Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 335–341

BIOORGANIC & MEDICINAL CHEMISTRY

N,N-Disubstituted Aminomethyl Benzofuran Derivatives: Synthesis and Preliminary Binding Evaluation

Sophie Boyé,[a] Bruno Pfeiffer,[b] Pierre Renard,[b] Marie-Claire Rettori,[c] Gérald Guillaumet[a] and Marie-Claude Viaud[a,*]

[a]*Institut de Chimie Organique et Analytique, associé au CNRS, Université d'Orléans, B.P. 6759, 45067 Orléans Cedex 2, France*
[b]*A.D.I.R., 1, rue Carle Hébert, 92415 Courbevoie Cedex, France*
[c]*I.R.I. Servier, 6, place des Pléiades, 92415 Courbevoie Cedex, France*

Received 23 June 1998; accepted 5 October 1998

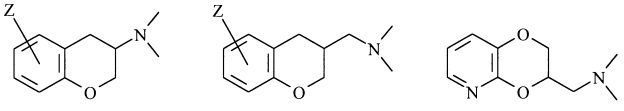
Abstract—A series of new *N*-substituted 2,3-dihydro-2-aminomethyl-2*H*-1-benzofuran derivatives was prepared and evaluated for affinity at 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, D_2, and D_3 receptors. Compound **9**, 8-[4-[*N*-propyl-*N*-(7-hydroxy-2,3-dihydro-2*H*-1-benzofuran-2-yl)methyl]aminobutyl]-8-azaspiro[4,5]decane-7,9-dione, bound at 5-HT_{1A} sites with nanomolar affinity (IC_{50} = 1.5 nM) and high selectivity over 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, D_2, and D_3 receptors.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that mediates a wide variety of physiological responses in both the peripheral and central nervous systems.[1–3] The receptors that are activated by 5-HT have been divided into at least seven classes (5-HT_{1-7}) and each class has been further subdivided into different subtypes (A, B,. . .).[4–6] Of the serotonin receptor subtypes, the 5-HT_{1A} receptor subtype is the best studied and it is generally accepted that it is involved in psychiatric disorders such as depression[7,8] and anxiety.[9,10] The early discovery of 8-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin[11] (8-OH-DPAT) a highly selective and potent 5-HT_{1A} agonist, enabled the search for new selective compounds for the 5-HT_{1A} subtype. This search has led to the discovery of several serotoninergic ligands of different chemical classes[6] (indoles, aminotetralines, arylpiperazines, and benzodioxans). Buspirone, an arylpiperazine derivative, was the first agent to be approved for chemical use as an antianxiety agent.[12,13]

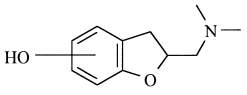
Our interest in the development of such therapeutic agents that display high affinity for 5-HT_{1A} receptor sites has recently led us to synthesize several derivatives[14–17] of 3,4-dihydro-3-amino-2*H*-1-benzopyran **I**, 3,4-dihydro-3-amino-methyl-2*H*-1-benzopyran **II** and (2,3-dihydro-1,4-dioxino[2,3-*b*]pyridinyl)-methanamine **III**.

One of those (+)-8-[4-[*N*-propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro-[4,5]decane-7,9-dione (S 20499, Alnespirone) is today under clinical development.[14]



I **II** **III**

In continuation of our previous works, we report, in this paper, the preparation and receptor binding profile of a series of compounds **A** which possess the aminomethyl benzofuran structure.



