

3,4-Dihydro-3-amino-2H-1-benzopyran Derivatives as 5-HT_{1A} Receptor Ligands and Potential Anxiolytic Agents. 1. Synthesis and Structure-Activity Relationship Studies

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A series of 3,4-dihydro-3-amino-2H-1-benzopyran derivatives were prepared in order to determine the necessary structural requirements for good affinity for 5-HT_{1A} receptors and high selectivity versus other receptors. Modifications of the extracyclic amino substituents, the length of the alkyl side chains, and their substituents were explored. The best compounds (**9g**, **9k**, **15b**, **15d**) possess imido or sulfonamido functional groups with a preferential length of four methylenes for the side chain. After resolution, the dextrorotatory enantiomers showed better affinity and selectivity for 5-HT_{1A} receptors. These compounds have been proven to be full agonists. **9g** and its enantiomers showed anxiolytic activity *in vivo* in various comportemental models. The compound (+)-**9g** is currently under clinical investigation.

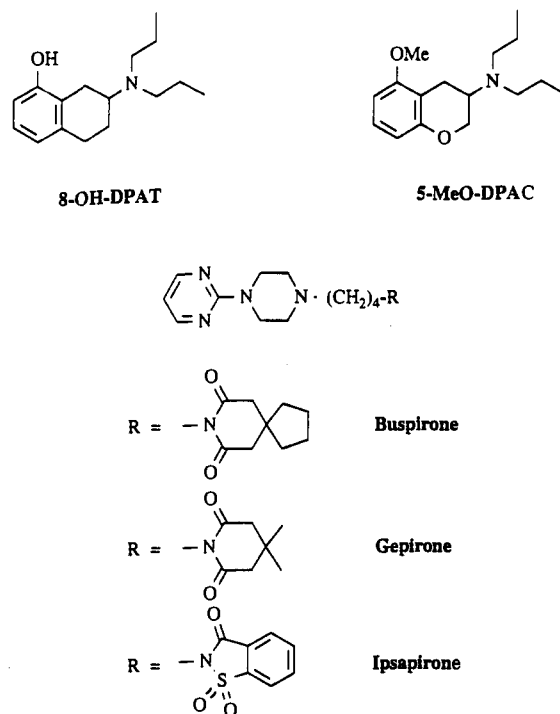
Introduction

During the last decade, serotonin (5-hydroxytryptamine, 5-HT) has been implicated in various behavioral disorders such anxiety, depression, and insomnia.¹⁻³ The discovery of multiple populations of central serotonin binding sites has rekindled a new interest in this neurotransmitter.^{4,5} Until recently, three main types of 5-HT receptors (5-HT₁, 5-HT₂, and 5-HT₃) have been described,⁶ but now there is also evidence of another type, the 5-HT₄ receptor.⁷ The 5-HT₁ class has been further subdivided into four accepted subtypes 5-HT_{1A}, 5-HT_{1B}, and more recently 5-HT_{1D} and 5-HT_{1E};⁸ the previous 5-HT_{1C} receptor was reclassified in the 5-HT₂ category as 5-HT_{2C}.⁹ Of the 5-HT₁ receptors, only the 5-HT_{1A} receptor, found predominantly in the hippocampus and dorsal raphe nucleus,¹⁰ possesses a selective and potent agonist: 8-OH-DPAT [8-hydroxy-2-(*N,N*-dipropylamino)tetralin]¹¹ (Chart 1).

In recent years, a growing body of literature has attributed the activity of the non-benzodiazepine anxiolytic agent buspirone (Chart 1) to an activation of the 5-HT_{1A} receptor,¹² but with a rather low selectivity versus D₂ receptors. Despite this poor selectivity, this discovery has created much interest in alternative, non-benzodiazepine treatment of anxiety, and consequently, synthetic efforts have been devoted by various authors¹³⁻¹⁶ in an attempt to obtain potent ligands with high affinity and relative selectivity for the 5-HT_{1A} receptor subtype such as gepirone or ipsapirone (Chart 1).

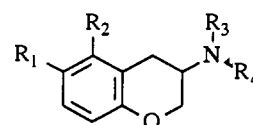
Our interest in the development of such therapeutic agents that exhibit weak or moderate activity at the D₂ receptor binding sites and display high affinity for 5-HT_{1A} receptor sites has recently led us to synthesize several derivatives of 3,4-dihydro-3-amino-2H-1-benzopyran.^{17,18} One of these, 5-MeO-DPAC [5-methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyran] (Chart 1), which is closely related to 8-OH-DPAT, acts in the nanomolar range

Chart 1



on 5-HT_{1A} sites but very poorly recognizes other 5-HT₁ sites and D₂ sites in rat brain membranes.

In this paper, we report the synthesis, receptor-binding profile, and behavioral activity of a series of compounds, analogs of the 5-MeO-DPAC, which possess the aminobenzopyran structure with various substitutions on the aromatic ring as well as on the extracyclic nitrogen atom.



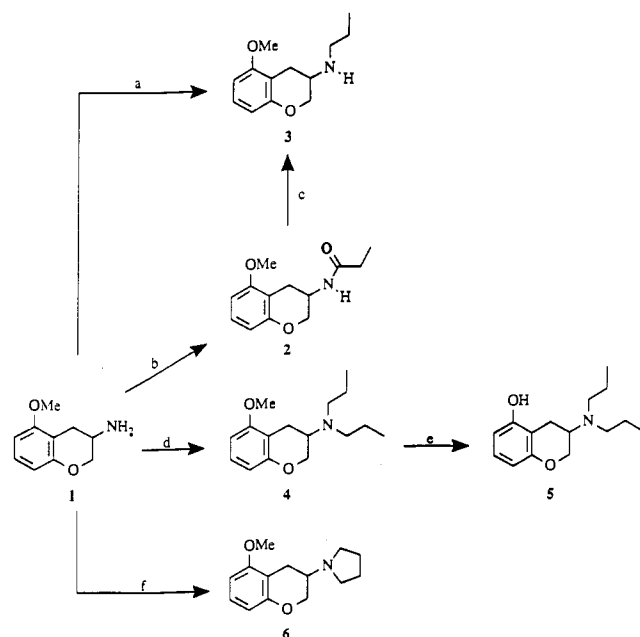
In order to reinforce the serotonergic properties of 5-MeO-DPAC, we associated imidic or bioisosteric groups

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Scheme 1^a

^a (a) DMF, *n*-PrI (1 equiv), K₂CO₃, 60 °C; (b) CH₂Cl₂, ClCOEt, Et₃N, 20 °C; (c) (i) THF, BH₃·Me₂S, (ii) MeOH, HCl, reflux; (d) DMF, *n*-PrI (3 equiv), K₂CO₃, 60 °C; (e) AcOH, HBr, reflux; (f) DMF, Br(CH₂)₄Br, Et₃N, KI, 60 °C.

such as those of buspirone, gepirone, ipsapirone, and analogues to the 3-amino-3,4-dihydro-2*H*-1-benzopyran serotonergic pharmacophore *via* an alkyl linkage. Chemical modulations were systematically carried out in order to determine the necessary structural requirements for good affinity on the 5-HT_{1A} receptors and high selectivity versus other receptors, and more particularly the D₂ receptors.

Chemistry

The synthesis of compounds 3–6 is illustrated in Scheme 1. The *N*-monopropyl derivative 3 is obtained by two different synthetic pathways from 5-methoxy-3,4-dihydro-3-amino-2*H*-1-benzopyran (1)¹⁸ either by *N*-monoalkylation with 1-iodopropane in dimethylformamide in the presence of potassium carbonate (75% yield) or by reduction of amide 2 which was prepared from propionyl chloride, with borane–methyl sulfide complex¹⁹ in tetrahydrofuran, in an overall yield of 64%. Compound 4 was synthesized in good yield (82%) by *N,N*-dialkylation of primary amine with 1-iodopropane in dimethylformamide. *O*-Demethylation of 4 by refluxing bromhydric acid in acetic acid²⁰ provided the desired aminophenol 5 in 95% yield. The amine 6 was synthesized from compound 1 by substitution with 1,4-dibromobutane in dimethylformamide in 54% yield.

The preparation of compounds 9–11 is described in Scheme 2. The treatment of compound 7, commercially available or obtained by known procedures,^{21,22} with 5-methoxy-3,4-dihydro-3-amino-2*H*-1-benzopyran (1) provided 8*a–d,f,m*, which were subsequently reacted with 1-iodopropane to give the desired substituted amines 9*a–d,f,m* in 21–57% yields. From 3,4-dihydro-3-amino-2*H*-1-benzopyran (21*a*), an analogous synthetic sequence allowed us to successively obtain substituted derivatives 8*n* and 9*n*. However, the reaction of 1 with 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione does not give the expected product 8*e* but corresponding *N*-(2-hydroxy-

ethyl)iminoglutarimide²³ in 68% yield. The synthetic problem was resolved by condensation of 3,3-tetramethyleneglutaric anhydride with amine 14*a* in refluxing toluene. This sequence provided amine 9*e* in 74% yield. The *O*-demethylation of 9*g* with boron tribromide in dichloromethane²⁴ gave the phenol 10 in 58% yield. On the other hand, the treatment of the same compound 9*g* with methyl iodide in dichloromethane provided the corresponding ammonium 11 in 70% yield.

Scheme 3 shows the various procedures used to synthesize amides and sulfonamides 15. The treatment of the *N*-monopropyl derivative 3 with chloroacetonitrile or 4-bromobutyronitrile in dimethylformamide in presence of potassium carbonate and potassium iodide gave compounds 13*a* and 13*b* in 73 and 79% yields, respectively. Reduction of these nitriles using lithium aluminum hydride²⁵ in tetrahydrofuran gave amines 14*a* and 14*b* in 69 and 72% yield. Condensation of these products with different acid chlorides or sulfonamides gave amides and sulfonamides 15 in 76–89% yields. The compound 15*c* is isolated in 65% yield by condensation in dimethylformamide of the monopropyl derivative 3 with the appropriate bromo sulfonamide 12.²⁶

Scheme 4 illustrates the synthesis of cyclic amines 18*a* and 18*b*. Condensation of 4-chlorobutyryl chloride with amine 3 in dichloromethane in presence of triethylamine gives compound 16 in 94% yield. Substitution of 16 by piperidine or morpholine provide the expected amides 17*a* and 17*b* in 64 and 66% yields, respectively, which by reduction with borane–dimethyl sulfide complex¹⁹ give compounds 18*a* and 18*b* in 66% yield in both cases.

The benzopyrans 22*a* and 22*b* were prepared from the corresponding nitro derivatives 19*a* and 19*b*²⁷ by known procedures^{17,18} (Scheme 5). Reduction of the unsaturated bond was carried out in a mixture of chloroform and 2-propanol by sodium borohydride in presence of silica gel.²⁸ Access to amines 21*a* and 21*b* was accomplished by using the hydrazine with Raney nickel.²⁹ The *N,N*-dipropyl compounds 22*a* and 22*b* were synthesized according to the usual procedure using propyl iodide in dimethylformamide in presence of potassium carbonate.

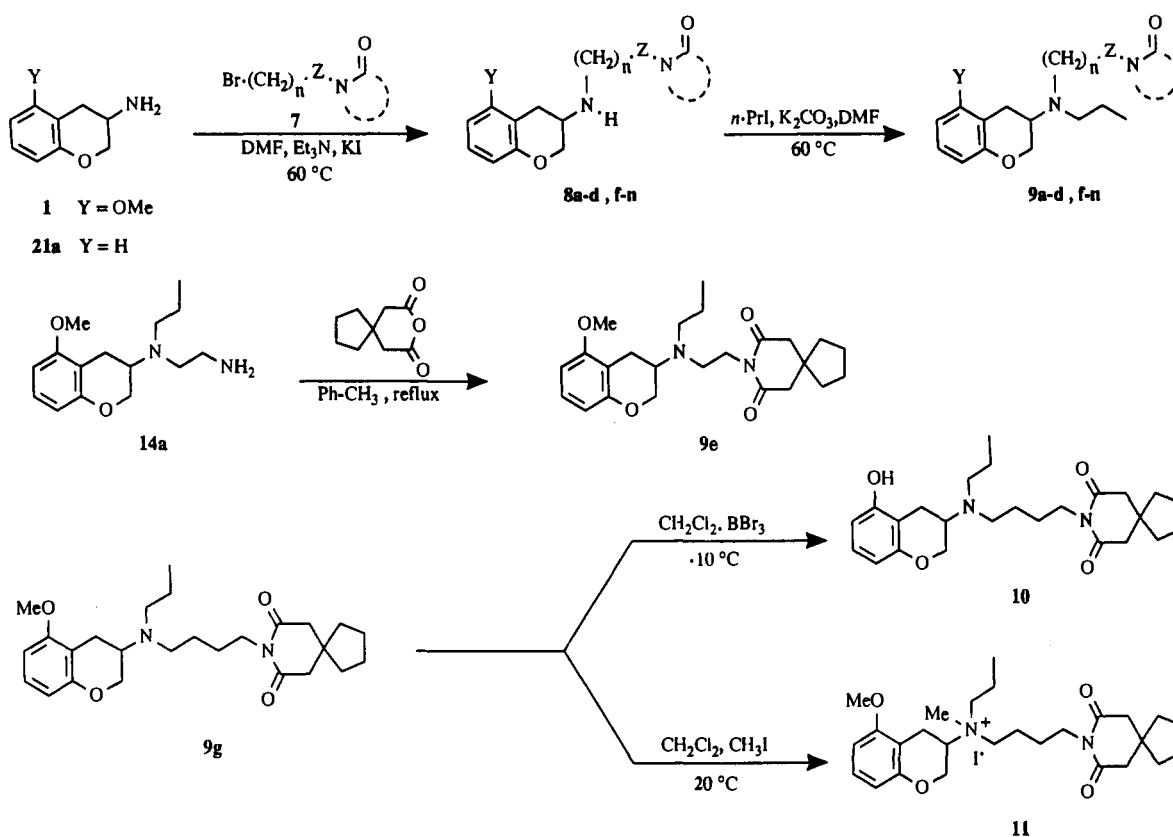
Indeed, compound 8*g* (Scheme 2) can also be obtained by reductive amination³⁰ from ketone 24,³¹ which was obtained from 2-hydroxy-6-methoxybenzaldehyde according to the procedure described by Wise et al.³² and 8-(4-aminobutyl)-8-azaspiro[4.5]decane-7,9-dione hydrochloride (23)³³ which was synthesized according to the method described by Gould et al.³⁴ (Scheme 6).

Both enantiomers of compounds 4, 9*g,k*, and 15*b,d* were obtained using similar procedures from the corresponding enantiomers of 5-methoxy-3,4-dihydro-3-amino-2*H*-1-benzopyran (1).

Results and Discussion

Forty-one 3,4-dihydro-3-amino-2*H*-1-benzopyran derivatives were designed, prepared, and evaluated to try to improve both the affinity for the 5-HT_{1A} receptor and the selectivity compared to other receptors, especially the D₂ receptor (Table 4). In this perspective, structural modulations were systematically carried out, in order, to determine (a) the importance of the 5-methoxy group, (b) the importance of the imide group's type (spiranic, aromatic, mono- or bicyclic), and (c) the optimal length between the benzopyran's basic nitrogen atom and the imide's nitrogen atom.

Scheme 2



In the same way, the following were also studied: (a) the influence of the amine group's type (secondary, tertiary, or ammonium) and (b) the replacement of the imide function by bioisosteric groups such as sulfonamides or carboxamides.

Diamino compounds were also prepared in order to determine the possible interest of two basic nitrogen atoms.

It rapidly appeared that (a) 5-methoxy, 5-hydroxy, and non-5-substituted compounds have about the same affinity for 5-HT_{1A} receptors, but only the 5-methoxy group gives simultaneously both good affinity and selectivity (compounds **9g,n** and **10**); (b) quaternarization of the amine (compound **11**) results in a dramatic decrease in affinity for 5-HT_{1A} receptor; and (c) replacement of tertiary amines by secondary amines results in a slighter decrease in affinity and selectivity.

Sulfonamides (**15b,c**) and amides (**15e,f**) have about the same good affinity for 5-HT_{1A} receptors, but amides have a rather low selectivity between the 5-HT_{1A} and D₂ receptors.

When the length of the alkyl spacer remains the same, aromatic imides (phthalimides **9a-c, 8c**) are lower affinity and selectivity ligands than aliphatic mono- or bicyclic imides, among which spiranic imides **9g** are a good affinity/selectivity compromise, and also than the sulfonamide bioisosteres **15d**.

When the substituent is a sulfonamide, the affinities remain the same with an alkyl spacer from two to four methylene units. With an imide substituent, the best affinity is obtained with a four methylene unit alkyl spacer as for tetralin analogs.³⁵ The incorporation of an oxygen atom in the spacer (compound **9m**) results in a decrease of both affinity and selectivity.

With replacement of the nonsalifiable amide groups by an amine morpholine, **18b**, or a piperidine, **18a**, we obtain

good affinity for the 5-HT_{1A} receptor but low selectivity between the 5-HT_{1A} and D₂ receptors.

When resolved, dextrorotatory enantiomers of imide (**9g,k**) or sulfonamide (**15b,d**) derivatives have always shown better affinity and selectivity than their levorotatory antipodes.

