SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW ANTIINFLAMMATORY 1-BENZOTHIOPHENE-2-CARBOXANILIDES

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Received January 26, 2000
Accepted March 27, 2000

3-Substituted 1-benzothiophene-2-carboxanilides **2**–**5** and their corresponding sulfones **6**–**8** were synthesized. The antiinflammatory effect of compounds **2**–**8** was evaluated in tests of LTB_4 biosynthesis, carrageenin edema and ear inflammation. With the exception of 3-hydroxyamides **5a**–**5c**, low inhibitory activities against COX and LT biosynthesis were observed.

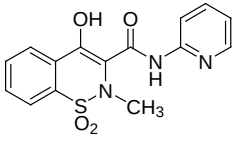
Key words: Benzothiophenes; Sulfones; Antiinflammatory activity; 5-LO inhibition; Calculated log *P* values.

Nonsteroidal antiinflammatory drugs (NSAIDs) possessing antiinflammatory, analgesic, and antipyretic activities have been widely used in treatment of acute and subchronic inflammatory conditions[1]. In early 1970s it was reported that NSAIDs prevent the production of prostaglandins (PGs) by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) to prostaglandins[2,3]. For many years it was believed that COX was a single enzyme (COX-1) constitutively expressed in most tissues. In contrast to COX-1, COX-2 is an inducible isoenzyme, which is essentially undetectable under normal physiological conditions; however, its expression is markedly elevated during inflammation. It was shown[4] that compounds inhibiting selectively COX-2 do not cause ulcers in stomach or intestines. The observation supports the hypothesis that the constitutive COX-1 isoenzyme protects the gastrointestinal tract whereas the inducible COX-2 isoform mediates inflammatory PG production.

Leukotrienes (LTs) represent another class of arachidonic acid metabolites, synthesized by leucocytes in response to a variety of inflammatory

and immunological stimuli. 5-Lipoxygenase (5-LO) starts the metabolism of arachidonic acid[5] through LTA_4 to LTB_4, a potent chemotactic agent for leucocytes that was thought to be a key component in a variety of inflammation diseases, and peptidoleukotrienes LTC_4, LTD_4, and LTE_4, which are implicated in allergic hyperactivity disorders such as asthma. Elevated levels of these LTs, associated with several inflammatory and allergic disorders, have been found in various pathological tissues. Thus, compounds restricting LT synthesis by inhibition of 5-LO will have therapeutic utility in such pathological conditions. Recently it has been shown[6,7] that some hydroxamic acids, *e.g.* zileuton possessing the 1-benzothiophene moiety, can be strong 5-LO inhibitors.

Classical NSAIDs, such as ibuprofen, have been found active primarily *via* inhibition of COX pathways. Piroxicam **1**, an enol-carboxamide type of NSAID, is also a potent COX inhibitor. Tenidap[8] [5-chloro-2-oxo-3-(2-thenoyl)indoline-1-carboxamide] containing a similar fragment, is distinguished by the inhibition of both COX and 5-LO. In our research on new antiinflammatory agents with dual mechanism of 5-LO and COX inhibition, we decided to study a new type of enol-amide compounds based on replacement of the 1,2-benzothiazine moiety of piroxicam by the 1-benzothiophene skeleton. In our preceding paper[9] we reported synthesis of 3-substituted 1-benzothiophene-2-carboxanilides **2**–**5**. While compounds **5** contain the HO–C=C–CONHAr fragment responsible for the activity of piroxicam, the hydroxy group in compounds **3** and **4** was masked by substitution with chlorine and methoxy group, respectively, or was completely removed as in **2**. Some preliminary results of the biological activity tests of compounds **2**–**5** were also presented. The aim of this paper is to report syntheses of new oxidized derivatives **6**–**8** and to show full results of biological screening of this class of substances.



