SYNTHESIS AND ANALGESIC ACTIVITY OF SOME SUBSTITUTED 1-BENZOFURANS AND 1-BENZOTHIOPHENES

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2-Benzoyl- and 2-(pyridylcarbonyl)-1-benzofuran-3-amines were prepared from 2-hydroxybenzonitrile and corresponding bromoethanone derivatives. 2-Benzoyl- and 2-(pyridylcarbonyl)-1-benzothiophene-3-amines were prepared analogously from 2-sulfanylbenzonitrile. 2-Benzoyl-1-benzofuran-3-amine treated with acetic anhydride or ethyl chloroformate provided the corresponding *N*-acetyl or *N*-ethoxycarbonyl derivatives. These *N*-activated compounds were alkylated with ethyl bromoacetate to provide ethyl *N*-acetyl-*N*-(2-benzoyl-1-benzofuran-3-yl)glycinate and ethyl *N*-(2-benzoyl-1-benzofuran-3-yl)-*N*-ethoxycarbonylglycinate, respectively. Their mild hydrolysis gave the corresponding glycine derivatives. Methylation of ethyl *N*-(2-benzoyl-1-benzofuran-3-yl)carbamate gave the corresponding *N*-methyl carbamate, which was hydrolyzed to *N*-methyl-(2-benzoyl-1-benzofuran-3-yl)amine. 2-Benzoyl-7-methoxy-1-benzofuran-3-amine and 2-(4-methoxybenzoyl)-1-benzofuran-3-amine were demethylated with boron tribromide to the corresponding hydroxy derivatives; their *O*-alkylation with ethyl bromoacetate than gave ethyl [(3-amino-2-benzoyl-1-benzofuran-7-yl)oxy]acetate and ethyl {4-[(3-amino-1-benzofuran-2-yl)carbonyl]phenoxy}acetate, respectively. The mild hydrolysis of these esters provided corresponding acids. Similarly, alkylation of the hydroxy derivatives with (dimethylamino)propyl chloride gave corresponding (dimethylamino)propoxy derivatives. 2-Hydroxybenzonitrile treated with 2-bromo-1-(2-, 3-, or 4-pyridyl)ethan-1-one provided the respective 2-(pyridylcarbonyl)-1-benzofuran-3-amine. Similar 2-(pyridylcarbonyl)-1-benzothiophene-3-amines were prepared analogously from 2-sulfanylbenzonitrile. 2-Benzoyl-3-(bromomethyl)-1-benzofuran treated with dimethylamine, 1-methylpiperazine, and sodium 1-methylpiperidine-4-thiolate gave the corresponding alkylation products. Several compounds were found to exhibit considerable analgesic activity.

Key words: Benzofurans; Benzothiophenes; Heterocyclizations; Demethylations; Alkylations; Antinociceptive activity; Analgesics.

Antinociceptive activity of 2-(4-bromobenzoyl)-4,6-dimethoxy-3-methylbenzofuran[1,2] (**1**) inspired us to prepare a series of similar 3-amino substi-

tuted 1-benzofurans, 1-benzothiophenes, and indoles[3]. Similarly to **1**, all of these compounds were found active only after intraperitoneal or subcutaneous application and slightly active or inactive after oral application. These new types of analgesics showed some intrinsic potential and therefore preparation of analogs of **1** with a better pharmacological profile could be fruitful. Since the initial set[3] contains compounds with a relatively wide range of lipophilicity, we decided to try to modify the bioavailability of the compounds by changing their acid-base character and to prepare compounds that could form salts either under acidic or alkaline conditions.

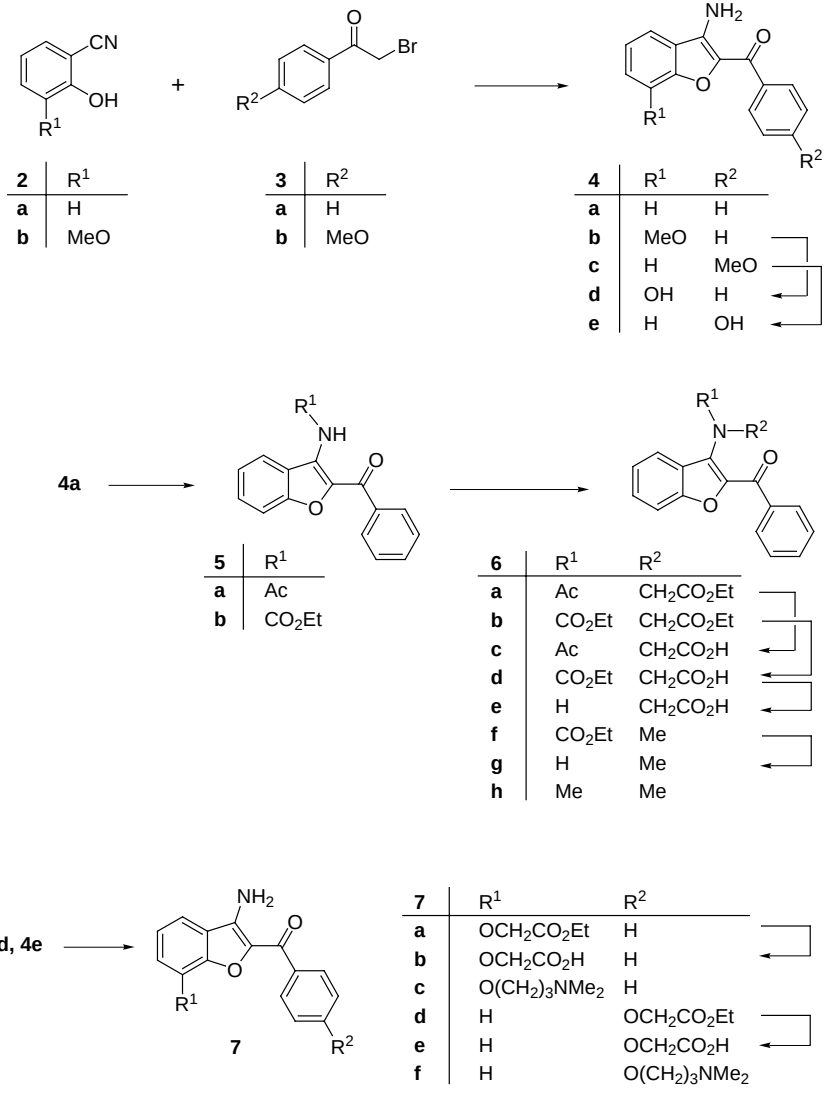
We chose the carboxymethyl group as a suitable group for ionization under alkaline conditions and (dimethylamino)propyl group as a substituent ionizable under acidic conditions. Our synthetic efforts were focused on the 1-benzofuran derivatives containing these substituents attached to the heterocyclic skeleton either through the 3-amino group (compounds **6c–6e**), or through an ether oxygen attached to position 7 (compounds **7b** and **7c**) or 4′ (compounds **7e** and **7f**).

