Synthesis of Novel 5-Substituted 3-Amino-3,4-dihydro-2*H*-1-benzopyran Derivatives and Their Interactions with the 5-HT_{1A} Receptor

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A series of new enantiomerically pure 3-amino-3,4-dihydro-2*H*-1-benzopyrans (3-aminochromans) has been synthesized from (*R*)- and (*S*)-5-methoxy-3-amino-3,4-dihydro-2*H*-1-benzopyran. The absolute configuration of the respective (*R*)- and (*S*)-enantiomers was deduced from X-ray crystallography of (*R*)-3-(*N*-isopropylamino)-5-methoxy-3,4-dihydro-2*H*-1-benzopyran, (*R*)-**9a**. Various 5-substituents were introduced via palladium-catalyzed carbonylation of *N*-substituted 3-amino-5-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-1-benzopyran. The effect of *N*- and 5-substitution on affinity for the 5-HT_{1A} receptor was evaluated in competition experiments using rat hippocampal membranes and [^{3}H]8-OH-DPAT as radioligand. Selected compounds were also tested for their affinity to the D_1 (rat striatum), D_2 (rat striatum), D_{2A} (human cloned), and 5-HT_{2A} (rat cortex) receptors. The intrinsic activity of the compounds was evaluated by measuring their effect on VIP-stimulated cAMP production in GH_4ZD10 cells stably transfected with the 5-HT_{1A} receptor. High-affinity compounds with high selectivity for the 5-HT_{1A} receptor were found among structures substituted with carboxylate esters, amides, and ketones in the 5-position. Primary and secondary amines bound with lower affinity than tertiary amines. Larger substituents were well-tolerated by the receptor, but the smaller *N*-ethyl-*N*-isopropyl bound with lower affinity. Generally, the (*R*)-enantiomers displayed higher affinity for the 5-HT_{1A} receptor than the corresponding (*S*)-enantiomers. In the present series of compounds, both full and partial agonists were found.

Introduction

The great success of using selective serotonin reuptake inhibitors (SSRIs) for alleviating the symptoms of depression and anxiety[1−3] has clearly demonstrated the importance of serotonergic transmission in psychiatric diseases. Even though the treatment with the new SSRIs with fewer side effects[4−6] seems at least as efficacious as the older regimen of tricyclic antidepressants, the reuptake inhibitors typically have a 3-week delay from start of treatment until a clinical effect can be observed.[7] The mechanism behind this delay is far from elucidated, but desensitization of presynaptic receptor function in order to obtain the therapeutic effect has been implicated.[8,9] Activation of the somatodendritic 5-HT_{1A} autoreceptor inhibits the firing of 5-HT from the serotonergic nerve terminals, and it can be hypothesized that the increase in synaptic serotonin has to await the functional down-regulation of the presynaptic 5-HT_{1A} receptor.

From the available data it is hard to clearly demonstrate what subtype or which subtypes of serotonergic receptors are involved in the antidepressant and anxiolytic effect of SSRIs, but the postsynaptic 5-HT_{1A} receptor has been proposed.[9,10] It has also been hypothesized that drugs acting directly on the postsynaptic 5-HT_{1A} receptor would lack the delayed onset of action and in that respect be superior to the SSRIs in treating depression and anxiety.[11]

The full elucidation of the involvement of the 5-HT_{1A} serotonergic receptor in these diseases still awaits the proper pharmacological tools. Although a number of compounds with high affinity for the 5-HT_{1A} receptor have been described in the past, few are both selective and highly efficacious at the receptor.

In this study we explored the pharmacological profile of a set of compounds structurally related to 8-OH-DPAT with the prospect of finding highly selective 5-HT_{1A} full agonists. (*R*)-8-OH-DPAT is a selective and efficacious 5-HT_{1A} agonist, but first-pass metabolism makes the compound unsuitable as a drug.[12] We have designed a series of 3-aminochromans and evaluated the structure−activity relationships by varying the substituents in the 5-position of the aromatic ring. Furthermore, the effects on potency and affinity obtained by changing the *N*-alkyl substituents were examined.

The new compounds were tested in vitro for their affinity to the 5-HT_{1A} receptor by competition experiments using rat hippocampal membranes and [^{3}H]8-OH-DPAT as radioligand. Selected compounds were also tested for their affinity to the 5-HT_{2A} (rat cortex), D_{2A} (human cloned receptor expressed in Ltk^- cells), D_1 (rat striatum), and D_2 (rat striatum) receptors. Efficacy data was obtained by measuring cAMP levels in GH_4ZD10

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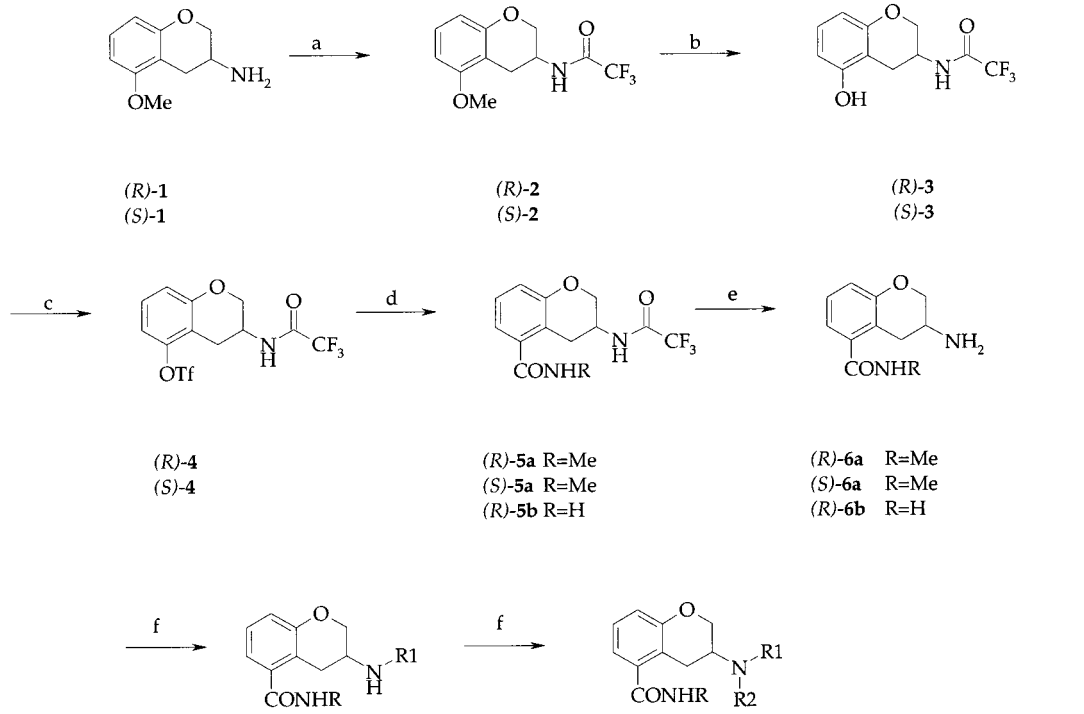
Scheme 1[a]



(R)-**1**
(S)-**1**

(R)-**2**
(S)-**2**

(R)-**3**
(S)-**3**

(R)-**4**
(S)-**4**

(R)-**5a** R=Me
(S)-**5a** R=Me
(R)-**5b** R=H

(R)-**6a** R=Me
(S)-**6a** R=Me
(R)-**6b** R=H

(R)-**7a**	R=Me R_1=cyclopentyl	*(R)*-**8a** R=Me R_1=cyclopentyl	R_2=Pr
(S)-**7a**	R=Me R_1=cyclopentyl	*(S)*-**8a** R=Me R_1=cyclopentyl	R_2=Pr
(R)-**7b**	R=Me R_1=2,2-dimethylpropyl	*(R)*-**8b** R=Me R_1=2,2-dimethylpropyl	R_2=Pr
(S)-**7b**	R=Me R_1=2,2-dimethylpropyl	*(S)*-**8b** R=Me R_1=2,2-dimethylpropyl	R_2=Pr
(R)-**7c**[g]	R=Me R_1=butyl-8-azaspiro[4.5]deca-7,9-dione	*(R)*-**8c** R=Me R_1=butyl-8-azaspiro[4.5]deca-7,9-dione	R_2=Pr
(S)-**7c**[g]	R=Me R_1=butyl-8-azaspiro[4.5]deca-7,9-dione	*(S)*-**8c** R=Me R_1=butyl-8-azaspiro[4.5]deca-7,9-dione	R_2=Pr
(R)-**7d**	R=Me R_1=2-methylpropyl	*(S)*-**8d** R=Me R_1=butyl-8-azaspiro[4.5]deca-7,9-dione	R_2=2-methylpropyl
(R)-**7e**[h]	R=H R_1=Pr	*(R)*-**8e** R=Me R_1=2-methylpropyl	R_2=Pr
(R)-**7f**	R=H R_1=^{i}Pr		

[a] Reagents: (a) trifluoroacetic acid, Et_3N, CH_2Cl_2; (b) BBr_3, CH_2Cl_2; (c) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2; (d) $Pd^{II}(OAc)_2$, dppp, CO, RNH_2; (e) NaOH, $CHCl_3$; (f) RCHO, AcOH, MeOH, $NaCNBH_3$; (g) 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione, K_2CO_3, KI, DMF; (h) 1-iodopropane, K_2CO_3, DMF.

cells stably transfected with the rat 5-HT_{1A} receptor, in the presence of vasoactive intestinal polypeptide (VIP) and test compounds.

Chemistry

The synthesis of compounds **2**−**14** is delineated in Schemes 1 and 2, and the associated physical data are presented in Table 2.

In brief, racemic (*R*/*S*)-**1**[13] was mixed with D-tartaric acid, and the precipitated salt was crystallized three times from water to give the pure (*S*)-**1**. The supernatant was made basic to isolate crude (*R*)-**1**. Addition of L-tartaric acid to (*R*)-**1** gave a salt that was crystallized as above to afford the pure (*R*)-enantiomer.

The pure enantiomers were transformed into trifluoroacetamides (*S*)-**2** and (*R*)-**2**, respectively, by reaction with trifluoroacetic anhydride in dichloromethane at low temperature. After *O*-demethylation with boron tribromide, the phenols were converted to the corresponding triflates (*R*)-**4** and (*S*)-**4**, by reaction with triflic anhydride in the presence of base. The triflate was subsequently subjected to a Pd-catalyzed carbonylation, affording the desired 5-substituent. After *N*-deacylation, the base was alkylated by reductive amination to give the *N*-alkyl-substituted derivatives. In a similar way, the enantiomerically pure (*S*)-**1** and (*R*)-**1**, respectively, were reductively alkylated to afford the desired *N*-alkyl substituents.

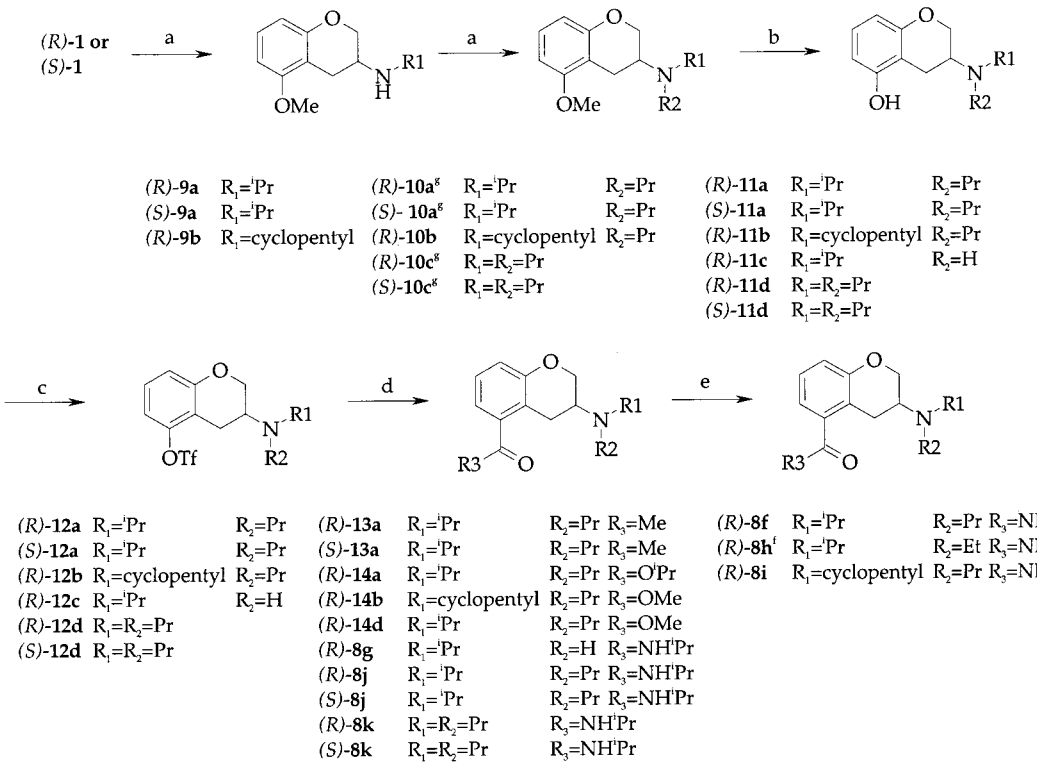
Transformation of the methyl ethers **9** and **10** to the triflate, as described above, gave access to an intermediate (**12**) from which the 5-substituent could be varied through Pd-catalyzed carbonylation reactions.

To elucidate the absolute configuration of the enantiomerically pure compound, (*R*)-**9a** was synthesized via reaction of (*R*)-**1** with acetone and sodium cyanoborohydride. After conversion of the base into the hydrochloride, (*R*)-**9a** was submitted to X-ray analysis. This assigned the series emanating from (*R*)-**1** to be of the (*R*)-configuration.

Results and Discussion

In the present series we have explored the influence of the 5-substituent and the *N*-substituents on affinity, selectivity, and efficacy at the 5-HT_{1A} receptor. From previous studies[13] it was apparent that in addition to the affinity for serotonergic receptors a dopaminergic effect resides within the class of 3-aminochromans. 8-Hydroxy-3-(*N*,*N*-dipropylamino)chroman is a potent dopamine agonist, and the corresponding 5-hydroxy-3-(*N*,*N*-dipropylamino)chroman is also endowed with a substantial affinity for the dopamine D_2 receptor.

Scheme 2[a]



[a] Reagents: (a) RCHO, AcOH, MeOH, $NaCNBH_3$; (b) BBr_3, CH_2Cl_2; (c) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2; (d) $Pd^{II}(OAc)_2$, dppp and ethyl vinyl ether or CO followed by RNH_2 or ROH; (e) NaOH followed by (i) $SOCl_2$, (ii) NH_3; (f) from (*R*)-**8g** and CH_3CHO, AcOH, MeOH, $NaCNBH_3$; (g) 1-iodopropane, K_2CO_3, DMF.

