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C5-Substituted Derivatives of 5-OMe-BPAT: Synthesis and Interactions with Dopamine D_2 and Serotonin 5-HT_{1A} Receptors

Evert J. Homan,[a,*] Martin Th. M. Tulp,[b] Jonas E. Nilsson,[c] Håkan V. Wikström[a] and Cor J. Grol[a]

[a]*Department of Medicinal Chemistry, University Centre for Pharmacy, University of Groningen, Antonius Deusinglaan 1, NL-9713 AV Groningen, The Netherlands*

[b]*Department of Pharmacology, Solvay Pharmaceuticals B.V., PO Box 900, NL-1380 DA Weesp, The Netherlands*

[c]*Department of Structural Chemistry, Pharmacia & Upjohn AB, S-751 82 Uppsala, Sweden*

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Abstract—Eight new C5-substituted derivatives of the potential atypical antipsychotic agent 5-methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin (5-OMe-BPAT, **1**) have been prepared by chemical conversion of the 5-trifluoromethylsulfonyloxy (triflate) analogue **4** via various Stille-type cross-couplings, a Heck reaction, and an amidation in moderate to good yields. The 5-acetyl, 5-cyano, 5-methyl, 5-(2-furyl), 5-phenyl, methyl 5-carboxylate, and the 5-carboxamido analogues **5**–**11** thus obtained, the previously disclosed 5-methoxy, 5-hydroxy, and 5-unsubstituted analogues **1**–**3**, and the 5-triflate analogue **4** were evaluated for their ability to compete for [^{3}H]-spiperone binding to rat striatal membranes containing dopamine D_2 receptors, and their ability to compete for [^{3}H]-8-OH-DPAT binding to rat frontal cortex membranes containing serotonin 5-HT_{1A} receptors in vitro. Compounds **1**–**11** displayed weak to high affinities for dopamine D_2 receptors, with K_i-values ranging from 550 nM for the 5-carboxamido analogue to 4.9 nM for the 5-hydroxy analogue. The relative affinities of the 5-methoxy, 5-hydroxy, and 5-unsubstituted analogues suggested that these compounds may bind to the same site and in a similar way as the 5-oxygenated DPATs, with the 5-methoxy substituent of **1** functioning as a hydrogen bond acceptor. The serotonin 5-HT_{1A} receptor tolerated more structural diversity at the C5-position of **1**, as revealed by the higher K_i-values of **1**–**11**, which ranged from 60 nM for the 5-carboxamido analogue to 1.0 nM for the 5-unsubstituted analogue. Partial least-squares (PLS) analysis of a set of 24 molecular descriptors, generated for each analogue, revealed no significant correlation between the dopamine D_2 receptor affinities of **1**–**11** and their molecular properties, supporting the view that they may have different binding modes at this receptor subtype. A PLS model with moderate predictability ($Q^2 = 0.49$) could be derived for the serotonin 5-HT_{1A} receptor affinities of **1**–**11**. According to the model, a relatively lipophilic, nonpolar C5-substituent should be optimal for a high affinity at this receptor subtype.

Introduction

Preclinical[1–4] and post-mortem[5–8] studies suggest that compounds, which simultaneously block dopamine D_2 receptors and stimulate serotonin 5-HT_{1A} receptors, may possess atypical antipsychotic properties. Promising results from preclinical studies have recently been reported for several novel compounds with the indicated pharmacological profile.[9–11] 2-Aminotetralin-derived benzamides comprise a novel class of compounds with mixed dopamine D_2, D_3 and serotonin 5-HT_{1A} receptor binding properties.[12,13] The enantiomers of 5-methoxy-2-[*N*-2-(benzamidoethyl)-*N*-*n*-propylamino]tetralin (5-OMe-BPAT, **1**) were shown to possess different pharmacological profiles: whereas both enantiomers behave as full serotonin 5-HT_{1A} receptor agonists, (*R*)-**1** appears to block dopamine D_2 receptors, while (*S*)-**1** possesses dopamine D_2 receptor-stimulating properties.[14] Using molecular modeling studies, we were able to rationalise these differences in pharmacological behaviour by showing that (*R*)- and (*S*)-**1** may have different modes of binding to the dopamine D_2 receptor.[15] Specifically, differences were observed in the interactions of the 5-methoxy substituents of both compounds and a serine residue (Ser193) in transmembrane domain (TM) 5 of the dopamine D_2 receptor, which may explain the differences in intrinsic efficacy at this receptor subtype.

In order to further explore the differences in structural requirements of the dopamine D_2 and serotonin 5-HT_{1A}

Key words: Dopamine; serotonin; atypical antipsychotic; triflate; QSAR.

* Corresponding author. Present address: Pharmacopeia, Inc., CN 5350, Princeton, NJ 08543-5350, USA. Tel.: +1-609-452-3753; fax: +1-732-422-0156; e-mail: ehoman@pharmacop.com

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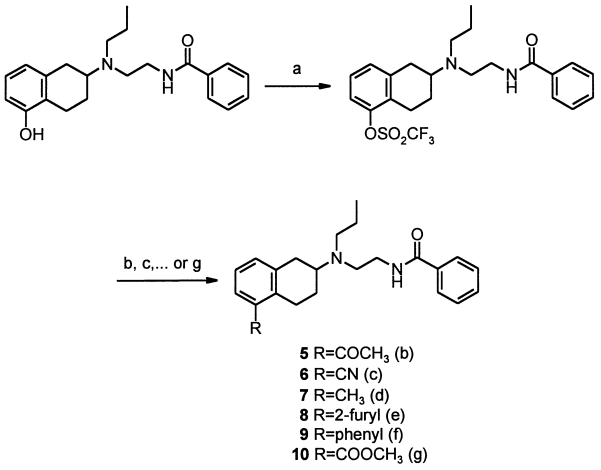
receptor with respect to the C5-substituent of the 2-aminotetralin-derived benzamides, the 5-triflate, 5-acetyl, 5-cyano, 5-methyl, 5-(2-furyl), 5-phenyl, methyl 5-carboxylate, and the 5-carboxamido analogues of **1** were prepared and their affinities for dopamine D_2 and serotonin 5-HT_{1A} receptors were determined in vitro.