It is a well-known fact that pK_a and log *P* (and for ionizable compounds log *D*) values are useful parameters for use in understanding the behavior of drug molecules. These parameters may be used to predict the distribution of a drug compound in a biological system. Factors such as absorption, excretion and penetration of the CNS may be related to them. Therefore we estimated these parameters using well-proven prediction methods of Advanced Chemistry Development (ACD/log *P* v4.5, ACD/log *D* v4.5 and ACD/pK_a v4.5). The results were obtained using the ACD/I-Lab service, which is available at http://www2.acdlabs.com/ilab. The prediction of pK_a is based on the choice of the dominant ionic form in the system at the equilibrium state under standard conditions (25 °C and zero ionic strength). For the synthesized compounds the mentioned parameters are given in Table I.

The starting benzofuran derivatives **4a–4c** were prepared by a known procedure from the appropriate benzonitrile **2** and bromo derivative **3** (Scheme 1). Compounds **4a** (refs[3–5]) and **4b** (ref.[3]) have been described. The starting 2-hydroxy-3-methoxybenzonitrile was prepared from commercially available 2-hydroxy-3-methoxybenzaldehyde **2b** *via* the corresponding oxime, which was dehydrated *in situ* with formic acid to the required benzonitrile[3].

For the synthesis of compounds **6**, 3-amino group of the starting benzofuran **4a** should be activated by an electron-withdrawing group. Such compounds **5a** and **5b** were prepared from **4a** by acetylation with acetic anhydride and direct reaction with ethyl chloroformate, respectively. These compounds were alkylated with ethyl bromoacetate, using either sodium

hydride in DMF or potassium carbonate in butanone, to provide compounds **6a** and **6b**. Mild hydrolysis of **6a** with sodium hydroxide at room temperature then provided acid **6c**; no deacetylation under the used conditions was observed and a complex mixture was obtained after prolonged heating. Similarly, the same treatment of **6b** led to acid **6d** as the only product. On the other hand, a medium yield of acid **6e** was isolated from



SCHEME 1

TABLE I
Estimated values of pK_a, log *P*, and log *D* (pH 7) of the prepared compounds

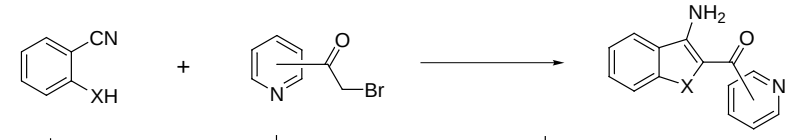
Compound	pK_a	log *P*	log *D*
4a	–0.55 ± 0.33	3.02 ± 0.83	3.0 ± 1.0
4b	–0.62 ± 0.4	2.84 ± 1.30	2.8 ± 1.0
4c	0.88 ± 0.33	3.07 ± 0.83	3.1 ± 1.0
4d	8.70 ± 0.40	2.28 ± 1.42	2.3 ± 1.0
4e	7.55 ± 0.15	2.71 ± 0.83	2.6 ± 1.0
5a	14.19 ± 0.50	3.25 ± 0.83	3.2 ± 1.0
5b	10.60 ± 0.50	4.46 ± 0.87	4.5 ± 1.0
6a	–7.09 ± 0.70	2.12 ± 0.88	2.1 ± 1.0
6b	–7.96 ± 0.70	3.45 ± 0.91	3.5 ± 1.0
6c	3.42 ± 0.10	1.12 ± 0.87	–2.3 ± 1.0
6d	3.67 ± 0.10	2.46 ± 0.90	–0.8 ± 1.0
6e	3.90 ± 0.10	2.78 ± 0.85	–0.3 ± 1.0
6f	–7.58 ± 0.70	2.82 ± 0.87	2.8 ± 1.0
6g	3.38 ± 0.50	3.76 ± 0.83	3.8 ± 1.0
7a	–0.77 ± 0.40	2.64 ± 1.30	2.6 ± 1.0
7b	3.13 ± 0.40	2.04 ± 1.31	–1.6 ± 1.0
7c	9.30 ± 0.28	3.01 ± 1.31	0.8 ± 1.0
7d	0.76 ± 0.33	2.88 ± 0.85	2.9 ± 1.0
7e	3.00 ± 0.10	2.28 ± 0.85	–1.5 ± 1.0
7f	9.28 ± 0.28	3.25 ± 0.85	1.0 ± 1.0
10a	0.85 ± 0.12	1.94 ± 0.84	1.9 ± 1.0
10b	2.91 ± 0.10	1.95 ± 0.83	1.9 ± 1.0
10c	2.87 ± 0.10	1.73 ± 0.83	1.7 ± 1.0
10d	0.77 ± 0.12	3.94 ± 0.83	3.9 ± 1.0
10e	2.87 ± 0.10	3.95 ± 0.83	3.9 ± 1.0
10f	2.72 ± 0.10	3.73 ± 0.82	3.7 ± 1.0
13a	7.99 ± 0.28	3.02 ± 0.44	2.0 ± 1.0
13b	7.42 ± 0.30	2.32 ± 0.51	1.7 ± 1.0
13c	9.00 ± 0.40	4.17 ± 0.54	2.2 ± 1.0

the same reaction mixture after prolonged heating. Compound **5b** was smoothly alkylated with iodomethane using potassium carbonate in acetonitrile to give compound **6f**. Alkaline hydrolysis of this compound then provided *N*-methyl derivative **6g** (Scheme 1). In attempts to prepare dimethylamino derivative **6h**, we failed to alkylate compound **6g** both with iodomethane and dimethyl sulfate under various conditions. Therefore we decided to use reductive methylation of **4a** with formaldehyde and sodium cyanoborohydride, a method known for its selectivity and efficacy even with arylamines[6]. We used the conditions described in the literature even for dimethylation of nitroanilines[7] as well as carbonyl group-containing anilines[8]. Unlike the easy alkylations of compounds **5** described above, we failed to alkylate these compounds with 3-(dimethylamino)propyl chloride under various conditions (NaH–DMF; potassium carbonate–potassium iodide in various solvents). The prolonged treatment usually provided complex mixtures, the only identified compound being 3-amino derivative **4a**.

Synthesis of compounds **7** started from methoxy derivatives **4b** and **4c**. Their demethylation to the respective hydroxy derivatives **4d** and **4e** was smoothly achieved using BBr_3 under common conditions. Both compounds, treated with ethyl bromoacetate in the presence of potassium carbonate, provided the corresponding esters **7a** and **7d**, which were hydrolyzed to acids **7b** and **7e**, respectively. Compounds **4d** and **4e** treated with 3-(dimethylamino)propyl chloride hydrochloride in the presence of potassium iodide and an excess of potassium carbonate in butanone provided the respective 3-(dimethylamino)propoxy derivatives **7c** and **7f** (Scheme 1).

Another possibility to change pK_a of the benzofurans is to prepare pyridine-containing benzofurans **10a**–**10c** (Table I). The compounds were prepared from 2-hydroxybenzonitrile (**2a**) and corresponding 2-bromo-1-pyridylethan-1-ones **9a**–**9c**. We used an excess of potassium carbonate in DMF, basically the same conditions outlined for the preparation of the corresponding opened intermediates[3]. In this case, hydrobromides of the starting 2-bromo-1-pyridylethan-1-ones were used and benzofurans **10a–10c** were directly formed (Scheme 2). Analogously, benzothiophenes **10d–10f** were prepared from 2-sulfanylbenzonitrile (**8**).