These above-mentioned results prove the important contribution of the 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran to the interaction with the 5-HT_{1A} receptor.

The length of the alkyl spacer between the two nitrogen atoms seems to have more influence in the selectivity than in the affinity for the 5-HT_{1A} receptor.

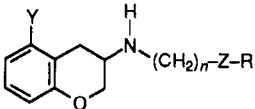
Whatever the structural modifications carried out, the only inactive compound was obtained *via* a bulky substitution of the benzopyran's 5-position (compound **22b**).

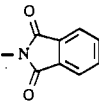
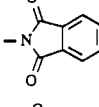
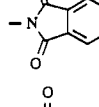
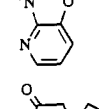
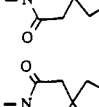
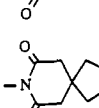
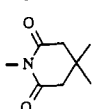
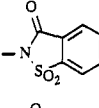
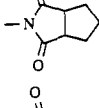
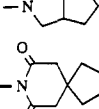
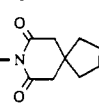
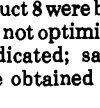
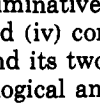
The conclusion of these structure-activity relationships studies is that the chemical modulation carried out led to the obtention of new compounds, among which the compound (+)-**9g**, with both greater affinity and higher selectivity for the 5-HT_{1A} receptors than buspirone and ipsapirone (Table 4).

Pharmacology

Among the high 5-HT_{1A} binding sites and selective compounds, **9g** has been selected and its enantiomers separated in order to (i) determine *in vitro* their agonistic or antagonistic activity at both presynaptic (inhibition of DRN firing) and postsynaptic (inhibition cAMP forskolin induced in hippocampus) levels, (ii) determine *in vivo* their activity with comportemental tests, related either to postsynaptic activity or to presynaptic activity, (iii) evaluate their *in vivo* anxiolytic-like activity using three behavioral tests which have been described to be very sensitive to 5-HT_{1A} agonist, like 8-OH-DPAT or buspirone

Table 1. Physical Data for Compounds 8

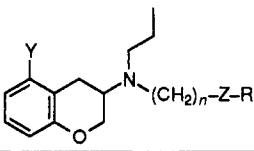


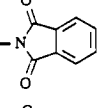
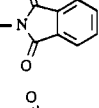
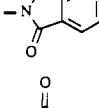
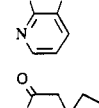
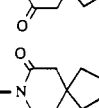
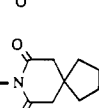
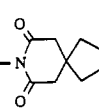
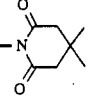
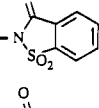
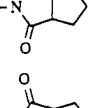
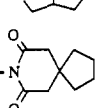
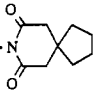
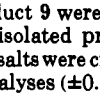

compd	Y	n	Z	R	yield ^a (%)	mp (°C)	formula ^b
8a	OMe	1	CH ₂		30	oil	C ₂₀ H ₂₀ N ₂ O ₄
8b	OMe	2	CH ₂		70	oil	C ₂₁ H ₂₂ N ₂ O ₄
8c	OMe	3	CH ₂		67	170	C ₂₂ H ₂₄ N ₂ O ₄ · C ₂ H ₂ O ₄
8d	OMe	3	CH ₂		53	oil	C ₂₀ H ₂₃ N ₃ O ₄
8f	OMe	2	CH ₂		58	oil	C ₂₂ H ₃₀ N ₂ O ₄
8g	OMe	3	CH ₂		65	135	C ₂₃ H ₃₂ N ₂ O ₄ · C ₂ H ₂ O ₄
8h	OMe	4	CH ₂		64	oil	C ₂₄ H ₃₄ N ₂ O ₄
8i	OMe	3	CH ₂		58	oil	C ₂₁ H ₃₀ N ₂ O ₄
8j	OMe	3	CH ₂		60	oil	C ₂₁ H ₂₄ N ₂ O ₅ S
8k	OMe	3	CH ₂		66	oil	C ₂₁ H ₃₈ N ₂ O ₄
8l	OMe	3	CH ₂		58	oil	C ₂₁ H ₃₀ N ₂ O ₃
8m	OMe	3	O		56	oil	C ₂₂ H ₃₀ N ₂ O ₅
8n	H	3	CH ₂		57	oil	C ₂₂ H ₃₀ N ₂ O ₃

^a Yields of isolated product 8 were based on corresponding primary amines 1 and 21a and were not optimized. ^b C₂H₂O₄ indicates oxalate salt unless otherwise indicated; satisfactory elemental analyses ($\pm 0.4\%$) for C, H, N were obtained for all compounds.

(anticonflict and discriminative stimulus effect, light/dark choice procedure), and (iv) compare the potency of the racemic compound and its two enantiomers on binding and on electrophysiological and behavioral activities in order to select the most potent compound for therapeutic development.

Table 2. Physical Data for Compounds 9



compd	Y	n	Z	R	yield ^a (%)	mp ^c (°C)	formula ^d
9a	OCH ₃	1	CH ₂		70	168	C ₂₃ H ₂₆ N ₂ O ₄ · HCl
9b	OCH ₃	2	CH ₂		76	74	C ₂₄ H ₂₈ N ₂ O ₄ · C ₂ H ₂ O ₄
9c	OCH ₃	3	CH ₂		81	72	C ₂₅ H ₃₀ N ₂ O ₄ · C ₂ H ₂ O ₄
9d	OCH ₃	3	CH ₂		65	85	C ₂₃ H ₂₉ N ₃ O ₄ · 2HCl
9e	OCH ₃	1	CH ₂		75 ^b	56	C ₂₄ H ₃₄ N ₂ O ₄ · C ₂ H ₂ O ₄
9f	OCH ₃	2	CH ₂		52	82	C ₂₅ H ₃₆ N ₂ O ₄ · C ₂ H ₂ O ₄
9g	OCH ₃	3	CH ₂		72	68	C ₂₆ H ₃₈ N ₂ O ₄ · C ₂ H ₂ O ₄
9h	OCH ₃	4	CH ₂		61	60	C ₂₇ H ₄₀ N ₂ O ₄ · C ₂ H ₂ O ₄
9i	OCH ₃	3	CH ₂		77	64	C ₂₄ H ₃₆ N ₂ O ₄ · C ₂ H ₂ O ₄
9j	OCH ₃	3	CH ₂		57	85	C ₂₄ H ₃₀ N ₂ O ₅ S· C ₂ H ₂ O ₄
9k	OCH ₃	3	CH ₂		78	65	C ₂₄ H ₃₄ N ₂ O ₄ · C ₂ H ₂ O ₄
9l	OCH ₃	3	CH ₂		70	55	C ₂₄ H ₃₆ N ₂ O ₃ · C ₂ H ₂ O ₄
9m	OCH ₃	3	O		68	55	C ₂₅ H ₃₆ N ₂ O ₅ · C ₂ H ₂ O ₄
9n	H	3	CH ₂		62	82	C ₂₅ H ₃₆ N ₂ O ₃ · C ₂ H ₂ O ₄

^a Yields of isolated product 9 were based on 8a-d,f-n and were not optimized. ^b Yield of isolated product 9e was based on 14a. ^c Oxalate and chlorhydrate salts were crystallized in dry diethyl ether. ^d Satisfactory elemental analyses ($\pm 0.4\%$) C, H, N were obtained for all compounds.

Scheme 3

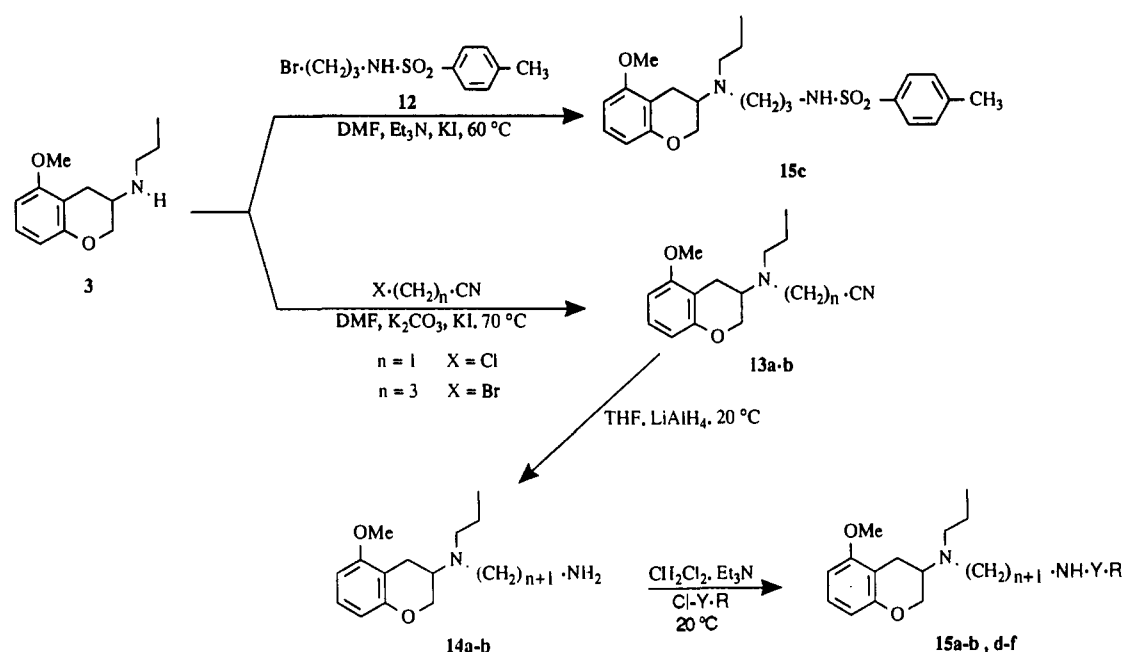


Table 3. Physical Data for Compounds 15

compd	Y	n	R	yield ^a (%)	mp ^c (°C)	formula ^d
15a	C=O	1	CH ₃	90	54	C ₁₇ H ₂₆ N ₂ O ₃ ·C ₂ H ₂ O ₄
15b	SO ₂	1		88	132	C ₂₂ H ₃₀ N ₂ O ₄ S·C ₂ H ₂ O ₄
15c	SO ₂	2		65 ^b	128	C ₂₃ H ₃₂ N ₂ O ₄ S·C ₂ H ₂ O ₄
15d	SO ₂	3		89	95	C ₂₄ H ₃₄ N ₂ O ₄ S·C ₂ H ₂ O ₄
15e	C=O	3		76	82	C ₂₄ H ₃₁ N ₂ O ₃ ·C ₂ H ₂ O ₄
15f	C=O	3		83	66	C ₂₅ H ₃₄ N ₂ O ₄ ·C ₂ H ₂ O ₄

^a Yields of isolated product 15 were based on amines 14a or 14b and were not optimized. ^b Yield of isolated product 15c was calculated on compound 3 and was not optimized. ^c Oxalate salts were crystallized in dry diethyl ether. ^d Satisfactory elemental analyses ($\pm 0.4\%$) C, H, N were obtained for all compounds.

Pharmacology: Results. The results of **9g** and its two enantiomers are shown in Table 5. The racemate **9g** and its two enantiomers (+)-**9g** and (-)-**9g** inhibited forskolin-activated adenylate cyclase in rat hippocampi in a concentration-dependent manner, with a similar maximal effect (maximal inhibition = -25%) for the three compounds. The enantiomer (+)-**9g** was more potent than **9g** and (-)-**9g**, with IC₅₀ values of 10.2 ± 2.7 , 26.3 ± 5.8 , and 248 ± 31 nM (mean \pm SEM, $n = 3$), respectively.³⁶ These data suggest simulation of the 5-HT_{1A} receptors located postsynaptically.

Both (+)-**9g** and (-)-**9g** were able to produce a long-lasting and concentration-dependent inhibition of the firing of DRN serotonergic neurons. Comparison of the concentration-response curves showed that (+)-**9g** (IC₅₀ \approx 6 nM) was \approx 20 times more potent than (-)-**9g** (IC₅₀ =

130 nM).³⁶ The conclusion of this data results from stimulation of the somatodendritic 5-HT_{1A} autoreceptors.

In the forepaw treading test, (+)-**9g** dose-dependently induced forepaw treading with a statistically significant effect at the lowest dose tested (8 mg/kg ip). With (-)-**9g**, a statistically significant effect was first observed at 32 mg/kg ip. In this test (+)-**9g** was 4 times more potent than (-)-**9g**.³⁷

In the lower lip retraction test, (+)-**9g** induced a clear lower lip retraction at the lowest dose tested (4 mg/kg ip). The effects observed with (-)-**9g** were clearly dose-dependent with a statistically significant effect from 8 mg/kg. In this test, (+)-**9g** was also at least 2 times more potent than (-)-**9g**.³⁷

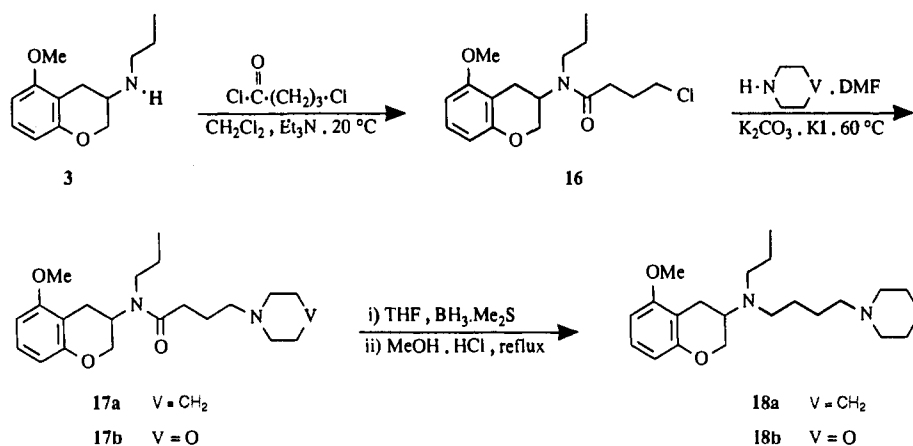
In the anticonflict test in pigeons, (+)-**9g** was approximately 10 times more potent than (-)-**9g** in producing maximal increases in punished responding. The racemate **9g** was comparable in potency to (-)-**9g** in producing maximal increases in punished responding. The lowest dose which induces an increase of punished responding was 0.03 mg/kg for (+)-**9g**, close to 0.06 mg/kg for **9g**,³⁸ and close to 1 mg/kg for (-)-**9g**. The dose giving the maximal increase in punished responding was approximately 0.1 mg/kg for (+)-**9g**.

In the drug-discrimination procedure, all three compounds, substituted for 8-OH-DPAT in a dose-dependent manner, differed in potency in the punishment studies. The enantiomer (+)-**9g** was again the most potent of the three compounds tested, producing >80% response on the key correlated with 8-OH-DPAT at 0.1 mg/kg. Substitution with **9g** and (-)-**9g** did not occur when doses of 0.3 and 3 mg/kg, respectively, were administered.³⁸

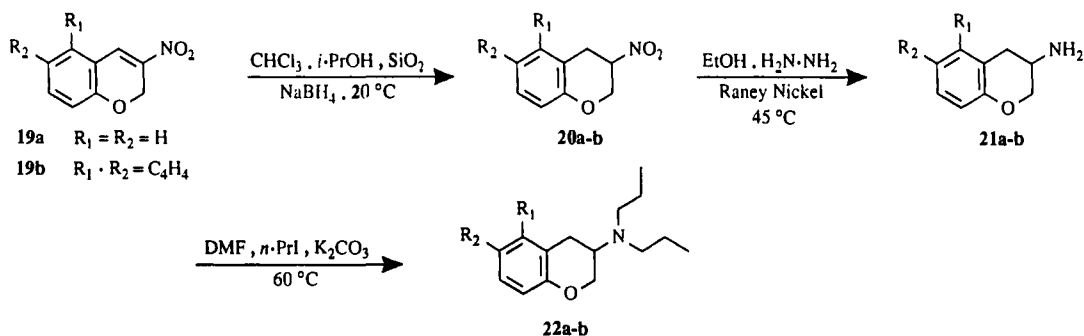
In the dark/light choice procedure, the three compounds induced anxiolytic-like effects at doses which were devoid of sedative properties. The dose corresponding to an amount of time spent in the lit box of longer than 60 s were respectively 1 mg/kg for (+)-**9g**, 2 mg/kg for **9g** and >2 mg/kg for (-)-**9g**.³⁹

Taken as a whole, the results of the *in vitro* and *in vivo* studies reported in Table 5 clearly demonstrate the difference in the potency of the three compounds: (+)-**9g**

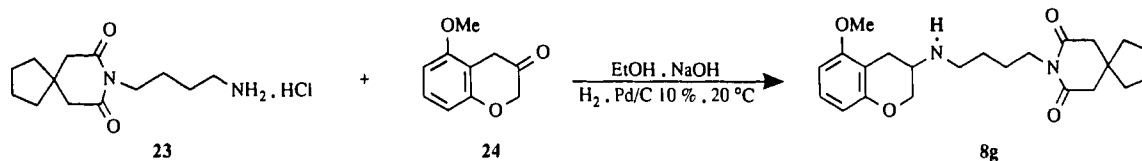
Scheme 4



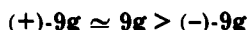
Scheme 5



Scheme 6



being slightly more active than **9g** and distinctly more active than (-)-**9g**.



