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Synthesis and Pharmacology of the Enantiomers of the Potential Atypical Antipsychotic Agents 5-OMe-BPAT and 5-OMe-(2,6-di-OMe)-BPAT

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Abstract—The optically pure enantiomers of the potential atypical antipsychotic agents 5-methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin (5-OMe-BPAT, **5**) and 5-methoxy-2-{*N*-[2-(2,6-dimethoxy)benzamidoethyl]-*N*-*n*-propylamino}tetralin [5-OMe-(2,6-di-OMe)-BPAT, **6**] were synthesized and evaluated for their in vitro binding affinities at α_1-, α_2-, and β-adrenergic, muscarinic, dopamine D_1, D_{2A}, and D_3, and serotonin 5-HT_{1A} and 5-HT_2 receptors. In addition, their intrinsic efficacies at serotonin 5-HT_{1A} receptors were established in vitro. (*S*)- and (*R*)-**5** had high affinities for dopamine D_{2A}, D_3, and serotonin 5-HT_{1A} receptors, moderate affinities for α_1-adrenergic and serotonin 5-HT_2 receptors, and no affinity ($K_i > 1000$ nM) for the other receptor subtypes. (*S*)- and (*R*)-**6** had lower affinities for the dopamine D_{2A} and the serotonin 5-HT_{1A} receptor, compared to (*S*)- and (*R*)-**5**, and hence showed some selectivity for the dopamine D_3 receptor. The interactions with the receptors were stereospecific, since the serotonin 5-HT_{1A} receptor preferred the (*S*)-enantiomers, while the dopamine D_{2A} and D_3 receptors preferred the (*R*)-enantiomers of **5** and **6**. The intrinsic efficacies at the serotonin 5-HT_{1A} receptor were established by measuring their ability to inhibit VIP-induced cAMP production in GH_4ZD10 cells expressing serotonin 5-HT_{1A} receptors. Both enantiomers of **5** behaved as full serotonin 5-HT_{1A} receptor agonists in this assay, while both enantiomers of **6** behaved as weak partial agonists. The potential antipsychotic properties of (*S*)- and (*R*)-**5** were evaluated by establishing their ability to inhibit *d*-amphetamine-induced locomotor activity in rats, while their propensity to induce extrapyramidal side-effects (EPS) in man was evaluated by determining their ability to induce catalepsy in rats. Whereas (*R*)-**5** was capable of blocking *d*-amphetamine-induced locomotor activity, indicative of dopamine D_2 receptor antagonism, (*S*)-**5** even enhanced the effect of *d*-amphetamine, suggesting that this compound has dopamine D_2 receptor-stimulating properties. Since both enantiomers also were devoid of cataleptogenic activity, they are interesting candidates for further exploring the dopamine D_2/serotonin 5-HT_{1A} hypothesis of atypical antipsychotic drug action.

Introduction

The outcome of both preclinical and clinical investigations suggest that compounds which combine serotonin 5-HT_{1A} receptor agonism with dopamine D_2 receptor antagonism may have potential as atypical antipsychotic agents. In preclinical behavioural and neurochemical models selective serotonin 5-HT_{1A} receptor agonists have been shown to interact with antipsychotic agents. For example, several selective serotonin 5-HT_{1A} receptor agonists, including 8-hydroxy-2-(*N*,*N*-*n*-dipropylamino)tetralin (8-OH-DPAT), flesinoxan, buspirone, ipsapirone and gepirone, have consistently been shown to reverse catalepsy induced by dopamine D_2 receptor antagonists, such as haloperidol and raclopride, in rats[1–8] and monkeys.[9,10] Furthermore, 8-OH-DPAT has been shown to possess antipsychotic-like properties[11,12] and to enhance the antipsychotic properties of raclopride in animal models with predictive value for antipsychotic activity.[6] Interestingly, the standard atypical antipsychotic agent clozapine was recently shown to behave as partial serotonin 5-HT_{1A} receptor agonist in vivo,[13] a feature which may contribute to its unique clinical profile. In addition, several clinical observations suggest a role for the serotonin 5-HT_{1A} receptor in schizophrenia. First, post-mortem studies on the brains

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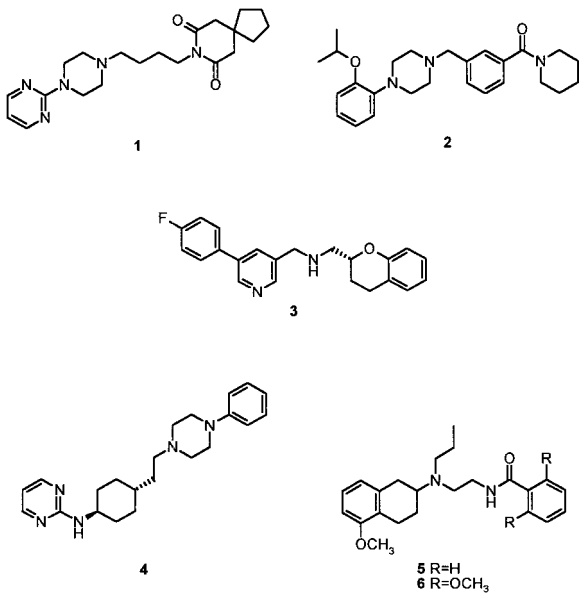


Chart 1.

of schizophrenic patients have revealed increased densities of serotonin 5-HT_{1A} receptors in the frontal cortex, which were unrelated to the medication history of the patients.[14–17] Second, clinical studies with buspirone (**1**, Chart 1), a compound with mixed dopamine D_2 receptor antagonistic and partial serotonin 5-HT_{1A} receptor agonistic properties,[18] suggest that it may have an atypical antipsychotic profile.[19–23] Finally, it has been suggested that a serotonin 5-HT_{1A} receptor agonistic component may be beneficial in relieving the anxiety that can trigger psychotic episodes in schizophrenics.[24] Several promising compounds with the indicated pharmacological profile, including mazapertine (**2**),[25] EMD 128130 (**3**),[26,27] and PD 158771 (**4**),[28] have recently been reported.

In a previous report, we have disclosed a new class of compounds with mixed dopamine D_2, D_3, and serotonin 5-HT_{1A} receptor binding properties.[29] The lead compound of this series, 5-methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin (5-OMe-BPAT, **5**), had high affinities for all three receptor subtypes, while its 2,6-dimethoxy substituted analogue, 5-methoxy-2-{*N*-[2-(2,6-dimethoxy)benzamidoethyl]-*N*-*n*-propylamino}tetralin [5-OMe-(2,6-di-OMe)-BPAT, **6**], showed some preference for the dopamine D_3 receptor. The basic skeleton for the series was conceived by combining the structural, and hence pharmacological features of the *N*,*N*-di-*n*-propyl-substituted 2-aminotetralins (DPATs) and the 2-pyrrolidinylmethyl-derived class of substituted benzamides into one structural hybrid. Since both classes of compounds display highly stereoselective pharmacological properties, it may be expected that the enantiomers of the 2-aminotetralin-derived benzamides will also behave differently. Herein we report the synthesis, the receptor binding profiles, and the intrinsic efficacies at serotonin 5-HT_{1A} receptors of the enantiomers of **5** and **6**. In addition, the enantiomers of **5** were evaluated for their potential antipsychotic activity and side-effect liability in vivo.