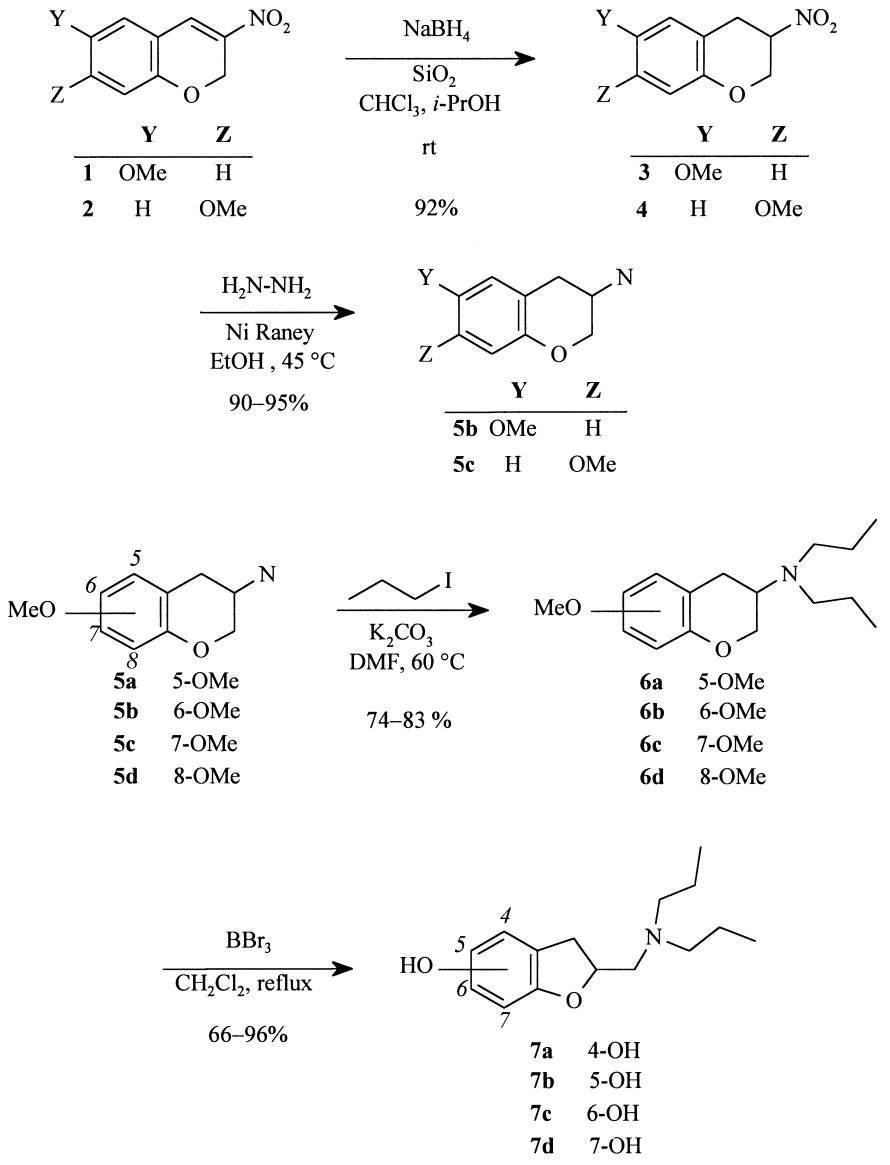
A

Chemistry

The benzopyrans **5b** and **5c** were prepared from the corresponding nitro derivatives **1** and **2** by known procedure[18] (Scheme 1). The unsaturated nitro compounds **1** or **2** reacted with sodium borohydride in the presence of silica gel in a mixture of chloroform and 2-propanol to give the saturated derivatives **3** and **4**.[19] These products were easily converted into the amines **5b** and **5c** by means of a modified procedure using hydrazine in the presence of Raney nickel.[20] The *N,N*-dipropyl compounds **6a–d** were synthesized in good yields by treatment of amines

Key words: 2,3-Dihydro-2-aminomethyl-2*H*-1-benzofurans; ring contraction; serotoninergic and dopaminergic receptor binding.
*Corresponding author. Tel.: +33 2 38 49 45 80; fax: +33 2 38 41 70 78; e-mail. Marie-Claude.Viaud@univ-orleans.fr

0968-0896/99/$ - see front matter
PII: S0968-0896(98)00239-9



Scheme 1.

5a–d with propyl iodide in *N,N*-dimethylformamide in the presence of potassium carbonate.[14]

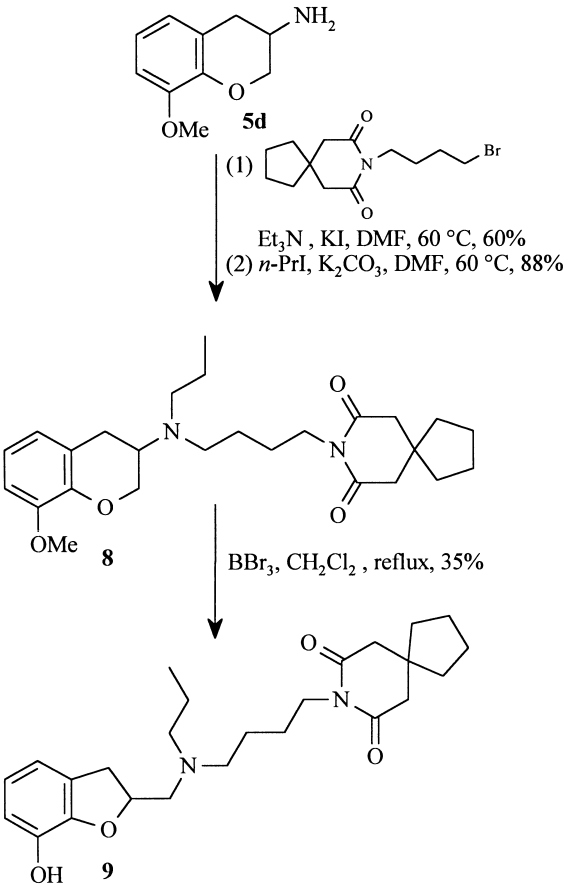
The treatment of benzopyrans **6a–d** by boron tribromide in methylene chloride under reflux provide an unexpected rearrangement.[21] This methodology furnishes the demethylated benzofurans **7a–d** in 67–96 % yields. Starting from **6a** and **6c**, the reaction of the demethylation is also observed and so the corresponding hydroxybenzopyrans **10a** and **10c** are obtained with 22 and 13% yields, respectively. The preparation of the compound **9** is described in Scheme 2. The treatment of 8-(4-bromobutyl)-8-azaspiro[4,5]decane-7,9-dione, obtained by known procedure,[14] with 8-methoxy-3,4-dihydro-3-amino-2*H*-1-benzopyran **5d**[18] in *N,N*-dimethylformamide in the presence of triethylamine and potassium iodide provided the corresponding *N*-monosubstituted amino derivative. This compound was subsequently treated with 1-iodopropane to give the desired benzopyran **8** in satisfactorily overall yield. The treatment of this compound by boron tribromide according to the procedure described for the synthesis of **7** furnish compound **9** in 35% yield. Regardless of the conditions used, a relatively large amount of the demethylated benzopyran product was always obtained.