These data parallel very well with the potency observed with the *in vitro* binding assays reported by different authors. For example Kidd et al.³⁶ reported that the derivatives bound with high affinity to 5-HT_{1A} sites in rat hippocampal membranes with values of 0.19 nM for (+)-**9g**, 0.35 nM for **9g**, and 0.95 nM for (-)-**9g**. This order of potency parallels the IC₅₀ values reported in the pigeons by Barrett et al.⁴⁰ for 5-HT_{1A} binding sites with IC₅₀ (nM) of 2.79 for (+)-**9g**, 2.87 for **9g**, and 20.30 for (-)-**9g**.

Conclusion

The structure-activity relationships we have established with our compounds proved the interest in associating two moieties known as good 5-HT_{1A} pharmacophores: 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran and imides, preferably spiranic. Experimental *in vitro* and *in vivo* data have shown higher activities for the dextrorotatory enantiomers. One of these compounds, (+)-**9g** is currently under clinical investigation. Further chemical modifications are currently being performed in order to define more accurately other structural requirements.

Experimental Section

Chemistry. General Comments. Melting points (uncorrected) were determined on a Kofler hot-stage apparatus.

Infrared spectra were determined with a Perkin-Elmer 297 spectrometer. The proton NMR spectra were obtained on a Bruker AM 300 spectrometer (300 MHz). Chemical shifts are reported in parts per million (δ , ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. The deuterated NMR solvents contained 99.8% deuterium with 1% TMS (v/v) were obtained from Aldrich-Chimie (Strasbourg, France). ¹H NMR coupling constants (*J* values) are listed in hertz (Hz), and spin multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). Chemical ionization mass spectral data (MS) were acquired on a R10-10C 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 Chemicals*; Pergamon: Oxford, 1986) or were purchased from the Aldrich Chimie or Janssen Chimica. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotatory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light or an alcohol solution of ammonium cerium(IV) nitrate. Column chromatography was performed with Kieselgel 60 (70–230 mesh) silica gel for gravity columns and Kieselgel 60 (230–400 mesh) silica gel (Merck) for flash columns. Where analyses in the tables are indicated by symbols of the elements, analytical results obtained for those elements were $\pm 0.4\%$ of the theoretical values. All nonaqueous reactions were performed in oven-dried glassware under an atmosphere of argon. The column chromatography solvents employed were glass distilled, and solvent mixtures are reported as volume to volume ratios. *N*-(Bromoalkyl)phthalimides **7a-c** were commercially available and used as received.

General Procedure for the Preparation of Bromo Compounds 7d-n. Method A. Potassium carbonate (7.43 g, 53.8

Table 4. IC₅₀ (M) Values in the Binding Tests

compd	5-HT _{1A}	5-HT _{1B}	5-HT ₂	D ₁	D ₂	α ₁	α ₂
4	2 × 10 ⁻⁶	2 × 10 ⁻⁵	6 × 10 ⁻⁵	1 × 10 ⁻⁴	5 × 10 ⁻⁶	8 × 10 ⁻⁵	4 × 10 ⁻⁶
(+)-4	2 × 10 ⁻⁹	5.1 × 10 ⁻⁷	9.7 × 10 ⁻⁶	>10 ⁻⁴	1.4 × 10 ⁻⁷	2.3 × 10 ⁻⁶	9.1 × 10 ⁻⁶
(-)-4	1 × 10 ⁻⁹	1 × 10 ⁻⁶	4 × 10 ⁻⁶	>10 ⁻⁴	2.1 × 10 ⁻⁷	3.5 × 10 ⁻⁶	7.8 × 10 ⁻⁷
5	4 × 10 ⁻⁹	>10 ⁻⁴	>10 ⁻⁴	1 × 10 ⁻⁴	4 × 10 ⁻⁷	1 × 10 ⁻⁴	2 × 10 ⁻⁶
6	7 × 10 ⁻⁹	1 × 10 ⁻⁴	6 × 10 ⁻⁵	>10 ⁻⁴	2.5 × 10 ⁻⁶	4 × 10 ⁻⁵	3 × 10 ⁻⁶
8c	9 × 10 ⁻⁶	7 × 10 ⁻⁶	6 × 10 ⁻⁷	3 × 10 ⁻⁵	5 × 10 ⁻⁶	>10 ⁻⁴	4 × 10 ⁻⁶
8g	2 × 10 ⁻⁶	2 × 10 ⁻⁵	1 × 10 ⁻⁶	2 × 10 ⁻⁵	9 × 10 ⁻⁷	1 × 10 ⁻⁵	2 × 10 ⁻⁵
9a	8 × 10 ⁻⁷	>10 ⁻⁴	>10 ⁻⁴	>10 ⁻⁴	1 × 10 ⁻⁵	>10 ⁻⁴	>10 ⁻⁴
9b	1 × 10 ⁻⁷	3 × 10 ⁻⁶	8 × 10 ⁻⁶	4 × 10 ⁻⁵	8 × 10 ⁻⁶	4 × 10 ⁻⁶	1 × 10 ⁻⁶
9c	5 × 10 ⁻⁶	4 × 10 ⁻⁷	3 × 10 ⁻⁵	4 × 10 ⁻⁵	3 × 10 ⁻⁶	5 × 10 ⁻⁶	2 × 10 ⁻⁶
9d	5 × 10 ⁻⁹	1 × 10 ⁻⁶	6 × 10 ⁻⁶	3 × 10 ⁻⁵	1 × 10 ⁻⁷	3 × 10 ⁻⁶	5 × 10 ⁻⁶
9e	3 × 10 ⁻⁶	>10 ⁻⁴	>10 ⁻⁴	>10 ⁻⁴	3 × 10 ⁻⁶	>10 ⁻⁴	>10 ⁻⁴
9f	1 × 10 ⁻⁹	2 × 10 ⁻⁵	8 × 10 ⁻⁷	1 × 10 ⁻⁵	6 × 10 ⁻⁷	8 × 10 ⁻⁶	6 × 10 ⁻⁶
9g	2 × 10 ⁻¹⁰	5 × 10 ⁻⁶	1 × 10 ⁻⁶	4 × 10 ⁻⁵	1 × 10 ⁻⁶	6 × 10 ⁻⁶	1 × 10 ⁻⁵
(+)-9g	3 × 10 ⁻¹⁰	1 × 10 ⁻⁵	3 × 10 ⁻⁶	4 × 10 ⁻⁵	3 × 10 ⁻⁶	4 × 10 ⁻⁵	2 × 10 ⁻⁶
(-)-9g	2 × 10 ⁻⁹	6 × 10 ⁻⁶	5 × 10 ⁻⁶	2 × 10 ⁻⁵	1 × 10 ⁻⁶	2 × 10 ⁻⁵	2 × 10 ⁻⁶
9h	1 × 10 ⁻⁹	2 × 10 ⁻⁵	3 × 10 ⁻⁶	6 × 10 ⁻⁵	6 × 10 ⁻⁶	5 × 10 ⁻⁶	1 × 10 ⁻⁷
9i	4 × 10 ⁻⁹	1 × 10 ⁻⁵	6 × 10 ⁻⁶	8 × 10 ⁻⁵	4 × 10 ⁻⁶	6 × 10 ⁻⁶	4 × 10 ⁻⁷
9j	1 × 10 ⁻⁹	1 × 10 ⁻⁶	1 × 10 ⁻⁵	5 × 10 ⁻⁵	9 × 10 ⁻⁶	1 × 10 ⁻⁶	4 × 10 ⁻⁵
9k	2 × 10 ⁻⁹	2 × 10 ⁻⁵	9 × 10 ⁻⁶	4 × 10 ⁻⁵	2 × 10 ⁻⁶	7 × 10 ⁻⁶	5 × 10 ⁻⁶
(+)-9k	8 × 10 ⁻⁹	1 × 10 ⁻⁵	1 × 10 ⁻⁵	5 × 10 ⁻⁵	1 × 10 ⁻⁷	3 × 10 ⁻⁶	5 × 10 ⁻⁶
(-)-9k	1 × 10 ⁻⁹	3 × 10 ⁻⁵	3 × 10 ⁻⁶	3 × 10 ⁻⁵	1 × 10 ⁻⁶	8 × 10 ⁻⁶	5 × 10 ⁻⁶
9l	1 × 10 ⁻⁹	3 × 10 ⁻⁵	2 × 10 ⁻⁶	6 × 10 ⁻⁵	3 × 10 ⁻⁹	5 × 10 ⁻⁶	4 × 10 ⁻⁶
9m	1 × 10 ⁻⁹	4 × 10 ⁻⁵	4 × 10 ⁻⁶	2 × 10 ⁻⁵	2 × 10 ⁻⁶	9 × 10 ⁻⁶	2 × 10 ⁻⁶
9n	2 × 10 ⁻⁹	3 × 10 ⁻⁵	2 × 10 ⁻⁶	4 × 10 ⁻⁵	4 × 10 ⁻⁹	7 × 10 ⁻⁶	1 × 10 ⁻⁵
10	1 × 10 ⁻⁹	3 × 10 ⁻⁵	4 × 10 ⁻⁶	1 × 10 ⁻⁴	8 × 10 ⁻⁹	1 × 10 ⁻⁵	2 × 10 ⁻⁵
11	3 × 10 ⁻⁷	>10 ⁻⁴	>10 ⁻⁴	1 × 10 ⁻⁴	1 × 10 ⁻⁶	7 × 10 ⁻⁵	>10 ⁻⁴
15a	4 × 10 ⁻⁶	6 × 10 ⁻⁵	>10 ⁻⁴	>10 ⁻⁴	6 × 10 ⁻⁷	>10 ⁻⁴	1 × 10 ⁻⁵
15b	2 × 10 ⁻⁹	>10 ⁻⁴	1 × 10 ⁻⁶	5 × 10 ⁻⁵	1 × 10 ⁻⁷	1 × 10 ⁻⁴	>10 ⁻⁴
(+)-15b	8 × 10 ⁻⁹	>10 ⁻⁴	>10 ⁻⁴	1 × 10 ⁻⁴	5 × 10 ⁻⁷	1 × 10 ⁻⁴	5 × 10 ⁻⁵
(-)-15b	5 × 10 ⁻⁹	>10 ⁻⁴	1 × 10 ⁻⁵	6 × 10 ⁻⁵	5 × 10 ⁻⁶	>10 ⁻⁴	1 × 10 ⁻⁵
15c	3 × 10 ⁻⁹	2 × 10 ⁻⁶	6 × 10 ⁻⁶	2 × 10 ⁻⁵	3 × 10 ⁻⁶	3 × 10 ⁻⁶	5 × 10 ⁻⁷
15d	2 × 10 ⁻⁹	8 × 10 ⁻⁶	1 × 10 ⁻⁵	3 × 10 ⁻⁵	2 × 10 ⁻⁷	3 × 10 ⁻⁶	1 × 10 ⁻⁵
(+)-15d	7 × 10 ⁻¹⁰	9 × 10 ⁻⁶	8 × 10 ⁻⁶	2 × 10 ⁻⁵	1 × 10 ⁻⁷	3 × 10 ⁻⁶	2 × 10 ⁻⁶
(-)-15d	2 × 10 ⁻⁶	2 × 10 ⁻⁵	5 × 10 ⁻⁶	2 × 10 ⁻⁵	6 × 10 ⁻⁶	7 × 10 ⁻⁶	2 × 10 ⁻⁶
15e	4 × 10 ⁻¹⁰	3 × 10 ⁻⁶	3 × 10 ⁻⁶	2 × 10 ⁻⁵	7 × 10 ⁻⁹	2 × 10 ⁻⁶	4 × 10 ⁻⁶
15f	1 × 10 ⁻⁹	1 × 10 ⁻⁶	4 × 10 ⁻⁶	ND	1 × 10 ⁻⁶	3 × 10 ⁻⁶	1 × 10 ⁻⁷
18a	2 × 10 ⁻⁹	5 × 10 ⁻⁵	>10 ⁻⁴	1 × 10 ⁻⁴	2 × 10 ⁻⁶	5 × 10 ⁻⁶	1 × 10 ⁻⁵
18b	8 × 10 ⁻⁹	>10 ⁻⁴	1 × 10 ⁻⁵	1 × 10 ⁻⁴	3 × 10 ⁻⁶	1 × 10 ⁻⁵	4 × 10 ⁻⁶
22a	4 × 10 ⁻⁷	>10 ⁻⁴	8 × 10 ⁻⁵	>10 ⁻⁴	6 × 10 ⁻⁶	>10 ⁻⁴	2 × 10 ⁻⁶
22b	2 × 10 ⁻⁵	3 × 10 ⁻⁵	1 × 10 ⁻⁵	4 × 10 ⁻⁵	1 × 10 ⁻⁷	2 × 10 ⁻⁶	1 × 10 ⁻⁵
8-OH-DPAT	2.4 × 10 ⁻⁹	ND	4.9 × 10 ⁻⁵	>10 ⁻⁴	8 × 10 ⁻⁷	3 × 10 ⁻⁵	1 × 10 ⁻⁶
bupirone	6 × 10 ⁻⁶	ND	1 × 10 ⁻⁵	2.7 × 10 ⁻⁵	4 × 10 ⁻⁶	1.6 × 10 ⁻⁵	1 × 10 ⁻⁵
ipsapirone	3.5 × 10 ⁻⁶	5 × 10 ⁻⁵	7.5 × 10 ⁻⁶	1.2 × 10 ⁻⁵	>10 ⁻⁴	1.2 × 10 ⁻⁶	2.8 × 10 ⁻⁶

Table 5. Effects of 9g and Its Enantiomers on Electrophysiological and Comportemental Studies

compd	agonist activity determination IC ₅₀ (nM)		<i>in vivo</i> comportemental tests				
	forskolin ^a	DRN firing ^b	FPT ^c msad (mg/kg ip)	LLR ^d msad (mg/kg ip)	punishment test msad (mg/kg im)	DDT ^e msad (mg/kg im)	DLBT ^f (mg/kg ip) ^g
9g	26.3 ± 5.8	-	-	-	0.06	0.3	2
(-)-9g	248 ± 31	~130	32	8	1	3	>2
(+)-9g	10.2 ± 2.7	~6	8	4	0.03	0.1	1
8-OH-DPAT	~8	~5	-	-	0.1	-	-

^a Inhibition of forskolin-activated adenylate cyclase.³⁶ ^b Inhibition of firing in the dorsal raphe nucleus.³⁶ ^c Forepaw treading test.³⁷ ^d Lower lip retraction.³⁷ ^e Drug discrimination test.³⁸ ^f Dark/light box test.³⁹ ^g Dose corresponding to an amount of time spent in the lit box longer than 60 s. msad = minimum significant active dose.

mmol), a catalytic amount of potassium iodide, and 1,ω-dibromoalkane (19.73 mmol) were added to a mixture of 8-azaspiro[4.5]decane-7,9-dione (3 g, 17.9 mmol) in acetonitrile (20 mL). The mixture was stirred at 60 °C for 6 h and then cooled to room temperature. The solvent was evaporated to dryness, and the product was extracted after aqueous hydrolysis with dichloromethane. The organic phase was dried (MgSO₄) and evaporated. The resulting oil was then purified by chromatography on a silica gel column by elution with dichloromethane to give the pure product.

Method B. 8-Azaspiro[4.5]decane-7,9-dione (17.9 mmol) was added in one portion to a suspension of NaH (50% oil dispersion, 0.65 g, 26.9 mmol, THF washed) in DMF (30 mL). The mixture was stirred at 60 °C for 1 h, and then 1,ω-dibromoalkane (107.6 mmol) and a catalytic amount of potassium iodide were added. Stirring was continued for 1 h, and the reaction mixture was cooled to room temperature. The solvent was removed in vacuo

and the residue taken up in dichloromethane (30 mL). The organic phase was washed with water (20 mL), dried (MgSO₄), and concentrated. The residue was chromatographed over silica gel using dichloromethane as eluent.

3-(4-Bromobutyl)oxazolo[4,5-*b*]pyridin-2(3*H*)-one (7d): method B (64%); IR (neat) 1775 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 2.41–2.51 (m, 4H, CH₂CH₂CH₂Br), 3.47 (t, 2H, J = 6.7 Hz, CH₂Br), 4.10 (t, 2H, J = 6.7 Hz, CH₂NCO), 7.08 (dd, 1H, J¹ = 8 Hz, J² = 5.1 Hz, pyridine), 7.41 (d, 1H, J = 8 Hz, pyridine), 8.11 (d, 1H, J = 5.1 Hz, pyridine).

8-(2-Bromoethyl)-8-azaspiro[4.5]decane-7,9-dione (7e): method B (63%); IR (neat) 1715 and 1660 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.46–1.54 (m, 4H, CH₂), 1.67–1.76 (m, 4H, CH₂), 2.62 (s, 4H, CH₂CO), 3.48 (t, 2H, J = 6.9 Hz, CH₂Br), 4.20 (t, 2H, J = 6.9 Hz, CH₂CH₂Br).

