SYNTHESIS AND ANALGESIC ACTIVITY OF SOME 1-BENZOFURANS, 1-BENZOTHIOPHENES AND INDOLES

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3-Unsubstituted 1-benzofurans **1e** and **1f**, 3-methyl-1-benzofurans **1a**–**1d**, and 3-amino-1-benzofurans **2a**–**2l**, as well as 3-amino-1-benzothiophenes **3a**, **3b** and 3-aminoindoles **4a**–**4f**, **11a**, and **11b** were prepared and tested as analgesics. The 3-amino-1-benzofurans **2** were prepared from the corresponding 2-hydroxybenzonitriles **5** and phenacyl bromides **6** *via* intermediates **7**. Similar treatment of 2-sulfanylbenzonitrile (**8**) provided 3-amino-1-benzothiophenes **3**. Appropriately substituted 2-aminobenzonitriles **9** then provided N-substituted 3-aminoindoles **4**. 1-(Ethoxycarbonyl)indoles **4e** and **4f** were successfully deprotected giving indoles **11a** and **11b**, respectively.

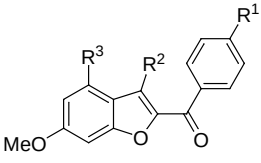
Key words: Benzofurans; Benzothiophenes; Indoles; Xanthoxyline analogs; Analgesics.

Antinociceptive activity of 2-(4-bromobenzoyl)-4,6-dimethoxy-3-methyl-1-benzofuran (**1a**) has recently been reported[1,2]. This compound, which was prepared from naturally occurring 1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (xanthoxyline), represents a new structural type exerting analgesic effect. Quite unusually, no other 1-benzofuran derivative of the active compound **1a** was mentioned and therefore we decided to prepare the compound itself and also its derivatives **1b**–**1f**.

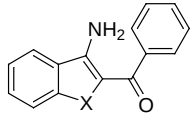
There are several well-documented methods of preparation of 3-unsubstituted and 3-methyl-2-benzoyl-1-benzofurans[3]. Synthesis of compound **1d** from the corresponding 6-hydroxy derivative has been published[4]. A low yield of compound **1f** was formed, in addition to several other products, during formylation of 2-(3,5-dimethoxyphenoxy)-1-phenylethan-1-one[5]. We decided to prepare all the compounds **1** from appropriate 2-hydroxyacetophenones or 2-hydroxybenzaldehydes and 2-bromo-1-phenylethan-1-ones by a modification of the published proce-

dure[6]. First we decided to prepare **1a** to prove the reported activity. The described methods of preparation of xanthoxyline are mostly nonselective and include the Friedel–Crafts acetylation of 3,5-dimethoxyphenole[7] or methylation of 1-(2,4,6-trihydroxyphenyl)ethan-1-one[8,9] under various conditions. Demethylation of 1-(2,4,6-trimethoxyphenyl)ethan-1-one with aluminum chloride is also nonselective providing a mixture of all possible mono-, di-, and trihydroxy derivatives[10]. We applied a published procedure[11] of selective demethylation of *ortho*-methoxy aromatic ketones. This procedure monodemethylated 1-(2,4,6-trimethoxyphenyl)ethan-1-one to give acceptable yields of xanthoxyline. This compound treated with 2-bromo-1-(4-bromophenyl)ethan-1-one in the presence of potassium hydroxide provided **1a**. Since the reported analgesic activity of **1a** was proved, compounds **1b**–**1d** were prepared from the corresponding 1-(2-hydroxyphenyl)ethan-1-ones by the same procedure. Similarly, starting from 2-hydroxy-4,6-dimethoxybenzaldehyde and the corresponding 2-bromo-1-phenylethan-1-ones, compounds **1e** and **1f** were prepared. In this case, the use of potassium carbonate in butan-2-one under reflux was sufficient for a smooth reaction.

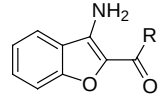
Analgesic screening found compound **1a** the most active of the series. However, all these compounds were found active only for i.p. or s.c. application and only slightly active or inactive after p.o. application. In order to obtain compounds with better pharmacological profile, we decided to prepare some more different analogs of **1a**. First we decided to prepare 3-amino-substituted 1-benzofurans **2**, 1-benzothiophenes **3**, and indoles **4**, since we expected that these compounds could form water-soluble salts.



1	R^1	R^2	R^3
a	Br	Me	MeO
b	H	Me	MeO
c	Br	Me	H
d	H	Me	H
e	Br	H	MeO
f	H	H	MeO



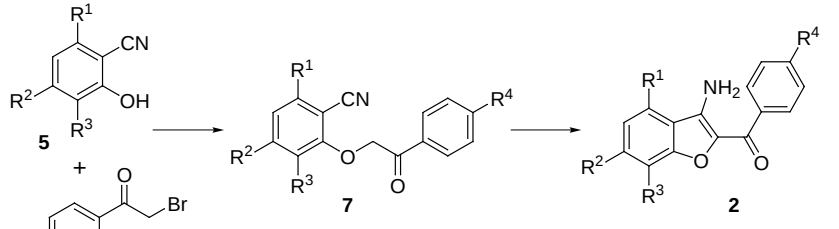
2, X = O
3, X = S
4, X = NR



12	R
a	Me
b	OEt

Synthesis of 1-benzofuran **2a** starting from 2-hydroxybenzonitrile (**5a**) and **6a** has been described[12,13]. When the reaction was done with sodium

hydroxide in 2-methoxyethan-1-ol, the intermediate benzoylmethoxy derivative **7a** was isolated and characterized[12]. Using potassium carbonate in acetone led directly to 1-benzofuran **2a**. We usually prepared 1-benzofuran derivatives **2a**–**2l** from the appropriate benzonitrile **5** and bromo derivative **6** *via* the corresponding benzoylmethoxy derivatives **7**, basically as described[12] for **2a**. We used sodium hydroxide in 2-methoxyethan-1-ol or sodium hydrogencarbonate in DMF at room temperature to get compounds **7**, which were after isolation cyclized with sodium methoxide or potassium *tert*-butoxide in methanol at room temperature to give good yields of compounds **2** (Scheme 1). Starting 2-hydroxy-3-methoxybenzonitrile (**5b**) and 2-hydroxy-4,6-dimethoxybenzonitrile (**5c**) were prepared from the appropriate commercially available benzaldehydes *via* the corresponding oximes, which were dehydrated *in situ* with formic acid to the required benzonitriles[14].



5	R^1	R^2	R^3
a	H	H	H
b	H	H	MeO
c	MeO	MeO	H

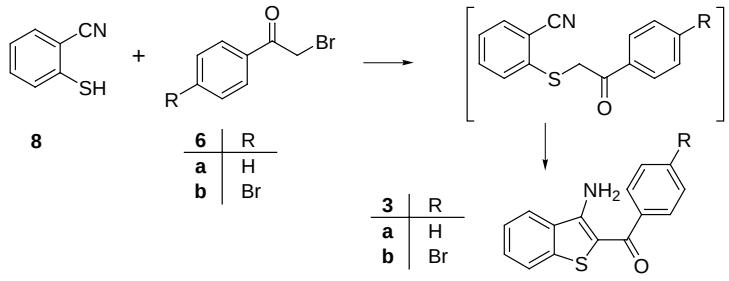
6	R^4
a	H
b	Br
c	Ph
d	2,4-$F_2C_6H_3$

2, 7	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	H	Br
c	H	H	H	Ph
d	H	H	H	2,4-$F_2C_6H_3$
e	H	H	MeO	H
f	H	H	MeO	Br
g	H	H	MeO	Ph
h	H	H	MeO	2,4-$F_2C_6H_3$
i	MeO	MeO	H	H
j	MeO	MeO	H	Br
k	MeO	MeO	H	Ph
l	MeO	MeO	H	2,4-$F_2C_6H_3$

SCHEME 1

Formation of **3a** from 2-sulfanylbenzonitrile (**8**) and 2-chloro-1-phenylethan-1-one in an aqueous sodium hydroxide solution has been reported without any experimental details[15]. We prepared 1-benzothiophene derivatives **3** under analogous conditions described above for the preparation of 1-benzofurans **2**. The reaction of 2-fluorobenzonitrile with phenylmethanethiol provided in good yield starting 2-(benzylsulfanyl)benzonitrile. Similar preparation of this compound from 2-nitrobenzonitrile has

been published[16]. The required 2-sulfanylbenzonitrile (**8**) was prepared by debenzylation of this compound with aluminum chloride. In our hands, this method provided purer product, which did not require distillation, than the described method[17] starting from 2-bromobenzonitrile and ethyl 3-sulfanylpropionate. In the case of 1-benzothiophenes, the expected open intermediates cannot be isolated and the target compounds **3a** and **3b** were directly formed under the used conditions (Scheme 2).

