester in **9** with amines failed even under forcing conditions due to the low reactivity of the ester. This result suggested that a more reactive compound, obtained by treatment of **7a** with phenyl chloroformate, could be appropriate. However, the synthesized carbamic acid ester **10** showed weak reactivity. Substitution of **10** with diamines either failed or proceeded to give the products in very low yields.

Because the 4-nitrophenyl ester moiety was expected to be highly reactive, amines **7a** and **7b** were treated with 4-nitro phenyl chloroformate to give the compounds **11a** and **11b** (Scheme 3). Doubling of ^1H and ^{13}C nmr signals for both compounds due to dynamic processes in the

desired target compounds **12a-12h** in good yields (Scheme 3). The reactions were carried out in tetrahydrofuran. Compound **12g** was synthesized by using the corresponding diamine as both a reactant and solvent. The diamino subunit-containing moieties, reaction conditions and salts are summarized in Table 1.

The target substances were insoluble in water and had to be converted into their salts with appropriate acids for pharmacological testings (Table 1). The pharmacological results are summarized in patent AT 403,918 [7]. The derivatives were compared with calcium antagonistic drugs. Most compounds showed a negative inotropic effect ranging from 1.4 - 40 µmol/l on isolated papillary muscles. The calcium antagonism occurred in a non-competitive manner, thus the compounds might also affect potassium and/or sodium channels. [8]

Scheme 3



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian UnityPlus-300 (300 MHz) or a Bruker Avance DPX 400 (400 MHz) spectrometer using deuteriochloroform as solvent, if not otherwise stated, and tetramethylsilane as internal standard. Mass spectra were obtained by using a Shimadzu GC/MS QP 1000 EX, Hewlett Packard (GC: 5890; MS: 5970) or Shimadzu QP 5000 spectrometer. High resolution mass spectra were measured on a Finnigan 8230 mass spectrometer. Column chromatography was performed using silica gel 60, 70-230 mesh ASTM (Merck). Solutions in organic solvents were dried over anhydrous sodium sulfate.

Ethyl 2-(5-acetyl-3-nitro-2-thienylsulfanyl)-2-methyl Propionate (**4b**).

To a suspension of 5.76 g (24 mmoles) of sodium sulfide nonahydrate in 80 ml absolute dimethylformamide 4.95 g (24 mmoles) of 5-acetyl-2-chlor-3-nitrothiophene were added and stirred under argon at room temperature. After 1 hour 9.36 g (48 mmoles) of ethyl 2-bromoisobutyrate were added dropwise and stirring was continued for 60 hours at 50°. The reaction mixture was poured into ice water and the precipitate filtered and crystallized from ethanol to yield 4.77 g (63%), mp 102-104°; ^1H nmr (deuteriochloroform): 8.12 (s, 1H, thiophene H), 4.25 (q, J = 7.2 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 1.79 (s, 6H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 188.9, 172.1, 150.3, 143.7, 139.9, 127.5, 62.6, 53.9, 26.0, 26.0, 25.8, 13.9; ms: m/z 317 (100), 244 (7), 203 (20), 186 (51), 115 (94), 87 (75), 59 (61).

Anal. Calcd. for $C_{12}H_{15}NO_5S_2$: C, 45.41; H, 4.76; N, 4.41. Found: C, 45.38; H, 4.49; N, 4.48.

6-Acetyl-2,3-dihydro-3,3-dimethyl-1*H*-thieno[2,3-*b*][1,4]thiazinone (**5b**).

To a solution of 4.76 g (15 mmoles) of **4b** in a mixture of 110 ml of glacial acetic acid, 11 ml of methanol and 11 ml of water was added portionwise 5.3 g of iron powder. The reaction mixture was heated at 60° for 3 hours and poured onto ice water. The crude product was recrystallized from 50 % ethanol to yield 2.76 g (76%), mp 180-183°; ^1H nmr (deuteriochloroform): 10.75 (s, 1H, NH), 7.36 (s, 1H, thiophene H), 2.48 (s, 3H, CH_3), 1.44 (s, 6H, CH_3); ^{13}C nmr (deuteriochloroform): 187.2, 165.9, 138.8, 135.6, 121.5, 118.0, 42.4, 24.4 (2C), 22.4; ms: m/z 241 (100), 226 (60), 198 (38).