8-(3-Bromopropyl)-8-azaspiro[4.5]decane-7,9-dione (7f): method A (70%); IR (neat) 1720 and 1665 cm⁻¹ (ν C=O); ¹H

NMR (CDCl₃) δ 1.45–1.56 (m, 4H, CH₂), 1.66–1.75 (m, 4H, CH₂), 2.06–2.15 (m, 2H, CH₂CH₂Br), 2.59 (s, 4H, CH₂CO), 3.36 (t, 2H, $J = 7.1$ Hz, CH₂Br), 3.89 (t, 2H, $J = 7.1$ Hz, CH₂NCO).

8-(4-Bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (7g): method A (69%); IR (neat) 1720 and 1660 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.45–1.52 (m, 4H, CH₂), 1.62–1.72 (m, 6H, CH₂), 1.79–1.90 (m, 2H, CH₂CH₂N), 2.60 (s, 4H, CH₂CO), 3.42 (t, 2H, $J = 7.1$ Hz, CH₂Br), 3.80 (t, 2H, $J = 7.1$ Hz, CH₂NCO).

8-(5-Bromopentyl)-8-azaspiro[4.5]decane-7,9-dione (7h): method A (50%); IR (neat) 1715 and 1655 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.35–1.73 (m, 12H, CH₂), 1.81–1.90 (m, 2H, CH₂), 2.57 (s, 4H, CH₂CO), 3.38 (t, 2H, $J = 7.1$ Hz, CH₂Br), 3.74 (t, 2H, $J = 7.1$ Hz, CH₂NCO).

1-(4-Bromobutyl)-4,4-dimethylpiperidine-2,6-dione (7i): method A (65%); IR (neat) 1715 and 1660 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.06 (s, 6H, CH₃C), 1.61–1.73 (m, 2H, CH₂), 1.80–1.91 (m, 2H, CH₂), 2.51 (s, 4H, CH₂CO), 3.41 (t, 2H, $J = 6.3$ Hz, CH₂Br), 3.80 (t, 2H, $J = 6.3$ Hz, CH₂N).

N-(4-Bromobutyl)-1,1-dioxo-1,2-benzisothiazol-3(2H)-one (7j): method A (60%); IR (neat) 1720 (ν C=O), 1300 and 1170 cm⁻¹ (n SO₂); ¹H NMR (CDCl₃) δ 1.95–2.05 (m, 4H, CH₂CH₂CH₂Br), 3.44 (t, 2H, $J = 7.1$ Hz, CH₂Br), 3.82 (t, 2H, $J = 7.1$ Hz, CH₂N), 7.78–8.05 (m, 5H, arom).

N-(4-Bromobutyl)-2,4-dioxo-3-azabicyclo[3.3.0]octane (7k): method A (58%); IR (neat) 1760 and 1685 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.15–1.38 (m, 2H, CH₂), 1.62–2.14 (m, 8H, CH₂), 3.12 (m, 2H, CHCO), 3.38 (t, 2H, $J = 6.6$ Hz, CH₂Br), 3.48 (t, 2H, $J = 6.6$ Hz, CH₂NCO).

N-(4-Bromobutyl)-2-oxo-3-azabicyclo[3.3.0]octane (7l): method B (52%); IR (neat) 1670 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.40–2.29 (m, 10H, CH₂), 2.70–2.95 (m, 2H, CH₂N), 3.00 (dd, 1H, $J^1 = 9.7$ Hz, $J^2 = 2.6$ Hz, CHCH₂), 3.20–3.40 (m, 2H, CH₂NCO), 3.44 (t, 2H, $J = 6.5$ Hz, CH₂Br), 3.58 (t, 1H, $J = 9.7$ Hz, CHCO).

8-[(3-Bromopropyl)oxy]-8-azaspiro[4.5]decane-7,9-dione (7m): By the procedure described by N. J. Hrib et al.,²² 8-hydroxy-8-azaspiro[4.5]decane-7,9-dione (5 g, 27.29 mmol) (prepared from 8-azaspiro[4.5]decane-7,9-dione) was converted into 7b (5.67 g, 68%) of the pure product: IR (neat) 1740 and 1690 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.51–1.61 (m, 4H, CH₂), 1.68–1.78 (m, 4H, CH₂), 2.21–2.31 (m, 2H, CH₂CH₂O), 2.68 (s, 4H, CH₂CO), 3.65 (t, 2H, $J = 6.3$ Hz, CH₂Br), 4.12 (t, 2H, $J = 6.3$ Hz, CH₂O).

5-Methoxy-3,4-dihydro-3-(*n*-propylamino)-2H-1-benzopyran (3): Method C. A mixture of 1 (4.85 g, 27 mmol), 1-iodopropane (5 g, 29.5 mmol), and potassium carbonate (11.19 g, 81 mmol) in DMF (15 mL) was warmed while stirring at 60 °C for 6 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. After aqueous hydrolysis, the product was extracted with diethyl ether, and the organic layer was dried (MgSO₄) and evaporated to dryness. Purification by column chromatography of the resulting crude product (diethyl ether/petroleum ether elution, 1:2) gave 4.5 g (75%) of pure compound 3 as a colorless oil: IR (neat) 1235 cm⁻¹ (ν C–O); ¹H NMR (CDCl₃) δ 0.94 (t, 3H, $J = 7.1$ Hz, CH₃CH₂), 1.07 (b, 1H, NH), 1.48–1.57 (m, 2H, CH₂CH₃), 2.47 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7$ Hz, CHAr), 2.70 (t, 2H, $J = 7.1$ Hz, CH₂N), 2.95 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.03–3.14 (m, 1H, CHN), 3.80–3.89 (m, 4H, CH₃O, CHO), 4.12–4.21 (m, 1H, CHO), 6.43 and 6.49 (2 d, 2H, $J = 8.2$ Hz, arom), 7.06 (t, 1H, $J = 8.2$ Hz, arom); MS *m/e* 221 (M⁺), 192, 163. Anal. (C₁₃H₁₉NO₂) C, H, N.

Method D. A solution of the primary amine 1 (0.179 g, 1 mmol) in dichloromethane (6 mL) containing triethylamine (0.22 g, 2.17 mmol) was treated with propanoyl chloride (0.092 g, 1 mmol). The mixture was stirred at room temperature for 30 min, and the dichloromethane solution was evaporated to dryness. The resulting crude was purified by column chromatography in 50% dichloromethane/diethyl ether to provide 0.21 g (90%) of 5-methoxy-3-propionamido-3,4-dihydro-2H-1-benzopyran (2) as a white solid: mp 125 °C; IR (KBr) 3300 (ν NH), 1630 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.12 (t, 3H, $J = 7.2$ Hz, CH₃CH₂), 2.16 (q, 2H, $J = 7.2$ Hz, CH₂CH₃), 2.72 (d, 1H, $J = 16.7$ Hz, CHAr), 2.87 (dd, 1H, $J^1 = 16.7$ Hz, $J^2 = 5.7$ Hz, CHAr), 3.80 (s, 3H, CH₃O), 4.02 and 4.10 (2d, 2H, $J = 11.3$ Hz, CH₂O), 4.45–4.55 (m,

1H, CHN), 5.86 (b, 1H, NHCO), 6.42 and 6.52 (2 d, 2H, $J = 8.3$ Hz, arom), 7.08 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₁₃H₁₇NO₃) C, H, N.

Compound 2 (0.15 g, 0.64 mmol) was dissolved in dry tetrahydrofuran (5 mL) and treated dropwise with borane-dimethyl sulfide complex (0.2 mL). The solution was heated under reflux for 4 h in an atmosphere of argon and evaporated to dryness. The residue was heated on a steam bath for 1.5 h with 2 M HCl (10 mL) and methanol (5 mL). The solution was cooled and basified with 2 M NaOH, and the product was extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL), dried (MgSO₄), and evaporated to dryness. The residue was purified by column chromatography (methanol/dichloromethane, 1:9) to yield 0.12 g (85%) of 3 which was identical to that obtained from method C.

5-Methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyran (4): The title compound was prepared from amine 1 (3 g, 16.8 mmol), iodopropane (8.5 g, 50.4 mmol), and potassium carbonate (7 g, 50.4 mmol) in DMF (15 mL) according to method C. Column chromatography of the resulting residue (diethyl ether/petroleum ether elution, 1:2) provide the title compound (3.62 g, 82%) as a colorless oil: IR (neat) 1230 cm⁻¹ (ν C–O); ¹H NMR (CDCl₃) δ 0.87 (t, 6H, $J = 7.9$ Hz, CH₃), 1.40–1.50 (m, 4H, CH₂CH₃), 2.45–2.56 (m, 5H, CH₂N, CHAr), 2.85 (d, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.08–3.15 (m, 1H, CHN), 3.75 (t, 1H, $J = 10.3$ Hz, CHO), 3.80 (s, 3H, CH₃O), 4.21–4.30 (m, 1H, CHO), 6.43 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.05 (t, 1H, $J = 8.3$ Hz, arom); MS *m/e* 263 (M⁺), 234, 163. Anal. (C₁₈H₂₅NO₂HCl) C, H, N, Cl.

(+)-4: $[\alpha]_D^{25} = +96^\circ$ ($c = 0.83$, CHCl₃).

(-)-4: $[\alpha]_D^{25} = -97^\circ$ ($c = 0.75$, CHCl₃).

5-Hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyran (5): Hydrobromic acid (48%, 1 mL) was added to a solution of 4 (0.1 g, 0.38 mmol) in acetic acid (2 mL). The mixture was refluxed at 130–140 °C for 4 h, cooled, and then poured with agitation into a mixture of 50 mL of saturated sodium bicarbonate, 50 mL of dichloromethane, and 50 g of ice. After decanting, the aqueous phase was extracted several times with dichloromethane. The unified organic layers were dried (MgSO₄), and the solvent was evaporated under reduced pressure. The crude was purified by short silica gel column chromatography (dichloromethane elution) to yield 0.09 g (95%) of pure compound 5 as a clear oil: IR (neat) 1230 cm⁻¹ (ν C–O); ¹H NMR (CDCl₃) δ 0.89 (t, 6H, $J = 7.9$ Hz, CH₃CH₂), 1.43–1.52 (m, 4H, CH₂CH₃), 2.51–2.60 (m, 5H, CH₂N, CHAr), 2.86 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.15–3.20 (m, 1H, CHN), 3.78 (t, 1H, $J = 10.3$ Hz, CHO), 4.23–4.33 (m, 1H, CHO), 6.37 and 6.44 (2 d, 2H, $J = 8.3$ Hz, arom), 6.93 (t, 1H, $J = 8.3$ Hz, arom); MS *m/e* 249 (M⁺), 220, 149. Anal. (C₁₅H₂₃NO₂HCl) C, H, N, Cl.

5-Methoxy-3-(pyrrolidin-1-yl)-3,4-dihydro-2H-1-benzopyran (6): A mixture of 0.5 g (2.79 mmol) of 1, 0.66 g (3.07 mmol) of 1,4-dibromobutane, 0.85 (8.37 mmol) of triethylamine, and a catalytic amount of potassium iodide in 6 mL of DMF was warmed with stirring at 60 °C for 24 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The product was extracted from the resulting crude after aqueous hydrolysis with dichloromethane. The organic solvent was dried (MgSO₄) and evaporated to dryness. The residual oil was chromatographed on silica gel column (diethyl ether/dichloromethane elution, 1:1) to give a white solid: mp 76 °C; IR (KBr) 1230 cm⁻¹ (ν C–O); ¹H NMR (CDCl₃) δ 1.79–1.88 (m, 4H, CH₂), 2.47–2.67 (m, 2H, CHN and CH₂Ar), 2.67–2.79 (m, 4H, CH₂N), 3.02 (ddd, 1H, $J = 3.0$ Hz, $J = 15.0$ Hz, $J = 5.0$ Hz, CH₂Ar), 3.79 (t, 1H, $J = 10.3$ Hz, CHO), 3.84 (s, 3H, CH₃O), 4.37 (dt, 1H, $J = 10.3$ Hz, $J = 3.0$ Hz, CHO), 6.43 and 6.48 (2 d, 2H, $J = 8.3$ Hz, arom), 7.05 (t, 1H, $J = 8.3$ Hz, arom); MS *m/e* 233 (M⁺), 97. Anal. (C₁₄H₁₉NO₂C₂H₅O₄) C, H, N.

General Procedure for the Preparation of Amines 8a–c. A mixture of 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran 1 (0.392 g, 2.2 mmol), N-(ω -bromoalkyl) phthalimide (2.4 mmol), potassium carbonate (0.907 g, 6.6 mmol) and potassium iodide (0.001 g, 0.06 mmol) in DMF (6 mL) was placed in a one-necked 50 mL conical flask. The solution was heated at 60 °C (oil bath) whilst stirring for 6 h and then cooled to room temperature. The solvent was removed under reduced pressure and the material

was partitioned between dichloromethane (10 mL) and water (5 mL). The organic phase was dried (MgSO₄) and the solvent was removed in vacuo to yield a crude oil which was chromatographed on a silica gel column using diethyl ether-petroleum ether (5:95) as eluent to give the expected pure products. The yields were calculated from primary amine 1.

5-Methoxy-3,4-dihydro-3-[N-(2-phthalimidoethyl)amino]-2H-1-benzopyran (8a). The title compound (0.06 g) was prepared in 30% yield from **7a** (0.157 g, 0.616 mmol) according to the general procedure: pale oil; IR (neat) 1765 and 1755 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.48 (b, 1H, NH), 2.44 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 7$ Hz, CHAr), 2.88 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 6$ Hz, CHAr), 3.03 (t, 2H, $J = 7.9$ Hz, CH₂NH), 3.10–3.20 (m, 1H, CHN), 3.78 (s, 3H, CH₃O), 3.76–3.86 (m, 3H, CH₂NCO, CHO), 4.05–4.15 (m, 1H, CHO), 6.40 and 6.44 (2 d, 2H, $J = 8.2$ Hz, arom), 7.02 (t, 1H, $J = 8.2$ Hz, arom), 7.71–7.85 (m, 4H, arom). Anal. (C₂₀H₂₀N₂O₄) C, H, N.

5-Methoxy-3,4-dihydro-3-[N-(3-phthalimidopropyl)amino]-2H-1-benzopyran (8b). Bystarting from **7b** (0.834 g, 4.96 mmol), this compound (0.73 g) was prepared according to the general procedure (70% yield): colorless oil; IR (neat) 1760 and 1690 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.56 (b, 1H, NH), 1.82–1.92 (m, 2H, CH₂CH₂N), 2.44 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7.1$ Hz, CHAr), 2.79 (t, 2H, $J = 6.6$ Hz, CH₂NH), 2.90 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6.6$ Hz, CHAr), 3.01–3.11 (m, 1H, CHN), 3.73–3.83 (m, 6H, CH₃O, CH₂NCO, CHO), 4.07–4.17 (m, 1H, CHO), 6.40 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.04 (t, 1H, $J = 8.2$ Hz, arom), 7.71–7.83 (m, 4H, arom). Anal. (C₂₁H₂₂N₂O₄) C, H, N.

5-Methoxy-3,4-dihydro-3-[N-(4-phthalimidobutyl)amino]-2H-1-benzopyran (8c). This compound (0.56 g) was synthesized from **7c** (0.677 g, 2.41 mmol) according to the general procedure (67% yield): colorless oil; IR (neat) 1760 and 1700 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.51–1.61 (m, 3H, CH₂CH₂N, NH), 1.70–1.80 (m, 2H, CH₂CH₂NCO), 2.47 (dd, 1H, $J^1 = 16.9$ Hz, $J^2 = 7$ Hz, CHAr), 2.75 (t, 2H, $J = 7.9$ Hz, CH₂NH), 2.92 (dd, 1H, $J^1 = 16.9$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.04–3.14 (m, 1H, CHN), 3.62 (t, 2H, $J = 7.9$ Hz, CH₂NCO), 3.80 (s, 3H, CH₃O), 3.84 (t, 1H, $J = 10.2$ Hz, CHO), 4.08–4.18 (m, 1H, CHO), 6.42 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.05 (t, 1H, $J = 8.2$ Hz, arom), 7.69–7.83 (m, 4H, arom). Anal. (C₂₂H₂₄N₂O₄·C₂H₂O₄) C, H, N.

General Procedure for the Preparation of Amines 8d,f-n. A mixture of 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran (**1**) (1.1 g, 6.14 mmol), bromo compounds **7** (6.75 mmol), triethylamine (1.86 g, 18.42 mmol), and potassium iodide (0.001 g, 0.06 mmol) in 15 mL of DMF was warmed with stirring at 60 °C for 24 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The product was extracted from the resulting crude after aqueous hydrolysis with CH₂Cl₂ (4 × 20 mL). The solvent was dried (MgSO₄) and evaporated to dryness under reduced pressure. Purification by column chromatography of the resulting crude was performed to give the expected pure products. The yields were calculated from primary amine 1.

