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Substituted 3-Amino and/or 3-Aminomethyl-3,4-dihydro-2*H*-1-benzopyrans: Synthesis and Biological Activity

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Abstract—A series of new 3-amino, 3-aminomethyl-5-alkoxy-3,4-dihydro-2*H*-1-benzopyran and 5′-alkoxy-3′,4′-dihydrospiro-[piperazine-2,3′(2′*H*)-benzopyran] derivatives was prepared and evaluated for affinity at 5-HT_{1A}, 5-HT_{2A} and D_2 receptors. Two of the compounds (**1f** and **2b**) can be considered as potent and selective 5-HT_{2A} ligands. One compound (**1g**) demonstrated high affinity for 5-HT_{1A} and D_2 receptor binding sites and one compound (**1d**) proved to be a mixed 5-HT_{1A}/5-HT_{2A} ligand.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was discovered as a central neurotransmitter about 40 years ago. 5-HT has been implicated in the aetiology of many disease states and may be particularly important in mental illness, such as depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder (OCD), migraine and panic disorder.[1–9] Indeed, many currently used treatments of these disorders are thought to act by modulating serotoninergic tone.

During the last decade, 5-HT receptors were classified in seven types (5-HT_{1-7}) and several families has been further subdivided into different subtypes (A, B, C...).[10–16] One of them, the 5-HT_{1A} receptor type is the best studied and it was shown to be involved in psychiatric disorders such as depression[17–20] and anxiety.[21,22] Buspirone (Fig. 1), an arylpiperazine derivative with high affinity for the 5-HT_{1A} receptor, was the first agent to be approved for clinical use.[23–30] On the other hand, the 5-HT_2 family of serotonin receptors includes three subtypes. The 5-HT_{2A} subtype is the best characterised with respect to distribution and function. It is involved in various cardiovascular and mental disorders. Ketanserin (Fig. 1), which is a potent 5-HT_{2A} antagonist, was clinically evaluated for its potential use in the treatment of hypertension.[31–34] However, this compound is not selective and its affinity for the α_1 receptor subtype could explain some of its cardiovascular effects.

Ritanserin (Fig. 1), a potent and selective 5-HT_{2A}/5-HT_{2C} central antagonist, was also found to improve the symptoms of generalized anxiety disorders.[35,36] Recent studies established that in the search of anxiolytics with reduced side effects, combination of 5-HT_{1A} and 5-HT_{2A} central antagonism could lead to a new therapeutic concept. Several works in this field confirm this hypothesis.[37,38]

Furthermore, its has been recently reported that (1,2-benzoisothiazole-3-yl) piperazine derivatives and benzisothiazole-3-carboxamide derivatives **I** and **II** (Fig. 2) are 5-HT_{1A}, 5-HT_{2A} and D_2 receptors ligands and exhibit antipsychotic activity in animal models.[39–41] Such compounds would be atypical antipsychotics which elicit their psychotherapeutic effects with lower neurological side effects.

In connection with our research towards the elaboration of products liable to affect the central nervous system (CNS),[42–48] we had prepared new ligands **1a**, **1b**, **1c**, **2a**, **3a** and **3b** with 3,4-dihydro-2*H*-1-benzopyran moiety that showed high affinity and selectivity for the 5-HT_{1A} receptors (Figs 3, 4 and 5). The aim of the present work was to modify these ligands in order to provide them with a mixed affinity for 5-HT_{1A} and 5-HT_{2A} receptors.

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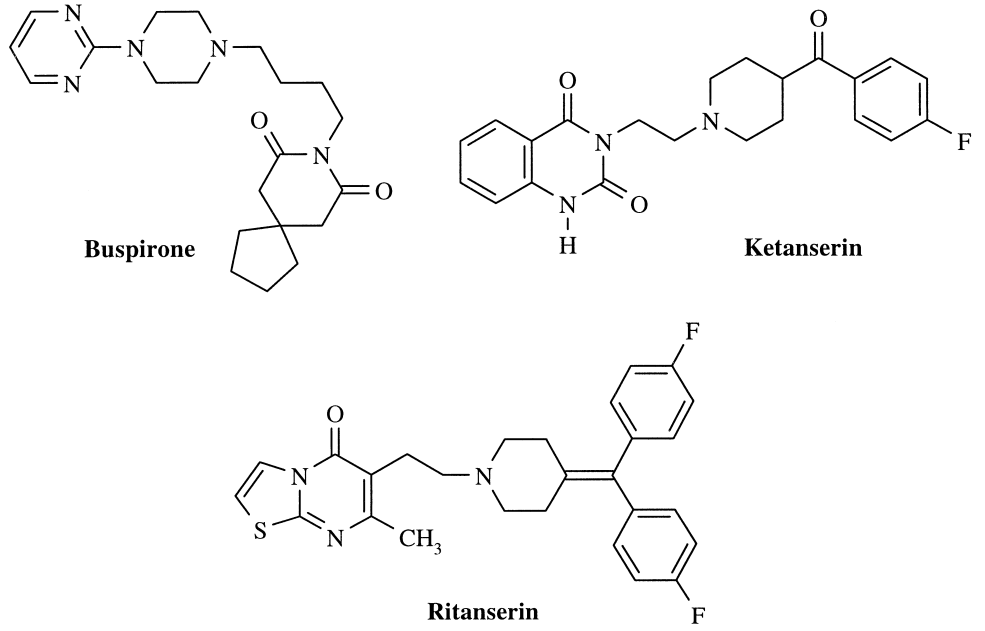


Figure 1. Structure of buspirone, ketanserin and ritanserin.

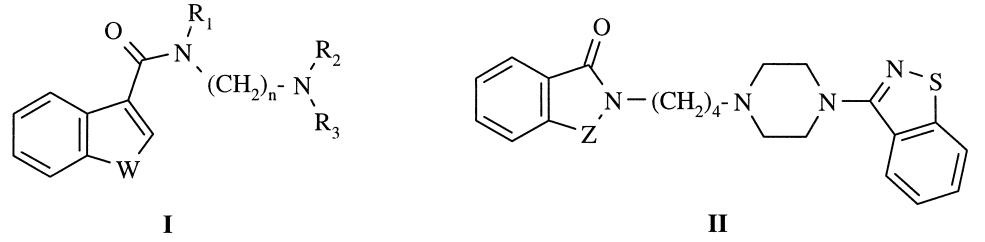


Figure 2. Structure of (1,2-benzoisothioazole-3-yl) piperazine derivatives **I** and benzoisothiazole-3-carboxamide derivatives **II**.

We report, here, the synthesis and the biological evaluation of 16 potential mixed ligands. Theses products belongs to four families of benzopyran derivatives:

N-Substituted-3-amino-5-alkoxy-3,4-dihydro-2*H*-1-benzopyrans **1** (Fig. 3).

N-Substituted-3-aminomethyl-5-alkoxy-3,4-dihydro-2*H*-1-benzopyrans **2** (Fig. 4).

N-Substituted-5′-methoxy-3′,4′-dihydrospiro[piperidine-2,3′(2′*H*) benzopyrans] **3** (Fig. 5).

N,N-Disubstituted-5′-methoxy-3′,4′-dihydrospiro[piperazine-2,3′(2′*H*)-benzopyrans] **4** (Fig. 6).

Chemistry

The first part of our study dealing with the synthesis of various *O*-and *N*-substituted 3-amino-5-alkoxybenzopyrans **1** (Fig. 3) is outlined in Schemes 1–3.

O-Demethylation of 5-methoxy-3,4-dihydro-2*H*-1-benzopyran (**1a**) by refluxing bromhydric acid in acetic acid (HBr/AcOH) provided the desired aminophenol (**5**) in 95% yield.[46] *O*-Alkylation of **5** with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione, in the presence of potassium carbonate (K_2CO_3) and a catalytic amount of potassium iodide (KI), in *N,N*-dimethylformamide (DMF) as solvent, gave the expected compound **1c** in 79% yield (Scheme 1).[46]

On the other hand, by treatment with the boron tribromide–dimethylsulfide complex ($BBr_3{\cdot}Me_2S$)[49] in dichloroethane ($C_2H_4Cl_2$), the 3,4-dihydro-2*H*-1-benzopyran **1b** afforded the desired phenol **6** in 81% yield. In previous work,[46] demethylation of **1b** was performed with BBr_3. This methodology afforded compound **6** in lower yield due to the concomitant formation of a benzofuran by-product.[50] *O*-Alkylation of **6** with 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine **7**, in the presence of potassium carbonate and a catalytic amount of potassium iodide, in *N,N*-dimethylformamide gave the expected benzopyran **1d** in good yield. Concerning the synthesis of **1e**, phenol **6** reacted with 1,3-dibromopropane in toluene, in the presence of potassium carbonate and *n*-tetrabutylammonium bromide as phase transfer agent,[51] to give the corresponding monobromide in 84% yield. Then, treatment of this latter compound with 2-aminoindane hydrochloride, in the presence of *N,N*-diisopropylethylamine (*i*-Pr_2NEt) and a catalytic amount of potassium iodide in *N,N*-dimethylformamide, afforded the expected benzopyran (**1e**) in moderate yield (Scheme 2).