Pharmacology

The compounds were evaluated for in vitro 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, D_2, and D_3 receptor affinity by radioligand binding assays. All the compounds were used in the form of oxalate salts and were water-soluble.

Results and Discussion

None of the synthesized compounds shows any affinity for the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, D_2, and D_3 receptors, with the exception of compound **9** which exhibits moderate affinity for the 5-HT_{2A} and D_2 receptors.

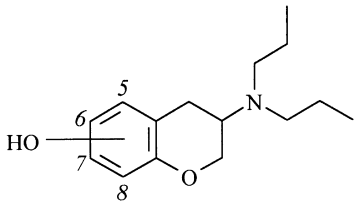


Scheme 2.

However, all these compounds present moderate to high affinity for the 5-HT_{1A} receptors.

The study of the data reported in Table 1 shows that: (1) Among the *N,N*-dipropylated derivatives **7**, compound **7d**, which is substituted by a hydroxyl group in 7-position, exhibits a good affinity for the 5-HT_{1A} receptors ($IC_{50} = 10$ nM) with a good selectivity toward the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3 ($IC_{50} > 10{,}000$ nM), D_2, and D_3 receptors ($IC_{50} > 1{,}000$ nM). (2) Replacement of one propyl moiety of compound **7d** by an imidobutyl group results in a selective high affinity 5-HT_{1A} ligand (compound **9** $IC_{50} = 1.5$ nM). Nevertheless, this compound exhibits moderate but significant affinity for D_2 receptors ($IC_{50} = 190$ nM).

The 2-aminomethylbenzofuran derivatives were also compared with their 3-aminobenzopyran "parents" **10**.



10a 5-OH
10b 6-OH
10c 7-OH
10d 8-OH

Among these, only compound **10a** shows a high affinity ($IC_{50} = 4$ nM) for the 5-HT_{1A} receptors. The results are in agreement with those obtained with aminomethyl benzofuran series since the relative position of the hydroxyl group toward the amino moiety is the same for the compounds **10a**, **7d**, and **9**. Compounds **10b** and **10d** exhibit high affinity for D_2 and D_3 receptors, respectively (**10b**, $IC_{50} = 1.2$ nM; **10d**, $IC_{50} = 7$ nM) in opposition to derivatives **7** which are devoid of any affinity for the receptors precited.

Conclusion

In conclusion, we have synthesized and evaluated a new family of potential 5-HT_{1A} ligands having a 2-aminomethyl benzofuran skeleton. Compound **9** exhibits excellent nanomolar affinity for the 5-HT_{1A} receptor with a high selectivity (> 100) toward the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and D_2 receptors. According to these in vitro results, compound **9** could be a promising candidate for future development.

Experimental

Chemistry

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Proton NMR were recorded on a Bruker 300 spectrometer. The coupling constants are recorded in hertz (Hz) and the chemical shifts are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. Infrared spectra were obtained with Perkin–Elmer spectrophotometer 297. Mass spectra were recorded on a R 10-10 C Nermag (70 eV) apparatus. Organic solvents were purified when necessary by the methods described by D. D. Perrin, W. L. F. Armarego and D. R. Perrin (*Purification of Laboratory*

Table 1 In vitro binding values of compounds **7a–d** and **9**[a]

Compound	$IC_{50} \pm SE$ (nM)					
	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_3	D_2	D_3
7a	270 ± 52	> 10 000	> 10 000	> 10 000	> 1 000	> 1 000
7b	1600 ± 200	> 10 000	ND[b]	> 10 000	> 1 000	> 1 000
7c	93 ± 9	> 10 000	ND[b]	> 10 000	> 1 000	> 1 000
7d	10 ± 3	> 10 000	> 10 000	> 10 000	> 1 000	> 1 000
9	1.5 ± 0.3	890 ± 47	7 000 ± 500	> 10 000	190 ± 29	ND[b]

[a]All compounds tested were racemic forms and used as oxalate.
[b]ND: Not determined.

Chemicals; Pergamon: Oxford, 1986) or purchased from Aldrich Chimie. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Buchi rotatory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F_{254}), and spots were visualised with UV light or an alcohol solution of ammonium cerium (IV) nitrate. Column chromatography was performed with Kieselgel 60 (70–230 mesh) silica gel (Merck) for gravity columns and Kieselgel 60 (230–400 mesh) silica gel (Merck) for flash columns. When analyses are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. The column chromatography solvents employed were distilled and solvent mixtures were reported as volume to volume ratios.