Anal. Calcd. for $C_{10}H_{11}NO_2S_2$: C, 49.77; H, 4.59; N, 5.80. Found: C, 49.60; H, 4.42; N, 5.84.

6-Ethyl-2,3-dihydro-3,3-dimethyl-1*H*-thieno[2,3-*b*][1,4]thiazinone (**6b**).

To a solution of 2.41 g (10 mmoles) of **5b** in 12 ml of trifluoroacetic acid 7.8 ml of triethylsilane were added dropwise and the whole stirred at room temperature for 12 hours. The reaction mixture was cooled, poured onto ice water and neutralized with solid sodium bicarbonate. The precipitate was filtered and crystallized from ethanol to yield 1.57 g (69%), mp 155-157°; ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): 10.39 (broad s, 1H, NH), 6.48 (s, 1H, thiophene H), 2.73 (q, J = 7.5 Hz, 2H, CH_2), 1.38 (s, 6H, CH_3), 1.24 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): 166.7, 143.2, 134.3, 114.0, 102.5, 41.9, 22.1 (2C), 21.6, 13.8; ms: m/z 227 (100), 212 (84), 184 (41), 158 (26).

Anal. Calcd. for $C_{10}H_{13}NOS_2$: C, 52.83; H, 5.76; N, 6.16. Found: C, 53.12; H, 5.53; N, 6.18.

General Procedure for the Preparation of **7a**, **7b** and **8**:

To an ice-cooled solution of **6a** or **6b** respectively in absolute tetrahydrofuran a 1.0 *M* solution of lithium aluminium hydride in tetrahydrofuran was added dropwise. After stirring at room temperature for 2-4 hours ethyl acetate was added carefully and the mixture then concentrated. The residue was diluted in ethyl acetate and washed with water. If necessary, by-products were removed by filtration and the organic layer dried and evaporated *in vacuo*. The products were purified by column chromatography.

6-Ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine (**7a**).

Reagents: 7.96 g (40 mmoles) of **6a** in 130 ml of absolute tetrahydrofuran, 50 ml of a 1.0 *M* solution of lithium aluminium hydride in tetrahydrofuran. Reaction time: 3 hours. Eluent: toluene/ethyl acetate 6/4. Yield: 6.33 g (86%) of an oil; ^{1}H nmr (deuteriochloroform): 6.20 (t, J = 1.1 Hz, 1H, thiophene H), 3.64-3.42 (m, 3H, NCH_2, NH), 2.99-2.93 (m, 2H, SCH_2), 2.68 (dq, J = 1.1 Hz, J = 7.5 Hz, 2H, CH_2), 1.23 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 142.7, 138.2, 117.1, 117.0, 43.5, 26.6, 23.5, 15.6; ms: m/z 185 (100), 170 (99), 136 (13).

Anal. Calcd. for $C_8H_{11}NS_2$: C, 51.85; H, 5.98; N, 7.56. Found: C, 51.91; H, 5.74; N, 7.64.

6-Ethyl-2,3-dihydro-3,3-dimethyl-1*H*-thieno[2,3-*b*][1,4]thiazine (**7b**).

Reagents: 2.27 g (10 mmoles) of **6b** in 40 ml of absolute tetrahydrofuran, 12 ml of a 1.0 *M* solution of lithium aluminium hydride in tetrahydrofuran. Reaction time: 4 hours. Eluent: toluene/ethyl acetate 8/2. Yield: 1.84 g (87%) of an oil; ^{1}H nmr (deuteriochloroform): 6.25 (s, 1H, thiophene H), 3.80 (broad s, 1H, NH), 3.15 (s, 2H, CH_2), 2.69 (q, J = 7.5 Hz, 2H, CH_2), 1.38 (s, 6H, CH_3), 1.24 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 142.9, 136.5, 116.7, 100.0, 55.6, 40.0, 26.7 (2C), 23.6, 15.5; ms: m/z 213 (55), 198 (4), 170 (100), 158 (23).