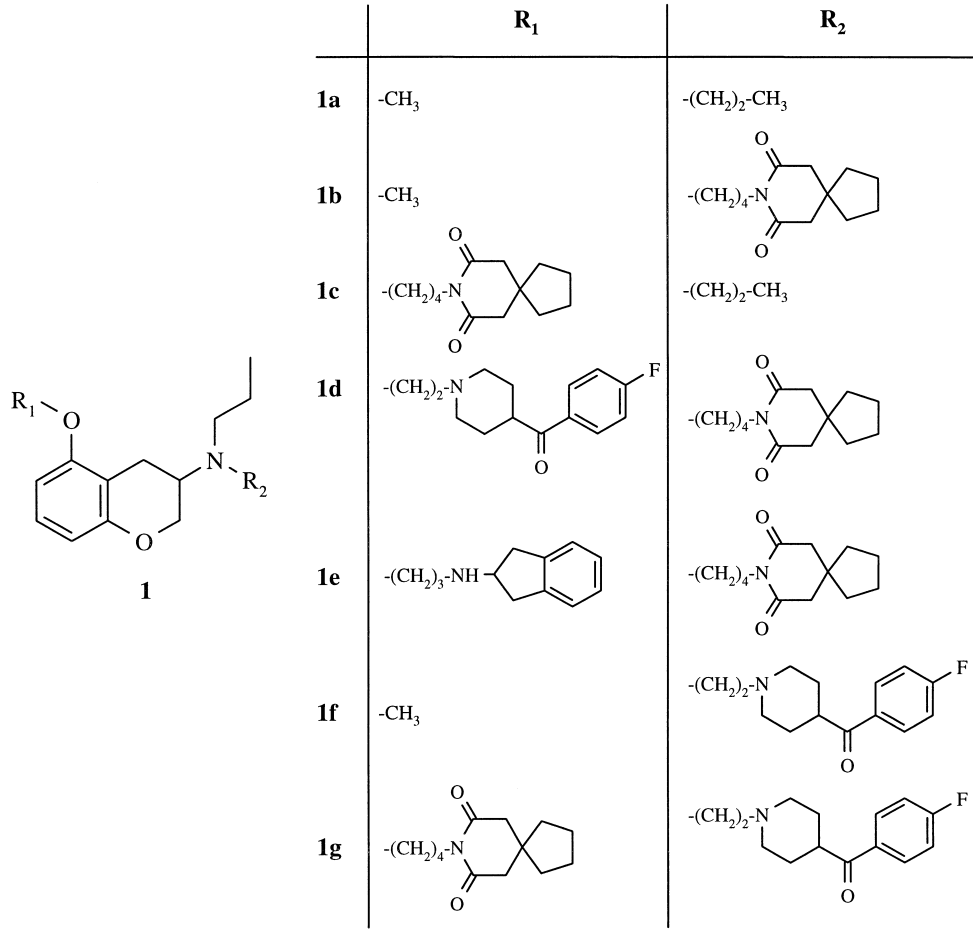


Figure 3. Structure of *N*-substituted-3-amino-5-alkoxy-3,4-dihydro-2*H*-1-benzopyran derivatives **1**.

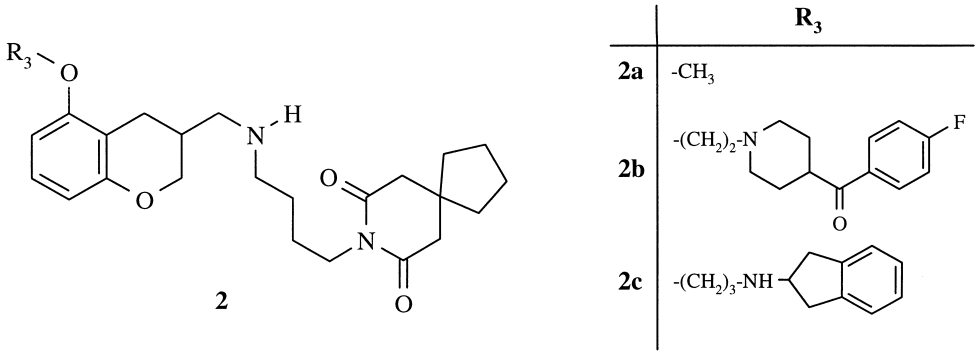


Figure 4. Structure of *N*-substituted-3-aminomethyl-5-alkoxy-3′,4-dihydro-2*H*-1-benzopyran derivatives **2**.

Moreover, derivatives **1f** and **g** were prepared starting from the 3-*n*-propylamino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran (**8**),[46] as shown in Scheme 3. *N*-Acylation of amine **8** with sodium hydroxide and chloroacetyl chloride in dichloromethane gave the expected amide **9** in 76% yield. Reduction of **9** with borane–dimethylsulfide complex ($BH_3.Me_2S$)[52] in refluxing tetrahydrofuran (THF) afforded the chloroethylamine **10** in 52% yield.[53] This compound reacted with 4-(4-fluorobenzoyl)piperidine in the presence of potassium carbonate and a catalytic amount of potassium iodide, in *N,N*-dimethylformamide, to afford the compound **1f** in excellent yield (94%). Afterwards, demethylation of **1f** was carried out in a 48% aqueous bromhydric acid/acetic acid solution in 67% yield. The *O*-alkylation of this obtained phenol in usual conditions (K_2CO_3, DMF, KI) with 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione gave the compound **1g** in 58% yield.

The second part of our present work concerned the elaboration of the compounds **2b** and **2c** (Fig. 4, Scheme 4). Synthesis of precursor, the 3-aminomethyl-5-methoxy-3,4-dihydro-2*H*-1-benzopyran (**2a**), has been described in a recent paper.[46] After demethylation of **2a**, in 60% yield, using boron tribromide–dimethylsulfide complex in dichloroethane, the obtained aminophenol was treated

with *t*-butyloxycarbonyl anhydride (Boc_2O) in the presence of triethylamine (Et_3N) in dichloromethane to afford the *N*-protected derivative **11** in 82% yield. *O*-Alkylation of **11** with chloro derivative **7**, in the presence of potassium carbonate in *N,N*-dimethylformamide, followed by a reaction with trifluoroacetic acid (TFA) in dichloromethane, gave the expected compound **2b** in good yield.

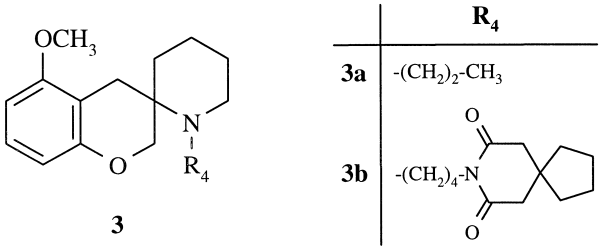


Figure 5. Structure of *N*-substituted-5′-methoxy-3′,4′-dihydrospiro [piperidine-2,3′(2′*H*)-benzopyran] derivatives **3**.

Compound **2c** was obtained in three steps. At first, the phenol **11** was treated with 1,3-dibromopropane in the presence of potassium carbonate and *n*-tetrabutylammonium bromide in toluene to afford the expected bromide in 82% yield. This compound reacted with 2-aminoindane hydrochloride in the presence of diisopropylethylamine and a catalycic amount of potassium iodide, in *N,N*-dimethylformamide, to give the desired *O*-alkylated benzopyran in moderate yield (34%). Then, *N*-deprotection of this benzopyran, using trifluoroacetic acid in dichloromethane, yielded the expected derivative **2c** in 77% yield.

The last series studied was the 5-methoxy-3,4-dihydro-*N,N*-disubstituted spiro[piperazine-2,3′(2′*H*)-benzopyrans] (**4a–d**) (Fig. 6). Preparation of the benzopyran **12**, a precursor of these derivatives **4a–d**, has been described in a recent paper.[54] As shown in scheme 5, *N*-alkylations of amine **12** were performed with *n*-propyl iodide, 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione and 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine (**7**) in the

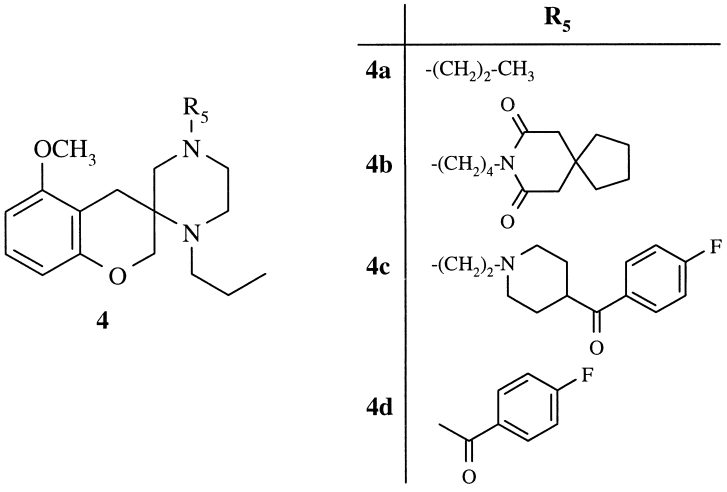
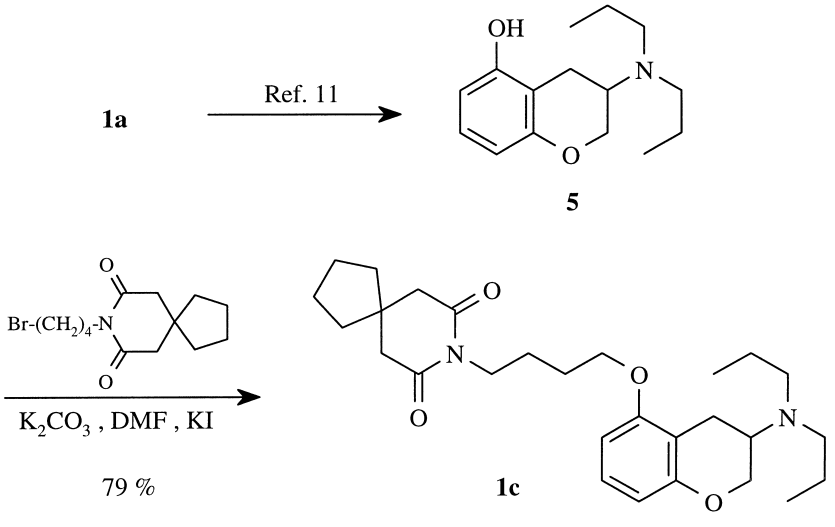
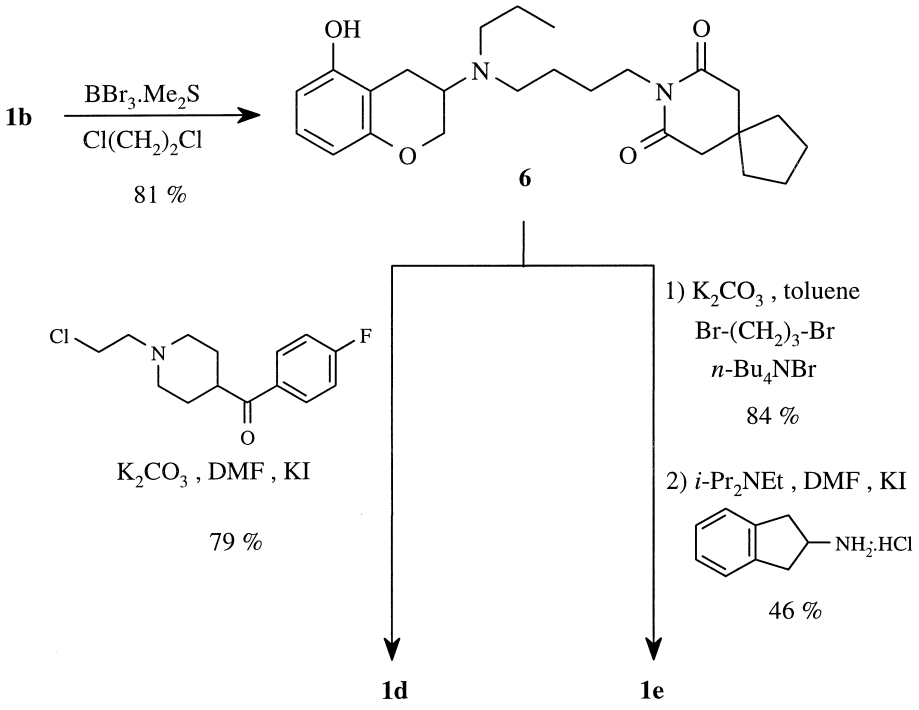