3-[4-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]oxazolo[4,5-b]pyridin-2(3H)-one (8d). Using the general procedure described above, bromo compound **7d** (1.99 g, 7.37 mmol) was converted into **8d**. The resulting residue was purified by silica gel column chromatography and elution with dichloromethane/methanol (98:2) to give 1.31 g (53%) of pure product **8d** as a pale oil: IR (neat) 1775 (ν C=O), 1240 cm⁻¹ (ν C-O); ¹H NMR (CDCl₃) δ 1.34 (b, 1H, NH), 1.58–1.68 (m, 2H, CH₂), 1.86–1.95 (m, 2H, CH₂), 2.48 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7$ Hz, CHAr), 2.78 (t, 2H, $J = 7.2$ Hz, CH₂N), 2.92 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.02–3.13 (m, 1H, CHN), 3.82 (s, 3H, CH₃O), 3.84 (t, 1H, $J = 10.2$ Hz, CHO), 3.97 (t, 2H, $J = 7.2$ Hz, CH₂NCO), 4.09–4.19 (m, 1H, CHO), 6.44 and 6.49 (2 d, 2H, $J = 8.3$ Hz, arom), 7.40–8.10 (m, 4H, arom). Anal. (C₂₀H₂₂N₃O₄) C, H, N.

3-[3-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]propyl]-8-azaspiro[4.5]decane-7,9-dione (8f). The title compound was prepared from **7f** (1.95 g, 6.75 mmol) according to the general procedure. The crude product was purified by flash chromatography using diethyl ether/dichloromethane (1:1) as eluent to provide 1.38 g (58%) of **8f** as an oil: IR (neat) 1720 and 1665 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.44–1.82 (m, 11H, CH₂, NH), 2.48 (dd, 1H, $J^1 = 16.8$ Hz, $J^2 = 6.9$ Hz, CHAr), 2.57

(s, 4H, CH₂CO), 2.65 (t, 2H, $J = 7.4$ Hz, CH₂N), 2.94 (dd, 1H, $J^1 = 16.8$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.04–3.14 (m, 1H, CHN), 3.79–3.89 (m, 6H, CH₃O, CH₂NCO, CHO), 4.12–4.20 (m, 1H, CHO), 6.43 and 6.48 (2 d, 2H, $J = 8.3$ Hz, arom), 7.05 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₂₂H₃₀N₂O₄) C, H, N.

8-[4-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-5-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (8g). This compound was synthesized from **7g** (2.04 g, 6.75 mmol) according to the general procedure. The crude product was chromatographed on silica gel and eluted with dichloromethane/diethyl ether (1:1) to give 1.6 g (65%) of **8g** as an oil: IR (neat) 1715 and 1660 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.45–1.85 (m, 13H, NH, CH₂), 2.46 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7$ Hz, CHAr), 2.59 (s, 4H, CH₂CO), 2.74 (t, 2H, $J = 7$ Hz, CH₂N), 2.92 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.01–3.09 (m, 1H, CHN), 3.76–3.85 (m, 6H, CH₃O, CH₂NCO, CHO), 4.08–4.18 (m, 1H, CHO), 6.41 and 6.48 (2 d, 2H, $J = 8.3$ Hz, arom), 7.04 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₂₃H₃₂N₂O₄·C₂H₂O₄) C, H, N.

(+)-**8g**: [α]_D²⁰ = +15.3° (c = 0.16, CHCl₃).

(-)-**8g**: [α]_D²⁰ = -15.6° (c = 0.16, CHCl₃).

8-[5-[N-(5-Methoxy-3,4-dihydroxy-2H-1-benzopyran-3-yl)amino]pentyl]-8-azaspiro[4.5]decane-7,9-dione (8h). By the general procedure described above, **7h** (1.35 g, 4.27 mmol) was converted into **8h**. The crude mixture was purified by silica gel column chromatography using dichloromethane/diethyl ether (1:1) as eluent to give 1.14 g (64%) of **8h** as a colorless oil: IR (neat) 1715 and 1650 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.32–1.41 (m, 2H, CH₂), 1.45–1.56 (m, 9H, CH₂, NH), 1.67–1.78 (m, 4H, CH₂), 2.45 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7.5$ Hz, CHAr), 2.57 (s, 4H, CH₂CO), 2.72 (t, 2H, $J = 7.1$ Hz, CH₂N), 2.91 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.5$ Hz, CHAr), 3.03–3.13 (m, 1H, CHN), 3.70–3.86 (m, 6H, CH₃O, CH₂NCO, CHO), 4.10–4.20 (m, 1H, CHO), 6.40 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.03 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₂₄H₃₄N₂O₄) C, H, N.

5-Methoxy-3-[N-[4-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)butyl]amino]-3,4-dihydro-2H-1-benzopyran (8i). This compound was obtained from **7i** (1.97 g, 7.2 mmol) using to the general procedure. The crude material was chromatographed on silica gel using dichloromethane/diethyl ether (1:1) as the eluent to give 1.4 g (58%) of pure **8i** as an oil: IR (neat) 1715 and 1660 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.06 (s, 6H, CH₃), 1.52–1.60 (m, 5H, CH₂, NH), 2.39 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 7$ Hz, CHAr), 2.41 (s, 4H, CH₂CO), 2.70 (t, 2H, $J = 7.1$ Hz, CH₂N), 2.90 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 6$ Hz, CHAr), 3.04–3.15 (m, 1H, CHN), 3.71–3.83 (m, 6H, CH₃O, CHO, CH₂NCO), 4.12–4.22 (m, 1H, CHO), 6.40 and 6.45 (2 d, 2H, $J = 8.3$ Hz, arom), 7.06 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₂₁H₃₀N₂O₄) C, H, N.

2-[4-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-1,1-dioxo-1,2-benzisothiazol-3(2H)-one (8j). This compound was synthesized from **7j** (0.92 g, 2.88 mmol) using the general procedure. The crude product was purified by silica gel column chromatography (dichloromethane/diethyl ether, 2:1) to give 0.66 g (60%) of **8j** as a colorless oil: IR (neat) 1720 (ν C=O), 1300 and 1170 cm⁻¹ (ν SO₂); ¹H NMR (CDCl₃) δ 1.27 (b, 1H, NH), 1.46–1.57 (m, 2H, CH₂CH₂NH), 2.79 (t, 2H, $J = 7.1$ Hz, CH₂NH), 2.93 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.7$ Hz, CHAr), 3.06–3.15 (m, 1H, CHN), 3.79–3.87 (m, 6H, CH₃O, CH₂NCO, CHO), 4.10–4.19 (m, 1H, CHO), 6.42 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.06 (t, 1H, $J = 8.2$ Hz, arom), 7.78–8.06 (m, 4H, arom). Anal. (C₂₁H₂₄N₂O₅S) C, H, N, S.

3-[4-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane (8k). Via the general procedure, **7k** (2.02 g, 7.36 mmol) was converted to **8k**. The crude mixture was chromatographed on silica gel using dichloromethane/methanol (99.5:0.5) as the eluent to give 1.65 g (66%) of **8k** as an oil: IR (neat) 1760 and 1680 cm⁻¹ (ν C=O); ¹H NMR (CDCl₃) δ 1.18–2.19 (m, 11H, CH₂, NH), 2.54 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 7$ Hz, CHAr), 2.72–2.82 (m, 2H, CH₂N), 2.88 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 6$ Hz, CHAr), 3.24–3.34 (m, 3H, CHCO, CHN), 3.50 (t, 2H, $J = 7.1$ Hz, CH₂NCO), 3.81 (s, 3H, CH₃O), 3.87 (t, 1H, $J = 10.3$ Hz, CHO), 4.31–4.41 (m, 1H, CHO), 6.43 and 6.50 (2 d, 2H, $J = 8.3$ Hz, arom), 7.06 (t, 1H, $J = 8.3$ Hz, arom). Anal. (C₂₁H₂₈N₂O₄) C, H, N.

(+)-**8k**: [α]_D²⁰ = +12° (c = 0.75, CHCl₃).

(-)-**8k**: [α]_D²⁰ = -12° (c = 0.75, CHCl₃).

3-[4-[*N*-(5-Methoxy-3,4-dihydroxy-2*H*-1-benzopyran-3-yl)amino]butyl]-2-oxo-3-azabicyclo[3.3.0]octane (81). This compound was obtained from 71 (1.92 g, 7.37 mmol) using the general procedure. The crude material was purified by silica gel column chromatography (dichloromethane/methanol, 99.5:0.5) to give 1.4 g (58%) of 81 as a pale yellow oil: IR (neat) 3400–3200 (ν NH), 1655 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 1.40–2.05 (m, 11H, CH_2 , NH), 2.55 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 7.1$ Hz, CHAr), 2.62–3.00 (m, 6H, CH_2 N, CHCHCO, CHAr), 3.16–3.26 (m, 3H, CHN, CH_2NCO), 3.56 (t, 1H, $J = 9.3$ Hz, CHCO), 3.82 (s, 3H, CH_3O), 3.91 (t, 1H, $J = 10.6$ Hz, CHO), 4.12–4.22 (m, 1H, CHO), 6.42 and 6.48 (2 d, 2H, $J = 8.3$ Hz, arom), 7.06 (t, 1H, $J = 8.3$ Hz, arom). Anal. ($\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_5$) C, H, N.

8-[3-[*N*-(5-Methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]propyl]oxy]-8-azaspiro[4.5]decane-7,9-dione (8m). This compound was synthesized from 7m (2.8 g, 9.21 mmol) using the general procedure. The crude mixture was purified by silica gel column chromatography (dichloromethane/diethyl ether, 1:1) to give 1.9 g (56%) of pure 8m as an oil: IR (neat) 1745 and 1700 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 1.49–1.76 (m, 9H, CH_2 , NH), 1.87–1.97 (m, 2H, $\text{CH}_2\text{CH}_2\text{O}$), 2.46 (dd, 1H, $J^1 = 16.6$ Hz, $J^2 = 7.9$ Hz, CHAr), 2.67 (s, 4H, CH_2CO), 2.91–3.01 (m, 3H, CH_2N , CHAr), 3.08–3.18 (m, 1H, CHN), 3.80 (s, 3H, CH_3O), 3.83 (t, 1H, $J = 10.3$ Hz, CHO), 4.08 (t, 2H, $J = 6.3$ Hz, CH_2O), 4.18–4.28 (m, 1H, CHO), 6.41 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.04 (t, 1H, $J = 8.3$ Hz, arom). Anal. ($\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_5$) C, H, N.

8-[4-[*N*-(3,4-Dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (8n). This compound was prepared from 7g (2.67 g, 8.85 mmol) using the general procedure. The crude mixture was chromatographed on a silica gel column using dichloromethane/diethyl ether (1:1) as the eluent to give 1.7 g (57%) of 8n as an oil: IR (neat) 3300 (ν NH), 1710 and 1650 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 1.35–1.75 (m, 13H, NH, CH_2), 2.58 (s, 4H, CH_2CO), 2.65 (dd, 1H, $J^1 = 16$ Hz, $J^2 = 7.4$ Hz, CHAr), 2.75 (t, 2H, $J = 7.1$ Hz, CH_2N), 3 (dd, 1H, $J^1 = 16$ Hz, $J^2 = 5.3$ Hz, CHAr), 3.08–3.18 (m, 1H, CHN), 3.78 (t, 2H, $J = 7.1$ Hz, CH_2NCO), 3.88 (dd, 1H, $J^1 = 10.7$ Hz, $J^2 = 6.4$ Hz, CHO), 4.20 (d, 1H, $J = 10.7$ Hz, CHO), 6.77–7.12 (m, 4H, arom). Anal. ($\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_5$) C, H, N.

General Procedure for the Preparation of Bisubstituted Amines 9a–d,f–n. A mixture of 5-methoxy-3,4-dihydro-3-[*N*-(*p*-phthalimidodethyl)amino]-2*H*-1-benzopyran 8 (1.5 mmol), 1-iodopropane (0.765 g, 4.5 mmol), and potassium carbonate (0.620 g, 4.5 mmol) was heated with stirring at 60 °C in DMF (10 mL) for 24 h. 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 (10 mL), and the product was extracted with CH_2Cl_2 (4 \times 15 mL). The combined organic fractions were dried (MgSO_4) and evaporated to dryness under reduced pressure. The resulting oil was chromatographed on a silica gel column to give the pure expected products. The oxalate salt was prepared by addition of an ethereal solution of amine 9 to a solution of oxalic acid in diethyl ether.

5-Methoxy-3,4-dihydro-3-[*N*-propyl-*N*-(2-phthalimidodethyl)amino]-2*H*-1-benzopyran (9a). Using the general procedure described above, 8a (0.06 g, 0.17 mmol) was converted into 9a. The crude product was purified by silica gel column chromatography using methanol/dichloromethane (0.5:99.5) as the eluent to give 0.048 g (70%) as a white solid: mp 114–115 °C; IR (KBr) 1760 and 1700 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.79 (t, 3H, $J = 7.2$ Hz, CH_3CH_2), 1.35–1.45 (m, 2H, CH_2CH_3), 2.45–2.55 (m, 3H, CH_2N , CHAr), 2.79–2.89 (m, 3H, CH_2N , CHAr), 3.14–3.24 (m, 1H, CHN), 3.66–3.76 (m, 3H, CH_2NCO , CHO), 4.11–4.19 (m, 1H, CHO), 6.40 and 6.44 (2 d, 2H, $J = 8.2$ Hz, arom), 7.02 (t, 1H, $J = 8.2$ Hz, arom), 7.69–7.83 (m, 4H, arom); MS m/e 394 (M^+), 351, 310, 234, 163. Anal. ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4\cdot\text{HCl}$) C, H, N, Cl.

5-Methoxy-3,4-dihydro-3-[*N*-propyl-*N*-(3-phthalimidopropyl)amino]-2*H*-1-benzopyran (9b). This compound was obtained from 8b (0.61 g, 1.67 mmol) using the general procedure. The crude material was purified by silica gel column chromatography (methanol/dichloromethane, 0.5:99.5) to give 0.45 g (76%) of 9b as a colorless oil: IR (neat) 1765 and 1700 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.90 (t, 3H, $J = 7.1$ Hz, CH_3), 1.41–1.51 (m, 2H, CH_2CH_3), 1.76–1.86 (m, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 2.45–2.55

(m, 3H, CH_2N , CHAr), 2.59–2.69 (m, 2H, CH_2N), 2.82 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.05–3.15 (m, 1H, CHN), 3.67–3.75 (m, 3H, CH_2NCO , CHO), 3.79 (s, 3H, CH_3O), 4.18–4.28 (m, 1H, CHO), 6.40 and 6.46 (2 d, 2H, $J = 8.2$ Hz, arom), 7.02 (t, 1H, $J = 8.2$ Hz, arom), 7.69–7.83 (m, 4H, arom); MS m/e 408 (M^+), 379, 234, 163. Anal. ($\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_4\cdot\text{C}_2\text{H}_2\text{O}_4$) C, H, N.

5-Methoxy-3,4-dihydro-3-[*N*-propyl-*N*-(4-phthalimidobutyl)amino]-2*H*-1-benzopyran (9c). This compound was synthesized from 8c (0.55 g, 1.46 mmol) using the general procedure. The crude mixture was chromatographed on a silica gel column using methanol/dichloromethane (0.5:99.5) as the eluent to give 0.50 g (81%) of 9c as an oil: IR (neat) 1760 and 1700 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.88 (t, 3H, $J = 7.2$ Hz, CH_3CH_2), 1.43–1.53 (m, 4H, $\text{CH}_2\text{CH}_2\text{N}$), 1.67–1.77 (m, 2H, $\text{CH}_2\text{CH}_2\text{NCO}$), 2.45–2.55 (m, 5H, CH_2N , CHAr), 2.88 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.07–3.17 (m, 1H, CHN), 3.65–3.75 (m, 3H, CH_2NCO , CHO), 3.80 (s, 3H, CH_3O), 4.19–4.29 (m, 1H, CHO), 6.42 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.05 (t, 1H, $J = 8.2$ Hz, arom), 7.64–7.84 (m, 4H, arom); MS m/e 422 (M^+), 261, 234, 163. Anal. ($\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4\cdot\text{C}_2\text{H}_2\text{O}_4$) C, H, N.

3-[4-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-one (9d). This compound was obtained from 8d (1.28 g, 3.45 mmol) using the general procedure. The crude material was purified by silica gel column chromatography (dichloromethane/methanol, 99:1) to give 0.93 g (65%) of 9d as a colorless oil: IR (neat) 1830 (ν C=O), 1260 cm^{-1} (ν C–O); ^1H NMR (CDCl_3) δ 0.84 (t, 3H, $J = 7.2$ Hz, CH_3), 1.38–1.42 (m, 2H, CH_2), 1.45–1.53 (m, 2H, CH_2), 1.80–1.89 (m, 2H, CH_2), 2.45–2.65 (m, 5H, CH_2N , CHAr), 2.83 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.03–3.13 (m, 1H, CHN), 3.66 (t, 1H, $J = 10.4$ Hz, CHO), 3.81 (s, 3H, CH_3O), 3.94 (t, 2H, $J = 7.2$ Hz, CH_2NCO), 4.18–4.28 (m, 1H, CHO), 6.48 and 6.53 (2 d, 2H, $J = 8.3$ Hz, arom), 7.40–8.10 (m, 4H, arom); MS m/e 411 (M^+), 370, 260, 222, 163. Anal. ($\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_4\cdot 2\text{HCl}$) C, H, N, Cl.

