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2-Aminotetralin-derived Substituted Benzamides with Mixed Dopamine D_2, D_3, and Serotonin 5-HT_{1A} Receptor Binding Properties: A Novel Class of Potential Atypical Antipsychotic Agents

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Abstract—A new chemical class of potential atypical antypsychotic agents, based on the pharmacological concept of mixed dopamine D_2 receptor antagonism and serotonin 5-HT_{1A} receptor agonism, was designed by combining the structural features of the 2-(N,N-di-*n*-propylamino)tetralins (DPATs) and the 2-pyrrolidinylmethyl-derived substituted benzamides in a structural hybrid. Thus, a series of 35 differently substituted 2-aminotetralin-derived substituted benzamides was synthesized and the compounds were evaluated for their ability to compete for [^{3}H]-raclopride binding to cloned human dopamine D_{2A} and D_3 receptors, and for [^{3}H]-8-OH-DPAT binding to rat serotonin 5-HT_{1A} receptors in vitro. The lead compound of the series, 5-methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]tetralin (**12a**), displayed high affinities for the dopamine D_{2A} receptor ($K_i = 3.2$ nM), the dopamine D_3 receptor ($K_i = 0.58$ nM) as well as the serotonin 5-HT_{1A} receptor ($K_i = 0.82$ nM). The structure–affinity relationships of the series suggest that the 2-aminotetralin moieties of the compounds occupy the same binding sites as the DPATs in all three receptor subtypes. The benzamidoethyl side chain enhances the affinities of the compounds for all three receptor subtypes, presumably by occupying an accessory binding site. For the dopamine D_2 and D_3 receptors, this accessory binding site may be identical to the binding site of the 2-pyrrolidinylmethyl-derived substituted benzamides.

Introduction

In the search for new atypical antipsychotic agents, which combine a superior clinical efficacy with a low incidence risk in causing extrapyramidal side-effects (EPS) and tardive dyskinesias (TD), compounds with mixed dopaminergic and serotonergic properties have been the subject of many investigations during the last decade. Based on cluster analyses, performed on the receptor binding profiles of a number of classical and supposedly atypical antipsychotic agents, Meltzer and co-workers hypothesized that compounds which combine 5-HT_2 receptor antagonism and dopamine D_2 receptor antagonism in an appropriate ratio (5-HT_2/D_2 pK_i ratio ≥ 1.12) should possess atypical antipsychotic properties. This hypothesis should thus account for the superior clinical profile of clozapine, the standard atypical antipsychotic agent.[1,2] Based on this concept of mixed 5-HT_2/dopamine D_2 receptor antagonism, several

Key words: Dopamine; serotonin; atypical antipsychotics; 2-aminotetralins; benzamides.

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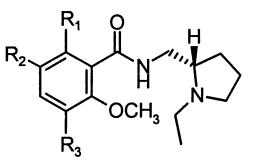
new potential atypical antipsychotic agents have been developed during recent years, including risperidone,[3] seroquel,[4] and sertindole.[5] Risperidone, which is now clinically available, has been show to possess improved efficacy against the negative symptoms of schizophrenia and a reduced EPS liability.[6]

Selective serotonin 5-HT_{1A} receptor agonists have been shown to interact with antipsychotic agents in behavioural and neurochemical models. For example, 8-hydroxy-2-(N,N-di-*n*-propylamino)tetralin (8-OH-DPAT, **7**, Chart 1) has been reported to reverse catalepsy, induced by haloperidol[7–11] or raclopride[12] in rats. Furthermore, 8-OH-DPAT has been shown to possess antipsychotic-like properties in models predictive of antipsychotic activity[13,14] and to enhance some antipsychotic-like effects of raclopride in rats.[12] In addition, it has been suggested that serotonin 5-HT_{1A} receptor agonism may be beneficial in relieving the anxiety that can trigger psychotic episodes in schizophrenics.[15] Taken together, these findings suggest that compounds which combine dopamine D_2 receptor antagonism with serotonin 5-HT_{1A} receptor agonism may have enhanced antipsychotic activity and a reduced EPS liability. Recently, several laboratories have disclosed new compounds with the indicated receptor binding profiles and demonstrable atypical antipsychotic-like properties in preclinical models.[15–18]