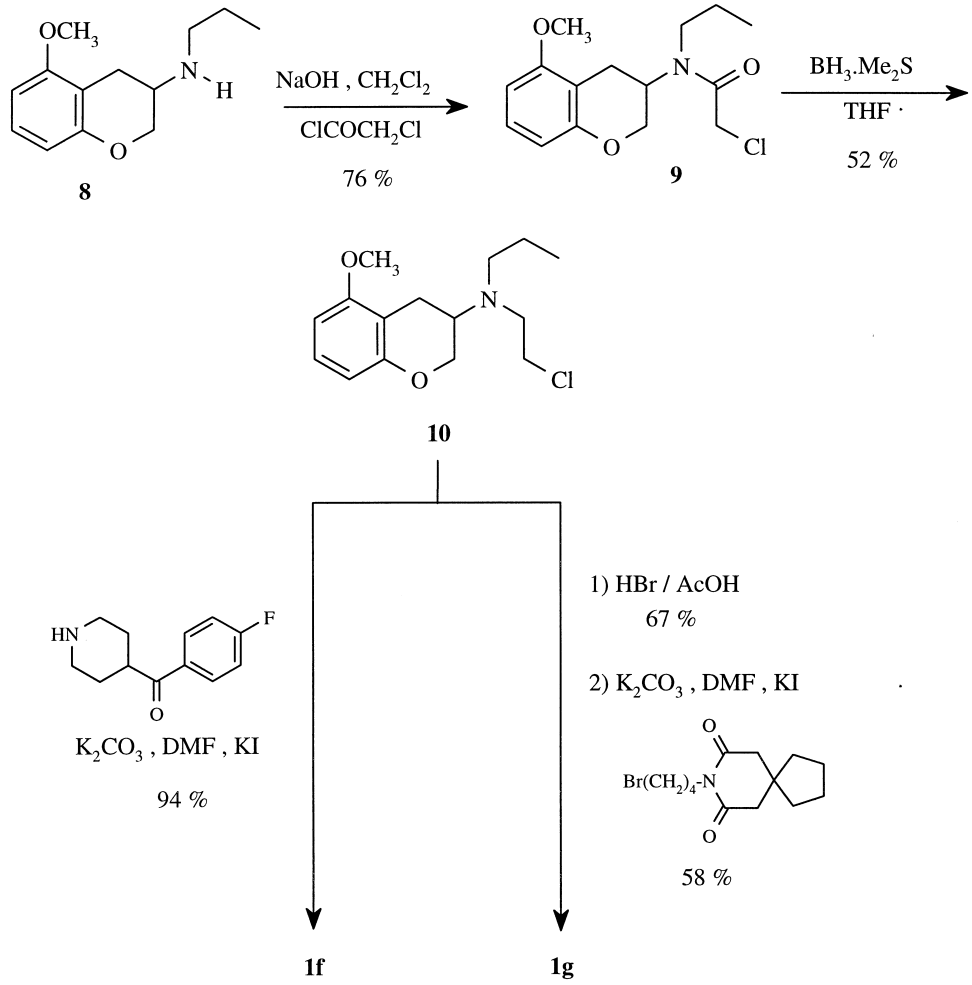
Figure 6. Structure of *N,N*-disubstituted-5′-methoxy-3′,4′-dihydrospiro[piperazine-2,3′(2′*H*)-benzopyran] derivatives **3**.



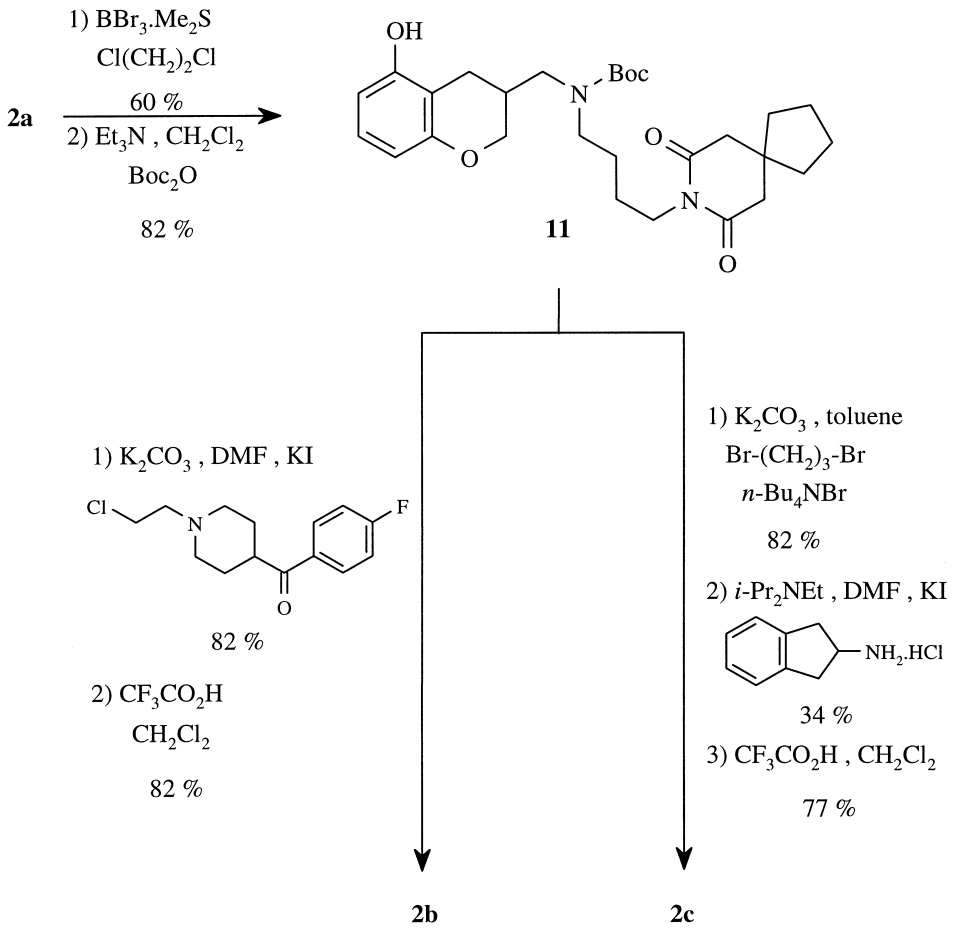
Scheme 1.



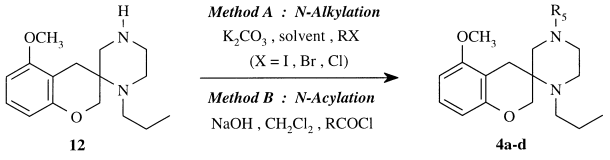
Scheme 2.

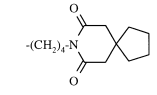
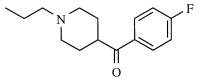
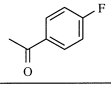


Scheme 3.



Scheme 4.



Compounds	R_5	Method	Yield %[a]
4a	$-(CH_2)_2-CH_3$	*A*[b,c]	70
4b		*A*[b,c]	85
4c		*A*[d]	86
4d		*B*	86

Scheme 5. [a]Yields of isolated products based on amine **12**, after purification by column chromatography. [b]For the synthesis of **4a** and **4b** see ref 54. [c]Acetone was the solvent. [d]Acetonitrile was used as solvent in the presence of a catalytic amount of potassium iodide.

presence of potassium carbonate, in acetone or acetonitrile as solvents, to afford the expected compounds **4a**, **4b** and **4c** in 70%, 85% and 86% yields, respectively. *N*-Acetylation of **12** using 4-fluorobenzoylchloride in the presence of sodium hydroxide in dichloromethane gave the expected product **4d** in good yield (86%).

Biological Results and Discussion

As explained in Introduction, our concept was to modify compounds already known for their high affinity for the 5-HT_{1A} receptors in order to provide them with an additional good affinity for 5-HT_{2A} receptors.

All the synthesized compounds were evaluated for their affinity for the 5-HT_{1A}, 5-HT_{2A} receptor, and then for some of them, 5-HT_{2C} and D_2 receptors (see Table 1 and Experimental).

In a first step, four derivatives were prepared in the *N*-substituted-3-amino-5-alkoxy-3,4-dihydro-2*H*-1-benzopyran series which, in previous works,[46] had led us to the obtention of potent and selective 5-HT_{1A} ligands, with among others, compounds **1a** and **1b** (Fig. 3).

We validated our concept with compound **1f** which is an analogue of compound **1a**, substituted on the basic nitrogen atom by the 2-[4-(4-fluorobenzoyl)piperidine]ethyl moiety of ketanserin. As expected, compound **1f** was found to be a high affinity ligand for both 5-HT_{1A} and 5-HT_{2A} receptors with IC_{50} values of

Table 1. Binding values of compounds **1**, **2**, **3** and **4** (IC_{50} values, M)[a]