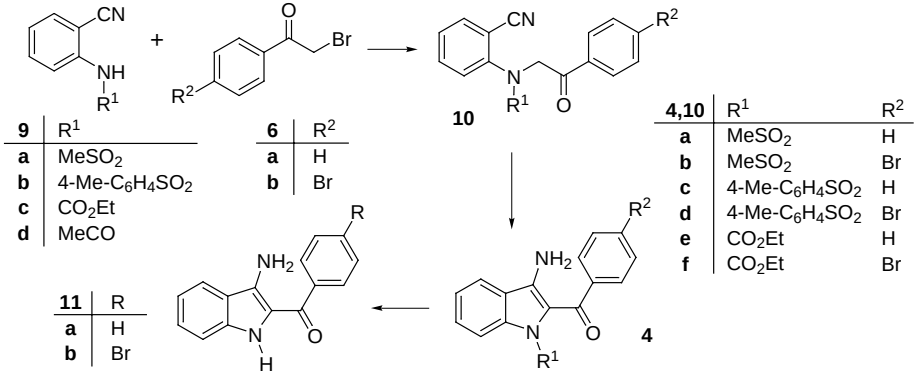


SCHEME 2

The use of addition of an activated CH_2 group to a nitrile functionality for the synthesis of 3-aminoindoles is rare[18]. Our attempts to use N-unsubstituted 2-aminobenzonitrile for similar preparation of indole derivatives failed. The reaction with 2-bromo-1-(4-bromophenyl)ethan-1-one under milder conditions did not proceed; under more harsh conditions, it provided complex mixtures. Therefore, we prepared N-activated derivatives **9a**–**9d** as suitable starting compounds. Reaction of **9a** or **9b** with bromo derivatives **6a** or **6b** provided smoothly intermediates **10**, together with small amounts of the corresponding indoles **4**. The same treatment of **9c** provided directly indoles **4e** and **4f**, respectively. On the other hand, the same reaction of acetyl derivative **9d** under different conditions provided complex mixtures. Compounds **10** were purified by crystallization and then cyclized into indoles **4** with sodium methoxide. With compounds **10c** and **10d**, the use of triethylamine in ethanol provided cleaner reaction mixtures and higher yields of indoles **4c** and **4d**, respectively. We tried to deprotect compounds **4** to get the corresponding N-unsubstituted indoles under various conditions. After several failures we succeeded in deprotection of *N*-ethoxycarbonyl derivatives **4e** and **4f** by alkaline hydrolysis to yield N-unsubstituted indoles **11a** and **11b**, respectively (Scheme 3).

Analogously to compounds **2**, the known 2-acetyl-3-amino-1-benzofuran (**12a**) and ethyl 3-amino-1-benzofuran-2-carboxylate (**12b**) were prepared

from 2-hydroxybenzonitrile (**5a**) and chloroacetone or ethyl bromoacetate, by modifications of the published procedures[12,13].



SCHEME 3

Structures of all new compounds were proved by elemental analysis and NMR spectroscopy. IR and UV spectra of selected compounds were also measured. In these cases, IR spectra showed characteristic vibrations of the functional groups present. UV spectra of all measured 1-benzofurans, 1-benzothiophenes, and indoles were found to exhibit similar patterns.

All the prepared target compounds, *i.e.* 1-benzofurans **1**, **2**, and **12**, 1-benzothiophenes **3** as well as indoles **4** and **11**, 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. Analgesic activity of compounds having at least in one of the tests activity higher than 30% is shown in Table I. It is evident that the model compound **1a** is highly active after subcutaneous application and only slightly active after oral application. The same pattern is observed also with other compounds **1**. In this subset, only compounds having the 4,6-dimethoxy substituents are fairly active. No such pattern can be seen in the group of 3-amino-1-benzofurans **2**, where the good analgesic activity after subcutaneous application was found in compound **2a**, as well as in 7-methoxy derivative **2e** and 4,6-dimethoxy derivative **2k**. Both tested compounds **12a** and **12b**, which do not contain the 2-benzoyl group, were found only slightly active. Also both tested 1-benzothiophenes **3a** and **3b** were only slightly active. No improvement in the analgesic activity was found also in indoles **4**, compound **4f** being the only active N-substituted indole of this group. On the other hand, both N-unsubstituted indoles **11** were active. However, their activity was not quite convincing.

In conclusion, a series of new 1-benzofurans, 1-benzothiophenes, and indoles were synthesized and tested as analgesics. Some of them, *e.g.*, compounds **2a**, **2k**, **4f**, **11a**, and **11b**, are in doses of 30 mg/kg active in the used analgesic models. However, their activity is not high enough 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. IR spectra (KBr) were recorded on a Unicam SP 2006 spectrometer, wavenumbers are given in cm^{-1}. UV spectra were measured on a Shimadzu UV-260 spectrometer in ethanol, wavelengths are given in nm. Flash chromatography was done on 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: 1-(biphenyl-4-yl)-2-bromoethan-1-one[19] (**6c**), 2-bromo-1-(2′,4′-difluorobiphenyl-4-yl)ethan-1-one[20] (**6d**), *N*-(2-cyanophenyl)methanesulfonamide[21] (**9a**), *N*-(2-cyanophenyl)-4-methyl benzenesulfonamide[22] (**9b**), ethyl *N*-(2-cyanophenyl)carbamate[23] (**9c**), and *N*-(2-cyanophenyl)acetamide[24] (**9d**). The known 1-benzofurans **12a** and **12b** were prepared analogously as described in the literature[12,13].

TABLE I
Analgesic activity[a] of active compounds **1**–**4**, **11**

Compound	Hot plate, %	Writhing, %	Tail flick, %
1a	–/63	22/–	–/47
1e	–/27	1/–	–/32
1f	–/7	15/–	–/45
2a	14/39	7/37	–/52
2e	5/44	33/–	–/–
2k	–/44	–/70	–/–
4f	–/29	33/–	1/93
11a	–/27	32/–	10/–
11b	18/17	31/–	3/–

[a] – p.o./s.c., 30 mg/kg.

1-(2-Hydroxy-4,6-dimethoxyphenyl)ethan-1-one

Butyllithium (10 ml of a 2.5 M solution in hexanes, 25 mmol) was added to a toluene solution (25 ml) of 1-methylpiperazine (2.5 g, 25 mmol) under argon at 0 °C and the mixture was stirred at room temperature for 20 min. The mixture was cooled to 0 °C and a solution of 1-(2,4,6-trimethoxyphenyl)ethan-1-one (4.2 g, 20 mmol) in toluene (50 ml) was added dropwise keeping the temperature below 15 °C. After addition of butyllithium (10 ml of a 2.5 M solution in hexanes, 25 mmol), the mixture was stirred at room temperature for 30 min and then at 80 °C for 10 h. The cold mixture was quenched with 5% hydrochloric acid (20 ml) and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with magnesium sulfate, the residue after evaporation (2.7 g) was crystallized twice from hexane to give the required product (2.7 g, 71%) as white crystals; m.p. 84–85 °C (ref.[25] 87 °C). ^{1}H NMR ($CDCl_3$): 2.61 s, 3 H (CH_3); 3.82 s, 3 H (CH_3O); 3.85 s, 3 H (CH_3O); 5.92 d, 1 H, *J* = 2.5 (H-5); 6.06 d, 1 H, *J* = 2.5 (H-3); 14.01 s, 1 H (OH).

Preparation of 2-Benzoyl-3-methyl-1-benzofurans **1a**–**1d**. General Procedure

A solution of an appropriate 2-bromo-1-phenylethan-1-one (10 mmol) in ethanol (20 ml) was added to a stirred solution of 1-(2-hydroxyphenyl)ethan-1-one (10 mmol) and potassium hydroxide (1 g, 18 mmol) in ethanol (30 ml) and the mixture was stirred overnight. The insoluble portion was filtered off and crystallized from ethanol (charcoal) to give **1**.

2-(4-Bromobenzoyl)-4,6-dimethoxy-3-methyl-1-benzofuran (**1a**). Yield 82%; m.p. 180–184 °C (ref.[2] 185 °C). For $C_{18}H_{15}BrO_4$ (375.2) calculated: 57.62% C, 4.03% H, 21.30% Br; found: 57.67% C, 4.54% H, 21.62% Br. ^{1}H NMR ($CDCl_3$): 2.75 s, 3 H (CH_3); 3.86 s, 3 H (CH_3O); 3.90 s, 3 H (CH_3O); 6.29 d, 1 H, *J* = 1.9 (H-5); 6.56 d, 1 H, *J* = 1.9 (H-7); 7.63 dt, 2 H, *J* = 8.7, 2.2 (benzoyl); 7.91 dt, 2 H, *J* = 8.7, 2.2 (benzoyl).

2-Benzoyl-4,6-dimethoxy-3-methyl-1-benzofuran (**1b**). Yield 88%; m.p. 123–126 °C. For $C_{18}H_{16}O_4$ (296.3) calculated: 72.96% C, 5.44% H; found: 73.27% C, 5.55% H. ^{1}H NMR ($CDCl_3$): 2.74 s, 3 H (CH_3); 3.85 s, 3 H (CH_3O); 3.90 s, 3 H (CH_3O); 6.29 d, 1 H, *J* = 1.9 (H-5); 6.58 d, 1 H, *J* = 1.9 (H-7); 7.38–7.63 m, 3 H (benzoyl); 8.01 m, 2 H (benzoyl).