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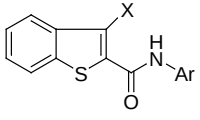
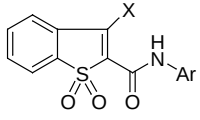


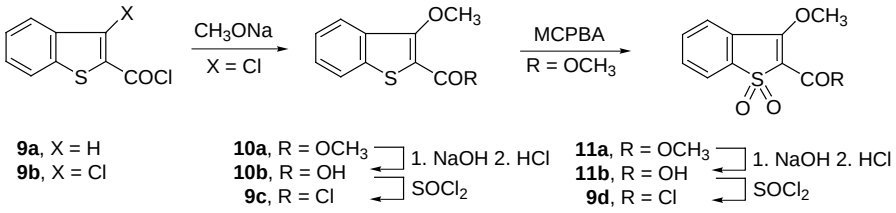
2, X = H
3, X = Cl
4, X = OCH_3
5, X = OH



6, X = Cl
7, X = OCH_3
8, X = OH

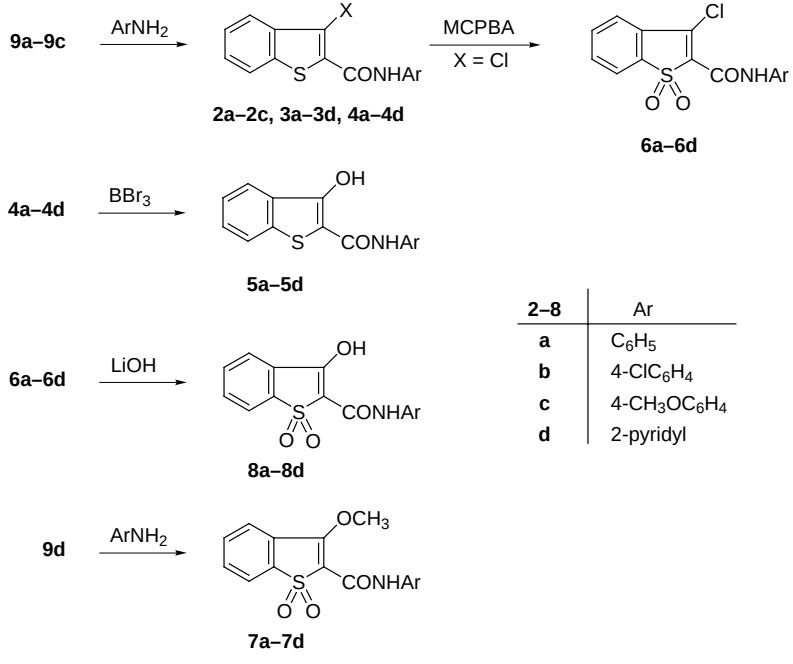
Synthesis of amides **2**–**5** started with easily accessible[10,11] 1-benzothiophene-2-carbonyl chloride (**9a**) and its 3-chloro derivative **9b** (Scheme 1). To introduce the methoxy and hydroxy functions in position 3, substitution

of chlorine in **9b** with sodium methoxide in *N*,*N*-dimethylformamide was successfully accomplished and ester **10a** was subsequently hydrolyzed to the corresponding acid **10b**. Treatment of acid **10b** with thionyl chloride under standard conditions afforded 3-methoxy chloride **9c**.



SCHEME 1

Aminolysis of chlorides **9a**–**9c** with 4-substituted anilines (H, Cl, CH_3O) and 2-aminopyridine led to amides **2a**–**2c**, **3a**–**3d** and **4a**–**4d** (Scheme 2). Deprotection of the 3-methoxy group in **4a**–**4d** with boron tribromide in dichloromethane afforded the required 3-hydroxyamides **5a**–**5d**. Experimental details of these transformations were described in the preceding paper[9].



2–8	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3OC_6H_4$
d	2-pyridyl

SCHEME 2

For the preparation of a series of oxidized amides **6**–**8**, we intended to make use of amides **2**–**5** (Scheme 2). Oxidation of sulfur in 1-benzothiophene compounds can be achieved by various methods[12]. In our case, oxidation of 3-chloroamides **4a**–**4d** with 3-chloroperoxybenzoic acid (MCPBA) in 1,2-dichloroethane proceeded smoothly providing good yields (58–80%) of amides **6a**–**6d**.