Compounds	5-HT_{1A}[b]	5-HT_{2A}[c]	5-HT_{2C}[d]	D_2[e]
1a	2.0×10^{-8}	6.0×10^{-5}	—	5.0×10^{-8}
1b[f]	2.0×10^{-10}	1.0×10^{-6}	—	1.0×10^{-8}
1c[f]	4.0×10^{-9}	10^{-4}	10^{-4}	1.0×10^{-5}
1d[f]	$(8.8\pm0.5)\times10^{-8}$	$(7.4\pm0.4)\times10^{-8}$	$(3.0\pm0.8)\times10^{-6}$	$(3.1\pm0.5)\times10^{-7}$
1e[h]	$(4.3\pm0.3)\times10^{-9}$	$(1.1\pm0.3)\times10^{-6}$	$(5.0\pm1.2)\times10^{-6}$	$(5.7\pm0.4)\times10^{-7}$
1f[f]	$(6.8\pm0.4)\times10^{-8}$	$(1.1\pm0.1)\times10^{-9}$	$(3.0\pm0.5)\times10^{-6}$	$(7.3\pm0.4)\times10^{-8}$
1g[f]	$(8.7\pm0.9)\times10^{-7}$	$(6.0\pm0.7)\times10^{-9}$	$(8.0\pm1.3)\times10^{-7}$	$(1.2\pm0.2)\times10^{-8}$
2a[f]	$(1.29\pm0.12)\times10^{-10}$	$(4.96\pm0.79)\times10^{-8}$	$(1.71\pm0.20)\times10^{-7}$	$(2.96\pm0.2)\times10^{-8}$
2b[g]	$(1.2\pm0.2)\times10^{-6}$	$(2.4\pm0.1)\times10^{-9}$	$(1.0\pm0.5)\times10^{-6}$	$(7.1\pm0.7)\times10^{-8}$
2c[f]	$(2.5\pm0.3)\times10^{-8}$	$(1.4\pm05)\times10^{-6}$	10^{-5}	$(6.6\pm0.8)\times10^{-7}$
3a[f]	$(4.2\pm0.23)\times10^{-7}$	$(4.14\pm0.59)\times10^{-5}$	—	$(1.47\pm0.07)\times10^{-5}$
3b[f]	$(8.81\pm0.23)\times10^{-9}$	$(2.91\pm0.47)\times10^{-5}$	—	$(2.84\pm0.95)\times10^{-6}$
4a[f]	$(2.4\pm0.6)\times10^{-6}$	$(6.9\pm2.8)\times10^{-6}$	$(1.5\pm0.6)\times10^{-5}$	$(2.4\pm0.9)\times10^{-5}$
4b[f]	$(1.2\pm0.4)\times10^{-5}$	$(7.6\pm3.1)\times10^{-6}$	$(1.5\pm0.4)\times10^{-5}$	10^{-4}
4c[f]	10^{-4}	10^{-4}	—	–
4d[g]	$(8.1\pm1.2)\times10^{-6}$	$(4.5\pm0.6)\times10^{-7}$	—	–
Buspirone[i]	2.0×10^{-8}	8.12×10^{-7}	3.8×10^{-6}	9.6×10^{-8}
Ritanserin[i]	1.05×10^{-6}	0.25×10^{-9}	0.58×10^{-9}	3.6×10^{-8}
Ketanserin[i]	$\sim10^{-5}$	2.0×10^{-9}	1.0×10^{-7}	3.98×10^{-7}

[a]Results are expressed as $IC_{50}\pm$SEM (concentration inhibiting 50% of the specific binding).
[b–e]Radioligands and tissue preparation for affinity determination. [b][^{3}H] 8-OH-DPAT, bovine frontal cortex and hippocampus; [c][^{3}H] ketanserin, bovine frontal cortex; [d][^{3}H] *N*-methyl-mesolergine, pig choroide plexus; [e][^{3}H] raclopride, bovine striatum.
[f–h]The compounds were tested as: [f]oxalate; [g]free base; or [h]fumarate.
[i]Results expressed as K_i in M.[60–63]

6.8×10^{-8} M and 1.1×10^{-9} M, respectively, compared to IC_{50} values of 2.0×10^{-8} M and 6.0×10^{-5} M, respectively, for compound **1a** (almost no decrease of the 5-HT_{1A} affinity and a 10,000-fold increase of 5-HT_{2A} affinity).

We then prepared compounds combining both the 2-(4-fluorobenzoyl)piperidine moiety of ketanserine and the 8-azaspiro[4,5]decane-7,9-dione substituent of buspirone.

This was archieved by substitution of compound **1c** and **1b** respectively on the basic amino moiety (compound **1g**) and on the 5-position of the benzopyran skeleton (compound **1d**).

In the case of compound **1g**, we observed a very clear improvement (100,000-fold) of the 5-HT_{2A} affinity with IC_{50} values of 6.0×10^{-9} M compared to 1.0×10^{-4} M for **1c**.

Compound **1d** proved also to be a better $5HT_{2a}$ ligand with an IC_{50} of 7.4×10^{-8} M compared to 1.0×10^{-6} M for its counterpart **1b**.

Unfortunately, and despite the 8-azaspiro[4.5]decane-7,9-dione moiety, both compounds **1g** and **1d** exhibited lower 5-HT_{1A} affinity (IC_{50} of 8.7×10^{-7} and 8.8×10^{-8} M, respectively) than their 'parent' counterpart **1c** ($IC_{50}=4.0\times10^{-9}$ M) and **1b** ($IC_{50}=2.0\times10^{-10}$ M).

A possible explanation for this difference of recognition by the 5-HT_{1A} and 5-HT_{2A} receptor subtype could be connected to different structural requirements in term of steric hindrance. This requirements seems to be more critical for the 5-HT_{1A} subtype.

According to unpublished personal results a 5-[3-(2,3-dihydro-1*H*-2-indenylamino)propoxy] moiety was 'added' to the compound **1b** structure in order to provide it with 5-HT_{2C} affinity. In this way we obtained compound **1e** which retains high 5-HT_{1A} affinity ($IC_{50}=4.3\times10^{-9}$ M) but exhibits only moderate to low affinities for both 5-HT_{2A} and 5-HT_{2C} receptors with IC_{50} of 1.1×10^{-6} M and 5.0×10^{-6} M, respectively.

The same pharmacomodulations were also performed in the 3-aminomethyl-5-alkoxy-3,4-dihydro-2*H*-1-benzopyran series with as start point compound **2a** (Fig. 4), already described as a very potent 5-HT_{1A} ligand ($IC_{50}=1.29\times10^{-10}$ M) having also a significant affinity ($IC_{50}=4.96\times10^{-8}$ M) for the 5-HT_{2A} receptors.[48]

As in the previous series, introduction in the 5-position of the benzopyran of the 2-[4-(4-fluorobenzoyl)piperidine]ethyl moiety of ketanserin (compound **2b**) results in a significant increase (20-fold) of the 5-HT_{2A} affinity with IC_{50} values of 2.35×10^{-9} M compared to 4.90×10^{-8} M for the 'parent' derivative **2a** but at the cost of a drastic decrease (10,000-fold) of the 5-HT_{1A} affinity ($IC_{50}=1.2\times10^{-6}$ M for **2b** compared to 1.29×10^{-10} M for **2a**).

Compound **2c**, which is substituted by the same 2-aminoindane moiety than compound **1e**, is devoided of any significant 5-HT_{2C} affinity.

Four compounds were also synthesized and evaluated in an original new *N*,*N*′-disubstituted-5′-methoxy-3′,4′-dihydrospiro[piperazin-2,3′(2′*H*)-benzopyran] series (Fig. 6) directly inspired from previously described 5-HT_{1A} selective spiro[piperidine-2,3′(2′*H*)-benzopyran] ligands,[47] with among others compounds **3a** and **3b** (Fig. 5). Whatever the substitution on the piperazine's nitrogen (propyl compound **4a**; 4-(7,9-dioxo-8-azaspiro[4′,5′]decanyl)butyl compound **4b**; 2-[4-(4-fluorobenzoyl)piperidino]ethyl compound **4c** and 4-fluorobenzoyl compound **4d**), none of the prepared compounds exhibits high affinity for 5-HT_{1A} and/or 5-HT_{2A} receptors. The

best results are these of benzopyran **4d** with IC_{50} values of 8.1×10^{-6} M for 5-HT_{1A} and 4.5×10^{-7} M for 5-HT_{2A}.

Due to their good affinity for 5-HT_{1A} and/or 5-HT_{2A} receptors, compounds belonging to the 3-amino and 3-aminomethylbenzopyran series were, in a second time, investigated on the dopamine D_2 receptors. All of them exhibit IC_{50} values between 6.6×10^{-7} M and 1.2×10^{-8} M.

Compound **1g** can be considered as a mixed 5-HT_{2A} ($IC_{50}=6\times10^{-9}$ M) and D_2 ($IC_{50}=1.2\times10^{-8}$ M) ligand with a selectivity higher than 60 times towards the $5HT_{1A}$ and $5HT_{2C}$ receptors.

Conclusion

In conclusion, among the 10 synthesized compounds, two of them (**2b** and **1f**) can be considered as potent and selective 5-HT_{2A} ligands with IC_{50} values in the nanomolar range and one (compound **1g**) as a mixed 5-HT_{2A}/D_2 ligand. One of them (compound **1d**) proved to be a mixed 5-HT_{1A}/5-HT_{2A} ligand with similar affinities ($IC_{50}\simeq 8.0\times10^{-8}$ M) for both receptors.

In a next step complementary studies will be performed to assess the central 5-HT_2 antagonist activity. The compounds will also be evaluated in the light/dark box test in mice which is predictive of anxiolytic activity

Experimental

Chemistry

Melting points (mp) (uncorrected) were determined on a Köfler hot-stage apparatus. Infrared spectra were given with a Perkin–Elmer 297 spectrometer. The proton NMR spectra were obtained on a Bruker AM 300 spectrometer (300 MHz). Chemical shift are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) which was used as an internal standard. The deuterated NMR solvents containing 99.8% deuterium with 1% (v/v) TMS were obtained from Aldrich-Chimie. ^{1}H NMR coupling constants (J values) are listed in hertz (Hz), and spin multiplicies are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad signal (br s). Chemical ionization mass spectral data (MS) were reported on a R10-10C Nermag (70 eV) apparatus using chemical ionization (CI/NH_3) or electronic impact (EI) methods. Organic solvents were purified when necessary by methods described by D. D. Perrin, WLF. Armarego, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or were purchased from Aldrich or Acros. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotarory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silical gel, $60F_{254}$) and spots were visualised with UV light or alcohol solution of ammonium cerium (IV) nitrate. Column chromatography was performed with Kiesegel 60 (70–230 mesh) silica gel (Merck) for gravity columns and Kieselgel 60 (230–400 mesh) silical gel (Merck) for flash columns. Analytical results were within 0.4% of the theoretical values. All nonaqueous reactions were performed in oven-dried glassware under an atomosphere or argon. The column chromatography eluents employed were glass distilled, and solvent mixtures are reported as volume to volume ratios. The compounds **1a**, **1b** and **2a**, were prepared by published procedure.[46,48] The synthesis of *N*-substituted-5′-methoxy-3,4′-dihydrospiro [piperidine-2,3′-(2′*H*)-benzopyran] derivatives **3a** and **3b** (Fig. 5) was described in a recent article.[47]

5-Hydroxy-3,4-dihydro-3,3-di-*N*-*n*-propylamino-2*H*-1-benzopyran (5). The preparation of compound **5** was described in a recent paper.[46]