The compounds **1** and **2** were prepared by published procedure.[22] The compounds **5a** and **5d** have been described in literature.[18] The hydroxy derivatives **10** were obtained, in very good yields, by treatment of the compounds **6** with 48% hydrobromic acid at reflux or boron tribromide at low temperature.[14,23–25]

6-Methoxy-3-nitro-3,4-dihydro-2*H*-1-benzopyran 3. Under inert atmosphere, 7-methoxy-3-nitro-2*H*-1-benzopyran 1 (6.3 g, 30.4 mmol) was dissolved in a mixture of chloroform (195 mL) and 2-propanol (65 mL). While maintaining vigorous stirring, silica gel (70–230 mesh, ASTM, 15.4 g) was then poured into the flask and powdered sodium borohydride (2.90 g, 76.0 mmol) was added portionwise over a period of 15 min. The mixture was stirred for an additional 15 min, and the reaction was stopped by dropwise addition of acetic acid (4.8 mL). The reaction mixture was stirred for an additional 15 min. The insoluble material was filtered by suction and washed with dichloromethane, and then the solvent was removed in vacuo. The crude was purified by flash chromatography using petroleum ether/dichloromethane, 1/1 as eluent to give 5.87 g (92%) of **3** as a pale-yellow solid: mp 92 °C; IR (KBr) ν 1560, 1210–1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (dd, 1H, $J=6.1$, 17.4 Hz, H_4), 3.53 (dd, 1H, $J=5.5$, 17.4 Hz, H_4), 3.76 (s, 3H, OCH_3), 4.37 (dd, 1H, $J=2.9$, 11.5 Hz, H_2), 4.59 (dd, 1H, $J=5.8$, 11.5 Hz, H_2), 4.88–4.96 (m, 1H, H_3), 6.64 (d, 1H, $J=3.0$ Hz, H_5), 6.72 (dd, 1H, $J=3.0$, 8.8 Hz, H_7), 6.79 (d, 1H, $J=8.8$ Hz, H_8). Anal. ($C_{10}H_{11}NO_4$) C,H,N.

7-Methoxy-3-nitro-3,4-dihydro-2*H*-1-benzopyran 4. This compound was synthesized from **2** (3.13 g, 30.4 mmol) according to the method used for **3**. The crude product was chromatographed on a silica gel column using dichloromethane as eluent to give 2.9 g (92%) of **4** as a pale-yellow solid: mp 72–73 °C; IR (KBr) ν 1561, 1282, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (dd, 1H, $J=5.9$, 16.3 Hz, H_4), 3.47 (dd, 1H, $J=5.5$, 16.3 Hz, H_4), 3.75 (s, 3H, OCH_3), 4.36–4.44 (m, 1H, H_2), 4.60 (dd, 1H, $J=5.9$, 11.8 Hz, H_2), 4.86–4.94 (m, 1H, H_3), 6.41 (d, 1H, $J=2.2$, H_8), 6.54 (dd, 1H, $J=2.2$, 8.8 Hz, H_6), 7.01 (d, 1H, $J=8.8$ Hz, H_5). Anal. ($C_{10}H_{11}NO_4$) C,H,N.

6-Methoxy-3-amino-3,4-dihydro-2*H*-1-benzopyran 5b. Under inert atmosphere, benzopyran **3** (2.0 g, 9.6 mmol) was dissolved in ethanol (150 mL) by heating to 80 °C, and then the solution was cooled to 45 °C. Wet Raney nickel (1.90 g) was introduced, and 5.50 mL of 98% hydrazine hydrate was added portionwise for 1 h with vigorous stirring. The mixture was stirred at 45 °C for an additional 30 min, at which time the reaction was complete, monitored by TLC. After cooling, the reaction mixture was filtered on Celite and the remaining catalyst washed with ethanol. The solvent was evaporated to dryness, and the crude was purified by flash chromatography (eluent: dichloromethane then dichloromethane/methanol, 9/1) to afford 1.62 g (95%) of **5b** as a yellow oil: IR (neat) ν 3570–3100, 1190–1230 cm^{-1}; ^1H NMR ($CDCl_3$), 1.43 (br s, 2H, NH_2), 2.55 (dd, 1H, $J=6.8$, 16.3 Hz, H_4), 3.04 (dd, 1H, $J=5.3$, 16.3 Hz, H_4), 3.29–3.37 (m, 1H, H_3), 3.74 (s, 3H, OCH_3), 3.78 (dd, 1H, $J=6.9$, 10.6 Hz, H_2), 4.06–4.12 (m, 1H, H_2), 6.58 (d, 1H, $J=3.0$ Hz, H_5), 6.68 (dd, 1H, $J=3.0$, 8.9 Hz, H_7), 6.76 (d, 1H, $J=8.9$ Hz, H_8). Anal. ($C_{10}H_{13}NO_2$) C,H,N.