Chemistry

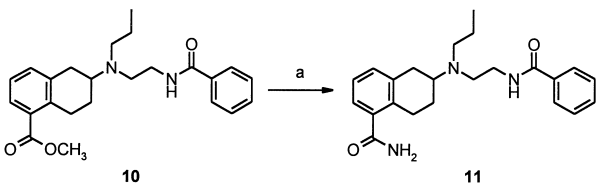
The synthetic steps employed to access the different 5-substituted analogues of **1** are outlined in Schemes 1 and 2. The 5-triflate analogue **4**, which served as the starting point for the preparation of the other derivatives, was prepared from the previously reported hydroxy analogue **2**[12] by reaction with *N,N*-bis(trifluoromethane-sulfonyl) aniline (*N*-phenyltriflimide) in dichloromethane, employing triethylamine as a base.[16]

A Heck reaction between **4** and vinyl butyl ether in the presence of 1,3-bis(diphenylphosphino)propane (dppp) and a catalytic amount of palladium(II) acetate, employing triethylamine as a base and DMF as a solvent, followed by hydrolysis with 5% aqueous hydrochloric acid solution, was used to prepare the 5-acetyl analogue **5**.[17]

The 5-cyano analogue **6** was prepared according to a procedure reported by Hedberg et al.,[18] which is a modification of the procedure originally described by Chambers and Widdowson.[19] Thus, reaction of **4** with potassium cyanide in the presence of zinc dust, triphenylphosphine and bistriphenylphosphine-nickel(II) chloride as a catalyst, employing DMF as a solvent, gave complete conversion to **6** after 48 h at 120°C.



Scheme 1. Reagents and conditions: (a) *N*-phenyltriflimide, Et_3N, CH_2Cl_2, rt; (b) butyl vinyl ether, $Pd(OAc)_2$, dppp, Et_3N, DMF, Δ; 5% HCl, Δ; (c) KCN, $(PPh_3)_2NiCl_2$, PPh_3, Zn, DMF, Δ; (d) tetramethylstannane, $(PPh_3)_2PdCl_2$, PPh_3, LiCl, 2,6-di-*tert*-butyl-4-methylphenol, DMF, Δ; (e) tributyl(2-furyl)stannane, $(PPh_3)_2PdCl_2$, PPh_3, LiCl, 2,6-di-*tert*-butyl-4-methylphenol, DMF, Δ; (f) tributylphenylstannane, $Pd(PPh_3)_4$, LiCl, 2,6-di-*tert*-butyl-4-methylphenol, DMF, Δ; (g) $CO_{(g)}$, MeOH, $Pd(OAc)_2$, dppp, Et_3N, DMSO, Δ.



Scheme 2. Reagents and conditions: (a) formamide, 30% $NaOCH_3$, DMF, Δ.

Stille reactions, employing the modifications reported by Saá et al. for hindered electron-rich aryl triflates,[20] were performed for the preparation of the 5-methyl (**7**), 5-(2-furyl) (**8**) and 5-phenyl (**9**) analogues. Thus, reaction of **4** with the appropriate organostannane reagent (tetramethylstannane, tributyl(2-furyl)stannane and tributylphenylstannane, respectively) in the presence of excess lithium chloride, triphenylphosphine, and catalytic amounts of bistriphenylphosphine-palladium(II) chloride and 2,6-di-*tert*-butyl-4-methylphenol (radical scavenger), employing DMF as a solvent and elevated reaction temperatures, gave the desired products **7**, **8** and **9** in acceptable yields.

Since the carboxamide moiety has been shown to be an interesting bioisostere for aromatic hydroxy and methoxy substituents in structurally related serotonergic ligands,[21] we wanted to prepare the 5-carboxamide analogue of **1**. However, different attempts to convert the 5-cyano analogue (**6**) directly to the 5-carboxamido analogue (**11**), employing different mild hydrolytic conditions, failed in our hands. Thus, reaction with manganese dioxide in CH_2Cl_2,[22] mercury(II) acetate in glacial acetic acid,[23] aqueous sodium perborate without[24] or with[25] methanol, or hydrogen peroxide[26] gave only starting material. Application of stronger reaction conditions, such as refluxing in aqueous sulfuric acid,[18] resulted in the hydrolysis of both the nitrile group and the benzamide moiety. As an alternative route for the preparation of **11**, the methyl 5-carboxylate analogue **10** was prepared from **4** by a palladium-catalyzed crosscoupling with carbon monoxide in the presence of excess methanol[27] (Scheme 1). The resulting methyl ester could be converted efficiently to the carboxamide **11** by reaction with formamide and 30% methanolic sodium methoxide[28] (Scheme 2).

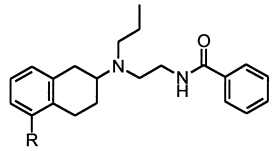
Pharmacology

The newly prepared C5-substituted analogues **4–11**, as well as the previously described 5-methoxy, 5-hydroxy, and 5-hydrido analogues **1**, **2** and **3** were evaluated for their ability to compete for [^{3}H]-spiperone binding to rat striatal membranes containing dopamine D_2 receptors, and their ability to compete for [^{3}H]-8-OH-DPAT binding to rat frontal cortex membranes containing serotonin 5-HT_{1A} receptors in vitro. The results of these binding studies are shown in Table 1. In order to characterise the binding assay, the affinities of spiperone and 8-OH-DPAT have been included as well.