8-[4-(3,4-Dihydro-3,3-di-*N*-*n*-propylamino-2*H*-1-benzopyran-5-yl)butyloxy]-8-azaspiro[4.5]decane-7,9-dione (1c). A solution of phenol **5** (3.460 g, 13.90 mmol) in dry *N*,*N*-dimethylformamide (DMF) (40 mL), 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (4.200 g, 13.90 mmol), potassium carbonate (5.750 g, 41.70 mmol) and a catalytic amount of potassium iodide was heated at 60 °C for 17 h. Then, the mixture was cooled to room temperature, solvent was evaporated and the residue was diluted with water and crude product was extracted with dichloromethane (CH_2Cl_2) (40 mL). After purification by column chromatography (eluent: Et_2O: CH_2Cl_2, 1:9) the expected compound **1c** was obtained as an oil (5.160 g) in 79% yield, IR (film) ν (cm^{-1}): 1715 and 1660 (NCO), 1230 (COC); ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, **CH_3**, $J=7.1$ Hz), 1.40–1.84 (m, 16H, **CH_2**), 2.32–2.62 (m, 9H, **CH_2**CO, **CH_2**N, Ar**CH_2**), 2.84 (dd, 1H, Ar**CH_2**, $J=6.0$, 17.2 Hz), 3.07–3.18 (m, 1H, **CH**N), 3.75 (t, 1H, O**CH_2**, $J=10.3$ Hz), 3.83 (t, 2H, **CH_2**NCO, $J=7.1$ Hz), 3.91–4.01 (m, 2H, O**CH_2**), 4.20–4.30 (m, 1H, O**CH_2**), 6.38 (d, 1H, **H_{arom}**, $J=8.3$ Hz), 6.44 (d, 1H, **H_{arom}**, $J=8.3$ Hz), 7.00 (t, 1H, **H_{arom}**, $J=8.3$ Hz); MS (EI) m/z 470 (M^+); anal. $C_{28}H_{42}N_2O_4$, $C_2H_2O_4$: (C, H, N).

8-[4-[*N*-*n*-Propyl-*N*-(5-hydroxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (6). A mixture of 5-methoxychroman **1b**[46] (2.000 g, 4.52 mmol) in 1,2-dichloroethane (20 mL) and boron tribromide–dimethylsulfide complex ($BBr_3.Me_2S$) (1.840 g, 5.88 mmol) was refluxed for 3 h. After evaporation of the solvent, the residue was treated with water and a saturated solution of sodium hydrogenocarbonate was added to maintain the pH at about 9–10. After evaporation with CH_2Cl_2 and a purification by column chromatography (eluent: CH_2Cl_2:Et_2O, 2:1), the expected phenol **6** was obtained as an oil (1.570 g) in 81% yield, IR (film) ν (cm^{-1}): 3680–3100 (OH), 1650 (NCO); 1230 (COC); ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, 3H, **CH_3**, $J=7.3$ Hz), 1.38–1.73 (m, 14H, **CH_2**), 2.44–2.63 (m, 5H, **CH_2**, Ar**CH_2**), 2.60 (s, 4H, NCO**CH_2**), 2.83 (dd, 1H, Ar**CH_2**, $J=5.1$, 16.6 Hz), 3.09–3.22 (m, 1H, **CH**N), 3.69–3.82 (m, 3H, O**CH_2**, **CH_2**NCO), 4.24–4.32 (m, 1H, O**CH_2**), 5.87 (br s, 1H, **OH**), 6.39 (d, 1H, **H_{arom}**, $J=8.1$ Hz), 6.42 (d, 1H, **H_{arom}**, $J=8.1$ Hz), 6.95 (t, 1H, **H_{arom}**, $J=8.1$ Hz); MS (CI/NH_3) m/z 429 ($M+1$); anal. $C_{25}H_{36}N_2O_4$: (C, H, N).

1-(2-Chloroethyl)-4-(4-fluorobenzoyl)piperidine (7). To a solution of 4-(4-fluorobenzoyl)piperidine (0.500 g, 2.05 mmol) in a 0.4 M ethanolic sodium hydroxide solution (12.80 mL, 5.13 mmol) was added 2-bromoethanol (0.36 mL, 5.13 mmol). The reaction mixture was refluxed for 2 h. After cooling to room temperature, the mineral solid was filtered, the organic layer was concentrated and washed with water (5 mL). Then, the crude product was extracted with dichloromethane (CH_2Cl_2) (15 mL). After purification by chromatography (eluent: CH_2Cl_2:MeOH, 9:1), the expected 1-(2-hydroxyethyl)-4(4-fluorobenzoyl)piperidine was obtained as an amorphous solid (0.445 g) in 86% yield, IR (KBr) ν (cm^{-1}): 3580–3000 (OH), 1670 (CO); ^1H NMR ($CDCl_3$) δ: 1.64 (br s, 1H, **OH**), 1.78–1.93 (m, 4H, $NCH_2\mathbf{CH_2}$), 2.20–2.30 (m, 1H, **CH**CO), 2.59 (t, 2H, $\mathbf{CH_2}N$,$J=5.4$ Hz), 2.98–3.05 (m, 2H, $N\mathbf{CH_2}$), 3.18–3.30 (m, 2H, $N\mathbf{CH_2}$), 3.63 (t, 2H, $\mathbf{CH_2}OH$, $J=5.4$ Hz), 7.15 (t, 2H, $\mathbf{H_{arom}}$, $J=8.8$ Hz), 7.98 (dd, 2H, $\mathbf{H_{arom}}$, $J=5.3$, 8.8 Hz).

To a solution of pyridine (12 mL) and carbone tetrachloride (CCl_4) (1.70 mL, 17.80 mmol) were added the 1-(2-hydroxyethyl)-4-(4-fluorobenzoyl) piperidine (0.445 g, 1.77 mmol) and triphenylphosphine (0.931 g, 3.55 mmol), at 0 °C. The mixture was stirred at room temperature for 1 h, then the reaction was quenched with methanol (MeOH) (1.5 mL). After evaporation of the solvents, an acido-basic work up removed the triphenylphosphine oxide. The expected 1-(2-chloroethyl)-4(4-fluorobenzoyl) piperidine **7** was obtained after a column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) as an amorphous solid (0.370 g) in 77% yield; IR (KBr) ν (cm^{-1}): 1670 (CO); ^1H NMR ($CDCl_3$) δ: 1.82–1.90 (m, 4H, $NCH_2\mathbf{CH_2}$), 2.22–2.30 (m, 1H, **CH**CO), 2.77 (t, 2H, $\mathbf{CH_2}N$,$J=7.2$ Hz), 2.97–3.05 (m, 2H, $N\mathbf{CH_2}$), 3.15–3.25 (m, 2H, $N\mathbf{CH_2}$), 3.60 (t, 2H, $Cl\mathbf{CH_2}$,$J=7.2$ Hz), 7.16 (t, 2H, $\mathbf{H_{arom}}$, $J=8.7$ Hz), 7.96 (dd, 2H, $\mathbf{H_{arom}}$, $J=5.5$, 8.7 Hz).

8-{4-[*N*-*n*-Propyl-*N*-{5-[2-(4-(4-fluorobenzoyl)piperidine) ethoxy]-3,4-dihydro-2*H*-1-benzopyran-3-yl}amino]butyl}-8 -azaspiro[4.5]decane-7,9-dione (1d). To a solution of phenol **6** (0.500 g, 1.17 mmol) in *N,N*-dimethylformamide (DMF) (8 mL) were added carbonate potassium (0.967 g, 7.00 mmol), 1-(2-chloroethyl)-4-(4-fluorobenzoyl) piperidine **7** (0.630 g, 2.34 mmol) in DMF (6 mL) and a catalytic amount of potassium iodide. The mixture was heated to 60 °C for 12 h. After evaporation of the solvent and addition of water, the crude product was extracted with CH_2Cl_2 and purified by column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) to give the derivative **1d** as an oil (0.607 g) in 79% yield, IR (film) ν (cm^{-1}): 1720 and 1660 (NCO, CO), 1230 (COC); ^1H NMR ($CDCl_3$) δ: 0.86 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.37–1.73 (m, 14H, $\mathbf{CH_2}$), 1.82–1.90 (m, 4H, $\mathbf{CH_2}$), 2.26–2.40 (m, 1H, **CH**CO), 2.44–2.62 (m, 5H, $\mathbf{CH_2}$, $Ar\mathbf{CH_2}$), 2.56 (s, 4H, $NCO\mathbf{CH_2}$), 2.80–2.90 (m, 3H, $Ar\mathbf{CH_2}$, $\mathbf{CH_2}N$), 3.05–3.27 (m, 5H, **CH**N, $N\mathbf{CH_2}$), 3.69–3.78 (m, 3H, $O\mathbf{CH_2}$, $\mathbf{CH_2}NCO$), 4.06–4.17 (m, 2H, $O\mathbf{CH_2}$), 4.20–4.26 (m, 1H, $O\mathbf{CH_2}$), 6.40 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 6.46 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 7.01 (t, 2H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 7.13 (t, 2H, $\mathbf{H_{arom}}$, $J=8.7$ Hz), 7.96 (dd, 2H, $\mathbf{H_{arom}}$, $J=5.5$, 8.7 Hz); MS (CI/NH_3) *m*/*z* 662 (M + 1); anal. $C_{39}H_{52}N_3O_5$, 1.6 $C_2H_2O_4$. (C, H, N).

8-{4-[*N*-*n*-Propyl-*N*-[5-(3-aminoindane)propyloxy]-3,4-dihydro-2*H*-1-benzopyran-3-yl]amino]butyl}-8-azaspiro[4.5]-decane-7,9-dione (1e). A mixture of phenol **6** (0.800 g, 1.87 mmol) and carbonate potassium (2.580 g, 18.70 mmol) was refluxed in toluene (10 mL) for 30 min. Then, 1,3-dibromopropane (1.132 g, 5.61 mmol) and *n*-tetrabutylammonium bromide (0.120 g, 0.37 mmol) were added. The reactional solution was heated to reflux for 12 h. After filtration on Celite, evaporation of toluene and addition of water, the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:Et_2O, 2:1) to give the desired bromide as an oil (0.860 g) in 84% yield, IR (film) ν (cm^{-1}): 1650 (NCO), 1240 (COC); ^1H NMR ($CDCl_3$) δ: 0.87 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.37–1.73 (m, 14H, $\mathbf{CH_2}$), 2.30–2.40 (m, 2H, $\mathbf{CH_2}$), 2.42–2.65 (m, 5H, $\mathbf{CH_2}$, $N\mathbf{CH_2}$, $Ar\mathbf{CH_2}$), 2.59 (s, 4H, $NCO\mathbf{CH_2}$), 2.84 (dd, 1H, $Ar\mathbf{CH_2}$, $J=4.8$, 16.6 Hz), 3.05–3.16 (m, 1H, **CH**N), 3.62 (t, 2H, $\mathbf{CH_2}Br$, $J=6.5$ Hz), 3.71–3.81 (m, 3H, $O\mathbf{CH_2}$, $\mathbf{CH_2}NCO$), 4.05–4.16 (m, 2H, $\mathbf{CH_2}O$), 4.20–4.27 (m, 1H, $O\mathbf{CH_2}$), 6.42 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 6.45 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 7.03 (t, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz).