7-Methoxy-3-amino-3,4-dihydro-2*H*-1-benzopyran 5c. This compound was obtained from **4** (2.71 g, 12.9 mmol) according to the method used for **5b**. The crude residue was purified by column chromatography (eluent: dichloromethane/methanol, 9/1) to give 2.1 g (90%) of **5c** as an oil: IR (neat) ν 3400–3180, 1270, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (br s, 2H, NH_2), 2.46 (dd, 1H, $J=7.0$, 15.8 Hz, H_4), 2.94 (dd, 1H, $J=4.8$, 15.8 Hz, H_4), 3.25–3.37 (m, 1H, H_3), 3.71 (s, 3H, OCH_3), 3.76 (dd, 1H, $J=7.0$, 10.7 Hz, H_2), 4.03–4.13 (m, 1H, H_2), 6.34 (d, 1H, $J=2.2$ Hz, H_8), 6.42 (dd, 1H, $J=2.2$, 8.8 Hz, H_6), 6.89 (d, 1H, $J=8.8$ Hz, H_5). Anal. ($C_{10}H_{13}NO_2$) C,H,N.

Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyrans 6. General procedure. A mixture of amines **5**, 1-iodopropane (3 equiv) and potassium carbonate (3 equiv) in DMF (10 mL) was warmed with stirring at 60 °C for 6 h, under inert atmosphere. The reaction mixture was isolated to room temperature, and the solvent was removed under reduced pressure. After aqueous hydrolysis, the product was extracted with ethyl acetate and the organic layer was dried ($MgSO_4$), and evaporated to dryness. Purification by column chromatography (eluent: petroleum ether/ethyl acetate, 9/1) gave the pure compounds **6**.

5-Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran 6a.[14] By starting from **5a** (1.0 g, 5.58 mmol), this compound (1.21 g) was prepared in DMF (10 mL) according to the general procedure (82% yield).

6-Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran 6b. The title compound (1.40 g) was prepared in 83 % yield from **5b** (1.14 g, 6.38 mmol) in DMF (10 mL) according to the general procedure; colorless oil; IR (neat) ν 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 6H, $J=7.3$ Hz, CH_3), 1.34–1.47 (m, 4H, CH_2), 2.38–2.54 (m, 4H, NCH_2), 2.77 (d, 2H, $J=9.6$ Hz, H_4), 3.06–3.17 (m, 1H, H_3), 3.69 (s, 3H, OCH_3), 3.72 (t, 1H, $J=10.3$ Hz, H_2), 4.20 (ddd, 1H, $J=15.4$, 10.3 Hz, H_2), 6.56 (d, 1H, $J=2.9$ Hz, H_5), 6.61 (dd, 1H, $J=2.9$,

8.8 Hz, H_7), 6.68 (d, 1H, $J = 8.8$ Hz, H_8). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

7-Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran 6c. This compound (2.30 g) was synthesized from **5c** (2.1 g, 11.8 mmol) in DMF (20 mL) according to the general procedure (74% yield); colorless oil; IR (neat) ν 1288–1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 6H, $J = 7.3$ Hz, CH_3), 1.33–1.49 (m, 2H, CH_2), 2.38–2.53 (m, 2H, NCH_2), 2.72 (d, 2H, $J = 8.1$ Hz, H_4), 3.03–3.15 (m, 1H, H_3), 3.70 (s, 3H, OCH_3), 3.74 (t, 1H, $J = 10.3$ Hz, H_2), 4.22 (dd, 1H, $J = 3.7$, 10.3 Hz, H_2), 6.32 (d, 1H, $J = 2.2$ Hz, H_8), 6.40 (dd, 1H, $J = 2.2$, 8.1 Hz, H_6), 6.90 (d, 1H, $J = 8.1$ Hz, H_5). Anal. ($C_{16}H_{25}NO_2$) C,H,N.

8-Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran 6d. The title compound (2.30 g) was obtained in 78% yield from **5d** (2.0 g, 11.16 mmol) in DMF (20 mL) according to the general procedure; colorless oil; IR (neat) ν 1213, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 6H, $J = 7.3$ Hz, CH_3), 1.35–1.47 (m, 4H, CH_2), 2.44–2.50 (m, 4H, NCH_2), 2.80 (d, 2H, $J = 9.1$ Hz, H_4), 3.09–3.19 (m, 1H, H_3), 3.80 (t, 1H, $J = 9.8$ Hz, H_2), 3.81 (s, 3H, OCH_3), 4.38 (dd, 1H, $J = 3.0$, 9.8 Hz, H_2), 6.62–6.78 (m, 3H, H_5, H_6, H_7). Anal. ($C_{16}H_{25}NO_2$) C, H, N.

Hydroxy-2,3-dihydro-2-(di-*n*-propylaminomethyl)-2*H*-1-benzofurans 7. General procedure. **Method A**. To a stirred solution of benzopyrans **6** (0.5 mmol) in dichloromethane (5 ml) was added dropwise boron tribromide (0.05 ml, 0.55 mmol) in dichloromethane (2 mL) at room temperature under inert atmosphere. The reaction mixture was heated with stirring at reflux for 2 h, then was cooled to room temperature. The mixture was neutralized with saturated aqueous solution of sodium hydrogenocarbonate, and the product was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was purified by chromatography on a silica gel column (eluent: dichloromethane, then dichloromethane/methanol, 9/1). **Method B**. The benzopyran derivatives **6** were treated by boron tribromide (2.1 equiv) for 24 h according to the Method A described above.