Chemistry

The synthetic route employed to obtain the enantiomers of **5** and **6** is outlined in Scheme 1. As starting points served optically pure (*S*)- and (*R*)-5-methoxy-2-aminotetralin, (*S*)- and (*R*)-**7**, which were treated with propionyl chloride in the biphasic medium sodium hydroxide/dichloromethane, according to the Schotten–Baumann procedure. The resulting propionamides, (*S*)- and (*R*)-**8**, were reduced with $LiAlH_4$ in boiling THF to give the *N*-*n*-propyl analogues (*S*)- and (*R*)-**9**, respectively. *N*-Alkylation with bromoacetonitrile in boiling acetone, employing K_2CO_3 as a base, gave the corresponding *N*-cyanomethyl analogues (*S*)- and (*R*)-**10**. Reduction of the nitriles with $LiAlH_4$ in boiling THF resulted in the corresponding primary amine derivatives (*S*)- and (*R*)-**11**, respectively. Finally, acylation of (*S*)- and (*R*)-**11** with the appropriately substituted benzoyl chloride in the biphasic medium sodium hydroxide/dichloromethane, according to the Schotten–Baumann procedure, gave the pure enantiomers of **5** and **6**.

Pharmacology

The enantiomers of **5** and **6** were evaluated in the following in vitro receptor binding assays: α_1-, α_2-, and

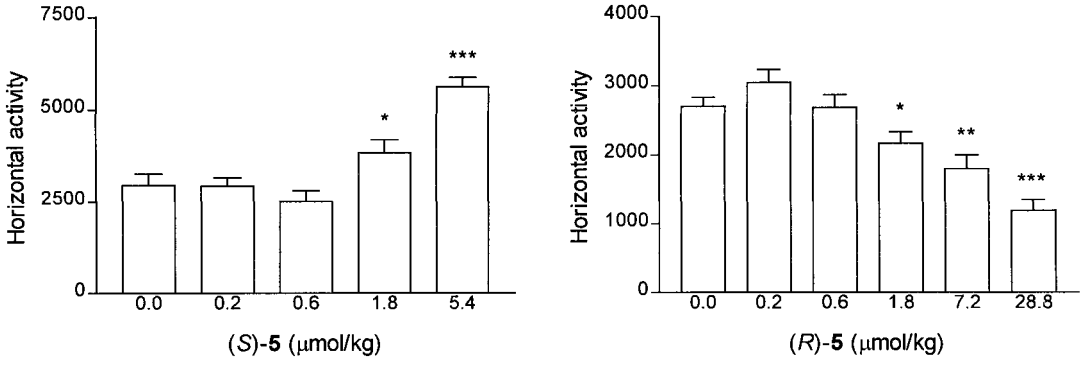
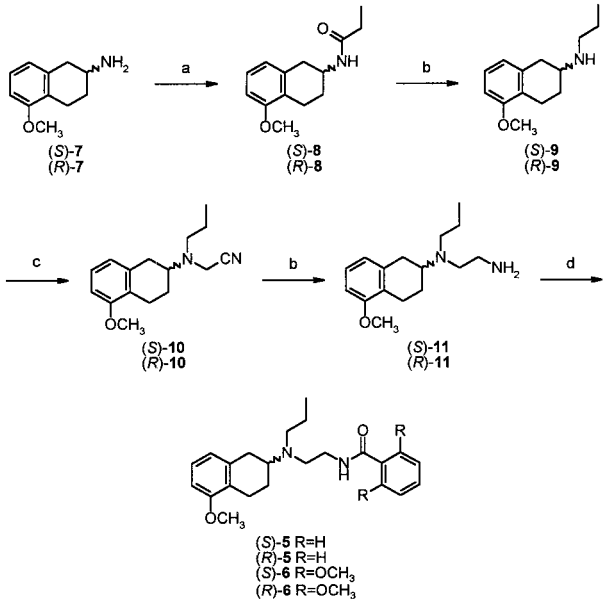


Figure 1. Dose-dependent effects (mean + SEM, $n = 7$-12; $^{**}p < 0.05$; $^{***}p < 0.01$; $^{***}px < 0.001$) of the enantiomers of **5** on *d*-amphetamine-induced locomotor activity in rats.



Scheme 1. Reagents and conditions: (a) propionyl chloride, 10% NaOH, CH_2Cl_2, rt; (b) $LiAlH_4$, THF, Δ; (c) $BrCH_2CN$, K_2CO_3, KI, acetone, Δ; (d) ArCOCl, 10% NaOH, CH_2Cl_2, rt.

β-adrenergic, muscarinic, dopamine D_1, D_{2A}, and D_3, and serotonin 5-HT_{1A} and 5-HT_2. The results of these binding studies are shown in Table 1. For comparison purposes, the previously reported affinities of racemic **5** and **6** for dopamine D_{2A}, D_3, and serotonin 5-HT_{1A} receptors,[29] as well as the receptor binding data of six reference antipsychotic agents, which were evaluated under the same assay conditions and have been previously reported by Hacksell et al.,[30] have been included. In addition, the intrinsic efficacies of the compounds at serotonin 5-HT_{1A} receptors were determined in vitro, by testing the ability of the compounds to inhibit VIP-induced cAMP production in GH_4ZD10 cells expressing serotonin 5-HT_{1A} receptors.[31] Potential antipsychotic activity of the enantiomers of **5** was determined by testing the ability of the compounds to inhibit *d*-amphetamine-induced locomotor activity in rats, while their EPS liability was established by measuring their ability to induce catalepsy in rats.

Results and Discussion

The optically pure enantiomers of 5-methoxy-2-aminotetralin, (−)-**7** and (+)-**7**, served as starting materials for the synthesis of the desired end products. These compounds are known to possess the absolute (*S*)- and (*R*)-configuration at the C2 carbon atom, respectively.[32] In view of the reaction conditions employed during the various synthetic steps, it is unlikely that inversion of stereochemistry has taken place. Therefore it is safe to assume that (−)-**5** and (−)-**6** have the (*S*)-configuration, while (+)-**5** and (+)-**6** have the (*R*)-configuration at the C2 carbon atom.