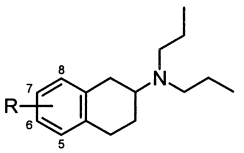
This promising new approach in the search for atypical antipsychotic agents encouraged us to develop a new chemical class of compounds with mixed dopamine D_2 and serotonin 5-HT_{1A} receptor binding properties. The benzamide moiety was chosen as a starting point for the design of this series. Substituted benzamides, in particular those of the 2-pyrrolidinylmethyl class, are known for their high affinity and selectivity towards dopamine D_2 and D_3 receptors. Some of these compounds (e.g. sulpiride (**1**), remoxipride (**2**) and raclopride (**3**)) possess atypical antipsychotic properties.[19–21] In order to incorporate serotonergic activity into the benzamide moiety, we decided to combine this pharmacophore with the 2-aminotetralin system in one structural hybrid. The semi-rigid 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) system has been successfully applied as a template for the development of dopaminergic,[22] serotonergic,[23] adrenergic,[24,25] and melatonergic[26] agents in the past. Particularly, the hydroxylated N,N-di-*n*-propyl-substituted 2-aminotetralins (DPATs) have been shown to possess intriguing structure–activity relationships with regard to dopaminergic and serotonergic receptors. For example, 5-hydroxy-2-(N,N-di-*n*-propylamino)tetralin (5-OH-DPAT, **4**), 6-hydroxy-2-(N,N-di-*n*-propylamino)tetralin (6-OH-DPAT, **5**) and 7-hydroxy-2-(N,N-di-*n*-propylamino)tetralin (7-OH-DPAT, **6**) are highly potent to weak dopamine D_2 receptor agonists, in the potency order of $\mathbf{4} \geqslant \mathbf{6} > \mathbf{5}$,[27–30] whereas the 8-hydroxy analogue (8-OH-DPAT, **7**) is a potent serotonin 5-HT_{1A} receptor agonist devoid of dopaminergic activity.[23] Furthermore, the unsubstituted analogue 2-(N,N-di-*n*-propylamino)tetralin (DPAT, **8**) has been shown to possess mixed dopaminergic and serotonergic properties.[31] Thus, the activity profile of the DPATs can be tuned by the substitution pattern on the aromatic nucleus. Taken together, we conceived it possible to develop compounds with the desired receptor binding profile by linking the basic nitrogen of differently substituted 2-aminotetralins via a two-carbon chain to the amide nitrogen of differently substituted benzamide moieties (Fig. 1). Therefore, a series of N-(2-benzamidoethyl)-substituted 2-(N-*n*-propylamino)tetralins with various substitution patterns at the aromatic nuclei of the 2-aminotetralin and benzamide moieties was synthesized, and the ability of these compounds to compete for [^{3}H]-raclopride binding to cloned human dopamine D_{2A} and D_3 receptors and [^{3}H]-8-OH-DPAT binding to rat serotonin 5-HT_{1A} receptors in vitro was determined.

Chemistry

The synthetic pathway employed to obtain the target compounds is outlined in Scheme 1. The appropriately substituted 2-(N-*n*-propylamino)tetralins **9a–e**, known from the literature,[32–34] served as starting points for the



1 R_1=H, R_2=SO_2NH_2, R_3=H (Sulpiride)
2 R_1=OCH_3, R_2=Br, R_3=H (Remoxipride)
3 R_1=OH, R_2=Cl, R_3=Cl (Raclopride)



4 R=5-OH (5-OH-DPAT)
5 R=6-OH (6-OH-DPAT)
6 R=7-OH (7-OH-DPAT)
7 R=8-OH (8-OH-DPAT)
8 R=H (DPAT)

Chart 1.

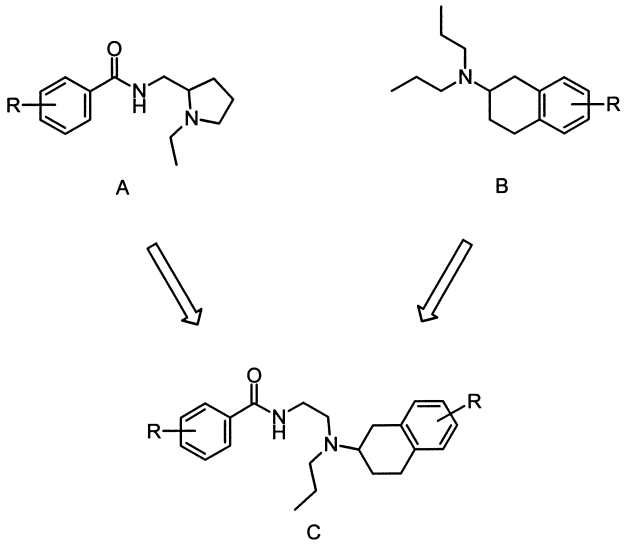
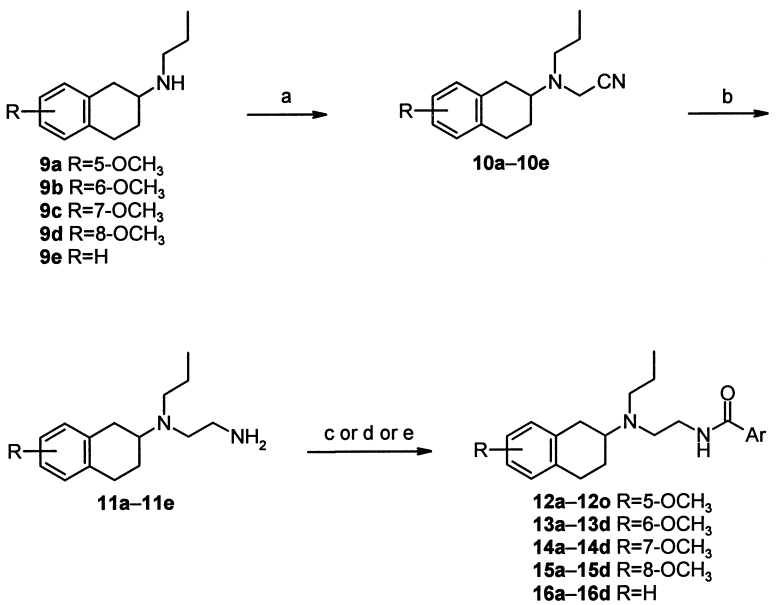


Figure 1. Schematic representation of the structural hybridization of 2-pyrrolidinylmethyl-derived substituted benzamides (A) and 2-(N,N-di-*n*-propylamino)tetralins (DPATs, B), resulting in the concept of 2-aminotetralin-derived benzamides (C).