4-Hydroxy-2,3-dihydro-2(di-*n*-propylaminomethyl)-2*H*-1-benzofuran 7a. The title compound (84 mg) was prepared in 67% yield from **6a** (132 mg) according to the general procedure (**Method B**). In this case, 27.5 mg (22%) of benzopyran **10a** was also obtained; yellow oil; IR (neat) ν 3660–3000, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 6H, $J = 7.3$ Hz, CH_3), 1.41–1.55 (m, 4H, CH_2), 2.52 (t, 4H, $J = 7.3$ Hz, NCH_2 CH_2), 2.65 (dd, 1H, $J = 5.6$, 13.5 Hz, NCH_2), 2.84 (dd, 1H, $J = 6.8$, 15.3 Hz, NCH_2), 2.90 (dd, 1H, $J = 7.2$, 15.3 Hz, H_3), 3.21 (dd, 1H, $J = 9.1$, 15.3 Hz, H_3), 4.33 (br s, 1H, OH), 4.87–4.98 (m, 1H, H_2), 6.29 and 6.36 (2d, 2H, $J = 8.0$ Hz, H_5 and H_7), 6.95 (t, 1H, $J = 8.0$ Hz, H_6); MS (IC/NH_3) m/z 250 (M + 1). Anal. ($C_{15}H_{22}NO_2$) C,H,N.

5-Hydroxy-2,3-dihydro-2(di-*n*-propylaminomethyl)-2*H*-1-benzofuran 7b. This compound (120 mg) was prepared in 96% yield from **6b** (132 mg) according to the general procedure (**Method B**); yellow oil; IR (neat) ν 3660–3095, 1199 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 0.86 (t, 6H, $J = 7.3$ Hz, CH_3), 1.38–1.54 (m, 4H, CH_2), 2.47 (t, 4H, $J = 7.3$ Hz, NCH_2), 2.59 (dd, 1H, $J = 5.9$, 13.6 Hz, NCH_2), 2.78 (dd, 1H, $J = 6.6$, 13.6 Hz, NCH_2), 2.93 (dd, 1H, $J = 7.3$, 15.4 Hz, H_3), 3.19 (dd, 1H, $J = 8.8$, 15.4 Hz, H_3), 4.78–4.90 (m, 1H, H_2), 6.53 (dd, 1H, $J = 2.2$, 8.3 Hz, H_6), 6.60 (d, 1H, $J = 8.3$ Hz, H_7), 6.67 (d, 1H, $J = 2.2$ Hz, H_4); MS (IC/NH_3) m/z 250 (M + 1). Anal. ($C_{15}H_{23}NO_2$) C,H,N.

6-Hydroxy-2,3-dihydro-2-(di-*n*-propylaminomethyl)-2*H*-1-benzofuran 7c. This compound (82.5 mg) was synthesized in 66% yield from **6c** (132 mg) according to the general procedure (**Method B**). In this case, 16 mg (13%) of benzopyran **10c** was also obtained; yellow oil; IR (neat) ν 3575–3150, 1142 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 0.87 (t, 6H, $J = 7.3$ Hz, CH_3), 1.40–1.55 (m, 4H, CH_2), 2.48 (t, 4H, $J = 7.3$ Hz, NCH_2), 2.59 (dd, 1H, $J = 5.5$, 13.4 Hz, CH_2N), 2.79 (dd, 1H, $J = 6.6$, 13.4 Hz, CH_2N), 2.85 (dd, 1H, $J = 7.0$, 15.3 Hz, H_3), 3.16 (dd, 1H, $J = 8.8$, 15.3 Hz, H_3), 4.83–4.94 (m, 1H, H_2), 6.24–6.32 (m, 2H, H_5 and H_7), 6.95 (d, 1H, $J = 8.1$ Hz, H_4); MS (IC/NH_3) m/z 250 (M + 1). Anal. ($C_{15}H_{23}NO_2$) C, H,N.

7-Hydroxy-2,3-dihydro-2-(di-*n*-propylaminomethyl)-2*H*-1-benzofuran 7d. The title compound (96 mg) was prepared in 77% yield from **6d** (132 mg) according to the general procedure (**Method A**); yellow oil; IR (neat) n 3670–3120 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 0.87 (t, 6H, $J = 7.3$ Hz, CH_3), 1.40–1.54 (m, 4H, CH_2), 2.50 (t, 4H, $J = 7.3$ Hz, NCH_2), 2.60 (dd, 1H, $J = 5.1$, 13.2 Hz, CH_2N), 2.82 (dd, 1H, $J = 7.3$, 13.2 Hz, CH_2N), 2.98 (dd, 1H, $J = 7.3$, 15.4 Hz, H_3), 3.28 (dd, 1H, $J = 8.8$, 15.4 Hz, H_3), 4.87–5.00 (m, 1H, H_2), 6.72 (s, 3H, H_4, H_5, and H_6); MS (IC/NH_3) m/z 250 (M + 1). Anal. ($C_{15}H_{23}NO_2$) C,H,N.