However, this method failed for the preparation of the series of 3-methoxyamides **7a**–**7d**. Attempted oxidation of amide **4a** with MCPBA both at room and at elevated temperatures always afforded complex mixtures of products from which amide **7a** can be isolated in low yields of about 18%. The yield could not be improved by application of hydrogen peroxide in acetic acid or by urea–hydrogen peroxide complex. That is why we searched for a new strategy for the synthesis of methoxyamides **7a**–**7d**. Oxidation of ester **10a** with MCPBA led selectively to sulfone **11a**, which was obtained in 65% yield (Scheme 1). The ester group of **11a** was carefully hydrolyzed with aqueous sodium hydroxide to give 56% yield of rather unstable 3-methoxy-1-benzothiophene-2-carboxylic acid 1,1-dioxide (**11b**). Acid **11b** was also obtained by direct oxidation of acid **10b** with 30% hydrogen peroxide in acetic acid, though only in a moderate yield. Subsequently, acid **11b** was treated with thionyl chloride to afford the corresponding chloride **9d**, which was immediately transformed by aminolysis with aromatic amines (*vide infra*) to give amides **7a**–**7d** in satisfactory yields.

In order to obtain 3-hydroxyamides **8a**–**8d**, we tried to deprotect[13] the methoxy group of amides **7a**–**7d**. Attempted reaction of amide **7a** with boron tribromide, unlike that of amides **4a**–**4d**, did not proceed at all and the starting compound was recovered even after long-term heating with an excess of boron tribromide in dichloromethane.

Finally, we used for introduction of the hydroxy group the well-known reactivity[14] of the vinyl sulfone moiety of thiophene derivatives, where halogens in position 3 are prone to nucleophilic substitution. Thus, reaction of amides **6a**–**6c** with lithium hydroxide in 1,4-dioxane at room temperature proceeded smoothly and amides **8a**–**8c** were obtained in good yields.

The antiinflammatory effect of compounds **2**–**8** was assessed by tests measuring their influence on inhibition of LTB_4 biosynthesis, carrageenin edema and ear inflammation (Table I). On the basis of the results it can be emphasised that *in vivo* antiinflammatory effect of compounds under study is not presumably related to their inhibition of LT synthesis. Some compounds being highly active in the inhibition of the ear edema, *e.g.* com-

TABLE I
Log *P* values and biological activities of compounds **2–8**

Compound	log*P*[a]		LTB_4 inh[b] %[e]/IC_{50}[f]	CE inh[c], %	EE inh[d], %	
	A	B			C	D
2a	3.70	3.73	0/–	nd[g]	9	34
2b	4.35	4.44	0/–	9	1(s)[h]	8
2c	3.78	3.66	0/–	nd	10	3[i]
3a	4.34	4.44	22/–	nd	6(s)	0
3b	4.99	5.15	15/–	13	3(s)	9
3c	4.42	4.37	11/–	50	4(s)	19
3d	3.71	3.88	12/>100	11	14	3[i]
4a	3.78	3.66	0/–	nd	13	14
4b	4.43	4.37	0/–	nd	9	6[i]
4c	3.86	3.59	8/–	nd	nd	nd
4d	3.15	3.09	17/>100	11	6[i]	7[i]
5a	3.52	4.06	94/1.24	16	14	39
5b	4.17	4.77	99/1.46	nd	2(s)	17
5c	3.60	3.99	93/1.82	13	10	23
5d	2.89	3.49	13/>100	nd	6[i]	7[i]
6a	1.95	3.60	98/3.33	12	3(s)	3[i]
6b	2.60	4.31	86/2.55	16	16	3[i]
6c	2.03	3.53	98/5.56	26	6[i]	12
6d	1.32	3.03	0/–	48	22(s)	12
7a	0.75	2.82	20/–	61	10	12
7b	1.40	2.82	30/>100	18	12	10
7c	0.83	2.75	0/–	30	2[i]	10
7d	0.12	2.25	0/–	26	24	19
8a	0.57	3.22	13/–	9	5[i]	36
8b	1.22	3.93	21/–	25	11	6[i]
8c	0.65	3.15	0/–	27	17	0
Zileuton			100/0.17	46	9	13
Piroxicam			nd	67[j]	22	68
Tenidap			100/1.04	61	14	

[a] Log *P* values were calculated, *A*: by the use of KOWWIN program, *B*: by the fragment method using log *P* experimental values available for the greatest fragments. [b] Inhibition of LT B_4 biosynthesis. [c] Carrageenin edema inhibition after a dose of 100 mg/kg. [d] Ear edema inhibition after a dose of 200 mg/kg, *C*: ear lobe weight, *D*: degree of ear lobe hyperemia. [e] Dose of 20 μM. [f] Given in μM. [g] Not determined. [h] Stimulation of ear lobe weight. [I] Significance level $p > 0.05$. [j] Dose of 10 mg/kg.

pounds **6d** and **7d**, are completely inactive as LTB_4 synthesis inhibitors. Only hydroxy substituted derivatives **5a**–**5c** showed an indication for such a relation; it is likely to be rather a random effect, because with analogously substituted sulfones **8a**–**8c** no relation was observed between the mentioned effects.

