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

Tchao Podona,† Béatrice Guardiola-Lemaître,‡ Daniel-Henri Caignard,§ Gérard Adam,§ Bruno Pfeiffer,§ Pierre Renard,§ and Gérald Guillaumet*,†

Laboratoire de Chimie Bioorganique et Analytique, associé au CNRS, Université d'Orléans, B.P. 6759, 45067 Orleans Cedex 2, France, IRI Servier, 6, place des Pléiades, 92415 Courbevoie Cedex, France, and ADIR, 1, rue Carle Hébert, 92415 Courbevoie Cedex, France

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A series of 3,4-dihydro-3-amino-2*H*-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.

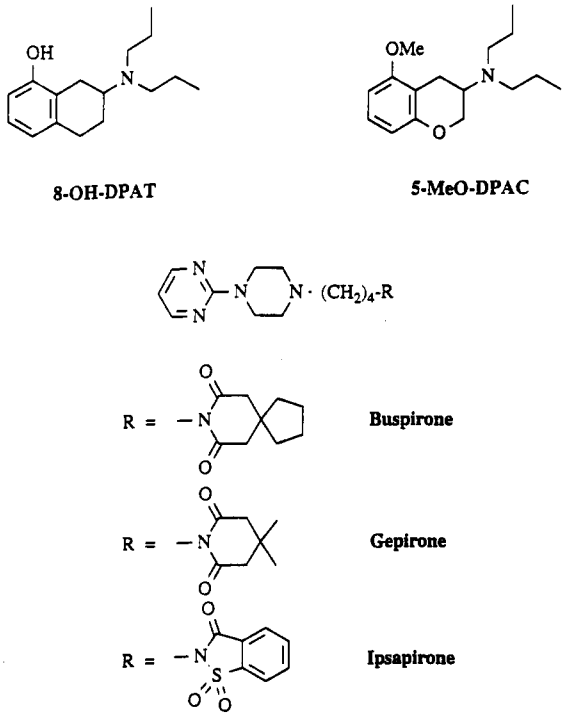
Introduction

During the last decade, serotonin (5-hydroxytryptamine, 5-HT) has been implicated in various behavorial 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-HT_1, 5-HT_2, and 5-HT_3) have been described,[6] but now there is also evidence of another type, the 5-HT_4 receptor.[7] The 5-HT_1 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 reclassed in the 5-HT_2 category as 5-HT_{2C}.[9] Of the 5-HT_1 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).

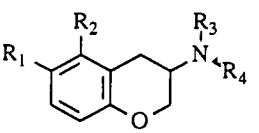
In recent years, a growing body of literature has attribued the activity of the non-benzodiazepine anxiolytic agent buspirone (Chart 1) to an activation of the 5-HT_{1A} receptor,[12] but with a rather low selectivity versus D_2 receptors. Despite this poor selectivity, this discovery has created much interest in alternative, non-benzodiazepine treatment of anxiety, and consequently, synthetic efforts have been devoted by various authors[13-16] 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 D_2 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-2*H*-1-benzopyran.[17,18] One of these, 5-MeO-DPAC [5-methoxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran] (Chart 1), which is closely related to 8-OH-DPAT, acts in the nanomolar range on 5-HT_{1A} sites but very poorly recognizes other 5-HT_1 sites and D_2 sites in rat brain membranes.

Chart 1



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 serotoninergic properties of 5-MeO-DPAC, we associated imidic or bioisosteric groups

† Laboratoire de Chimie Bioorganique et Analytique.
‡ IRI Servier.
§ ADIR.
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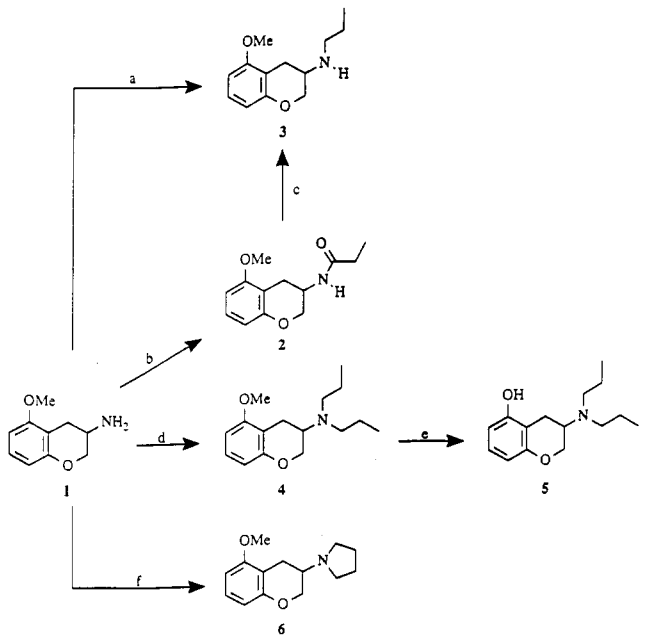
Scheme 1[a]



[a] (a) DMF, *n*-PrI (1 equiv), K_2CO_3, 60 °C; (b) CH_2Cl_2, ClCOEt, Et_3N, 20 °C; (c) (i) THF, BH_3·Me_2S, (ii) MeOH, HCl, reflux; (d) DMF, *n*-PrI (3 equiv), K_2CO_3, 60 °C; (e) AcOH, HBr, reflux; (f) DMF, $Br(CH_2)_4Br$, Et_3N, KI, 60 °C.

such as those of buspirone, gepirone, ipsapirone, and analogues to the 3-amino-3,4-dihydro-2*H*-1-benzopyran serotoninergic 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 D_2 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 complex[19] 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 acid[20] 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 **8a–d,f–m**, which were subsequently reacted with 1-iodopropane to give the desired substituted amines **9a–d,f–m** in 21–57% yields. From 3,4-dihydro-3-amino-2*H*-1-benzopyran (**21a**), an analogous synthetic sequence allowed us to successively obtain substituted derivatives **8n** and **9n**. However, the reaction of **1** with 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione does not give the expected product **8e** but corresponding *N*-(2-hydroxyethyl)iminoglutarimide[23] in 68% yield. The synthetic problem was resolved by condensation of 3,3-tetramethyleneglutaric anhydride with amine **14a** in refluxing toluene. This sequence provided amine **9e** in 74% yield. The O-demethylation of **9g** with boron tribromide in dichloromethane[24] gave the phenol **10** in 58% yield. On the other hand, the treatment of the same compound **9g** 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 **13a** and **13b** in 73 and 79% yields, respectively. Reduction of these nitriles using lithium aluminum hydride[25] in tetrahydrofuran gave amines **14a** and **14b** 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 **15c** 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 **18a** and **18b**. 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 **17a** and **17b** in 64 and 66% yields, respectively, which by reduction with borane–dimethyl sulfide complex[19] give compounds **18a** and **18b** in 66% yield in both cases.

The benzopyrans **22a** and **22b** were prepared from the corresponding nitro derivatives **19a** and **19b**[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 **21a** and **21b** was accomplished by using the hydrazine with Raney nickel.[29] The *N,N*-dipropyl compounds **22a** and **22b** were synthesized according to the usual procedure using propyl iodide in dimethylformamide in presence of potassium carbonate.