By replacing the 5-hydroxyl with a 5-carbonyl, compounds with little or no affinity for dopaminergic receptors were obtained. On the other hand, chromans substituted by amides, esters, ethers, and ketones as well as hydroxyl all retained affinity for the 5-HT_{1A} receptor, giving access to ligands with high affinity and good selectivity.

Very small effects on affinity resulted from changing the 5-substituent. The acetyl ((*R*)-**13a**), primary amide ((*R*)-**8f**), and methoxycarbonyl ((*R*)-**14d**) derivatives all have high affinity for the 5-HT_{1A} receptor. Only by increasing the steric bulk by addition of an isopropylcarboxy ester ((*R*)-**14a**) or an isopropylcarboxamide ((*R*)-**8j**) did a 50- and 15-fold, respectively, decrease in affinity result.

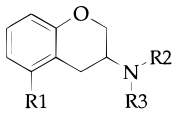
To the contrary, the substituents at the 3-position markedly influence the affinity for the 5-HT_{1A} receptor. The primary amine (*R*)-**6b** is almost devoid of 5-HT_{1A} affinity, whereas the corresponding *n*-propyl (*R*)-**7e** and isopropyl (*R*)-**7f** show a 30- and 7-fold increased affinity, respectively. By further *N*-substitution by cyclopentyl ((*R*)-**8i**) or *n*-propyl groups ((*R*)-**8f**), the affinity was additionally increased 350 and 800 times, respectively.

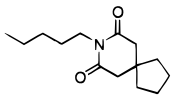
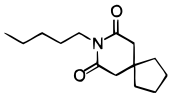
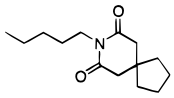
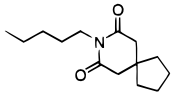
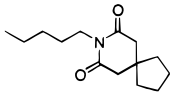
Interestingly, in the series of 5-isopropylcarboxamides, the ethyl-substituted (*R*)-**8h** shows a 25-fold reduction in its affinity for the 5-HT_{1A} receptor compared to the corresponding *n*-propyl derivative (*R*)-**8j**. In addition, the fairly low affinity of the *N*-butyl-8-azaspiro[4.5]decane-7,9-dione derivative (*R*)-**7c** is increased more than 1500-fold when an *n*-propyl group is added as in (*R*)-**8c**. These observations support the existence of a propyl pocket for the 5-HT_{1A} receptor as previously has been described for dopamine receptors.[14] The pocket available for binding seems to give restricted spatial access to the ligand since only the propyl and cyclopentyl *N*-substituents are well-tolerated and compounds with the branched 2-propyl, 2-methylpropyl, and 2,2-dimethylpropyl *N*-substitutents all lose affinity.

The stereospecific requirements for binding to the 5-HT_{1A} receptor were evaluated by preparing enantiomeric pairs of the compounds. In general, the (*R*)-enantiomers had the higher affinity with one notable exception, (*S*)-**8b**. Both enantiomers of the substituted *N*-butyl-8-azaspiro[4.5]decane-7,9-dione **8c** had high affinity for the 5-HT_{1A} receptor, and no enantioselectivity was observed. As has been reported previously for the analogous 5-fluoro-8-methoxy-2-aminotetralines[15] and 5-methoxy-3-aminochromans,[16] the substituted *N*-butyl-8-azaspiro[4.5]decane-7,9-diones were surprisingly potent 5-HT_{1A} ligands with eudismic ratios ranging from 7 to 200. In the present series of compounds, branching of the *N*-alkyl chain gave stereoselectivity favoring the (*R*)-enantiomer over the corresponding (*S*)-enantiomer. A different stereochemical preference has been reported for a number of substituted tetralins,[16] where the compounds of the opposite geometry (still (*R*)-enantiomers) have higher affinity for the 5-HT_{1A} receptor. It is notable, though, that (*S*)-tetralins substituted with a methoxycarbonyl or acetyl in the corresponding 8-position show higher affinity for the receptor than the (*R*)-enantiomers.

To test the efficacy of the new compounds, their effect on vasoactive intestinal polypeptide-induced (VIP-induced) cAMP formation was assessed in GH_4ZD10 cells expressing the rat 5-HT_{1A} receptor. The ability of the novel compounds to affect the intracellular production of cAMP was measured relative to the maximum response elicited by 5-HT and reported as efficacy. The

Table 1. Physical Data of Novel Compounds



compd	R1	R2	R3	mp (°C)	[α] (deg)	C[f]	anal.
(R)-**6b**	$CONH_2$	H	H	186−190	−36[d]	1	$C_{10}H_{12}N_2O_2$
(S)-**7c**	CONHMe		H	126 dec			$C_{24}H_{33}N_3O_4 \cdot HCl \cdot 0.5H_2O$
(R)-**7c**	CONHMe		H	126 dec	−60[d]	0.2	$C_{24}H_{33}N_3O_4 \cdot HCl \cdot 0.25H_2O$
(R)-**7e**	$CONH_2$	H	Pr	160−161	−27[d]	0.4	$C_{13}H_{18}N_2O_2$
(R)-**7f**	$CONH_2$	H	^{i}Pr	170−171	−37[d]	0.02	$C_{13}H_{18}N_2O_2$
(S)-**8a**	CONHMe	*c*-pentyl	Pr	90 dec	+98[a,e]	0.2	$C_{19}H_{28}N_2O_2 \cdot HCl \cdot 0.5H_2O$
(R)-**8a**	CONHMe	*c*-pentyl	Pr	90 dec	−96[a,e]	0.2	$C_{19}H_{28}N_2O_2 \cdot HCl \cdot 0.5H_2O$
(S)-**8b**	CONHMe	2,2-diMePr	Pr	111−113	+126[a,e]	0.2	$C_{19}H_{30}N_2O_2$
(R)-**8b**	CONHMe	2,2-diMePr	Pr	110−112	−122[a,e]	0.2	$C_{19}H_{30}N_2O_2 \cdot HCl \cdot 0.25H_2O$
(R)-**8c**	CONHMe		Pr	106 dec	−56[e]	0.3	$C_{27}H_{39}N_3O_4 \cdot HCl$
(S)-**8c**	CONHMe		Pr	105 dec	+52[e]	0.2	$C_{27}H_{39}N_3O_4 \cdot HCl \cdot 0.5H_2O$
(S)-**8d**	CONHMe		2-MePr	105 dec	+52[e]	0.2	$C_{28}H_{41}N_3O_4 \cdot HCl \cdot 0.5H_2O$
(R)-**8e**	CONHMe	2-MePr	Pr	60 dec	−15		$C_{18}H_{28}N_2O_2 \cdot HCl$
(R)-**8f**	$CONH_2$	^{i}Pr	Pr	121−122.5	−116[e]	1	$C_{16}H_{24}N_2O_2$
(R)-**8g**	CONH^{i}Pr	^{i}Pr	H	99−101	−26[e]	2.8	$C_{16}H_{24}N_2O_2$
(R)-**8h**	CONH^{i}Pr	^{i}Pr	Et	96−97	−113[e]	0.2	$C_{18}H_{28}N_2O_2$
(R)-**8i**	$CONH_2$	*c*-pentyl	Pr	121.5−122	−128[a,d]	3.8	$C_{18}H_{26}N_2O_2$
(R)-**8j**	CONH^{i}Pr	^{i}Pr	Pr	94−95.5	−87[d]	0.3	$C_{19}H_{30}N_2O_2$
(S)-**8j**	CONH^{i}Pr	^{i}Pr	Pr	94−95	+90[d]	0.3	$C_{19}H_{30}N_2O_2$
(S)-**8k**	CONH^{i}Pr	Pr	Pr	106.6−108.8	+77[d]	3.2	$C_{19}H_{30}N_2O_2$
(R)-**8k**	CONH^{i}Pr	Pr	Pr	101.4−103.0	−71[d]	0.2	$C_{19}H_{30}N_2O_2$
(R)-**10a**	OMe	^{i}Pr	Pr	108−120[b]	−96[a,d]	2.6	$C_{16}H_{25}NO_2 \cdot HCl$[c]
(S)-**10a**	OMe	^{i}Pr	Pr	91−101[b]	+96[a,d]	2.6	$C_{16}H_{25}NO_2 \cdot HCl$
(S)-**13a**	COMe	^{i}Pr	Pr	oil	+169[a,d]	0.4	oil
(R)-**13a**	COMe	^{i}Pr	Pr	142−145	−153[a,d]	2.8	$C_{17}H_{25}NO_2 \cdot HCl$
(R)-**14a**	$CO_2{}^i$Pr	^{i}Pr	Pr	153−154.4	−111[a,d]	3.2	$C_{19}H_{29}NO_3 \cdot HCl$
(R)-**14b**	CO_2Me	*c*-pentyl	Pr	oil	−128[d]	1	$C_{19}H_{27}NO_3$
(R)-**14d**	CO_2Me	^{i}Pr	Pr	125.5−127.4	−132[a,e]	1	$C_{17}H_{25}NO_3 \cdot HCl$

[a] Free base. [b] Hygroscopic. [c] C: calcd, 64.1; found, 63.5/63.5. [d] MeOH. [e] CH_2Cl_2. [f] Concn: g/100 mL.

corresponding reduction caused by the agonist 5-HT was used for comparison. Compounds reducing the formation of cAMP with 85% or more when tested alone and having no inhibitory effect when tested together with 5-HT were considered to be full agonists.

None of the compounds in the present series were found to be an antagonist. Both (*R*)- and (*S*)-isomers were agonists at the 5-HT_{1A} receptor. Interestingly, for some compounds such as **13a** and **8b** both enantiomers were full agonists.

Generally, the efficacy was higher for the (*S*)-enantiomer than for the corresponding (*R*)-enantiomer. Thus in these cases it seems like the (*S*)-enantiomers bind somewhat better to the active high-affinity agonist receptor conformation than to the low-affinity inactive conformation.

Quantitative Structure−Activity Relationships. We attempted to rationalize the affinity and efficacy of these compounds using QSAR. Thus, the program TSAR[17] was used to calculate a number of physicochemical descriptors of the compounds, reflecting their size, lipophilicity, and some electronic properties (see Table 3). The structures were imported into TSAR and converted into 3D using Corina. They were then energy-optimized using the Cosmic force field.[17] Subsequently, all the compounds were minimized using the semiempirical program VAMP[17] with the AM1 Hamiltonian. Three different substituents on the (*R*)-3-aminochroman moiety were defined in TSAR: the 5-substituent (S1) and the two *N*-alkyl groups (S2 and S3). TSAR descriptors were calculated for each of these three groups separately together with some descriptors of the complete molecule. The *N*-alkyl groups were defined such that, e.g., *N*-propyl groups were always considered as the same substituent in all the compounds (S2). The resulting data matrix was imported into Simca 7.0[18a] where further data analysis using PLS (partial least-squares) was performed. All variables were autoscaled to give each descriptor equal weighting in the PLS analysis. The model for the affinities for the (*R*)-3-aminochromans was based on a set of 33 descriptors generated by TSAR. The two (*R*)-*N*-butyl-8-azaspiro[4.5]-

Table 2. Receptor Binding Affinities (K_i)[a] and Efficacies[b] (% of maximum response by 5-HT) of Novel 3-Aminochromans

compd	K_i (nM) 5-HT$_{1A}$	5-HT$_2$	D$_{2A}$	D$_1$	efficacy (%)
(R)-**6b**	2930 ± 430	>1000	>1000	>1000	ne
(S)-**7c**	24.3 ± 4.7				82
(R)-**7c**	525 ± 28				61
(R)-**7e**	98.4 ± 7.1	>1000	>1000	>1000	42
(R)-**7f**	397 ± 25	>1000	>1000	>1000	20
(S)-**8a**	18.5 ± 2.2				110
(R)-**8a**	<0.3				70
(S)-**8b**	3.96 ± 0.57				91[c]
(R)-**8b**	31.0 ± 1.5				88
(S)-**8c**	<0.3				103
(R)-**8c**	0.34 ± 0.07				62
(S)-**8d**	2.48 ± 0.08				123
(R)-**8e**	2.37 ± 0.59	>50000			96
(R)-**8i**	<0.3	>1000	>1000	>4000	80[c]
(R)-**8g**	4300 ± 180	>10000	>1000	>1000	ne
(R)-**8h**	200 ± 25	>1000	>1000	>1000	34[c]
(R)-**8f**	0.48 ± 0.06	>1000	>50000	>1000	75
(R)-**8j**	7.77 ± 1.48	>10000	>50000	>50000	74
(S)-**8j**	1060 ± 210	>10000	>50000	>50000	ne
(R)-**10a**	3.1[e]				
(S)-**10a**	134[e]				
(S)-**13a**	11.9 ± 0.1		30100[d]		128
(R)-**13a**	0.30 ± 0.01				
(R)-**14a**	18[e]				
(R)-**14b**	0.41 ± 0.21				
(R)-**14d**	0.32 ± 0.01				128
(S)-**8k**	64[e]				95
(R)-**8k**	14.0 ± 4.3	>1000	>1000	>1000	58

[a] Values are means ± SEM of at least two experiments performed in duplicate. [b] Inhibition of VIP-stimulated cAMP production in GH$_4$ZD10 cells at 50 μM compound concentration is presented as percent (%) of the maximum response by 5-HT (efficacy). [c] Efficacy at 10 μM compound concentration. [d] Rat striatum. [e] $n = 1$, modified method using rat cortex + hippocampus; ne = no effect.

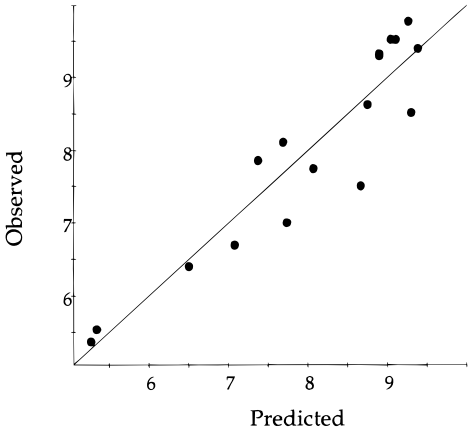


Figure 1. Predicted versus observed affinities (pK_i) at the 5-HT$_{1A}$ receptor.

decane-7,9-dione derivatives were excluded because they represent a structurally different series. This produced a PLS model with $r^2 = 0.87$ and cross-validated[18b] r^2 (q^2) = 0.78 using two significant components,[19] Figure 1.