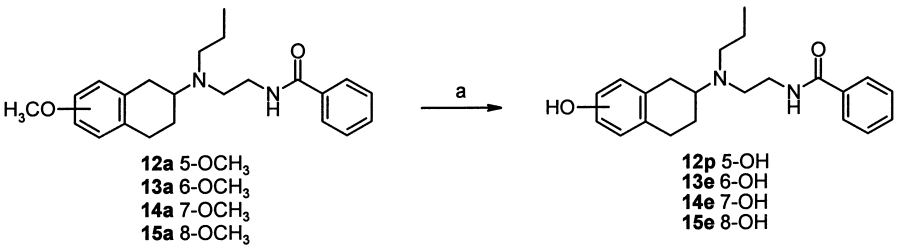
synthesis of the target compounds. N-alkylation with bromoacetonitrile in boiling acetone, employing potassium carbonate as a base and potassium iodide as a catalyst, gave the cyanomethyl intermediates **10a–e** in good yields, which subsequently were reduced almost quantitatively with $LiAlH_4$ to the corresponding amines **11a–e**. Three different methods were employed to obtain the amides **12a–o, 13a–d, 14a–d, 15a–d** and **16a–d**. First, the appropriate acid chloride (either commercially available or readily obtained from the corresponding carboxylic acid using standard procedures) was employed in the presence of sodium hydroxide and the biphasic medium water/dichloromethane according to the Schotten–Baumann procedure (Method A).[26] Second, the appropriate acid chloride was allowed to react with the appropriate primary amine in boiling chloroform, without addition of a base (Method B).[35] Third, the appropriate carboxylic acid was converted into a mixed anhydride using ethyl chloroformate and was then allowed to react with the appropriate primary amine in the presence of triethylamine and acetone as the solvent (Method C).[36] Since in the DPAT series the hydroxy-substituted congeners usually have the highest affinities, compounds **12a, 13a, 14a** and **15a** were demethylated with boron tribromide in dichloromethane,[37] resulting in the corresponding hydroxy analogues **12p, 13e, 14e** and **15e**, respectively (Scheme 2).

Pharmacology

Compounds **12a–p, 13a–e, 14a–e, 15a–e**, and **16a–d** were evaluated for their ability to compete for [^{3}H]-raclopride binding to cloned human dopamine D_{2A} receptors (expressed in Ltk$^-$ cells) and cloned human dopamine D_3 receptors (expressed in CHO cells), and their ability to compete for [^{3}H]-8-OH-DPAT binding to



Scheme 1. Reagents and conditions: (a) $BrCH_2CN$, K_2CO_3, KI, acetone, Δ; (b) $LiAlH_4$, THF, Δ; (c) ArCOCl, 10% NaOH, CH_2Cl_2; (d) ArCOCl, $CHCl_3$, Δ; (e) ArCOOH, EtOCOCl, Et_3N, acetone.



Scheme 2. Reagents: (a) BBr_3, CH_2Cl_2, $-50\,^{\circ}C$.

rat hippocampal membranes containing serotonin 5-HT_{1A} receptors in vitro. Haloperidol and clozapine were evaluated in the same assays for comparison purposes. The results of these binding studies are shown in Table 1.

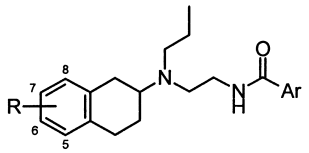
Results and discussion

By linking differently substituted benzamide moieties, as present in the 2-pyrrolidinylmethyl-derived class of substituted benzamides, with their amide nitrogen atom via a 2-carbon chain to the basic nitrogen atoms of differently substituted 2-N-*n*-propylaminotetralins, we have attempted to combine the pharmacological properties of these two distinct classes of compounds into a new chemical class of compounds (i.e. the 2-aminotetralin-derived benzamides). The results of the binding assays in Table 1 show that most compounds display moderate to high affinities for dopamine D_{2A} and D_3, and serotonin 5-HT_{1A} receptors.