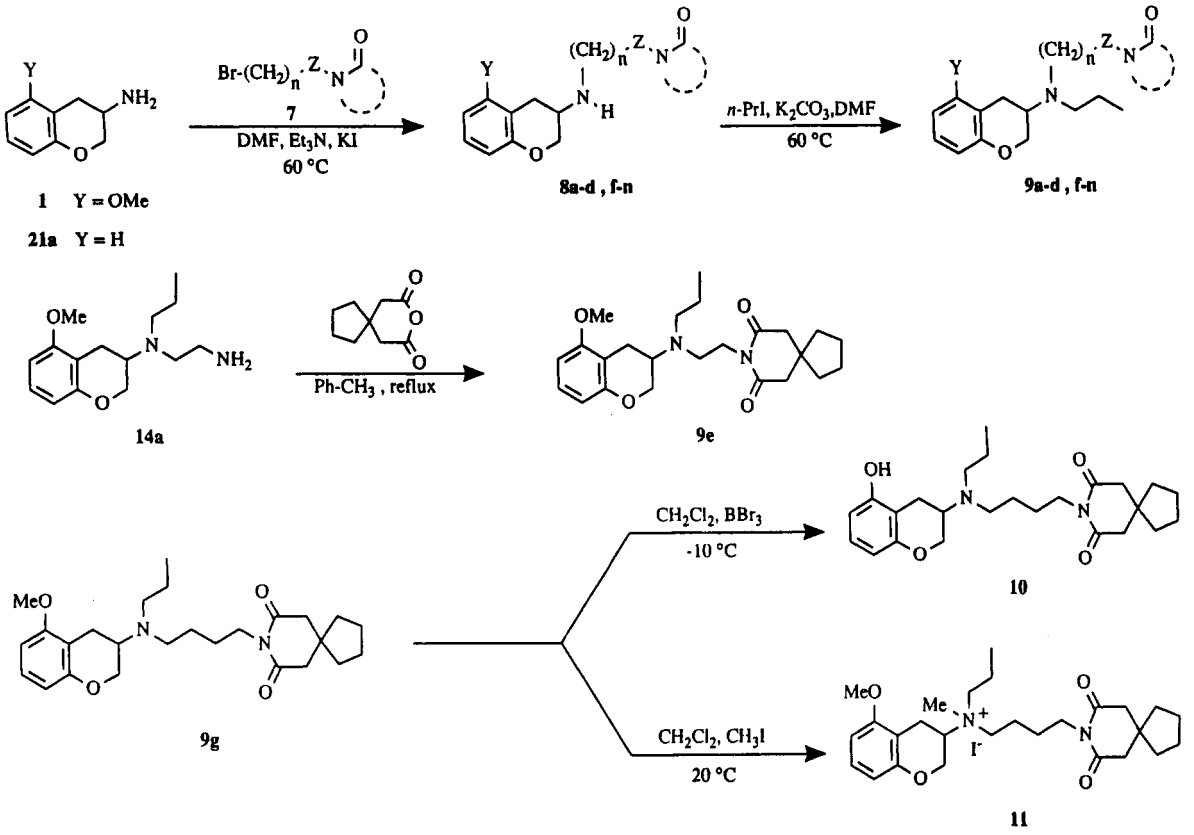
Indeed, compound **8g** (Scheme 2) can also be obtained by reductive amination[30] from ketone **24**,[31] which was obtained from 2-hydroxy-6-methoxybenzaldehyde according to the procedure described by Wise et al.[32] and 8-(4-aminobutyl)-8-azaspiro[4.5]decane-7,9-dione hydrochloride (**23**)[33] which was synthesized according to the method described by Gould et al.[34] (Scheme 6).

Both enantiomers of compounds **4**, **9g,k**, and **15b,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 D_2 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 D_2 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 D_2 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-2*H*-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.

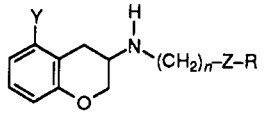
Whatever the structural modifications carried out, the only inactive compound was obtained *via* a bulky substitution of the benzopyran's 5-position (compound **22b**).

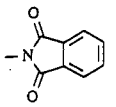
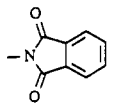
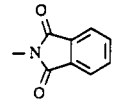
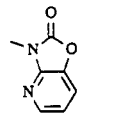
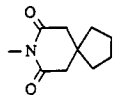
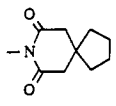
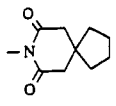
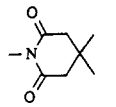
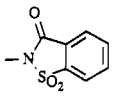
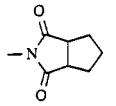
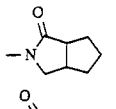
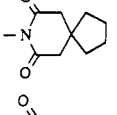
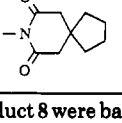
The conclusion of these structure–activity relationships studies is that the chemical modulation carried out led to the obtention of new compounds, among which the compound (+)-**9g**, with both greater affinity and higher selectivity for the 5-HT_{1A} receptors than buspirone and ipsapirone (Table 4).

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

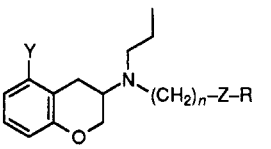


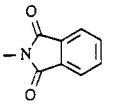
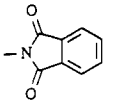
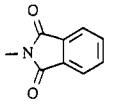
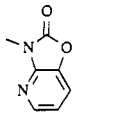
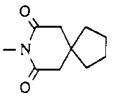
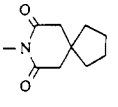
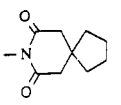
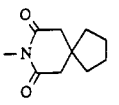
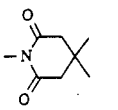
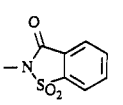
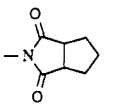
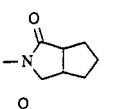
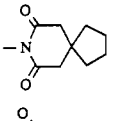
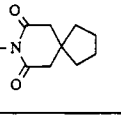
compd	Y	n	Z	R	yield[a] (%)	mp (°C)	formula[b]
8a	OMe	1	CH_2		30	oil	$C_{20}H_{20}N_2O_4$
8b	OMe	2	CH_2		70	oil	$C_{21}H_{22}N_2O_4$
8c	OMe	3	CH_2		67	170	$C_{22}H_{24}N_2O_4 \cdot C_2H_2O_4$
8d	OMe	3	CH_2		53	oil	$C_{20}H_{23}N_3O_4$
8f	OMe	2	CH_2		58	oil	$C_{22}H_{30}N_2O_4$
8g	OMe	3	CH_2		65	135	$C_{23}H_{32}N_2O_4 \cdot C_2H_2O_4$
8h	OMe	4	CH_2		64	oil	$C_{24}H_{34}N_2O_4$
8i	OMe	3	CH_2		58	oil	$C_{21}H_{30}N_2O_4$
8j	OMe	3	CH_2		60	oil	$C_{21}H_{24}N_2O_5S$
8k	OMe	3	CH_2		66	oil	$C_{21}H_{28}N_2O_4$
8l	OMe	3	CH_2		58	oil	$C_{21}H_{30}N_2O_3$
8m	OMe	3	O		56	oil	$C_{22}H_{30}N_2O_5$
8n	H	3	CH_2		57	oil	$C_{22}H_{30}N_2O_3$

[a] Yields of isolated product 8 were based on corresponding primary amines 1 and 21a and were not optimized. [b] $C_2H_2O_4$ indicates oxalate salt unless otherwise indicated; satisfactory elemental analyses (±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	$C_{23}H_{26}N_2O_4 \cdot HCl$
9b	OCH_3	2	CH_2		76	74	$C_{24}H_{28}N_2O_4 \cdot C_2H_2O_4$
9c	OCH_3	3	CH_2		81	72	$C_{25}H_{30}N_2O_4 \cdot C_2H_2O_4$
9d	OCH_3	3	CH_2		65	85	$C_{23}H_{29}N_3O_4 \cdot 2HCl$
9e	OCH_3	1	CH_2		75[b]	56	$C_{24}H_{34}N_2O_4 \cdot C_2H_2O_4$
9f	OCH_3	2	CH_2		52	82	$C_{25}H_{36}N_2O_4 \cdot C_2H_2O_4$
9g	OCH_3	3	CH_2		72	68	$C_{26}H_{38}N_2O_4 \cdot C_2H_2O_4$
9h	OCH_3	4	CH_2		61	60	$C_{27}H_{40}N_2O_4 \cdot C_2H_2O_4$
9i	OCH_3	3	CH_2		77	64	$C_{24}H_{36}N_2O_4 \cdot C_2H_2O_4$
9j	OCH_3	3	CH_2		57	85	$C_{24}H_{30}N_2O_5S \cdot C_2H_2O_4$
9k	OCH_3	3	CH_2		78	65	$C_{24}H_{34}N_2O_4 \cdot C_2H_2O_4$
9l	OCH_3	3	CH_2		70	55	$C_{24}H_{36}N_2O_3 \cdot C_2H_2O_4$
9m	OCH_3	3	O		68	55	$C_{25}H_{36}N_2O_5 \cdot C_2H_2O_4$
9n	H	3	CH_2		62	82	$C_{25}H_{36}N_2O_3 \cdot C_2H_2O_4$

[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 (±0.4%) C, H, N were obtained for all compounds.