The results of the receptor binding studies (Table 1) show that both enantiomers of **5** bind with high affinities to dopamine D_{2A} and D_3, as well as to serotonin 5-HT_{1A} receptors. In addition, both compounds have moderate affinities for α_1-adrenergic and serotonin 5-HT_2 receptors, and no affinity for α_2- and β-adrenergic, dopamine D_1, and muscarinic receptors. The enantiomers of **6** bind weakly to α_1-adrenergic and serotonin 5-HT_2 receptors, and like (*S*)- and (*R*)-**5**, have no affinity for α_2- and β-adrenergic, dopamine D_1, and muscarinic receptors. Furthermore, (*S*)- and (*R*)-**6** have somewhat lower affinities for the dopamine D_{2A} and serotonin 5-HT_{1A} receptors than (*S*)- and (*R*)-**5**, and hence, in consistency with racemic **5**, show a certain selectivity for the dopamine D_3 receptor. As anticipated, the enantiomers of both **5** and **6** display stereoselectivity in their receptor binding properties, although the absolute differences between the affinities of the two pairs of enantiomers are not large. Nevertheless, the (*S*)-enantiomers, when compared to their optical antipodes, have the highest affinities for the serotonin 5-HT_{1A} receptor, while the (*R*)-enantiomers are preferred by the dopamine D_{2A} and D_3 receptors.

Remoxipride has the cleanest receptor binding profile of the reference antipsychotic agents: it has moderate affinity for dopamine D_{2A} receptors only, and is inactive at the other receptor subtypes. All other reference compounds have high affinities for α_1-adrenergic and serotonin 5-HT_2 receptors. In addition, chlorpromazine,

Table 1. Receptor binding data (K_i values in nM)[a] of the racemates and enantiomers of **5** and **6**, and six reference antipsychotic agents[b]

Compound	D_1	D_{2A}	D_3	α_1	α_2	β	M	5-HT_{1A}	5-HT_2
5	ND[c]	3.2	0.58	ND	ND	ND	ND	0.82	ND
(*S*)-**5**	> 1000	3.4	0.42	156	> 1000	> 1000	> 1000	0.20	121
(*R*)-**5**	> 1000	0.77	0.14	124	> 1000	> 1000	> 1000	3.8	136
6	ND	48	2.6	ND	ND	ND	ND	27	ND
(*S*)-**6**	> 1000	58	1.6	560	> 1000	> 1000	> 1000	32	453
(*R*)-**6**	> 1000	15	0.89	594	> 1000	> 1000	> 1000	56	> 1000
Chlorpromazine	22	1.1	1.2	0.75	300	> 1000	47	980	4.9
Haloperidol	79	0.67	2.7	8.4	> 1000	> 1000	> 1000	> 1000	31
Thioridazine	22	2.3	2.3	1.1	180	> 1000	10	140	11
Risperidone	270	1.7	6.7	0.50	1.6	> 1000	> 1000	180	0.34
Clozapine	170	60	83	2.5	450	> 1000	15	300	9.5
Remoxipride	> 1000	130	970	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000

[a] Means of at least two independent experiments in duplicate.
[b] Adapted from ref 30.
[c] ND: not determined.

haloperidol, thioridazine and risperidone have high affinities for dopamine D_{2A} and D_3 receptors. The latter compound also has high affinity for the α_2-adrenergic receptor, while the former three possess considerable affinity for the dopamine D_1 receptor. Chlorpromazine, thioridazine and clozapine share a relatively high affinity for the muscarinic receptor. Only thioridazine and risperidone show moderate affinity for the serotonin 5-HT_{1A} receptor. As previously noted by Hacksell et al.,[30] it is virtually impossible to derive a common denominator responsible for the antipsychotic activity of these drugs from these receptor binding data.

Serotonin 5-HT_{1A} receptors are known to be functionally coupled to G_i-proteins mediating the inhibition of adenylate cyclase, the enzyme which catalyzes the conversion of ATP into cAMP.[33] Vasoactive intestinal peptide (VIP) stimulates the formation of cAMP in GH_4ZD10 cells.[34] Stimulation of rat serotonin 5-HT_{1A} receptors, brought to expression in these cells, counteracts the VIP-induced cAMP formation, and this system can be utilized to establish the intrinsic efficacy of serotonin 5-HT_{1A} receptor ligands.[31] Both enantiomers of **5** caused complete inhibition of VIP-induced cAMP production (Table 2), indicating that they behave as full serotonin 5-HT_{1A} receptor agonists in this in vitro assay. Although (*S*)- and (*R*)-**5** were less potent than the reference serotonin 5-HT_{1A} agonists 5-HT, 8-OH-DPAT, and flesinoxan in this assay, as illustrated by their lower IC_{50} values, they were the only compounds whose efficacy matched that of 5-HT. The enantiomers of **6** behaved as weak partial agonists in this assay, both having an intrinsic efficacy of 0.3. In accordance with their affinities for the serotonin 5-HT_{1A} receptor, the (*S*)-enantiomers were more potent in this assay than the (*R*)-enantiomers. In our previous report we hypothesized, based on the similarities in the SAFIRs of the 2-aminotetralin-derived benzamides and oxygenated 2-(*N*,*N*-di-*n*-propylamino)tetralins (DPATs), that the 2-aminotetralin moieties of these two classes of compounds may occupy the same binding sites in the dopamine D_2 and D_3 receptors.[29] The present finding that the (*R*)-enantiomers of **5** and **6** have higher affinities for the dopamine D_2 and D_3 receptors than their optical antipodes supports this hypothesis, since this is consistent with the stereoselectivity of the enantiomers of 5-methoxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (5-OMe-DPAT).[35] The 5-methoxy substituents play a role in this stereoselectivity, since the stereoselectivity of the enantiomers of 5-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (5-OH-DPAT) is reversed: at both receptor subtypes (*S*)-5-OH-DPAT has the highest affinities of the two.[35–37]

Table 2. Effects of serotonin receptor agonists and the enantiomers of **5** and **6** on serotonin 5-HT_{1A} receptor-mediated inhibition of VIP-induced cAMP production in GH_4ZD10 cells[a]

Compound	Efficacy[b]	IC_{50} (nM)
5-HT	100	60
(*R*-8-OH-DPAT	87	30
(*S*)-8-OH-DPAT	62	40
Flesinoxan	79	10
Buspirone	43	100
(*S*)-**5**	100	< 100
(*R*)-**5**	100	100
(*S*)-**6**	30	300
(*R*)-**6**	30	1000

[a] Data of reference compounds taken from ref 31.
[b] Results are presented as relative 'efficacy', indicating the ratio of the effect of the test compound to the maximum response of 5-HT in percentage.

Inhibition of *d*-amphetamine-induced locomotor activity in rodents is a common denominator of all clinically effective antipsychotic agents, an effect which is mediated by their dopamine D_2 receptor-blocking properties.[38] Based on the receptor binding profiles and their high intrinsic efficacies at serotonin 5-HT_{1A} receptors in vitro, the enantiomers of **5** were selected for evaluation in this in vivo assay. (*R*)-**5** significantly inhibited the locomotor activity induced by *d*-amphetamine, indicative of dopamine D_2 receptor antagonism, with an estimated EC_{50} of 2.6 μmol/kg. In contrast, (*S*)-**5** enhanced the *d*-amphetamine-induced locomotor activity. At 5.4 μmol/kg (highest dose tested) the activity increased with 189% ($p < 0.01$) compared to animals treated with *d*-amphetamine only, suggesting that (*S*)-**5** has dopamine D_2 receptor-stimulating properties. These opposing effects of (*S*)- and (*R*)-**5** in vivo suggest that they may have different binding modes at the dopaminergic receptors, despite the small differences in absolute affinities.