3-[(Dimethylamino)methyl] derivative **13a** represents a different type of amine-containing 2-benzoyl-1-benzofurans. The compound was prepared from dimethylamine and 2-benzoyl-3-(bromomethyl)-1-benzofuran (**12**), obtained from the corresponding 3-methyl derivative **11**by radical bromination. Since many piperazine-containing heteroaromatic derivatives are known to exert analgesic activity[9–13], also piperazine derivative **13b** was analogously prepared. Various analogs of anpirtoline[14,15] containing



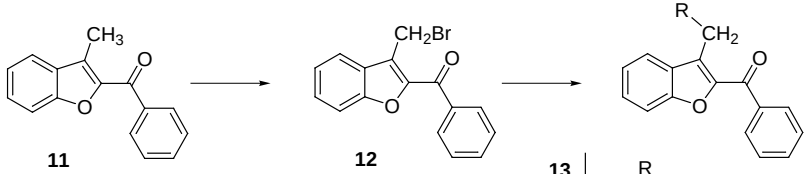
	X
2a	O
8	S

9	Position
a	1
b	2
c	3

10	X	Position
a	O	2
b	O	3
c	O	4
d	S	2
e	S	3
f	S	4

SCHEME 2

piperidin-4-ylsulfanyl heteroaromatic fragment have recently been described and some of them were found analgesically active[16–19]. Therefore, also compound **13c** was prepared from bromo derivative **12** and 1-methylpiperidine-4-thiol (Scheme 3).



13	R
a	Me_2N
b	Me–N N
c	Me–N S

SCHEME 3

All the prepared target compounds, *i.e.* benzofurans **4**–**7**, **10a**–**10c**, and **13**, as well as benzothiophenes **10d**–**10f**, were evaluated for their antinociceptive activity in two basic tests, the hot-plate test and intraperitoneal writhing test in mice. Selected compounds were tested also in the tail-flick test in rats. The analgesic activity of compounds having activity higher than 30% at least in one of the tests is shown in Table II. It is evident that the model compound **1** is highly active after subcutaneous application and only slightly active after oral application. Unfortunately, none of the structural modifications done with 1-benzofuran-3-amines and 1-benzothiophen-3-amines described in this work led to compounds with better bioavailability and/or higher activity after oral application. Better results

were found with compounds **13**; activity of compound **13b** after subcutaneous application was proved in several other models of experimental analgesia. The compound was found nontoxic in mice (200 mg/kg p.o., 100 mg/kg s.c.) and was not mutagenic *in vitro* in the Ames test (results not shown).

In conclusion, a series of new benzofurans and benzothiophenes was synthesized and tested as analgesics. Some of them, such as compounds **4a**, **13a** and **13b**, are active in the used analgesic models in doses of 30 mg/kg. However, their activity is not so significant to justify their further development as analgesic agents.

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker instrument (250 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. UV spectra were measured on a Shimadzu UV-260 spectrometer in ethanol, wavelengths are given in nm. Flash and vacuum chromatography were done on

TABLE II
Analgesic activity of active compounds (p.o./s.c., 30 mg/kg)

Compound	Hot plate, %	Writhing, %	Tail flick, %
1	–/63	22/–	–/47
4a	14/39	7/37	–/52
4b	4/44	34/–	–/–
4c	–/51	2/–	–/77
4e	39/38	10/–	–/67
7d	30/11	20/–	–/84
10a	6/54	–/–	–/–
10c	16/44	10/–	38/–
10d	34/72	1/–	–/–
10e	56/–	7/–	–/–
10f	31/26	25/–	–/–
13a	24/27	30/37	–/–
13b	20/56	30/73	–/79
13c	25/14	15/35	–/–

silica gel 60 (230–400 mesh) and preparative TLC on pre-coated PLC plates (silica gel 60) from EM Science.

The following starting compounds were prepared by the previously described methods: 2-benzoyl-1-benzofuran-3-amine[3] (**4a**), 2-benzoyl-7-methoxy-1-benzofuran-3-amine[3] (**4b**), 2-bromo-1-(4-methoxyphenyl)ethan-1-one[20] (**3a**), 2-sulfanylbenzonitrile[3] (**8**), 2-bromo-1-(2-pyridyl)ethan-1-one hydrobromide[21] (**9a**), 2-bromo-1-(3-pyridyl)ethan-1-one hydrobromide[22] (**9b**), 2-bromo-1-(4-pyridyl)ethan-1-one hydrobromide[23] (**9c**), 2-benzoyl-3-methyl-1-benzofuran[24] (**11**), 1-methylpiperidine-4-thiol[25].

2-[2-(4-Methoxyphenyl)-2-oxoethoxy]benzonitrile

A mixture of hydroxybenzonitrile **2a** (1.9 g, 16 mmol), bromo derivative **3b** (4.6 g, 20 mmol), and potassium carbonate (2.8 g, 20 mmol) in DMF (50 ml) was stirred at room temperature for 2 h and then left to stand overnight. The mixture was poured into water (300 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol to give the title compound as white crystals (3.7 g, 87%); m.p. 140–143 °C (ethanol). For $C_{16}H_{13}NO_3$ (267.3) calculated: 71.90% C, 4.90% H, 5.24% N; found: 71.81% C, 4.72% H, 5.44% N. ^{1}H NMR ($CDCl_3$): 3.89 s, 3 H (CH_3); 5.35 s, 2 H (CH_2); 6.84 d, 1 H, *J* = 8.7 (H-3); 6.97 dt, 2 H, *J* = 9.1, 2.4 (H-3′, H-5′); 7.03 dd, 1 H, *J* = 7.5, 1.0 (H-5); 7.45 ddd, 1 H, *J* = 8.7, 7.5, 1.8 (H-4); 7.57 dd, 1 H, *J* = 7.7, 1.8 (H-6); 8.01 dt, 2 H, *J* = 9.1, 2.4 (H-2′, H-6′).

2-(4-Methoxybenzoyl)-1-benzofuran-3-amine (**4c**)

Sodium methoxide (2.7 g, 50 mmol) was added to a stirred suspension of 2-[2-(4-methoxyphenyl)-2-oxoethoxy]benzonitrile (11.2 g, 42 mmol) in methanol (150 ml) and the mixture was stirred at room temperature for 1 h. The mixture was poured into water (1 l), the insoluble portion was filtered off, washed with water and crystallized from ethanol to give **4c** (3.7 g, 33%) as yellow crystals; m.p. 130–132 °C. For $C_{16}H_{13}NO_3$ (267.3) calculated: 71.90% C, 4.90% H, 5.24% N; found: 71.76% C, 5.23% H, 5.08% N. ^{1}H NMR ($CDCl_3$): 3.89 s, 3 H (CH_3); 5.98 bs, 2 H (NH_2); 7.02 dt, 2 H, *J* = 8.0, 0.5 (H-3′, H-5′); 7.25 ddd, 1 H, *J* = 8.0, 6.4, 1.7 (H-6); 7.47 m, 2 H (H-5, H-7); 7.61 dt, 1 H, *J* = 7.8, 0.7 (H-4); 8.13 dt, 2 H, *J* = 8.0, 0.5 (H-2′, H-6′).