Scheme 3

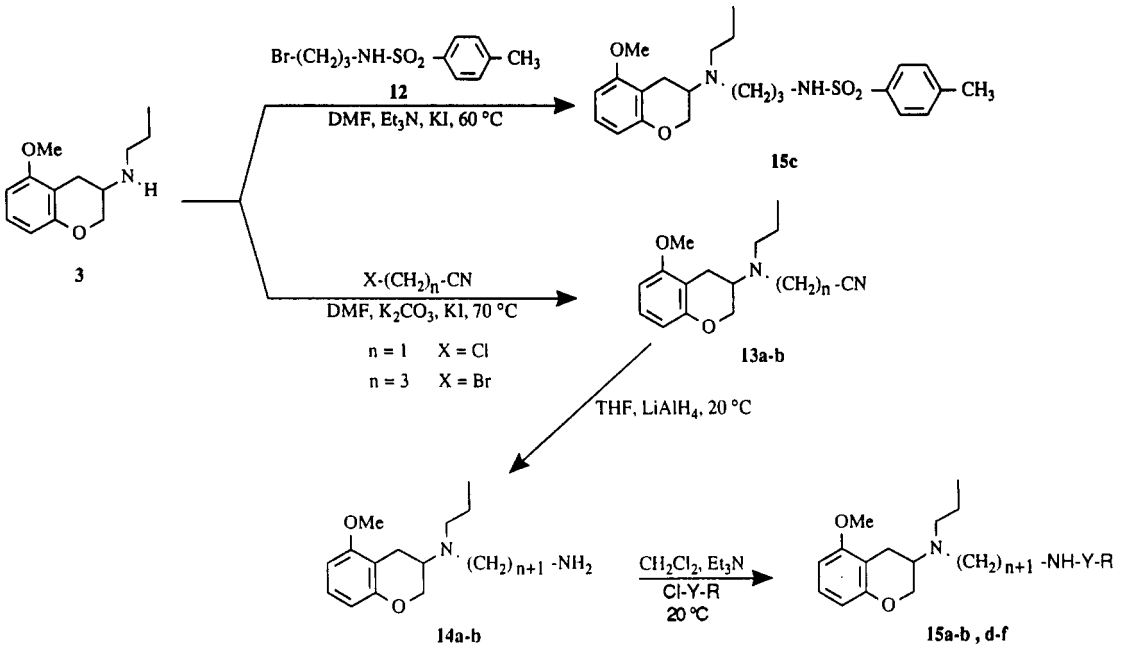
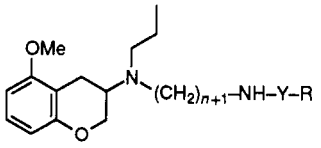
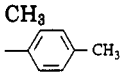
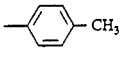
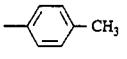
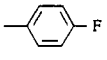


Table 3. Physical Data for Compounds **15**



compd	Y	n	R	yield[a] (%)	mp[c] (°C)	formula[d]
15a	C=O	1	CH_3	90	54	$C_{17}H_{26}N_2O_3 \cdot C_2H_2O_4$
15b	SO_2	1		88	132	$C_{22}H_{30}N_2O_4S \cdot C_2H_2O_4$
15c	SO_2	2		65[b]	128	$C_{23}H_{32}N_2O_4S \cdot C_2H_2O_4$
15d	SO_2	3		89	95	$C_{24}H_{34}N_2O_4S \cdot C_2H_2O_4$
15e	C=O	3		76	82	$C_{24}H_{31}N_2O_3 \cdot C_2H_2O_4$
15f	C=O	3		83	66	$C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4$

[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 (±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 IC_{50} values of 10.2 ± 2.7, 26.3 ± 5.8, and 248 ± 31 nM (mean ± 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 serotoninergic neurons. Comparison of the concentration–response curves showed that (+)-**9g** (IC_{50} ≃ 6 nM) was ≃20 times more potent than (−)-**9g** (IC_{50} = 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]

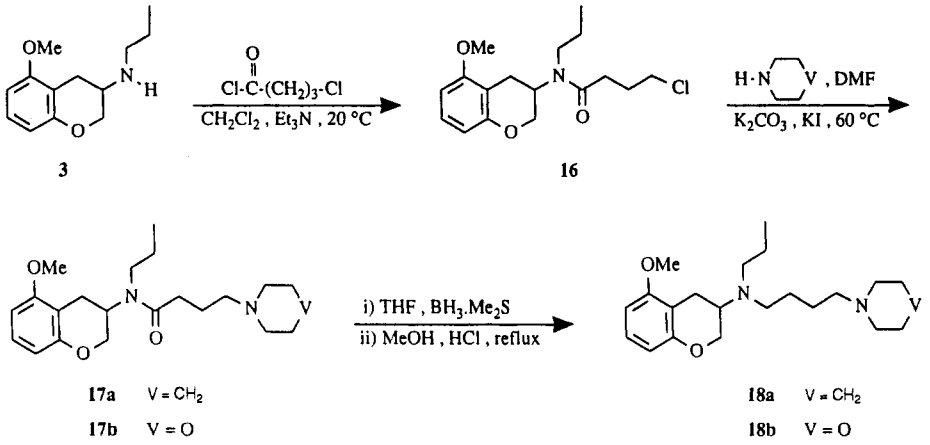
In the anticonflict test in pigeons, (+)-**9g** was approximately 10 times more potent than (−)-**9g** in producing *maximal increases* in punished responding. The racemate **9g** was comparable in potency to (−)-**9g** in producing maximal increases in punished responding. The lowest dose which induces 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

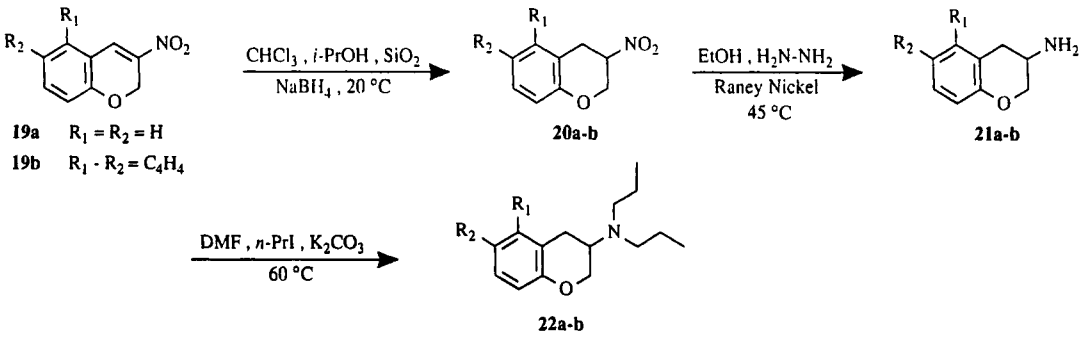


3 16

17a V = CH_2 18a V = CH_2

17b V = O 18b V = O

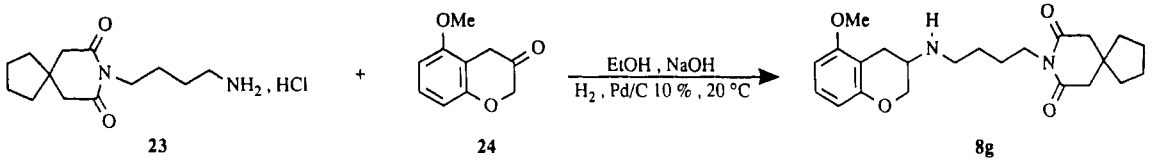
Scheme 5



19a $R_1 = R_2 = H$ 20a-b 21a-b

19b $R_1 - R_2 = C_4H_4$ 22a-b

Scheme 6



23 24 8g

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

$$(+)\text{-}\mathbf{9g} \simeq \mathbf{9g} > (-)\text{-}\mathbf{9g}$$

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 IC_{50} values reported in the pigeons by Barrett et al.[40] for 5-HT_{1A} binding sites with IC_{50} (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-2*H*-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 been 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 singulet (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 ±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. IC_{50} (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^{-8}	2×10^{-5}	6×10^{-5}	1×10^{-4}	5×10^{-8}	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^{-8}	7×10^{-6}	6×10^{-7}	3×10^{-5}	5×10^{-6}	$>10^{-4}$	4×10^{-6}
8g	2×10^{-8}	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^{-8}	4×10^{-6}	1×10^{-6}
9c	5×10^{-8}	4×10^{-7}	3×10^{-5}	4×10^{-5}	3×10^{-8}	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^{-8}	$>10^{-4}$	$>10^{-4}$	$>10^{-4}$	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^{-8}	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^{-8}
(−)-**9g**	2×10^{-9}	6×10^{-6}	5×10^{-6}	2×10^{-5}	1×10^{-8}	2×10^{-5}	2×10^{-6}
9h	1×10^{-9}	2×10^{-5}	3×10^{-6}	6×10^{-5}	6×10^{-8}	5×10^{-6}	1×10^{-7}
9i	4×10^{-9}	1×10^{-5}	6×10^{-6}	8×10^{-5}	4×10^{-8}	6×10^{-6}	4×10^{-7}
9j	1×10^{-9}	1×10^{-6}	1×10^{-5}	5×10^{-5}	9×10^{-8}	1×10^{-6}	4×10^{-5}
9k	2×10^{-9}	2×10^{-5}	9×10^{-6}	4×10^{-5}	2×10^{-8}	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^{-8}	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^{-8}	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^{-8}	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^{-8}	$>10^{-4}$	1×10^{-5}
15c	3×10^{-9}	2×10^{-6}	6×10^{-6}	2×10^{-5}	3×10^{-8}	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^{-8}	2×10^{-5}	5×10^{-6}	2×10^{-5}	6×10^{-8}	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^{-8}	3×10^{-6}	1×10^{-7}
18a	2×10^{-9}	5×10^{-5}	$>10^{-4}$	1×10^{-4}	2×10^{-8}	5×10^{-6}	1×10^{-5}
18b	8×10^{-9}	$>10^{-4}$	1×10^{-5}	1×10^{-4}	3×10^{-8}	1×10^{-5}	4×10^{-6}
22a	4×10^{-7}	$>10^{-4}$	8×10^{-5}	$>10^{-4}$	6×10^{-8}	$>10^{-4}$	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}
buspirone	6×10^{-8}	ND	1×10^{-5}	2.7×10^{-5}	4×10^{-6}	1.6×10^{-5}	1×10^{-5}
ipsapirone	3.5×10^{-8}	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 Enantiomeres on Electrophysiological and Comportemental Studies