Results and Discussion

In three previous reports we have elaborated on the structure–affinity relationships (SAFIRs) of a series of

Table 1. Receptor binding data of compounds **1**–**11**, spiperone, and 8-OH-DPAT



Compound	R	K_i (nM)[a] D_2	K_i (nM)[a] 5-HT_{1A}	D_2/5-HT_{1A}
1	OCH_3	6.3	2.4	2.6
2	OH	4.9	6.5	0.8
3	H	160	1.0	163
4	OSO_2CF_3	16	6.3	2.5
5	$COCH_3$	120	9.3	13
6	CN	25	36	0.7
7	CH_3	35	1.3	27
8	2-Furyl	30	12	2.5
9	Phenyl	120	8.3	14
10	$COOCH_3$	110	8.3	13
11	$CONH_2$	550	60	9.2
Spiperone	—	0.15	98	0.002
8-OH-DPAT	—	> 1000	2.5	> 400

[a] Mean values of 1–3 determinations.

2-aminotetralin-derived benzamides and structurally closely related analogues with mixed dopamine D_2, D_3 and serotonin 5-HT_{1A} receptor binding properties.[12–14] The SAFIRs suggested that the 2-aminotetralin moieties of the compounds may share the same binding sites in these receptor subtypes as the class of *N,N*-di-*n*-propyl-aminotetralins (DPATs). In the present study the effects of introduction of different substituents at the C5-position of the lead compound of the series, 5-OMe-BPAT (**1**) on the affinities for the dopamine D_2 and serotonin 5-HT_{1A} receptor have been investigated. Chemical diversity at this position was introduced by chemical transformation of the 5-triflate analogue **4**, using several Stille-type crosscouplings and a Heck reaction. All reactions proceeded in moderate to good yields, ranging from 52 to 82%. Aryl triflates have been shown to be efficiently hydrogenated to their unsubstituted analogues in the presence of a palladium catalyst, when tributylamine is employed as the hydride source.[29] This observation may explain why hydrogenolysis is sometimes observed as a side-reaction of palladium-catalysed crosscouplings of aryl triflates, in cases where triethylamine is added as a base.[30] However, there was no indication of the formation of C5-unsubstituted by-product during the preparation of **10**.

Compounds **1**, **2** and the 5-unsubstituted analogue **3** have been characterised previously under different assay conditions.[12] The affinities found in the present investigation are somewhat lower than those previously reported. Particularly, **3** shows a low affinity for the dopamine D_2 receptor ($K_i = 160$ nM), whereas at cloned human dopamine D_2 receptors, using [^{3}H]-raclopride as a radioligand, it had an affinity of 10 nM. These differences are likely to be the result of differences in the assay conditions ([^{3}H]-spiperone versus [^{3}H]-raclopride as a radioligand, tissue versus cloned receptors). Nevertheless, the affinity ranking of **1**–**3** at both receptor subtypes was the same under both assay conditions: at the dopamine D_2 receptor, the ranking is **2** > **1** > **3**, while at the serotonin 5-HT_{1A} receptor, the ranking is **3** > **1** > **2**. Compound **3** has the highest affinity for the serotonin 5-HT_{1A} receptor, and due to its low affinity for the dopamine D_2 receptor, it is also the most selective serotonin 5-HT_{1A} receptor ligand of this series under these assay conditions. The dopamine D_2 receptor affinity ranking, but also the relative affinities of **1**–**3** are consistent with what may be expected for 5-substituted DPAT analogues: the hydroxy-substituted congeners usually have the highest affinities, followed by the methoxy analogues, while unsubstituted analogues have only weak to moderate affinities.[31–35] Presumably, the hydroxy group at the C5-position functions both as hydrogen bond donor and acceptor, while a methoxy group can only act as a hydrogen bond acceptor while interacting with the dopamine D_2 receptor.[34] Unsubstituted DPATs are incapable of forming hydrogen bonds, which would explain their lower affinity for the dopamine D_2 receptor.

As no relationships between the nature of the C5-substituents of **1–11** and the affinities of the compounds for the two receptor subtypes were obvious at first sight, we applied partial least-squares projections to latent structures (PLS)[36] in an attempt to derive quantitative structure–activity relationships (QSARs). Thus, 24 different physicochemical descriptors, describing either whole molecule or C5-substituent properties, were generated for each compound. PLS analysis of the descriptor matrix (11×24; 11 compounds and 24 descriptors) and the corresponding receptor affinities revealed no statistically significant correlation between the molecular properties of **1–11** and their dopamine D_2 receptor affinities, as reflected by a negative values of Q^2. In contrast, for the serotonin 5-HT_{1A} receptor affinities a statistically significant model was obtained, with the first two latent variables of the PLS model accounting for 80% of the variance in the affinities. Figure 1 shows the correlation between the fitted and the observed (i.e. experimental) pK_i values of **1–11** at the serotonin 5-HT_{1A} receptor. The predictability of the model was evaluated by leave-one-out crossvalidation,[37] resulting in a Q^2 value of 0.49 after two components (Fig. 1). Inspection of the regression coefficients revealed that a relatively lipophilic C5-substituent is beneficial for a high serotonin 5-HT_{1A} receptor affinity, while the affinity decreases with a larger dipole moment of the C5-substituent. Size-related properties appeared to have little effect on the serotonin 5-HT_{1A} receptor affinity. Taken together, these findings clearly demonstrate that the serotonin 5-HT_{1A} receptor tolerates considerable structural diversity at the 5-position of **1** and that **1–11** may share a common mode of binding at this receptor subtype, as opposed to the dopamine D_2 receptor. The results from a previously reported molecular modeling study on the binding modes of the enantiomers of **1** to the dopamine D_2 and serotonin 5-HT_{1A} receptor[15] may provide a plausible explanation for this phenomenon. It was shown that both enantiomers of **1** could form specific interactions between their protonated tertiary amine moieties, their amide carbonyl oxygen atom, their amide hydrogen atom, and the phenyl ring of their benzamide moieties, and certain amino acid residues in