To evaluate the structure–activity relationships at a semiquantitative level, log *P* values for all derivatives **2**–**8** were estimated using two methods of calculations; by the KOWWIN program and by the fragment method (Table I). Inconsistent results of calculations by the two applied methods were registered; especially the log *P* values calculated for sulfones **6**–**8** by the KOWWIN method are not quite correct. The software considers too low values of correction for the interactions between SO_2 and CONH hydrophilic groups and uses aliphatic fragment constants also for heterocyclic substituents and therefore the calculated log *P* values of the mentioned sulfones are too low. Verification of correct total lipophilicity of compounds under study by an independent experimental method is in progress. Therefore, the influence of lipophilicity on activity can be studied only separately in the groups of either 1-benzothiophenes **2**–**5** or their sulfones **6**–**8**. The inhibition of LTB_4 biosynthesis in the series of compounds **2**–**5** depends only marginally on the total lipophilicity. However, the inhibitory activity was substantially increased by introducing of the hydrophilic 3-hydroxy group in compounds **5a**–**5c**. The presence of the local region of low lipophilicity could be probably the reason of the observed increase. The second possibility, *i.e.* the presence of enol-carboxamide moiety, is obviously not necessary, as it is demonstrated by the relatively high inhibitory activity of chloro derivatives **6a**–**6c**. In their structure the mentioned fragment is missing but other local low lipophilic region is present. It can be shown by low inhibitory activities of derivatives **8a**–**8c**, that the presence of another hydrophilic region in their structure acts obviously contradictory. The inhibition of carrageenin edema is characteristic of COX inhibitors. It is evidently supported by the change from thiophene derivatives **2**–**5** to sulfones **6**–**8**, which is accompanied by a decrease of lipophilicity of the molecules.

A new type of potentially antiinflammatory compounds based on the enol-amide structure has been synthesized. Several compounds studied have shown an inhibitory activity against 5-LO apparently without the relation to the presence of enol-carboxamide moiety.

EXPERIMENTAL

Melting points were determined on a Boetius block and are uncorrected. ^{1}H NMR spectra were taken on spectrometers Varian-Gemini 300 HC. Deuteriochloroform and DMSO-d_6 (compounds **6b**, **6d**, **7b**, **7c**) were used as solvents, their signals serving as internal standards. Chemical shifts are given in the δ-scale (ppm), coupling constants ^3J(H,H) in Hz. IR spectra (λ in nm) were recorded on a Nicolet FTIR 740 spectrometer in chloroform or KBr (compounds **6d**, **7a**–**7d**).

Calculation of log *P*

The program KOWWIN Version 1.6 (Syracuse Res. Corp. (NY), U.S.A.) was used in the calculations. For the above-mentioned approximations used by the program, we also calculated log *P* by the fragment method[15]. Calculations of log *P* of compounds **2a**, **3d**, and **6a** are given as examples:

$$\log P_{calc}\ (\mathbf{2a}) = \log P(\text{1-benzothiophene}) + \log P(\text{benzene}) + f^{\Phi\Phi}(\text{–CONH–}) - 2\,f(\text{H}) = 3.12 + 2.13 - 1.06 - 0.46 = 3.73$$

$$\log P_{calc}\ (\mathbf{3d}) = \log P(\text{1-benzothiophene}) + \log P(\text{pyridine}) + f^{\Phi\Phi}(\text{–CONH–}) + f(\text{Cl}) - 3\,f(\text{H}) - 0.42\,[f(\text{–CONH–}) + f(\text{–N=})] = 3.12 + 0.65 - 1.06 + 0.94 - 0.69 + 0.42\,(1.06 + 1.12) = 3.88$$

$$\log P_{calc}\ (\mathbf{6a}) = \log P(\text{1-benzothiophene 1,1,-dioxide}) + \log P(\text{benzene}) + f^{\Phi\Phi}(\text{–CONH–}) + f(\text{Cl}) - 3\,f(\text{H}) - 0.42\,[f(\text{–CONH–}) + f^{\Phi}(\text{SO}_2)] = 0.92 + 2.13 - 1.06 + 0.94 - 0.69 + 1.36 = 3.60$$