When considering the effects of differently substituted benzamide moieties, several consistent trends can be observed in the binding data: compounds with a 2,3-dimethoxy substitution pattern on the benzamide moiety (**12c, 14b, 15b**, and **16b**) always have a higher affinity for the dopamine D_{2A} receptor than for the dopamine D_3 receptor, whereas for compounds with a 2,6-dimethoxy substitution pattern (**12d, 14c, 15c**, and **16c**) the opposite is the case (i.e. they prefer the dopamine D_3 receptor to the dopamine D_2 receptor). These remarkable consistencies in affinities towards the two dopamine receptor subtypes should probably be explained by differences in conformational behaviour of the two types of substituted benzamides. Compounds with one methoxy substituent positioned *ortho* towards the benzamide carbonyl group presumably adopt a conformation in which the *ortho*-methoxy group is oriented in a coplanar fashion with respect to the plane of the aromatic ring and amide group, while forming a hydrogen bond between its oxygen atom and the amide hydrogen atom (Fig. 2). Benzamides with a 2,6-dimethoxy substitution pattern cannot adopt such a coplanar system due to steric hindrance between the second *ortho*-methoxy group and the carbonyl oxygen atom, resulting in an out-of-plane conformation of the entire aromatic ring with respect to the amide functionality. These assumptions are supported by X-ray and molecular modeling studies performed on 2-pyrrolidinylmethyl-derived benzamides with comparable substitution patterns.[19–21] It should be noted, however, that the dopamine D_{2A}/D_3 receptor affinity ratio is also affected by substituents at other positions of the benzamide moiety. This becomes obvious when the affinities of compounds **12a–c, 12e, 12f, 12i**, and **12k** for these receptor subtypes are compared. Introduction of an *ortho*-methoxy group in **12a**, resulting in **12b**, decreases the affinities for both receptor subtypes considerably. Introduction of an additional methoxy group at the 3-position, as in **12c**, restores the high affinity for the dopamine D_{2A} receptor (cf. **12a**), but decreases the dopamine D_3 receptor affinity even more (cf. **12b**). Thus, the preference of compounds **12c, 13b, 14b**, and **15b** for the dopamine D_{2A} receptor, as compared to their 2,6-dimethoxy-substituted analogues **12d, 13c, 14c**, and **15c**, seems not only to be accounted for by the ability of **12c, 13b, 14b**, and **15b** to form an intramolecular hydrogen bond, as opposed to **12d, 13c, 14c**, and **15c**, but also by the presence of the 3-methoxy group, which enhances the dopamine D_{2A} receptor affinity and at the same time decreases the dopamine D_3 receptor affinity. The affinities of compounds **12e, 12f, 12i**, and **12k** reveal that substitution of the benzamide 5-position, in combination with an *ortho*-methoxy group (cf. **12g** and **h**), also restores some of the affinity for the dopamine D_{2A} receptor (cf. **12b**). These observations are in line with SAR and QSAR studies performed on 2-pyrrolidinylmethyl-derived benzamides, which have shown that a 2,3-dimethoxy substitution pattern,[38–40] and the presence of a lipophilic and/or bulky substituent at the 5-position[19,41,42] are favourable for high dopamine D_2 receptor affinity. Therefore, the benzamide moieties of the 2-aminotetralin-derived benzamides presented here may occupy the same binding site as the 2-pyrrolidinylmethyl-derived benzamides.

Whereas 2-pyrrolidinylmethyl-derived substituted benzamides generally need several lipophilic substituents on the aromatic nucleus for high affinity, this is not

Table 1. Receptor binding data of compounds **12a–p, 13a–e, 14a–e, 15a–e**, and **16a–d**, haloperidol, and clozapine