The first component, which explains about 72% of the variance in *Y*, is mainly due to size and lipophilicity of the *N*-alkyl substituents. The major influence comes from S2, which indicates the importance of this group (Figure 3). The second component, which explains an additional 11%, is mainly related to the properties of the C-5 substituent and electronic parameters as calculated by VAMP (Figure 4). The model indicates that

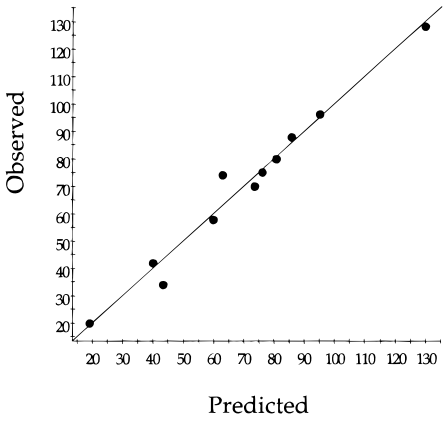


Figure 2. Predicted versus observed efficacies (%) at the 5-HT$_{1A}$ receptor.

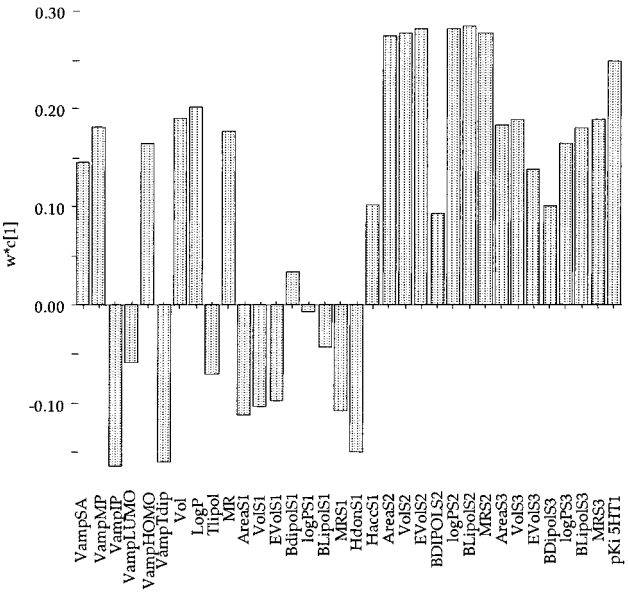


Figure 3. Loadings plot of first component.

for high affinity at the 5-HT$_{1A}$ receptor the C-5 substituents should be small and hydrophilic. In addition substituents that are only hydrogen bond acceptors should be preferred above those that are also donors, a reflection of the higher affinity of the 5-acetyl and 5-methoxycarbonyl derivatives compared to the 5-carboxamide derivatives. The model also confirms that the S2 derivative should be large and lipophilic, which is in agreement with preference of an *N*-propyl group for high-affinity binding. Preference for high-HOMO and low-LUMO energies for high-affinity binding indicates that the aromatic nucleus may be involved in a charge-transfer interaction with the receptor.

A similar model was constructed for the efficacy of the same set of (*R*)-3-aminochromans where efficacy data was available and using the same *X*-matrix. In this model the affinities of the compounds at the 5-HT$_{1A}$ receptor were also included as an *X*-variable. The resulting PLS model had a $r^2 = 0.98$ and $q^2 = 0.76$ with three significant components,[20] Figure 2. The model indicates that for high efficacy the 5-substituent should be small and preferably lipophilic and that the *N*-alkyl groups should be large and lipophilic. In addition, high 5-HT$_{1A}$ affinity also appears to be important for high efficacy.

Table 3. Methods Used To Generate Descriptors for the QSAR

calculation method	descriptor
Vamp-calculated descriptor	surface area (VampSA), mean polarizability (VampMP), ionization potential (VampIP), HOMO, LUMO, total dipole (Tdipol)
Tsar-generated descriptors of the complete molecule	volume (Vol), logP, total lipole (Tlipol), molecular refractivity (MR)
Tsar-generated descriptors for 5-substituent and the two *N*-substituents (S1, S2, S3)	surface area (AreaSX), volume (VolSX), ellipsoid volume (EvolSX), substituent bond dipole (BdipolSX), logP (logPSX), substituent bond lipole (BlipolSX), molecular refractivity (MRSX), number of H-bond acceptors (HaccS1), number of H-bond donors (HdonS1)

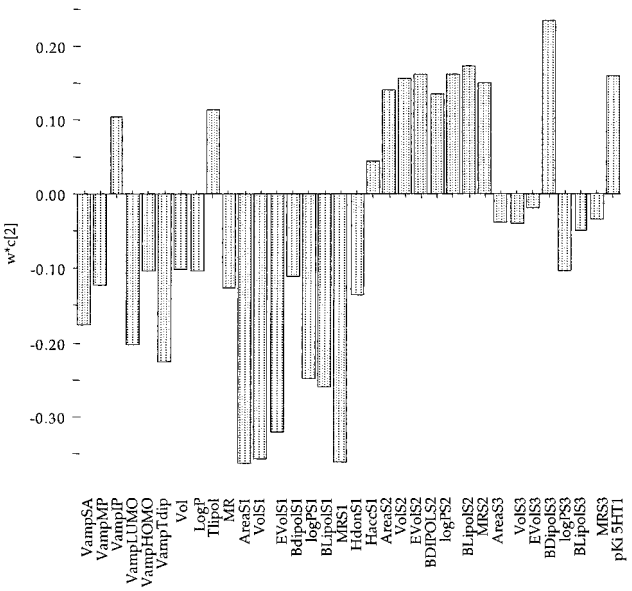


Figure 4. Loadings plot of second component.

Experimental Section

Chemistry. Melting points were determined on a Büchi SMP-20 apparatus. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Varian Unity 400 or Varian Gemini 300 instrument. Chemical shifts are given in ppm from internal standards. For ^{1}H and ^{13}C NMR spectra the internal references were tetramethylsilane (δ 0.0 ppm), $CDCl_3$ (δ 7.26 or 77.0 ppm), CD_3OD (δ 3.38 or 49.3 ppm) or DMSO-d_6 (δ 2.49 or 39.5 ppm), respectively. Coupling constants are given in Hertz, and the splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; hept, heptet; sext, sextet; oct, octet; and app, apparent. Mass spectra were obtained on a LKB 2091 (ELI, 70 eV or CI/CH_4) or Finnigan-MAT TSQ 70 (thermospray) spectrometer. Elemental analyses were performed by MIKRO KEMI AB, Uppsala, Sweden. The values were within ±0.4% of theoretical if not otherwise indicated.

(*S*)-3-Amino-3,4-dihydro-5-methoxy-2*H*-1-benzopyran [(*S*)-1]. To racemic 5-methoxy-3-amino-3,4-dihydro-2*H*-1-benzopyran (43.5 g, 0.24 mol) dissolved in MeOH (200 mL) was added D-(−)-tartaric acid (36.4 g, 0.23 mol) in H_2O. The salt was recrystallized three times from water. Finally the pure salt was added to 2 N NaOH and the aqueous phase was extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford 13.5 g (62%) of the title compound: $[\alpha]_D^{22} = +25°$ ($c = 2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.07 (t, $J = 8.1$ Hz, 1H), 6.44 (d, $J = 7.8$ Hz, 1H), 6.44 (d, $J = 7.8$ Hz, 1H), 4.46 (d, $J = 8.1$ Hz, 1H), 4.34 (br s, 1H), 4.09 (d, $J = 10.8$ Hz, 1H), 4.04 (d, $J = 10.8$ Hz, 1H), 3.84 (m, 1H), 3.81 (s, 3H), 2.87 (dd, $J = 17.3$, 5.6 Hz, 1H), 2.67 (br d, $J = 18.2$ Hz, 1H).

(*R*)-3-Amino-3,4-dihydro-5-methoxy-2*H*-1-benzopyran [(*R*)-1]: $[\alpha]_D^{22} = -21°$ ($c = 2$, CH_2Cl_2); ^{1}H NMR ((*R*)-**1**·HCl, MeOH) δ 7.12 (t, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 6.51 (d, $J = 8.3$ Hz, 1H), 4.5 (br s, 2H), 4.22 (d, $J = 10.8$ Hz, 1H), 4.14 (d, $J = 10.9$ Hz, 1H), 3.84 (m, 1H), 3.82 (s, 3H), 3.07 (dd, $J = 18.1$, 6.0 Hz, 1H), 2.80 (br d, $J = 18.1$ Hz, 1H).

***N*-((*R*)-3,4-Dihydro-5-methoxy-2*H*-1-benzopyran-3-yl)-trifluoroacetamide [(*R*)-2].** To (*R*)-**1** (2.34 g, 13.1 mmol) and pyridine (1.55 g, 19.6 mmol) in CH_2Cl_2 under nitrogen atmosphere was added trifluoroacetic anhydride (3.84 g, 18.3 mmol) dropwise at −65 °C. The mixture was stirred for 30 min while the temperature was raised to ambient temperature. The solution was washed with H_2O (25 mL) and the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The remainder was purified on a short column (SiO_2, EtOAc−hexane 2:3) affording 3.42 g (95%) of the title compound: mp 111−114 °C; $[\alpha]_D^{21} = -11°$ ($c = 2.8$, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.12 (t, $J = 8.3$ Hz, 1H), 6.63 (br s, 1H), 6.53 (d, $J = 8.2$ Hz, 1H), 6.49 (d, $J = 8.2$ Hz, 1H), 4.53 (br s, 1H), 4.19 (m, 1H), 4.07 (d, $J = 10.0$ Hz, 1H), 3.82 (s, 3H), 2.96 (dd, $J = 17.7$, 5.8 Hz, 1H), 2.80 (d, $J = 17.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.9 (q, $J_F = 38$ Hz), 154.3, 127.8, 115.6 (q, $J_F = 288$ Hz), 109.6, 107.6, 102.9, 66.8, 55.5, 42.9, 25.3; MS (EI, 70 eV) *m*/*z* 275. Anal. ($C_{12}H_{12}F_3NO_3$) C, H, N.

***N*-((*S*)-3,4-Dihydro-5-methoxy-2*H*-1-benzopyran-3-yl)-trifluoroacetamide [(*S*)-2].** As for (*R*)-**2** (76%): mp 112−113 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 7.12 (t, $J = 8.2$ Hz, 1H), 6.63 (br, 1H), 6.53 (d, $J = 8.3$ Hz, 1H), 6.49 (d, $J = 8.1$ Hz, 1H), 4.53 (br, 1H), 4.19 (m, 1H), 4.07 (d, $J = 11.0$ Hz, 1H), 3.82 (s, 3H), 2.96 (dd, $J = 18.0$, 5.9 Hz, 1H), 2.80 (d, $J = 18.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.9 (q, $J_F = 38$ Hz), 154.3, 127.8, 115.6 (q, $J_F = 288$ Hz), 109.6, 107.6, 102.9, 66.8, 55.5, 42.9, 25.3; MS (EI, 70 eV) *m*/*z* 275.

***N*-((*R*)-5-Trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)trifluoroacetamide [(*R*)-4].** To (*R*)-**2** (3.37 g, 12.2 mmol) in CH_2Cl_2 (100 mL) under nitrogen atmosphere was added boron tribromide (6.42 g, 25.6 mmol) at −75 °C. The mixture was stirred for 6 h while the temperature was raised to 0 °C. The solution was washed with saturated $NaHCO_3$ and the organic phase was dried and evaporated under reduced pressure to give 2.7 g (84%) of (*R*)-3-trifluoroacetamido-3,4-dihydro-2*H*-1-benzopyran-5-ol, (*R*)-**3**: mp 33−39 °C; $[\alpha]_D^{21} = -9.0°$ ($c = 0.1$, MeOH). To (*R*)-**3** in CH_2Cl_2 (100 mL) and under nitrogen atmosphere were added triethylamine (2.7 mL), *N*,*N*-(dimethylamino)pyridine (2 mg, cat.) and trifluoromethanesulfonic anhydride (4.17 g, 14.8 mmol) at −68 °C. The mixture was stirred for 30 min while the temperature was raised to 0 °C. The solution was washed with H_2O (25 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The remainder was purified by chromatography (SiO_2, hexanes−EtOAc 6:1) affording 2.7 g (67%) of the title compound: $[\alpha]_D^{21} = -7°$ ($c = 3.9$, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.26 (t, $J = 8.3$ Hz, 1H), 6.95 (d, $J = 7.7$ Hz, 2H), 6.58 (br d, 1H), 4.58 (m, 1H), 4.31−4.25 (m, 1H), 4.18 (d, $J = 11.4$ Hz, 1H), 3.16 (dd, $J = 17.5$, 5.5 Hz, 1H). 2.96 (d, $J = 17.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 157.1 (q, J_F=38 Hz), 155.0, 148.3, 128.7, 118.5 (q, $J_F = 320$ Hz), 117.3, 115.5 (q, $J_F = 288$ Hz), 114.3, 112.8, 67.0, 42.2, 25.6; MS (EI, 70 eV) *m*/*z* 393. Anal. ($C_{12}H_9F_6NO_5S$) H, N; C: calcd, 38.0; found, 36.8.

(*S*)-3,4-Dihydro-*N*-methyl-3-trifluoroacetamido-2*H*-1-benzopyran-5-carboxamide [(*S*)-5a]. To a solution of (*S*)-3-trifluoroacetamido-5-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-1-benzopyran, (*S*)-**4** (6 g, 15 mmol), prepared as for (*R*)-**4,** in dioxane were added palladium acetate (75 mg, 0.33 mmol), 1,3-bis(diphenylphosphino)propane (150 mg, 0.36 mmol) and methylamine (50 mL, 1 M in dioxane). The solution was transferred to a Parr flask and CO was added. The solution was shaken for 8 h at 70 °C and 1.5 atm pressure. The solvent was evaporated under reduced pressure and the remainder was purified by flash chromatography (SiO_2, EtOAc−hexane

1:1) to give 2.3 g (50%) of the title compound: mp 175−176 °C; ^{13}C NMR (DMSO-d_6) δ 169.5, 157.2 (q, J_F = 37 Hz), 154.2, 138.4, 128.0, 120.4, 116.4 (q, J_F = 288 Hz), 118.5, 66.6, 44.0, 28.4, 26.7; MS (EI, 70 eV) *m/z* (M + 1) 303. Anal. ($C_{13}H_{13}F_3N_2O_3$) C, H, N.