For 1-benzothiophenes **2**–**5**, the calculated values are in good agreement with log *P* values calculated by the fragment method where available experimental log *P* values[15] are used. However, we quoted great differences between both methods for calculation of log *P* values of sulfones **6**–**8** (Table I).

3-Chloro-*N*-phenyl-1-benzothiophene-2-carboxamide 1,1-Dioxide (**6a**)

A mixture of amide **3a** (ref.[9]) (3.20 g, 11.1 mmol), 85% 3-chloroperoxybenzoic acid (5.64 g, 32.7 mmol) (MCPBA), and 1,2-dichloroethane (150 ml) was stirred at 60 °C for 6 h. After cooling, the solution was washed with saturated aqueous sodium hydrogencarbonate (2 × 50 ml) and dried with anhydrous magnesium sulfate. The residue after evaporation of the solvent was crystallized from xylene to afford 2.83 g (80%) of amide **6a**, m.p. 188–190 °C. For $C_{15}H_{10}ClNO_3S$ (319.8) calculated: 56.34% C, 3.15% H, 11.09% Cl, 4.38% N, 10.03% S; found: 56.03% C, 3.21% H, 11.18% Cl, 4.21% N, 10.04% S. IR ($CHCl_3$): 3 369 (NH), 1 687 (CO), 1 154 (SO_2). ^{1}H NMR ($CDCl_3$): 7.21 t, 1 H, J = 7.5 (H-4′); 7.39 t, 2 H (H-3′); 7.65 d, 2 H, J = 8.0 (H-2′); 7.45 m, 2 H (H-5 and H-6); 7.49 m, 2 H (H-4 and H-7); 8.31 s, 1 H (NH).

In an analogous way the following compounds were obtained:

3-Chloro-N-(4-chlorophenyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**3b**). Yield 67%. M.p. 221–223 °C (xylene). For $C_{15}H_9Cl_2NO_3S$ (354.2) calculated: 50.86% C, 2.56% H, 20.02% Cl, 3.95% N, 9.05% S; found: 50.30% C, 2.62% H, 20.21% Cl, 3.64% N, 9.05% S.

IR ($CHCl_3$): 3 367 (NH), 1 690 (CO), 1 155 (SO_2). ^{1}H NMR (DMSO-d_6): 7.47 d, 2 H, J = 8.8; 7.71 d, 2 H; 7.84–7.94 m, 3 H; 8.12 d, 1 H, J = 7.0 (H-7); 11.02 s, 1 H (NH).

3-Chloro-N-(4-methoxyphenyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**3c**). Yield 74%. M.p. 205–207 °C (xylene). For $C_{16}H_{12}ClNO_4S$ (349.8) calculated: 54.94% C, 3.46% H, 10.14% Cl, 4.00% N, 9.17% S; found: 55.24% C, 3.45% H, 10.48% Cl, 3.98% N, 9.35% S. IR ($CHCl_3$): 3 371 (NH), 1 681 (CO), 1 155 (SO_2). ^{1}H NMR ($CDCl_3$): 3.82 s, 3 H (OCH_3); 6.91 d, 2 H, J = 8.8; 7.57 d, 2 H; 7.74–7.80 m, 2 H (H-5 and H-6); 7.80–7.86 m, 2 H (H-4 and H-7); 10.34 s, 1 H (NH).

3-Chloro-N-(2-pyridyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**3d**). Yield 58%. M.p. 232–234 °C (xylene). For $C_{14}H_9ClN_2O_3S$ (320.7) calculated: 52.43% C, 2.83% H, 11.05% Cl, 8.73% N, 10.00% S; found: 52.25% C, 2.95% H, 11.01% Cl, 8.67% N, 9.91% S. IR (KBr): 3 360 (NH), 1 662 (CO), 1 151 (SO_2). ^{1}H NMR (DMSO-d_6): 7.26 dt, 1 H, J_1 = 7.2, J_2 = 1.6; 7.54 t, 1 H, J = 7.7; 7.65 m, 2 H; 7.99 dd, 1 H, J_1 = 6.2, J_2 = 2.8; 8.17 dd, 1 H; 8.42 dd, 1 H, J_1 = 8.2, J_2 = 1.6; 8.49 d, 1 H, J = 6.0; 11.82 s, 1 H (NH).