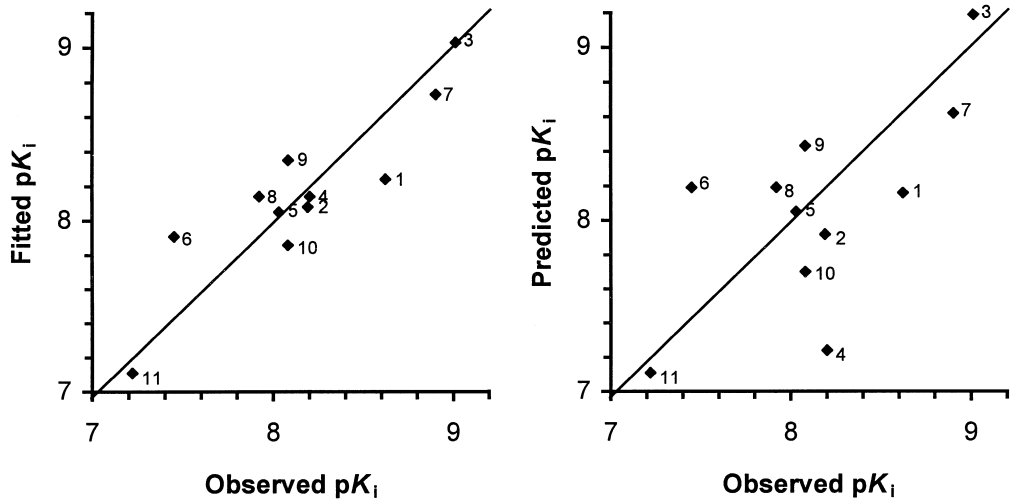


Figure 1. Plots showing (left) the observed versus fitted and the (right) observed versus predicted pK_i values of compounds **1**–**11** at the serotonin 5-HT_{1A} receptor after two PLS components.

the 7-transmembrane domains of the dopamine D_2 receptor model. This multipoint interaction mode of the benzamidoethyl side-chain, which is supported by SAFIRs derived from relevant structural modifications,[13] imposes certain restrictions on the way the 2-aminotetralin moiety of **1** can occupy the agonist binding site, and hence is likely to decrease the tolerance of the dopamine D_2 receptor to structural variation on the phenyl ring of the 2-aminotetralin moiety of **1**. In contrast, the amide moieties of the enantiomers of **1** were not involved in specific interactions in the serotonin 5-HT_{1A} receptor model, the only interaction points being the protonated tertiary amines and the benzamide phenyl rings. Presumably this allows for more conformational adaptation of the ligands, required for the agonist binding site to be able to accommodate aminotetralin moieties with structurally diverse substituents.

Conclusions

The 5-methoxy substituent of **1** plays a role in the binding of the compound to the dopamine D_2 receptor, since replacement of this substituent by other moieties affects the affinity for this receptor subtype. However, no clear structure–affinity relationship could be derived from the limited set of C5-substituted analogues. The 5-methoxy, 5-hydroxy and 5-unsubstituted analogues probably share their binding sites and binding modes with the 5-oxygenated DPATs, but the other analogues may bind to the dopamine D_2 receptor in a completely different way. The serotonin 5-HT_{1A} receptor tolerates more structural diversity at the C5-position of **1**. For high affinity at this receptor subtype, the C5-substituent should be relatively lipophilic and nonpolar.

Experimental

Chemistry

General remarks. Unless otherwise indicated, all materials were purchased 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, 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. All chemical ionisation mass spectra were recorded on a NERMAG R 3010 triple quadrupole mass spectrometer equipped with a home-built atmospheric pressure ionisation source and ionspray interface. Elemental analyses (C, H and N) for target compounds were performed at the Micro Analytical Department, University of Groningen.

5-{[(Trifluoromethyl)sulfonyl]oxy}-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin oxalate (4). Triethylamine (2.87 g, 28.4 mmol) was added to a stirred solution of *N*-phenyltriflimide (6.09 g, 17.0 mmol) and **2**[13] (5.00 g, 14.2 mmol) in CH_2Cl_2 (100 mL). The reaction mixture

was stirred overnight at room temperature under a nitrogen atmosphere. H_2O (50 mL) was added to the reaction mixture, the phases were separated and the organic layer was subsequently washed with 10% aq Na_2CO_3 solution (3×50 mL), H_2O (50 mL) and brine (50 mL). After drying (Na_2SO_4) and filtration of the organic layer, the solvent was evaporated, which gave the crude triflate as a brown oil. Chromatographic purification [eluent: EtOAc:petroleum ether (bp 40-–60), 1:2 (v/v)] gave 5.68 g (11.7 mmol, 83%) of the pure base of **4** as a light yellow oil: mp 147–149°C (acetone); IR: cm^{-1} 3377, 2973, 2880, 2651 (b), 2504 (b), 1718, 1660, 1579, 1525, 1417, 1210; ^1H NMR (base, 300 MHz, $CDCl_3$): δ 0.85 (t, $J=7.3$ Hz, 3H), 1.40–1.55 (m, 3H), 1.97–2.01 (m, 1H), 2.45–2.50 (dd, $J=7.0$ Hz, 7.7 Hz, 2H), 2.60–3.02 (m, 7H), 3.37–3.43 (m, 2H), 6.97–7.10 (m, 3H), 7.25–7.41 (m, 4H), 7.77 (dd, $J=8.3$ Hz, 1.3 Hz, 2H); ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 11.7, 22.0, 24.1, 24.8, 32.1, 38.5, 48.8, 52.4, 55.7, 118.3, 118.6 (q, $J=320$ Hz), 126.9, 128.4, 129.4, 131.2, 134.6, 140.0, 148.1, 167.3; MS (CI with AcOH): m/z 486 (M + 1). Anal. calcd for $C_{25}H_{27}N_2O_4SF_3 \cdot C_2H_2O_4$: C 52.25, H 5.10, N 4.88; obsd C 51.87, H 5.04, N 5.36.