(*R*)-3-Trifluoroacetamido-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide [(*R*)-5b]. To a solution of (*R*)-**4** (1 g, 2.5 mmol) in dioxane (15 mL) were added palladium acetate (50 mg, 0.22 mmol), 1,3-bis(diphenylphosphino)propane (100 mg, 0.24 mmol) and dioxane saturated with ammonia (20 mL). The solution was flushed with CO and the mixture was stirred at 70 °C overnight under CO atmosphere (1 atm). The solvent was evaporated under reduced pressure and the remainder was dissolved in diethyl ether and the organic phase was washed with 2 N NH_4OH, dried and evaporated under reduced pressure. The crude material was purified by flash chromatography (SiO_2, CH_2Cl_2−EtOAc 4:1) to give after crystallization 0.25 g (34%) of the title compound: mp 178−180 °C (CH_2Cl_2−hexane); ^{1}H NMR (CD_3OD) δ 7.18 (t, *J* = 7.7 Hz, 1 H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 4.38−4.35 (m, 1H), 4.22−4.08 (m, 2H), 3.22 (dd, *J* = 17, 5 Hz, 2H), 3.03 (dd, *J* = 17, 7 Hz, 1H); ^{13}C NMR (CD_3OD) δ 174.5, 159.1(q, J_F = 37 Hz), 155.6, 138.2, 128.6, 121.1, 119.8, 118.8, 117.4 (J_F = 286 Hz), 67.5, 45.1, 29.1; MS (EI, 70 eV) *m/z* 288. Anal. ($C_{12}H_{11}F_3N_2O_3$) C, H, N.

(*R*)-3-Amino-3,4-dihydro-*N*-methyl-2*H*-1-benzopyran-5-carboxamide [(*R*)-6a]. 1,3-Bis(diphenylphosphino)propane (0.20 g, 0.49 mmol), palladium acetate (94 mg, 0.42 mmol) and methylamine (70.1 mL, 175.2 mmol) in dioxane were added to a solution of (*R*)-**4** (6.89 g, 17.5 mmol) in dioxane (50 mL). The mixture was flushed with CO and then stirred at 70 °C overnight under CO atmosphere (1 atm). The solvent was evaporated under reduced pressure and the remainder dissolved in CH_2Cl_2 (200 mL). To the organic phase was added 2 N NaOH (20 mL) and the heterogeneous system was stirred for 1 h. The organic phase was collected, dried and evaporated under reduced pressure. The remainder was purified on a short column (SiO_2, EtOAc−EtOH 1:1) affording 2.48 g (69%) of the title compound: mp 188−190 °C (EtOAc); $[\alpha]_D^{21}$ = −39° (*c* = 2.1, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.11 (br s, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.85 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.07 (ddd, *J* = 10.1, 3.5, 2.0 Hz, 1H), 3.56 (t app, *J* = 7.4 Hz, 1H), 3.07−3.01 (m, 1H), 2.91 (ddd, *J* = 15.0, 3.4, 1.6 Hz, 1H), 2.71 (d, *J* = 4.6 Hz, 3H), 2.49 (m, 3H), 1.65 (br, 2H); ^{13}C NMR (DMSO-d_6) δ 168.8, 153.8, 138.3, 126.5, 119.1, 118.8, 117.0, 70.9, 43.6, 32.3, 25.8; MS (EI, 70 eV) *m/z* 206.

(*S*)-3-Amino-3,4-dihydro-*N*-methyl-2*H*-1-benzopyran-5-carboxamide [(*S*)-6a]. To (*S*)-**5a** (2.7 g, 9.0 mmol) in $CHCl_3$ (25 mL) was added 2 N NaOH (25 mL). The two-phase system was stirred for 30 min at room temperature. The organic phase was collected, dried (Na_2SO_4), filtered and then evaporated under reduced pressure to afford 1.7 g (95%) of the title compound: mp 190−192 °C ($CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.11 (br s, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.85 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.07 (ddd, *J* = 10.1, 3.5, 2.0 Hz, 1H), 3.56 (t app, *J* = 7.4 Hz, 1H), 3.07−3.01 (m, 1H), 2.91 (ddd, *J* = 15.0, 3.4, 1.6 Hz, 1H), 2.71 (d, *J* = 4.6 Hz, 3H), 2.49 (m, 3H), 1.65 (br, 2H); ^{13}C NMR (DMSO-d_6) δ 168.8, 153.8, 138.3, 126.5, 119.1, 118.8, 117.0, 70.9, 43.6, 32.3, 25.8; MS (EI, 70 eV) *m/z* 206. Anal. ($C_{11}H_{14}N_2O_2$) C, H, N; O: calcd, 15.5; found, 16.2.

(*R*)-3-Amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide [(*R*)-6b]. The title compound was prepared from (*R*)-**5b** according to the procedure for (*S*)-**6a** (97%): mp 186−190 °C; $[\alpha]_D^{22}$ = −36° (*c* = 1, MeOH); ^{1}H NMR (CD_3OD) δ 7.13 (t, *J* = 7.7 Hz, 1 H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.18−4.14 (m, 1H), 3.78 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.30−3.12 (m, 2H), 2.70 (m, 1H), 1.89 (s, 2H); ^{13}C NMR (CD_3OD) δ 174.7, 155.7, 138.7, 128.2, 120.6, 119.6, 119.4, 71.6, 45.0, 33.0; MS (EI, 70 eV) *m/z* 192. Anal. ($C_{10}H_{12}N_2O_2$) C, H, N.

(*S*)-8-[4-[*N*-(3,4-Dihydro-5-*N*-methylcarbamoyl-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride [(*S*)-7c]. A solution of (*S*)-**6a** (1.3 g, 6.3 mmol), 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione[21] (2.5 g, 7.5 mmol), potassium iodide (50 mg, 0.30 mmol) and potassium carbonate (0.4 g, 3 mmol) in DMF was stirred at 80 °C for 40 h. The solvent was evaporated under reduced pressure and CH_2Cl_2 was added. The organic phase was extracted with 2 N HCl and the aqueous phase was rendered basic by the careful addition of 2 N NaOH. The aqueous phase was then extracted with CH_2Cl_2, the organic phase was washed with H_2O, dried, filtered and evaporated under reduced pressure. The remainder was purified by flash chromatography (SiO_2, EtOAc−EtOH 9:1) to give 1.5 g (56%) of (*S*)-**7c** as the free base. The amine was dissolved in diethyl ether and ethereal hydrogen chloride was added affording 1.5 g (50%) of the title compound: mp 126 °C (EtOAc−EtOH−diethyl ether); MS (TSP) *m/z* (M + 1) 428. Anal. ($C_{24}H_{33}N_3O_4$·HCl·$^1/_2H_2O$) C, H, N.

(*R*)-8-[4-[*N*-(3,4-Dihydro-5-*N*-methylcarbamoyl-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride [(*R*)-7c]. From (*R*)-**6a** according to the procedure for (*S*)-**7c** (36%): mp 126 °C (diethyl ether−EtOAc). Anal. ($C_{24}H_{33}N_3O_4$·HCl·0.25H_2O) C, H, N.

(*R*)-3,4-Dihydro-*N*-methyl-3-(2-methylpropylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-7d]. To a solution of (*R*)-**6a** (145 mg, 0.70 mmol), isobutyraldehyde (60 mg, 0.77 mmol) and a few drops of acetic acid in MeOH (5 mL) was added sodium cyanoborohydride (62 mg, 0.98 mmol) in portions. The solution was stirred at room temperature for 3 h when the solvent was evaporated under reduced pressure. The remainder was dissolved in diethyl ether (25 mL) and the organic phase was washed with 1 N NH_4OH (5 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, EtOAc) affording 112 mg (61%) of the title compound: mp 111−113 °C; $[\alpha]_D^{22}$ = −33° (*c* = 2.6, MeOH); ^{1}H NMR ($CDCl_3$) 7.08 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.02 (br s, 1H), 4.19 (m, 1H), 3.82 (dd, *J* = 10.4, 7.5 Hz, 1H), 3.15 (dd, *J* = 17.4, 4.1 Hz, 1H), 3.08−3.00 (m, 1H), 2.95 (d, *J* = 4.8 Hz, 3H), 2.72 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.51 (d, *J* = 6.8 Hz, 2H), 1.70 (app hept, *J* = 6.8 Hz, 1H), 1.31 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 169.9, 154.7, 137.4, 127.0, 119.2, 118.9, 118.4, 68.9, 55.3, 50.0, 30.3, 28.6, 26.5, 20.5; MS (EI, 70 eV) *m/z* 262. Anal. ($C_{15}H_{22}N_2O_2$) C, H, N.

***(R)*-3,4-Dihydro-3-(propylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-7e].** To (*R*)-**6b** (0.2 g, 1.0 mmol) in DMF (20 mL) were added potassium carbonate (0.29 g, 2.1 mmol) and 1-iodopropane (0.25 g, 1.5 mmol). The solution was stirred at room temperature for 15 h, and then the solvent was evaporated under reduced pressure. To the remainder was added diethyl ether, the organic phase was filtered, and the combined organic phase was washed with H_2O, dried and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, EtOAc−EtOH 10:1) affording after crystallization 0.10 g (41%) of the title compound: mp 160−161 °C (diethyl ether−hexane); $[\alpha]_D^{22}$ = −27° (*c* = 0.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.10 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.37 (br s, 1H), 6.21 (br s, 1H), 4.20 (d, *J* = 10.1 Hz, 1H), 3.94 (dd, *J* = 10.7, 7.0 Hz, 1H), 3.26−3.13 (m, 2H), 2.90−2.77 (m, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 1.53 (app sext, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.6, 151.7, 136.0, 127.2, 119.5, 119.1, 119.0, 68.0, 49.9, 49.0, 29.8, 23.0, 11.6; MS (EI, 70 eV) *m/z* 234. Anal. ($C_{13}H_{18}N_2O_2$) C, H, N.

(*R*)-3,4-Dihydro-3-isopropylamino-2*H*-1-benzopyran-5-carboxamide [(*R*)-7f]. From (*R*)-**6b** and acetone (3 mL) according to the procedure for (*R*)-**7d** (62%): mp 170−171 °C (diethyl ether−hexane); $[\alpha]_D^{21}$ = −37° (*c* = 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.12 (t, *J* = 7.8 Hz, 1 H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.31 (br s, 1H), 6.01 (br s, 1H), 4.19 (app d, 1H), 3.86−3.80 (m, 1H), 3.22−3.16 (m, 2H), 3.03 (app sept, 1H), 2.82−2.76 (m, 1H), 1.38 (br, 1H), 1.07 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 171.5, 154.8, 136.2, 127.1, 119.4, 119.2, 118.9, 69.3, 46.9, 45.7, 30.6, 23.4, 23.2; MS (EI, 70 eV) *m/z* 234. Anal. ($C_{13}H_{18}N_2O_2$) C, H, N.

(*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-*N*-methyl-2*H*-1-benzopyran-5-carboxamide Hydrochloride

[(*R*)-8a]). To (*R*)-**6a** (0.3 g, 1.46 mmol), cyclopentanone (0.6 g, 7.14 mmol) and AcOH (0.1 g, 1.67 mmol) in methanol (25 mL) was added sodium cyanoborohydride (0.3 g, 4.7 mmol) in portions. The mixture was stirred at room temperature overnight when the solvent was evaporated under reduced pressure. The remainder was dissolved in diethyl ether and the organic phase washed with 2 N NH_4OH, dried and evaporated under reduced pressure to give 0.37 g (93%) of (*S*)-**7a**. MeOH (30 mL), propionaldehyde (0.23 g, 4.0 mmol), AcOH (0.1 g, 1.7 mmol) and sodium cyanoborohydride (0.3 g, 4 mmol) were added in portions during 30 min and the solution was stirred overnight at room temperature. The remainder was evaporated under reduced pressure and the resulting syrup was purified by flash chromatography (SiO_2, EtOAc−hexane 1:1) to give the free base. The amine was dissolved in diethyl ether and ethereal hydrogen chloride was added to give 0.4 g (78%) of the title compound: mp 90 °C dec; $[\alpha]_D^{21} = -96°$ (c = 0.2, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.7, 1.3 Hz, 1H), 6.85 (dd, J = 8.1, 1.1 Hz, 1H), 5.81 (s, 1H), 4.26 (ddd, J = 10.3, 3.5, 2.2 Hz, 1H), 3.81 (app t, J = 10.3 Hz, 1H), 3.22 (m, 2H), 2.99 (d, J = 4.9 Hz, 3H), 2.95 (m, 2H), 2.48 (m, 2H), 1.8−1.5 (m, 4H), 1.5−1.4 (m, 6H); ^{13}C NMR ($CDCl_3$, free base) δ 170.0, 155.0, 137.7, 127.0, 120.8, 118.7, 118.4, 68.6, 61.5, 52.9, 49.6, 30.9, 30.8, 27.0, 26.6, 24.6, 24.0, 23.8, 11.6. Anal. ($C_{19}H_{28}N_2O_2$·HCl·$^1/_2H_2O$) C, H, N.

(*S*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-*N*-methyl-2*H*-1-benzopyran-5-carboxamide Hydrochloride [(*S*)-8a]. From (*S*)-**6a** according to the procedure for (*R*)-**8a** (44%): mp 90 °C; $[\alpha]_D^{21} = +98°$ (c = 0.2, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.7, 1.3 Hz, 1H), 6.85 (dd, J = 8.1, 1.1 Hz, 1H), 5.81 (s, 1H), 4.26 (ddd, J = 10.3, 3.5, 2.2 Hz, 1H), 3.81 (app t, J = 10.3 Hz, 1H), 3.22 (m, 2H), 2.99 (d, J = 4.9 Hz, 3H), 2.95 (m, 2H), 2.48 (m, 2H), 1.8−1.5 (m, 4H), 1.5−1.4 (m, 6H); ^{13}C NMR ($CDCl_3$, free base) δ 170.0, 155.0, 137.7, 127.0, 120.8, 118.7, 118.4, 68.6, 61.5, 52.9, 49.6, 30.9, 30.8, 27.0, 26.6, 24.6, 24.0, 23.8, 11.6; MS (TSP) m/z (M + 1) 317. Anal. ($C_{19}H_{28}N_2O_2$·HCl·$^1/_2H_2O$) C, H, N.

(*R*)-3,4-Dihydro-3-*N*-(2,2-dimethylpropyl-*N*-propylamino)-*N*-methyl-2*H*-1-benzopyran-5-carboxamide Hydrochloride [(*R*)-8b]). From (*S*)-**6a** and pivalylaldehyde, followed by propionaldehyde according to the procedure for (*R*)-**8a** (87%): mp 110 °C dec; $[\alpha]_D^{21} = -122°$ (c = 0.2, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 5.91 (s, 1H), 4.27 (dd, J = 10.2, 3.0 Hz, 1H), 3.79 (app t, J = 10.3 Hz, 1H), 3.09 (m, 1H), 3.0 (m, 5H), 2.57 (m, 1H), 2.43 (m, 1H), 2.30 (app q, J = 14.7 Hz, 2H), 1.44 (m, 2H), 0.85 (m, 12H); ^{13}C NMR ($CDCl_3$, free base) δ 170.1, 155.0, 137.7, 127.0, 120.8, 118.7, 118.5, 67.9, 64.1, 54.8, 54.6, 32.9, 28.3, 26.6, 25.1, 22.8, 11.6. Anal. ($C_{19}H_{30}N_2O_2$·HCl·0.25H_2O) C, H, N.