Catalepsy has been generally accepted as a model for EPS in man,[39] and the ability of a potential antipsychotic agent to induce catalepsy in rats is considered to be a measure for its liability to induce EPS in man.[38] Both enantiomers were evaluated in this in vivo assay, but neither of them induced any sign of catalepsy at doses up to 60 μmol/kg (data not shown), suggesting that they will have a low propensity to induce EPS in humans. The lack of cataleptogenic activity of (*S*)-**5** is not surprising, in view of its locomotor-stimulating properties. The inability of (*R*)-**5** to induce catalepsy, despite its ability to inhibit *d*-amphetamine-induced locomotor activity, probably stems from its serotonin 5-HT_{1A} receptor-stimulating properties.

Since it has been generally accepted that dopamine D_2 receptor antagonism is required for a compound to exert antipsychotic effects, (*R*)-**5** seems to be the most promising candidate for further development as a potential atypical antipsychotic agent. However, for compounds which combine dopamine D_2 and serotonin 5-HT_{1A} receptor-binding properties, the optimal combination of intrinsic efficacies, as well as the optimal affinity ratio at the two receptor subtypes, required for an optimal clinical profile, remain to be established. In this respect, it is noteworthy that compounds which combine dopamine D_2 receptor antagonism with full serotonin 5-HT_{1A} receptor agonism, such as EMD 128130 (**3**),[26,27] but also mixed partial dopamine D_2/serotonin 5-HT_{1A} receptor agonists, such as PD 158771 (**4**),[28] have been reported to show beneficial properties in preclinical models with predictability for antipsychotic efficacy and EPS liability.

Conclusions

The clean receptor binding profiles of the enantiomers of **5**, together with their efficacies at dopamine D_2 and serotonin 5-HT_{1A} receptors, makes these compounds interesting pharmacological tools for further exploring the dopamine D_2/serotonin 5-HT_{1A} hypothesis of atypical antipsychotic drug action. The lack of cataleptogenic activity of (*R*)-**5**, in combination with its dopamine D_2 receptor antagonistic and serotonin 5-HT_{1A} receptor-stimulating properties, suggest that this compound in particular may possess enhanced antipsychotic efficacy and a low propensity to cause EPS in man.

Experimental

Chemistry

General remarks. Unless otherwise indicated, all materials were puchased from commercial suppliers and used without further purification. All basic amine products were converted to their corresponding hydrochloride or oxalate salts by adding an equimolar amount of a 1 M ethereal HCl solution or an ethanolic solution of oxalic acid to a solution of the free base in ether. All chemical data, except for TLC analyses and electron impact mass spectra, were obtained on the salt forms, unless otherwise stated. TLC analyses were carried out on aluminium plates (Merck) precoated with silica gel 60 F_{254} (0.2 mm), and spots were visualised with UV light and I_2. Gravity column chromatography was performed using silica gel (Merck 60). Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on an ATI-Mattson Genesis Series FT–IR spectrophotometer, and only the important absorptions are indicated. Broad peaks (b) have been indicated as such. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini-200 spectrometer or at 300 MHz on a Varian VXR-300 spectrometer. ^{1}H NMR chemical shifts are denoted in δ units (ppm) relative to $CDCl_3$ (7.26) and converted to the TMS scale. The following abbreviations are used to indicate spin multiplicities: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). ^{13}C NMR spectra were recorded at 50 MHz on a Varian Gemini-200 spectrometer or at 75 MHz on a Varian VXR-300 spectrometer. ^{13}C NMR chemical shifts are denoted in δ units (ppm) relative to $CDCl_3$ (76.91) and converted to the TMS scale. Specific optical rotations were measured in methanol ($c = 1.0$) at 22°C on a Perkin–Elmer 241 polarimeter. Electron impact (EI) mass spectra were recorded on a Unicam Automass mass spectrometer in conjunction with a gas chromatograph. Chemical ionization (CI) mass spectra were recorded on a NERMAG R 3010 mass spectrometer equipped with a home-built atmospheric pressure ionization source and ionspray interface. Elemental analyses (C, H, and N) for the final compounds were performed at the Micro Analytical Department, University of Groningen.

General procedure for the preparation of (*S*)-8 and (*R*)-8. The method adopted for the synthesis of (*S*)-5-methoxy-2-propionamidotetralin [(*S*)-**8**] is described: a solution of propionyl chloride (3.25 g, 35.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise to an ice-cooled, vigorously stirred mixture of (*S*)-**7**·HCl (3.00 g, 14.0 mmol), 10% aqueous NaOH solution (90 mL) and CH_2Cl_2 (100 mL). The mixture was allowed to warm to room temperature and stirring was continued for 18 h at room temperature. The reaction mixture was poured into H_2O (100 mL) and the phases were separated. The H_2O layer was extracted with CH_2Cl_2 (2×50 mL), the organic layers were combined and subsequently washed with a saturated aqueous $NaHCO_3$ solution (3×50 mL) and H_2O (50 mL). After drying over $MgSO_4$, the CH_2Cl_2 layer was filtered and evaporated under reduced pressure which gave the crude amide as a white solid, which was recrystallized from acetone/*n*-hexane to give the pure amide as colourless needles.

(*S*)-5-Methoxy-2-propionamidotetralin [(*S*)-8]. Yield 93%; mp 141–143°C; $[\alpha]_D^{22}$ −53°; IR: cm^{-1} 3300 (b), 2937, 2848, 1637, 1587, 1535; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, $J = 7.7$ Hz, 3H), 1.72–1.83 (m, 1H), 1.97–2.05 (m, 1H), 2.17 (q, $J = 7.7$ Hz, 2H), 2.56–2.78 (m, 3H), 3.08 (dd, $J = 16.2$ Hz, 4.7 Hz, 1H), 3.80 (s, 3H), 4.21–4.30 (m, 1H), 5.71 (bs, 1H), 6.66 (d, $J = 8.1$ Hz, 2H), 7.09 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.9, 21.0, 28.0, 29.8, 35.6, 44.5, 55.2, 107.2, 121.5, 124.4, 126.4, 135.4, 157.2, 173.3; MS (EI, 70 eV): *m*/*z* (rel. intensity) 74 (24), 91 (20), 104 (17), 115 (12), 129 (21), 145 (21), 160 (100), 233 (2, M^+).

(*R*)-5-Methoxy-2-propionamidotetralin [(*R*)-8]. This compound was prepared as described for (*S*)-**8**, starting from (*R*)-**7**. Yield 78%: mp 142–143 (C; $[\alpha]_D^{22}$ +53°; IR: cm^{-1} 3298 (b), 2939, 2850, 1633, 1587, 1543; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (t, $J = 7.7$ Hz, 3H), 1.66–1.77 (m, 1H), 1.95–2.04 (m, 1H), 2.15 (q, $J = 7.7$ Hz, 2H), 2.54–2.77 (m, 3H), 3.05 (dd, $J = 16.2$ Hz, 4.7 Hz, 1H), 3.78 (s, 3H), 4.17–4.25 (m, 1H), 5.94 (bs, 1H), 6.63 (d, $J = 8.6$ Hz, 2H), 7.06 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.0, 21.2, 28.1, 29.8, 35.7, 44.6, 55.2, 107.2, 121.5, 124.4, 126.4, 135.5, 157.2, 173.4; MS (EI, 70 eV): *m*/*z* (rel. intensity) 74 (25), 91 (20), 104 (18), 115 (13), 129 (22), 145 (20), 160 (100), 233 (2, M^+).