2-(4-Bromobenzoyl)-6-methoxy-3-methyl-1-benzofuran (**1c**). Yield 90%; m.p. 117–119 °C. For $C_{17}H_{13}BrO_3$ (345.2) calculated: 59.15% C, 3.80% H, 23.15% Br; found: 58.88% C, 3.70% H, 22.66% Br. UV, λ (log ε): 205 (4.51), 244 (4.00), 264 (4.11), 349 (4.40). ^{1}H NMR ($CDCl_3$): 2.63 s, 3 H (CH_3); 3.88 s, 3 H (CH_3O); 6.93–7.03 m, 2 H (H-5, H-7); 7.55 dd, 1 H, *J* = 8.3, 0.9 (H-4); 7.65 dt, 2 H, *J* = 8.6, 1.9 (benzoyl); 7.96 dt, 2 H, *J* = 8.6, 1.9 (benzoyl).

2-Benzoyl-6-methoxy-3-methyl-1-benzofuran (**1d**). Yield 54%; m.p. 74–75 °C (ref.[4] 76 °C). For $C_{17}H_{14}O_3$ (266.3) calculated: 76.68% C, 5.30% H; found: 76.34% C, 4.92% H. IR (KBr): 1 621 (C=O). UV, λ (log ε): 205 (4.42), 241 (4.03), 256 (4.11), 344 (4.33). ^{1}H NMR ($CDCl_3$): 2.61 s, 3 H (CH_3); 3.88 s, 3 H (CH_3O); 6.94 m, 2 H (H-5, H-7); 7.46–7.63 m, 4 H (H-4, benzoyl); 8.02 m, 2 H (benzoyl).

Preparation of 2-Benzoyl-1-benzofurans **1e**, **1f.** General Procedure

A mixture of 2-hydroxy-4,6-dimethoxybenzaldehyde (1.8 g, 10 mmol), an appropriate 2-bromo-1-phenylethan-1-one (10 mmol), potassium carbonate (2 g, 14 mmol) and butan-2-one (50 ml) was refluxed for 6 h. The insoluble portion was filtered off, the filtrate was evaporated and crystallized twice from ethanol (charcoal) to give the required product.

2-(4-Bromobenzoyl)-4,6-dimethoxy-1-benzofuran (**1e**). Yield 53%; m.p. 179–181 °C. For $C_{17}H_{13}BrO_4$ (361.2) calculated: 56.53% C, 3.63% H, 22.12% Br; found: 56.72% C, 3.52% H, 21.78% Br. UV, λ (log ε): 207 (4.56), 230 (3.92), 255 (4.04), 286 (3.89). ^{1}H NMR ($CDCl_3$): 3.87 s, 3 H (CH_3O); 3.91 s, 3 H (CH_3O); 6.34 d, 1 H, *J* = 1.9 (H-5); 6.69 dd, 1 H, *J* = 1.9, 1.0 (H-7); 7.52 d, 1 H, *J* = 1.0 (H-3); 7.64 dt, 2 H, *J* = 8.8, 2.0 (benzoyl); 7.88 dt, 2 H, *J* = 8.8, 2.0 (benzoyl).

2-Benzoyl-4,6-dimethoxy-1-benzofuran (**1f**). Yield 57%; m.p. 135–136 °C (ref.[5] 140–141 °C). For $C_{17}H_{14}O_4$ (282.3) calculated: 72.33% C, 5.00% H; found: 72.50% C, 5.33% H. IR (KBr): 1 631 (C=O). UV, λ (log ε): 205 (4.44), 254 (4.14), 352 (4.28). ^{1}H NMR ($CDCl_3$): 3.87 s, 3 H (CH_3O); 3.91 s, 3 H (CH_3O); 6.34 d, 1 H, *J* = 1.9 (H-5); 6.70 dd, 1 H, *J* = 1.9, 0.9 (H-7); 7.50 m, 3 H (benzoyl); 7.54 d, 1 H, *J* = 0.9 (H-3); 7.94 m, 2 H (benzoyl).

2-Hydroxy-3-methoxybenzonitrile (**5b**)

A mixture of 2-hydroxy-3-methoxybenzaldehyde (7.6 g, 50 mmol), hydroxylamine hydrochloride (4.4 g, 63 mmol), dry sodium acetate (4.5 g, 55 mmol), and anhydrous formic acid (60 ml) was refluxed under nitrogen for 3 h. The mixture was evaporated under reduced pressure, the residue was poured into water, the mixture was extracted with ether, the organic layer was washed with brine and dried with magnesium sulfate. The residue was purified by flash chromatography (petroleum ether–acetone, from 20 : 1 to 8 : 2) followed by crystallization from hexane to give 5.6 g (75%) of white crystals, m.p. 56–57 °C (ref.[14] 47–48 °C; ref.[26] 59 °C). For $C_8H_7NO_2$ (149.1) calculated: 64.42% C, 4.73% H, 9.39% N; found: 64.03% C, 4.83% H, 9.24% N. ^{1}H NMR ($CDCl_3$): 3.93 s, 3 H (CH_3); 6.63 bs, 1 H (OH); 6.89 dd, 1 H, *J* = 8.4, 7.8 (H-5); 7.05 m, 2 H (H-4, H-6).

2-Hydroxy-4,6-dimethoxybenzonitrile (**5c**)

A mixture of 2-hydroxy-4,6-dimethoxybenzaldehyde (10 g, 55 mmol), hydroxylamine hydrochloride (4.4 g, 63 mmol), dry sodium acetate (4.5 g, 55 mmol), and anhydrous formic acid (40 ml) was refluxed under nitrogen for 3 h. The mixture was worked up as above and purified by flash chromatography (petroleum ether–acetone, 20 : 1) to give 3.35 g (33.5%) of the starting aldehyde and 4.0 g (40%) of white crystals, m.p. 203–206 °C (ethanol–water, 1 : 1). For $C_9H_9NO_3$ (179.2) calculated: 60.33% C, 5.06% H, 7.82% N; found: 60.12% C, 5.28% H, 7.56% N. ^{1}H NMR ($CDCl_3$): 3.87 s, 3 H (CH_3); 3.95 s, 3 H (CH_3); 6.05 d, 1 H, *J* = 2.0 (H-3 or H-5); 6.08 d, 1 H, *J* = 2.0 (H-3 or H-5); 10.95 bs, 1 H (OH). ^{13}C NMR ($CDCl_3$): 55.54 (CH_3), 56.12 (CH_3), 88.88 (C-1), 90.20 (C-5), 93.46 (C-3), 114.85 (CN), 162.52 (C-2), 163.01 (C-4), 164.73 (C-6).

Preparation of 2-(2-Oxo-2-phenylethoxy)benzonitriles **7**. General Procedure

Method A. A solution of sodium hydroxide (1 g, 25 mmol) in water (2 ml) was added to a stirred mixture of an appropriate 2-hydroxybenzonitrile **5** (25 mmol) and a 2-bromo-1-phenylethan-1-one **6** (10 mmol) in 2-methoxyethan-1-ol (20 ml) and the mixture was refluxed for 15 min. Then the mixture was cooled, the insoluble portion was filtered and crystallized from ethanol to give **7**.

Method B. A mixture of 2-hydroxybenzonitrile **5** (10 mmol), 2-bromo-1-phenylethan-1-one **6** (11 mmol), and potassium carbonate (1.5 g, 15 mmol) in DMF (20 ml) was

stirred at room temperature for 2 h. The mixture was poured into water (100 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol to give pure **7**.

2-(2-Oxo-2-phenylethoxy)benzonitrile (**7a**). Yield 83% (Method *A*), 79% (Method *B*); white crystals, m.p. 147–148 °C (ref.[12] 148–149 °C). For $C_{15}H_{11}NO_2$ (237.3) calculated: 75.94% C, 4.67% H, 5.90% N; found: 75.57% C, 4.74% H, 6.01% N. ^{1}H NMR ($CDCl_3$): 5.43 s, 2 H (CH_2); 6.83 d, 1 H, *J* = 8.5 (H-3); 7.03 dt, 1 H, *J* = 7.5, 1.0 (H-5); 7.54 m, 5 H (H-4, H-6, H-3′, H-4′, H-5′); 8.01 bd, 2 H (H-2′, H-6′).

2-[2-(4-Bromophenyl)-2-oxoethoxy]benzonitrile (**7b**). Yield 57% (Method *A*); white crystals, m.p. 141–150 °C (ref.[12] 164–165 °C; crystallized from $CHCl_3$–CCl_4). For $C_{15}H_{10}BrNO_2$ (316.1) calculated: 56.99% C, 3.19% H, 25.27% Br, 4.43% N; found: 56.67% C, 3.44% H, 24.89% Br, 4.57% N. IR (KBr): 1 692 (C=O), 2 223 (CN).