To a solution of this bromide (0.850 g, 1.55 mmol) in DMF (8 mL) were added diisopropylethylamine (1.08 mL, 6.19 mmol), 2-aminoindane hydrochloride (0.394 g, 3.32 mmol) in DMF (4 mL) and a catalytic amount of potassium iodide. The solution was heated at 80 °C for 40 h. After evaporation of solvent and hydrolysis, the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 95:5) to afford the expected compound **1e** as an oil (0.430 g) in 46% yield, IR (film) ν (cm^{-1}); 3640–3220 (NH), 1640 (NCO), 1240 (COC); ^1H NMR ($CDCl_3$, D_2O) δ: 0.89 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.38–7.71 (m, 14H, $\mathbf{CH_2}$), 2.16–2.29 (m, 2H, $\mathbf{CH_2}$), 2.48–2.66 (m, 5H, $\mathbf{CH_2}$, $N\mathbf{CH_2}$, $Ar\mathbf{CH_2}$), 2.54 (s, 4H, $NCO\mathbf{CH_2}$), 2.82–2.92 (m, 1H, $Ar\mathbf{CH_2}$), 2.99–3.20 (m, 5H, $\mathbf{CH_2}$, **CH**N), 3.27 (d, 1H, $\mathbf{CH_2}$, $J=7.3$ Hz), 3.33 (d, 1H, $\mathbf{CH_2}$, $J=7.3$ Hz), 3.68–3.93 (m, 4H, $O\mathbf{CH_2}$, $\mathbf{CH_2}NCO$, N**CH**), 4.04–4.15 (m, 2H, $O\mathbf{CH_2}$), 4.23–4.30 (m, 1H, $O\mathbf{CH_2}$), 6.40 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 6.47 (d, 1H, $\mathbf{H_{arom}}$,$J=8.1$ Hz), 7.03 (t, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 7.13–7.23 (m, 4H, $\mathbf{H_{arom}}$); MS (CI/NH_3) *m*/*z*: 602 (M + 1); anal. $C_{37}H_{51}N_3O_4$ $1.7C_4H_4O_4$: (C, H, N).

5-Methoxy-3-[*N*-*n*-propyl-*N*-(2-chloroethanoyl)amino]-3,4-dihydro-2*H*-1-benzopyran (9). To a solution of 5-methoxy-3-*N*-*n*-propylamino-3.4-dihydro-2*H*-1-benzopyran **8**[46] (4.000 g, 18.10 mmol) in CH_2Cl_2 (40 mL) was added a 1 N sodium hydroxide solution (27 mL). The mixture was cooled to 0 °C and 2-chloroacetyl chloride (2.16 mL, 27.15 mmol) was added. After stirring 30 min at room temperature, a 1 N sodium hydroxide solution was added until to obtain a pH about 9–10. The two layers were separated and, after evaporation of the organic layer, the crude product was purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 99:1) to give the amide **9** as an oil (4.100 g) in 76% yield, IR (film) ν (cm^{-1}): 1640 (NCO), 1240 (COC); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.50–1.80 (m, 2H, $\mathbf{CH_2}$), 2.72–3.40 (m, 5H, $\mathbf{CH_2}$, **CH**N, $Ar\mathbf{CH_2}$), 3.83 (s, 3H, $O\mathbf{CH_3}$), 3.90–4.50 (m, 4H, $O\mathbf{CH_2}$, $\mathbf{CH_2}Cl$), 6.40–6.55 (m,

2H, $\mathbf{H_{arom}}$), 7.02–7.06 (m, 1H, $\mathbf{H_{arom}}$); anal. $C_{15}H_{20}NO_3Cl$: (C, H, N).

5-Methoxy-3-[*N*-*n*-propyl-*N*-(2-chloroethyl)amino]-3,4-dihydro-2*H*-1-benzopyran (10). A mixture of amide **9** (0.240 g, 0.81 mmol) in tetrahydrofuran (THF) (6 mL) and borane–dimethylsulfide complex ($BH_3{\cdot}Me_2S$) (0.81 mL, 1.61 mmol) was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in MeOH (8 mL) and a 2 N hydrochloric acid solution (16 mL) was added. The solution was refluxed for 2 h. After cooling, the mixture was basified with a saturated sodium hydrogenocarbonate solution. The product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 99:1) to afford the desired amine **10** as an oil (0.120 g) in 52% yield, IR (film) ν (cm^{-1}); 1240 (COC); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.40–1.55 (m, 2H, $\mathbf{CH_2}$), 2.46–2.68 (m, 3H, $\mathbf{CH_2}$, Ar$\mathbf{CH_2}$), 2.85–2.93 (m, 3H, $\mathbf{CH_2}$, Ar$\mathbf{CH_2}$), 3.08–3.20 (m, 1H, **CH**N), 3.42–3.49 (m, 2H, $\mathbf{CH_2}$Cl), 3.75 (t, 1H, O$\mathbf{CH_2}$, $J=10.3$ Hz), 3.82 (s, 3H, O$\mathbf{CH_3}$), 4.20–4.27 (m, 1H, O$\mathbf{CH_2}$), 6.42 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 6.46 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 7.06 (t, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz); MS (CI/NH_3) m/z 284 (M + 1); anal. $C_{15}H_{22}NO_2Cl$: (C, H, N).

5-Methoxy-3-{*N*-*n*-propyl-*N*-[2-(4-(4-fluorobenzoyl)piperidine)ethyl]amino}-3,4-dihydro-2*H*-1-benzopyran (1f). A solution of chloroethylamine **10** (0.080 g, 0.28 mmol) and 4-(4-fluorobenzoyl)piperidine (0.117 g, 0.56 mmol) in DMF (4 mL), potassium carbonate (0.117 g, 0.85 mmol) and a catalytic amount of potassium iodide was heated at 60 °C for 1 h. After evaporation of the solvent and dilution with water, the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 95:5) to afford the expected compound **1f** as an oil (0.120 g) in 94% yield, IR (film) ν (cm^{-1}): 1670 (CO), 1230 (COC); ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.41–1.54 (m, 2H, $\mathbf{CH_2}$), 1.80–1.89 (m, 4H,$\mathbf{CH_2}$), 2.10–2.22 (m, 1H, **CH**CO), 2.43–2.65 (m, 5H, Ar$\mathbf{CH_2}$, $\mathbf{CH_2}$, $\mathbf{CH_2}$N), 2.71–2.80 (m, 2H, N$\mathbf{CH_2}$), 2.90 (ddd, 1H, Ar$\mathbf{CH_2}$,$J=1.7$, 5.5, 16.7 Hz), 2.96–3.06 (m, 2H, N$\mathbf{CH_2}$), 3.09–3.25 (m, 3H, **CH**N, N$\mathbf{CH_2}$), 3.78 (t, 1H, O$\mathbf{CH_2}$, $J=10.2$ Hz), 3.82 (s, 3H, O$\mathbf{CH_3}$), 4.22–4.30 (m, 1H, O$\mathbf{CH_2}$), 6.43 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 6.47 (d, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 7.05 (t, 1H, $\mathbf{H_{arom}}$, $J=8.2$ Hz), 7.13 (t, 2H, $\mathbf{H_{arom}}$,$J=8.7$ Hz); 7.96 (dd, 2H, $\mathbf{H_{arom}}$, $J=5.6$, 8.7 Hz); MS (CI/NH_3) m/z 455 (M + 1); anal. $C_{27}H_{35}N_2O_3F$, $1.37C_2H_2O_4$: (C, H, N).

8-{4-[3-[*N*-*n*-Propyl-*N*-(2-(4-(4-fluorobenzoyl)piperidine)ethyl)amino]-3,4-dihydro-2*H*-1-benzopyran-3-yl]butyloxy}-8-azaspiro[4.5]decane-7,9-dione (1g). To a solution of methoxychroman **1f** (2.000 g, 4.40 mmol) in acetic acid (AcOH) (30 mL) was added a 48% aqueous bromhydric acid solution (HBr) (15 mL). The mixture was heated at 130–140 °C for 4 h. After evaporation of the solvents, the residue was dissolved in ethyl acetate (AcOEt) (40 mL) and the organic layer was washed with a saturated sodium hydrogenocarbonate solution. The crude product was extracted with AcOEt and chromatographied (eluent: CH_2Cl_2:MeOH, 9:1) to give the desired phenol as a sticky solid (1.300 g) in 67% yield; IR (KBr) ν (cm^{-1}): 3500–3000 (OH), 1650 (CO), 1215 (COC); ^1H NMR ($CDCl_3$, D_2O) δ: 0.88 (t, 3H, $\mathbf{CH_3}$, $J=7.3$ Hz), 1.40–1.52 (m, 2H, $\mathbf{CH_2}$), 1.83–1.92 (m, 4H, $\mathbf{CH_2}$), 2.17–2.31 (m, 1H, **CH**CO), 2.43–2.62 (m, 5H, Ar$\mathbf{CH_2}$, $\mathbf{CH_2}$, $\mathbf{CH_2}$N), 2.71–2.80 (m, 2H, N$\mathbf{CH_2}$), 2.86 (dd, 1H, Ar$\mathbf{CH_2}$, $J=5.0$, 16.1 Hz), 3.01–3.27 (m, 5H, N$\mathbf{CH_2}$, **CH**N), 3.61 (t, 1H, O$\mathbf{CH_2}$, $J=10.2$ Hz), 4.15–4.21 (m, 1H, O$\mathbf{CH_2}$), 6.31 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 6.49 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 7.12 (t, 2H, $\mathbf{H_{arom}}$, $J=5.6$, 8.6 Hz).