	agonist activity determination IC_{50} (nM)		*in vivo* comportemental tests				
compd	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 ($MgSO_4$) 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 ($MgSO_4$), 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 ($CDCl_3$) δ 2.41–2.51 (m, 4H, $CH_2CH_2CH_2Br$), 3.47 (t, 2H, J = 6.7 Hz, CH_2Br), 4.10 (t, 2H, J = 6.7 Hz, CH_2NCO), 7.08 (dd, 1H, J^1 = 8 Hz, J^2 = 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 ($CDCl_3$) δ 1.46–1.54 (m, 4H, CH_2), 1.67–1.76 (m, 4H, CH_2), 2.62 (s, 4H, CH_2CO), 3.48 (t, 2H, J = 6.9 Hz, CH_2Br), 4.20 (t, 2H, J = 6.9 Hz, CH_2CH_2Br).

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 ($CDCl_3$) δ 1.45–1.56 (m, 4H, CH_2), 1.66–1.75 (m, 4H, CH_2), 2.06–2.15 (m, 2H, CH_2CH_2Br), 2.59 (s, 4H, CH_2CO), 3.36 (t, 2H, J = 7.1 Hz, CH_2Br), 3.89 (t, 2H, J = 7.1 Hz, CH_2NCO).

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 ($CDCl_3$) δ 1.45–1.52 (m, 4H, CH_2), 1.62–1.72 (m, 6H, CH_2), 1.79–1.90 (m, 2H, CH_2CH_2N), 2.60 (s, 4H, CH_2CO), 3.42 (t, 2H, J = 7.1 Hz, CH_2Br), 3.80 (t, 2H, J = 7.1 Hz, CH_2NCO).

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 ($CDCl_3$) δ 1.35–1.73 (m, 12H, CH_2), 1.81–1.90 (m, 2H, CH_2), 2.57 (s, 4H, CH_2CO), 3.38 (t, 2H, J = 7.1 Hz, CH_2Br), 3.74 (t, 2H, J = 7.1 Hz, CH_2NCO).

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 ($CDCl_3$) δ 1.06 (s, 6H, CH_3C), 1.61–1.73 (m, 2H, CH_2), 1.80–1.91 (m, 2H, CH_2), 2.51 (s, 4H, CH_2CO), 3.41 (t, 2H, J = 6.3 Hz, CH_2Br), 3.80 (t, 2H, J = 6.3 Hz, CH_2N).

***N*-(4-Bromobutyl)-1,1-dioxo-1,2-benzisothiazol-3(2*H*)-one (7j)**: method A (60%); IR (neat) 1720 (ν C=O), 1300 and 1170 cm^{-1} (n SO_2); ^1H NMR ($CDCl_3$) δ 1.95–2.05 (m, 4H, $CH_2CH_2CH_2Br$), 3.44 (t, 2H, J = 7.1 Hz, CH_2Br), 3.82 (t, 2H, J = 7.1 Hz, CH_2N), 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 ($CDCl_3$) δ 1.15–1.38 (m, 2H, CH_2), 1.62–2.14 (m, 8H, CH_2), 3.12 (m, 2H, CHCO), 3.38 (t, 2H, J = 6.6 Hz, CH_2Br), 3.48 (t, 2H, J = 6.6 Hz, CH_2NCO).

***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 ($CDCl_3$) δ 1.40–2.29 (m, 10H, CH_2), 2.70–2.95 (m, 2H, CH_2N), 3.00 (dd, 1H, J^1 = 9.7 Hz, J^2 = 2.6 Hz, $CHCH_2$), 3.20–3.40 (m, 2H, CH_2NCO), 3.44 (t, 2H, J = 6.5 Hz, CH_2Br), 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 ($CDCl_3$) δ 1.51–1.61 (m, 4H, CH_2), 1.68–1.78 (m, 4H, CH_2), 2.21–2.31 (m, 2H, CH_2CH_2O), 2.68 (s, 4H, CH_2CO), 3.65 (t, 2H, J = 6.3 Hz, CH_2Br), 4.12 (t, 2H, J = 6.3 Hz, CH_2O).

5-Methoxy-3,4-dihydro-3-(*n*-propylamino)-2*H*-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 ($MgSO_4$) 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 ($CDCl_3$) δ 0.94 (t, 3H, J = 7.1 Hz, CH_3CH_2), 1.07 (b, 1H, NH), 1.48–1.57 (m, 2H, CH_2CH_3), 2.47 (dd, 1H, J^1 = 17 Hz, J^2 = 7 Hz, CHAr), 2.70 (t, 2H, J = 7.1 Hz, CH_2N), 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, CH_3O, 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. ($C_{13}H_{19}NO_2$) 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-2*H*-1-benzopyran (**2**) as a white solid: mp 125 °C: IR (KBr) 3300 (ν NH), 1630 cm^{-1} (ν C=O); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J = 7.2 Hz, CH_3CH_2), 2.16 (q, 2H, J = 7.2 Hz, CH_2CH_3), 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, CH_3O), 4.02 and 4.10 (2d, 2H, J = 11.3 Hz, CH_2O), 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. ($C_{13}H_{17}NO_3$) 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 ($MgSO_4$), 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)-2*H*-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 ($CDCl_3$) δ 0.87 (t, 6H, J = 7.9 Hz, CH_3), 1.40–1.50 (m, 4H, CH_2CH_3), 2.45–2.56 (m, 5H, CH_2N, 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, CH_3O), 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. ($C_{16}H_{25}NO_2HCl$) C, H, N, Cl.

(+)-4: $[\alpha]^{18}_D$ = +96° (c = 0.83, $CHCl_3$).

(−)-4: $[\alpha]^{18}_D$ = −97° (c = 0.75, $CHCl_3$).

5-Hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-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 ($MgSO_4$), 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 ($CDCl_3$) δ 0.89 (t, 6H, J = 7.9 Hz, CH_3CH_2), 1.43–1.52 (m, 4H, CH_2CH_3), 2.51–2.60 (m, 5H, CH_2N, 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. ($C_{15}H_{23}NO_2$·HCl) C, H, N, Cl.

5-Methoxy-3-(pyrrolidin-1-yl)-3,4-dihydro-2*H*-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 ($MgSO_4$) 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 ($CDCl_3$) δ 1.79–1.88 (m, 4H, CH_2), 2.47–2.67 (m, 2H, CHN and CH_2Ar), 2.67–2.79 (m, 4H, CH_2N), 3.02 (ddd, 1H, J = 3.0 Hz, J = 15.0 Hz, J = 5.0 Hz, CH_2Ar), 3.79 (t, 1H, J = 10.3 Hz, CHO), 3.84 (s, 3H, CH_3O), 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. ($C_{14}H_{19}NO_2$·$C_2H_2O_4$) C, H, N.

General Procedure for the Preparation of Amines 8a–c. A mixture of 5-methoxy-3,4-dihydro-3-amino-2*H*-1-benzopyran **1** (0.392 g, 22 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 ($MgSO_4$) 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]-2*H*-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 ($CDCl_3$) 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, **CH_2NH**), 3.10–3.20 (m, 1H, **CHN**), 3.78 (s, 3H, **CH_3O**), 3.76–3.86 (m, 3H, **CH_2NCO, 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. ($C_{20}H_{20}N_2O_4$) C, H, N.