2-[2-(Biphenyl-4-yl)-2-oxoethoxy]benzonitrile (**7c**). Yield 82% (Method *A*); white crystals, m.p. 148–151 °C. For $C_{21}H_{15}NO_2$ (313.4) calculated: 80.49% C, 4.82% H, 4.47% N; found: 80.19% C, 5.01% H, 4.43% N. IR (KBr): 1 688 (C=O), 2 226 (CN). UV, λ (log ε): 207 (4.72), 291 (4.52). ^{1}H NMR ($CDCl_3$): 5.44 s, 2 H (CH_2); 6.85 d, 1 H, *J* = 7.8 (H-3); 7.02 dt, 1 H, *J* = 7.8, 1.6 (H-4); 7.46 m, 4 H (H-5, H-2″, H-4″, H-6″); 7.57 dd, 1 H, *J* = 7.5, 1.6 (H-6); 7.62 bd, 2 H (H-3″, H-5″); 7.72 d, 2 H, *J* = 8.5 (H-3′, H-5′); 8.08 d, 2 H, *J* = 8.5 (H-2′, H-6′).

2-[2-(2′,4′-Difluorobiphenyl-4-yl)-2-oxoethoxy]benzonitrile (**7d**). Yield 49% (Method *B*); white crystals, m.p. 141–143 °C. For $C_{21}H_{13}F_2NO_2$ (349.3) calculated: 72.20% C, 3.75% H, 10.88% F, 4.01% N; found: 72.13% C, 4.09% H, 10.57% F, 3.57% N. ^{1}H NMR ($CDCl_3$): 5.44 s, 2 H (CH_2); 6.86 d, 1 H, *J* = 8.5 (H-3); 6.99 m, 3 H (H-5, H-3″, H-5″); 7.46 m, 2 H (H-4, H-6″); 7.59 dd, 1 H, *J* = 7.9, 1.9 (H-6); 7.65 dd, 2 H, *J* = 8.5, 1.6 (H-3′, H-5′); 8.09 d, 2 H, *J* = 8.5 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –109.68 (F-2″), –113.21 (F-4″).

3-Methoxy-2-(2-oxo-2-phenylethoxy)benzonitrile (**7e**). Yield 67% (Method *B*); white crystals, m.p. 83–84 °C. For $C_{16}H_{13}NO_3$ (267.3) calculated: 71.90% C, 4.90% H, 5.24% N; found: 71.66% C, 4.68% H, 5.02% N. ^{1}H NMR ($CDCl_3$): 3.77 s, 3 H (CH_3); 5.50 s, 2 H (CH_2); 7.09–7.17 m, 3 H (H-4, H-5, H-6); 7.49 m, 2 H (H-3′, H-5′); 7.60 m, 1 H (H-4′); 7.97 m, 2 H (H-2′, H-6′).

3-Methoxy-2-[2-(4-bromophenyl)ethoxy-2-oxo]benzonitrile (**7f**). Yield 79% (Method *B*); white crystals, m.p. 132–133 °C. For $C_{16}H_{12}BrNO_3$ (346.2) calculated: 55.51% C, 3.49% H, 23.08% Br, 4.05% N; found: 55.49% C, 3.68% H, 23.55% Br, 3.60% N. ^{1}H NMR ($CDCl_3$): 3.78 s, 3 H (CH_3); 5.41 s, 2 H (CH_2); 7.09–7.17 m, 3 H (H-4, H-5, H-6); 7.63 d, 2 H, *J* = 8.7 (H-3′, H-5′); 7.86 d, 2 H, *J* = 8.7 (H-2′, H-6′).

2-[2-(Biphenyl-4-yl)-2-oxoethoxy]-3-methoxybenzonitrile (**7g**). Yield 87% (Method *B*); white crystals, m.p. 122–125 °C. For $C_{22}H_{17}NO_3$ (343.4) calculated: 76.95% C, 4.99% H, 4.08% N; found: 76.82% C, 5.33% H, 3.71% N. IR (KBr): 1 693 (C=O), 2 231 (CN). UV, λ (log ε): 208 (4.68), 289 (4.41). ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 5.52 s, 2 H (CH_2); 7.09–7.18 m, 3 H (H-4, H-5, H-6); 7.45 m, 3 H (H-3″, H-4″, H-5″); 7.63 m, 2 H (H-2″, H-6″); 7.71 d, 2 H, *J* = 8.3 (H-3′, H-5′); 8.06 d, 2 H, *J* = 8.3 (H-2′, H-6′).

2-[2-(2′,4′-Difluorobiphenyl-4-yl)-2-oxoethoxy]-3-methoxybenzonitrile (**7h**). Yield 77% (Method *B*); white crystals, m.p. 126–128 °C. For $C_{22}H_{15}F_2NO_3$ (379.4) calculated: 69.65% C, 3.99% H, 10.02% F, 3.69% N; found: 69.57% C, 4.24% H, 9.67% F, 3.51% N. IR (KBr): 1 674 (C=O), 232 (CN). UV, λ (log ε): 209 (4.72), 282 (4.30). ^{1}H NMR ($CDCl_3$): 3.80 s, 3 H (CH_3); 5.51 s, 2 H (CH_2); 6.97 m, 2 H (H-3″, H-5″); 7.10–7.18 m, 3 H (H-4, H-5, H-6); 7.44 m, 1 H (H-6″); 7.63 dd, 2 H, *J* = 8.8, 1.6 (H-3′, H-5′); 8.06 d, 2 H, *J* = 8.8 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –109.76 (F-2″), –113.19 (F-4″).

4,6-Dimethoxy-2-(2-oxo-2-phenylethoxy)benzonitrile (**7i**). Yield 95% (Method *B*); white crystals, m.p. 148–150 °C. For $C_{17}H_{15}NO_4$ (297.3) calculated: 68.68% C, 5.09% H, 4.71% N; found: 68.86% C, 5.24% H, 4.62% N. IR (KBr): 1 701 (C=O), 2 220 (CN). UV, λ (log ε): 205 (4.57), 216 (4.60), 250 (4.44). ^{1}H NMR ($CDCl_3$): 3.78 s, 3 H (CH_3O); 3.87 s, 3 H (CH_3O); 5.33 s, 2 H (CH_2); 5.96 d, 1 H, *J* = 1.9 (H-3 or H-5); 6.08 d, 1 H, *J* = 1.9 (H-3 or H-5); 7.50 bt, 2 H (H-3′, H-5′); 7.62 bt, 1 H (H-4′); 8.01 bd, 2 H (H-2′, H-6′).

2-[2-(4-Bromophenyl)-2-oxoethoxy]-4,6-dimethoxybenzonitrile (**7j**). Yield 99% (Method *B*); white crystals, m.p. 191–192 °C. For $C_{17}H_{14}BrNO_4$ (376.2) calculated: 54.28% C, 3.75% H, 21.24% Br, 3.72% N; found: 54.59% C, 3.84% H, 21.09% Br, 3.59% N. IR (KBr): 1 694 (C=O), 2 217 (CN). UV, λ (log ε): 205 (4.44), 216 (4.62), 258 (4.52). ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 3.87 s, 3 H (CH_3); 5.26 s, 2 H (CH_2); 5.96 d, 1 H, *J* = 2.2 (H-3 or H-5); 6.08 d, 1 H, *J* = 2.2 (H-3 or H-5); 7.65 d, 2 H, *J* = 8.5 (H-3′, H-5′); 7.90 d, 2 H, *J* = 8.5 (H-2′, H-6′).

2-[2-(Biphenyl-4-yl)-2-oxoethoxy]-4,6-dimethoxybenzonitrile (**7k**). Yield 29% (Method *B*); creamy crystals, m.p. 142–143 °C. For $C_{23}H_{19}NO_4$ (373.4) calculated: 73.98% C, 5.13% H, 3.75% N; found: 73.65% C, 5.20% H, 3.94% N. IR (KBr): 1 688 (C=O), 2 219 (CN). ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 3.87 s, 3 H (CH_3); 5.35 s, 2 H (CH_2); 5.99 d, 1 H, *J* = 2.2 (H-3 or H-5); 6.08 d, 1 H, *J* = 2.2 (H-3 or H-5); 7.44 m, 3 H (H-3″, H-4″, H-5″); 7.63 m, 2 H (H-2″, H-6″); 7.72 d, 2 H, *J* = 8.2 (H-3′, H-5′); 8.10 d, 2 H, *J* = 8.2 (H-2′, H-6′).

2-[2-(2′,4′-Difluorobiphenyl-4-yl)-2-oxoethoxy]-4,6-dimethoxybenzonitrile (**7l**). Yield 44% (Method *B*); creamy crystals, m.p. 142–146 °C. For $C_{23}H_{17}F_2NO_4$ (409.4) calculated: 67.48% C, 4.19% H, 9.28% F, 3.42% N; found: 67.66% C, 4.34% H, 8.92% F, 3.25% N. IR (KBr): 1 689 (C=O), 2 215 (CN). UV, λ (log ε): 217 (4.67), 260 (4.41). ^{1}H NMR ($CDCl_3$): 3.79 s, 3 H (CH_3); 3.87 s, 3 H (CH_3); 5.35 s, 2 H (CH_2); 5.99 d, 1 H, *J* = 1.9 (H-3 or H-5); 6.08 d, 1 H, *J* = 1.9 (H-3 or H-5); 6.96 m, 2 H (H-3″, H-5″); 7.44 m, 1 H (H-6″); 7.64 dd, 2 H, *J* = 8.5, 1.6 (H-3′, H-5′); 8.09 d, 2 H, *J* = 8.5 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –109.80 (F-2″), –113.18 (F-4″).