(*S*)-3,4-Dihydro-3-(*N*-2,2-dimethylpropyl-*N*-propylamino)-*N*-methyl-2*H*-1-benzopyran-5-carboxamide [(*S*)-8b]. From (*R*)-**6a** according to the procedure for (*R*)-**8a** (58%): $[\alpha]_D^{20} = +126°$ (c = 0.2, CH_2Cl_2, free base); mp (HCl salt) 111−113 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 5.91 (s, 1H), 4.27 (dd, J = 10.2, 3.0 Hz, 1H), 3.79 (app t, J = 10.3 Hz, 1H), 3.09 (m, 1H), 3.0 (m, 5H), 2.57 (m, 1H), 2.43 (m, 1H), 2.30 (app q, J = 14.7 Hz, 2H), 1.44 (m, 2H), 0.85 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 170.1, 155.0, 137.7, 127.0, 120.8, 118.7, 118.5, 67.9, 64.1, 54.8, 54.6, 32.9, 28.3, 26.6, 25.1, 22.8, 11.6; MS (TSP) m/z (M + 1) 319. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

(*R*)-8-[4-[*N*-Propyl-*N*-(3,4-dihydro-5-methylcarbamoyl-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride [(*R*)-8c]. From (*R*)-**7c** and propionaldehyde according to the procedure for (*S*)-**7d** (SiO_2, EtOAc) (48%): mp 106 °C dec; $[\alpha]_D^{21} = -56°$ (c = 0.3, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.4, 1.2, Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 5.91 (s, 1H), 4.23 (ddd, J = 10.4, 3.3, 1.6 Hz, 1H), 3.85 (app t, J = 10.4 Hz, 1H), 3.74 (t, J = 7.1 Hz, 2H), 3.1 (m, 1H), 3.0 (d, J = 4.9 Hz, 2H), 2.94 (m, 2H), 2.57 (s, 3H), 2.50 (m, 5H), 1.70 (m, 4H), 1.50 (m, 6H), 1.40 (m, 4H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, free base) δ 172.2, 170.1, 155.0, 137.7, 127.0, 120.4, 118.7, 118.4, 67.9, 53.0, 52.7, 50.4, 45.0, 39.5, 39.4, 39.3, 37.6, 26.7, 26.4, 25.9, 25.7, 24.2, 21.9, 11.7; MS (EI, 70 eV) m/z 469. Anal. ($C_{27}H_{39}N_3O_4$·HCl) C, H, N.

(*S*)-8-[4-[*N*-Propyl-*N*-(3,4-dihydro-5-methylcarbamoyl-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride [(*S*)-8c]. From (*S*)-**7c** and propionaldehyde according to the procedure for (*S*)-**7d** (66%): mp 105 °C dec; $[\alpha]_D^{23} = +52°$ (c = 0.2, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 5.91 (s, 1H), 4.23 (ddd, J = 10.4, 3.3, 1.6 Hz, 1H), 3.85 (app t, J = 10.4 Hz, 1H), 3.74 (t, J = 7.1 Hz, 2H), 3.1 (m, 1H), 3.0 (d, J = 4.9 Hz, 2H), 2.94 (m, 2H), 2.57 (s, 3H), 2.50 (m, 5H), 1.70 (m, 4H), 1.50 (m, 6H), 1.40 (m, 4H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, free base) δ 172.2, 170.0, 154.9, 137.6, 126.9, 120.3, 118.7, 118.3, 67.9, 53.0, 52.6, 50.3, 44.9, 39.4, 39.3, 37.5, 26.6, 26.3, 25.8, 25.7, 24.2, 21.8, 11.7; MS (EI, 70 eV) m/z 469. Anal. ($C_{27}H_{39}N_3O_4$·HCl·$^1/_2H_2O$) C, H, N.

(*S*)-8-[4-[*N*-(2-Methylpropyl)-*N*-(3,4-dihydro-5-methylcarbamoyl-2*H*-1-benzopyran-3-yl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione Hydrochloride [(*S*)-8d]. From (*S*)-**7c** and isobutyraldehyde according to the procedure for (*S*)-**7c** (SiO_2, EtOAc−EtOH 4:1) (25%): mp 105 °C dec; $[\alpha]_D^{23} = +52°$ (c = 0.2, CH_2Cl_2, free base); ^{1}H NMR ($CDCl_3$, free base) δ 7.08 (app t, J = 7.8 Hz, 1H), 6.91 (dd, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 8.3, 1.3 Hz, 1H), 5.91 (s, 1H), 4.23 (ddd, J = 10.1, 3.5, 1.9 Hz, 1H), 3.82 (app t, J = 10.3 Hz, 1H), 3.74 (t, J = 7.3 Hz, 2H), 3.1 (m, 1H), 3.0 (d, J = 5.0 Hz, 2H), 2.90 (m, 2H), 2.58 (s, 3H), 2.50 (m, 2H), 2.30 (m, 2H), 1.70 (m, 4H), 1.60 (m, 2H), 1.48 (m, 3H), 1.38 (m, 2H), 0.84 (dd, J = 1.6, 1.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, free base) δ 172.2, 170.1, 155.0, 137.7, 127.0, 120.5, 118.7, 118.4, 67.9, 59.4, 52.9, 50.9, 45.0, 39.5, 39.4, 37.6, 27.5, 26.6, 26.4, 25.7, 25.2, 24.2, 20.6; MS (EI, 70 eV) m/z (M + 1) 484. Anal. ($C_{28}H_{41}N_3O_4$·HCl·$^1/_2H_2O$) C, H, N.

(*R*)-3,4-Dihydro-*N*-methyl-3-(*N*-2-methylpropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxamide Hydrochloride [(*R*)-8e]. From (*R*)-**7d** and propionaldehyde according to the procedure for (*R*)-**7d** (SiO2, EtOAc−hexane 1:1) (68%): mp 60 °C dec; $[\alpha]_D^{21} = -20°$ (c = 3.4, MeOH); ^{1}H NMR (DMSO-d_6) δ 10.1 (br s, 1H), 8.31 (d, J = 3.6 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 4.57 (t, J = 11.1 Hz, 1H), 4.82−4.28 (m, 1H), 3.84 (m, 1H), 3.31−3.28 (m, 2H), 3.20−2.92 (m, 4H), 2.74 (d, J = 4.4 Hz, 3H), 2.02 (m, 1H), 1.75 (m, 2H), 0.99 (app t, J = 7.0 Hz, 6H), 0.89 (t, J = 7.7 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 168.1, 153.8, 137.3, 127.4, 120.5, 118.0, 117.7, 63.2, 62.9, 58.3, 57.9, 56.0, 55.8, 53.9, 53.0, 26.0, 24.9, 24.8, 23.5, 22.8, 20.7, 20.6, 20.5, 17.1, 16.9, 10.9; MS (EI, 70 eV) m/z 304. Anal. ($C_{18}H_{28}N_2O_2$·HCl) C, H, N.

(*R*)-3,4-Dihydro-3-(*N*-isopropylamino)-5-methoxy-2*H*-1-benzopyran [(*R*)-9a]. From (*R*)-**1** and acetone according to the procedure for (*R*)-**7d** (99%): mp 285−286 °C (HCl salt, ethyl acetate−diethyl ether); $[\alpha]_D^{22} = -32°$ (c = 2.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.06 (app t, J = 8 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.15 (m, 1H), 3.83−3.77 (m, 1H), 3.80 (s, 3H), 3.20−3.17 (m, 1H), 3.06 (app sept, J = 6.2 Hz, 1H), 2.94 (m, 1H), 2.44 (dd, J = 16.8, 7.6 Hz, 1H), 1.37 (m, 1H), 1.09 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.8, 155.7, 127.7, 110.2, 109.8, 102.7, 69.8, 56.0, 47.6, 46.2, 27.6, 24.0, 23.9; MS (EI, 70 eV) m/z 221. Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

(*S*)-3,4-Dihydro-3-(*N*-isopropylamino)-5-methoxy-2*H*-1-benzopyran [(*S*)-9a]. From (*S*)-**1** and acetone, according to the procedure for (*R*)-**7d**: mp 285−286 °C (HCl salt); $[\alpha]_D^{22} = +32°$ (c = 2.2, MeOH). Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

(*S*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-5-methoxy-2*H*-1-benzopyran Hydrochloride [(*S*)-10a]. To (*S*)-**9a** (4.8 g, 21.7 mmol) and K_2CO_3 (6.0 g, 43 mmol) in DMF (40 mL) was added 1-iodopropane (14.7 g, 87 mmol), and the mixture was stirred at 60 °C for 48 h. The solvent was evaporated under reduced pressure and to the remainder was

diethyl ether and water added. The organic phase was collected, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in diethyl ether and ethereal hydrogen chloride was added affording 4.7 g (72%) of the title compound: mp 108−120 °C; $[\alpha]_D^{22} = +96°$ ($c = 2.6$, the base, MeOH); ^{1}H NMR (free base, $CDCl_3$) δ 7.04 (t, $J = 8.2$ Hz, 1H), 6.47 (d, $J = 8.3$ Hz, 1H), 6.41 (d, $J = 8.2$ Hz, 1H), 4.18 (ddd, $J = 10.1$, 2.1, 2.1 Hz, 1H), 3.8 (s, 3H), 3.71 (app t, $J = 10.5$ Hz, 1H), 3.18−3.02 (m, 2H), 2.80 (m, 1H), 2.62−2.45 (m, 3H), 1.40 (app sext, $J = 7.4$ Hz, 2H), 1.05 (app t, $J = 6.6$ Hz, 6H), 0.85 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (of the base, $CDCl_3$) δ 158.2, 155.2, 126.9, 111.1, 109.1, 101.8, 69.2, 55.4, 50.5, 48.4, 47.8, 24.7, 24.3, 21.2, 19.7, 11.6. Anal. ($C_{16}H_{25}NO_2$·HCl) C, H, N.

(*R*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-5-methoxy-2*H*-1-benzopyran Hydrochloride [(*R*)-10a]. From (*R*)-**9a** and 1-iodopropane according to the procedure for (*S*)-**10a**: mp 108−120 °C; $[\alpha]_D^{22} = -96°$ ($c = 2.6$, the base, MeOH); ^{1}H NMR (free base, $CDCl_3$) δ 7.04 (t, $J = 8.2$ Hz, 1H), 6.47 (d, $J = 8.3$ Hz, 1H), 6.41 (d, $J = 8.2$ Hz, 1H), 4.18 (ddd, $J = 10.1$, 2.1, 2.1 Hz, 1H), 3.8 (s, 3H), 3.71 (app t, $J = 10.5$ Hz, 1H), 3.18−3.02 (m, 2H), 2.80 (m, 1H), 2.62−2.45 (m, 3H), 1.40 (app sext, $J = 7.4$ Hz, 2H), 1.05 (app t, $J = 6.6$ Hz, 6H), 0.85 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (of the base, $CDCl_3$) δ 158.2, 155.2, 126.9. 111.1, 109.1, 101.8, 69.2, 55.4, 50.5, 48.4, 47.8, 24.7, 24.3, 21.2, 19.7, 11.6. Anal. ($C_{16}H_{25}NO_2$·HCl) H, N; C: calcd, 64.1; found, 63.5.

(*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-5-methoxy-2*H*-dihydro-1-benzopyran [(*R*)-10b]. From (*R*)-**1** and cyclopentanone, followed by propanal, according to the procedure for (*R*)-**8a** (92%) (SiO_2, EtOAc−hexane 1:9): $[\alpha]_D^{21} = -80°$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.05 (t, $J = 8.0$ Hz, 1H), 6.47 (d, $J = 8.2$ Hz, 1H), 6.42 (d, $J = 8.2$ Hz, 1H), 4.25 (split d, $J = 6.9$ Hz, 1H), 3.82 (s, 3H), 3.79−3.71 (m, 1H), 3.28−3.18 (m, 2H), 2.89−2.81 (m, 1H), 2.63−2.42 (m, 3H), 1.78−1.26 (m, 10 H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.4, 155.4, 127.0, 111.2, 109.2, 101.9, 68.5, 61.7, 55.3, 52.9, 49.7, 30.8, 30.5, 24.5, 23.8, 23.7, 23.2, 11.5; MS (EI, 70 eV) *m*/*z* 289. Anal. ($C_{18}H_{27}NO_2$) C, H, N.

***(S)*-3,4-Dihydro-3-(*N*,*N*-dipropylamino)-5-methoxy-2*H*-1-benzopyran [(*S*)-10c].** From (*S*)-**1** according to the method for (*R*)-**7e** (98%): mp 147−150 °C; $[\alpha]_D^{22} = +83$ ° ($c = 2.6$, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.04 (t, $J = 8.1$ Hz, 1H), 6.47 (d, $J = 8.3$ Hz, 1H), 6.42 (d, $J = 8.1$ Hz, 1H), 4.25 (m, 1H), 3.82 (s, 3H), 3.82−3.75 (m, 1H), 3.25−3.10 (m, 1H), 2.95−2.83 (m, 1H), 2.53 (app oct, $J = 7.6$ Hz, 5H), 1.47 (app sext, $J = 7.5$ Hz, 4H), 0.88 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 162.5, 158.3, 155.3, 126.9, 109.2, 102.0, 67.8, 55.4, 53.2, 52.8, 22.5, 21.9, 11.8. Anal. ($C_{16}H_{25}NO_2$·HCl) C, H, N.

***(R)*-3,4-Dihydro-3-(*N*,*N*-dipropylamino)-5-methoxy-2*H*-1-benzopyran [(*R*)-10c].** From (*R*)-**1** according to the procedure for (*R*)-**7e** (75%): mp 151−153 °C; $[\alpha]_D^{22} = -81°$ ($c = 2.6$, MeOH). Anal. ($C_{16}H_{25}NO_2$·HCl) C, H, N.

(*R*)-3,4-Dihydro-5-hydroxy-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran [(*R*)-11a]. To (*R*)-**10a** (15.5 g, 527 mmol) in CH_2Cl_2 (100 mL) under nitrogen atmosphere was added boron tribromide (27.23 g, 110 mmol) dropwise at −60 °C and the mixture was stirred for 6 h. The temperature was raised to 0 °C and the organic phase was then washed with NH_4OH, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc 5:1) to give 12.6 g (98%) of the title compound: mp 215−222 °C dec; $[\alpha]_D^{22} = -83°$ ($c = 0.1$, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.94 (t, $J = 8.1$ Hz, 1H), 6.40 (app t, $J = 7.8$ Hz, 2H), 5.20 (s, 1H), 4.23 (m, 1H), 3.81 (t, $J = 10$ Hz, 1H), 3.25−3.18 (m, 2H), 2.98 (m, 4H), 1.47 (app q, $J = 7.6$ Hz, 2 H), 1.10 (d, $J = 9.5$ Hz, 3H), 1.08 (d, $J = 9.3$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4, 154.5, 127.2, 109.5, 108.7, 106.9, 68.7, 51.0, 49.4, 48.0, 24.4, 23.9, 20.8, 19.5, 11.6. Anal. ($C_{15}H_{23}NO_2$·HCl) C, H, N.