8-[4-[*N*-Propyl-*N*-(8-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4,5]decane-7,9-dione 8. A mixture of aminobenzopyran **5d** (1.20 g, 6.70 mmol), 8-(4-bromobutyl)-8-azaspiro[4,5]decane-7,9-dione[14] (2.04 g, 6.70 mmol), triethylamine (2.8 mL, 20.2 mmol), and potassium iodide (333 mg, 2.01 mmol) in 30 mL of DMF was warmed with stirring at 60 °C for 24 h under inert atmosphere. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. After aqueous hydrolysis, the product was extracted from the resulting crude with ethyl acetate. The solvent was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The crude material was chromatographed on silica gel using ethyl acetate as eluent to give 1.75 g (65%) of pure desired compound as a yellow oil; IR (neat) ν 3320, 1723, 1663 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 1.42–1.74 (m, 12H, CH_2), 2.58 (s, 4H, $COCH_2$), 2.65 (dd, 1H, $J = 7.3$, 15.9 Hz, H_4), 2.70–2.81 (m, 2H, NCH_2), 3.01 (dd, 1H, $J = 5.2$, 15.9 Hz, H_4), 3.07–3.16 (m, 1H, H_3), 3.77 (t, 2H, $J = 7.1$ Hz, $CONCH_2$), 3.86 (s, 3H, OCH_3), 3.96 (dd, 1H, $J = 7.1$, 10.6 Hz, H_2), 4.27 (ddd, 1H, $J = 2.1$, 10.6 Hz, H_2), 6.68 and 6.71 (2d, 2H, $J = 7.6$ Hz, H_5 and H_7), 6.81 (t, 1H, $J = 7.6$ Hz, H_6).

A mixture of the compound described above (656 mg, 1.64 mol), 1-iodopropane (0.30 mL, 2.46 mmol), and potassium carbonate (680 mg, 4.91 mmol) was heated with stirring at 60 °C in DMF (8 mL) for 30 h under inert atmosphere. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to yield a yellow oil. The crude was diluted by the addition of water, and the product was extracted with ethyl acetate. The combined organic fractions were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The resulting crude material was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate, 6/4) to give 640 mg (88%) of **8** as yellow oil: IR (neat) ν 1725, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, $J = 7.4$ Hz, CH_3), 1.35–1.76 (m, 14H, CH_2), 2.43–2.66 (m, 4H, CH_2), 2.75 (s, 4H, $COCH_2$), 2.82 (d, 2H, $J = 8.8$ Hz, H_4), 3.09–3.25 (m, 1H, H_3), 3.76 (t, 2H, $J = 7.4$ Hz, $CONCH_2$), 3.82 (t, 1H, $J = 10.3$ Hz, H_2), 3.85 (s, 3H, OCH_3), 4.35–4.43 (m, 1H, H_2), 6.64–6.84 (m, 3H, H_{arom}). Anal. ($C_{26}H_{38}N_2O_4$) C,H,N.

8-[4-[*N*-Propyl-*N*-(7-hydroxy-2,3-dihydro-2*H*-1-benzofuran-2-yl)methyl]aminobutyl]-8-azaspiro[4,5]decane-7,9-dione 9. A solution of boron tribromide (0.10 mL, 1.1 mmol) in dichloromethane (2 mL) was added to a stirred solution of **8** (221 mg, 0.5 mmol) in 5 ml of dichloromethane at room temperature under inert atmosphere. The reaction mixture was heated with stirring at reflux for 24 h, cooled, and then neutralized with saturated aqueous solution of sodium hydrogenocarbonate. The product was extracted with dichloromethane. The solvent was dried ($MgSO_4$) and removed in vacuo. The crude material was purified by silica gel column chromatography (eluent: dichloromethane, then dichloromethane/methanol, 9/1) to give 120 mg (56%) of 8-[4-[*N*-propyl-*N*-(5-hydroxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4,5]decane-7.9-dione[14] and 75 mg (35%) of **9** as yellow oil. IR (neat) ν 3690–3105, 1724, 1679 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 0.87 (t, 3H, $J = 7.4$ Hz, CH_3), 1.37–1.76 (m, 14H, CH_2), 2.40–2.64 (m, 5H, CH_2 and CHN), 2.58 (s, 4H, $COCH_2$), 2.80 (dd, 1H, $J = 8.1$, 14.0 Hz, CH_2N), 2.89 (dd, 1H, $J = 7.4$, 15.4 Hz, H_3), 3.26 (dd, 1H, $J = 8.8$, 15.4 Hz, H_3), 3.69–3.88 (m, 2H, $CONCH_2$), 4.86–4.97 (m, 1H, H_2), 6.69–6.74 (m, 3H, H_{arom}); MS (IC/NH_3) *m*/*z* 429 (M + 1). Anal. ($C_{25}H_{36}N_2O_4$) C,H,N.