8-[2-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]ethyl]-8-azaspiro[4.5]decane-7,9-dione (9e). A mixture of 3,3-tetramethylene glutaric anhydride (3.43 g, 20.43 mmol), 5-methoxy-3,4-dihydro-3-[*N*-propyl-*N*-(2-aminoethyl)amino]-2*H*-1-benzopyran (15) (1.80 g, 6.8 mmol) in 55 mL of toluene was refluxed and stirred for a 1-h period. The reaction mixture was then cooled to room temperature, and the solvent was evaporated to dryness. The residual crude was basified (NaHCO_3 solution) and the product was extracted with dichloromethane. The organic solvent was dried (MgSO_4) and removed *in vacuo*. Flash chromatography of the resultant oil in 50% diethyl ether/petroleum ether gave 2.1 g of 9e as a colorless oil: IR (neat) 1720 and 1660 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.90 (t, 3H, $J = 7.7$ Hz, CH_3CH_2), 1.44–1.76 (m, 10H, CH_2), 2.47–2.72 (m, 9H, CH_2N , CH_2CO , CHAr), 2.86 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.13–3.23 (m, 1H, CHN), 3.76 (t, 1H, $J = 9.8$ Hz, CHO), 3.84 (s, 3H, CH_3O), 3.86 (t, 2H, $J = 6.8$ Hz, CH_2NCO), 4.20–4.30 (m, 1H, CHO), 6.43 and 6.48 (2 d, 2H, $J = 8.3$ Hz, arom), 7.05 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 414 (M^+), 234, 163. Anal. ($\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\cdot\text{C}_2\text{H}_2\text{O}_4$) C, H, N.

8-[3-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]propyl]-8-azaspiro[4.5]decane-7,9-dione (9f). This compound was synthesized from 8f (1.14 g, 2.95 mmol) using the general procedure. The residue was chromatographed on a silica gel column using petroleum ether/diethyl ether (1:2) as the eluent to give 0.66 g (52%) of 9f as an oil: IR (neat) 1720 and 1660 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.88 (t, 3H, $J = 7.3$ Hz, CH_3CH_2), 1.40–1.75 (m, 12H, CH_2), 2.45–2.60 (m, 9H, CH_2N , CH_2CO , CHAr), 2.86 (dd, 1H, $J^1 = 17.4$ Hz, $J^2 = 5.8$ Hz, CHAr), 3.07–3.17 (m, 1H, CHN), 3.71–3.83 (m, 6H, CH_3O , CH_2NCO , CHO), 4.20–4.30 (m, 1H, CHO), 6.41 and 6.46 (2 d, 2H, $J = 8.2$ Hz, arom), 7.05 (t, 1H, $J = 8.2$ Hz, arom); MS m/e 428 (M^+), 234, 163. Anal. ($\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_4\cdot\text{C}_2\text{H}_2\text{O}_4$) C, H, N.

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 (9g). This compound was obtained from 8g (1.5 g, 3.75 mmol) using the general procedure. The crude mixture was chromatographed on a silica gel column using petroleum ether/diethyl ether (1:2) as the eluent to give 1.26 g (72%) of 9g as a clear oil: IR (neat) 1715 and 1660 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.87 (t, 3H, $J = 7$ Hz, CH_3CH_2), 1.45–1.75 (m, 14H, CH_2), 2.50–2.70 (m, 9H,

CH₂CO, CH₂N, CHAr, 2.84 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.06–3.16 (m, 1H, CHN), 3.68–3.78 (m, 3H, CH₂NCO, CHO), 3.81 (s, 3H, CH₃O), 4.17–4.27 (m, 1H, CHO), 6.39 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.02 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 442 (M^+) 413, 234, 163. Anal. (C₂₆H₃₈N₂O₄·C₂H₂O₄) C, H, N.

(+)-**9g**: $[\alpha]^{20}_D = +45^\circ$ ($c = 0.65$, CHCl₃).

(-)-**9g**: $[\alpha]^{20}_D = -44.7^\circ$ ($c = 0.65$, CHCl₃).

8-[5-[N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]pentyl]-8-azaspiro[4.5]decane-7,9-dione (9h). This compound was synthesized from **8h** (0.2 g, 0.48 mmol) using the general procedure. The crude oil was purified by silica gel column chromatography (diethyl ether) to give 0.135 g (61%) of **9h** as a light yellow oil: IR (neat) 1715 and 1650 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, $J = 7.1$ Hz, CH₃), 1.25–1.35 (m, 2H, CH₂), 1.45–1.55 (m, 10H, CH₂), 1.67–1.77 (m, 4H, CH₂), 2.45–2.55 (m, 5H, CH₂N, CHAr), 2.59 (s, 4H, CH₂CO), 2.85 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.5$ Hz, CHAr), 3.11 (m, 1H, CHN), 3.72–3.82 (m, 3H, CH₂NCO, CHO), 3.83 (s, 3H, CH₃O), 4.19–4.29 (m, 1H, CHO), 6.41 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.04 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 456 (M^+), 427, 233, 163. Anal. (C₂₇H₄₀N₂O₄·C₂H₂O₄) C, H, N.

5-Methoxy-3-[N-propyl-N-[4-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)butyl]amino]-3,4-dihydro-2H-1-benzopyran (9i). This compound was prepared from **8i** (1.28 g, 3.42 mmol) using the general procedure. The residue was chromatographed on a silica gel column (ethyl acetate/petroleum ether, 1:1) to give 1.1 g (77%) of **9i** as a clear oil: IR (neat) 1715 and 1660 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, $J = 7$ Hz, CH₃), 1.06 (s, 6H, CH₃), 1.43–1.53 (m, 6H, CH₂), 2.47–2.57 (m, 9H, CH₂N, CH₂CO, CHAr), 2.84 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.08–3.16 (m, 1H, CHN), 3.70–3.80 (m, 3H, CH₂NCO, CHO), 3.83 (s, 3H, CH₃O), 4.21–4.31 (m, 1H, CHO), 6.42 and 6.47 (2 d, 2H, $J = 8.3$ Hz, arom), 7.05 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 416 (M^+), 387, 234. Anal. (C₂₄H₃₆N₂O₄·C₂H₂O₄) C, H, N.

2-[4-[N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-1,1-dioxo-1,2-benzisothiazol-3(2H)-one (9j). This compound was obtained from **8j** (2 g, 4.8 mmol) using the general procedure. The crude oil was purified by silica gel column chromatography (dichloromethane/methanol, 98:2) to give 1.25 g (57%) of **9j** as a colorless oil: IR (neat) 1720 (ν C=O), 1300 and 1170 cm^{-1} (ν SO₂); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, $J = 7.2$ Hz, CH₃), 1.40–1.64 (m, 4H, CH₂CH₃, CH₂CH₂N), 1.85–1.95 (m, 2H, CH₂CH₂NCO), 2.43–2.72 (m, 5H, CH₂N, CHAr), 2.88 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.09–3.19 (m, 1H, CHN), 3.71–3.81 (m, 6H, CH₃O, CH₂NCO, CHO), 4.20–4.30 (m, 1H, CHO), 6.42 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.04 (t, 1H, $J = 8.2$ Hz, arom), 7.76–8.06 (m, 4H, arom); MS m/e 458 (M^+), 163. Anal. (C₂₄H₃₀N₂O₅·C₂H₂O₄) C, H, N, S.

3-[4-[N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane (9k). This compound was synthesized from **8k** (1.65 g, 4.43 mmol) using the general procedure. The residue was chromatographed on a silica gel column (ethyl acetate/petroleum ether, 1:1) to give 1.43 g (78%) of **9k** as a colorless oil: IR (neat) 1760 and 1690 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.88 (t, 3H, $J = 7.1$ Hz, CH₃), 1.18–2.18 (m, 12H, CH₂), 2.47–2.57 (m, 5H, CH₂N, CHAr), 2.84 (dd, 1H, $J^1 = 17.2$ Hz, $J^2 = 6$ Hz, CHAr), 3.07–3.17 (m, 3H, CHCO, CHN), 3.48 (t, 2H, $J = 7.1$ Hz, CH₂NCO), 3.74 (t, 1H, $J = 10.3$ Hz, CHO), 3.82 (s, 3H, CH₃O), 4.16–4.26 (m, 1H, CHO), 6.41 and 6.47 (2 d, 2H, $J = 8.2$ Hz, arom), 7.06 (t, 1H, $J = 8.2$ Hz, arom); MS m/e 414 (M^+) 385, 251, 234, 222, 163. Anal. (C₂₄H₃₄N₂O₄·C₂H₂O₄) C, H, N.

(+)-**9k**: $[\alpha]^{20}_D = +57.4^\circ$ ($c = 0.60$, CHCl₃).

(-)-**9k**: $[\alpha]^{20}_D = -57.7^\circ$ ($c = 0.60$, CHCl₃).

3-[4-[N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-2-oxo-3-azabicyclo[3.3.0]octane (9l). This compound was obtained from **8l** (1.4 g, 3.9 mmol) using the general procedure. The crude product was chromatographed on a silica gel column (dichloromethane/diethyl ether, 1:1) to give 1.1 g (70%) of **9l** as a clear oil: IR (neat) 1665 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.86 (t, 3H, $J = 7.4$ Hz, CH₃), 1.35–2.05 (m, 12H, CH₂), 2.44–2.90 (m, 8H, CH₂NCO, CH₂Ar, CH₂NCH), 2.97 (dd, 1H, $J^1 = 9.4$ Hz, $J^2 = 2.6$ Hz, CHCHCO), 3.04–3.38 (m, 3H, CH₂NCO, CHN), 3.56 (t, 1H, $J = 9.4$ Hz, CHCO), 3.76 (t, 1H, $J = 10.3$ Hz, CHO), 3.82 (s, 3H, CH₃O), 4.17–4.27 (m, 1H, $J =$

10.3 Hz, CHO), 6.40 and 6.45 (2 d, 2H, $J = 8.3$ Hz, arom), 7.02 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 400 (M^+), 371, 234, 163. Anal. (C₂₄H₃₆N₂O₃·C₂H₂O₄) C, H, N.

8-[3-[N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-5-yl)amino]propyl]oxy]-8-azaspiro[4.5]decane-7,9-dione (9m). This compound was synthesized from **8m** (1.5 g, 3.7 mmol) using the general procedure. The residue was chromatographed on a silica gel column using diethyl ether as the eluent to give 1.12 g (68%) of **9m** as a colorless oil: IR (neat) 1740 and 1700 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.87 (t, 3H, $J = 7.1$ Hz, CH₃), 1.39–1.76 (m, 6H, CH₂), 1.85–1.95 (m, 2H, CH₂CH₂O), 2.41–2.51 (m, 3H, CH₂N, CHAr), 2.66 (s, 4H, CH₂CO), 2.76 (t, 2H, $J = 6.9$ Hz, CH₂N), 2.92 (dd, 1H, $J^1 = 16.3$ Hz, $J^2 = 4$ Hz, CHAr), 3.07–3.17 (m, 1H, CHN), 3.77 (t, 1H, $J = 10.4$ Hz, CHO), 3.82 (s, 3H, CH₃O), 4.03 (t, 2H, $J = 6.3$ Hz, CH₂O), 4.19–4.29 (m, 1H, CHO), 6.40 and 6.44 (2 d, 2H, $J = 8.3$ Hz, arom), 7.04 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 444 (M^+), 280, 234, 222, 163. Anal. (C₂₅H₃₆N₂O₅·C₂H₂O₄) C, H, N.

8-[4-[N-Propyl-N-(3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (9n). This compound was prepared from **8n** (1.64 g, 4.43 mmol) using the general procedure. The crude mixture was chromatographed on a silica gel column (diethyl ether/petroleum ether, 1:1) to give 1.13 g (62%) of **9n** as a yellow pale oil: IR (neat) 1715 and 1650 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.90 (t, 3H, $J = 7.4$ Hz, CH₃CH₂), 1.43–1.78 (m, 14H, CH₂), 2.50–2.63 (m, 8H, CH₂N, CH₂CO), 2.87 (d, 2H, $J = 8.3$ Hz, CH₂Ar), 3.13–3.23 (m, 1H, CHN), 3.78–3.88 (m, 3H, CH₂NCO, CHO), 4.32 (dd, 1H, $J^1 = 10.4$ Hz, $J^2 = 3.8$ Hz, CHO), 6.81–7.15 (m, 4H, arom); MS m/e 412 (M^+), 383, 204, 131. Anal. (C₂₅H₃₆N₂O₃·C₂H₂O₄) C, H, N.

8-[4-[N-Propyl-N-(5-hydroxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-8-azaspirodecane-7,9-dione (10). Boron tribromide (0.35 mL) was added to a stirred solution of **9g** (1.4 g, 3.16 mmol) in 100 mL of dry dichloromethane at -10°C . The reaction mixture was stirred for 15 min, and 10 mL of water was added. The solution was basified, and the product was extracted with dichloromethane (4 × 15 mL). The solvent was dried (MgSO₄) and removed in vacuo, and the resulting crude was chromatographed on a silica gel column and eluted with diethyl ether/dichloromethane (1:2) to give (0.78 g, 58%) as a clear oil: IR (neat) 3500–3200 (ν OH), 1720 and 1665 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 0.87 (t, 3H, $J = 7.4$ Hz, CH₃), 1.39–1.74 (m, 14H, CH₂), 2.50–2.70 (m, 9H, CH₂N, CH₂CO, CHAr), 2.85 (dd, 1H, $J^1 = 16.3$ Hz, $J^2 = 5.6$ Hz, CHAr), 3.09–3.19 (m, 1H, CHN), 3.71–3.81 (m, 3H, CH₂NCO, CHO), 4.23–4.33 (m, 1H, CHO), 6.39 and 6.42 (2 d, 2H, $J = 8.3$ Hz, arom), 6.94 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 428 (M^+), 220, 149, 139. Anal. (C₂₅H₃₆N₂O₄·C₂H₂O₄) C, H, N.

8-[4-[N-Methyl-N-propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Iodide (11). Methyl iodide (4 g, 29 mmol) was added to a stirred solution of **9g** (1.3 g, 2.9 mmol) in 25 mL of dichloromethane. The reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under reduced pressure, and the resulting crude was purified by flash chromatography using dichloromethane/methanol (95:5) as the eluent to give 1.2 g (70%) of **11** as a white solid: mp 100–101 $^\circ\text{C}$; IR (KBr) 1720 and 1665 cm^{-1} (ν C=O); ¹H NMR (CDCl₃) δ 1.02 and 1.06 (2 t, 3H, $J = 7.1$ Hz, CH₃CH₂), 1.45–1.55 (m, 4H, CH₂), 1.65–1.75 (m, 6H, CH₂), 1.84–1.94 (m, 4H, CH₂), 2.71 and 2.73 (2 s, 4H, CH₂CO), 3.08 (d, 1H, $J = 18$ Hz, CHAr), 3.24 (dd, 1H, $J^1 = 18$ Hz, $J^2 = 6$ Hz, CHAr), 3.26 and 3.28 (2 s, 3H, CH₃N), 3.38–3.48 (m, 2H, CH₂N), 3.51–3.61 (m, 2H, CH₂N), 3.78–3.81 (m, 2H, CH₂NCO), 3.84 (s, 3H, CH₃O), 4.45–4.58 (m, 3H, CH₂O, CHN), 6.50 (d, 2H, $J = 8.3$ Hz, arom), 7.10 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 442, 415, 236, 163. Anal. (C₂₇H₄₁N₂O₄·I) C, H, N.

5-Methoxy-3-[N-propyl-N-(cyanomethyl)amino]-3,4-dihydro-2H-1-benzopyran (13a). A mixture of the secondary amine **3** (1.5 g, 6.78 mmol), 2-chloroacetonitrile (1.5 g, 20.3 mmol), potassium carbonate (2.8 g, 20.3 mmol), and a catalytic amount of potassium iodide was heated while being stirred at 60 $^\circ\text{C}$ in DMF (10 mL) for 24 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The product was extracted from the resulting crude after aqueous hydrolysis with dichloromethane (3 × 20 mL). The organic combined solvent was dried (MgSO₄) and evaporated to

dryness. The residue was chromatographed on a silica gel column (dichloromethane/methanol, 99.5:0.5) to give 1.4 g (79%) of **13a** as a light yellow oil: IR (neat) 1235 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.92 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 1.47–1.57 (m, 2H, CH_2CH_3), 2.63–2.73 (m, 3H, CH_2N , CHAr), 2.98 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.05–3.15 (m, 1H, CHN), 3.70 (s, 2H, CH_2CN), 3.84 (s, 3H, CH_3O), 3.91 (t, 1H, $J = 10.3$ Hz, CHO), 4.24–4.34 (m, 1H, CHO), 6.45 and 6.49 (2 d, 2H, $J = 8.2$ Hz, arom), 7.08 (t, 1H, $J = 8.2$ Hz, arom). Anal. ($\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$) C, H, N.

(+)-**13a**: $[\alpha]_D^{20} = +72^\circ$ ($c = 0.65$, CHCl_3).

(-)-**13a**: $[\alpha]_D^{20} = -72^\circ$ ($c = 0.65$, CHCl_3).