Preparation of 2-Benzoyl-1-benzofuran-3-amines **2**. General Procedure

Sodium methoxide (0.55 g, 10 mmol) was added to a stirred solution of **7** (10 mmol) in methanol (20 ml) and the mixture was stirred at room temperature for 30 min. The mixture was poured into water (25 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol to give **2**.

2-Benzoyl-1-benzofuran-3-amine (**2a**). Yield 89%; yellow crystals, m.p. 124–126 °C (ref.[12] 125–126 °C). For $C_{15}H_{11}NO_2$ (237.3) calculated: 75.94% C, 4.67% H, 5.90% N; found: 76.11% C, 4.53% H, 5.97% N. IR (KBr): 1 621 (C=O); 3 296, 3 422 (NH_2). UV, λ (log ε): 208 (4.13), 252 (4.23), 312 (3.99), 380 (4.26).

2-(4-Bromobenzoyl)-1-benzofuran-3-amine (**2b**). Yield 90%; yellow crystals, m.p. 198–200°C (ref.[12] 203–204 °C). For $C_{15}H_{10}BrNO_2$ (316.1) calculated: 56.99% C, 3.19% H, 25.27% Br, 4.43% N; found: 56.90% C, 3.26% H, 24.88% Br, 4.03% N. IR (KBr): 1 613 (C=O); 3 297, 3 420 (NH_2). UV, λ (log ε): 203 (4.32), 221 (4.10), 357 (4.28), 314 (3.98), 385 (4.33). ^{1}H NMR ($CDCl_3$, 60 °C): 5.83 bs, 2 H (NH_2); 7.30 m, 1 H (H-5); 7.47 m, 1 H (H-7); 7.56 m, 1 H (H-6); 7.65 m, 1 H (H-4); 7.69 d, 2 H, *J* = 8.8 (benzoyl); 8.17 d, 2 H, *J* = 8.8 (benzoyl).

2-(Biphenyl-4-ylcarbonyl)-1-benzofuran-3-amine (**2c**). Yield 87%; yellow crystals, m.p. 167–169 °C. For $C_{21}H_{15}NO_2$ (313.4) calculated: 80.49% C, 4.82% H, 4.47% N; found: 80.38% C, 5.00% H, 4.29% N. IR (KBr): 1 615 (C=O); 3 316, 3 418 (NH_2). UV, λ (log ε): 206 (4.56), 226 (4.19), 249 (4.12), 295 (4.22), 387 (4.31). ^{1}H NMR ($CDCl_3$, 60 °C): 6.01 bs, 2 H (NH_2);

7.22 m, 1 H (H-5); 7.41 m, 4 H (H-6, H-7, H-3″, H-4″, H-5″); 7.61 m, 3 H (H-4, H-2″, H-6″); 7.72 d, 2 H, *J* = 8.2 (H-3′, H-5′); 8.33 d, 2 H, *J* = 8.2 (H-2′, H-6′).

2-[(2′,4′-Difluorobiphenyl-4-yl)carbonyl]-1-benzofuran-3-amine (**2d**). Yield 51%; yellow crystals, m.p. 173–176 °C. For $C_{21}H_{13}F_2NO_2$ (349.3) calculated: 72.20% C, 3.75% H, 10.88% F, 4.01% N; found: 72.13% C, 4.02% H, 10.98% F, 3.75% N. IR (KBr): 1 613 (C=O); 3 304, 3 406 (NH_2). UV, λ (log ε): 204 (4.57), 224 (4.22), 258 (4.24), 284 (4.18), 386 (4.33). ^{1}H NMR ($CDCl_3$, 60 °C): 6.03 bs, 2 H (NH_2); 6.94 m, 2 H (H-3″, H-5″); 7.24 bt, 1 H (H-5); 7.46 m, 3 H (H-6, H-7, H-6″); 7.63 m, 3 H (H-4, H-3′, H-5′); 8.33 d, 2 H, *J* = 8.2 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –110.91 (F-2″), –113.06 (F-4″).

2-Benzoyl-7-methoxy-1-benzofuran-3-amine (**2e**). Yield 75%; yellow crystals, m.p. 166–168 °C. For $C_{16}H_{13}NO_3$ (267.3) calculated: 71.90% C, 4.90% H, 5.24% N; found: 71.99% C, 5.01% H, 5.26% N. IR (KBr): 1 621 (C=O); 3 316, 3 442 (NH_2). UV, λ (log ε): 204 (4.39), 251 (4.34), 319 (3.90), 380 (4.25). ^{1}H NMR ($CDCl_3$): 3.99 s, 3 H (CH_3); 6.01 bs, 2 H (NH_2); 6.96 dd, 1 H, *J* = 6.8, 2.0 (H-6); 7.16 m, 2 H (H-4, H-5); 7.49 dd, 3 H, *J* = 5.2, 1.9 (H-3′, H-5′); 8.27 m, 2 H (H-2′, H-6′).

2-(4-Bromobenzoyl)-7-methoxy-1-benzofuran-3-amine (**2f**). Yield 64%; yellow crystals, m.p. 201–204°C. For $C_{16}H_{12}BrNO_3$ (346.2) calculated: 55.51% C, 3.49% H, 23.08% Br, 4.05% N; found: 55.30% C, 3.60% H, 23.27% Br, 3.88% N. IR (KBr): 1 620 (C=O); 3 322, 3 440 (NH_2). ^{1}H NMR ($CDCl_3$, 60 °C): 4.01 s, 3 H (CH_3); 5.94 bs, 2 H (NH_2); 6.98 m, 1 H (H-6); 7.18 m, 2 H (H-4, H-5); 7.65 d, 2 H, *J* = 7.9 (H-3′, H-5′); 8.16 d, 2 H, *J* = 7.9 (H-2′, H-6′).

2-(Biphenyl-4-ylcarbonyl)-7-methoxy-1-benzofuran-3-amine (**2g**). Yield 92%; yellow crystals, m.p. 208–210 °C. For $C_{22}H_{17}NO_3$ (343.4) calculated: 76.95% C, 4.99% H, 4.08% N; found: 77.27% C, 5.39% H, 3.92% N. ^{1}H NMR ($CDCl_3$): 4.03 s, 3 H (CH_3); 5.99 bs, 2 H (NH_2); 7.00 m, 1 H (H-6); 7.20 m, 2 H (H-4, H-5); 7.39 tt, 1 H (H-4″); 7.48 m, 2 H (H-3″, H-5″); 7.68 m, 2 H (H-2″, H-6″); 7.76 bd, 2 H, *J* = 8.6 (H-3′, H-5′); 8.37 bd, 2 H, *J* = 8.6 (H-2′, H-6′).

2-[(2′,4′-difluorobiphenyl-4-yl)carbonyl]-7-methoxy-1-benzofuran-3-amine (**2h**). Yield 97%; yellow crystals, m.p. 178–180 °C. For $C_{22}H_{15}F_2NO_3$ (379.4) calculated: 69.65% C, 3.99% H, 10.02% F, 3.69% N; found: 69.27% C, 4.22% H, 9.79% F, 3.49% N. IR (KBr): 1 617 (C=O); 3 348, 3 449 (NH_2). UV, λ (log ε): 204 (4.58), 253 (4.22), 281 (4.22), 321 (3.92), 387 (4.34). ^{1}H NMR ($CDCl_3$, 60 °C): 4.03 s, 3 H (CH_3); 6.02 bs, 2 H (NH_2); 6.96 m, 2 H (H-3″, H-5″); 7.00 m, 1 H (H-6); 7.20 m, 2 H (H-4, H-5); 7.48 m, 1 H (H-6″); 7.67 bdd, 2 H, *J* = 8.5, 1.6 (H-3′, H-5′); 8.36 bd, 2 H, *J* = 8.5 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –110.98 (F-2″), –113.28 (F-4″).

2-Benzoyl-4,6-dimethoxy-1-benzofuran-3-amine (**2i**). Yield 92%; yellow crystals, m.p. 112–113 °C. For $C_{17}H_{15}NO_4$ (297.3) calculated: 68.68% C, 5.09% H, 4.71% N; 68.54% C, 5.27% H, 4.73% N. IR (KBr): 1 624 (C=O); 3 333, 3 435 (NH_2). UV, λ (log ε): 204 (4.44), 255 (4.20), 311 (3.90), 384 (4.41). ^{1}H NMR ($CDCl_3$, 60 °C): 3.83 s, 3 H (CH_3O); 3.92 s, 3 H (CH_3O); 6.20 d, 1 H, *J* = 1.6 (H-5); 6.39 bs, 2 H (NH_2); 6.47 d, 1 H, *J* = 1.6 (H-7); 7.47 m, 3 H (benzoyl); 8.17 m, 2 H (benzoyl).