N-(2-Benzoyl-1-benzofuran-3-yl)acetamide (**5a**)

A mixture of **4a** (8 g, 34 mmol), acetic anhydride (320 ml), and of 4-(dimethylamino)-pyridine (0.25 g, 2 mmol) was stirred at room temperature for 48 h. The mixture was cooled, the insoluble portion was filtered off and crystallized from ethanol to give **5a** as yellow needles (7.2 g, 76%); m.p. 140–142 °C. For $C_{17}H_{13}NO_3$ (279.3) calculated: 73.11% C, 4.69% H, 5.02% N; found: 72.95% C, 4.76% H, 4.78% N. UV, λ (log ε): 204 (4.31), 241 (4.13), 328 (4.26). ^{1}H NMR ($CDCl_3$): 2.36 s, 3 H (CH_3); 7.33–7.55 m, 4 H (H-5, H-6, H-7, H-4′); 7.70 m, 2 H (H-3′, H-5′); 8.13 dt, 2 H, *J* = 8.9, 0.6 (H-2′, H-6′), 8.57 d, 1 H, *J* = 8.0 (H-4); 10.68 bs, 1 H (NH).

Ethyl *N*-(2-Benzoyl-1-benzofuran-3-yl)carbamate (**5b**)

A mixture of compound **4a** (1.2 g, 5 mmol) and ethyl chloroformate (10 ml) was refluxed for 2 h. The residue after evaporation of ethyl chloroformate was crystallized from ethanol

to give **5b** (1.4 g, 91%); m.p. 95–96 °C. For $C_{18}H_{15}NO_4$ (309.3) calculated: 69.89% C, 4.89% H, 4.53% N; found: 69.76% C, 5.12% H, 4.44% N. ^{1}H NMR ($CDCl_3$): 1.37 t, 3 H, *J* = 7.2 (CH_3); 4.30 q, 2 H, *J* = 7.2 (CH_2); 7.29 ddd, 1 H, *J* = 8.2, 6.2, 1.8 (H-4′); 7.43–7.63 m, 5 H (H-5, H-6, H-7, H-3′, H-5′); 8.21 m, 2 H (H-2′, H-6′); 8.58 d, 1 H, *J* = 8.2 (H-4); 10.15 bs, 1 H (NH).

Ethyl *N*-Acetyl-*N*-(2-benzoyl-1-benzofuran-3-yl)glycinate (**6a**)

Sodium hydride (0.25 g, 50% dispersion in mineral oil, 5 mmol) was added to a stirred solution of **5a** (1.4 g, 5 mmol) in DMF (25 ml) and the mixture was stirred under nitrogen for 1 h. Then ethyl bromoacetate (1.7 g, 10 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was poured into water (200 ml) and the mixture was extracted with dichloromethane, the extract was washed with brine (2 × 20 ml) and dried with anhydrous magnesium sulfate. The residue after evaporation was crystallized from ethanol to give **6a** (1.2 g, 66%) as yellow crystals; m.p. 94–97 °C. For $C_{21}H_{19}NO_5$ (365.4) calculated: 69.03% C, 5.24% H, 3.83% N; found: 68.71% C, 5.45% H, 3.75% N. UV, λ (log ε): 204 (4.32), 225 (4.27), 248 (4.21), 296 (4.18), 311 (4.18), 381 (4.52). ^{1}H NMR ($CDCl_3$): 1.23 t, 3 H, *J* = 7.2 (ethyl CH_3); 2.02 s, 3 H (CH_3); 3.97 d, 1 H, *J* = 17.6 (CH_2); 4.15 q, 2 H, *J* = 7.2 (ethyl CH_2); 5.03 d, 1 H, *J* = 17.6 (CH_2); 7.56 bm, 6 H (H-5, H-6, H-7, H-3′, H-4′, H-5′); 8.02 m, 1 H (H-4); 8.13 m, 2 H (H-2′, H-6′).

N-Acetyl-*N*-(2-benzoyl-1-benzofuran-3-yl)glycine (**6c**)

A suspension of **6a** (1.85 g, 5 mmol) in a solution of sodium hydroxide (1.6 g, 40 mmol) in methanol (50 ml) and water (30 ml) was stirred at room temperature for 2 h. The mixture was introduced onto a column of Zerolite 220 (40 g) in H cycle and the column was washed with 50% aqueous methanol. The fractions containing the product were evaporated and the residue was crystallized from ethanol to give **6c** monohydrate (1.4 g, 83%) as yellowish crystals; m.p. 87–90 °C. For $C_{19}H_{17}NO_6$ (355.4) calculated: 64.22% C, 4.82% H, 3.94% N; found: 64.11% C, 5.01% H, 3.88% N. ^{1}H NMR ($CDCl_3$): 2.01 s, 3 H (CH_3); 4.03 d, 1 H, *J* = 17.6 (CH_2); 4.94 d, 1 H, *J* = 17.6 (CH_2); 7.42–7.66 bm, 6 H (H-5, H-6, H-7, H-3′, H-4′, H-5′); 7.96 d, 1 H, *J* = 8.0 (H-4); 8.13 bd, 2 H, *J* = 7.2 (H-2′, H-6′).

Ethyl *N*-(2-Benzoyl-1-benzofuran-3-yl)-*N*-(ethoxycarbonyl)glycinate (**6b**)

A mixture of **5b** (1.55 g, 5 mmol), potassium carbonate (1.4 g, 10 mmol), ethyl bromoacetate (1.0 g, 6 mmol), and butanone (30 ml) was refluxed for 30 h. Then additional potassium carbonate (0.5 g, 4 mmol) and ethyl bromoacetate (0.5 g, 3 mmol) were added and the mixture was refluxed for 12 h (TLC). The insoluble portion was filtered off, the filtrate was evaporated and the residue was purified by flash chromatography (silica gel, petroleum ether–acetone, 10 : 1) followed by crystallization from hexane to give **6b** as white crystals (0.95 g, 48%); m.p. 77–79 °C. For $C_{22}H_{21}NO_6$ (395.4) calculated: 66.83% C, 5.35% H, 3.54% N; found: 66.54% C, 5.01% H, 3.76% N. ^{1}H NMR ($CDCl_3$): 1.20 t, 3 H, *J* = 7.2 (ethyl CH_3); 1.35 t, 3 H, *J* = 7.2 (ethyl CH_3); 4.30 m, 4 H (ethyl CH_2); 4.48 s, 2 H (CH_2); 7.32 ddd, 1 H, *J* = 8.0, 6.0, 1.6 (H-4′); 7.40–7.55 m, 5 H (H-5, H-6, H-7, H-3′, H-5′); 7.88 m, 1 H (H-4); 8.13 m, 2 H (H-2′, H-6′).