5-Acetyl-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (5). $Pd(OAc)_2$ (6 mg, 0.03 mmol), dppp (11 mg, 0.03 mmol), Et_3N (0.20 g, 1.98 mmol), and butyl vinyl ether (0.50 g, 5.0 mmol) were added to a solution of the free base of **4** (0.24 g, 0.50 mmol) in dry DMF (2 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 15 min. Then the reaction vessel was sealed and the reaction mixture was heated at 120°C for 24 h. After cooling to ~90°C, 5% aq HCl solution (3 mL) was added to the reaction mixture and stirring was continued for 15 min at ambient temperature. The reaction mixture was then cooled to room temperature, poured into H_2O (25 mL) and solid $NaHCO_3$ was added until basic. The mixture was extracted with CH_2Cl_2 (3×25 mL), the organic layers were collected and subsequently washed with H_2O (3×25 mL) and brine (25 mL). After drying (Na_2SO_4) and filtering, the organic layer was concentrated under reduced pressure to give the crude product as a brown oil. Purification by column chromatography (eluent: EtOAc) yielded 0.154 g (0.4 mmol, 82%) of the pure base of **5** as a colourless oil: mp 81–83°C; IR: cm^{-1} 3256 (b), 2963, 2494 (b), 1676, 1654, 1601, 1578, 1533; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, $J=7.3$ Hz, 3H), 1.46–1.64 (m, 3H), 1.95–2.10 (m, 1H), 2.51 (s, 3H), 2.58–2.66 (m, 2H), 2.81–3.13 (m, 7H), 3.51–3.55 (m, 2H), 7.15 (d, $J=5.4$ Hz, 2H), 7.35–7.51 (m, 5H), 7.80 (dd, $J=7.7$ Hz, 1.8 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 20.8, 25.1, 27.7, 29.7, 32.1, 37.4, 48.8, 52.4, 56.0, 125.4, 126.8, 127.0, 128.4, 131.3, 132.8, 134.2, 135.7, 137.0, 137.7, 167.2; MS (CI with AcOH): m/z 379 (M + 1). Anal. calcd for $C_{24}H_{30}N_2O_2 \cdot HCl \cdot \frac{3}{4}H_2O$: C 67.26, H 7.66, N 6.54; obsd C 67.03, H 7.32, N 6.44.

5-Cyano-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (6). Zn (dust, 103 mg, 1.6 mmol), $(PPh_3)_2NiCl_2$ (172 mg, 0.3 mmol), PPh_3 (140 mg, 0.5 mmol) and KCN (83 mg, 1.27 mmol) were added to a solution of the free base of **4** (0.50 g, 1.03 mmol) in dry DMF (5 mL). The mixture was stirred under a nitrogen atmosphere at room temperature for 15 min. Then the reaction vessel was sealed and stirring was continued at 120°C for 48 h. After cooling to room temperature, the reaction mixture was poured into H_2O (25 mL) and the mixture was extracted with Et_2O (3×25 mL). The organic layers were collected and washed with brine (25 mL). After drying (Na_2SO_4), the organic solution was concentrated in vacuo which gave the crude nitrile as an orange oil. Purification by column chromatography (eluent: EtOAc) yielded 0.260 g (0.72 mmol, 70%) of the pure base of **6** as a colourless oil: mp 117–120°C; IR: cm^{-1} 3421 (b), 3246 (b), 3058, 2937, 2880, 2475 (b), 2224, 1654, 1578, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.86 (t, $J=7.3$ Hz, 3H), 1.39–1.70 (m, 3H), 1.96–2.05 (m, 1H), 2.45–2.52 (m, 2H), 2.68–3.15 (m, 7H), 3.33–3.47 (m, 2H), 7.05–7.43 (m, 7H), 7.75 (d, $J=7.1$ Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.8, 24.8, 28.2, 31.8, 38.0, 48.5, 52.1, 55.3, 111.9, 117.8, 126.0, 126.7, 128.4, 130.2, 131.2, 133.9, 134.5, 137.8, 139.6, 167.2; MS (CI with AcOH): m/z 362 (M + 1). Anal. calcd for $C_{23}H_{27}N_3O \cdot HCl \cdot \frac{1}{4}H_2O$: C 68.63, H 7.15, N 10.44; obsd C 68.55, H 7.14, N 9.84.