General procedure for the preparation of (*S*)-9 and (*R*)-9. The method adopted for the synthesis of (*S*)-5-methoxy-2-(*N*-*n*-propylamino)tetralin hydrochloride [(*S*)-**9**] is described: a solution of (*S*)-**8** (2.98 g, 12.8 mmol) in dry THF (75 mL) was added to a stirred suspension of $LiAlH_4$ (3.00 g) in dry THF (75 mL) and the reaction mixture was refluxed under a nitrogen atmosphere for 42 h. After cooling, excess $LiAlH_4$ was quenched with H_2O and 4 N aqueous NaOH solution, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The resulting oil was taken up in CH_2Cl_2 and dried over $MgSO_4$. After filtration, the solvent was evaporated, which gave the pure base of (*S*)-**9** as a colourless oil. The corresponding hydrochloride salt was recrystallized from EtOH, yielding colourless needles.

(*S*)-5-Methoxy-2-(*N*-*n*-propylamino)tetralin hydrochloride [(*S*)-9]. Yield 95%; mp 276–278°C dec (EtOH) [lit.[40] mp 278–280°C]; $[\alpha]_D^{22}$ −73° [lit.[40] −63°]; IR: cm^{-1} 2967, 2835, 2793, 2735, 2525, 2443, 2588; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.97 (t, $J=7.3$ Hz, 3H), 1.51–1.67 (m, 3H), 1.80 (bs, 1H), 2.05–2.13 (m, 1H), 2.55–2.74 (m, 4H), 2.85–3.05 (m, 3H), 3.81 (s, 3H), 6.69 (dd, $J=11.1$ Hz, 7.7 Hz, 2H), 7.11 (t, $J=8.1$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.2, 23.6, 29.2, 36.8, 49.1, 53.2, 55.2, 107.0, 121.5, 125.1, 126.2, 136.7, 157.2; MS (CI with AcOH): m/z 220 (M + 1).

(*R*)-5-Methoxy-2-(*N*-*n*-propylamino)tetralin hydrochloride [(*R*)-9]. This compound was prepared as described for (*S*)-**9**, starting from (*R*)-**8**. Yield 91%; mp 275–277°C dec (EtOH) [lit.[40] mp 278–280°C]; $[\alpha]_D^{22}$ +71° [lit.[40] +70°]; IR: cm^{-1} 2967, 2835, 2791, 2734, 2525, 2443, 1588; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.97 (t, $J=7.3$ Hz, 3H), 1.34 (bs, 1H), 1.50–1.61 (m, 3H), 2.06–2.13 (m, 1H), 2.54–2.74 (m, 4H), 2.85–3.07 (m, 3H), 3.82 (s, 3H), 6.67 (dd, $J=9.0$ Hz, 9.0 Hz, 2H), 7.11 (t, $J=8.1$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.2, 23.6, 29.3, 36.9, 49.1, 53.2, 55.2, 107.0, 121.5, 125.1, 126.1, 136.8, 157.2; MS (CI with AcOH): m/z 220 (M + 1).

General procedure for the preparation of (*S*)-10 and (*R*)-10. The method adopted for the preparation of (*S*)-5-methoxy-2-(*N*-cyanomethyl-*N*-*n*-propylamino)tetralin hydrochloride [(*S*)-**10**] is described: bromoacetonitrile (3.55 g, 29.6 mmol) was added dropwise to a stirred suspension of K_2CO_3 (4.10 g, 29.6 mmol) and (*S*)-**9** (2.60 g, 11.9 mmol) in acetone (150 mL), and the reaction mixture was refluxed under a nitrogen atmosphere for 24 h. After cooling, the precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting crude oil was purified by column chromatography (eluent: CH_2Cl_2), yielding 2.62 g (10.1 mmol, 85%) of the pure base of (*S*)-**10** as a colourless oil, which was converted to the corresponding hydrochloride salt.

(*S*)-5-Methoxy-2-(*N*-cyanomethyl-*N*-*n*-propylamino)-tetralin hydrochloride [(*S*)-10]. Yield 85%; mp 189–191°C; $[\alpha]_D^{22}$ −66°; IR: cm^{-1} 2922, 2833, 2737, 2368 (b), 2322 (b), 1590; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.96 (t, $J=7.3$ Hz, 3H), 1.45–1.72 (m, 3H), 2.12–2.22 (m, 1H), 2.59–3.06 (m, 7H), 3.68 (s, 2H), 3.83 (s, 3H), 6.71 (dd, $J=8.3$ Hz, 8.3 Hz, 2H), 7.17 (t, $J=7.9$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 20.9, 22.9, 26.5, 33.2, 38.6, 52.1, 55.2, 57.7, 107.2, 116.9, 121.5, 124.8, 126.3, 136.3, 157.1; MS (CI with AcOH): m/z (rel. intensity) 220 (100), 259 (86, M + 1).

(*R*)-5-Methoxy-2-(*N*-cyanomethyl-*N*-*n*-propylamino)-tetralin hydrochloride [(*R*)-10]. This compound was prepared as described for (*S*)-**10**, starting from (*R*)-**9**. Yield 85%; mp 186–188°C; $[\alpha]_D^{22}$ +66°; IR: cm^{-1} 2922, 2834, 2367 (b), 2330 (b), 1590; ^1H NMR (base, 200 MHz, $CDCl_3$): δ0.96 (t, $J=7.3$ Hz, 3H), 1.49–1.72 (m, 3H), 2.15 (m, 1H), 2.60–3.06 (m, 7H), 3.68 (s, 2H), 3.83 (s, 3H), 6.71 (dd, $J=8.3$ Hz, 8.3 Hz, 2H), 7.13 (t, $J=7.7$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 20.9, 22.9, 26.5, 33.2, 38.6, 52.1, 55.2, 57.7, 107.2, 116.9, 121.5, 124.8, 126.3, 136.3, 157.1; MS (CI with AcOH): m/z (rel. intensity) 220 (31), 259 (100, M + 1).

General procedure for the preparation of (*S*)-11 and (*R*)-11. The method adopted for the preparation of (*S*)-5-methoxy-2-[*N*-(2-aminoethyl)-*N*-*n*-propylamino]tetralin dihydrochloride [(*S*)-**11**] is described: a solution of the free base of (*S*)-**10** (2.35 g, 9.1 mmol) in dry THF (75 mL) was added to a stirred suspension of $LiAlH_4$ (3.00 g) in dry THF (75 mL). After refluxing for 24 h under a nitrogen atmosphere, the reaction mixture was cooled to room temperature and excess $LiAlH_4$ was decomposed by adding H_2O and 4 N aqueous NaOH solution. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, the solution was dried over Na_2SO_4 and subsequently filtered. Removal of the solvent under reduced pressure gave the pure base of (*S*)-**11** as a colourless oil, which was converted to the corresponding dihydrochloride salt.