N-(2-Benzoyl-1-benzofuran-3-yl)-*N*-(ethoxycarbonyl)glycine (**6d**)

An aqueous solution (5 ml) of sodium hydroxide (1 g, 25 mmol) was added to a stirred solution of compound **6b** (1 g, 2.5 mmol) in methanol (25 ml) and the mixture was stirred at room temperature for 24 h. The residue after evaporation was dissolved in water (30 ml) and acidified with acetic acid. The separated insoluble portion was extracted with chloroform (5 × 25 ml) and the extract was dried with anhydrous magnesium sulfate. The residue after evaporation was purified by flash chromatography on silica gel (dichloromethane–methanol, 20 : 1) and crystallization from cyclohexane to give **6d** (0.5 g, 68%) as slightly yellowish crystals; m.p. 112–115 °C. For $C_{20}H_{17}NO_6$ (367.4) calculated: 65.39% C, 4.66% H, 3.81% N; found: 65.12% C, 5.01% H, 3.55% N. ^{1}H NMR ($CDCl_3$): 1.06 t, 3 H, *J* = 7.1 (CH_3); 4.14 q, 2 H, *J* = 7.1 (CH_2); 4.42 s, 2 H (CH_2); 7.25–7.65 m, 5 H (H-5, H-6, H-7, H-3′, H-4′, H-5′); 7.85 m, 1 H (H-4); 8.18 m, 2 H (H-2′, H-6′).

N-(2-Benzoyl-1-benzofuran-3-yl)glycine (**6e**)

The same reaction mixture described above in the preparation of **6d** was refluxed for 24 h, the reaction mixture was cooled and left in a refrigerator overnight. The insoluble portion was filtered off and crystallized from acetone–water (4 : 1) to give sodium salt of **6e** (0.6 g, 76%) as yellow crystals; m.p. 228–233 °C. A sample was dissolved in water and acidified with acetic acid, the precipitate was filtered off and crystallized from ethanol to give **6e** as yellow crystals; m.p. 218–220 °C. For $C_{17}H_{13}NO_4$ (295.3) calculated: 69.15% C, 4.44% H, 4.74% N; found: 68.72% C, 4.65% H, 4.27% N. ^{1}H NMR (DMSO-d_6): 2.52 bs, 1 H (NH or COOH); 4.60 d, 2 H, *J* = 5.8 (CH_2); 7.32 m, 1 H (H-4′); 7.47–7.70 m, 5 H (H-5, H-6, H-7, H-3′, H-5′); 7.98 d, 1 H, *J* = 7.8 (H-4); 8.12 d, 2 H, *J* = 7.8 (H-2′, H-6′).

Ethyl *N*-(2-Benzoyl-1-benzofuran-3-yl)-*N*-methylcarbamate (**6f**)

A mixture of compound **5b** (2.8 g, 10 mmol), potassium carbonate (5 g, 36 mmol), iodomethane (2 ml), and acetonitrile (50 ml) was refluxed for 24 h. The insoluble portion was filtered off, washed with acetonitrile and the combined filtrates were evaporated. The residue was crystallized from hexane to give **6f** (2.5 g, 77%); m.p. 79–81 °C. For $C_{19}H_{17}NO_4$ (323.4) calculated: 70.58% C, 5.30% H, 4.33% N; found: 70.20% C, 5.38% H, 4.22% N. ^{1}H NMR ($CDCl_3$): 1.13 t, 3 H, *J* = 7.2 (ethyl CH_3); 3.26 s, 3 H (CH_3); 4.11 q, 2 H, *J* = 7.2 (CH_2); 7.33 td, 1 H, *J* = 7.3, 1.4 (H-4′); 7.44–7.67 m, 6 H (H-4, H-5, H-6, H-7, H-3′, H-5′); 8.02 d, 2 H, *J* = 7.2 (H-2′, H-6′).

N-Methyl-(2-benzoyl-1-benzofuran-3-yl)amine (**6g**)

An aqueous solution (10 ml) of sodium hydroxide (3 g, 75 mmol) was added to a stirred solution of compound **6f** (1 g, 3.1 mmol) in ethanol (20 ml) and the mixture was refluxed for 40 h. The residue after evaporation was crystallized from propan-2-ol to give **6g** (0.35 g, 45%) as yellow-brown crystals; m.p. 115–116 °C. For $C_{16}H_{13}NO_2$ (251.3) calculated: 76.48% C, 5.21% H, 5.57% N; found: 76.22% C, 5.05% H, 5.19% N. ^{1}H NMR ($CDCl_3$): 3.46 s, 3 H (CH_3); 7.22 dd, 1 H, *J* = 8.4, 0.9 (H-7); 7.40–7.57 m, 5 H (H-5, H-6, H-3′, H-4′, H-5′); 8.00 d, 1 H, *J* = 8.1 (H-4); 8.20 m, 2 H (H-2′, H-6′); 8.30 bs, 1 H (NH).

3-Amino-2-benzoyl-1-benzofuran-7-ol (**4d**)

A solution of boron tribromide (2.5 g, 10 mmol) in dichloromethane (10 ml) was added dropwise to a solution of **4b** (1 g, 3.7 mmol), the mixture was stirred at room temperature for 7 h and left to stand overnight. The mixture was poured into an ice–water mixture (800 ml) and extracted with diethyl ether. The extract was dried with anhydrous magnesium sulfate, the residue after evaporation was crystallized from methanol and the formed crystals were thoroughly dried in a desiccator over P_2O_5 to give (0.4 g, 42%); m.p. 234–237 °C (methanol). For $C_{15}H_{11}NO_3$ (253.3) calculated: 71.14% C, 4.38% H, 5.53% N; found: 71.32% C, 4.27% H, 5.27% N. UV, λ (log ε): 204 (4.22), 251 (4.27), 322 (3.80), 385 (4.22). ^{1}H NMR (DMSO-d_6): 5.30 bs, 3 H (NH_2, OH); 6.99 dt, 1 H, *J* = 7.7, 1.6 (H-6); 7.04 t, 1 H, *J* = 7.7 (H-5); 7.35 dd, 1 H, *J* = 7.4, 1.6 (H-4); 7.52 m, 3 H (H-3′, H-4′, H-5′); 8.27 m, 2 H (H-2′, H-6′).

2-(4-Hydroxybenzoyl)-1-benzofuran-3-amine (**4e**)

According to the procedure described for **4d**, compound **4c** was demethylated to give 87% of **4e** as yellow crystals; m.p. 202–205 °C (methanol). For $C_{15}H_{11}NO_3$ (253.3) calculated: 71.14% C, 4.38% H, 5.53% N; found: 70.77% C, 4.01% H, 5.72% N. UV, λ (log ε): 204 (4.15), 253 (4.01), 244 (3.99), 300 (3.94), 311 (3.94), 379 (4.29). ^{1}H NMR ($CDCl_3$): 5.30 bs, 2 H (NH_2); 6.93 dt, 2 H, *J* = 8.8, 2.1 (H-3′, H-5′); 7.26–7.33 m, 1 H (H-6); 7.53 m, 2 H (H-5, H-7); 8.03 dt, 1 H, *J* = 7.9, 1.1 (H-4); 8.11 dt, 2 H, *J* = 8.8, 2.1 (H-2′, H-6′).