Anal. Calcd. for $C_{10}H_{15}NS_2$: C, 56.30; H, 7.09; N, 6.56. Found: C, 56.18; H, 7.07; N, 6.49.

2,2-Dideutero-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine (**8**).

Reagents: 398 mg (2 mmoles) of **6a** in 10 ml of absolute tetrahydrofuran, 2.5 ml of a 1.0 *M* solution of lithium aluminium deuteride in tetrahydrofuran. Reaction time: 2 hours. Eluent: toluene/ethyl acetate 8/2. Yield: 283 mg (76%) of an oil; ^{1}H nmr (deuteriochloroform): 6.21 (s, 1H, thiophene H), 3.39 (broad s, 1H, NH), 2.96 (s, 2H, SCH_2), 2.68 (q, J = 7.5 Hz, 2H, CH_2), 1.23 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 142.7, 138.3, 117.0, 26.5, 23.5, 15.6; ms: m/z 187 (93), 172 (100), 158 (4); 1 C could not be detected.

General Procedure for the Preparation of **9**, **10**, **11a** and **11b**:

A solution of **7a** or **7b** respectively in absolute tetrahydrofuran was treated with triethylamine followed by either ethyl chloroformate, phenyl chloroformate or 4-nitrophenyl chloroformate respectively. After stirring at room temperature for 1-2.5 hours the solvent was removed under vacuum. The residue was diluted with ethyl acetate and washed with a 5 % aqueous sodium hydrogen carbonate solution. The organic layer was dried, evaporated and purified.

Ethyl 6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-1-carboxylate (**9**).

Reagents: 1.11 g (6 mmoles) of **7a** in 25 ml of dry tetrahydrofuran, 0.60 g (6 mmoles) of triethylamine, 1.3 g (12 mmoles) of ethyl chloroformate. Reaction time: 1.5 hours. Purification: column chromatography (toluene/ethyl acetate 9/1). Yield: 1.39 g (90%) of an oil; ^{1}H nmr (deuteriochloroform): 7.04 (broad s, 1H, thiophene H), 4.24 (q, J = 7.1 Hz, 2H, CH_2), 4.09-3.99 (m, 2H, NCH_2), 3.16-3.07 (m, 2H, SCH_2), 2.68 (q, J = 7.5 Hz, 2H, CH_2), 1.33 (t, J = 7.1 Hz, 3H, CH_3), 1.26 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 141.0, 121.0, 62.2, 43.6, 27.4, 23.6, 15.5, 14.5; ms: m/z 257 (100), 229 (36), 228 (5), 184 (30), 170 (34), 151 (16); 3 C could not be detected.

Anal. Calcd. for $C_{11}H_{15}NO_2S_2$: C, 51.33; H, 5.87; N, 5.44. Found: C, 51.29; H, 5.69; N, 5.54.

Phenyl 6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-1-carboxylate (**10**).

Reagents: 0.74 g (4 mmoles) of **7a** in 20 ml of dry tetrahydrofuran, 0.40 g (4 mmoles) of triethylamine, 1.25 g (8 mmoles) of phenyl chloroformate. Reaction time: 1 hour. Purification: column chromatography (toluene/ethyl acetate 9 + 1). Yield: 1.12 g (91%) of a brown oil; ^{1}H nmr (deuteriochloroform): 7.51-7.07 (m, 6H, phenyl H), 4.39-3.99 (m, 2H, NCH_2), 3.28-3.16 (m, 2H, SCH_2), 2.73 (q, J = 7.5 Hz, 2H, CH_2), 1.25 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 150.9, 141.5, 129.4 (2C), 125.7 (2C), 121.6, 120.8, 27.5, 23.5, 15.5; ms: m/z 305 (8), 214 (67), 169 (30), 157 (26), 141 (60), 94 (49), 77 (100).