Compound **1g** was prepared according to the method used for **1d** from the phenol described above (1.000 g, 2.27 mmol) in DMF (8 mL), potassium carbonate (0.941 g, 6.82 mmol), 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (0.834 g, 2.73 mmol) and a catalytic amount of potassium iodide. The expected product was obtained after a column chromatography (eluent: CH_2Cl_2: MeOH, 95:5) as an oil (0.870 g) in 58% yield, IR (film) ν (cm^{-1}): 1720 and 1650 (NCO, CO), 1230 (COC); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, $\mathbf{CH_3}$, $J=7.3$), 1.40–2.00 (m, 18H, $\mathbf{CH_2}$), 2.20–2.40 (m, 1H, **CH**CO), 2.46–2.65 (m, 5H, Ar$\mathbf{CH_2}$, N$\mathbf{CH_2}$, $\mathbf{CH_2}$), 2.60 (s, 4H, NCO$\mathbf{CH_2}$), 2.74–2.94 (m, 3H, Ar$\mathbf{CH_2}$, $\mathbf{CH_2}$N), 3.00–3.34 (m, 5H, **CH**N, N$\mathbf{CH_2}$), 3.70–3.88 (m, 3H, O$\mathbf{CH_2}$, $\mathbf{CH_2}$NCO), 3.91–4.04 (m, 2H, O$\mathbf{CH_2}$), 4.20–4.30 (m, 1H, O$\mathbf{CH_2}$), 6.40 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 6.42 (d, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 7.02 (t, 1H, $\mathbf{H_{arom}}$, $J=8.1$ Hz), 7.14 (t, 2H, $\mathbf{H_{arom}}$, $J=8.6$ Hz), 7.98 (dd, 2H, $\mathbf{H_{arom}}$, $J=5.3$, $J=8.6$ Hz); MS (CI/NH_3) m/z 662 (M + 1); anal. $C_{39}H_{52}N_3O_5F$, $C_2H_2O_4$: (C, H, N).

8-{4-[*N*-(5-Hydroxy-3,4-dihydro-2*H*-1-benzopyran-3-ylmethyl)-*N*-*t*-butyloxycarbonylamino]butyl}-8-azaspiro[4.5]decane-7,9-dione (11). This phenol was prepared according to the method used for **6** from the methoxychroman **2a**[48] (0.250 g, 0.60 mmol) in dichloroethane (7 mL) and boron tribromide–dimethylsulfide complex ($BBr_3{\cdot}Me_2S$) (0.283 g, 0.91 mmol). The expected product was obtained after a column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) as a sticky solid (0.150 g) in 60% yield; IR (KBr) ν (cm^{-1}): 3600–3060 (OH, NH), 1640 (NCO), 1240 (COC); ^1H NMR ($CDCl_3$), D_2O) δ 1.44–1.76 (m, 12H, $\mathbf{CH_2}$), 2.21–2.34 (m, 1H, **CH**CH_2N), 2.49 (dd, 1H, Ar$\mathbf{CH_2}$, $J=8.1$, 16.5 Hz), 2.60 (s, 4H, NCO$\mathbf{CH_2}$), 2.62–2.80 (m, 4H, $\mathbf{CH_2}$N), 2.91 (dd, 1H, Ar$\mathbf{CH_2}$,$J=5.5$, 16.5 Hz), 3.74–3.82 (m, 2H, $\mathbf{CH_2}$NCO), 3.84 (dd, 1H, O$\mathbf{CH_2}$, $J=8.1$, 10.0 Hz), 4.22 (dd, 1H, O$\mathbf{CH_2}$, $J=3.0$, 10.0 Hz), 6.38 (d, 1H, $\mathbf{H_{arom}}$, $J=7.9$ Hz), 6.42 (d, 1H, $\mathbf{H_{arom}}$, $J=7.9$ Hz), 6.94 (t, 1H, $\mathbf{H_{arom}}$, $J=7.9$ Hz); MS (CI/NH_3) m/z 401 (M + 1).

To a solution of the phenol described above (1.330 g, 3.32 mmol) in CH_2Cl_2 (25 mL) were added triethylamine (1.007 g, 9.97 mmol) and, at 0 °C, di-*t*-butyldicarbonate (0.762 g, 3.49 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 3 h. Then, the solution was washed with water and the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 95:5). The expected compound **11** was afforded as an amorphous solid (1.360 g) in 82% yield; IR (KBr) ν (cm^{-1}): 3600–3060 (OH), 1650 (NCO), 1250 (COC); ^1H NMR ($CDCl_3$) δ: 1.36–1.74 (m, 21H, $\mathbf{CH_2}$, $\mathbf{CH_3}$), 2.30–2.47 (m, 2H, **CH**CH_2N, Ar$\mathbf{CH_2}$), 2.58 (s, 4H, NCO$\mathbf{CH_2}$),

2.70–2.82 (m, 1H, Ar**CH$_2$**), 3.10–3.33 (m, 4H, **CH$_2$**N), 3.77 (t, 2H, **CH$_2$**NCO,J = 7.0 Hz), 3.84 (dd, 1H, O**CH$_2$**, J = 8.1, 11.0 Hz), 4.16 (d, 1H, O**CH$_2$**, J = 11.0 Hz), 5.46 (br s, 1H, **OH**), 6.36 (d, 1H, **H$_{arom}$**, J = 8.1 Hz), 6.41 (d, 1H, **H$_{arom}$**, J = 8.1 Hz), 6.94 (t, 1H, **H$_{arom}$**,J = 8.1 Hz); anal. $C_{28}H_{40}N_2O_6$: (C, H, N).

8-{4-[*N*-(5-(2-(4-(4-Fluorobenzoyl)piperidine)ethyloxy)-3,4-dihydro-2*H*-1-benzopyran-3-ylmethyl]amino]butyl}-8-azaspiro[4.5]decane-7,9-dione (2b). The 8-{4-[*N*-(5-(2-(4-(4-fluorobenzoyl)piperidine)ethyloxy)-3,4-dihydro-2*H*-1-benzopyran-3-ylmethyl]-*N*-(*t*-butyloxycarbonyl)amino]-butyl}-8-azaspiro[4.5]decane-7,9-dione was prepared according to the method used for **1d** from the phenol **11** (0.650 g, 1.30 mmol) in DMF (8 mL), potassium carbonate (0.540 g, 3.90 mmol), 1-(2-chloroethyl)-4-(4-fluorobenzoyl)piperidine **7** (0.525 g, 1.95 mmol) and a catalytic amount of potassium iodide. The expected product was obtained after a column chromatography (eluent: CH_2Cl_2:MeOH, 95:5) as an oil (0.780 g) in 82% yield, IR (film) ν (cm^{-1}): 1650 (NCO, CO), 1240 (COC); ^{1}H NMR ($CDCl_3$) δ: 1.37–1.72 (m, 21H, **CH$_2$**, **CH$_3$**), 1.81–1.90 (m, 4H, **CH$_2$**), 2.24–2.37 (m, 3H, **CH**CH$_2$N, Ar**CH$_2$**, **CH**CO), 2.56 (s, 4H, NCO**CH$_2$**), 2.70–2.81 (m, 1H, Ar**CH$_2$**), 2.86 (t, 2H, N**CH$_2$**, J = 5.9 Hz), 3.05–3.28 (m, 8H, **CH$_2$**N), 3.71–3.85 (m, 3H, O**CH$_2$**, **CH$_2$**NCO), 4.08–4.19 (m, 3H, O**CH$_2$**, **CH$_2$**O), 6.41 (d, 1H, **H$_{arom}$**, J = 8.2 Hz), 6.48 (d, 1H, **H$_{arom}$**, J = 8.2 Hz), 7.02 (t, 1H, **H$_{arom}$**,J = 8.2 Hz), 7.13 (t, 2H, **H$_{arom}$**, J = 8.6 Hz), 7.98 (dd, 2H, **H$_{arom}$**, J = 5.6, 8.6 Hz).

To a solution of the *N*-*t*-butyloxycarbonylamine described above (0.780 g, 1.06 mmol) in CH_2Cl_2 (10 mL) was added dropwise trifluoroacetic acid (1.23 mL, 15.96 mmol). The mixture was stirred for 16 h at room temperature and, then, a saturated sodium hydrogenocarbonate solution was added. The compound was chromatographied (eluent: CH_2Cl_2:MeOH, 95:5) to afford the expected derivative **2b** as an oil (0.550 g) in 82% yield, IR (film) ν (cm^{-1}): 3640–3100 (NH), 1650 (NCO, CO), 1230 (COC); ^{1}H NMR ($CDCl_3$, D_2O) δ: 1.44–1.76 (m, 12H, **CH$_2$**), 1.85–1.98 (m, 4H, **CH$_2$**), 2.22–2.46 (m, 3H, **CH**CH$_2$N, Ar**CH$_2$**, **CH**CO), 2.59 (s, 4H, NCO**CH$_2$**), 2.66–2.78 (m, 4H, **CH$_2$**N), 2.85 (dd, 1H, Ar**CH$_2$**, J = 5.5, 17.2 Hz), 2.90 (t, 2H, N**CH$_2$**, J = 5.7 Hz), 3.08–3.43 (m, 4H, **CH$_2$**N), 3.72–3.80 (m, 2H, **CH$_2$**NCO), 3.88 (dd, 1H, O**CH$_2$**, J = 7.5, 10.7 Hz), 4.07–4.17 (m, 2H, O**CH$_2$**), 4.20–4.28 (m, 1H, O**CH$_2$**), 6.40 (d, 1H, **H$_{arom}$**, J = 8.2 Hz), 6.46 (d, 1H, **H$_{arom}$**, J = 8.2 Hz), 7.02 (t, 1H, **H$_{arom}$**, J = 8.2 Hz), 7.13 (t, 2H, **H$_{arom}$**, J = 8.6 Hz), 7.97 (dd, 2H, **H$_{arom}$**,J = 5.6, 8.6 Hz); MS (CI/NH_3) m/z 634 (M + 1); anal. $C_{37}H_{48}N_3O_5F$: (C, H, N, F).

8-{4-[*N*-[5-(3-(2-Aminoindane)propyloxy)-3,4-dihyro-2*H*-1-benzopyran-3-ylmethyl]amino]butyl}-8-azaspiro[4.5]decane-7,9-dione (2c). A mixture of phenol **11** (0.710 g, 1.42 mmol) in toluene (10 mL) and carbonate potassium (1.960 g, 14.20 mmol) was refluxed for 30 min. Then, 1,3-dibromopropane (0.860 g, 4.26 mmol) and *n*-tetrabutylammonium bromide (0.092 g, 0.28 mmol) were added. The reactional solution was heated to reflux for 12 h. After filtration on Celite, evaporation of toluene and addition of water, the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 99:1) to give the desired bromide as an oil (0.720 g) in 82% yield, IR (film) ν (cm^{-1}): 1650 (NCO), 1240 (COC); ^{1}H NMR ($CDCl_3$) δ: 1.39–1.74 (m, 21H, **CH$_2$**, **CH$_3$**), 2.24–2.40 (m, 4H, **CH**CH$_2$N, Ar**CH$_2$**, **CH$_2$**), 2.58 (s, 4H, NCO**CH$_2$**), 2.67–2.81 (m, 1H, Ar**CH$_2$**), 3.16–3.30 (m, 4H, **CH$_2$**N), 3.60 (t, 2H, Br**CH$_2$**, J = 6.4 Hz), 3.77 (t, 2H, **CH$_2$**NCO, J = 6.8 Hz), 3.82 (dd, 1H, O**CH$_2$**, J = 8.5, 10.4 Hz), 4.10 (t, 2H, **CH$_2$**O, J = 5.6 Hz), 4.13–4.20 (m, 1H, O**CH$_2$**), 6.41 (d, 1H, **H$_{arom}$**, J = 8.2 Hz), 6.47 (d, 1H, **H$_{arom}$**,J = 8.2 Hz), 7.05 (t, 1H, **H$_{arom}$**, J = 8.2 Hz).