Methyl 3-methoxy-1-benzothiophene-2-carboxylate 1,1-dioxide (**11a**). Yield 65%. M.p. 164–165 °C (methanol); ref.[16] m.p. 162–163 °C. For $C_{11}H_{10}O_5S$ (254.3) calculated: 51.96% C, 3.96% H, 12.61% S; found: 51.88% C, 3.90% H, 12.76% S. IR ($CHCl_3$): 1 718 (CO), 1 156 (SO_2). ^{1}H NMR ($CDCl_3$): 3.97 s, 3 H (OCH_3); 4.44 s, 3 H (OCH_3); 7.66 dt, 1 H, J_1 = 7.2, J_2 = 1.2; 7.71 dt, 1 H; 7.75 dd, 1 H, J_1 = 7.2, J_2 = 1.3; 7.79 dd, 1 H.

3-Methoxy-1-benzothiophene-2-carboxylic Acid 1,1-Dioxide (**11b**)

Method A. Ester **11a** (ref.[9]) (12.02 g, 47.3 mmol) was added to a solution of sodium hydroxide (5.67 g, 142 mmol) in aqueous methanol (700 ml, 1 : 1 v/v) and the mixture was stirred at 40 °C for 2 h. The mixture was diluted with water (200 ml), acidified with concentrated hydrochloric acid, extracted with chloroform (2 × 250 ml), the organic layer was washed with water and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave 10.44 g (92%) of pure acid **11b**, m.p. 166–167 °C (decomp.). For $C_{10}H_8O_5S$ (240.2) calculated: 50.00% C, 3.36% H, 13.35% S; found: 49.70% C, 3.35% H, 12.98% S. IR ($CHCl_3$): 2 700–3 150 (COOH), 1 165 (SO_2). ^{1}H NMR ($CDCl_3$): 4.03 s, 3 H (OCH_3); 7.72 t, 1 H, J = 7.2; 7.74 t, 1 H; 7.82 d, 1 H; 7.85 d, 1 H.

Method B. Aqueous 30% hydrogen peroxide (1.64 ml, 20.8 mmol) was added to a solution of acid **10b** (0.50 g, 2.08 mmol) in acetic acid (10 ml), the mixture was stirred at 50 °C for 30 h and evaporated to dryness. The residue was purified by column chromatography (silica gel, chloroform–methanol, 99 : 1) to give 0.32 g (56%) of acid **11b**.

3-Methoxy-1-benzothiophene-2-carbonyl Chloride 1,1-Dioxide (**9d**)

Thionyl chloride (37.5 ml, 0.52 mol) was added dropwise under stirring at room temperature to a slurry of acid **11b** (17.90 g, 74.5 mmol) in toluene (400 ml). The mixture was stirred at 75–80 °C for 2.5 h and the solvent was evaporated to afford 18.53 g (96%) of chloride **9d**, m.p. 215–217 °C (toluene). This product was used for preparation of amides **7a**–**7d** without further purification. ^{1}H NMR ($CDCl_3$): 4.06 s, 3 H (OCH_3); 7.77 t, 1 H, J = 7.2; 7.81 t, 1 H; 7.86 d, 1 H; 7.93 d, 1 H.