Pharmacology

Binding experiments. Receptor binding assays were conducted using methods previously reported in the literature. Briefly, 5-HT_{1A} assays used rat hippocampus membranes, [^{3}H]-8-OH-DPAT, and buspirone for nonspecific binding (NSB).[26] 5-HT_{2A} assays used calf frontal cortex, [^{3}H]ketanserin, and spiperone for NSB.[27] 5-HT_{2C} assays used pig choroid plexus, [^{3}H]-*N*-methyl-mesulergine, and mianserine for NSB.[28] 5-HT_3 assays used NG 10815 cells, [^{3}H]-BRC 36694, and ICS 205930 for NSB.[29] D_2 assays used calf caudate nucleus, [3H]-SDZ205-501, and butaclamol for NSB.[30] D_3 assays used cloned rat receptors, [^{3}H]-R-(+)-7-OH-DPAT, and spiperone for NSB.[31]

The concentration of the radioligands used in competition studies were approximately equal to the K_D of the binding system. The affinity of the ligands tested to these receptors was expressed as IC_{50} (concentration inhibiting 50% of the specific binding) and calculated using LUNDON 2 software. The results obtained are reported in Table 1.

Acknowledgements

The authors thank Mrs M. M. Le Floch and M. Obert for typing the manuscript.

References

1. Zifa, E.; Fillion, G. *Pharmacol. Rev.* **1992**, *44*, 401.
2. Humphrey, P. P. A. In *Serotonin Receptor Subtypes: Pharmacological Significance and Clinical Investigations*; Langer, S. Z.; Brunello, N.; Racagni, G.; Mendlewicz, J.; Eds.; Karger: Basel 1992; Vol. 1, p 129.
3. Saudou, F.; Hen, R. *Med. Chem. Res.* **1994**, *4*, 16.
4. Martin, G. R.; Humphrey, P. P. A. *Neuropharmacology* **1994**, *33*, 261.
5. Hoyer, D.; Martin, G. R. *Behav. Brain Res.* **1996**, *73*, 263.
6. Olivier, B.; Van Wijngaarden, I.; Soudijn, W. *Serotonin Receptors and their Ligands*; Elsevier: Amsterdam, 1997.
7. Artigas, F. *Trends Pharmacol. Sci.* **1993**, *14*, 262.
8. Blier, P.; Montigny, C. *Trends Pharmacol. Sci.* **1994**, *15*, 220.
9. Barrett, J. E.; Vanover, K. E. *Psycopharmacology* **1993**, *112*, 1.
10. Hamon, M. *Trends Pharmacol. Sci.* **1994**, *15*, 36.
11. Middlemis, D. N.; Fozard, J. R. *Eur. J. Pharmacol.* **1983**, *90*, 151.
12. Harrington, T. M.; Albrecht, D.; David, D.; Downey, D. B.; Freeman, A.; Miller, E.; Norton, J.; Roth, D.; Rumbo, N.; Shehan, D.; Weart, W. *Drug Invest.* **1989**, *1*, 1.
13. Böhm, C.; Placchi, M.; Stallone, F.; Gammans, R. E.; Alms, D. E.; Shrotriya, R. C.; Robinson, D. S. J. *Clin. Psychopharmacol.* **1990**, *10 (Suppl. 3)*, 38.
14. Podona, T.; Guardiola-Lemaître, B.; Caignard, D. H; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779.
15. Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D. H.; Renard, P.; Rettori, M. C.; Adam, G.; Guardiola-Lemaître, B. *J. Med. Chem.* **1996**, *39*, 4285.
16. Marot, C; Comoy, C.; Viaud, M. C.; Rettori, M. C.; Pfeiffer, B.; Morin-Allory, L.; Guillaumet, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1077.
17. Comoy, C.; Benarab, A.; Monteil, A.; Leinot, M.; Massingham, R.; Guillaumet, G. *Med. Chem. Res.* **1996**, *6*, 392.
18. Al Neirabeyeh, M.; Reynaud, D.; Podona, T.; Ou, L.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L.; Gharib, A.; Sarda, N. *Eur. J. Med. Chem.* **1991**, *26*, 497.
19. Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227.
20. Hamacher, H. *Arzneim. Forsch. Drug Res.* **1979**, *29*, 463.
21. Boyé, S.; Guillaumet, G.; Viaud, M. C. to be published.
22. Al Neirabeyeh, M.; Koussini, R.; Guillaumet, G. *Synth. Commun.* **1990**, *20*, 783.
23. Dijkstra, D.; Mulder, T. B. A.; Rollema, H.; Tepper, P. G.; Van der Weide, J.; Horn, A. S. *J. Med. Chem.* **1988**, *31*, 2178.
24. Wise, L. D.; De Wald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A. *J. Med. Chem.* **1988**, *31*, 688.
25. Horn, A. S.; Kaptein, B.; Vermue, N. A.; De Vries, J. B.; Mulder, T. B. A. *Eur. J. Med. Chem.* **1988**, *23*, 325.

26. Hoyer, D.; Engel, G.; Kalkman, H. O. *Eur. J. Pharmacol.* **1985**, *118*, 13.
27. Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.
28. Sanders-Busch, E.; Breeding, M. *J. Pharmacol. Exp.* **1988**, *247*, 169.
29. Hoyer, D.; Neijt, H. C. *Eur. J. Pharmacol.* **1987**, *143*, 291.
30. Köhler, C.; Hall, H.; Ogren, J. V.; Gawell, L. *Biochem. Pharmacol.* **1985**, *34*, 2251.
31. Martres, M. P.; Bouthenet, M. L.; Salès, N.; Sokoloff, P.; Schwartz, J. C. *Science* **1985**, *228*, 752.