Anal. Calcd. for $C_{15}H_{15}NO_2S_2$: C, 58.99; H, 4.95; N, 4.59. Found: C, 59.07; H, 4.72; N, 4.32.

4-Nitrophenyl 6-Ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-1-carboxylate (**11a**).

Reagents: 5.56 g (30 mmoles) of **7a** in 110 ml of absolute tetrahydrofuran, 3.03 g (30 mmoles) triethylamine, 6.06 g (30 mmoles) 4-nitrophenyl chloroformate. Reaction time: 1.5 hours. Purification: vacuum flash chromatography (toluene/ethyl acetate 9/1) followed by recrystallisation from ethanol to yield 9.1 g (87%), mp 105-108°; ^{1}H nmr (deuteriochloroform): 8.27 (A-part of an AB-system, J = 9.2 Hz, 2H, phenyl H), 7.37 (B-part of an AB-system, J = 9.2 Hz, 2H, phenyl H), 7.30-6.68 (m, 1H, thiophene H), 4.43-3.89 (m, 2H, NCH_2), 3.31-3.16 (m, 2H, SCH_2), 2.75 (q, J = 7.5 Hz, 2H, CH_2), 1.26 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 156.1, 145.6, 142.4, 125.6 (2C), 122.8 (2C), 121.3, 120.5, 45.8, 44.3, 28.0, 24.1, 16.0; ms: m/z 350 (62), 227 (20), 184 (100), 170 (42); 2 C could not be detected.

Anal. Calcd. for $C_{15}H_{14}N_2O_4S_2$: C, 51.41; H, 4.03; N, 7.99. Found: C, 51.56; H, 3.83; N, 8.01.

4-Nitrophenyl 6-ethyl-2,3-dihydro-3,3-dimethyl-1*H*-thieno[2,3-*b*]-[1,4]thiazine-1-carboxylate (**11b**).

Reagents: 1.065 g (6 mmoles) of **7b** dissolved in 25 ml of dry tetrahydrofuran, 0.5 g (5 mmoles) triethylamine, 1.01 g (5 mmoles) 4-nitrophenyl chloroformate. Reaction time: 2.5 hours. Purification: crystallizing from ethanol. Yield: 1.25 g (66 %), mp 80-84°; ^{1}H nmr (deuteriochloroform): 8.34-8.23 (m, 2H, phenyl H), 7.44-7.28 (m, 2H, phenyl H), 6.91 (broad s, 1H, thiophene H), 4.03-3.77 (m, 2H, NCH_2), 2.75 (q, J = 7.5 Hz, 2H, CH_2), 1.52 (s, 6H, CH_3), 1.27 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.6, 145.1, 142.0, 125.1 (2C), 122.2 (2C), 120.1, 119.7, 56.0, 55.4, 42.6, 26.9, 23.6, 15.5; ms: m/z 378 (100), 335 (59), 240 (12), 212 (49), 184 (39), 170 (57); 2 C could not be detected.

Anal. Calcd. for $C_{17}H_{18}N_2O_4S_2$: C, 53.95; H, 4.79; N, 7.40. Found: C, 53.81; H, 4.78; N, 7.30.

N-[2-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methylamino]ethyl]-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-1-carboxamide (**12a**).