			K_i (nM)[a]		
Compd	R	Ar	D_{2A}	D_3	5-HT_{1A}
12a	5-OCH_3	Ph[b]	3.2 ± 0.2	0.58 ± 0.05	0.82 ± 0.11
12b	5-OCH_3	2-OCH_3-Ph	22.9 ± 8.4	19.7 ± 5.6	15.2 ± 6.9
12c	5-OCH_3	2,3-di-OCH_3-Ph	6.7 ± 2.7	24.3 ± 1.4	12.7 ± 4.5
12d	5-OCH_3	2,6-di-OCH_3-Ph	47.9 ± 16.0	2.6 ± 0.1[c]	27.3 ± 1.6
12e	5-OCH_3	5-Br-2-OCH_3-Ph	9.4 ± 1.0	17.4 ± 0.5	38.5 ± 23.0
12f	5-OCH_3	5-I-2-OCH_3-Ph	6.9 ± 2.3	16.3 ± 0.7	75 ± 45
12g	5-OCH_3	5-Br-2-OH-Ph	79.8 ± 2.0	ND[d]	10.4 ± 1.6
12h	5-OCH_3	2-OH-5-I-Ph	266 ± 110	ND	21.9 ± 0.4
12i	5-OCH_3	2-OCH_3-5-SO_2NH_2-Ph	14.7 ± 2.7	20.3 ± 1.1	34.4 ± 6.4
12j	5-OCH_3	5-Br-2,6-di-OCH_3-Ph	42.8 ± 3.2	ND	53.9 ± 20.6
12k	5-OCH_3	4-NH_2-5-Cl-2-OCH_3-Ph	2.9 ± 0.5	2.5 ± 0.2	40.5 ± 1.5
12l	5-OCH_3	2-Thienyl	3.6 ± 0.2	0.69 ± 0.05	1.1 ± 0.1
12m	5-OCH_3	3-Thienyl	5.4 ± 1.8	ND	4.6 ± 0.5
12n	5-OCH_3	1-Napthyl	21.9 ± 0.3	ND	13.0 ± 2.8
12o	5-OCH_3	2-Naphthyl	18.5 ± 2.9	ND	20.2 ± 3.8
12p	5-OH	Ph	1.4 ± 0.2	0.28 ± 0.03	1.5 ± 0.4
13a	6-OCH_3	Ph	70.8 ± 7.6	ND	16.8 ± 4.3
13b	6-OCH_3	2,3-di-OCH_3-Ph	10.1 ± 1.0	ND	72.8 ± 12.4
13c	6-OCH_3	2,6-di-OCH_3-Ph	1070 ± 70	ND	93.0 ± 23.7
13d	6-OCH_3	2-Thienyl	112 ± 11	ND	61.1 ± 8.3
13e	6-OH	Ph	13.4 ± 2.4	ND	17.4 ± 4.7
14a	7-OCH_3	Ph	60.7 ± 0.9	14.3 ± 0.7[c]	4.2 ± 1.1
14b	7-OCH_3	2,3-di-OCH_3-Ph	3.7 ± 0.1	6.8 ± 0.4	12.7 ± 1.2
14c	7-OCH_3	2,6-di-OCH_3-Ph	366 ± 51	56.2 ± 0.2	32.8 ± 0.6
14d	7-OCH_3	2-Thienyl	110 ± 4	32.7 ± 6.6	12.2 ± 0.4
14e	7-OH	Ph	3.7 ± 0.1	0.50 ± 0.03	3.0 ± 1.2
15a	8-OCH_3	Ph	54.9 ± 1.8	4.5 ± 0.7	< 0.3
15b	8-OCH_3	2,3-di-OCH_3-Ph	1.0 ± 0.1	14.6 ± 0.4	0.76 ± 0.11
15c	8-OCH_3	2,6-di-OCH_3-Ph	89.5 ± 1.3	15.0 ± 2.0	1.0 ± 0.1
15d	8-OCH_3	2-Thienyl	60.3 ± 4.1	9.8 ± 1.8	0.73 ± 0.19
15e	8-OH	Ph	55.2 ± 2.2	6.8 ± 2.3[c]	< 0.3
16a	H	Ph	10.0 ± 0.8	0.46 ± 0.01	0.56 ± 0.05
16b	H	2,3-di-OCH_3-Ph	0.63 ± 0.1	7.4 ± 0.1	3.5 ± 0.3
16c	H	2,6-di-OCH_3-Ph	59.8 ± 9.3	2.6 ± 0.1	3.7 ± 0.4
16d	H	2-Thienyl	106 ± 18	ND	1.8 ± 0.3
Haloperidol			0.67 ± 0.11	2.7 ± 0.6	2,213 ± 585
Clozapine			59.8 ± 7.8	83.3 ± 9.9	304 ± 184

[a]Mean values ± SEM of two to four independent experiments.
[b]Ph: phenyl.
[c]Two binding sites significant.
[d]ND: not determined.

necessary for the 2-aminotetralin-derived benzamides: comparison of the affinities of **12a** with those of **12b–k** shows that attachment of substituents on the benzamide nucleus generally leads to somewhat lower affinities. Furthermore, the benzene ring of the benzamide moiety of **12a** can be replaced by aromatic isosteres of comparable size, such as 2-thiophene (**12l**) and 3-thiophene (**12m**) without seriously affecting the affinities for the receptors. A similar isosteric replacement in **15a** does not affect the receptor binding (cf. **15d**) either, but in **13a, 14a**, and **16a** it results in lower affinities (cf. **13d, 14d** and **16d**, respectively). Replacement by larger

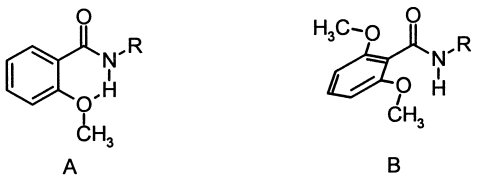


Figure 2. Conformational differences between 2-methoxy (A) and 2,6-dimethoxy-substituted (B) benzamides: intramolecular hydrogen bond formation in A results in a coplanar benzene ring and amide, whereas in B the presence of a second *ortho*-methoxy group causes steric hindrance with the carbonyl oxygen atom and hence an out-of-plane twisted benzene ring.

aromatic systems, such as 1-naphthalene (**12n**) or 2-naphthalene (**12o**) results in somewhat lower affinities when compared to their benzene analogue (**12a**). Apparently, these groups are too bulky to be accommodated optimally by the receptors.