(*S*)-3,4-Dihydro-5-hydroxy-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran [(*S*)-11a]. From (*S*)-**10a**, according to the procedure for (*R*)-**10a** (96%): mp 208−220 °C (HCl salt, dec); $[\alpha]_D^{22} = +87°$ ($c = 0.1$, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.94 (t, $J = 8.1$ Hz, 1H), 6.40 (app t, $J = 8.2$ Hz, 2H), 5.20 (s, 1H), 4.23 (m, 1H), 3.81 (t, $J = 10$ Hz, 1H), 3.25−3.18 (m, 2H), 2.98 (m, 4H), 1.47 (app q, $J = 7.6$ Hz, 2 H), 1.10 (d, $J = 9.5$ Hz, 3H), 1.08 (d, $J = 9.3$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4, 154.5, 127.2, 109.5, 108.7, 106.9, 68.7, 51.0, 49.4, 48.0, 24.4, 23.9, 20.8, 19.5, 11.6. Anal. ($C_{15}H_{23}NO_2$·HCl) C, H, N.

(*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-5-hydroxy-2*H*-1-benzopyran [(*R*)-11b]. Demethylation of (*R*)-**10b** according to the procedure for (*R*)-**10a** (SiO_2, EtOAc−hexane 1:4→ EtOAc−hexane 1:3) (98%): $[\alpha]_D^{21} = -80°$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.95 (t, $J = 8.0$ Hz, 1H), 6.43 (d, $J = 8.2$ Hz, 1H), 6.35 (d, $J = 8.0$ Hz, 1H), 4.28 (split d, $J = 6$ Hz, 1H), 3.77 (t, $J = 10.5$ Hz, 1H), 3.33−3.19 (m, 2H), 2.85 (dd, $J = 16.2$, 5.5 Hz, 1H), 2.64 (dd, $J = 16.3$, 10.7 Hz, 1H), 2.56−2.44 (m, 2H), 1.80−1.39 (m, 10 H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.7, 154.6, 127.2, 109.8, 108.9, 106.7, 68.4, 61.7, 53.0, 49.7, 30.7, 30.5, 24.3, 23.8, 23.7, 23.2, 11.5; MS (EI, 70 eV) *m*/*z* 275. Anal. ($C_{17}H_{25}NO_2$) C, H, N.

(*R*)-3,4-Dihydro-5-hydroxy-3-(*N*-isopropylamino)-2*H*-1-benzopyran [(*R*)-11c]. Demethylation of (*R*)-**9a**·HCl according to the procedure for (*R*)-**11a** (93%): mp 177−179 °C; $[\alpha]_D^{21} = -32°$ ($c = 2.1$, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.41 (br s, 1H) 6.83 (t, $J = 8.0$ Hz, 1H), 6.36 (d, $J = 7.7$ Hz, 1H), 6.20 (d, $J = 8.2$ Hz, 1H), 4.09 (d, $J = 9.2$ Hz, 1H), 3.60 (t, $J = 8.7$ Hz, 1H), 3.07−2.95 (m, 2 H), 2.82 (dd, $J = 16.5$, 4.5 Hz, 1H), 2.24 (dd, $J = 16.5$, 8.5 Hz, 1H), 1.02 (d, $J = 6.1$ Hz, 3H), 1.01 (d, $J = 6.1$ Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 156.0, 155.1, 126.6, 108.5, 106.8, 106.6, 68.3, 46.8, 45.2, 26.6, 22.8, 22.8; MS (EI, 70 eV) *m*/*z* 207. Anal. ($C_{12}H_{17}NO_2$) C, H, N.

***(R)*-3,4-Dihydro-5-hydroxy-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran Hydrochloride [(*R*)-11d].** Demethylation of (*R*)-**10c** according to the procedure for (*R*)-**11a** (73%): $[\alpha]_D^{21} = -74°$ ($c = 0.1$, MeOH). The base was dissolved in diethyl ether and ethereal hydrogen chloride was added to afford the title compound: mp 232−234 °C; ^{1}H NMR ($CDCl_3$, free base) δ 6.93 (t, $J = 8.1$ Hz, 1 H), 6.41 (d, $J = 8.2$ Hz, 1H), 6.32 (d, $J = 7.9$ Hz, 1H), 4.29 (app d, $J = 9.8$ Hz, 1H), 3.78 (app t, $J = 10.3$ Hz, 1H), 3.22 (m, 1H), 2.93−2.82 (m, 1H), 2.63−2.46 (m, 5H), 1.47 (app sext, $J = 7.5$ Hz, 4H), 0.88 (t, $J = 7.1$ Hz, 6H); MS (EI, 70 eV) *m*/*z* 249. Anal. ($C_{15}H_{23}NO_2$·HCl) H, N; C: calcd, 63.0; found, 62.1.

***(S)*-3,4-Dihydro-5-hydroxy-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran Hydrochloride [(*S*)-11d].** Demethylation of (*S*)-**10c** according to the procedure for (*R*)-**11a**: mp 232−235 °C; $[\alpha]_D^{24} = +81°$ ($c = 0.1$, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 6.93 (t, $J = 8.1$ Hz, 1 H), 6.41 (d, $J = 8.2$ Hz, 1H), 6.32 (d, $J = 7.9$ Hz, 1H), 4.29 (app d, $J = 9.8$ Hz, 1H), 3.78 (app t, $J = 10.3$ Hz, 1H), 3.22 (m, 1H), 2.93−2.82 (m, 1H), 2.63−2.46 (m, 5H), 1.47 (app sext, $J = 7.5$ Hz, 4H), 0.88 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$, free base) δ 155.6, 154.7, 127.0, 109.6, 108.6, 106.8, 67.7, 65.9, 53.2, 52.7, 22.5, 21.6, 15.1, 11.7; MS (EI, 70 eV) *m*/*z* 249. Anal. ($C_{15}H_{23}NO_2$·HCl) C, H, N.

(*R*)-5-Trifluoromethanesulfonyloxy-3,4-dihydro-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran [(*R*)-12a]. To (*R*)-**11a** (4 g, 16 mmol) and *syn*-collidine (2.5 g, 21 mmol) in CH_2Cl_2 (100 mL) was added trifluoromethanesulfonic anhydride (5.4 g, 19 mmol) in CH_2Cl_2 (50 mL) dropwise at −70 °C. The mixture was stirred for 1 h while the temperature was raised to 0 °C. The organic phase was washed with NH_4OH, dried ($MgSO_4$) and evaporated under reduced pressure. The remainder was purified by chromatography (SiO_2, CH_2Cl_2) affording 5.2 g (85%) of the title compound, as an oil: $[\alpha]_D^{22} = -78°$ ($c = 3.8$, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16 (t, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 2H), 4.23 (m, 1H), 3.80 (t, $J = 10.5$ Hz, 1H), 3.20 (m, 1H), 3.08 (app pent, $J = 6.6$ Hz, 1H), 2.88−2.77 (m, 2H), 2.49 (app t, $J = 8.0$ Hz, 2H), 1.41 (app hext, $J = 7.2$ Hz, 2H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.05 (d, $J = 6.5$ Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1, 148.4, 127.6, 118.6 (q, $J_F = 324$ Hz), 116.5, 116.3, 112.8, 69.4, 49.6, 49.0, 47.6, 25.1, 24.1, 21.0, 19.9, 11.5; MS (EI, 70 eV) *m*/*z* 381. Anal. ($C_{16}H_{22}F_3NO_4S$) C, H, N.

(*S*)-5-Trifluoromethanesulfonyloxy-3,4-dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran [(*S*)-12a]. From (*S*)-**11a**, according to the procedure for (*R*)-**12a**: $[\alpha]_D^{21}$

= +78° (*c* = 3.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 2H), 4.23 (m, 1H), 3.80 (t, *J* = 10.5 Hz, 1H), 3.20 (m, 1H), 3.08 (app pent, *J* = 6.6 Hz, 1H), 2.88−2.77 (m, 2H), 2.49 (app t, *J* = 8.0 Hz, 2H), 1.41 (app hext, *J* = 7.2 Hz, 2H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1, 148.4, 127.6, 118.6 (q, J_F = 324 Hz), 116.5, 116.3, 112.8, 69.4, 49.6, 49.0, 47.6, 25.1, 24.1, 21.0, 19.9, 11.5. Anal. ($C_{16}H_{22}F_3NO_4S$) C, H, N.

(*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-5-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-1-benzopyran [(*R*)-12b]. From (*R*)-**11b**, according to the procedure for (*R*)-**12a** (80%) (SiO_2, CH_2Cl_2): $[\alpha]_D^{21}$ = −76° (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.14 (t, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 4.29 (d split, 1H), 3.83 (t, *J* = 10.4 Hz, 1H), 3.30−3.15 (m, 2H), 2.94 (split d, 1H), 2.75 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.49 (t, *J* = 7.7 Hz, 2H), 1.76−1.37 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.2, 148.6, 127.7, 118.7 (q, J_F= 320 Hz), 116.6, 116.4, 112.9, 68.7, 61.6, 52.0, 49.3, 30.8, 30.4, 24.4, 23.8, 11.5; MS (EI, 70 eV) *m*/*z* 407. Anal. ($C_{18}H_{24}F_3NO_4S$) C, H, N.

(*R*)-5-Trifluoromethanesulfonyloxy-3,4-dihydro-3-(*N*-isopropylamino)-2*H*-1-benzopyran [(*R*)-12c]. From (*R*)-**11c**, according to the procedure for (*R*)-**12a** (SiO_2, hexanes−EtOAc 3:2) (59%): $[\alpha]_D^{21}$ = −34° (*c* = 3.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 4.21 (m, 1H), 3.88 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.26−3.19 (m, 1H), 3.07−2.99 (m, 2H), 2.63 (dd, *J* = 16.5, 7.4 Hz, 1H), 1.09 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 155.9, 148.5, 127.7, 118.6 (q, J_F = 320 Hz), 116.6, 114.9, 113.0, 69.5, 46.2, 45.6, 27.3, 23.3; MS (EI, 70 eV) *m*/*z* 339. Anal. ($C_{13}H_{16}F_3NO_4S$) C, H, N.

***(R)*-5-Trifluoromethanesulfonyloxy-3,4-dihydro-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran [(*R*)-12d].** From (*R*)-**11d**, according to the procedure for (*R*)-**12a** (SiO_2, CH_2Cl_2) (60%): $[\alpha]_D^{24}$ = −65° (*c* = 3.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.13 (t, *J* = 8.2 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.32−4.28 (m, 1H), 3.85 (t, *J* = 10.3 Hz, 1H), 3.16−3.13 (m, 1H), 2.94−2.92 (m, 1H), 2.73 (dd, *J* = 16.5, 10.8 Hz, 1H), 2.51 (app oct, *J* = 5.9 Hz, 4H), 1.45 (app sext, *J* = 7.3 Hz, 4H), 0.88 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.1, 148.5, 127.6, 118.6 (q, J_F = 319 Hz) 116.5, 116.1, 112.8, 68.0, 52.6, 52.3, 23.1, 21.8, 11.6; MS (EI, 70 eV) *m*/*z* 381. Anal. ($C_{16}H_{22}F_3NO_4S$) C, H, N.

***(S)*-5-Trifluoromethanesulfonyloxy-3,4-dihydro-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran [(*S*)-12d].** From (*S*)-**11d**, according to the procedure for (*R*)-**12a** (70%): $[\alpha]_D^{24}$ = +64° (*c* = 3.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.13 (t, *J* = 8.2 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.32−4.28 (m, 1H), 3.85 (t, *J* = 10.3 Hz, 1H), 3.16−3.13 (m, 1H), 2.94−2.92 (m, 1H), 2.73 (dd, *J* = 16.5, 10.8 Hz, 1H), 2.51 (app oct, *J* = 5.9 Hz, 4H), 1.45 (app sext, *J* = 7.3 Hz, 4H), 0.88 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.1, 148.5, 127.6, 118.6 (q, J_F = 319 Hz) 116.5, 116.1, 112.8, 68.0, 52.6, 52.3, 23.1, 21.8, 11.6; MS (EI, 70 eV) *m*/*z* 381. Anal. ($C_{16}H_{22}F_3NO_4S$) C, H, N.

[(*R*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-yl]methyl Ketone Hydrochloride [(*R*)-13a]. To (*R*)-**12a** (1.8 g, 4.7 mmol) and triethylamine (0.95 g, 9.4 mmol) in DMF (15 mL) were added 1,3-bis(diphenylphosphino)propane (60 mg, 0.15 mmol), palladium acetate (30 mg, 0.13 mmol) and ethyl vinyl ether (2.0 g, 28 mmol) and the mixture was heated at 80 °C for 4 h. 2 N HCl (1 mL) was added and stirring was continued for 20 min. The mixture was extracted with diethyl ether, the organic phase was washed with 2 N NH_4OH, dried and evaporated under reduced pressure. The remainder was purified by flash chromatography (SiO_2, CH_2Cl_2−EtOAc 10:1) affording the base. The amine was dissolved in diethyl ether and ethereal hydrogen chloride was added affording 1.35 g (92%) of the title compound: mp 142−145 °C (diethyl ether); $[\alpha]_D^{22}$ = −153° (the base, *c* = 2.8, MeOH); ^{1}H NMR ($CDCl_3$, free base) δ 7.27 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 4.24−4.16 (m, 1H), 3.76 (t, *J* = 10.1 Hz, 1H), 3.15−2.98 (m, 4H), 2.54 (s, 3H), 2.52−2.42 (m, 2H), 1.38 (app sext, *J* = 7.3 Hz, 2H), 1.03 (t, *J* = 6.6 Hz, 6H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, free base) δ 201.1, 155.0, 138.4, 126.4, 122.3, 121.8, 120.2, 69.0, 50.6, 48.7, 47.5, 29.5, 29.2, 24.1, 20.9, 19.8, 11.4. Anal. ($C_{17}H_{25}NO_2$·HCl) C, H, N.