2-(4-Bromobenzoyl)-4,6-dimethoxy-1-benzofuran-3-amine (**2j**). Yield 95%; yellow crystals, m.p. 225–226 °C. For $C_{17}H_{14}BrNO_4$ (376.2) calculated: 54.28% C, 3.75% H, 21.24% Br, 3.72% N; found: 54.56% C, 3.85% H, 21.06% Br, 3.66% N. IR (KBr): 1 624 (C=O); 3 331, 3 452 (NH_2). UV, λ (log ε): 204 (4.37), 259 (4.17), 312 (3.84), 388 (4.35). ^{1}H NMR ($CDCl_3$): 3.84 s, 3 H (CH_3); 3.92 s, 3 H (CH_3); 6.20 d, 1 H, *J* = 1.9 (H-5); 6.42 bs, 2 H (NH_2); 6.46 d, 1 H, *J* = 1.9 (H-7); 7.60 d, 2 H, *J* = 8.5 (H-3′, H-5′); 8.06 d, 2 H, *J* = 8.5 (H-2′, H-6′).

2-(Biphenyl-4-ylcarbonyl)-4,6-dimethoxy-1-benzofuran-3-amine (**2k**). Yield 75%; yellow crystals, m.p. 177–183 °C. For $C_{23}H_{19}NO_4$ (373.4) calculated: 73.98% C, 5.13% H, 3.75% N;

found: 73.94% C, 5.20% H, 4.02% N. IR (KBr): 1 624 (C=O); 3 333, 3 456 (NH_2). UV, λ (log ε): 205 (4.77), 224 (4.29), 260 (4.20), 285 (4.35), 391 (4.37). ^{1}H NMR ($CDCl_3$, 60 °C): 3.86 s, 3 H (CH_3); 3.98 s, 3 H (CH_3); 6.20 d, 1 H, *J* = 1.8 (H-5); 6.44 bs, 2 H (NH_2); 6.50 d, 1 H, *J* = 1.8 (H-7); 7.34–7.52 m, 3 H (H-3′, H-5′, H-4″); 7.65–7.82 m, 4 H (H-2″, H-3″, H-5″, H-6″); 8.28 bd, 2 H, *J* = 8.4 (H-2′, H-6′).

2-[(2′,4′-Difluorobiphenyl-4-yl)carbonyl]-4,6-dimethoxy-1-benzofuran-3-amine (**2l**). Yield 55%; yellow crystals, m.p. 199–201 °C. For $C_{23}H_{17}F_2NO_4$ (409.4) calculated: 67.48% C, 4.19% H, 9.28% F, 3.42% N; found: 67.18% C, 4.15% H, 9.26% F, 3.10% N. IR (KBr): 1 628 (C=O); 3 326, 3 428 (NH_2). UV, λ (log ε): 205 (4.55), 261 (4.28), 278 (4.28), 390 (4.42). ^{1}H NMR ($CDCl_3$, 60 °C): 3.85 s, 3 H (CH_3); 3.94 s, 3 H (CH_3); 6.43 bs, 2 H (NH_2); 6.22 d, 1 H, *J* = 1.9 (H-5); 6.49 d, 1 H, *J* = 1.9 (H-7); 6.94 m, 2 H (H-3″, H-5″); 7.45 m, 1 H (H-6″); 7.61 dd, 2 H, *J* = 8.2, 1.6 (H-3′, H-5′); 8.26 d, 2 H, *J* = 8.2 (H-2′, H-6′). ^{19}F NMR ($CDCl_3$): –111.30 (F-2″), –113.17 (F-4″).

2-(Benzylsulfanyl)benzonitrile

A mixture of 2-fluorobenzonitrile (12 g, 0.1 mol), phenylmethanethiol (13.7 g, 0.11 mmol), potassium carbonate (35 g, 0.25 mol), and butan-2-one (125 ml) was stirred at room temperature under nitrogen. The insoluble portion was filtered off, the filtrate was evaporated to dryness and purified twice by flash chromatography (silica gel, petroleum ether–acetone, from 40 : 1 to 10 : 1) followed by crystallization from hexane to give 5.45 g (24%) of the title compound; m.p. 59–61 °C (ref.[27] 57–58 °C; ref.[16] 62–64 °C). For $C_{14}H_{11}NS$ (225.3) calculated: 74.63% C, 4.93% H, 6.22% N, 14.23% S; found: 74.92% C, 5.24% H, 6.37% N, 14.17% S.

2-Sulfanylbenzonitrile (**8**)

A solution of 2-(benzylsulfanyl)benzonitrile (6.45 g, 28.6 mmol) in benzene (50 ml) was added dropwise to a suspension of aluminum chloride (5.8 g, 43 mmol) in benzene (50 ml) stirred under argon and the mixture was stirred at room temperature for 30 h. The mixture was poured into cold water (150 ml) and the organic layer was washed with 5% solution of sodium hydroxide (2 × 50 ml). The combined aqueous solution was acidified with 10% hydrochloric acid and the mixture was extracted with ether (2 × 60 ml, 2 × 30 ml). The organic extract was dried with anhydrous magnesium sulfate to give 3.6 g (93%) of the title compound, which was used for further reactions without purification.

Preparation of 2-Benzoyl-1-benzothiophen-3-amines **3**. General Procedure

Sodium hydride (0.5 g, 50% dispersion in mineral oil, 10 mmol) was added to a solution of 2-sulfanylbenzonitrile (**8**) (10 mmol) in DMF (30 ml) and the mixture was stirred under argon for 1 h. Then a solution of an appropriate 2-bromo-1-phenylethan-1-one **6** (10 mmol) was added and the mixture was stirred at room temperature for 24 h. The mixture was poured into water (250 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol.

2-Benzoyl-1-benzothiophen-3-amine (**3a**). Yield 52%; yellow crystals, m.p. 124–125 °C (ref.[15] gives a different m.p. 103–104 °C). For $C_{15}H_{11}NOS$ (253.3) calculated: 71.12% C, 4.38% H, 5.53% N, 12.66% S; found: 71.28% C, 4.77% H, 5.47% N, 12.49% S. IR (KBr): 1 598 (C=O); 3 321, 3 433 (NH_2). UV, λ (log ε): 204 (4.40), 279 (4.18), 310 (3.84), 319 (3.92), 404 (4.00).

^{1}H NMR ($CDCl_3$): 7.04 bs, 2 H (NH_2); 7.35 td, 1 H, *J* = 7.3, 1.2 (H-4′); 7.43–7.53 m, 4 H (H-2′, H-3′, H-5′, H-6′); 7.70 m, 2 H (H-5, H-6); 7.98 dd, 2 H, *J* = 7.3, 1.5 (H-4, H-7).

2-(4-Bromobenzoyl)-1-benzothiophen-3-amine (**3b**). Yield 41%; yellow crystals, m.p. 119–124 °C. For $C_{15}H_{10}BrNOS$ (332.2) calculated: 54.23% C, 3.03% H, 24.05% Br, 4.22% N, 9.65% S; found: 54.55% C, 3.17% H, 24.48% Br, 4.07% N, 9.58% S. IR (KBr): 1 602 (C=O); 3 318, 3 430 (NH_2). UV, λ (log ε): 205 (4.33), 274 (4.11), 322 (3.82), 404 (4.12). ^{1}H NMR ($CDCl_3$): 7.05 bs, 2 H (NH_2); 7.37–7.50 m, 2 H (H-2′, H-6′); 7.60–7.69 m, 4 H (arom. H, H-3′, H-5′); 7.75 m, 2 H (arom. H).

Preparation of Benzonitriles **10**. General Procedure

Sodium hydride (0.5 g, 50% dispersion in mineral oil, 10 mmol) was added to a stirred *N*-substituted 2-aminobenzonitrile **9** (10 mmol) in DMF (30 ml) and the mixture was stirred for 1 h. Then a solution of an appropriate 2-bromo-1-phenylethan-1-one **6** (10 mmol) was added and the mixture was stirred at room temperature for 2–24 h (TLC). The mixture was poured into water (250 ml), the insoluble portion was filtered off, washed with water and crystallized from a suitable solvent.

N-(2-Cyanophenyl)-N-(2-oxo-2-phenylethyl)methanesulfonamide (**10a**). Yield 86%; white crystals, m.p. 189–192 °C (ethanol). For $C_{16}H_{14}N_2O_3S$ (314.4) calculated: 61.13% C, 4.49% H, 8.91% N, 10.20% S; found: 61.55% C, 4.32% H, 8.68% N, 9.92% S. IR (KBr): 1 153, 1 340 (SO_2); 1 709 (C=O); 2 237 (CN). UV, λ (log ε): 204 (4.52), 243 (4.18). ^{1}H NMR ($CDCl_3$): 3.25 s, 3 H (CH_3); 5.28 s, 2 H (CH_2); 7.48 m, 3 H (arom. H); 7.62–7.75 m, 3 H (arom. H); 7.93 d, 2 H, *J* = 7.5 (H-2, H-6, benzoyl); 8.00 d, 1 H, *J* = 8.5 (H-3, cyanophenyl).