(*S*)-5-Methoxy-2-[*N*-(2-aminoethyl)-*N*-*n*-propylamino]-tetralin dihydrochloride [(*S*)-11]. Yield 90%; mp 111–112°C; $[\alpha]_D^{22}$ −53°; IR: cm^{-1} 3399 (b), 2939, 2881, 2836, 2633, 2519, 1588; ^1H NMR (base, 200 MHz, CDCl3): δ 0.90 (t, $J=7.3$ Hz, 3H), 1.39–1.69 (m, 3H), 1.80 (bs, 2H), 1.98–2.08 (m, 1H), 2.28–3.07 (m, 11H), 3.82 (s, 3H), 6.69 (dd, $J=11.7$ Hz, 7.9 Hz, 2H), 7.10 (t, $J=7.9$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.3, 23.9, 25.5, 32.8, 40.6, 52.6, 53.0, 55.2, 56.2, 106.8, 121.6, 125.2, 126.1, 138.1, 157.2; MS (CI with AcOH): m/z (rel. intensity) 220 (2), 263 (100, M + 1).

(*R*)-5-Methoxy-2-[*N*-(2-aminoethyl)-*N*-*n*-propylamino]-tetralin dihydrochloride [(*R*)-11]. This compound was prepared as described for (*S*)-**11**, starting from (*R*)-**10**. Yield 97%; mp 111–113°C; $[\alpha]_D^{22}$ +54°; IR: cm^{-1} 3400 (b), 2939, 2882, 2837, 2639, 2525, 1588; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, $J=7.3$ Hz, 3H), 1.42–1.68 (m, 3H), 1.84 (bs, 2H), 1.99–2.08 (m, 1H), 2.46–2.67 (m, 5H), 2.70–3.07 (m, 5H), 3.81 (s, 3H), 6.69 (dd, $J=12.2$ Hz, 7.9 Hz, 2H), 7.10 (t, $J=7.7$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.3, 23.9, 25.5, 32.2, 40.6, 52.6, 53.0, 55.2, 56.2, 106.8, 121.6, 125.2, 126.1, 138.1, 157.2; MS (CI with AcOH): m/z (rel. intensity) 220 (5), 263 (100, M + 1).

General procedure for the preparation of (*S*)-5, (*R*)-5, (*S*)-6, and (*R*)-6. The method adopted for the preparation of (*S*)-5-methoxy-2-[*N*-(2-(benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride [(*S*)-**5**] is described: benzoyl chloride (0.52 g, 3.7 mmol), dissolved in CH_2Cl_2 (10 mL), was added dropwise to a vigorously stirred mixture of (*S*)-**11** (0.50 g, 1.5 mmol), 10% aqueous NaOH solution (12 mL) and CH_2Cl_2 (50 mL). After stirring at room temperature for 3 h, the reaction mixture was poured into H_2O (50 mL) and the organic phase was separated. The H_2O layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were subsequently washed with saturated aqueous $NaHCO_3$ (3×50 mL), H_2O (50 mL) and brine (50 mL). After drying over Na_2SO_4 the organic layer was concentrated

in vacuo to obtain the crude amide as an orange oil. Purification by column chromatography [eluent: MeOH: CH_2Cl_2, 1:15 (v/v)] yielded the pure base of (*S*)-**5** as a colourless oil, which was converted to the corresponding hydrochloride salt.

(*S*)-5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride [(*S*)-5]. Yield 86%; mp 91–93°C; $[\alpha]_D^{22}$ −37°; IR: cm^{-1} 3255 (b), 2939, 2835, 2598 (b), 2502 (b), 1655, 1588, 1533; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.93 (t, $J=7.3$ Hz, 3H), 1.47–1.64 (m, 3H), 2.00–2.05 (m, 1H), 2.52–2.62 (m, 3H), 2.74–2.83 (m, 4H), 2.92–3.09 (m, 2H), 3.45–3.55 (m, 2H), 3.79 (s, 3H), 6.67 (t, $J=8.8$ Hz, 2H), 7.10 (t, $J=7.9$ Hz, 1H), 7.23 (bs, 1H), 7.38–7.48 (m, 3H), 7.84 (dd, $J=7.9$ Hz, 8.8 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.1, 23.8, 25.6, 32.3, 38.2, 48.6, 52.3, 55.2, 56.0, 107.0, 121.6, 125.0, 126.3, 126.9, 128.5, 131.2, 137.5, 157.2, 167.2; MS (CI with AcOH): *m*/*z* 367 (M + 1); Anal. calcd for $C_{23}H_{30}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$: C 67.04, H 7.84, N 6.80; obsd C 66.70, H 7.76, N 6.75.

(*R*)-5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride [(*R*)-5]. This compound was prepared as described for (*S*)-**5**, starting from (*R*)-**11**. Yield 91%; mp 91–93°C; $[\alpha]_D^{22}$ +38°; IR: cm^{-1} 3261 (b), 2939, 2836, 2619 (b), 1655, 1589, 1535; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, $J=7.3$ Hz, 3H), 1.47–1.65 (m, 3H), 1.97–2.06 (m, 1H), 2.47–2.60 (m, 3H), 2.75–2.82 (m, 4H), 2.95–3.04 (m, 2H), 3.42–3.56 (m, 2H), 3.80 (s, 3H), 6.67 (t, $J=8.2$ Hz, 2H), 6.96 (bs, 1H), 7.08 (t, $J=8.1$ Hz, 1H), 7.42–7.53 (m, 3H), 7.78 (dd, $J=8.1$ Hz, 1.5 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.8, 23.5, 25.3, 31.9, 37.7, 48.3, 51.9, 55.0, 55.6, 106.9, 121.4, 124.9, 126.2, 126.7, 128.4, 131.2, 134.6, 137.4, 157.1, 167.1; MS (CI with AcOH): *m*/*z* 367 (M + 1); Anal. calcd for $C_{23}H_{30}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$: C 67.04, H 7.84, N 6.80; obsd C 67.18, H 7.71, N 6.80.

(*S*)-5-Methoxy-2-{*N*-[2-(2,6-dimethoxy)benzamidoethyl]-*N*-*n*-propylamino}tetralin oxalate [(*S*)-6]. This compound was prepared as described for (*S*)-**5**. Yield 74%; mp 78–80°C; $[\alpha]_D^{22}$ −32°; IR: cm^{-1} 3259 (b), 2939, 2840, 2642 (b), 2530 (b), 1655, 1597, 1523; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.86 (t, $J=7.3$ Hz, 3H), 1.41–1.69 (m, 3H), 1.97–2.06 (m, 1H), 2.42–2.59 (m, 3H), 2.77–2.83 (m, 4H), 2.93–3.05 (m, 2H), 3.42–3.59 (m, 2H), 3.78 (s, 9H), 6.56 (d, $J=8.5$ Hz, 2H), 6.66 (dd, $J=6.6$ Hz, 6.6 Hz, 2H), 7.08 (t, $J=7.8$ Hz, 1H), 7.26 (dd, $J=8.4$ Hz, 8.4 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 21.4, 23.5, 25.0, 31.5, 37.5, 49.0, 52.1, 55.0, 55.6, 56.2, 103.7, 106.8, 115.9, 121.4, 124.8, 126.2, 130.3, 137.3, 157.1, 157.3, 165.8; MS (CI with AcOH): 427 (M + 1); Anal. calcd for $C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4$: C 62.76, H 7.04, N 5.42; obsd C 63.09, H 7.37, N 5.45.