[(*S*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-yl]methyl Ketone [(*S*)-13a]. From (*S*)-**12a** according to the procedure for (*R*)-**13a** (78%): $[\alpha]_D^{22}$ = +169° (*c* = 0.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 4.24−4.16 (m, 1H), 3.76 (t, *J* = 9.9 Hz, 1H), 3.15−2.98 (m, 4H), 2.54 (s, 3H), 2.52−2.42 (m, 2H), 1.38 (app sext, *J* = 7.3 Hz, 2H) 1.03 (t, *J* = 6.3 Hz, 6H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.1, 155.0, 138.4, 126.4, 122.3, 121.8, 120.2, 69.0, 50.6, 48.7, 47.5, 29.5, 29.2, 24.1, 20.9, 19.8, 11.4

Isopropyl (*R*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxylate Hydrochloride [(*R*)-14a]. To (*R*)-**12a** (0.4 g, 1.0 mmol) and triethylamine (0.22 g, 2.2 mmol) in a mixture of DMF (6 mL) and 2-propanol (2 mL) were added 1,3-bis(diphenylphosphino)propane (20 mg, 0.05 mmol) and palladium acetate (8 mg, 0.04 mmol). The mixture was flushed with CO and the solution was heated at 80 °C for 7 h in CO atmosphere (1 atm). The solvents were evaporated under reduced pressure and the remainder was dissolved in diethyl ether. The organic phase was washed with 2 N NH_4OH, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting oil was purified by chromatography (SiO_2, CH_2Cl_2−EtOAc 10:1) affording the free base. The amine was dissolved in diethyl ether and ethereal hydrogen chloride was added to give after crystallization from EtOAc−diethyl ether 0.21 g (56%) of the title compound: mp 153−154 °C; $[\alpha]_D^{22}$ = −110° (*c* = 3.2, the base, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.21 (app hept, *J* = 6.2 Hz, 1H), 4.74−4.05 (br m, 4H), 3.97−3.91 (br m, 2H), 3.67−3.41 (br m, 2H), 3.20−3.11 (br m, 1H), 1.76−1.74 (br m, 2H), 1.51−1.38 (br m, 3H), 1.37 (d, *J* = 6.2 Hz, 6H), 1.01−0.83 (br m, 3H); MS (EI, 70 eV) *m*/*z* 319. Anal. ($C_{19}H_{29}NO_3$·HCl) C, H, N.

Methyl (*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-2*H*-1-benzopyran-5-carboxylate [(*R*)-14b]. From (*R*)-**12b** according to the procedure for (*R*)-**14d** (84%): (EtOAc−hexane 1:9); $[\alpha]_D^{21}$ = −128° (*c* = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.13 (app t, *J* = 7.7 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.1 Hz, 1H), 4.28 (split d, *J* = 9.9 Hz, 1H), 3.88 (s, 3H), 3.80 (app t, *J* = 9.9 Hz, 1H), 3.27−3.05 (m, 4H), 2.50 (t, *J* = 7.7 Hz, 2H), 1.80−1.37 (m, 10H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.8, 155.2, 130.8, 126.6, 124.3, 123.1, 120.8, 68.4, 61.6, 52.9, 51.8, 49.5, 30.8, 30.6, 27.9, 24.5, 23.8, 23.7, 11.5; MS (EI, 70 eV) *m*/*z* 317. Anal. ($C_{19}H_{27}NO_3$) C, H, N.

Methyl (*R*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxylate [(*R*)-14d]. To a solution of (*R*)-**12a** (4 g, 10.5 mmol) in DMF (36 mL) and MeOH (14 mL) were added palladium acetate (66 mg, 0.29 mmol), 1,3-bis-(diphenylphosphino)propane (114 mg, 0.28 mmol) and triethylamine (2.3 g, 23.1 mmol). The solution was flushed with CO and then stirred at 70 °C for 9 h under CO atmosphere (1 atm). The solvent was evaporated under reduced pressure, and the remainder was dissolved in diethyl ether. The organic phase was washed with 1 N NH_4OH, dried and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (SiO_2, CH_2Cl_2−EtOAc 10:1) to afford 2.5 g (82%) of the title compound: $[\alpha]_D^{22}$ = −132° (*c* = 3, MeOH); mp (HCl salt) 126−127 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 4.23−4.19 (m, 1H), 3.87 (s, 3H), 3.78−3.74 (m, 1H), 3.15−3.07 (m, 4H), 2.53−2.47 (m, 2H), 1.41 (m, *J* = 7.3 Hz, 2H), 1.06 (dd, *J* = 6.6, 3.8 Hz, 6H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.6, 155.0, 130.5, 126.5, 124.2, 123.0, 120.6, 69.1, 51.8, 50.6, 48.8, 47.7, 29.3, 24.3, 21.0, 19.9, 11.5; MS (EI, 70 eV) *m*/*z* 291. Anal. ($C_{17}H_{25}NO_3$) C, H, N.

(*R*)-3,4-Dihydro-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-8f]. To (*R*)-**14d** (1.65 g, 5.7 mmol) in methanol (40 mL) was added NaOH (0.25 g, 6.2 mmol) in water (12 mL), and the mixture was refluxed for 3.5 h. The solvent was evaporated under reduced pressure and the remainder was coevaporated two times with toluene. To

the crude acid was thionyl chloride (15 mL) added. The solution was refluxed for 1 h and the excess reagent was evaporated under reduced pressure. The acid chloride was coevaporated with toluene and CH_2Cl_2 (30 mL) was added. NH_3(g) was gently added during 1 min, and the mixture was stirred for 30 min. CH_2Cl_2 (50 mL) was added, and the organic phase was washed with water, dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product. The remainder was purified by chromatography (SiO_2, diethyl ether−ethyl acetate 10:1) affording after crystallization 0.21 g (58%) of the title compound (diethyl ether/hexane): mp 121−122 °C; $[\alpha]_D^{21} = -116°$ (c = 2.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.11 (t, J = 7.7 Hz, 1 H), 7.09 (d, J = 6.2 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 5.82 (br s, 2H), 4.24−4.19 (m, 1H), 3.80 (t, J = 10.3 Hz, 1H), 3.19−2.99 (m, 4H), 2.49 (m, 2H), 1.40 (m, J = 7.3 Hz, 2H), 1.04 (t, J = 6.3 Hz, 6H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 155.5, 136.9, 127.5,121.4, 119.5, 119.4, 69.9, 51.1, 49.4, 48.2, 29.0, 24.8, 21.6, 20.6, 12.1; MS (EI, 70 eV) m/z 276. Anal. ($C_{16}H_{24}N_2O_2$) C, H, N.

(*R*)-3,4-Dihydro-*N*-isopropyl-3-(*N*-isopropylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-8g]. To a solution of (*R*)-**12c** (0.95 g, 2.8 mmol) and 2-propylamine (0.83 g, 14.0 mmol) in dioxane (20 mL) were added 1,3-bis(diphenylphosphino)-propane (29 mg, 0.07 mmol) and palladium acetate (15 mg, 0.07). The solution was flushed with CO and the mixture was then heated at 75 °C for 5 h under CO atmosphere (1 atm). Diethyl ether was added and the organic phase was washed with 1 N NH_4OH (20 mL), dried and evaporated under reduced pressure. The remainder was purified on a short column (SiO_2, EtOAc−THF 1:1) affording after crystallization from hexanes 0.64 g (82%) of the title compound: mp 99−101 °C (petroleum ether 60−80); $[\alpha]_D^{21} = -26°$ (c = 2.8, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.10 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.64 (br s, 1H), 4.28−4.17 (m, 2H), 3.84 (dd, J = 10.3, 7.3 Hz, 1H), 3.20−3.13 (m, 2H), 3.03 (app sept, J = 6.2 Hz, 1H), 2.71 (dd, J = 18.1, 9.2 Hz, 1H), 1.25 (d, J = 6.6 Hz, 6 H), 1.08 (d, J = 6.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.4, 154.8, 137.8, 127.1, 119.1, 118.8, 118.3, 69.4, 47.1, 45.7, 41.7, 30.4, 23.4, 23.4, 22.8; MS (EI, 70 eV) m/z 276. Anal. ($C_{16}H_{24}N_2O_2$) C, H, N.

(*R*)-3,4-Dihydro-3-(*N*-ethyl-*N*-isopropylamino)-*N*-isopropyl-2*H*-1-benzopyran-5-carboxamide [(*R*)-8h]. From (*R*)-**8g** and acetaldehyde according to the procedure for (*R*)-**7d** (SiO_2, EtOAc−hexane 1:1) (66%): mp 96−97 °C; $[\alpha]_D^{21} = -113°$ (c = 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.08 (t, J = 7.7 Hz, 1H), 6.90 (dd, J = 7.4, 1.1 Hz, 1H), 6.85 (dd, J = 8.1, 1.1 Hz, 1H), 5.60 (d, J = 7.5 Hz, 1H), 4.25 (m, 2H), 3.81 (app t, J = 10.3 Hz, 1H), 3.18 (m, 2H), 2.94 (m, 2H), 1.25 (dd, J = 10.0, 6.0 Hz, 6H), 1.02 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 168.6, 154.9, 137.9, 127.0, 120.4, 118.5, 118.1, 69.3, 50.8, 48.8, 41.7, 39.6, 28.3, 22.8, 21.1, 19.8, 17.0; MS (EI, 70 eV) m/z 304; IR (cm^{-1}): 2975, 1690, 1489, 1458, 1242, 1188. Anal. ($C_{18}H_{28}N_2O_2$) C, H, N.

(*R*)-3-(*N*-Cyclopentyl-*N*-propylamino)-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide [(*R*)-8i]. According to (*R*)-**8f** from (*R*)-**14b** (93%) (SiO_2, EtOAc−hexane 1:9): mp 121.5−122.0 °C; $[\alpha]_D^{21} = -128°$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.11 (t, J = 7.7 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.18 (br s, 1H), 5.89 (br s, 1H), 4.28 (split d, J = 10.2 Hz, 1H), 3.81 (app t, J = 10.2 Hz, 1H), 3.27−3.10 (m, 2H), 3.02 (d, J = 9.1 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 1.77−1.36 (m, 10H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.1, 136.4, 127.0, 121.0, 119.0, 118.9, 68.5, 61.4, 52.8, 49.4, 30.8, 30.6, 27.0, 24.4, 23.8, 23.7, 11.5; MS (EI, 70 eV) m/z 302. Anal. ($C_{18}H_{26}N_2O_2$) C, H, N.

(*R*)-3,4-Dihydro-*N*-isopropyl-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-8j]. From (*R*)-**12a** according to the procedure for (*R*)-**8g** (SiO_2, EtOAc−CH_2Cl_2 1:10) (35%): $[\alpha]_D^{21} = -87°$ (c = 3.2, MeOH); mp 94−96 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (app t, J = 8.2 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.63 (br s, 1H), 4.27−4.20 (m, 2H), 3.79 (app t, J = 10.2 Hz, 1H), 3.18−2.89 (m, 4H), 2.48 (app t, J = 7.3 Hz, 2H), 1.39 (app sext, J = 7.3 Hz, 2H), 1.26 (d, J = 6.5 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.6, 154.8, 137.9, 127.0, 120.3, 118.5, 118.1, 69.3, 50.5, 48.9, 47.7, 41.7, 28.2, 24.3, 22.8, 21.0, 19.8, 11.6; MS (EI, 70 eV) m/z 318. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

(*S*)-3,4-Dihydro-*N*-isopropyl-3-(*N*-isopropyl-*N*-propylamino)-2*H*-1-benzopyran-5-carboxamide [(*S*)-8j]. As for (*R*)-**8j**: mp 94−96 °C; $[\alpha]_D^{21} = +93°$ (c = 3.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.08 (t, J = 8.2 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.63 (br s, 1H), 4.27−4.20 (m, 2H), 3.79 (app t, J = 10.5 Hz, 1H), 3.18−2.89 (m, 4H), 2.48 (app t, J = 7.3 Hz, 2H), 1.39 (app sext, J = 7.3 Hz, 2H), 1.26 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.02 (app t, J = 6.8 Hz, 3H), 0.84 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.6, 154.8, 137.9, 127.0, 120.3, 118.5, 118.1, 69.3, 50.5, 48.9, 47.7, 41.7, 28.2, 24.3, 22.8, 21.0, 19.8, 11.6. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

(*R*)-3,4-Dihydro-*N*-isopropyl-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran-5-carboxamide [(*R*)-8k]. From (*R*)-**12d** according to the procedure for (*R*)-**8g** (SiO_2, CH_2Cl_2−EtOAc 10:3) (69%): mp 100−101 °C (diethyl ether−hexane); $[\alpha]_D^{22} = -71°$ (c = 2.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.03 (t, J = 7.7 Hz, 1 Hz), 6.86 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.98 (d, J = 7.9 Hz, 1H), 4.25−4.17 (m, 2H), 3.77 (t, J = 10.2 Hz, 1H), 3.08−3.05 (m, 1H), 2.96−2.82 (m, 2H), 2.48 (app hept, J = 7.6 Hz, 4H), 1.43 (app sext, J = 7.3 Hz, 4H), 1.23 (app t, J = 6.8 Hz, 6H), 0.86 (t, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) 168.4, 154.6, 137.8, 126.7, 119.9, 118.5, 117.8, 67.6, 52.9, 52.5, 41.4, 25.8, 22.5, 21.7, 11.5; MS (EI, 70 eV) m/z 318. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N

(*S*)-3,4-Dihydro-*N*-isopropyl-3-(*N*,*N*-dipropylamino)-2*H*-1-benzopyran-5-carboxamide [(*S*)-8k]. From (*S*)-**12d** according to the procedure for (*R*)-**8g** (64%): mp 107−108 °C; $[\alpha]_D^{22} = +77°$ (c = 3.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.03 (t, J = 7.7 Hz, 1 Hz), 6.86 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.98 (d, J = 7.9 Hz, 1H), 4.25−4.17 (m, 2H), 3.77 (t, J = 10.2 Hz, 1H), 3.08−3.05 (m, 1H), 2.96−2.82 (m, 2H), 2.48 (app hept, J = 7.6 Hz, 4H), 1.43 (app sext, J = 7.3 Hz, 4H), 1.23 (t, J = 6.8 Hz, 6H), 0.86 (t, J = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 168.4, 154.6, 137.8, 126.7, 119.9, 118.5, 117.8, 67.6, 52.9, 52.5, 41.4, 25.8, 22.5, 21.7, 11.5; MS (EI, 70 eV) m/z 318. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

Determination of the Absolute Configuration of (*R*)-9a by X-ray Diffraction. An enantiomerically pure, colorless single crystal of (*R*)-**9a** ($C_{13}H_{19}NO_2$·HCl, MW = 257.76, mp 284.6−285.4 °C) showed orthorhombic ($P2_12_12_1$) symmetry with four molecules per unit cell [D_c = 1.2332(2) g cm^{-3}, F(000) = 552]. The cell dimensions, a = 7.556(1), b = 7.720(1), and c = 23.800(1) Å, were refined using θ values of 46 well-centered reflections with $24 < 2\theta < 52°$. Intensities of 1736 reflections (Cu Kα radiation, $\theta < 70°$) were collected and corrected for background, Lorentz, polarization, and absorption effects (μ = 23.8 cm^{-1}). The absorption correction was carried out by numerical integration (program STOEABS);[22] the transmission factors varied between 0.46 and 0.64.