5-Methyl-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (7). A solution of the free base of **4** (250 mg, 0.5 mmol) in dry DMF (3 mL) was added to a mixture of $(PPh_3)_2PdCl_2$ (42 mg, 0.06 mmol), LiCl (181 mg, 4.27 mmol) and PPh_3 (82 mg, 0.31 mmol) in dry DMF (7 mL). The reaction mixture was stirred at room temperature for 10 min, and then $(CH_3)_4Sn$ (0.29 mL, 2.09 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol were added. The reaction vessel was sealed and the reaction mixture was stirred overnight at 120°C. After cooling, the reaction mixture was partitioned between $CHCl_3$ and 10% aqueous $NaHCO_3$ solution. The combined organic layers were subsequently washed with 10% aqueous KF solution, H_2O and brine. After drying (Na_2SO_4) and filtering the organic layer, the solvent was evaporated, which gave the crude product as a brown oil. Purification by column chromatography [eluent: MeOH:CH_2Cl_2, 1:20 (v/v)] yielded 150 mg (0.43 mmol, 82%) of the pure base of **7** as a colourless oil: mp 122–124°C; IR: cm^{-1} 3249 (b), 2965, 2467 (b), 1655, 1601, 1578, 1533; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, $J=7.3$ Hz, 3H), 1.43–1.79 (m, 3H), 2.04–2.10 (m, 1H), 2.21 (s, 3H), 2.57 (dd, $J=7.3$ Hz, 7.3 Hz, 2H), 2.65–3.08 (m, 7H), 3.46–3.56 (m, 2H), 6.92–7.09 (m, 4H), 7.41–7.56 (m, 3H), 7.80 (dd, $J=7.7$ Hz, 1.6 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 19.4, 21.6, 25.8, 27.0, 32.3, 37.5, 48.2, 51.9, 55.5, 125.5, 126.7, 127.2, 128.4, 131.2, 134.5, 134.6, 135.8, 136.2, 167.1; MS (CI with AcOH): m/z 351 (M + 1). Anal. calcd for $C_{23}H_{30}N_2O \cdot HCl \cdot \frac{3}{4}H_2O$: C 68.97, H 8.20, N 7.00; obsd C 69.16, H 8.03, N 7.07.

5-(2-Furyl)-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (8). A mixture of $(PPh_3)_2PdCl_2$ (43 mg, 0.1 mmol), LiCl (175 mg, 4.1 mmol), PPh_3 (80 mg, 0.3 mmol) and the free base of **4** (220 mg, 0.45 mmol) in dry DMF (4 mL) was stirred at room temperature under a nitrogen atmosphere. After 5 min a solution of tributyl(2-furyl)stannane (0.325 mL, 1.03 mmol) in dry DMF (6 mL) was added, followed by a few crystals of 2,6-di-*tert*-butyl-4-methylphenol. After stirring for 45 min at 120°C under a nitrogen atmosphere, the reaction

mixture was cooled and partitioned between CH_2Cl_2 and 10% aqueous $NaHCO_3$ solution. The organic solution was subsequently washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (eluent: EtOAc), which yielded 140 mg (0.35 mmol, 77%) of the pure base of **8** as a colourless oil: mp 127–130°C; IR: cm^{-1} 3416 (b), 3246 (b), 3057, 2939, 2880, 2611, 2475, 1654, 1578, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, $J=7.3$ Hz, 3H), 1.46–1.67 (m, 3H), 2.03–2.09 (m, 1H), 2.53–2.60 (m, 2H), 2.75–3.11 (m, 7H), 3.46–3.56 (m, 2H), 6.48 (s, 2H), 7.03–7.06 (m, 2H), 7.18 (t, $J=7.7$ Hz, 1H), 7.39–7.54 (m, 5H), 7.80 (dd, $J=7.7$ Hz, 1.8 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.7, 25.9, 28.6, 32.6, 37.6, 48.2, 51.9, 55.3, 108.8, 111.0, 125.4, 125.6, 126.7, 128.4, 129.1, 130.1, 131.2, 133.3, 134.6, 136.8, 141.6, 153.3, 167.1; MS (CI with AcOH): m/z 403 (M + 1). Anal. calcd for $C_{26}H_{30}N_2O_2{\cdot}HCl{\cdot}\frac{1}{2}H_2O$: C 69.69, H 7.21, N 6.25; obsd C 69.64, H 7.18, N 6.25.

5-Phenyl-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]-tetralin hydrochloride (9). A solution of tributylphenylstannane (228 mg, 0.62 mmol) in 1,4-dioxane (9 mL) was added to a mixture of the free base of **4** (250 mg, 0.52 mmol), LiCl (68 mg, 1.60 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) in dry DMF (3 mL). Then a few crystals of 2,6-di-*tert*-butyl-4-methylphenol were added and the reaction mixture was stirred overnight at 120°C under a nitrogen atmosphere. After cooling, the solids were removed from the reaction mixture by filtration (Celite®) and the filtrate was poured into H_2O (25 mL). The aqueous solution was extracted with $CHCl_3$ (3×25 mL) and the extracts were combined. The organic solution was subsequently washed with aqueous $NaHCO_3$ solution (3×25 mL), H_2O (25 mL) and brine. After drying (Na_2SO_4) and filtering, the organic solution was concentrated under reduced pressure, which gave the crude product as a brown oil. Purification by silica column chromatography [eluent: MeOH:CH_2Cl_2, 1:20 (v/v)] yielded 110 mg (0.27 mmol, 52%) of the pure base of **9** as a colourless oil: mp 103–105°C; IR: cm^{-1} 3256 (b), 3057, 2965, 2479 (b), 1654, 1601, 1578, 1533; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (as, 3H), 1.77–1.80 (m, 1H), 1.99–2.06 (m, 2H), 2.32–2.47 (m, 1H), 2.69–2.79 (m, 2H), 3.05–3.22 (m, 4H), 3.31–3.44 (m, 1H), 3.51–3.60 (m, 1H), 3.64–3.74 (m, 1H), 3.79–3.87 (m, 1H), 4.02–4.11 (m, 1H), 6.93–7.54 (m, 12H), 8.06–8.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 21.3, 25.6, 28.2, 32.0, 37.4, 48.6, 52.2, 56.2, 125.6, 126.8, 127.4, 127.9, 128.5, 128.6, 129.0, 131.2, 133.6, 134.4, 135.9, 141.6, 141.8, 167.1; MS (CI with AcOH): m/z 413 (M + 1). Anal. calcd for $C_{28}H_{32}N_2O{\cdot}\ HCl{\cdot}\frac{1}{2}H_2O$: C 73.41, H 7.50, N 6.12; obsd C 73.14, H 7.70, N 6.28.