(*R*)-5-Methoxy-2-{*N*-[2-(2,6-dimethoxy)benzamidoethyl]-*N*-*n*-propylamino}tetralin oxalate [(*R*)-6]. This compound was prepared as described for (*S*)-**5**, starting from (*R*)-**11**. Yield 72%; mp 79–81°C; $[\alpha]_D^{22}$ +29°; IR: cm^{-1} 3406 (b), 2938, 2838, 2627 (b), 2504 (b), 1654, 1596, 1542; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.85 (t, $J=7.3$ Hz, 3H), 1.37–1.66 (m, 3H), 1.95–2.04 (m 1H), 2.41–2.59 (m, 3H), 2.72–2.80 (m, 4H), 2.87–3.05 (m, 2H), 3.47–3.56 (m, 2H), 3.79 (s, 9H), 6.43 (bs, 1H), 6.56 (d, $J=8.3$ Hz, 2H), 6.65 (dd, $J=6.8$ Hz, 6.8 Hz, 2H), 7.07 (t, $J=7.9$ Hz, 1H), 7.27 (dd, $J=9.0$ Hz, 7.8 Hz, 1H); ^{13}C NMR (base, 50 MHz, CDC_{l3}): (11.5, 21.7, 23.6, 25.1, 31.7, 37.6, 48.8, 52.0, 55.0, 55.6, 55.9, 103.7, 106.8, 116.0, 121.4, 124.9, 126.1, 130.3, 137.6, 157.1, 157.3, 165.6; MS (CI with AcOH): *m*/*z* 427 (M + 1); Anal. calcd for $C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4$: C 62.76, H 7.04, N 5.42; obsd C 62.80, H 7.40, N 5.53.

Pharmacology

Radioligand binding studies. The receptor binding assays were essentially performed as described by Malmberg et al.[41] and Jackson et al.[42] The following receptors and radioligands were used: D_1, rat striatum and [^{3}H]-SCH23390; D_{2A} and D_3, cloned human receptors (expressed in Ltk^- and CHO cells, respectively) and [^{3}H]-raclopride; α_1, rat cortex and [^{3}H]-prazosin; α_2, rat cortex and [^{3}H]-RX821002; β, rat cortex and [^{3}H]-DHA; M, rat cortex and [^{3}H]-QNB; 5-HT_{1A}, rat hippocampus and [^{3}H]-8-OH-DPAT; 5-HT_2, rat cortex and [^{3}H]-ketanserin.

Inhibition of VIP-stimulated cAMP production in GH_4ZD10 cells. This assay was performed essentially as described by Johansson et al.[43] Briefly, the GH_4ZD10 (rat pituitary tumor) cells (obtained from Dr. O. Civelli, Vollum Institute for Advanced Biomedical Research, Oregon Health Sciences University, Portland, OR) were cultured in 175 cm^2 flasks in Ham's medium with 1 mM L-glutamine supplemented with 10% FCS, 10 mM HEPES, penicillin and streptomycin at 37°C. Cells in passages 8 to 11 were used. Geneticin (G418 sulfate, 700 μg/L) was used for selection of cells transfected with receptors. The test compounds were dissolved to a 20 mM concentration in dimethyl sulfoxide and stored at −20°C until further use. The stock solutions were further diluted with water containing 0.01% ascorbic acid and 0.1 mM IBMX. The 5-HT was freshly prepared in the solution above. The cAMP assay was performed according to the method described by Dorflinger and Schonbrunn[34] with some minor modifications.[31] The cells were detached from the cultured flasks with Earle's balanced salt solution 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 250×*g* for 6 min at room temperature. The pellets were resuspended to a density of 10^7 cells/mL in medium containing 0.01% ascorbic acid and 0.1 mM IBMX. Cells were preincubated in this solution for 1 h at 37°C and then diluted to a final density of 10^6 cells/mL. Aliquots (0.4 mL) of the cell suspension were added to Eppendorf tubes containing 0.1 mL VIP at a final concentration of 30 nM 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 to 5 min at 4°C, the supernatants were decanted, frozen and stored at −20°C until analyzed. Cyclic AMP levels were

determined according to the method of Brown and Elkins[44] as modified by Nordstedt and Fredholm,[45] in which free [^{3}H]-cAMP/cAMP is separated from that bound to the bovine adrenocortical protein kinase A on glass fiber filters with a semiautomatic cell harvester (Skatron AS, Tranby, Norway). Results are presented as percentages of the VIP-stimulated response, set to 100%, or as relative 'efficacy', which indicates the ratio of the effect of the test compound to maximum response of 5-HT in percentage.

Inhibition of *d*-amphetamine-induced locomotor activity in rats. This assay was performed essentially as described by Ericson et al.[46] Briefly, male Sprague–Dawley rats were administered saline or test compound subcutaneously (sc) followed by *d*-amphetamine (5 mg/kg sc) after 60 min, and their horizontal activity was measured in automated cages during 60 min. Dose-dependent effects were tested for significance compared to control treatment by one-way ANOVA followed by Dunnett's test.

Catalepsy in rats. Male Sprague–Dawley rats were administered saline or test compound sc and tested for catalepsy at $^1/_2$, 1, 2, 4, 8, and 24 h after injection, using the grid test. Catalepsy time was defined as the time until the animals moved one paw. The maximal catalepsy time was set to 3 min. Dose-dependent effects were tested for significance compared to control treatment by one-way ANOVA followed by Mann–Whitney U-test (two-tailed).