The structure was solved by application of direct methods (SHELXS)[23] and was refined by full-matrix least-squares calculations (SHELX-76)[24] based on 1228 reflections with $I/\sigma(I) > 3$. The hydrogens were located from difference electron density ($\Delta\rho$) maps and were held riding on their parent atoms during the subsequent calculations. In the last stage of the refinement the non-hydrogen atoms were treated anisotropically, and isotropic vibration parameters were refined for the H positions. Moreover, an empirical extinction correction factor,[25] x, was refined [x = 0.030(1)] and applied on F_{calc} [$F^* = F(1 - 0.001xF^2/\sin\theta)$]. The weights of the structure factors were assumed[24] as $w = [\sigma^2(F) + 0.007F^2]^{-1}$.

The final refinement calculation (of 176 variables, using 1228 F values) was carried out twice, assuming (*R*)- and (*S*)-absolute configurations, respectively, for the chiral C(3) atom. Refinement of (*R*)-**9a** ended with R = 0.028, wR = 0.039, and wR_{tot} = 0.041, whereas that for (*S*)-**9a** converged to R = 0.044, wR = 0.061, and wR_{tot} = 0.069. The wR_{tot} values were calculated using all 1468 unique reflections. According to statistical tests of the crystallographic $wR_{(R)}/wR_{(S)}$ ratios,[25,26]

the structure model with the (*S*)-configuration can be rejected at a significance level of $\alpha \ll 10^{-10}$. The assignment of absolute configuration was also proved by the Bijvoet method,[27] i.e., by comparison of the calculated and observed Bijvoet differences X [$X = 2(I_{h,k,l} - I_{-h,-k,-l})/(I_{h,k,l} + I_{-h,-k,-l})$], determined from the structure model of (*R*)-**9a** (X_{calc}) and from carefully measured intensities of selected Friedel pair reflections (X_{obs}), respectively (Table VII, Supporting Information crystallographic data). The significant differences between corresponding *R* indexes and the very high value of estimated probability of right assignment[25,26] together with the agreement between related $X_{obs} - X_{calc}$ values clearly indicate that the studied crystal was composed of the (*R*)-**9a** enantiomer. Supporting Information crystallographic data list the atomic coordinates referring to the right (*R*)-enantiomer of compound **9a**.

Pharmacology. 1. 5-HT$_{1A}$ Receptor Binding Assay. The 5-HT$_{1A}$ receptor binding assays were performed as previously described.[28,29] In brief, male Sprague−Dawley rats (weighing 150−220 g; B&K Universal AB, Sollentuna, Sweden) were decapitated, and the hippocampi were dissected out on ice. The tissue was homogenized in 50 mM Tris-HCl (pH 7.4) containing 10 mM EDTA using an Ultra-Turrax followed by centrifugation for 10 min at 48000*g* and 5 °C. The pellet was resuspended in 50 mM Tris-HCl and centrifuged. The final pellet was frozen in sucrose (0.32 M) and stored at −70 °C. On the day of the experiment the frozen homogenate was thawed, homogenized, and suspended in Tris-HCl (50 mM), $CaCl_2$ (2 mM), $MgCl_2$ (1 mM), and $MnCl_2$ (1 mM), pH 7.4, to a final concentration of 2.5 mg original wet weight/0.5 mL. The competition experiments were carried out in duplicate using 1−2 nM [^{3}H]8-OH-DPAT (New England Nuclear, Boston, MA) and 10−12 concentrations of the test compounds at 37 °C for 45 min. The nonspecific binding was defined with 100 μM 5-HT (Sigma Chemical Co., St. Louis, MO). The radioligand and the various compounds were dissolved in ascorbic acid (final concentration 0.01%). The incubations were terminated by rapid filtration through Whatman GF/B filters and subsequent washing with cold buffer (50 mM Tris-HCl, pH 7.4) using a cell harvester (Brandel). Scintillation cocktail (Packard Ultima Gold, 4 mL) was added, and the radioactivity was determined in a Packard 2500TR liquid scintillation counter at about 50% efficiency. The binding curves were analyzed by nonlinear regression using the LIGAND program.[30] The dissociation constant (K_d) of [^{3}H]8-OH-DPAT for the 5-HT$_{1A}$ receptors, used to calculate the inhibition constants (K_i) of the various compounds, was 1.0 nM.

2. 5-HT$_{2A}$ Receptor Binding Assay. The 5-HT$_{2A}$ receptor binding assays were performed essentially as previously described.[31] In brief, male Sprague−Dawley rats (weighing 150−220 g; B&K Universal AB, Sollentuna, Sweden) were decapitated, and the cortices were dissected out on ice. The tissue was homogenized in 50 mM Tris-HCl (pH 7.7) using an Ultra-Turrax followed by centrifugation for 10 min at 48000*g* and 5 °C. The pellet was resuspended and centrifuged. The final pellet was frozen in 0.32 M sucrose and stored at −70 °C. On the day of the experiment the frozen homogenate was thawed, homogenized and suspended in 50 mM Tris-HCl (pH 7.7) to a final concentration of 2.5 mg original wet weight/2 mL. The competition experiments were carried out with 0.5−0.6 nM [^{3}H]ketanserin (New England Nuclear, Boston, MA) and 10−12 concentrations of the test compounds at 37 °C for 45 min. Nonspecific binding was defined with 10 μM methysergide (Sandoz AG, Basel, Switzerland). The various compounds were dissolved in ascorbic acid (final concentration 0.01%). The incubation was terminated, the radioactivity was determined, and the binding curves were analyzed as described for the [^{3}H]8-OH-DPAT binding assay. The dissociation constant (K_d) of [^{3}H]ketanserin for 5-HT$_{2A}$ receptors, used to calculate the inhibition constants (K_i) of the various compounds, was 0.6 nM.

3. DA D$_{2A}$ Receptor Binding Assay to Cloned DA D$_{2A}$ Receptors. The D$_{2A}$ receptor binding assays were performed as previously described[32] using human DA D$_{2A}$ receptors expressed in mouse fibroblast (Ltk$^-$) cells (obtained from Dr. O. Civelli, Vollume Institute, OR). In brief, the binding assays were carried out in duplicate in a total volume of 0.5 mL using 1.5 nM [^{3}H]raclopride (New England Nuclear, Boston, MA) and 10−12 concentrations of the test compounds. The binding reaction was initiated by the addition of membranes (0.03 mg protein) and carried out at 22 °C for 60 min. Nonspecific binding was defined with 1 μM (+)-butaclamol (Research Biochemicals Inc., Natick, MA). The radioligand and the various compounds were dissolved in ascorbic acid (final concentration 0.01%). The incubation was terminated, the radioactivity was determined, and the binding curves were analyzed as described above. The dissociation constant (K_d) of [^{3}H]raclopride for DA D$_{2A}$ receptors, used to calculate the inhibition constants (K_i) of the various compounds, was 1.2 nM.

4. DA D$_2$ Receptor Binding Assay to Rat Striatal Membranes. The DA D$_2$ receptor binding assay was performed as previously described.[32] In brief, male Sprague−Dawley rats (weighing 150−220 g; B&K Universal AB, Sollentuna, Sweden) were decapitated, and the striata were dissected out on ice and homogenized in 50 mM Tris-HCl (pH 7.7) using an Ultra-Turrax and centrifuged for 10 min at 48000*g* and 5 °C. The pellet was resuspended and centrifuged. The final pellet was suspended in 50 mM Tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.01 mM pargyline, and 0.1% ascorbic acid (pH 7.6) to a final concentration of 2.5 mg original wet weight/0.5 mL. To remove endogenous dopamine the striatal membranes were preincubated at 37 °C for 10 min. The competition experiments were carried out with 1−2 nM [^{3}H]raclopride (New England Nuclear, Boston, MA) and 10−12 concentrations of the test compounds at 25 °C for 60 min. Nonspecific binding was defined with 1 μM butaclamol. The various compounds were dissolved in ascorbic acid (final concentration 0.01%). The incubation was terminated, the radioactivity was determined, and the binding curves were analyzed as described above. The dissociation constant (K_d) of [^{3}H]raclopride for DA D$_2$ receptors, used to calculate the inhibition constants (K_i) of the various compounds, was 1.2 nM.

5. DA D$_1$ Receptor Binding Assay. The DA D$_1$ receptor binding assays were performed essentially as previously described.[16] In brief, male Sprague−Dawley rats (weighing 150−220 g; B&K Universal AB, Sollentuna, Sweden) were decapitated, and the striata were dissected out on ice, frozen in 0.32 M sucrose and stored at −70 °C. On the day of the experiment the tissue was thawed, homogenized in 50 mM Tris-HCl (pH 7.7) using an Ultra-Turrax and centrifuged for 10 min at 48000*g* and 5 °C. The pellet was resuspended and centrifuged. The final pellet was suspended in 50 mM Tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.01 mM pargyline, and 0.1% ascorbic acid (pH 7.6) to a final concentration of 1−2.5 mg original wet weight/2 mL. To remove endogenous dopamine, the striatal membranes were preincubated at 37 °C for 10 min. The competition experiments were carried out with 0.25 nM [^{3}H]SCH23390 (New England Nuclear, Boston, MA), test compounds (10−12 concentrations), and 40 nM ketanserin (to inhibit the binding to the 5-HT$_{2A}$ receptor) at 25 °C for 60 min. Nonspecific binding was defined with 1 μM flupentixol. The radioligand and the various compounds were dissolved in ascorbic acid (final concentration 0.01%). The incubation was terminated, the radioactivity was determined, and the binding curves were analyzed as described above. The dissociation constant (K_d) of [^{3}H]SCH23390 for DA D$_1$ receptors, used to calculate the inhibition constants (K_i) of the various compounds, was 0.29 nM.

6. Cyclic AMP Assay. GH_4ZD10 cells expressing 5-HT$_{1A}$ receptors were obtained from Dr. Olivier Civelli[33] (Vollum Institute for Advanced Biomedical Reseach, Oregon Health Sciences University, OR). The cells were grown and prepared as previously described.[34] Cells in passages 8−12 after arrival at AstraZeneca were used. Geneticin (G418 sulfate, 700 μg/L) was used for selection of cells expressing the 5-HT$_{1A}$ receptor.

The cAMP assays were carried out according to Dorflinger and Schonbrunn[35] with some minor modifications. Briefly, the cells were detached from the culture flasks with EBSS

supplemented with 1 mM EDTA (without Ca^{2+} and Mg^{2+}). The cells were suspended in FCS-free Ham's medium and the suspension was centrifuged at approximately 250*g* for 6 min at room temperature. The pellet was resuspended to a density of about 10^7 cells/mL in medium containing 0.01% ascorbic acid and 0.1 or 1 mM IBMX. The cells were preincubated in the above solution for 1 h at 37 °C and then diluted to a final density of $0.5-1.2 \times 10^6$ cells/mL. Aliquots (0.4 mL) of the cell suspension were added to Eppendorf tubes containing 0.1 mL of VIP (30 nM final concentration), along with the test compounds and incubated for 20 min at 37 °C. Each sample was carried out in duplicate. Reactions were stopped by placing the assay tubes in boiling water for 4 min after which the samples were transferred to ice water. The lysates were then centrifuged at 12 000 rpm for 4−5 min at 4 °C and the supernatants were stored frozen at −20 °C until analyzed.

cAMP levels were determined in triplicate according to the protein-binding method of Brown[36] and modified according to Nordstedt and Fredholm.[37] In brief, free [^{3}H]cAMP/cAMP was separated from that bound to the bovine adrenocortical protein kinase A on glass fiber filters using a semiautomatic cell harvester (Skatron AS, Tranby, Norway). Results are presented as relative "efficacy" which indicates the ratio of the effect of the test compound/maximum response of 5-HT in percent.

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Supporting Information Available: Crystal data, X-ray coordinates, bond distances, and bond angles for compound (*R*)-**9a** are available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) SIMCA 7.01; Umetri AB, Box 7960, S-907 19 Umeå, Sweden. (b) The cross-validation was performed according to the SIMCA 7.0 defaults. In short, parts of the data were kept out of the model development and subsequently predicted by the model and then compared with the actual values. This procedure is repeated until every observation has been kept out once. A component is considered significant if Q2(1.0 − PRESS (prediction error sum of squares))/SS (residual sum of squares of previous dimension) is greater than a significant limit (0.097).
(19) Coefficients for the unscaled PLS equation are: pK_i 5-HT_{1A} = 8.718 + 0.000225VampSA + 0.005979VampMP − 0.22291VampIP − 0.33964LUMO + 0.22291HOMO − 0.09746Tdipol + 0.001249Vol + 0.045927logP + 0.001181Tlipol + 0.002782MR − 0.00475AreaS1 − 0.00691VolS1 − 0.00234EVolS1 − 0.03079BdipolS1 − 0.1117logPS1 − 0.04736BLipolS1 − 0.02018MRS1 − 0.17818HdonS1 + 0.11657HaccS1 + 0.005035AreaS2 + 0.008016VolS2 + 0.007185EVolS2 + 0.38861BDIPOLS2 + 0.32498logPS2 + 0.099656BLipolS2 + 0.023759MRS2 + 0.002031AreaS3 + 0.003062VolS3 + 0.00254EVolS3 + 0.30028BDipolS3 + 0.072402logPS3 + 0.034971BLipolS3 + 0.00923MRS3
(20) Coefficients for the unscaled PLS equation are: efficacy (%) = 198.39 + 0.018238VampSA + 0.16118VampMP − 9.3313VampIP − 24.582VampLUMO + 9.3313VampHOMO − 3.5945VampTdipol + 0.028894Vol + 2.589logP − 2.7627 Tlipol + 0.07675MR − 0.044466AreaS1 − 0.060571VolS1 − 0.042385EvolS + 19.1324BdipolS1 + 1.6633ogPS1 + 2.3455BLipolS1 − 0.18716MRS1 − 13.607HdonS1 + 13.607HaccS1 + 0.087237AreaS2 + 0.13152VolS2 + 0.13591EVolS2 − 9.6552DIPOLS2 + 6.1673logPS2 + 1.9331BLipolS2 + 0.42296MRS2 + 0.04363AreaS3 + 0.065729VolS3 + 0.075185EVolS3 − 2.0062 BDipolS3 + 2.746logPS3 + 0.53758BLipolS3 + 0.17887MRS3 + 2.4736pK_i 5-HT_{1A}.
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