3-Methoxy-*N*-phenyl-1-benzothiophene-2-carboxamide 1,1-Dioxide (**7a**)

Method A. Aniline (2.34 g, 25.1 mmol) was added dropwise to a cooled (0 °C) solution of chloride **9d** (5.0 g, 19.3 mmol) in dry chloroform (100 ml), then triethylamine (4.02 ml, 29 mmol) was added and the mixture was stirred at room temperature for 6 h. The mixture was diluted with chloroform (100 ml) and subsequently washed with 2% aqueous hydrochloric acid (2 × 70 ml), saturated aqueous sodium hydrogencarbonate solution (50 ml), and water (50 ml) and then dried with anhydrous magnesium sulfate. The residue after evaporation of the solvent was crystallized from toluene to afford 4.02 g (66%) of amide **7a**, m.p. 183–185 °C. For $C_{16}H_{13}NO_4S$ (315.3) calculated: 61.45% C, 4.16% H, 4.44% N, 10.17% S; found: 61.40% C, 4.16% H, 4.40% N, 9.90% S. IR (KBr): 3 370 (NH), 1 683 (CO), 1 161 (SO_2). ^{1}H NMR ($CDCl_3$): 3.98 s, 3 H (OCH_3); 6.66 d, 1 H, J = 8.2; 7.26 t, 2 H (H-3′); 7.33 dd, 2 H, J_1 = 7.4, J_2 = 1.8 (H-2′); 7.49 m, 2 H (H-5 and H-6); 7.61 t, 1 H; 7.84 d, 1 H; 10.42 s, 1 H (NH).

Method B. A mixture of amide **4a** (0.50 g, 1.76 mmol), MCPBA (0.895 g, 5.19 mmol), and 1,2-dichloroethane (15 ml) was stirred at 50 °C for 16 h, diluted with chloroform (150 ml) and worked up as for **6a**. The crude product was purified by column chromatography (silica gel, chloroform–methanol, 99 : 1) to afford amide **7a** (0.099 g; 18%), m.p. 180–183 °C.

The following amides **7b**–**7d** were obtained by method *A*:

N-(4-Chlorophenyl)-3-methoxy-1-benzothiophene-2-carboxamide 1,1-dioxide (**7b**). Yield 62%. M.p. 148–150 °C (toluene). For $C_{16}H_{12}ClNO_4S$ (349.8) calculated: 54.94% C, 3.46% H, 10.14% Cl, 4.00 % N, 9.17% S; found: 55.20% C, 3.40% H, 10.11% Cl, 3.80% N, 9.09% S. IR (KBr): 3 368 (NH), 1 668 (CO), 1 163 (SO_2). ^{1}H NMR (DMSO-d_6): 3.97 s, 3 H (OCH_3); 6.74 d, 1 H, J = 7.7; 7.27 d, 2 H, J = 8.8; 7.33 t, 1 H, J = 7.7; 7.46 d, 2 H; 7.64 t, 1 H; 7.85 d, 1 H, J = 7.8; 10.30 s, 1 H (NH).

3-Methoxy-N-(4-methoxyphenyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**7c**). Yield 73%. M.p. 212–215 °C (toluene). For $C_{17}H_{15}NO_5S$ (345.4) calculated: 59.12% C, 4.38% H, 4.06% N, 9.28% S; found: 58.99% C, 4.39% H, 4.07% N, 9.13% S. IR (KBr): 3 370 (NH), 1 659 (CO), 1 160 (SO_2). ^{1}H NMR (DMSO-d_6): 3.88 s, 3 H (OCH_3); 3.96 s, 3 H (OCH_3); 6.64 d, 1 H, J = 8.2; 6.98 d, 2 H, J = 8.2; 7.23 d, 2 H; 7.27 t, 1 H, J = 7.7; 7.60 t, 1 H, J = 7.7; 7.82 d, 1 H; 10.30 s, 1 H (NH).

3-Methoxy-N-(2-pyridyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**7d**). Yield 34%. M.p. 220–223 °C (toluene). For $C_{15}H_{12}N_2O_4S$ (316.3) calculated: 56.95% C, 3.82% H, 8.86% N, 10.13% S; found: 57.12% C, 3.78% H, 8.58% N, 10.11% S. IR (KBr): 3 424 (NH), 1 718 (CO), 1 164 (SO_2). ^{1}H NMR ($CDCl_3$): 4.39 s, 3 H (OCH_3); 7.02 dt, 1 H, J_1 = 6.6, J_2 = 1.3; 7.38 dt, 1 H, J_1 = 7.2, J_2 = 1.6; 7.44 dt, 1 H; 7.50 dt, 1 H; 7.84 dd, 1 H, J_1 = 8.2, J_2 = 1.1; 7.96 dd, 1 H; 8.30 dd, 1 H, J_1 = 6.6, J_2 = 1.1; 8.61 dd, 1 H, J_1 = 8.2, J_2 = 1.7; 12.16 s, 1 H (NH).