When the effects of the differently substituted aminotetralin moieties are examined, several conclusions can be drawn. First, when comparing the dopaminergic affinities of 5-, 6- and 7-methoxy-substituted congeners with identically substituted benzamide moieties (e.g. **12a, 13a**, and **14a**), the general order of potency (except for the 2,3-dimethoxy-substituted benzamides) is 5-OCH_3 > 7-OCH_3 > 6-OCH_3. Furthermore, the hydroxy-substituted congeners (**12p, 13e**, and **14e**) all have higher affinitities than their methoxy-substituted analogues. In addition, all congeners with an 8-methoxy substitutent have a very high affinity for the serotonin 5-HT_{1A} receptor. Similar to 8-OH-DPAT,[43] replacement of the 8-methoxy group by a hydroxy group (cf. **15a** and **e**) does not affect the affinity for the serotonin 5-HT_{1A} receptor. Nevertheless, the binding data of compounds **16a–d** show that substituents on the aminotetralin nucleus are not a prerequisite for high affinities. Taken together, these structure–affinity relationships are consistent with those of the DPATs[23,27–29,31] and suggest that the 2-aminotetralin part of the molecules occupy the same binding sites as the DPATs.

Finally, the binding data suggest that attachment of a 2-benzamidoethyl side chain to the basic nitrogen atom of differently substituted 2-(N-*n*-propylamino)tetralins enhances the affinities for the dopamine D_2 and D_3, as well as for the serotonin 5-HT_{1A} receptor, when compared to their DPAT analogues. For example, whereas 5-OH-DPAT (**4**) and 7-OH-DPAT (**6**) have virtually no serotonergic activity, their benzamide analogues **12p** and **14e** have high affinities for the serotonin 5-HT_{1A} receptor. On the other hand, compound **15e** has moderate and high affinity for the dopamine D_2 and D_3 receptor, respectively, whereas 8-OH-DPAT (**7**) is devoid of dopaminergic activity. The observation that the large 2-benzamidoethyl side chain is tolerated well by the three receptor subtypes is constistent with the requirements for the nitrogen substituents of the DPATs, where only one substituent larger than *n*-propyl is allowed.[43–49] Taken together, the findings suggest that the 2-benzamidoethyl side chain may occupy an accessory binding site in all three receptor subtypes, thereby enhancing the affinities for the receptors. For the dopaminergic receptors, this accessory binding site may prove to be identical to the binding site of the 2-pyrrolidinylmethyl-derived substituted benzamides, as noted earlier.

Since both the DPATs and the 2-pyrrolidinylmethyl-derived substituted benzamides display high stereoselectivity in their interactions with the receptors, it may be anticipated that this will also be the case for the 2-aminotetralin-derived benzamides. Therefore, compounds **12a** and **d** were selected for enantiopure synthesis and assessment of the in vitro receptor binding profiles and the intrinsic efficacies at dopamine D_2, D_3 and serotonin 5-HT_{1A} receptors of their enantiomers.

Conclusions

A series of compounds with mixed dopamine D_2, D_3, and serotonin 5-HT_{1A} receptor binding profiles was designed by combining the structural and pharmacological features of two distinct classes of compounds, the 2-pyrrolidinylmethyl-derived substituted benzamides and the DPATs, into a new basic skeleton. Several compounds display high affinities for both dopamine D_2 and D_3, and serotonin 5-HT_{1A} receptors. Provided that they have the desired intrinsic efficacies at the indicated receptor subtypes, these compounds may be interesting candidates for further evaluation of the dopamine D_2/serotonin 5-HT_{1A} hypothesis of atypical antipsychotic activity.

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 etheral 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 (E. 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 (E. 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 the solvent and converted to the TMS scale, using 7.26 for $CDCl_3$ and 3.30 for CD_3OD. 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 the solvent and converted to the TMS scale, using 76.91 for $CDCl_3$ and 49.50 for CD_3OD. Chemical ionization (CI) mass spectra were recorded on a Finnegan 3300 quadrupole mass spectrometer. Ammonia was used as the reactant gas and samples were introduced into the ion source by means of the direct insertion probe. Alternatively, chemical ionization mass spectra were recorded on a NERMAG R 3010 triple quadrupole mass spectrometer equipped with a home-built atmospheric pressure ionization source and ionspray interface. Electron impact (EI) mass spectra were recorded on a Unicam 610/Automass 150 mass spectrometer in conjunction with a gas chromatograph. Elemental analyses (C, H, and N) for target compounds were performed at the Micro Analytical Department, University of Groningen, and unless otherwise indicated, the obtained results were within 0.4% of the theoretical values.

General procedure for the preparation of compounds 10a–e

The method adopted for the synthesis of 5-methoxy-2-(N-cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (**10a**) is described: bromoacetonitrile (1.17 g, 9.8 mmol) was added to a suspension of **9a**·HCl[33] (1.00 g, 3.9 mmol), K_2CO_3 (1.35 g, 9.8 mmol) and KI (0.16 g, 0.1 mmol) in acetone (50 mL). The reaction mixture was refluxed for 18 h under a nitrogen atmosphere. After cooling, the solids were removed by filtration and the filtrate was concentrated under reduced pressure, which yielded the crude nitrile as a dark brown oil. Purification by column chromatography (eluent: CH_2Cl_2) gave 0.86 g (3.3 mmol) of the pure base of **10a** as a colourless oil, which was converted to the hydrochloride salt.