Methyl 2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin-5-carboxylate hydrochloride (10). Methanol (3.32 mL, 131 mmol) was added to a mixture of the free base of **4** (1.00 g, 2.1 mmol), $Pd(OAc)_2$ (14 mg, 0.1 mmol), dppp (26 mg, 0.1 mmol), Et_3N (0.42 g, 4.2 mmol) and DMSO (15 mL). The mixture was flushed with nitrogen until all reagents were dissolved (1 h) and then the reaction mixture was saturated with CO gas (caution: highly toxic!) by flushing it at room temperature during 1 h. Then the reaction mixture was heated at 70°C under an atmosphere of CO. After 24 and 48 h of heating, the reaction mixture was cooled to room temperature, resaturated with CO and extra MeOH (1.0 mL) was added in order to complete the reaction. After 72 h of heating at 70°C TLC analysis revealed absence of starting material. The reaction mixture was cooled to room temperature and poured into H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (5×15 mL), and the collected organic layers were washed with H_2O (5×15 mL) and brine (15 mL). After drying (Na_2SO_4) and filtering of the organic layer, the solvent was evaporated, yielding the crude ester as a brown oil. Purification by column chromatography [eluent: MeOH:CH_2Cl_2, 1:20 (v/v)] yielded 0.50 g (1.3 mmol, 61%) of the pure base of **10** as a colourless oil: mp 90–91°C; IR: cm^{-1} 3400 (b), 3247 (b), 3057, 2965, 2880, 2626 (b), 2492 (b), 1718, 1654, 1578, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, $J=7.3$ Hz, 3H), 1.43–1.62 (m, 3H), 1.99–2.05 (m, 1H), 2.53 (dd, $J=7.3$ Hz, 7.3 Hz, 2H), 2.72–3.10 (m, 6H), 3.28–3.49 (m, 3H), 3.84 (s, 3H), 7.04 (bs, 1H), 7.12–7.21 (m, 2H), 7.36–7.47 (m, 3H), 7.66–7.79 (m, 3H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.7, 25.6, 28.0, 32.6, 37.7, 48.3, 51.6, 51.9, 55.2, 125.2, 126.7, 128.1, 128.4, 129.6, 131.1, 133.3, 134.6, 137.4, 137.7, 161.1, 168.2; MS (CI with AcOH): m/z (relative intensity) 337 (8), 395 (100, M + 1). Anal. calcd for $C_{24}H_{30}N_2O_3{\cdot}HCl{\cdot}\frac{1}{2}H_2O$: C 65.51, H 7.35, N 6.37; obsd C 65.35, H 7.32, N 6.48.

5-Carboxamido-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (11). Formamide (69 mg, 1.6 mmol) was added to a solution of the free base of **10** (150 mg, 0.4 mmol) in dry DMF (20 mL). The reaction mixture was heated at 100°C under a nitrogen atmosphere and then 30% $NaOCH_3$ solution in MeOH (0.1 mL) was added dropwise via a syringe. Heating was continued at 100°C for 1 h and then the reaction mixture was allowed to cool to room temperature. After concentrating the reaction mixture under reduced pressure, the residue was dissolved in CH_2Cl_2 (25 mL), and the resulting solution was subsequently washed with 10% aqueous $NaHCO_3$ solution (3×25 mL), H_2O (25 mL) and brine (25 mL). After drying (Na_2SO_4) and filtering, the solvent was evaporated, which gave the crude carboxamide as a yellow oil. Purification by silica column chromatography [eluent: MeOH:CH_2Cl_2, 1:10 (v/v)] yielded 110 mg (0.3 mmol, 76%) of the pure base of **11** as a colourless oil: mp 190–192°C; IR: cm^{-1} 3297 (b), 3169 (b), 2965, 2611 (b), 2520 (b), 1655, 1578, 1533; ^1H NMR (base, 200 MHz, $CHCl_3$): δ 0.88 (t, $J=7.3$ Hz, 3H), 1.39–1.67 (m, 3H), 1.97–2.02 (m, 1H), 2.52 (dd, $J=7.4$ Hz, 7.4 Hz, 2H), 2.71–3.16 (m, 7H), 3.42–3.47 (m, 2H), 6.05 (bs, 1H), 6.26 (bs, 1H), 7.07–7.12 (m, 3H), 7.19–7.24 (m, 1H), 7.36–7.52 (m, 3H), 7.75 (dd, $J=7.9$ Hz, 1.6 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.6, 25.3, 27.0, 32.3, 37.6, 48.3, 52.0, 55.4, 124.4, 125.5, 126.7, 128.4, 131.2, 131.4, 134.2, 134.4, 135.1, 137.3, 167.2, 172.4; MS (CI with AcOH): m/z (rel. intensity) 288 (3), 380 (100, M + 1). Anal. calcd for $C_{23}H_{29}N_3O_2{\cdot}HCl{\cdot}\frac{1}{4}H_2O$: C 65.69, H 7.33, N 9.99; obsd C 65.37, H 7.33, N 9.93.