3-Hydroxy-*N*-phenyl-1-benzothiophene-2-carboxamide 1,1-Dioxide (**8a**)

A solution of lithium hydroxide (0.22 g, 9.38 mmol) in water (20 ml) was added dropwise to a solution of amide **6a** (1.00 g, 3.13 mmol) in 1,4-dioxane (50 ml), the mixture was stirred at room temperature for 6 h and extracted with dichloromethane (100 ml). The formed aqueous layer was acidified with 5% hydrochloric acid (pH 3) and extracted with dichloromethane (3 × 30 ml). Combined organic extracts were dried with anhydrous magnesium sulfate and evaporated to dryness. After crystallization from ethanol, 0.60 g (63%) of amide **8a** was obtained, m.p. 166–168 °C. For $C_{15}H_{11}NO_4S$ (301.3) calculated: 59.79% C, 3.68% H, 4.65% N, 10.64% S; found: 59.27% C, 3.69% H, 4.54% N, 10.60% S. IR (KBr): 3 340 (OH),

1 637 (CO), 1 158 (SO_2). ^{1}H NMR ($CDCl_3$): 5.28 bs, 1 H (OH); 7.22 t, 1 H, *J* = 7.7 (H-4′); 7.40 t, 2 H (H-3′); 7.59 dd, 2 H (H-2′); 7.74 m, 2 H (H-5 and H-6); 7.85 m, 2 H (H-4 and H-7).

Amides **8b** and **8c** were obtained in an analogous way.

N-(4-Chlorophenyl)-3-hydroxy-1-benzothiophene-2-carboxamide 1,1-dioxide (**8b**). Yield 61%. M.p. 194–196 °C (ethanol). For $C_{15}H_{10}ClNO_4S$ (335.8) calculated: 53.66% C, 3.00% H, 10.56% Cl, 4.17% N, 9.55% S; found: 53.34% C, 3.04% H, 10.38% Cl, 4.07% N, 9.59% S. IR (KBr): 3 342 (OH), 1 636 (CO), 1 159 (SO_2). ^{1}H NMR ($CDCl_3$): 7.35 d, 2 H, *J* = 8.8; 7.53 d, 2 H; 7.75 dt, 1 H, J_1 = 7.4, J_2 = 1.6; 7.78 dt, 1 H; 7.83 dd, J_1 = 7.6, J_2 = 1.6; 7.86 dd, 1 H.

3-Hydroxy-N-(4-methoxyphenyl)-1-benzothiophene-2-carboxamide 1,1-dioxide (**8c**). Yield 54%. M.p. 169–171 °C (ethanol). For $C_{16}H_{13}NO_5S$ (331.3) calculated: 58.00% C, 3.95% H, 4.23% N, 9.68% S; found: 57.87% C, 4.11% H, 4.16% N, 9.93% S. IR (KBr): 3 339 (OH), 1 633 (CO), 1 152 (SO_2). ^{1}H NMR ($CDCl_3$): 3.82 s, 3 H (OCH_3); 5.75 bs, 1 H (OH); 6.92 d, 2 H, *J* = 8.8; 7.47 d, 2 H; 7.76 m, 2 H; 7.84 m, 2 H.

Biological Evaluation

Inhibition of carrageenin edema was evaluated by the method of Winter[17]. The experimental conditions have been described elsewhere[18]. Arachidonic acid-induced ear inflammation in mice was achieved using the method of Opas[19], ear lobe inflammation was induced by application of 20 µl arachidonic acid solution in acetone. The substance was administered orally 16 h before edema induction. The degree of ear lobe hyperemia and the ear lobe weight were evaluated 1 h after application of arachidonic acid. The results were expressed in terms of percentage inhibition relative to the untreated control. Inhibition of LTB_4 biosynthesis was evaluated by determination of the LTB_4 production in rat polymorphonuclear cells from pleural exudate induced by heat-activated rat serum[20]. The cells were stimulated with Ca ionophore A 23187 (Sigma) and incubated with various concentrations of the substances tested. LTB_4 was determined in supernatant using a commercial RIA kit (Amersham).

This project was supported by the Grant Agency of Czech Republic (grant No. 203/97/0212).

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