5-Methoxy-3,4-dihydro-3-[*N*-(3-phthalimidopropyl)amino]-2*H*-1-benzopyran (8b). By starting 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 ($CDCl_3$) δ 1.56 (b, 1H, **NH**), 1.82–1.92 (m, 2H, **CH_2CH_2N**), 2.44 (dd, 1H, J^1 = 17 Hz, J^2 = 7.1 Hz, **CHAr**), 2.79 (t, 2H, J = 6.6 Hz, **CH_2NH**), 2.90 (dd, 1H, J^1 = 17 Hz, J^2 = 6 Hz, **CHAr**), 3.01–3.11 (m, 1H, **CHN**), 3.73–3.83 (m, 6H, **CH_3O, CH_2NCO, 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. ($C_{21}H_{22}N_2O_4$) C, H, N.

5-Methoxy-3,4-dihydro-3-[*N*-(4-phthalimidobutyl)amino]-2*H*-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 ($CDCl_3$) δ 1.51–1.61 (m, 3H, **CH_2CH_2N, NH**), 1.70–1.80 (m, 2H, **CH_2CH_2NCO**), 2.47 (dd, 1H, J^1 = 16.9 Hz, J^2 = 7 Hz, **CHAr**), 2.75 (t, 2H, J = 7.9 Hz, **CH_2NH**), 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, **CH_2NCO**), 3.80 (s, 3H, **CH_3O**), 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. ($C_{22}H_{24}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

General Procedure for the Preparation of Amines 8d,f–n. A mixture of 5-methoxy-3,4-dihydro-3-amino-2*H*-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 CH_2Cl_2 (4 × 20 mL). The solvent was dried ($MgSO_4$) 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-2*H*-1-benzopyran-3-yl)amino]butyl]oxazolo[4,5-*b*]pyridin-2(3*H*)-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 ($CDCl_3$) δ 1.34 (b, 1H, **NH**), 1.58–1.68 (m, 2H, **CH_2**), 1.86–1.95 (m, 2H, **CH_2**), 2.48 (dd, 1H, J^1 = 17 Hz, J^2 = 7 Hz, **CHAr**), 2.78 (t, 2H, J = 7.2 Hz, **CH_2N**), 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, **CH_3O**), 3.84 (t, 1H, J = 10.2 Hz, **CHO**), 3.97 (t, 2H, J = 7.2 Hz, CH_2NCO), 4.09–4.19 (m, 1H, **CHO**), 6.44 and 6.49 (2d, 2H, J = 8.3 Hz, arom), 7.40–8.10 (m, 4H, arom). Anal. ($C_{20}H_{23}N_3O_4$) C, H, N.

8-[3-[*N*-(5-Methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 1.44–1.82 (m, 11H, **CH_2, NH**), 2.48 (dd, 1H, J^1 = 16.8 Hz, J^2 = 6.9 Hz, **CHAr**), 2.57 (s, 4H, **CH_2CO**), 2.65 (t, 2H, J = 7.4 Hz, **CH_2N**), 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, **CH_3O, CH_2NCO, 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. ($C_{22}H_{30}N_2O_4$) C, H, N.

8-[4-[*N*-(5-Methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 1.45–1.85 (m, 13H, **NH, CH_2**), 2.46 (dd, 1H, J^1 = 17 Hz, J^2 = 7 Hz, **CHAr**), 2.59 (s, 4H, **CH_2CO**), 2.74 (t, 2H, J = 7 Hz, **CH_2N**), 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, **CH_3O, CH_2NCO, 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. ($C_{23}H_{32}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

(+)-**8g**: $[\alpha]^{20}_D$ = +15.3° (c = 0.16, $CHCl_3$).

(–)-**8g**: $[\alpha]^{20}_D$ = –15.6° (c = 0.16, $CHCl_3$).

8-[5-[*N*-(5-Methoxy-3,4-dihydroxy-2*H*-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 ($CDCl_3$) δ 1.32–1.41 (m, 2H, **CH_2**), 1.45–1.56 (m, 9H, CH_2, **NH**), 1.67–1.78 (m, 4H, **CH_2**), 2.45 (dd, 1H, J^1 = 17 Hz, J^2 = 7.5 Hz, **CHAr**), 2.57 (s, 4H, **CH_2CO**), 2.72 (t, 2H, J = 7.1 Hz, **CH_2N**), 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, **CH_3O, CH_2NCO, 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. ($C_{24}H_{34}N_2O_4$), C, H, N.

5-Methoxy-3-[*N*-[4-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)butyl]amino]-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 1.06 (s, 6H, **CH_3**), 1.52–1.60 (m, 5H, **CH_2, NH**), 2.39 (dd, 1H, J^1 = 17.1 Hz, J^2 = 7 Hz, **CHAr**), 2.41 (s, 4H, **CH_2CO**), 2.70 (t, 2H, J = 7.1 Hz, **CH_2N**), 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, **CH_3O, CHO, CH_2NCO**), 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. ($C_{21}H_{30}N_2O_4$) C, H, N.

2-[4-[*N*-(5-Methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-1,1-dioxo-1,2-benzisothiazol-3(2*H*)-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 SO_2); ^1H NMR ($CDCl_3$) δ 1.27 (b, 1H, **NH**), 1.46–1.57 (m, 2H, **CH_2CH_2NH**), 2.79 (t, 2H, J = 7.1 Hz, **CH_2NH**), 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, **CH_3O, CH_2NCO, 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. ($C_{21}H_{24}N_2O_5S$) C, H, N, S.

3-[4-[*N*-(5-Methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 1.18–2.19 (m, 11H, **CH_2, NH**), 2.54 (dd, 1H, J^1 = 17.1 Hz, J^2 = 7 Hz, **CHAr**), 2.72–2.82 (m, 2H, **CH_2N**), 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, **CH_2NCO**), 3.81 (s, 3H, **CH_3O**), 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. ($C_{21}H_{28}N_2O_4$) C, H, N.

(+)-**8k**: $[\alpha]^{20}_D$ = +12° (c = 0.75, $CHCl_3$).

(–)-**8k**: $[\alpha]^{20}_D$ = –12° (c = 0.75, $CHCl_3$).

3-[4-[*N*-(5-Methoxy-3,4-dihydroxy-2*H*-1-benzopyran-3-yl)amino]butyl]-2-oxo-3-azabicyclo[3.3.0]octane (8l). This compound was obtained from **7l** (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 **8l** as a pale yellow oil: IR (neat) 3400–3200 (ν NH), 1655 cm^{-1} (ν C=O); ^{1}H 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_2N, 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. ($C_{21}H_{30}N_2O_3$) 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); ^{1}H NMR ($CDCl_3$) δ 1.49–1.76 (m, 9H, **CH_2, NH**), 1.87–1.97 (m, 2H, **CH_2CH_2O**), 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. ($C_{22}H_{30}N_2O_5$) 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); ^{1}H 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. ($C_{22}H_{30}N_2O_3$) 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*-(ω-phthalimidoalkyl)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 × 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-phthalimidoethyl)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); ^{1}H 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. ($C_{23}H_{26}N_2O_4$·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); ^{1}H 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, **CH_2CH_2N**), 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. ($C_{24}H_{28}N_2O_4$·$C_2H_2O_4$) 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); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz, **CH_3CH_2**), 1.43–1.53 (m, 4H, **CH_2CH_2N**), 1.67–1.77 (m, 2H, **CH_2CH_2NCO**), 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. ($C_{25}H_{30}N_2O_4$·$C_2H_2O_4$) 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); ^{1}H 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. ($C_{23}H_{29}N_3O_4$·2HCl) 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); ^{1}H 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. ($C_{24}H_{34}N_2O_4$·$C_2H_2O_4$) 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 **9d** as an oil: IR (neat) 1720 and 1660 cm^{-1} (ν C=O); ^{1}H 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. ($C_{25}H_{36}N_2O_4$·$C_2H_2O_4$) 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)); ^{1}H 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,

CH_2CO, CH_2N, 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, CH_2NCO, CHO), 3.81 (s, 3H, CH_3O), 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. ($C_{26}H_{38}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

(+)-**9g**: $[\alpha]^{20}_D$ = +45° (c = 0.65, $CHCl_3$).

(−)-**9g**: $[\alpha]^{20}_D$ = −44.7° (c = 0.65, $CHCl_3$).