N-[2-(4-Bromophenyl)-2-oxoethyl]- N-(2-cyanophenyl)methanesulfonamide (**10b**). Yield 88%; white crystals, m.p. 154-159 °C (ethanol). For $C_{16}H_{13}BrN_2O_3S$ (393.2) calculated: 48.87% C, 3.33% H, 20.32% Br, 7.12% N, 8.15% S; found: 48.44% C, 3.21% H, 20.72% Br, 6.87% N, 7.76% S. IR (KBr): 1 158, 1 345 (SO_2); 1 733 (C=O); 2 241 (CN). UV, λ (log ε): 205 (4.44), 248 (4.02). ^{1}H NMR ($CDCl_3$, 60 °C): 3.21 s, 3 H (CH_3); 5.20 s, 2 H (CH_2); 7.46 dt, 1 H, *J* = 7.5, 1.3 (H-4, cyanophenyl); 7.61 d, 2 H, *J* = 8.8 (H-3, H-5, benzoyl); 7.67 m, 2 H (H-5, H-6, cyanophenyl); 7.78 d, 2 H, *J* = 8.8 (H-2, H-6, benzoyl); 7.94 bd, 1 H (H-3, cyanophenyl).

N-(2-Cyanophenyl)-N-(2-oxo-2-phenylethyl)-4-methylbenzene-1-sulfonamide (**10c**). Yield 44%; white crystals, m.p. 146–148 °C (methanol). For $C_{22}H_{18}N_2O_3S$ (390.5) calculated: 67.68% C, 4.65% H, 7.17% N, 8.21% S; found: 67.33% C, 4.91% H, 7.03% N, 8.05% S. IR (KBr): 1 162, 1 345 (SO_2); 1 697 (C=O); 2 229 (CN). ^{1}H NMR ($CDCl_3$): 2.44 s, 3 H (CH_3); 5.24 s, 2 H (CH_2); 7.30 d, 2 H, *J* = 8.05 (H-3, H-5); 7.40 m, 1 H (H-5, cyanophenyl); 7.48 d, 2 H, *J* = 8.05 (H-2, H-6); 7.60 m, 5 H (H-4, H-6, cyanophenyl; H-3, H-4, H-5, benzoyl); 7.79 dd, 1 H (H-3, cyanophenyl); 7.92 m, 2 H (H-2, H-6, benzoyl).

N-[2-(4-Bromophenyl)-2-oxoethyl]-N-(2-cyanophenyl)-4-methylbenzenene-1-sulfonamide (**10d**). Yield 40%; white crystals, m.p. 162-166 °C (ethanol). For $C_{22}H_{17}BrN_2O_3S$ (469.3) calculated: 56.30% C, 3.65% H, 17.02% Br, 5.97% N, 6.83% S; found: 55.99% C, 3.72% H, 16.85% Br, 5.86% N, 7.03% S. IR (KBr): 1 145, 1 352 (SO_2); 1 694 (C=O); 2 235 (CN). ^{1}H NMR ($CDCl_3$): 2.44 s, 3 H (CH_3); 5.17 s, 2 H (CH_2); 7.26 m, 2 H (H-3, H-5); 7.31 t, 1 H, *J* = 7.8 (H-5, cyanophenyl); 7.61 m, 6 H (H-2, H-6, H-3, H-4, cyanophenyl; H-2, H-6, benzoyl); 7.80 m, 3 H (H-6, cyanophenyl; H-3, H-5, benzoyl).

Preparation of *N*-(Alkanesulfonyl)-2-benzoylindol-3-amines **4a**–**4d**. General Procedure

Method A. Sodium methoxide (55 mg, 1 mmol) was added to a stirred solution of **10** (1 mmol) in ethanol (5–20 ml) and the mixture was stirred at room temperature for 10 h. The mixture was poured into water (25 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol to give **4**.

Method B. Triethylamine (0.2 g, 2 mmol) was added to a stirred solution of **10** (1 mmol) in ethanol (5–20 ml) and the mixture was stirred at room temperature for 10 h. The mixture was evaporated to dryness and crystallized from ethanol to give **4**.

2-Benzoyl-1-(methanesulfonyl)indol-3-amine (**4a**). Yield 45% (Method *A*); yellow crystals, m.p. 190–191 °C. For $C_{16}H_{14}N_2O_3S$ (314.4) calculated: 61.13% C, 4.49% H, 8.91% N, 10.20% S; found: 60.68% C, 4.74% H, 8.57% N, 9.85% S. IR (KBr): 1 144, 1 339 (SO_2); 1 631 (C=O); 3 333, 3 449 (NH_2). UV, λ (log ε): 203 (4.44), 259 (4.08), 308 (3.67), 368 (4.13). ^{1}H NMR ($CDCl_3$): 2.43 s, 3 H (CH_3); 6.01 bs, 2 H (NH_2); 7.44 m, 4 H (H-4, H-5, H-6, H-4′); 7.62 m, 2 H (H-3′, H-5′); 7.93 dd, 2 H, *J* = 7.6, 1.9 (H-2′, H-6′); 8.04 d, 1 H, *J* = 8.2 (H-7).

2-(4-Bromobenzoyl)-1-(methanesulfonyl)indol-3-amine (**4b**). Yield 59% (Method *A*); yellow crystals, m.p. 208–212 °C. For $C_{16}H_{13}BrN_2O_3S$ (393.2) calculated: 48.87% C, 3.33% H, 20.32% Br, 7.12% N, 8.15% S; found: 48.43% C, 3.11% H, 19.87% Br, 7.36% N, 8.43% S. IR (KBr): 1 164, 1 345 (SO_2); 1 620 (C=O); 3 349, 3 461 (NH_2). UV, λ (log ε): 213 (4.41), 263 (4.24), 308 (3.80), 370 (4.19). ^{1}H NMR (DMSO-d_6): 2.51 s, 3 H (CH_3); 7.16 bs, 2 H (NH_2); 7.45 ddd, 1 H, *J* = 8.0, 7.3, 1.0 (H-6); 7.60 d, 2 H, *J* = 8.7 (H-3′, H-5′); 7.63 ddd, 1 H, *J* = 8.3, 7.3, 1.2 (H-5); 7.71 d, 2 H, *J* = 8.7 (H-2′, H-6′); 7.86 dt, 1 H, *J* = 8.3, 0.8 (H-4); 8.08 ddd, 1 H, *J* = 8.0, 1.2, 0.8 (H-7).

2-Benzoyl-1-(4-methylbenzene-1-sulfonyl)indol-3-amine (**4c**). Yield 46% (Method *A*), 85% (Method *B*); yellow crystals, m.p. 189–191 °C. For $C_{22}H_{18}N_2O_3S$ (390.5) calculated: 67.68% C, 4.65% H, 7.17% N, 8.21% S; found: 67.38% C, 4.84% H, 7.13% N, 8.08% S. IR (KBr): 1 172, 1 350 (SO_2); 1 626 (C=O); 3 339, 3 449 (NH_2). UV, λ (log ε): 203 (4.46), 257 (4.22), 308 (3.82), 372 (4.11). ^{1}H NMR ($CDCl_3$): 2.22 s, 3 H (CH_3); 5.90 bs, 2 H (NH_2); 6.96 d, 2 H, *J* = 8.0 (H-3, H-5, tosyl); 7.29 m, 4 H (H-4, H-5, H-2, H-6, tosyl); 7.49 m, 4 H (H-6, H-3′, H-4′, H-5′); 8.05 m, 2 H (H-2′, H-6′); 8.14 d, 1 H, *J* = 8.3 (H-7).

2-(4-Bromobenzoyl)-1-(4-methylbenzene-1-sulfonyl)indol-3-amine (**4d**). Yield 66% (Method *A*), 82% (Method *B*); yellow crystals, m.p. 187–195 °C. For $C_{22}H_{17}BrN_2O_3S$ (469.3) calculated: 56.30% C, 3.65% H, 17.02% Br, 5.97% N, 6.83% S; found: 55.87% C, 3.85% H, 16.77% Br, 5.77% N, 7.11% S. IR (KBr): 1 174, 1 355 (SO_2); 1 623 (C=O); 3 333, 3 442 (NH_2). UV, λ (log ε): 203 (4.56), 264 (4.31), 308 (3.71), 375 (4.10). ^{1}H NMR ($CDCl_3$): 2.23 s, 3 H (CH_3); 5.93 bs, 2 H (NH_2); 6.97 bd, 2 H, *J* = 8.3 (H-3, H-5, tosyl); 7.22–7.36 m, 4 H (H-5, H-6, H-2, H-6, tosyl); 7.60 m, 3 H (H-7, H-3′, H-5′); 7.93 dt, 2 H, *J* = 8.6, 2.3 (H-2′, H-6′); 8.14 d, 1 H, *J* = 8.2 (H-7).

Preparation of 2-Benzoyl-1-(ethoxycarbonyl)indole-3-amines **4e**, **4f.** General Procedure

Sodium hydride (0.5 g, 50% dispersion in mineral oil, 10 mmol) was added to a solution of 2-aminobenzonitrile **9** (10 mmol) in DMF (30 ml) and the mixture was stirred for 1 h. Then a solution of an appropriate 2-bromo-1-phenylethan-1-one **6** (10 mmol) was added and the mixture was stirred at room temperature for 24 h. The mixture was poured into water (250 ml), the insoluble portion was filtered off, washed with water and crystallized from ethanol.