To a solution of 700 mg (2 mmoles) of **11a** in 10 ml of dry tetrahydrofuran 476 mg (2 mmoles) of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methyl-ethane-1,2-diamine, dissolved in 1 ml dry tetrahydrofuran, were added dropwise. The reaction mixture was refluxed for 2 hours followed by concentration. The residue

was purified by column chromatography (ethyl acetate/triethylamine 7/1) to yield 632 mg (70%) of an oil; ^{1}H nmr (deuteriochloroform): 6.78-6.61 (m, 4H, phenyl H and thiophene H), 5.77-5.60 (m, 1H, NH), 4.02-3.92 (m, 2H, NCH_2), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.39-3.26 (m, 2H, CH_2), 3.15-3.02 (m, 2H, SCH_2), 2.73 (q, J = 7.5 Hz, 2H, CH_2), 2.68-2.47 (m, 6H, CH_2), 2.30 (s, 3H, NCH_3), 1.26 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.4, 148.7, 147.2, 142.5, 132.5, 131.8, 120.3, 119.6, 116.1, 111.7, 111.1, 59.4, 55.8, 55.7, 55.6, 41.6, 41.3, 38.1, 33.4, 27.6, 23.5, 15.4; ms: m/z 450 (95), 298 (100), 255 (100), 227 (28), 185 (83), 165 (100), 113 (57).

Anal. Calcd. for $C_{22}H_{31}N_3O_3S_2$: C, 58.77; H, 6.95; N, 9.35. Found: C, 58.53; H, 6.70; N, 9.13.

Compounds **12b** - **12f** and **12h** were obtained by the same method to that used for **12a**. The diamino moieties, reaction temperatures, reaction times and acquired salts of the compounds are listed in Table 1.

N-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isochinolyl)ethyl]-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine-1-carboxamide (**12b**).

The product was purified by column chromatography (ethyl acetate/triethylamine 9/1) to yield 578 mg (65%), mp 110°; ^{1}H nmr (deuteriochloroform): 6.62 (s, 1H, aromatic H), 6.59 (s, 1H, aromatic H), 6.52 (s, 1H, aromatic H), 6.02-5.82 (m, 1H, NH), 4.04-3.93 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2), 3.52-3.39 (m, 2H, CH_2), 3.15-3.04 (m, 2H, SCH_2), 2.80-2.60 (m, 6H, CH_2), 2.34 (q, J = 7.5 Hz, 2H, CH_2), 0.98 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform):155.4, 147.5, 147.2, 143.0, 131.7, 126.3, 126.0, 119.4, 116.2, 111.3, 109.3, 56.1, 55.9 (2C), 55.1, 50.6, 41.3, 37.6, 28.8, 27.6, 23.3, 15.4; ms: m/z 447 (1), 263 (21), 206 (43), 192 (21), 185 (100).

Anal. Calcd. for $C_{22}H_{29}N_3O_3S_2$: C, 59.03; H, 6.53; N, 9.39. Found: C, 59.24; H, 6.81; N, 9.35.

N-(3-Diethylaminopropyl)-6-ethyl-2,3-dihydro-1*H*-thieno-[2,3-*b*][1,4]thiazine-1-carboxamide (**12c**).

The product was purified by column chromatography (ethyl acetate/methanol/triethylamine 6/1/1) to yield 533 mg (78%) of an oil; ^{1}H nmr (deuteriochloroform): 6.70 (s, 1H, thiophene H), 6.46-6.32 (m, 1H, NH), 4.03-3.90 (m, 2H, NCH_2), 3.36 (dt, J = 6.2 Hz, J = 5.6 Hz, 2H, CH_2), 3.15-3.03 (m, 2H, SCH_2), 2.74 (q, J = 7.5 Hz, 2H, CH_2), 2.58-2.31 (m, 6H, CH_2), 1.64 (quint, J = 6.2 Hz, 2H, CH_2), 1.27 (t, J = 7.5 Hz, 3H, CH_3), 0.91 (t, J = 7.1 Hz, 6H, CH_3); ^{13}C nmr (deuteriochloroform): 156.4, 142.9, 132.5, 120.6, 117.0, 51.9, 47.2 (2C), 42.1, 41.3, 28.4, 26.6, 24.1, 15.9, 11.3 (2C); ms: m/z 342 (58), 185 (100), 170 (32), 157 (100), 129 (14).

Anal. Calcd. for $C_{16}H_{27}N_3OS_2$: C, 56.27; H, 7.97; N, 12.30. Found: C, 55.99; H, 7.81; N, 12.06.