8-[5-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.88 (t, 3H, J = 7.1 Hz, CH_3), 1.25–1.35 (m, 2H, CH_2), 1.45–1.55 (m, 10H, CH_2), 1.67–1.77 (m, 4H, CH_2), 2.45–2.55 (m, 5H, CH_2N, CHAr), 2.59 (s, 4H, CH_2CO), 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, CH_2NCO, CHO), 3.83 (s, 3H, CH_3O), 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. ($C_{27}H_{40}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-[4-(4,4-dimethyl-2,6-dioxo-1-piperidinyl)butyl]amino]-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.88 (t, 3H, J = 7 Hz, CH_3), 1.06 (s, 6H, CH_3), 1.43–1.53 (m, 6H, CH_2), 2.47–2.57 (m, 9H, CH_2N, CH_2CO, 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, CH_2NCO, CHO), 3.83 (s, 3H, CH_3O), 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. ($C_{24}H_{36}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

2-[4-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amino]butyl]-1,1-dioxo-1,2-benzisothiazol-3(2*H*)-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 SO_2); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.40–1.64 (m, 4H, CH_2CH_3, CH_2CH_2N), 1.85–1.95 (m, 2H, CH_2CH_2NCO), 2.43–2.72 (m, 5H, CH_2N, 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, CH_3O, CH_2NCO, 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 458 (M^+), 163. Anal. ($C_{24}H_{30}N_2O_5S \cdot C_2H_2O_4$) C, H, N, S.

3-[4-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.88 (t, 3H, J = 7.1 Hz, CH_3), 1.18–2.18 (m, 12H, CH_2), 2.47–2.57 (m, 5H, CH_2N, 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, CH_2NCO), 3.74 (t, 1H, J = 10.3 Hz, CHO), 3.82 (s, 3H, CH_3O), 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. ($C_{24}H_{34}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

(+)-**9k**: $[\alpha]^{20}_D$ = +57.4° (c = 0.60, $CHCl_3$).

(−)-**9k**: $[\alpha]^{20}_D$ = −57.7° (c = 0.60, $CHCl_3$).

3-[4-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.86 (t, 3H, J = 7.4 Hz, CH_3), 1.35–2.05 (m, 12H, CH_2), 2.44–2.90 (m, 8H, CH_2NCO, CH_2Ar, CH_2NCH), 2.97 (dd, 1H, J^1 = 9.4 Hz, J^2 = 2.6 Hz, CHCHCO), 3.04–3.38 (m, 3H, CH_2NCO, CHN), 3.56 (t, 1H, J = 9.4 Hz, CHCO), 3.76 (t, 1H, J = 10.3 Hz, CHO), 3.82 (s, 3H, CH_3O), 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. ($C_{24}H_{36}N_2O_3 \cdot C_2H_2O_4$) C, H, N.

8-[[3-[*N*-Propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.87 (t, 3H, J = 7.1 Hz, CH_3), 1.39–1.76 (m, 6H, CH_2), 1.85–1.95 (m, 2H, CH_2CH_2O), 2.41–2.51 (m, 3H, CH_2N, CHAr), 2.66 (s, 4H, CH_2CO), 2.76 (t, 2H, J = 6.9 Hz, CH_2N), 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, CH_3O), 4.03 (t, 2H, J = 6.3 Hz, CH_2O), 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. ($C_{25}H_{36}N_2O_5 \cdot C_2H_2O_4$) C, H, N.

8-[4-[*N*-Propyl-*N*-(3,4-dihydro-2*H*-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 ($CDCl_3$) δ 0.90 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.43–1.78 (m, 14H, CH_2), 2.50–2.63 (m, 8H, CH_2N, CH_2CO), 2.87 (d, 2H, J = 8.3 Hz, CH_2Ar), 3.13–3.23 (m, 1H, CHN), 3.78–3.88 (m, 3H, CH_2NCO, 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. ($C_{25}H_{36}N_2O_3 \cdot C_2H_2O_4$) C, H, N.

8-[4-[*N*-Propyl-*N*-(5-hydroxy-3,4-dihydro-2*H*-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 ($MgSO_4$) 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 ($CDCl_3$) δ 0.87 (t, 3H, J = 7.4 Hz, CH_3), 1.39–1.74 (m, 14H, CH_2), 2.50–2.70 (m, 9H, CH_2N, CH_2CO, 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, CH_2NCO, 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. ($C_{25}H_{36}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

8-[4-[*N*-Methyl-*N*-propyl-*N*-(5-methoxy-3,4-dihydro-2*H*-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 purifed 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 °C; IR (KBr) 1720 and 1665 cm^{-1} (ν C=O); ^1H NMR ($CDCl_3$) δ 1.02 and 1.06 (2 t, 3H, J = 7.1 Hz, CH_3CH_2), 1.45–1.55 (m, 4H, CH_2), 1.65–1.75 (m, 6H, CH_2), 1.84–1.94 (m, 4H, CH_2), 2.71 and 2.73 (2 s, 4H, CH_2CO), 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, CH_3N), 3.38–3.48 (m, 2H, CH_2N), 3.51–3.61 (m, 2H, CH_2N), 3.78–3.81 (m, 2H, CH_2NCO), 3.84 (s, 3H, CH_3O), 4.45–4.58 (m, 3H, CH_2O, 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. ($C_{27}H_{41}N_2O_4^+I^-$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-(cyanomethyl)amino]-3,4-dihydro-2*H*-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 °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 ($MgSO_4$) 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_3CH_2), 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. ($C_{15}H_{20}N_2O_2$) C, H, N.

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

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

5-Methoxy-3-[*N*-propyl-*N*-(cyanopropyl)amino]-3,4-dihydro-2*H*-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, CH_2CH_2CN), 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. ($C_{17}H_{24}N_2O_2$) C, H, N.

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

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

5-Methoxy-3-[*N*-propyl-*N*-(2-aminoethyl)amino]-3,4-dihydro-2*H*-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. ($C_{15}H_{24}N_2O_2$) C, H, N.

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

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

5-Methoxy-3-[*N*-propyl-*N*-(4-aminobutyl)amino]-3,4-dihydro-2*H*-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, CH_2CH_2N), 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. ($C_{17}H_{28}N_2O_2$) C, H, N.

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

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

5-Methoxy-3-[*N*-propyl-*N*-(2-acetamidoethyl)amino]-3,4-dihydro-2*H*-1-benzopyran (15a). Acetyl chloride (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. ($C_{17}H_{26}N_2O_3 \cdot C_2H_2O_4$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-[2-(4-tolylsulfonamido)ethyl]amino]-3,4-dihydro-2*H*-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. ($C_{22}H_{30}N_2O_4S \cdot C_2H_2O_4$) C, H, N, S.

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

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

5-Methoxy-3-[*N*-propyl-*N*-[3-(4-tolylsulfonamido)propyl]amino]-3,4-dihydro-2*H*-1-benzopyran (15c). A mixture of **3** (0.1 g, 0.54 mmol), **12**[26] (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 × 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, CH_2CH_2NH), 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. ($C_{23}H_{32}N_2O_4S \cdot C_2H_2O_4$) C, H, N, S.

5-Methoxy-3-[*N*-propyl-*N*-[4-(4-tolylsulfonamido)butyl]amino]-3,4-dihydro-2*H*-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 $CDCl_3$ d 0.84 (t, 3H, J = 7.3 Hz, CH_3CH_2), 1.35–1.57 (m, 6H, CH_2CH_2N), 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. ($C_{24}H_{34}N_2O_4S \cdot C_2H_2O_4$) C, H, N, S.

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

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

5-Methoxy-3-[*N*-propyl-*N*-[4-(4-fluoro-1-benzamido)butyl]amino]-3,4-dihydro-2*H*-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, CH_2CH_2N), 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. ($C_{24}H_{31}FN_2O_3 \cdot C_2H_2O_4$) C, H, N, F.

5-Methoxy-3-[*N*-propyl-*N*-[4-(2-methoxy-1-benzamido)butyl]amino]-3,4-dihydro-2*H*-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); ^1H NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.2 Hz, CH_3CH_2), 1.39–1.69 (m, 6H, CH_2CH_2N), 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. ($C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-(4-chlorobutanoyl)amino]-3,4-dihydro-2*H*-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-chlorobutyryl 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); ^1H 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, CH_2CH_2Cl), 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. ($C_{17}H_{24}ClNO_3$) C, H, N, Cl.

5-Methoxy-3-[*N*-propyl-*N*-[4-(1-piperidinyl)butanoyl]amino]-3,4-dihydro-2*H*-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); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.41–1.78 (m, 8H, CH_2), 1.95–2.05 (m, 2H, CH_2CH_2CO), 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. ($C_{22}H_{34}N_2O_3$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-[4-(1-piperidinyl)butyl]amino]-3,4-dihydro-2*H*-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); ^1H 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. ($C_{22}H_{36}N_2O_2 \cdot C_2H_2O_4$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-(4-morpholin-4-ylbutanoyl)amino]-3,4-dihydro-2*H*-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); ^1H 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, CH_2CH_2CO), 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. ($C_{21}H_{32}N_2O_4$) C, H, N.