Ethyl [(3-Amino-2-benzoyl-1-benzofuran-7-yl)oxy]acetate (**7a**)

A stirred mixture of **4d** (2.5 g, 10 mmol), potassium carbonate (2.8 g, 20 mmol), ethyl bromoacetate (2.5 g, 15 mmol), and butanone (60 ml) was refluxed for 12 h (TLC). The insoluble portion was filtered off, the filtrate was evaporated and the residue was crystallized from ethanol to give yellowish crystals (3.1 g, 91%); m.p. 121–122 °C. For $C_{19}H_{17}NO_5$ (339.4) calculated: 67.25% C, 5.05% H, 4.13% N; found: 66.87% C, 5.37% H, 3.99% N. ^{1}H NMR ($CDCl_3$): 1.26 t, 3 H, *J* = 7.2 (CH_3); 4.24 q, 2 H, *J* = 7.2 (ethyl CH_2); 4.89 s, 2 H (CH_2); 6.00 bs, 2 H (NH_2); 6.90 dd, 1 H, *J* = 7.7, 0.9 (H-6); 7.14 t, 1 H, *J* = 8.1 (H-5); 7.25 dd, 1 H, *J* = 8.1, 0.9 (H-4); 7.45–7.60 bm, 3 H (H-3′, H-4′, H-5′); 8.25 dd, 2 H, *J* = 8.2, 1.4 (H-2′, H-6′).

Ethyl {4-[(3-Amino-1-benzofuran-2-yl)carbonyl]phenoxy}acetate (**7d**)

Compound **4e** was alkylated according to the procedure described for the preparation of **7a**. The crude mixture was purified by flash chromatography (petroleum ether–ethyl acetate, 8 : 2) to give, after crystallization from ethanol, compound **7d** (68%) as yellow crystals; m.p. 87–90 °C. For $C_{19}H_{17}NO_5$ (339.4) calculated: 67.25% C, 5.05% H, 4.13% N; found: 67.02% C, 4.77% H, 4.28% N. ^{1}H NMR ($CDCl_3$): 1.31 t, 3 H, *J* = 7.2 (CH_3); 4.29 q, 2 H, *J* = 7.2 (ethyl CH_2); 4.71 s, 2 H (CH_2); 6.00 bs, 2 H (NH_2); 7.02 dt, 2 H, *J* = 8.8, 2.1 (H-3′, H-5′); 7.25 ddd, 1 H (H-6); 7.48 m, 2 H (H-5, H-7); 7.62 dt, 1 H, *J* = 7.9, 1.2 (H-4); 8.30 dt, 2 H, *J* = 8.6, 2.0 (H-2′, H-6′).

[(3-Amino-2-benzoyl-1-benzofuran-7-yl)oxy]acetic Acid (**7b**)

An aqueous solution (30 ml) of sodium hydroxide (1.6 g, 40 mmol) was added to a stirred suspension of **7a** (1.7 g, 5 mmol) in methanol (50 ml) and the mixture was stirred at room temperature for 24 h. The solution was acidified with dilute hydrochloric acid, the mixture was cooled and the insoluble portion was filtered off. Crystallization from ethanol provided **7b** (0.75 g, 48%) as yellowish crystals; m.p. 191–195 °C. For $C_{17}H_{13}NO_5$ (311.3) calculated: 65.59% C, 4.21% H, 4.50% N; found: 65.33% C, 4.48% H, 4.77% N. ^{1}H NMR (DMSO-d_6): 4.90 s, 2 H (CH_2); 7.08 bd, 1 H, J = 8.0, 0.9 (H-6); 7.19 t, 1 H, J = 7.8 (H-4′); 7.30 bs, 2 H (NH_2); 7.59 m, 4 H (H-4, H-5, H-3′, H-5′); 8.12 dd, 2 H, J = 7.8, 2.2 (H-2′, H-6′).

{4-[(3-Amino-1-benzofuran-2-yl)carbonyl]phenoxy}acetic Acid (**7e**)

According to the procedure described for the preparation of **7b**, compound **7d** was hydrolyzed to give **7e** (54%) as yellowish crystals; m.p. 215–218 °C (ethanol). For $C_{17}H_{13}NO_5$ (311.3) calculated: 65.59% C, 4.21% H, 4.50% N; found: 65.39% C, 4.36% H, 4.37% N. ^{1}H NMR (DMSO-d_6): 4.40 s, 2 H (CH_2); 7.10 dt, 2 H, J = 9.1, 2.7 (H-3′, H-5′); 7.26 bs, 2 H (NH_2); 7.31 m, 1 H (H-6); 7.53–7.59 m, 2 H (H-5, H-7); 8.04 d, 1 H, J = 7.9 (H-4); 8.18 dt, 2 H, J = 9.1, 2.7 (H-2′, H-6′).

2-Benzoyl-7-[3-(dimethylamino)propoxy]-1-benzofuran-3-amine (**7c**)

A stirred mixture of **4d** (2.5 g, 10 mmol), potassium carbonate (2.8 g, 20 mmol), 3-(dimethylamino)propyl chloride hydrochloride (2.0 g, 12.7 mmol), and 2-butanone (80 ml) was refluxed for 30 h (TLC monitoring). The insoluble portion was filtered off, the solid was washed with hot butanone and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether–acetone from 7 : 3 to 1 : 1) followed by crystallization from hexane to give **7c** as yellowish crystals (1.8 g, 53%); m.p. 87–91 °C. For $C_{20}H_{22}N_2O_3$ (338.4) calculated: 70.99% C, 6.55% H, 8.28% N; found: 71.25% C, 6.88% H, 8.30% N. ^{1}H NMR ($CDCl_3$): 2.08 m, 2 H (CH_2); 2.31 s, 6 H (CH_3); 2.58 t, 2 H, J = 7.3 (CH_2N); 4.27 t, 2 H, J = 6.3 (CH_2O); 5.96 bs, 2 H (NH_2); 7.01 dd, 1 H, J = 7.0, 1.9 (H-6); 7.16 t, 1 H, J = 7.8, 7.0 (H-5); 7.20 dd, 1 H, J = 7.8, 1.9 (H-4); 7.52 m, 3 H (H-3′, H-4′, H-5′); 8.29 m, 2 H (H-2′, H-6′).

A part of the base was converted to hydrogen maleate; m.p. 197–199 °C. For $C_{24}H_{26}N_2O_7$ (454.5) calculated: 63.43% C, 5.77% H, 6.16% N; found: 63.76% C, 6.01% H, 6.39% N.

2-{4-[3-(Dimethylamino)propoxy]benzoyl}-1-benzofuran-3-amine (**7f**)

According to the procedure described for the preparation of **7c**, using the same amount of **4e**, compound **7f** was prepared as yellow crystalline monohydrate (2.1 g, 59%); m.p. 73–78 °C (hexane). For $C_{20}H_{24}N_2O_4$ (356.4) calculated: 67.40% C, 6.79% H, 7.86% N; found: 67.19% C, 7.17% H, 7.65% N. ^{1}H NMR ($CDCl_3$): 2.03 q, 2 H (CH_2); 2.31 s, 6 H (CH_3); 2.53 t, 2 H, J = 7.3 (CH_2N); 4.13 t, 2 H, J = 6.3 (CH_2O); 5.95 bs, 2 H (NH_2); 7.01 d, 2 H, J = 9.0 (H-3′, H-5′); 7.27 ddd, 1 H, J = 8.1, 6.6, 1.6 (H-6); 7.49 m, 2 H (H-5, H-7); 7.62 d, 1 H, J = 7.8 (H-4); 8.29 d, 2 H, J = 9.0 (H-2′, H-6′).