Pharmacology

[^{3}H]-Spiperone binding to dopamine D_2 receptors. Male Wistar rats, weighing 200–300 g (TNO, The Netherlands), were decapitated and the striata were dissected. After

weighing, the striata were taken up in 20 volume amounts of 50 mM Tris–HCl buffer (pH 7.7) and homogenised using a Potter-Elvehjem homogenizer (10×600 rpm). The resulting homogenate was centrifuged at 4°C during 10 min at 50,000×*g* in a Sorvall RC-5 centrifuge. The supernatant was decanted and the pellet was resuspended in 20 volume amounts of 50 mM Tris–HCl buffer, using a Vortex mixer. The suspension was again homogenised (5×600 rpm) and centrifuged at 4°C during 10 min at 50,000×*g*. After having repeated this washing procedure two more times, the tissue was taken up in 20 volume amounts of incubation medium (47 mM Tris–HCl buffer, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, 5 μM pargyline, pH 7.7) and homogenised (5×600 rpm). The membrane fraction was then taken up in 100 volume amounts of incubation medium, to a final concentration of 10 mg original wet weight per mL. The homogenate was incubated batchwise at 37°C during 10 min (activation of pargyline), distributed in 96-well plates (0.5 mL per well) by a Tecan dilution robot, and stored at 4°C until further use. Half an hour prior to the incubation the tissue was allowed to warm to room temperature. About 15 min prior to the incubation 50 μL of test compound, dissolved in 0.1% ascorbic acid solution, or 0.1% ascorbic acid solution (determination of total binding) was added to the tissue. The incubation was then initiated by adding 50 μL of [^{3}H]-spiperone (New England Nuclear, Boston, MA; specific activity 20–40 Ci/mmol, $K_d = 0.12$ nM), dissolved in 0.1% ascorbic acid solution, resulting in a concentration of 0.5 nM during incubation. The incubation mixture was incubated at 25°C on a water bath during 20 min. Binding in the presence of haloperidol (0.1 μM) was defined as non-specific. The incubation was terminated by filtration of the plates through Whatman GF/B glassfiber filters and subsequent washing with 50 mM Tris–HCl buffer (2×5 mL) of 4°C, using Tomtek cell harvesters. The filters, each containing 96 samples, were dried and transferred in polyurethane envelopes, together with solid scintillation sheets. The envelops were heat-sealed and counted in a Wallac betaplate counter.

[^{3}H]-8-OH-DPAT binding to serotonin 5-HT$_{1A}$ receptors. Male Wistar rats, weighing 200–-300 g (TNO, The Netherlands), were decapitated and the frontal cortices were dissected. After weighing, the frontal cortices were taken up in 10 volume amounts of 0.32 M sucrose solution and homogenised using a Potter-Elvehjem homogeniser (10×600 rpm). The resulting homogenate was centrifuged at 4°C during 10 min at 700×*g* in a Sorvall RC-5 centrifuge. The supernatant was decanted and again centrifuged at 4°C during 10 min at 50,000×*g*. The pellet was resuspended in 10 volume amounts of 50 mM Tris–HCl buffer (pH 7.7), using a Vortex mixer and homogenised during 10 s using a Polytron (level 100). The resulting homogenate was incubated during 10 min at 37°C in order to remove endogenous serotonin. Again the homogenate was centrifuged at 4°C during 10 min at 50,000×*g*. The resulting pellet was resuspended in 10 volume amounts of incubation medium (50 mM Tris–HCl buffer, 4 mM $CaCl_2$, 0.1% ascorbic acid, 10 μM pargyline, pH 7.7) and homogenised (5×600 rpm). The membrane fraction was then taken up in 50 volume amounts of incubation medium, to a final concentration of 20 mg original wet weight per mL. The homogenate was incubated batchwise at 37°C during 15 min (activation of pargyline), distributed in 96-well plates (0.5 mL per well) by a Tecan dilution robot, and stored at 4°C until further use. Half an hour prior to the incubation the tissue was allowed to warm to room temperature. About 15 min prior to the incubation 50 μL of test compound, dissolved in 0.1% ascorbic acid solution, or 0.1% ascorbic acid solution (determination of total binding) was added to the tissue. The incubation was then initiated by adding 50 μL of [^{3}H]-8-OH-DPAT (New England Nuclear, Boston, MA; specific activity 158 Ci/mmol, $K_d = 2.0$ nM), dissolved in 0.1% ascorbic acid solution, resulting in a concentration of 1.0 nM during incubation. The incubation mixture (0.6 mL) was incubated at 37°C on a water bath during 10 min. Binding in the presence of serotonin (10 μM) was defined as non-specific. The incubations were terminated and the radioactivity was determined as described for the dopamine D_2 receptor binding assay.

Data analysis. Concentrations of unlabeled test compound causing 50% displacement of the specific binding of a labelled compound (IC_{50} values) were obtained by computerised log-probit linear regression analysis of data obtained in experiments in which four to six different concentrations of the test compound were used. Inhibition constants (K_i) were calculated using the Cheng–Prusoff equation.[38] Mean K_i values were calculated from at least three values obtained from independent experiments, that is, in experiments performed on different days with different membrane preparations. All incubations were done in triplicate.

Quantitative structure–activity relationships. All calculations were performed on an Octane R10,000 Silicon Graphics workstation running IRIX 6.4. The program Tsar[39] was used to generate 24 descriptors for compounds **1**–**11**. The following whole molecule descriptors were generated: molecular mass; molecular surface area; molecular volume; total dipole moment; number of heteroatoms; number of H-bond donors; number of H-bond acceptors; number of N atoms; number of O atoms; number of S atoms. In addition, the following descriptors were generated for the C5-substituents only: molecular mass; molecular surface area; molecular volume; Verloop L; Verloop B1; Verloop B2; Verloop B3; Verloop B4; Verloop B5; total dipole moment; log P; molecular refractivity; number of H-bond donors; number of H-bond acceptors. A matrix was formed by putting the descriptors in the columns and the compounds in the rows. The first two columns were formed by the dopamine D_2 and serotonin 5-HT$_{1A}$ pK_i values of the compounds. After mean-centring and autoscaling of the matrix, PLS analysis was performed using the PLS_Toolbox[40] for MatLab.[41]

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