5-Methoxy-3-[*N*-propyl-*N*-(4-morpholin-4-ylbutyl)amino]-3,4-dihydro-2*H*-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); ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.4 Hz, CH_3), 1.45–1.55 (m, 6H, CH_2CH_2N), 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. ($C_{21}H_{34}N_2O_3 \cdot C_2H_2O_4$) C, H, N.

3,4-Dihydro-3-nitro-2*H*-1-benzopyran (20a). 3-Nitro-2*H*-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 CO); ^1H 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. ($C_9H_9NO_3$) C, H, N.

3-Amino-3,4-dihydro-2*H*-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); ^1H 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. ($C_9H_{11}NO$) C, H, N.

3,4-Dihydro-3-nitro-2*H*-1-naphtho[1,2-*b*]pyran (20b). The method was exactly as for **20a**: yield 3.8 g (95%) from 3-nitro-2*H*-1-naphtho[1,2-*b*]pyran (**19b**) (4 g, 17.60 mmol) **25c**; mp 65 °C; IR (KBr) 1235 cm^{-1} (ν C–O); ^1H 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. ($C_{13}H_{11}NO_3$) C, H, N.

3-Amino-3,4-dihydro-2*H*-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); ^1H 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. ($C_{13}H_{13}NO$) C, H, N.

3,4-Dihydro-3-(di-*n*-propylamino)-2*H*-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); ^1H 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. ($C_{15}H_{23}NO \cdot C_2H_2O_4$) C, H, N.

3,4-Dihydro-3-(di-*n*-propylamino)-2*H*-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); ^1H 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. ($C_{19}H_{25}NO \cdot HCl$) C, H, N, Cl.

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 (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-2*H*-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 [^{3}H]-8-OH-DPAT, and buspirone for nonspecific binding (NSB). 5-HT_{1B} assays used rat cortex + striatum + globuspallidus, and [^{3}H]-5-OH-tryptamine and serotonin for NSB. 5-HT_2 assays used calf frontal cortex and [^{3}H]ketanserin, and spiperone for NSB. D_1 assays used calf striatum and [^{3}H]raclopide, and haloperidol for NSB. D_2 assays used calf caudate nucleus and [^{3}H]SDZ 205-501,[42] and butaclamol for NSB. α_1 assays used calf frontal cortex and [^{3}H]prazosin, and phentolamine for NSB. α_2 assays used calf frontal cortex and [^{3}H]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 IC_{50} (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 [^{32}P]-α-ATP into [^{32}P]cAMP at the end of a 20-min incubation at 30 °C. Concentration–effect curves were analyzed using SCTFIT, a nonlinear regression computer program[43] for the calculation of maximal inhibition and IC_{50} values.

Electrophysiological Experiments. The *in vitro* recordings of the electrical activity of dorsal raphe nucleus (DRN) serotoninergic 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 serotoninergic neurons were induced to fire by adding 3 μM phenylephrine (α_1 agonist) to the superfusion milieu. When a cell was recorded it was identified as serotoninergic 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 (−)-propanolol (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 schocks ("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 exploratery 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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References

(1) Johnston, A. L.; File, S. E. 5-HT and Anxiety: Promises and Pitfalls. *Pharmacol. Biochem. Behav.* **1986**, *24*, 1467–1470.
(2) Eison, M. S. Use of Animal Models: toward Anxioselective Drugs. *Psychopathology* **1984**, *17*, 37–44.
(3) Peroutka, S. J.; Snyder, S. H. [^{3}H] Mianserin: Differential Labelling of Serotonin$_2$ and Histamin$_1$ Receptors in Rat Brain. *J. Pharmacol. Exp. Ther.* **1981**, *216*, 142–148.
(4) Glennon, R. A. Central Serotonin Receptors as Targets for Drug Research. *J. Med. Chem.* **1987**, *30*, 1–12.
(5) Fozard, J. R. 5-HT_3 Receptors and Cytotoxic Drug-induced Vomitting. *Trends Pharmacol. Sci.* **1987**, *8*, 44–45.
(6) Saxena, P. R.; Ferrari, M. D. 5-HT_1-like Receptor Agonists and the Pathophysiology of Migraine. *Trends Pharmacol. Sci.* **1989**, *10*, 200–204.
(7) Clarke, D. E.; Craig, D. A.; Fozard, J. R. The 5-HT_4 Receptor: Naughty, but Nice. *Trends Pharmacol. Sci.* **1989**, *10*, 385–386.
(8) Saxena, P. R.; Villalon, C. M. 5-Hydroxytryptamine: a Chameleon in the Heart. *Trends Pharmacol. Sci.* **1991**, *12*, 223–227.