6-Ethyl-2,3-dihydro-*N*-(2-piperidinoethyl)-1*H*-thieno[2,3-*b*]-[1,4]thiazine-1-carboxamide (**12d**).

The product was purified by vacuum flash chromatography (ethyl acetate/triethylamine 9/1) to yield 826 mg (81%) of an oil; ^{1}H nmr (deuteriochloroform): 6.75 (s, 1H, thiophene H), 5.86 (broad s, 1H, NH), 4.06-3.93 (m, 2H, NCH_2), 3.40-3.23 (m, 2H, CH_2), 3.18-3.03 (m, 2H, SCH_2), 2.77 (q, J = 7.5 Hz, 2H, CH_2), 2.50-2.21 (m, 6H, CH_2), 1.60-1.33 (m, 6H, CH_2), 1.28 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.5, 142.8, 131.8, 119.7, 116.5, 57.1, 54.1 (2C), 41.3, 37.4, 27.6, 26.1 (2C), 24.3, 23.7, 15.7; ms: m/z 340 (77), 185 (100), 155 (81), 98 (60).

Anal. Calcd. for $C_{16}H_{25}N_3OS_2$: C, 56.60; H, 7.42; N, 12.38. Found: C, 56.51; H, 7.23; N, 12.26.

6-Ethyl-2,3-dihydro-*N*-[2-(4-morpholino)ethyl]-1*H*-thieno-[2,3-*b*][1,4]thiazine-1-carboxamide (**12e**).

The product was purified by vacuum flash chromatography (ethyl acetate/triethylamine 9/1) to yield 521 mg (76%), mp 70-75°; ^{1}H nmr (deuteriochloroform): 6.73 (s, 1H, thiophene H), 5.75 (broad s, 1H, NH), 4.05-3.91 (m, 2H, NCH_2), 3.75-3.59 (m, 4H, CH_2), 3.44-3.29 (m, 2H, CH_2), 3.19-3.05 (m, 2H, SCH_2), 2.78 (q, J = 7.5 Hz, 2H, CH_2), 2.59-2.34 (m, 6H, CH_2), 1.29 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.4, 142.9, 131.7, 119.5, 116.9, 67.0 (2C), 57.0, 53.1 (2C), 41.3, 36.9, 27.7, 23.7, 15.7; ms: m/z 341 (10), 185 (100), 157 (57), 100 (79).

Anal. Calcd. for $C_{15}H_{23}N_3O_2S_2$: C, 52.76; H, 6.79; N, 12.31. Found: C, 53.06; H, 6.68; N, 12.09.

6-Ethyl-2,3-dihydro-1-[(4-benzyl-1-piperazinyl)carbonyl]-1*H*-thieno[2,3-*b*][1,4]thiazine (**12f**).

The product was purified by column chromatography (toluene/ethyl acetate/triethylamine 6/3/1) to yield 481 mg (62%) of an oil; ^{1}H nmr (deuteriochloroform): 7.36-7.19 (m, 5H, phenyl H), 6.60 (s, 1H, thiophene H), 3.95-3.83 (m, 2H, NCH_2), 3.50 (s, 2H, CH_2), 3.40-3.27 (m, 4H, CH_2), 3.20-3.08 (m, 2H, SCH_2), 2.70 (q, J = 7.5 Hz, 2H, CH_2), 2.47-2.36 (m, 4H, CH_2), 1.24 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 159.1, 142.1, 137.5, 134.2, 129.1 (2C), 128.2 (2C), 127.1, 118.8, 110.4, 63.0, 52.7 (2C), 46.2 (2C), 44.3, 28.6, 23.5, 15.6; ms: m/z 387 (49), 203 (43), 185 (15), 91 (100).

HRMS Calcd. for $C_{20}H_{25}N_3OS_2$: 387.1439. Found: 387.1443.

N-(2-Dimethylaminoethyl)-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*]-[1,4]thiazine-1-carboxamide (**12g**).