2-Benzoyl-1-(ethoxycarbonyl)indol-3-amine (**4e**). Yield 68%; yellow crystals, m.p. 129–131 °C (ref.[18] 131–133 °C). For $C_{18}H_{16}N_2O_3$ (308.3) calculated: 70.12% C, 5.23% H, 9.09% N;

found: 69.98% C, 5.14% H, 8.68% N. IR (KBr): 1 612 (C=O); 1 726 (COO); 3 349, 3 467 (NH_2). ^{1}H NMR ($CDCl_3$): 0.84 t, 3 H, *J* = 7.2 (CH_3); 3.73 q, 2 H, *J* = 7.2 (CH_2); 5.19 bs, 2 H (NH_2); 7.31 ddd, 1 H, *J* = 7.8, 7.2, 0.9 (H-4′); 7.38–7.48 m, 3 H (H-5, H-3′, H-5′); 7.55 ddd, 1 H, *J* = 8.4, 7.2, 1.2 (H-6); 7.62 ddd, 1 H, *J* = 7.8, 1.2, 0.8 (H-4); 7.76 m, 2 H (H-2′, H-6′); 8.21 dt, 1 H, *J* = 8.4, 0.8 (H-7).

2-(4-Bromobenzoyl)-1-(ethoxycarbonyl)indol-3-amine (**4f**).Yield 67%; yellow crystals, m.p. 118–120 °C. For $C_{18}H_{15}BrN_2O_3$ (387.2) calculated: 55.83% C, 3.90% H, 20.63% Br, 7.23% N; found: 55.52% C, 4.15% H, 21.17% Br, 6.93% N. IR (KBr): 1 612 (C=O); 1 722 (COO); 3 350, 3 390 (NH_2). UV, λ (log ε): 213 (4.40), 263 (4.53), 308 (3.79), 370 (4.19). ^{1}H NMR ($CDCl_3$, 60 °C): 0.93 t, 3 H, *J* = 7.1 (CH_3); 3.84 q, 2 H, *J* = 7.1 (CH_2); 5.78 bs, 2 H (NH_2); 7.31 bt, 1 H, *J* = 7.4 (H-5); 7.56 m, 6 H (H-4, H-6, benzoyl); 8.20 d, 1 H, *J* = 8.3 (H-7).

2-Benzoylindol-3-amine (**11a**)

A solution of sodium hydroxide (0.4 g, 10 mmol) in water (2 ml) was added to a stirred solution of **4e** (0.31 g, 1 mmol) in ethanol (3 ml) and the mixture was refluxed for 10 min. The mixture was evaporated to dryness, the residue was triturated with water (5 ml) and extracted with dichloromethane (2 x 5 ml). The extract was washed with water to neutral reaction of the aqueous layer and dried with magnesium sulfate. The residue after evaporation was crystallized three times from hexane to give **11a** as a brown solid (0.15 g, 63%); m.p. 51–52 °C. The compound darkens on light. For $C_{15}H_{12}N_2O$ (236.3) calculated: 76.25% C, 5.12% H, 11.86% N; found: 76.26% C, 5.49% H, 11.45% N. ^{1}H NMR ($CDCl_3$): 5.57 bs, 2 H (NH_2); 7.06 dt, 1 H (H-7); 7.21 bd, 1 H, *J* = 8.4 (H-4); 7.35 dt, 1 H (H-5); 7.45–7.60 m, 5 H (H-1, H-6, benzoyl); 7.82 m, 2 H (benzoyl).

2-(4-Bromobenzoyl)indol-3-amine (**11b**)

According to the procedure described for compound **11a**, compound **11b** was obtained from **4f** as a brown solid (51%); m. p. 44–46 °C (cyclohexane). The compound darkens on light. For $C_{15}H_{11}BrN_2O$ (315.2) calculated: 57.16% C, 3.52% H, 25.35% Br, 8.89% N; found: 57.55% C, 3.64% H, 24.97% Br, 8.63% N. IR (KBr): 1 599 (C=O); 3 319, 3 435 (NH_2). UV, λ (log ε): 204 (4.74), 228 (4.23), 264 (4.29), 333 (4.20), 426 (3.91). ^{1}H NMR ($CDCl_3$): 5.53 bs, 2 H (NH_2); 7.04 dt, 1 H, *J* = 8.0, 0.8 (H-7); 7.22 m, 1 H (H-4); 7.35 dt, 1 H, *J* = 8.1, 0.8 (H-5); 7.55–7.70 m, 6 H (H-1, H-6, benzoyl).

Biological Evaluation

Hot-Plate Test

The hot-plate test was used to measure the response latencies according to the method described earlier[28], 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 to induce the licking reflex of the forepaws or jumping was recorded. The measurement was done 30 and 60 min after administration of 30 mg/kg of the tested compound and the results were expressed as prolongation of the licking latencies (%).

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 the administration of 30 mg/kg of the tested compound[29]. 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[30] was used. The animals (male Wistar–Hannover rats) were placed in a Ugo Basile (Varese, Italy) apparatus and the predrug latency to removal of the tail 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 the appropriate tested compound (30 mg/kg) and were placed in the holding apparatus. Thirty and sixty minutes later, a postdrug latency was measured. A postdrug latency was expressed as a decrease in latency of the control (%).

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REFERENCES

1. Vaz Z. R., Cechinel-Filho V., Yunes R. A., Calixto J. B.: *J. Pharmacol. Exp. Ther.* **1996**, *278*, 304.
2. Cechinel-Filho V., Vaz Z. R., Zunino L., Calixto J. B., Yunes R. A.: *Eur. J. Med. Chem.* **1996**, *31*, 833.
3. Livingstone R. in: *Rodd's Chemistry of Carbon Compounds* (S. Coffey, Ed.), Vol. IV, Part A, p. 83. Elsevier, Amsterdam 1973.
4. Mackenzie J. B. D., Robertson A., Bushra A., Towcis R.: *J. Chem. Soc.* **1949**, 2057.
5. Hirota T., Fujita H., Sasaki K., Namba T., Hayakawa S.: *Heterocycles* **1986**, 24, 771.
6. Bisagni M., Buu-Hoi N. P., Royer R.: *J. Chem. Soc.* **1955**, 3693.
7. Sonn A., Bülow W.: *Chem. Ber.* **1925**, *58*, 1691.
8. Dean F. M., Robertson A.: *J. Chem. Soc.* **1953**, 1241.
9. Srivastava S. D., Srivastava S. K.: *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26*, 57.
10. Malterud K. E., Undheim J., Erdal J. E.: *Tetrahedron Lett.* **1985**, *26*, 4807.
11. Gillies I., Loft M.: *Synth. Commun.* **1988**, *18*, 191.
12. Gewald K., Jansch H.-J.: *J. Prakt. Chem.* **1973**, *315*, 779.
13. Vaidya V. P., Mahajan S. B., Agasimundin Y. S. : *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1981**, *20*, 391.
14. Rahman L. K. A., Scrowton R. M.: *J. Chem. Soc., Perkin Trans. 1* **1983**, 2973.
15. Carrington D. E. L., Clarke K., Scrowston R. M.: *J. Chem. Soc. C* **1971**, 3903.
16. Beck J. R.: *J. Heterocycl. Chem.* **1978**, *15*, 513.
17. Beugelmans R., Bois-Choussy M., Boudet B.: *Tetrahedron* **1983**, *39*, 4153.
18. Garcia E. E., Benjamin L. E., Fryer R. I.: *J. Heterocycl. Chem.* **1973**, *10*, 51.
19. Pirkle W. H., Simmons K. A.: *J. Org. Chem.* **1983**, *48*, 2520.

20. Fišnerová L., Brůnová B., Kocfeldová Z., Tíkalová J., Matunová E., Grimová J.: *Collect. Czech. Chem. Commun.* **1991**, 56, 2373.
21. Abramovitch R. A., Knaus G. N., Uma V.: *J. Org. Chem.* **1974**, *39*, 1101.
22. Auwers K.: *Chem. Ber.* **1925**, 58, 2081.
23. Schroeder H. E., Rigby G. W.: *J. Am. Chem. Soc.* **1949**, *71*, 2205.
24. Auwers K., Frese E.: *Justus Liebigs Ann. Chem.* **1926**, *450*, 273.
25. Brandt E. V., Ferreira D., Roux D. G.: *J. Chem. Soc., Perkin Trans. 1* **1981**, 514.
26. Borsche W., Hahn-Weinheimer P.: *Justus Liebigs Ann. Chem.* **1950**, 570.
27. Bates D. K.: *J. Org. Chem.* **1977**, *42*, 3452.
28. Eddy N. B., Leimbach D.: *J. Pharmacol. Exp. Ther.* **1953**, *80*, 385.
29. Koster R., Anderson M., De Beer J.: *Fed. Proc.* **1959**, *18*, 412.
30. D'Amour F. E., Smith D. L. J.: *Pharmacol. Exp. Ther.* **1941**, *72*, 74.