A part of the base was converted to hydrogen maleate; m.p. 137–139 °C. For $C_{24}H_{26}N_2O_7$ (454.5) calculated: 63.43% C, 5.77% H, 6.16% N; found: 63.73% C, 5.91% H, 6.16% N.

Preparation of 2-(Pyridylcarbonyl)-1-benzofuran-3-amines **10a**–**10c.** General Procedure

A mixture of 2-hydroxybenzonitrile (**2a**; 10 mmol) and potassium carbonate (3.5 g, 25 mmol) in DMF (20 ml) was stirred at room temperature for 1 h. Then a solution of hydrobromide of an appropriate 2-bromo-1-pyridylethan-1-one **9** (10 mmol) in DMF (10 ml) was added and the mixture was stirred at room temperature for 24 h (**10a**, **10c**) or at 80 °C for 5 h (**10b**). The mixture was poured into water (500 ml), extracted with ethyl acetate and the extract was dried with anhydrous magnesium sulfate. The crude product was then crystallized from a suitable solvent to give pure compounds.

2-(2-Pyridylcarbonyl)-1-benzofuran-3-amine (**10a**). Yield 41%. Brown crystals, m.p. 141–144 °C (ethanol). For $C_{14}H_{10}N_2O_2$ (238.3) calculated: 70.58% C, 4.23% H, 11.76% N; found: 70.33% C, 4.55% H, 11.51% N. ^{1}H NMR (DMSO-d_6): 7.28 ddd, 1 H, J = 8.2, 7.0, 1.1 (H-5); 7.45–7.75 m, 5 H (H-6, H-7, H-5′, NH_2); 8.00–8.18 bm, 3 H (H-4, H-3′, H-4′); 8.78 bd, 1 H, J = 8.6 (H-6′).

2-(3-Pyridylcarbonyl)-1-benzofuran-3-amine (**10b**). Yield 37%. Brown crystals, m.p. 153–159 °C (ethanol). For $C_{14}H_{10}N_2O_2$ (238.3) calculated: 70.58% C, 4.23% H, 11.76% N; found: 70.21% C, 4.07% H, 11.55% N. ^{1}H NMR ($CDCl_3$, 60 °C): 6.17 bs, 2 H (NH_2); 7.25 ddd, 1 H, J = 8.0, 7.0, 1.1 (H-5); 7.48 m, 3 H (H-6, H-7, H-5′); 7.64 bd, 1 H, J = 8.0, 1.1 (H-4); 8.49 dt, 1 H, J = 8.0, 1.4 (H-4′); 8.77 bd, 1 H, J = 8.8 (H-6′); 9.50 bs, 1 H (H-2′).

2-(4-Pyridylcarbonyl)-1-benzofuran-3-amine (**10c**). Yield 52%. Ochre crystals, m.p. 204–206 °C (ethanol). For $C_{14}H_{10}N_2O_2$ (238.3) calculated: 70.58% C, 4.23% H, 11.76% N; found: 70.21% C, 4.66% H, 11.62% N. ^{1}H NMR (DMSO-d_6): 7.05–7.40 m, 4 H (arom. H); 7.44 m, 1 H (H-4); 7.98 m, 3 H (arom. H); 8.78 bs, 2 H (NH_2).

Preparation of 2-(Pyridylcarbonyl)-1-benzothiophene-3-amines **10d**–**10f**. General Procedure

A mixture of 2-sulfanylbenzonitrile (**8**; 1. 4 g, 10 mmol) and potassium carbonate (3.5 g, 25 mmol) in acetone (40 ml) was stirred at room temperature for 1 h. Then hydrobromide of an appropriate 2-bromo-1-pyridylethan-1-one **9** (10 mmol) was added in several portions and the mixture was stirred at room temperature for 5 h and then refluxed for 24 h. The mixture was evaporated to dryness, mixed with water and extracted with ethyl acetate. The extract was dried with anhydrous magnesium sulfate and the residue after evaporation was crystallized from a suitable solvent to give pure compounds **10d**–**10f**.

2-(2-Pyridylcarbonyl)-1-benzothiophen-3-amine (**10d**). Yield 65%. Brownish crystals, m.p. 137–139 °C (ethanol). For $C_{14}H_{10}N_2OS$ (254.3) calculated: 66.12% C, 3.96% H, 11.02% N, 12.61% S; found: 65.78% C, 4.11% H, 10.87% N, 12.39% S. ^{1}H NMR ($CDCl_3$): 7.30–7.53 m, 4 H (H-5, H-7, H-3′, H-4′); 7.88 td, 1 H, J = 7.6, 1.7 (H-5′); 8.25 bd, 1 H, J = 8.1 (H-6′); 8.79 bs, 2 H (NH_2).

2-(3-Pyridylcarbonyl)-1-benzothiophen-3-amine (**10e**). Yield 21%. Yellow crystals, m.p. 164–166 °C (toluene). For $C_{14}H_{10}N_2OS$ (254.3) calculated: 66.12% C, 3.96% H, 11.02% N, 12.61% S; found: 65.92% C, 4.22% H, 10.77% N, 12.44% S. ^{1}H NMR ($CDCl_3$): 7.14 bs, 2 H (NH_2); 7.36–7.46 m, 2 H (H-5, H-7); 7.52 td, 1 H, J = 8.1, 1.1 (H-5′); 7.71–7.76 m, 2 H (H-4, H-6); 8.17 ddd, 1 H, J = 8.1, 2.4, 1.8 (H-4′); 8.75 dd, 1 H, J = 9.8, 1.8 (H-6′); 9.13 d, 1 H, J = 1.8 (H-2′).

2-(4-Pyridylcarbonyl)-1-benzothiophen-3-amine (**10f**). Yield 65%. Ochre crystals, m.p. 230–232 °C (toluene). For $C_{14}H_{10}N_2OS$ (254.3) calculated: 66.12% C, 3.96% H, 11.02% N, 12.61% S; found: 65.93% C, 3.77% H, 11.13% N, 12.38% S. ^{1}H NMR ($CDCl_3$): 7.39 ddd, 1 H,

J = 8.2, 7.0, 1.2 (H-6); 7.52 ddd, 1 H, *J* = 8.2, 7.0, 1.2 (H-5); 7.65–7.72 m, 3 H (H-7, H-3′, H-5′); 8.00 bs, 2 H (NH_2); 8.08 d, 1 H, *J* = 8.1 (H-4); 8.76 bd, 2 H, *J* = 4.7 (H-2′, H-6′).