A solution of 700 mg (2 mmoles) of **7a** in 4 ml of *N,N*-dimethylethylenediamine was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated and purified by column chromatography (ethyl acetate/methanol/triethylamine 6/1/1) to yield 546 mg (88%) of an oil; ^{1}H nmr (deuteriochloroform): 6.74 (s, 1H, thiophene H), 5.80-5.69 (m, 1H, NH), 4.04-3.95 (m, 2H, NCH_2), 3.33 (dt, J = 6.0 Hz, J = 4.9 Hz, 2H, CH_2), 3.15-3.06 (m, 2H, SCH_2), 2.74 (q, J = 7.5 Hz, 2H, CH_2), 2.42 (t, J = 6.0 Hz, 2H, CH_2), 2.22 (s, 6H, CH_3), 1.27 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.4, 142.4, 131.79, 119.4, 116.0, 57.9, 45.0 (2C), 41.3, 38.2, 27.7, 23.5, 15.4; ms: m/z 299 (5), 185 (94), 170 (30), 136 (16), 115 (58).

Anal. Calcd. for $C_{13}H_{21}N_3OS_2$: C, 52.14; H, 7.07; N, 14.03. Found: C, 52.32; H, 6.96; N, 13.86.

N-[2-[*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methylamino]-ethyl]-6-ethyl-2,3-dihydro-3,3-dimethyl-1*H*-thieno[2,3-*b*]-[1,4]thiazine-1-carboxamide (**12h**).

The product was purified by column chromatography (ethyl acetate/triethylamine 9/1) to yield 630 mg (65%) of an oil; ^{1}H nmr (deuteriochloroform): 6.79-6.60 (m, 4H, phenyl H and thiophene H), 5.75 (broad s, 1H, NH), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.78 (s, 2H, NCH_2), 3.36 (dt, 2H, CH_2), 2.85-2.49 (m, 8H, CH_2), 2.31 (s, 3H, CH_3), 1.41 (s, 6H, CH_3), 1.26 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 155.9, 148.7, 147.2, 142.8, 132.5, 129.8, 120.3, 118.9, 116.7, 111.7, 111.1, 59.5, 56.0, 55.8, 55.7, 53.1, 44.7, 41.7, 38.2, 33.4, 27.3 (2C), 23.7, 15.5; ms: m/z 477 (3), 326 (29), 283 (63), 265 (19), 213 (100), 208 (20), 165 (70).

Anal. Calcd. for $C_{24}H_{35}N_3O_3S_2$: C, 60.35; H, 7.39; N, 8.80. Found: C, 60.06; H, 7.33; N, 8.75.

REFERENCES AND NOTES

[1] Part **16**: T. Erker, *J. Heterocyclic Chem.*, **35**, 1521 (1998).

[2a] K. Atwal and F. Ferrara, Canadian Patent Appl. CA 2,109,186 (Cl. C07D215/48); *Chem. Abstr.*, **121**, 230675v (1994); [b] K. Atwal, F. Ferrara, C. Ding, G. Grover, P. Sleph, *et al.*; *J.Med.Chem.*, **39**, 304 (1996).

[3] C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74**, 2965 (1952).

[4] I. Puschmann and T. Erker, *Heterocycles*, **36**, 1323 (1993).

[5] S. Gronowitz, Thiophene and its Derivatives, Part **I**, John Wiley and Sons (1985).

[6] T. Erker, *J. Heterocyclic Chem.*, **30**, 1089 (1993).

[7] T. Erker, P. Heistracher, R. Lemmens-Gruber, A. Lexer and M. Schreder, Austrian AT 403,918 (Cl. C07D513/04); *Chem. Abstr.*, **129**, 260468n (1998).

[8a] C. Studenik, R. Lemmens-Gruber and P. Heistracher, *Biol. Pharm. Bull.*, **22**, 453 (1999); [b] C. Studenik, R. Lemmens-Gruber and P. Heistracher, *Arzneimittelforschung*, in print (1999).