5-Methoxy-2-(N-cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (10a). Yield 85%; mp 183–186 °C; IR: cm^{-1} 2924, 2832, 2739, 2347 (b), 1590; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H), 1.46–1.75 (m, 3H), 2.14–2.22 (m, 1H), 2.52–3.07 (m, 7H), 3.68 (s, 2H), 3.84 (s, 3H), 6.72 (dd, J = 8.4 Hz, 8.4 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 20.9, 26.5, 33.2, 38.6, 52.1, 55.2, 57.7, 107.2, 116.9, 121.5, 124.8, 126.4, 136.4, 157.1; MS (EI, 70 eV) m/z (rel. intensity) 104 (47), 123 (60), 134 (64), 161 (100), 229 (33), 258 (58, M^+).

6-Methoxy-2-(N-cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (10b). Using the general procedure, this compound was prepared from **9b**·HCl.[34] Yield 30%; mp 138–140 °C; IR: cm^{-1} 2936, 2839, 2344 (b), 1611; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.93, (t, J = 7.3 Hz, 3H), 1.46–1.78 (m, 3H), 2.07–2.17 (m, 1H), 2.65–3.03 (m, 7H), 3.66 (s, 2H), 3.77 (s, 3H), 6.63 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 8.3 Hz, 2.7 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.3, 20.7, 26.5, 28.8, 32.1, 38.4, 51.9, 55.0, 58.1, 112.0, 113.0, 116.8, 126.8, 130.1, 136.8, 157.7; MS (EI, 70 eV): m/z (rel. intensity) 91 (41), 134 (98), 161 (100), 199 (15), 229 (52), 258 (61, M^+).

7-Methoxy-2-(N-cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (10c). This compound was synthesized from **9c**·HCl[33] using the general procedure. Yield 73%; mp 144–146 °C; IR: cm^{-1} 2922, 2832, 2737, 2365 (b), 1616; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.96 (t, J = 7.3 Hz, 3H), 1.44–1.71 (m, 3H), 2.09–2.17 (m, 1H), 2.66–3.00 (m, 7H), 3.64 (s, 2H), 3.77 (s, 3H), 6.64–6.74 (m, 2H), 7.00 (dd, J = 8.6 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.4, 20.7, 26.8, 27.8, 33.1, 38.4, 51.8, 55.0, 58.0, 112.3, 113.7, 116.9, 127.8, 129.3, 136.1, 156.7; MS (EI, 70 eV): m/z (rel. intensity) 91 (24), 134 (100), 161 (85), 218 (20), 229 (20), 258 (54, M^+).

8-Methoxy-2-(N-cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (10d). Using the general procedure, this compound was prepared from **9d**·HCl.[33] Yield 62%; mp 163–164 °C; IR: cm^{-1} 2943, 2839, 2305 (b), 1584; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.99 (t, J = 7.3 Hz, 3H), 1.48–1.75 (m, 3H), 2.13–2.20 (m, 1H), 2.53 (dd, J = 16.0 Hz, 9.6 Hz, 1H), 2.74 (dd, J = 7.2 Hz, 7.2 Hz, 2H), 2.84–3.13 (m, 4H), 3.68 (s, 2H), 3.85 (s, 3H), 6.72 (dd, J = 8.4 Hz, 8.4 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.4, 20.8, 26.1, 26.8, 29.0, 38.4, 52.0, 55.0, 57.9, 106.8, 116.9, 120.6, 123.7, 126.2, 137.2, 157.3; MS (EI, 70 eV): m/z (rel. intensity) 91 (16), 104 (27) 123 (20), 134 (28), 161 (100), 229 (24), 258 (47, M^+).

2-(N-Cyanomethyl-N-*n*-propylamino)tetralin hydrochloride (10e). Using the general procedure, this compound was prepared from **9e**·HCl.[32] Yield 69%; mp

158–160 °C; IR: cm^{-1} 3138, 3022, 2933, 2364 (b) 1578; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.3$ Hz, 3H), 1.44–1.83 (m, 3H), 2.12–2.20 (m, 1H), 2.73 (dd, $J = 7.5$ Hz, 7.5 Hz, 2H), 2.82–3.09 (m, 5H), 3.69 (s, 2H), 7.14 (s, 4H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 20.9, 26.8, 28.8, 33.1, 38.9, 52.1, 58.1, 116.9, 125.8, 126.0, 128.6, 129.4, 135.0, 135.9; MS (EI, 70 eV): *m/z* (rel. intensity) 104 (22), 131 (100), 199 (18), 228 (16, M^+).

General procedure for the preparation of compounds 11a–e

The method adopted for the synthesis of 5-methoxy-2-[N-(2-aminoethyl)-N-*n*-propylamino]tetralin dihydrochloride (**11a**) is described: a solution of the free base of **10a** (10.00 g, 38.7 mmol) in dry THF (75 mL) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (3 g) in dry THF (75 mL). When addition was complete, the reaction mixture was refluxed overnight under a nitrogen atmosphere. After cooling, excess $LiAlH_4$ was quenched by subsequent addition of H_2O (3 mL), 4 N aqueous NaOH solution (3 mL) and H_2O (9 mL). After drying over Na_2SO_4, the suspension was filtrated and the filtrate was concentrated under reduced pressure, yielding 10.09 g (38.5 mmol) of the pure base of **11a** as a clear yellow oil, which was converted to the dihydrochloride salt.