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References

1. Broekkamp, C. L. E.; Oosterloo, S. K.; Berendsen, H. H. G.; Van Delft, A. M. L. *Naunyn Schmiedebergs Arch. Pharmacol.* **1988**, *338*, 191.
2. McMillen, B. A.; Scott, S. M.; Davano, E. A. *J. Pharm. Pharmacol.* **1988**, *40*, 885.
3. Invernizzi, R. W.; Cervo, L.; Samanin, R. *Neuropharmacology* **1988**, *27*, 515.
4. Elliot, P. J.; Walsh, D. M.; Close, S. P.; Higgins, G. A.; Hayes, A. G. *Neuropharmacology* **1990**, *29*, 949.
5. Hicks, P. B. *Life Sci.* **1990**, *47*, 1609.
6. Wadenberg, M. L.; Ahlenius, S. *J. Neural Transm. Gen. Sect.* **1991**, *83*, 43.
7. Neal-Beliveau, B. S.; Joyce, J. N.; Lucki, I. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 207.
8. Lucas, G.; Bonhomme, N.; De Deurwaerdere, P.; Le Moal, M.; Spampinato, U. *Psychopharmacology Berl.* **1997**, *131*, 57.
9. Liebman, J. M.; Gerhardt, S. C.; Gerber, R. *Psychopharmacology Berl.* **1989**, *97*, 456.
10. Christoffersen, C. L.; Meltzer, L. T. *Neuropsychopharmacology* **1998**, *18*, 399.
11. Wadenberg, M. L.; Ahlenius, S. *J. Neural. Transm.* **1988**, *74*, 195.
12. Hillegaart, V.; Wadenberg, M. L.; Ahlenius, S. *Pharmacol. Biochem. Behav.* **1989**, *32*, 797.
13. Rollema, H.; Lu, Y.; Schmidt, A. W.; Zorn, S. H. *Eur. J. Pharmacol.* **1997**, *338*, 3.
14. Joyce, J. N. *Psychopharmacology Berl.* **1993**, *112*, S16.
15. Hashimoto, T.; Nishino, N.; Nakai, H.; Tanaka, C. *Life Sci.* **1991**, *48*, 355.
16. Hashimoto, T.; Kitamura, N.; Kajimoto, Y.; Shirai, Y.; Shirakawa, O.; Mita, T.; Nishino, N.; Tanaka, C. *Psychopharmacology Suppl.* **1993**, *112*, 35.
17. Sumiyoshi, T.; Stockmeier, C. A.; Overholser, J. C.; Dilley, G. E.; Meltzer, H. Y. *Brain Res.* **1996**, *708*, 209.
18. Taylor, D. P.; Eison, M. S.; Riblet, L. A.; Vandermaelen, C. P. *Pharmacol. Biochem. Behav.* **1985**, *23*, 687.
19. Wood, P. L.; Nair, N. P.; Lai, S.; Etienne, P. *Life Sci.* **1983**, *33*, 269.
20. McMillen, B. A. *J. Neural. Transm.* **1985**, *64*, 1.
21. Goff, D. C.; Midha, K. K.; Brotman, A. W.; McCormick, S.; Waites, M.; Amico, E. T. *J. Clin. Psychopharmacol.* **1991**, *11*, 193.
22. Luchins, D. J.; Dojka, D. M.; Hanrahan, P. *Am. J. Ment. Retard.* **1993**, *98*, 165.
23. D'Mello, D. A.; McNeil, J. A.; Harris, W. *J. Clin. Psychopharmacol.* **1989**, *9*, 151.
24. Norman, M. H.; Navas III, F.; Thompson, J. B.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 4692.
25. Reitz, A. B.; Bennett, D. J.; Blum, P. S.; Codd, E. E.; Maryanoff, C. A.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1994**, *37*, 1060.
26. Böttcher, H.; Bartoszyk, G. D.; Berthelon, J. J.; Brunet, M.; Devant, R.; Greiner, H. E.; Gottschlich, R.; März, J.; Seyfried, C. A.; Zeiller, J. J. SAR for novel chromanes: atypical neuroleptics with 5-HT_{1A} agonistic and D_2 antagonistic activity. *Soc. Neurosci. Abstr.* **1996**, *22*, 841.
27. Bartoszyk, G. D.; Greiner, H. E.; Seyfried, C. A. Pharmacological profile of EMD 128130: a putative atypical antipsychotic with dopamine D_2 antagonistic and serotonin 5-HT_{1A} agonistic properties. *Soc. Neurosci. Abstr.* **1997**, *23*, 530.
28. Wustrow, D.; Belliotti, T.; Glase, S.; Ross Kesten, S.; Johnson, D.; Colbry, N.; Rubin, R.; Blackburn, A.; Akunne, H.; Corbin, A.; Davis, M. D.; Georgic, L.; Whetzel, S.; Zoski, K.; Heffner, T.; Pugsley, T.; Wise, L. *J. Med. Chem.* **1998**, *41*, 760.
29. Homan, E. J.; Copinga, S.; Elfström, L.; Van der Veen, T.; Hallema, J.-P.; Mohell, N.; Unelius, L.; Johansson, R.; Wikström, H.; Grol, C. J. *Bioorg. Med. Chem.* **1998**, *6*, 2111.
30. Hacksell, U.; Jackson, D. M.; Mohell, N. *Pharmacol. Toxicol.* **1995**, *76*, 320.
31. Fowler, C. J.; Ahlgren, P. C.; Brännström, G. *Br. J. Pharmacol.* **1992**, *107*, 141.
32. Karlsson, A.; Björk, L.; Pettersson, C.; Andén, N.-E.; Hacksell, U. *Chirality* **1990**, *2*, 90.
33. Fargin, A.; Raymond, J. R.; Regan, J. W.; Coteccia, S.; Lefkowitz, R. J.; Caron, M. G. *J. Biol. Chem.* **1989**, *264*, 14848.
34. Dorflinger, L. J.; Schonbrunn, A. *Endocrinology* **1983**, *113*, 1541.
35. Malmberg, Å.; Nordvall, G.; Johansson, A. M.; Mohell, N.; Hacksell, U. *Mol. Pharmacol.* **1994**, *46*, 299.
36. Grol, C. J.; Nordvall, G.; Johansson, A. M.; Hacksell, U. *J. Pharm. Pharmacol.* **1991**, *43*, 481.
37. Van Vliet, L. A.; Tepper, P. G.; Dijkstra, D.; Damsma, G.; Wikstrm, H.; Pugsley, T. A.; Akunne, H. C.; Heffner, T. G.; Glase, S. A.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 4233.
38. Hoffman, D. C.; Donovan, H. *Psychopharmacology Berl.* **1995**, *120*, 128.
39. Niemegeers, C. J. E.; Janssen, P. A. J. *Life Sci.* **1979**, *24*, 2201.
40. Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L. -E.; Johansson, A. M.; Nilsson, J. L.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

41. Malmberg, Å.; Jackson, D. M.; Eriksson, A.; Mohell, N. *Mol. Pharmacol.* **1993**, *43*, 749.
42. Jackson, D. M.; Ryan, C.; Evenden, J.; Mohell, N. *Acta Psychiatr. Scand. Suppl.* **1994**, *380*, 41.
43. Johansson, L.; Sohn, D.; Thorberg, S.-O.; Jackson, D. M.; Kelder, D.; Larsson, L.-G.; ReÁnyi, L.; Ross, S. B.; Wallsten, C.; Eriksson, H.; Hu, P.-S.; Jerning, E.; Mohell, N.; Westlind-Danielsson, A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 216.
44. Brown, B. L.; Ekins, P. *Adv. Cyclic Nucleotide Res.* **1972**, *2*, 25.
45. Nordstedt, C.; Fredholm, B. B. *Anal. Biochem.* **1990**, *89*, 231.
46. Ericson, E.; Samuelsson, J.; Ahlenius, S. *J. Pharmacol. Methods* **1991**, *25*, 111.