A solution of the bromide described above (0.700 g, 1.13 mmol) in DMF (5 mL), diisopropylethylamine (0.583 g, 4.51 mmol), 2-aminoindane hydrochloride (0.287 g, 1.69 mmol) in DMF (5 mL) and a catalytic amount of potassium iodide was stirred 72 h at 60 °C. After evaporation of solvent and addition of water, the crude product was extracted with CH_2Cl_2 and purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 99:1) to afford the expected compound as an amorphous solid (0.260 g) in 34% yield, IR (KBr) ν (cm^{-1}): 3560–3160 (NH), 1640 (NCO), 1220 (COC); ^{1}H NMR ($CDCl_3$, D_2O) δ: 1.37–1.74 (m, 21H, **CH$_2$**, **CH$_3$**), 2.10–2.37 (m, 4H, **CH**CH$_2$N, Ar**CH$_2$**), 2.53 (s, 4H, NCO**CH$_2$**), 2.64–2.77 (m, 1H, Ar**CH$_2$**), 2.95–3.34 (m, 10H, **CH$_2$**, **CH$_2$**N, **CH$_2$**N(Boc)**CH$_2$**), 3.73 (t, 2H, **CH$_2$**NCO, J = 6.9 Hz), 3.78–3.86 (m, 2H, O**CH$_2$**, NH**CH**), 4.06 (t, 2H, O**CH$_2$**, J = 5.9 Hz), 4.09–4.18 (m, 1H, O**CH$_2$**), 6.39 (d, 1H, **H$_{arom}$**, J = 8.1 Hz), 6.47 (d, 1H, **H$_{arom}$**, J = 8.1 Hz), 7.01 (t, 1H, **H$_{arom}$**, J = 8.1 Hz), 7.12–7.23 (m, 4H, **H$_{arom}$**).

To a solution of the *N*-t-butyloxycarbonylamine described above (0.380 g, 0.56 mmol) in CH_2Cl_2 (8 mL) was added dropwise trifluoroacetic acid (0.90 mL, 11.30 mmol). The reaction mixture was stirred at room temperature for 16 h, then the solution was hydrolyzed with a saturated sodium hydrogenocarbonate solution. The product, extracted with CH_2Cl_2, was purified by a column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) to afford the expected compound **2c** as an oil (0.250 g) in 77% yield, IR (film) ν (cm^{-1}): 3620-3100 (NH), 1640 (NCO), 1230 (COC); ^{1}H NMR ($CDCl_3$, D_2O) δ: 1.40–1.85 (m, 12H, **CH$_2$**), 2.01–2.12 (m, 2H, **CH$_2$**), 2.19–2.40 (m, 2H, **CH**CH$_2$N, Ar**CH$_2$**), 2.57 (s, 4H, NCO**CH$_2$**), 2.60–2.98 (m, 9H, Ar**CH$_2$**, **CH$_2$**N, **CH$_2$**), 3.16–3.27 (m, 2H, **CH$_2$**), 3.68–3.86 (m, 4H, O**CH$_2$**, **CH$_2$**NCO, N**CH**), 3.98–4.07 (m, 2H, **CH$_2$**O), 4.19–4.26 (m, 1H, O**CH$_2$**), 6.38 (d, 1H, **H$_{arom}$**, J = 7.9 Hz), 6.45 (d, 1H, **H$_{arom}$**, J = 7.9 Hz), 7.01 (t, 1H, **H$_{arom}$**, J = 7.9 Hz), 7.10–7.23 (m, 4H, **H$_{arom}$**); MS (EI) m/z 573 (M^+); anal. $C_{35}H_{47}N_3O_4$, $C_2H_2O_4$: (C, H, N).

1-*N*-*n*-Propyl-4-[2-(4-(4-fluorobenzoyl)piperidine)ethoxy]-5′-methoxy-3′,4′-dihydrospiro[piperazin-2,3′(2′*H*)-benzopyran] (4c). A mixture of chroman **12**[54] (0.290 g, 1.05 mmol) in dry acetonitrile (CH_3CN) (5 mL), potassium carbonate (0.435 g, 3.15 mmol), chloro derivative **7** (0.425 g, 1.58 mmol) and potassium iodide (catalytic amount) were refluxed. After total consumption of the starting material, the mixture was hydrolyzed and the crude product was extracted with CH_2Cl_2 (15 mL).

After a purification by a column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) the expected compound **4c** was obtained as an oil (0.460 g) in 86% yield, IR (film) ν (cm^{-1}): 1676 (CO), 1235 (COC); ^1H NMR ($CDCl_3$) δ: 0.86 (t, 3H, **CH_3**, $J=7.3$ Hz), 1.36–1.47 (m, 2H, **CH_2**), 1.73–1.86 (m, 4H, **CH_2**), 2.06–2.21 (m, 1H, **CH**CO), 2.25–2.80 (m, 12H, Ar**CH_2**, N**CH_2**, **CH_2**), 2.63 (d, 1H, **CH_2**N, $J=17.4$ Hz), 2.86 (d, 1H, **CH_2**N, $J=17.4$ Hz), 2.93–3.00 (m, 2H, N**CH_2**), 3.10–3.22 (m, 2H, N**CH_2**), 3.80 (s, 3H, O**CH_3**), 3.95 (d, 1H, O**CH_2**, $J=10.4$ Hz), 4.04 (d, 1H, O**CH_2**, $J=10.4$ Hz), 6.42 (d, 1H, **H_{arom}**, $J=8.2$ Hz), 6.47 (d, 1H, **H_{arom}**, $J=8.2$ Hz), 7.04 (t, 1H, **H_{arom}**, $J=8.2$ Hz), 7.13 (t, 2H, **H_{arom}**, $J=8.4$ Hz), 7.94 (dd, 2H, **H_{arom}**, $J=5.6$, 8.4 Hz); MS (CI/NH_3) m/z 510 (M + 1); anal. $C_{30}H_{40}N_3O_3F$, $C_2H_2O_4$: (C, H, N).

1-*N*-*n*-Propyl-4-*p*-fluorobenzoyl-5′-methoxy-3′,4′-dihydrospiro[piperazin-2,3′(2′*H*)-benzopyran] (4d). A solution of **12**[54] (0.300 g, 1.09 mmol) in CH_2Cl_2 (6 mL) was vigorously stirred with a 1.2% sodium hydroxide solution (5.0 mL), then, *p*-fluorobenzoyl chloride (0.260 g, 1.63 mmol) was added dropwise at 0 °C. The same sodium hydroxide solution was then used drop by drop in order to maintain the pH about 9. When this value became stable, the separated organic layer was dried and the solvent was removed. After a column chromatography (eluent: CH_2Cl_2:MeOH, 9:1) the expected compound **4d** was obtained as a solid (0.372 g) in 86% yield, mp: 140-141 °C; IR (KBr) ν (cm^{-1}): 1630 (NCO), 1230 (COC); ^1H NMR (benzene-d_6) δ: 0.75 (t, 3H, **CH_3**, $J=7.3$ Hz), 1.09–1.27 (m, 2H, **CH_2**), 1.80–2.10 (m, 2H, **CH_2**), 2.26–2.60 (m, 3H, Ar**CH_2**, **CH_2**N), 2.87–3.22 (m, 5H, Ar**CH_2**, **CH_2**N), 3.38 (s, 3H, O**CH_3**), 3.42–4.30 (m, 2H, O**CH_2**), 6.13 (d, 1H, **H_{arom}**, $J=8.2$ Hz), 6.46–6.65 (m, 3H, **H_{arom}**), 6.90 (t, 1H, **H_{arom}**, $J=8.2$ Hz), 7.17 (dd, 2H, **H_{arom}**, $J=5.4$, 8.5 Hz); MS (CI/NH_3) m/z 399 (M + 1); anal. $C_{23}H_{17}N_2O_3F$: (C, H, N, F).

Biology: binding experiments

5-HT_{1A} receptor binding to bovine frontal cortex and hippocampus membranes was determined by modifications of the methods of Hoyer et al.[55] Membranes (0.5 mg/mL protein) were incubated at 23 °C for 40 min with 0.5 nM [^{3}H]8-OH- DPAT in 50 mM Tris–HCl buffer, pH 7.4, supplemented with 4 mM $CaCl_2$ and 10 μM pargyline. Nonspecific binding was determined in the presence of 10 μM buspirone.

5-HT_{2A} receptor binding to bovine frontal cortex membranes was determined by modification of the methods of Leysen et al.[56] Membranes (0.6 mg/mL protein) were incubated at 37 °C for 30 min with 0.8 nM [^{3}H] ketanserin and 100 nM WB4101 in 50 mM Tris–HC1 buffer, pH 7.4 supplemented with 5mM $MgCl_2$, 10 mM NaCl, 0.5 mM EDTA, and 10 μM pargyline. Nonspecific binding was determined in the presence of 10 μM spiperone.

5-HT_{2C} receptor binding to pig choroide plexus membranes was determined by modification of the methods of Sanders-Busch and Breading.[57] Membranes (0.2 mg/mL protein) were incubated at 25 °C for 60 min with 1.2 nM [^{3}H] *N*-methylmesulergine and 1 μM spiperone in 50 nM Tris–HCl buffer, pH 7.4, supplemented with 4 mM $CaCl_2$ and 10 μM pargyline. Nonspecific binding was determined in the presence of 10 μM mianserine.

D_2 receptor binding was determined using membranes prepared from bovine striatum. The receptor was labeled with 1.2 nM [^{3}H] raclopride by incubation at 25 °C for 30 min. Nonspecific binding was determined in the presence of 10 μM spiperone.[58,59]

The affinity of the ligands tested to these receptors was expressed as $IC_{50} \pm$ SEM (concentration inhibiting 50% of the specific binding) and calculated using LUNDON2 software. The results obtained are reported in Table 1.

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