(9) Humphrey, P. P. A.; Hartig, P.; Hoyer, D. A Proposed New Nomenclature for 5-HT Receptors. *Trends Pharmacol. Sci.* **1993**, *14*, 233–236.
(10) Pazos, A.; Palacios, J. M. Quantitative Autoradiographic Mapping of Serotonin Receptors in the Rat Brain. I. Serotonin-1 Receptors. *Brain Res.* **1985**, *346*, 205–230.
(11) Middlemis, D. N.; Fozard, J. R. 8-Hydroxy-2-(di-n-propylamino) tetralin. Discriminates between Subtypes of the 5-HT_1 Recognition Site. *Eur. J. Pharmacol.* **1983**, *90*, 151–153.
(12) Spencer, D. G., Jr.; Traber, J. The Interoceptive Discriminative Stimuli Induced by the Novel Putative Anxiolytic TVXQ 7821: Behavioral Evidence for the Specific Involvement of Serotonin 5-HT_{1A} Receptors. *Psychopharmacology* **1987**, *91*, 25–29.
(13) Abou-Gharbia, M.; Hoyer, J. A.; Patel, U.; Webb, M.; Schiehser, G.; Andree, T.; Haskins, J. T. Synthesis and Structure-Activity Relationship of Substituted Tetrahydro- and Hexahydro-1,2-benzisoxathiazol-3-one 1,1-Dioxides and Thiadiazinones: Potential Anxiolytic Agents. *J. Med. Chem.* **1989**, *32*, 1024–1033 and references cited therein.
(14) Cervo, L.; Samanin, R. Potential Antidepressant Properties of 8-Hydroxy-2-(di-n-propylamino) tetralin, a Selective Serotonin$_{1A}$ Receptor Agonist. *Eur. J. Pharmacol.* **1987**, *144*, 223–229.
(15) Macor, J. E.; Burkhart, C. A.; Heyin, J. M.; Ives, J. L.; Lebel, L. A.; Newman, M. E.; Nielsen, J. A.; Ryan, K.; Schulz, D. W.; Torgersen, K. L.; Koe, K. B. 3-(1,2,5,6-Tetrahydro-pyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one: A Potent and Selective Serotonin (5-HT_{1B}) Agonist and Rotationally Restricted Phenolic Analogue of 5-Methoxy-3-(1,2,5,6-tetrahydro-pyrid-4-yl) indole. *J. Med. Chem.* **1990**, *33*, 2087–2093 and references cited therein.
(16) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. Graphics Computed-Aided Receptor Mapping as a Predictive Tool for Drug Design: Development of Potent, Selective, and Stereospecific Ligands for the 5-HT_{1A} Receptor. *J. Med. Chem.* **1988**, *31*, 1087–1093.
(17) Cossery, J. M.; Gozlan, H.; Spampinato, U.; Perdicakis, C.; Guillaumet, G.; Pichat, L.; Hamon, M. The Selective Labelling of Central 5-HT_{1A} Receptor Binding Sites by [^{3}H]5-Methoxy-3-(di-n-propylamino) chroman. *Eur. J. Pharmacol.* **1987**, *140*, 143–155.
(18) Al Neirabeyeh, M.; Reynaud, D.; Podona, T.; Ou, L.; Perdicakis, C.; Coudert, G.; Guillaumet, G.; Pichat, L.; Gharib, A.; Sarda, N. Methoxy and Hydroxy Derivatives of 3,4-Dihydro-3-(di-n-propylamino)-2H-1-benzopyrans: New Synthesis and Dopaminergic Activity. *Eur. J. Med. Chem.* **1991**, *26*, 497–504.
(19) Lane, C. F. Selective Reductions Using Borane Complexes. *Aldrichimica Acta* **1977**, *10*, 41–51.
(20) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Fujii, M.; Ishihama, H.; Uchida, Y. Synthesis and Hypotensive Activity of Benzopyran Derivatives. *Chem. Pharm. Bull.* **1987**, *35*, 632–641.
(21) Temple, D. L.; Joseph, Y. Benzisothiazole and Benzisoxazole Piperazine Derivatives. Ger. Offen. DE 3 248 160, 1983; *Chem. Abstr.* **1983**, *99*, 195001a.
(22) Hrib, N. J.; Jurcak, J. G.; Huger, F. P.; Errico, C. L.; Dunn, R. W. Synthesis and Biological Evaluation of a Series of Substituted N-Alkoxyimides and -Amides as Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1991**, *34*, 1068–1072.
(23) Podona, T.; Lazar, S.; Coudert, G.; Guillaumet, G. Synthesis of N-(2-hydroxyethyl)iminoglutarimides from N-(2-bromoethyl)glutarimides. *Tetrahedron* **1993**, *21*, 4619–4626.
(24) McOmie, J. F. W.; West, D. E. 3,3-Dihydroxybiphenyl. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 412–414.
(25) Saxena, M.; Agarwal, K. S.; Patnaik, K. G.; Saxena, A. K. Synthesis, Biological Evaluation, and Quantitative Structure-Activity Relationship Analysis of [β-(Aroylamino)ethyl]piperazines and piperidines, and [2-[(Arylamino)carbonyl]ethyl]piperazines, -piperidines, -pyrazinopyridoindoles, and -pyrazinoisoquinolines. A New Class of Potent H_1 Antagonists. *J. Med. Chem.* **1990**, *33*, 2970–2976.
(26) Iwata, M.; Kuzuhara, H. Design and Synthesis of Macrocyclic Polyamines Composed of Natural Methylene Assays. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 198–210.
(27) (a) Al Neirabeyeh, M.; Koussini, R.; Guillaumet, G. New Direct Synthesis of 3-Nitro-2*H*-chromenes Using Nitroethylene. *Synth. Commun.* **1990**, *20*, 783–788. (b) Dauzonne, D.; Royer, R. A Convenient One-Pot Synthesis of 2-Unsubstituted 3-Nitro-2*H*-chromenes. *Synthesis* **1984**, 348–349. (c) Dauzonne, D.; Royer, R. Sur Quelques Analogues Pyranniques des Nitrobenzofurannes et des Nitronaphtofurannes. (On Some Pyranic Analogues of Nitrobenzofurans and Nitronaphthofurans.) *Eur. J. Med. Chem.* **1984**, *19*, 477–479.
(28) Sinhababu, A. K.; Borchardt, R. T. Silica-gel Assisted Reduction of Nitrostyrenes to 2-Aryl-1-nitroalkanes with Sodium Borohydride. *Tetrahedron Lett.* **1983**, *24*, 227–230.
(29) Hamacher, H. Potential Antineoplastics. Part 4. N-Mustard Derivatives of Estrone. *Arzneim.-Forsch.* **1979**, *29*, 463–466.
(30) Emerson, W. S. The Preparation of Amines by Reductive Alkylation. *Organic Reactions* **1948**, *4*, 175–244.
(31) Andersson, B.; Wikström, H.; Hallberg, A. Synthesis of 3-Dialkylaminochromans via Thallium (III)-Induced Cyclisation of Allyl Aryl Ethers. *Acta Chem. Scand.* **1990**, *44*, 1024–1028.
(32) Wise, D. L.; Dewald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Mettzer, L. T.; Pugsley, T. A. 6- and 8-Hydroxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyrans. Dopamine Agonists with Autoreceptor Selectivity. *J. Med. Chem.* **1988**, *31*, 688–691.
(33) (a) Casas, A. V.; Arechaga, S. J. Procedimiento de Preparacion de 8-[[4-(2-pirimidinil)-1-piperazinil]alquil]-8-azaspiro-[4,5]-decano-7,9-diona. (Methods of Preparation of the 8-[[4-(2-Pyrimidinyl)-1-piperazinyl]alkyl]-8-azaspiro-[4,5]-decane-7,9-diones.) Span., ES 549.014, 1986; *Chem. Abstr.* **1987**, *107*, 023360j. (b) Bilbao, J. I.; Sorolla, J. R.; Gerra, E. F. Process for the Preparation of N-(4-aminobutyl)-3,3-tetramethyleneglutarimide, Useful as a Buspirone Intermediate. Span., ES 552.060, 1987; *Chem. Abstr.* **1988**, *108*, 112254r.
(34) Prabhakaran, P. C.; Woo, N. T.; Yorgey, P. S.; Gould, S. J. Biosynthesis of Blasticidin S from L-α-arginine. Stereochemistry in the Arginine-2,3-aminomutase Reaction. *J. Am. Chem. Soc.* **1988**, *110*, 5785–5791.
(35) Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Smith, J. D.; Ismael, A. M.; Titeler, M.; Lyon, R. A. N-(Phtalimidoalkyl) Derivatives of Serotoninergic Agents: a Common Interaction at 5-HT_{1A} Serotonin Binding Sites. *J. Med. Chem.* **1989**, *32*, 1921–1926.
(36) Kidd, E. J.; Haj-Dahhane, S.; Jolas, T.; Lanfumey, L.; Fattacini, C. M.; Guardiola-Lemaitre, B.; Gozlan, H.; Hamon, M. New Methoxychroman Derivatives, 4[N-(5-Methoxychroman-3-yl)N-propylamino]butyl-8-azaspiro-(4,5)-decane-7,9-dione S20244 and its Enantiomers (+)-S20499 and (−)-S20500 with Potent Agonist Properties at Central 5-Hydroxytryptamine 1A Receptors. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 863–872.
(37) Porsolt, R.; Lenegre, A.; Caignard, D. H.; Pfeiffer, B.; Mocaer, E.; Guardiola-Lemaitre, B. Psychopharmacological Profile of a New Chroman Derivative with 5-Hydroxytryptamine 1A Agonist Properties: (+)-S20499. *Drug. Dev. Res.* **1992**, *27*, 389–402.
(38) Barrett, J. E.; Gleeson, S.; Gamble, E. H.; Zhang, L.; Guardiola-Lemaitre, B. Anticonflict and Discriminative Stimulus Effects in the Pigeon of a New Methoxy Chroman 5-HT_{1A} Agonist S20244 and its Enantiomers (+)-S20499 and (−)-S20500. *Psychopharmacology*, in press.
(39) Griebel, G.; Misslin, R.; Pawlowski, M.; Guardiola-Lemaitre, B.; Guillaumet, G.; Bizot-Espiard, J. Anxiolytic-Like Effects of a Selective 5-HT_{1A} Agonist S20244 and its Enantiomers in Mice. *Neuroreport* **1992**, *3*, 84–86.
(40) Barrett, J. E. Animal Behaviour Models in the Analysis and Understanding of Anxiolytic Drugs Activing on Serotonin Receptors. In *Animal Models in Psychopharmacology*; Olivier, B., Mos, J., Slange, J. L., Eds.; Birkauser Verlag AG: Basel, 1992; pp 37–52.
(41) Zifa, E.; Fillion, G. 5-Hydroxytryptamine Receptors. *Pharmacol. Rev.* **1992**, *44*, 401–458.
(42) Closse, A.; Frick, W.; Markstein, R.; Maurer, R.; Nordmann, R. [^{3}H] SDZ 205-501 A non Catechol Dopaminergic Agonist Labels Selectively and with High Affinity Dopamine D_2 Receptors. *J. Neural. Transm.* **1985**, *62*, 231–248.
(43) De Lean, A.; Stadel, J. M.; Lefkowitz, R. J. A Ternary Complex Model Explains the Agonist-Specific Binding Sites by [^{3}H]5-Methoxy-3-(di-n-propylamino)chroman. *Eur. J. Pharmacol.* **1987**, *140*, 143–155.
(44) Jolas, T.; Haj Dahmane, S.; Lanfumey, L.; Fattacini, C. M.; Kidd, E. J.; Adrien, J.; Gozlan, H.; Guardiola-Lemaître, B.; Hamon, M. (−)-Tertatolol is a Potent Antagonist at Pre and Postsynaptic Serotonin 5-HT_{1A} Receptors in the Brain. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1993**, *347*, 453–463.
(45) Arnt, J.; Hyttel, J. Facilitation of 8-OH-DPAT Induced Forepaw Treading of Rats by the 5-HT_2 Agonist DOI. *Eur. J. Pharmacol.* **1989**, *161*, 45–51.
(46) Berendsen, H. H. G.; Jenck, F.; Broekramp, C. L. E. Selective Activation of 5-HT_{1A} Receptors Induced Lower Lip Retraction in the Rat. *Pharmacol. Biochem. Behav.* **1989**, *33*, 821–827.