2-Benzoyl-3-(bromomethyl)-1-benzofuran (**12**)

N-Bromosuccinimide (3.8 g, 21.3 mmol) and dibenzoyl peroxide (0.21 g, mmol) were added to a solution of 2-benzoyl-3-methylbenzofuran (**11**; 5 g, 21 mmol) in tetrachloromethane (100 ml) and the mixture was refluxed for 5 h. The residue after evaporation was crystallized from hexane to give the title compound (5 g, 75%); m.p. 96–98 °C. For $C_{16}H_{11}BrO_2$ (315.2) calculated: 60.98% C, 3.52% H, 25.35% Br; found: 60.64% C, 3.25% H, 25.78% Br. ^{1}H NMR ($CDCl_3$): 5.08 s, 2 H (CH_2); 7.40 ddd, 1 H, *J* = 7.9, 6.6, 1.6 (H-6); 7.49–7.68 m, 5 H (H-5, H-7, H-3′, H-4′, H-5′); 7.88 ddd, 1 H, *J* = 7.8, 1.3, 0.8 (H-4); 8.13 m, 2 H (H-2′, H-6′).

2-Benzoyl-3-[(dimethylamino)methyl]-1-benzofuran Hydrogen Maleate (**13a**)

2-Benzoyl-3-(bromomethyl)-1-benzofuran (**12**; 1.6 g, 5 mmol) was dissolved in a solution of dimethylamine (1.2 g, 27 mmol) in ethanol (15 ml) and the mixture was stirred at room temperature for 1 h. The mixture was evaporated, the residue was dissolved in ethyl acetate (25 ml) and the solution was washed with brine. The extract was dried with anhydrous magnesium sulfate and the oily residue (1.5 g) was transformed to its hydrogen maleate, which was crystallized from ethanol to give **13a** (1.9 g, 48%) as white crystals; m.p. 146–148 °C. For $C_{22}H_{21}NO_6$ (395.4) calculated: 66.83% C, 5.35% H, 3.54% N; found: 66.57% C, 5.22% H, 3.71% N. ^{1}H NMR of the corresponding base ($CDCl_3$): 2.32 s, 6 H (CH_3); 4.04 s, 2 H (CH_2); 7.38 m, 1 H (H-6); 7.45–7.64 m, 5 H (H-5, H-7, H-3′, H-4′, H-5′); 8.05 m, 3 H (H-4, H-2′, H-6′).

2-Benzoyl-3-[(1-methylpiperazin-4-yl)methyl]-1-benzofuran Hydrogen Maleate (**13b**)

2-Benzoyl-3-(bromomethyl)-1-benzofuran (**12**; 1.6 g, 5 mmol) was added to a stirred solution of 1-methylpiperazine (1.1 g, 11 mmol) in acetone (25 ml) and the mixture was stirred at room temperature for 2 h. The mixture was evaporated, the residue was dissolved in ethyl acetate (30 ml) and the solution was washed successively with a 10% solution of sodium carbonate, water, and brine. The extract was dried with anhydrous magnesium sulfate and evaporated to give a slowly crystallizing oil (1.6 g, 96%). A small sample was crystallized from hexane to give slightly yellowish crystals; m.p. 91–93 °C. For $C_{21}H_{22}N_2O_2$ (334.4) calculated: 75.42% C, 6.63% H, 8.38% N; found: 75.07% C, 6.45% H, 8.72% N. ^{1}H NMR ($CDCl_3$): 2.28 s, 3 H (N-CH_3); 2.44 bm, 4 H (piperazine CH_2); 2.58 bm, 4 H (piperazine CH_2); 4.11 s, 2 H (CH_2); 7.32 ddd, 1 H, *J* = 7.9, 6.7, 1.4 (H-6); 7.43–7.65 m, 5 H (H-5, H-7, H-3′, H-4′, H-5′); 8.07 m, 2 H (H-2′, H-6′); 8.12 ddd, 1 H, *J* = 7.9, 1.3, 0.8 (H-4).

The residue (1.4 g) was transformed to hydrogen maleate, which was crystallized from 50% aqueous methanol to give slightly yellowish crystals (0.7 g, 36%); m.p. 196–199 °C. For $C_{25}H_{26}N_2O_6$ (450.5) calculated: 66.66% C, 5.82% H, 6.22% N; found: 66.48% C, 5.97% H, 6.02% N.

2-Benzoyl-3-{[(1-methylpiperidin-4-yl)sulfanyl]methyl}-1-benzofuran Hydrogen Maleate (**13c**)

A mixture of 1-methylpiperidin-4-thiol (0.8 g, 6.1 mmol), potassium carbonate (1.5 g, 10 mmol), and acetone (30 ml) was stirred at room temperature for 30 min. Then 2-benzoyl-3-(bromomethyl)benzofuran (1.7 g, 5.4 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was evaporated, the residue was mixed with water and extracted with ethyl acetate (4 × 25 ml). The combined extracts were washed with brine and water, dried with anhydrous magnesium sulfate and the oily residue after evaporation (1.8 g) was transformed to hydrogen maleate, which after crystallization from propan-2-ol provided white crystals (2.0 g, 48%); m.p. 148–152 °C. For $C_{26}H_{27}NO_6S$ (481.6) calculated: 64.85% C, 5.65% H, 2.91% N, 6.66% S; found: 64.47% C, 5.58% H, 2.84% N, 6.87% S. ^{1}H NMR ($CDCl_3$): 1.75 m, 2 H (piperidine H-3 and H-5); 1.9 m, 4 H (piperidine H-2, H-3, H-5, and H-6); 2.22 s, 3 H (N-CH_3); 2.80 m, 3 H (piperidine H-2, H-4, and H-6); 4.32 s, 2 H (CH_2); 7.15–7.65 bm, 6 H (arom. H); 7.98 bd, 1 H (H-4); 8.05–8.20 m, 2 H (H-2′, H-6′).

Biological Evaluation

Hot-plate test. The hot-plate test was used to measure the response latencies according to the method described earlier[26], with minor modifications. All animals (male NMRI mice) were selected on the basis of their reactivity in the model. The selected animals were placed into a glass cylinder and the plate temperature was maintained at 54 °C. The time necessary for appearance of the licking reflex of the forepaws or jumping was recorded. The measurement was done 30 and 60 min after oral administration of the tested compound and the results were expressed as prolongation of the licking latencies (%). Compounds were considered to have interesting antinociceptive properties if they produced a significant increase in threshold ($p < 0.05$).

Acetic acid-induced writhing. Writhing was induced by intraperitoneal injection of 0.2 ml of 0.7% solution of acetic acid to male NMRI mice 30 min after administration of the tested compound[27]. Writhings were counted for 20 min, compared with the control and expressed as decrease in the stretching movements (%).

Tail-flick test. A slightly modified method of D'Amour and Smith[28] was used. The animals (male Wistar–Hannover rats) were placed in a Ugo Basile (Varese, Italy) apparatus and the predrug latency of the tail removal from a radiant heat source (light beam focused 3 cm from the end of the tail) was determined twice for each rat. The animals were then administered a tested compound (30 mg/kg) and were again placed in the holding apparatus. Thirty and sixty minutes later, a postdrug latency was measured and expressed as a decrease in the latency of the control (%).

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