5-Methoxy-3-[N-propyl-N-(cyanopropyl)amino]-3,4-dihydro-2H-1-benzopyran (13b). This compound was obtained from **3** (0.1 g, 0.45 mmol) as described for **13a**. The optimal reaction time was 24 h at 60 °C when 0.27 g (1.8 mmol) of 4-bromobutyronitrile was used: yield 0.95 g (73%) as a clear oil; IR (neat) 2220 cm^{-1} (ν CN); ^1H NMR (CDCl_3) δ 0.91 (t, 3H, $J = 7.1$ Hz, CH_3), 1.43–1.53 (m, 2H, CH_2CH_3), 1.75–1.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CN}$), 2.42–2.78 (m, 7H, CH_2N , CH_2CN , CHAr), 2.89 (dd, 1H, $J^1 = 17.2$ Hz, $J^2 = 6$ Hz, CHAr), 3.11–3.21 (m, 1H, CHN), 3.80 (t, 1H, $J = 10.3$ Hz, CHO), 3.82 (s, 3H, CH_3O), 4.19–4.29 (m, 1H, CHO), 6.44 and 6.49 (2 d, 2H, $J = 8.2$ Hz, arom), 7.07 (t, 1H, $J = 8.2$ Hz, arom). Anal. ($\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$) C, H, N.

(+)-**13b**: $[\alpha]_D^{20} = +77^\circ$ ($c = 0.70$, CHCl_3).

(-)-**13b**: $[\alpha]_D^{20} = -77^\circ$ ($c = 0.70$, CHCl_3).

5-Methoxy-3-[N-propyl-N-(2-aminoethyl)amino]-3,4-dihydro-2H-1-benzopyran (14a). **13a** (1.4 g, 5.38 mmol) was dissolved in 30 mL of tetrahydrofuran. LiAlH_4 (0.408 g, 10.75 mmol) was added portionwise over a period of 5 min with stirring and under an inert atmosphere. The mixture was stirred at room temperature for 30 min, and then the reaction was stopped by dropwise addition of cold water (15 mL). The solid was filtered off, and the product was extracted with diethyl ether. The organic solution was dried (MgSO_4) and removed under reduced pressure. The crude product was purified by column chromatography (dichloromethane/methanol, 95:5) to yield 1.035 g (72%) of **14a** as a colorless oil: IR (neat) 3400–3200 cm^{-1} (ν NH_2); ^1H NMR (CDCl_3) δ 0.89 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.41–1.51 (m, 2H, CH_2CH_3), 2.44–2.71 (m, 8H, CH_2Ar , CH_2N), 3.09–3.19 (m, 1H, CHN), 3.43 (b, 2H, NH_2), 3.75–3.85 (m, 1H, CHO), 3.80 (s, 3H, CH_3O), 4.20–4.30 (m, 1H, CHO), 6.40 and 6.45 (2 d, 2H, $J = 8.3$ Hz, arom), 7.04 (t, 1H, $J = 8.3$ Hz, arom). Anal. ($\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$) C, H, N.

(+)-**14a**: $[\alpha]_D^{20} = +76.5^\circ$ ($c = 0.65$, CHCl_3).

(-)-**14a**: $[\alpha]_D^{20} = -76.5^\circ$ ($c = 0.65$, CHCl_3).

5-Methoxy-3-[N-propyl-N-(4-aminobutyl)amino]-3,4-dihydro-2H-1-benzopyran (14b). Using the same method as described for the preparation of **14a**, 0.95 g (3.3 mmol) of **13b** was converted into 0.67 g (69%) of **14b** as a colorless oil: IR (neat) 3500–3250 cm^{-1} (ν NH_2); ^1H NMR (CDCl_3) δ 0.81 (t, 3H, $J = 7.1$ Hz, CH_3CH_2), 1.36–1.46 (m, 6H, $\text{CH}_2\text{CH}_2\text{N}$), 2.34–2.68 (m, 9H, CH_2N , NH_2 , CHAr), 2.80 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.02–3.12 (m, 1H, CHN), 3.68 (t, 1H, $J = 10.3$ Hz, CHO), 3.76 (s, 3H, CH_3O), 4.13–4.23 (m, 1H, CHO), 6.33 and 6.40 (2 d, 2H, $J = 8.2$ Hz, arom), 6.98 (t, 1H, $J = 8.2$ Hz, arom). Anal. ($\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_2$) C, H, N.

(+)-**14b**: $[\alpha]_D^{20} = +85^\circ$ ($c = 0.60$, CHCl_3).

(-)-**14b**: $[\alpha]_D^{20} = -80^\circ$ ($c = 0.60$, CHCl_3).

5-Methoxy-3-[N-propyl-N-(2-acetamidoethyl)amino]-3,4-dihydro-2H-1-benzopyran (15a). Acetylchloride (0.065 g, 0.832 mmol) was added to benzopyran **14a** (0.2 g, 0.757 mmol) dissolved in dichloromethane (5 mL) containing triethylamine (0.23 g, 2.27 mmol). The mixture was stirred at room temperature for 30 min, and then the solvent was removed under reduced pressure. The resulting crude was chromatographed on a silica gel (dichloromethane as the eluent) to give 0.9 g (89%) of **15a** as a colorless oil: IR (neat) 3280 (ν NH), 1640 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.89 (t, 3H, $J = 7.5$ Hz, CH_3CH_2), 1.41–1.51 (m, 2H, CH_2CH_3), 1.96 (s, 3H, CH_3CO), 2.50–2.73 (m, 5H, CH_2N , CHAr), 2.83 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 6$ Hz, CHAr), 3.12–3.22 (m, 1H, CHN), 3.29 (q, 2H, $J = 7.2$ Hz, CH_2NH), 3.82 (s, 3H, CH_3O), 3.85 (t, 1H, $J = 10.2$ Hz, CHO), 4.15–4.25 (m, 1H, CHO), 6.00 (b, 1H, NH), 6.44 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.06 (t, 1H, $J = 8.2$ Hz, arom); MS m/e 306 (M^+), 234, 163. Anal. ($\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_5$) C, H, N.

5-Methoxy-3-[N-propyl-N-[2-(4-tolylsulfonamido)ethyl]amino]-3,4-dihydro-2H-1-benzopyran (15b). Tosyl chloride (0.8 g, 3.8 mmol) dissolved in dichloromethane (30 mL) was added to benzopyran **14a** (1 g, 38 mmol) dissolved in dichloromethane (10 mL) and triethylamine (12 g, 11.4 mmol). The mixture was stirred at room temperature for 30 min, and then the solvent was removed under reduced pressure. The resulting crude was chromatographed on a silica gel column by elution with dichloromethane to give 1.4 g (88%) of **15b** as a white solid: mp 123 °C; IR (KBr) 3250 (ν NH), 1320 and 1150 cm^{-1} (ν SO_2); ^1H NMR (CDCl_3) δ 0.76 (t, 3H, $J = 7.1$ Hz, CH_3CH_2), 1.27–1.37 (m, 2H, CH_2CH_3), 2.36–2.48 (m, 8H, CH_3Ar , CH_2N , CHAr), 2.74 (dd, 1H, $J^1 = 17.1$ Hz, $J^2 = 6.2$ Hz, CHAr), 2.87–2.97 (m, 3H, CHN , CH_2NH), 3.69 (t, 1H, $J = 10.2$ Hz, CHO), 3.82 (s, 3H, CH_3O), 4.05–4.15 (m, 1H, CHO), 5.11 (b, 1H, NHSO_2), 6.43 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.05 (t, 1H, $J = 8.2$ Hz, arom), 7.26 and 7.73 (2 d, 4H, $J = 8.2$ Hz, arom); MS m/e 418 (M^+), 265, 234, 222, 163. Anal. ($\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$) C, H, N, S.

(+)-**15b**: $[\alpha]_D^{20} = +48^\circ$ ($c = 0.75$, CHCl_3).

(-)-**15b**: $[\alpha]_D^{20} = -48^\circ$ ($c = 0.75$, CHCl_3).

5-Methoxy-3-[N-propyl-N-[3-(4-tolylsulfonamido)propyl]amino]-3,4-dihydro-2H-1-benzopyran (15c). A mixture of **3** (0.1 g, 0.54 mmol), **12²⁶** (0.1 g, 0.59 mmol), triethylamine (0.16 g, 1.6 mmol), and a catalytic amount of potassium iodide was heated with stirring at 60 °C in dimethylformamide (3 mL) for 72 h. The reaction mixture was then cooled to room temperature, the solvent was removed under reduced pressure, and the product was extracted from the resulting crude after aqueous hydrolysis with dichloromethane (3 \times 4 mL). The organic solvent was dried (MgSO_4) and evaporated to dryness under reduced pressure. The resulting oil was chromatographed on a silica gel column (dichloromethane/methanol, 99.5:0.5) to give 0.126 g (65%) of **15c** as a white solid: mp 128 °C; IR (KBr) 3280 (ν NH), 1310 and 1150 cm^{-1} (ν SO_2); ^1H NMR (CDCl_3) δ 0.88 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.40–1.50 (m, 2H, CH_2CH_3), 1.58–1.68 (m, 2H, $\text{CH}_2\text{CH}_2\text{NH}$), 2.40–2.70 (m, 8H, CH_2N , CH_3Ar , CHAr), 2.83 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.7$ Hz, CHAr), 3.03–3.13 (m, 3H, CH_2NH , CHN), 3.75 (t, 1H, $J = 10.1$ Hz, CHO), 3.83 (s, 3H, CH_3O), 4.12–4.22 (m, 1H, CHO), 6.25 (b, 1H, NH), 6.44 and 6.50 (2 d, 2H, $J = 8.2$ Hz, arom), 7.06 (t, 1H, $J = 8.2$ Hz, arom), 7.27 and 7.75 (2 d, 4H, $J = 7.9$ Hz, arom); MS m/e 432 (M^+), 403, 234, 163. Anal. ($\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$) C, H, N, S.

5-Methoxy-3-[N-propyl-N-[4-(4-tolylsulfonamido)butyl]amino]-3,4-dihydro-2H-1-benzopyran (15d). The method used was exactly the same as for **15b**: yield 0.90 g (89%) from **14b** (0.66 g, 2.26 mmol); oil; IR (neat) 3230 (ν NH), 1310 and 1150 cm^{-1} (ν SO_2); ^1H NMR (CDCl_3) δ 0.84 (t, 3H, $J = 7.3$ Hz, CH_3CH_2), 1.35–1.57 (m, 6H, $\text{CH}_2\text{CH}_2\text{N}$), 2.39–2.56 (m, 8H, CH_3Ar , CHAr , CH_2N), 2.83 (dd, 1H, $J^1 = 16.7$ Hz, $J^2 = 5.7$ Hz, CHAr), 2.94 (q, 2H, $J = 6.5$ Hz, CH_2NH), 3.01–3.12 (m, 1H, CHN), 3.73 (t, 1H, $J = 10.2$ Hz, CHO), 3.82 (s, 3H, CH_3O), 4.16–4.26 (m, 1H, CHO), 5.51 (b, 1H, NH), 6.41 and 6.46 (2 d, 2H, $J = 8$ Hz, arom), 7.03 (t, 1H, $J = 8$ Hz, arom), 7.27 and 7.75 (2 d, 4H, $J = 8$ Hz, arom); MS m/e 446 (M^+), 417, 291, 234, 163. Anal. ($\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_4\text{S}$) C, H, N, S.

(+)-**15d**: $[\alpha]_D^{20} = +52.5^\circ$ ($c = 0.60$, CHCl_3).

(-)-**15d**: $[\alpha]_D^{20} = -52.5^\circ$ ($c = 0.60$, CHCl_3).

5-Methoxy-3-[N-propyl-N-[4-(4-fluoro-1-benzamido)butyl]amino]-3,4-dihydro-2H-1-benzopyran (15e). 4-Fluorobenzoyl chloride (0.48 g, 3.01 mmol) dissolved in dichloromethane was added to benzopyran **14b** (0.8 g, 2.74 mmol) dissolved in dichloromethane (15 mL) and triethylamine (0.83 g, 8.22 mmol). The solution was stirred at room temperature for 30 min. The solvent was then removed under reduced pressure, and the residual oil was chromatographed on a silica gel using dichloromethane/methanol (99.5:0.5) as the eluent to give 0.86 g (76%) of **15e** as a light yellow oil: IR (neat) 3500–3140 (ν NH), 1630 cm^{-1} (ν C=O); ^1H NMR (CDCl_3) δ 0.87 (t, 3H, $J = 7.2$ Hz, CH_3CH_2), 1.40–1.70 (m, 6H, $\text{CH}_2\text{CH}_2\text{N}$), 2.46–2.67 (m, 5H, CH_2N , CHAr), 2.84 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.5$ Hz, CHAr), 3.09–3.19 (m, 1H, CHN), 3.45 (q, 2H, $J = 6.5$ Hz, CH_2NH), 3.77 (t, 1H, $J = 10.3$ Hz, CHO), 3.82 (s, 3H, CH_3O), 4.20–4.30 (m, 1H, CHO), 6.18 (b, 1H, NHCO), 6.44 and 6.48 (2 d, 2H, $J = 8.2$ Hz, arom), 7.04 (t, 1H, $J = 8.2$ Hz, arom), 7.10 (t, 2H, $J = 8.7$ Hz, arom), 7.73 and 7.77 (2 d, 2H, $J = 8.7$ Hz, arom); MS m/e 414 (M^+), 385, 233, 234, 163. Anal. ($\text{C}_{24}\text{H}_{31}\text{FN}_2\text{O}_5$) C, H, N, F.

5-Methoxy-3-[N-propyl-N-[4-(2-methoxy-1-benzamido)butyl]amino]-3,4-dihydro-2H-1-benzopyran (15f). This compound was obtained from 14b (0.8 g, 2.74 mmol) as described for 15e: yield (0.97 g, 83%); oil; IR (neat) 3600–3200 cm^{-1} (ν NH), 1635 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.98 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 1.39–1.69 (m, 6H, $\text{CH}_2\text{CH}_2\text{N}$), 2.47–2.64 (m, 5H, CH_2N , CHAr), 2.73 (dd, 1H, $J^1 = 17$ Hz, $J^2 = 5.5$ Hz, CHAr), 3.10–3.20 (m, 1H, CHN), 3.48 (q, 2H, $J = 6.7$ Hz, CH_2NH), 3.77 (t, 1H, $J = 10.3$ Hz, CHO), 3.81 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 4.20–4.30 (m, 1H, CHO), 6.41 and 6.45 (2 d, 2H, $J = 8.2$ Hz, arom), 7.05–7.15 (m, 3H, arom), 7.43 (t, 1H, $J = 7.8$ Hz, arom), 7.86 (b, 1H, NHCO), 8.21 (d, 1H, $J = 7.8$ Hz, arom); MS m/e 426 (M^+), 397, 265, 234, 163. Anal. ($\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_4 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

5-Methoxy-3-[N-propyl-N-(4-chlorobutanoyl)amino]-3,4-dihydro-2H-1-benzopyran (16). A solution of the secondary amine 3 (4 g, 18 mmol) in dichloromethane (140 mL) containing triethylamine (5.5 g, 54 mmol) was treated with 4-chlorobutyl chloride (2.8 g, 20 mmol). The mixture was stirred at room temperature for 30 min, and the dichloromethane solution was evaporated to dryness. The resulting crude was chromatographed on a silica gel using dichloromethane/diethyl ether (1:1) as the eluent to give 5.58 g (94%) of 16 as a pale yellow oil: IR (neat) 1670–1635 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.89 (t, 3H, $J = 7.5$ Hz, CH_3), 1.58–1.68 (m, 2H, CH_2CH_3), 2.09–2.19 (m, 2H, $\text{CH}_2\text{CH}_2\text{Cl}$), 2.50–2.60 (m, 2H, CH_2N), 2.85–2.95 (m, 2H, CH_2Ar), 3.13–3.23 (m, 2H, CH_2CO), 3.64 (t, 2H, $J = 6.3$ Hz, CH_2Cl), 3.80 and 3.85 (2 s, 3H, CH_3O), 4.09–4.29 (m, 2H, CH_2O), 4.45–4.55 (m, 1H, CHN), 6.43–6.53 (m, 2H, arom), 7.01–7.11 (m, 1H, arom). Anal. ($\text{C}_{17}\text{H}_{24}\text{ClNO}_3$) C, H, N, Cl.

5-Methoxy-3-[N-propyl-N-(4-(1-piperidinyl)butanoyl)amino]-3,4-dihydro-2H-1-benzopyran (17a). Potassium carbonate (1.3 g, 9.2 mmol), piperidine (0.43 g, 5 mmol), and a catalytic amount of potassium iodide were added to a solution of 16 (1.5 g, 4.6 mmol) in *N,N*-dimethylformamide (10 mL). The mixture was stirred at 60 °C for 24 h and then cooled. The solvent was removed under reduced pressure. After drying (MgSO_4), the residual oil was partitioned between dichloromethane and water, the dichloromethane was evaporated, and the residue was chromatographed on a silica gel using dichloromethane/methanol (9:1) as the eluent to give 1.1 g (64%) of 17a as an oil: IR (neat) 1670–1635 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.88 (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 1.41–1.78 (m, 8H, CH_2), 1.95–2.05 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 2.40–2.70 (m, 8H, CH_2), 2.86–2.96 (m, 2H, CH_2Ar), 3.12–3.22 (m, 2H, CH_2CO), 3.80 and 3.82 (2 s, 3H, CH_3O), 4.11–4.28 (m, 2H, CH_2O), 4.43–4.53 (m, 1H, CHN), 6.42–6.52 (m, 2H, arom), 7.01–7.11 (m, 1H, arom). Anal. ($\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_3$) C, H, N.

5-Methoxy-3-[N-propyl-N-(4-(1-piperidinyl)butyl)amino]-3,4-dihydro-2H-1-benzopyran (18a). This compound was prepared from 17a (1.1 g, 2.94 mmol) as described for 3: yield (0.7 g, 66%); oil; IR (neat) 1590 (ν C=C); $^1\text{H NMR}$ (CDCl_3) δ 0.85 (t, 3H, $J = 7.4$ Hz, CH_3), 1.35–1.61 (m, 12H, CH_2), 2.24–2.59 (m, 11H, CH_2 , CHAr), 2.84 (dd, 1H, $J^1 = 16.6$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.05–3.15 (m, 1H, CHN), 3.73 (t, 1H, $J = 10.1$ Hz, CHO), 3.80 (s, 3H, CH_3O), 4.17–4.27 (m, 1H, CHO), 6.40 and 6.44 (2 d, 2H, $J = 8.3$ Hz, arom), 7.02 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 360 (M^+), 236, 234, 163, 98. Anal. ($\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

5-Methoxy-3-[N-propyl-N-(4-morpholin-4-ylbutanoyl)amino]-3,4-dihydro-2H-1-benzopyran (17b). This compound was prepared from 16 (1.5 g, 4.6 mmol) as described for 17a: yield (1.15 g, 66%); oil; IR (neat) 1670–1635 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.88 (t, 3H, $J = 7.4$ Hz, CH_3), 1.55–1.65 (m, 2H, CH_2CH_3), 1.82–1.92 (m, 2H, $\text{CH}_2\text{CH}_2\text{CO}$), 2.35–2.45 (m, 6H, CH_2), 2.85–2.95 (m, 2H, CH_2Ar), 3.14–3.24 (m, 2H, CH_2CO), 3.63–3.73 (m, 4H, CH_2O), 3.73 and 3.75 (2 s, 3H, CH_3O), 4.10–4.30 (m, 2H, CH_2O), 4.45–4.55 (m, 1H, CHN), 6.43–6.53 (m, 2H, arom), 7.01–7.11 (m, 1H, arom); Anal. ($\text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_4$) C, H, N.

5-Methoxy-3-[N-propyl-N-(4-morpholin-4-ylbutyl)amino]-3,4-dihydro-2H-1-benzopyran (18b). This compound was prepared from 17b (1.1 g, 2.92 mmol) as described for 3: yield (0.7 g, 66%); oil; IR 1580 (ν C=C); $^1\text{H NMR}$ (CDCl_3) δ 0.86 (t, 3H, $J = 7.4$ Hz, CH_3), 1.45–1.55 (m, 6H, $\text{CH}_2\text{CH}_2\text{N}$), 2.28–2.62 (m, 11H, CH_2N , CHAr), 2.86 (dd, 1H, $J^1 = 16.6$ Hz, $J^2 = 5.9$ Hz, CHAr), 3.08–3.18 (m, 1H, CHN), 3.62–3.80 (m, 5H, CH_2O , CHO), 3.81 (s, 3H, CH_3O), 4.19–4.29 (m, 1H, CHO), 6.42 and 6.46 (2 d, 2H, $J = 8.3$ Hz, arom), 7.03 (t, 1H, $J = 8.3$ Hz, arom); MS m/e 362 (M^+), 222, 163. Anal. ($\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_3 \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

3,4-Dihydro-3-nitro-2H-1-benzopyran (20a). 3-Nitro-2H-1-benzopyran (19a) (4 g, 22.58 mmol) was dissolved in a mixture of chloroform (140 mL) and 2-propanol (40 mL). While maintaining vigorous stirring, silica gel (230–400 mesh, ASTM, 11 g) was then poured into the flask and powdered sodium borohydride (2.13 g, 56.45 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 (3.5 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 chromatographed on a silica gel column using dichloromethane as the eluent to give 4 g (99%) of 20a as a pale yellow solid: mp 86 °C; IR (KBr) 1235 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 3.33 (dd, 1H, $J^1 = 16.8$ Hz, $J^2 = 6$ Hz, CHAr), 3.56 (dd, 1H, $J^1 = 16.8$ Hz, $J^2 = 6$ Hz, CHAr), 4.44 (dd, 1H, $J^1 = 11.4$ Hz, $J^2 = 2$ Hz, CHO), 4.61 (dd, 1H, $J^1 = 11.4$ Hz, $J^2 = 6$ Hz, CHO), 4.88–4.98 (m, 1H, CHN), 6.85–7.19 (m, 4H, arom). Anal. ($\text{C}_9\text{H}_9\text{NO}_3$) C, H, N.

3-Amino-3,4-dihydro-2H-1-benzopyran (21a). Benzopyran 20a (3.6 g, 20.11 mmol) was dissolved in ethanol (300 mL) by heating to 80 °C, and then the solution was cooled to 45 °C. Wet Raney nickel (2 g) was introduced, and 11 mL of 40% hydrazine hydrate solution 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, as indicated by TLC (eluent: dichloromethane/methanol, 9:1). 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 column chromatography (dichloromethane/methanol, 9:1) to give 2.8 g (93%) of 21a as an oil: IR (neat) 3420–3120 (ν NH_2); $^1\text{H NMR}$ (CDCl_3) δ 1.33 (b, 2H, NH_2), 2.56 (dd, 1H, $J^1 = 16.3$ Hz, $J^2 = 6.9$ Hz, CHAr), 3.04 (dd, 1H, $J^1 = 16.3$ Hz, $J^2 = 5.4$ Hz, CHAr), 3.28–3.41 (m, 1H, CHN), 3.78 (dd, 1H, $J^1 = 10.9$ Hz, $J^2 = 6.9$ Hz, CHO), 4.13 (d, 1H, $J = 10.9$ Hz, CHO), 6.79–7.14 (m, 4H, arom). Anal. ($\text{C}_9\text{H}_{11}\text{NO}$) C, H, N.

3,4-Dihydro-3-nitro-2H-1-naphtho[1,2-b]pyran (20b). The method was exactly as for 20a: yield 3.8 g (95%) from 3-nitro-2H-1-naphtho[1,2-b]pyran (19b) (4 g, 17.60 mmol) 25c; mp 65 °C; IR (KBr) 1235 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 3.63 (dd, 1H, $J^1 = 17.4$ Hz, $J^2 = 6.5$ Hz, CHAr), 3.83 (dd, 1H, $J^1 = 17.4$ Hz, $J^2 = 5.7$ Hz, CHAr), 4.54 (dd, 1H, $J^1 = 11.4$ Hz, $J^2 = 2.8$ Hz, CHO), 4.70 (dd, 1H, $J^1 = 11.4$ Hz, $J^2 = 5.9$ Hz, CHO), 5.08–5.18 (m, 1H, CHN), 7.06–7.84 (m, 6H, arom). Anal. ($\text{C}_{13}\text{H}_{11}\text{NO}_3$) C, H, N.

3-Amino-3,4-dihydro-2H-1-naphtho[1,2-b]pyran (21b). Using the procedure described for 21a, 20b (3.3 g, 14.39 mmol) was converted into 2.3 g (80%) of 21b as a colorless oil: IR (neat) 3400–3200 cm^{-1} (ν NH_2); $^1\text{H NMR}$ (CDCl_3) δ 1.60 (b, 2H, NH_2), 2.77 (dd, 1H, $J^1 = 16.2$ Hz, $J^2 = 6.7$ Hz, CHAr), 3.32 (dd, 1H, $J^1 = 16.2$ Hz, $J^2 = 5.6$ Hz, CHAr), 3.43–3.53 (m, 1H, CHN), 3.85 (dd, 1H, $J^1 = 10.4$ Hz, $J^2 = 7.1$ Hz, CHO), 4.18 (d, 1H, $J = 10.4$ Hz, CHO), 7.02–7.78 (m, 6H, arom). Anal. ($\text{C}_{13}\text{H}_{13}\text{NO}$) C, H, N.

3,4-Dihydro-3-(di-n-propylamino)-2H-1-benzopyran (22a). This compound was synthesized from benzopyran 21a (0.8 g, 5.36 mmol) by the procedure described for compound 4: yield (0.91 g, 73%); oil; IR (neat) 1225 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.91 (t, 6H, $J = 7.3$ Hz, CH_3), 1.43–1.52 (m, 4H, CH_2CH_3), 2.49–2.59 (m, 4H, CH_2N), 2.86 (d, 2H, $J = 8.3$ Hz, CH_2Ar), 3.14–3.24 (m, 1H, CHN), 3.82 (t, 1H, $J = 10.4$ Hz, CHO), 4.30 (dd, 1H, $J^1 = 10.4$ Hz, $J^2 = 3.8$ Hz, CHO), 6.80–7.14 (m, 4H, arom); MS m/e 233 (M^+), 204, 160. Anal. ($\text{C}_{15}\text{H}_{23}\text{NO} \cdot \text{C}_2\text{H}_2\text{O}_4$) C, H, N.

3,4-Dihydro-3-(di-n-propylamino)-2H-1-naphtho[1,2-b]pyran (22b). This compound was prepared from benzopyran 23b (1.7 g, 8.53 mmol) as described for 4: yield (1.8 g, 74%); oil; IR (neat) 1230 cm^{-1} (ν C=O); $^1\text{H NMR}$ (CDCl_3) δ 0.92 (t, 6H, $J = 7.5$ Hz, CH_3CH_2), 1.45–1.55 (m, 4H, CH_2CH_3), 2.55–2.66 (m, 4H, CH_2N), 3.01 (dd, 1H, $J^1 = 16$ Hz, $J^2 = 10.8$ Hz, CHAr), 3.22 (dd, 1H, $J^1 = 16$ Hz, $J^2 = 5.5$ Hz, CHAr), 3.28–3.38 (m, 1H, CHN), 3.87 (t, 1H, $J = 10.3$ Hz, CHO), 4.34–4.44 (m, 1H, CHO), 7.02–7.86 (m, 6H, arom); MS m/e 283 (M^+), 242, 183. Anal. ($\text{C}_{19}\text{H}_{25}\text{NO} \cdot \text{HCl}$) C, H, N, Cl.

8-[4-(N-Propyl-N-(5-methoxy-3,4-dihydro-2H-1-benzopyran-3-yl)amino)butyl]-8-azaspiro[4.5]decane-7,9-dione (8g). Scheme 6. 8-(4-Aminobutyl)-8-azaspiro[4.5]decane-7,9-dione

hydrochloride (23) (1 g, 3.64 mmol) dissolved in ethanol (10 mL) and NaOH (0.145 g, 3.6 mmol) dissolved in ethanol (10 mL) were added to a stirred solution of 0.65 g (3.64 mmol) of 5-methoxy-2H-1-benzopyran-3-one (24) in dry ethanol (10 mL). The reaction mixture was stirred for 1 h at room temperature and filtered, and then 0.5 g of 10% Pd/C was added. The mixture was hydrogenated, at 40 psi, in a Parr shaker at room temperature for 16 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using dichloromethane/diethyl ether (1:1) as eluent to give 1.18 g (81%) of pure 8g.

Biology. Binding Experiments. Receptor binding assays were conducted using methods previously reported in the literature.⁴¹ Briefly 5-HT_{1A} assays used rat hippocampus membranes and [³H]-8-OH-DPAT, and buspirone for nonspecific binding (NSB). 5-HT_{1B} assays used rat cortex + striatum + globus pallidus, and [³H]-5-OH-tryptamine and serotonin for NSB. 5-HT₂ assays used calf frontal cortex and [³H]ketanserin, and spiperone for NSB. D₁ assays used calf striatum and [³H]raclopride, and haloperidol for NSB. D₂ assays used calf caudate nucleus and [³H]SDZ 205-501,⁴² and butaclamol for NSB. α₁ assays used calf frontal cortex and [³H]prazosin, and phenotolamine for NSB. α₂ assays used calf frontal cortex and [³H]rauwolscine, and yohimbine for NSB.

The concentrations 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 IC₅₀ (concentration inhibiting 50% of the specific binding) and calculated using LUNDON 2 Software. The results obtained are reported in the Table 4.

Adenylate Cyclase Experiments. Hippocampi of Sprague-Dawley rats previously treated with 5 mg/kg ip of reserpine (24 h before sacrifice) were dissected immediately after death, and tissues were homogenized, centrifuged, and then sedimented for adenylate cyclase assays as previously described.³⁶ The enzymatic activity was estimated from the conversion of [³²P]-α-ATP into [³²P]cAMP at the end of a 20-min incubation at 30 °C. Concentration-effect curves were analyzed using SCTFIT, a nonlinear regression computer program⁴³ for the calculation of maximal inhibition and IC₅₀ values.

Electrophysiological Experiments. The *in vitro* recordings of the electrical activity of dorsal raphe nucleus (DRN) serotonergic neurons were performed in mice brain of 7-week-old Sprague-Dawley rats (150 g) as previously described.³⁶ In brief, young rats were anesthetized, and their brains removed and placed in an ice-cold Krebs oxygenated solution. The DRN was cut into frontal sections (0.3 mm thick). A single slice was transferred to a recording chamber and the micropipette implanted into the DRN area.

The serotonergic neurons were induced to fire by adding 3 μM phenylephrine (α₁ agonist) to the superfusion milieu. When a cell was recorded it was identified as serotonergic using the following two criteria: biphasic action potentials of 2–3 ms duration and a slow (0.5–2.0 spikes/s) and regular pattern of discharge. (+)-9g (5–10–30 nM) or (-)-9g (10–30–300 nM) was perfused into the chamber containing the mice brains for 25 min and the baseline activity recorded for 10 min. Furthermore, (+)-9g (30 nM) was recorded while being superfused with (±)-tertatolol (1 μM) or (-)-propranolol (10 μM), two potent 5-HT_{1A} receptor antagonists.⁴⁴ The effects of the two compounds were evaluated by calculating the ratio (in percentage) of the total number of spikes for the 10-min period just following the end of the drug infusion over that for the 10-min period just preceding the treatment.

Data were analyzed statistically by one-way analysis of variance and, in the case of significance (*p* < 0.05), the Fisher's test for significant treatment effects was followed by a two-tailed Student's *t* test to compare the experimental groups with their control groups.

Forepaw Treading Test in Rats. First, behavioral indices of 5-HT_{1A} agonist activity were evaluated following the forepaw treading procedure.⁴⁵ Rats were injected with the test compound and immediately afterward were placed individually in transparent plexiglass cages (20 × 10 × 10 cm) covered by a perforated stainless steel lid. Forepaw treading was scored at 15, 30, 45, and 60 min according to a 3-point scale (0 = absent; 1 = periodic and

weak; 2 = continuous). Scores were cumulated per rat. Six rats were used per group. (+)-9g and (-)-9g were each tested at the following doses: 8, 16, and 32 mg/kg ip.

Lower Lip Retraction Test in Rats. Behavioral indices of 5-HT_{1A} agonist activity were then evaluated following the lower lip retraction procedure.⁴⁶ Rats were administered with the test compound and immediately afterward were placed individually in transparent plexiglass cages (20 × 10 × 10 cm) covered by a perforated stainless steel lid. Lower lip retraction was scored every 15 min for 3 h after injection according to a 3-point scale (0 = lower incisors not visible; 1 = lower incisors partly visible; 2 = lower incisors completely visible). Scores were cumulated per rat. Six rats were used per group. (+)-9g and (-)-9g were each tested at the following doses: 4, 8, and 16 mg/kg ip.

All quantitative data were analyzed for their overall statistical significance using parametric analysis of variance (one-factor or two-factor, depending on experiments) followed by individual comparisons with the vehicle control groups using Dunnett's *t* test (two-tailed).

Anxiolytic-like Activity. The anxiolytic-like activity of 9g, (+)-9g, and (-)-9g was tested using the anticonflict and discriminative procedures in pigeons according to the procedure detailed by J. E. Barrett.⁴⁰

In Brief, key-peck responding of pigeons was maintained by a 30-response fixed-ratio schedule of food delivery. In studies involving punished response, every 30th response during one key light stimulus also produced shocks ("conflict" procedure). In studies involving drug discrimination, pigeons were trained to discriminate the 5-HT_{1A} drug 8-OH-DPAT (3 mg/kg) from saline by differentially reinforcing responding following the administration of either 0.3 mg/kg im of 8-OH-DPAT or saline. The compounds were tested from 0.01 up to 3.0 mg/kg im for their ability to modify punished response or to substitute for 8-OH-DPAT in the drug discrimination procedure.

Light/Dark Choice Procedure. The anxiolytic-like activity of the compounds was tested using an unconditioned conflict test, the light/dark choice procedure behaviorally validated for detecting antianxiety agents in mice.³⁹

In brief, the apparatus consisted of two poly(vinyl chloride) tools covered by plexiglass. One of these boxes was darkened, and the other was lightened by a lamp. Mice were placed in the lit box to start the test session. The amount of time spent by mice in the lit box (TLB) and the number of transitions through the tunnel were recorded over a 5-min period, after the first entry in the dark box. A mouse with all four paws in the new box was considered as having changed boxes. The compounds were tested from 1 up to 4 mg/kg ip. The lack of sedative effect of the compounds at the tested doses was previously measured in a free exploratory test.

The statistical significance of differences between control and treated groups was ascertained by a combined analysis of variance and a Dunnett's or Bonferroni's posteriori *t* test.

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