5-Methoxy-2-[N-(2-aminoethyl)-N-*n*-propylamino]tetralin dihydrochloride (11a). Yield 99%; mp 112–114 °C (lit.[46] mp 110–112 °C); IR: cm^{-1} 3406 (b), 2965, 2836, 2631 (b), 2520 (b), 2063 (b), 1588; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.39–1.55 (m, 5H), 1.97–2.04 (m, 1H), 2.41–3.02 (m, 11H), 3.75 (s, 3H), 6.62 (dd, $J = 15.6$ Hz, 7.8 Hz, 2H), 7.04 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.1, 23.7, 25.2, 32.0, 40.5, 52.3, 52.9, 54.8, 55.9, 106.6, 121.5, 125.0, 126.0, 137.9, 157.1; MS (EI, 70 eV): *m/z* (rel. intensity) 72 (10), 161 (50), 232 (100), 262 (1, M^+).

6-Methoxy-2-[N-(2-aminoethyl)-N-*n*-propylamino]tetralin dihydrochloride (11b). Using the general procedure, this compound was prepared from **10b**. Yield 98%; mp 113–115 °C; IR: cm^{-1} 3414 (b), 2965, 2837, 2639 (b), 2517, 2055 (b), 1610; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.40–1.69 (m, 3H), 1.95–2.15 (m, 1H), 2.43–2.95 (m, 11H), 3.75 (s, 3H), 6.61 (d, $J = 2.2$ Hz, 1H), 6.66 (dd, $J = 8.3$ Hz, 2.7 Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.1, 25.5, 30.0, 31.0, 40.4, 52.4, 52.9, 55.0, 56.5, 111.8, 113.0, 128.5, 130.1, 137.4, 157.5; MS (CI with AcOH): *m/z* (rel. intensity) 220 (7), 234 (14), 263 (100, M + 1).

7-Methoxy-2-[N-(2-aminoethyl)-N-*n*-propylamino]tetralin oxalate (11c). Using the general procedure, this compound was prepared from **10c**. Yield 97%; mp 168–170 °C; IR: cm^{-1} 2937, 2836, 2670 (b), 2527 (b), 1719, 1612; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.40–1.65 (m, 3H), 1.93–2.02 (m, 3H), 2.43–2.59 (m, 4H), 2.67–2.96 (m, 7H), 3.75 (s, 3H), 6.61–6.69 (m, 2H), 6.95–6.99 (m, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.1, 25.7, 28.9, 32.2, 40.3, 52.3, 52.8, 55.0, 56.3, 111.9, 113.7, 128.4, 129.3, 137.6, 157.4; MS (CI with AcOH): *m/z* 220 (7), 234 (5), 263 (100, M + 1).

8-Methoxy-2-[N-(2-aminoethyl)-N-*n*-propylamino]tetralin dihydrochloride (11d). Using the general procedure, this compound was prepared from **10d**. Yield 97%; mp 155–157 °C; IR: cm^{-1} 3396 (b), 2939, 2837, 2637 (b), 2520 (b), 1587; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, $J = 7.3$ Hz, 3H), 1.39–1.70 (m, 3H), 1.80 (bs, 2H), 1.91–2.03 (m, 1H), 2.36–3.01 (m, 11H), 3.82 (s, 3H), 6.68 (dd, $J = 8.8$ Hz, 8.8 Hz, 2H), 7.08 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.4, 25.6, 30.3, 40.6, 52.6, 53.1, 55.1, 56.6, 106.7, 120.8, 125.3, 125.9, 137.8, 157.5; MS (CI with AcOH): *m/z* (rel. intensity) 220 (23), 234 (32), 263 (100, M + 1).

2-[N-(2-Aminoethyl)-N-*n*-propylamino]tetralin dihydrochloride (11e). Using the general procedure, this compound was prepared from **10e**. Yield 96%; mp 138–141 °C; IR: cm^{-1} 3402 (b), 2965, 2643 (b), 2522 (b), 2043 (b), 1607; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, $J = 7.3$ Hz, 3H), 1.39–1.68 (m, 5H), 1.96–2.06 (m, 1H), 2.46–3.01 (m, 11H), 7.10 (s, 4H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.3, 25.8, 29.9, 32.1, 40.7, 52.6, 53.1, 56.5, 125.6, 128.6, 129.4, 135.0, 135.5; MS (EI, 70 eV): *m/z* (rel. intensity) 72 (23), 131 (100), 202 (79), 232 (2, M^+).

General procedures for the preparation of compounds 12a–o, 13a–d, 14a–d, 15a–d and 16a–d

Method A. The method adopted for the synthesis of 5-methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (**12a**) is described: benzoyl chloride (4.70 g, 33.4 mmol), dissolved in CH_2Cl_2 (25 mL), was added dropwise to a firmly stirred mixture of CH_2Cl_2 (225 mL), 10% aqueous NaOH solution (40 mL) and **11a** (4.00 g, 11.9 mmol). After stirring overnight at room temperature, the reaction mixture was poured into H_2O (50 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL), the organic layers were combined and subsequently washed with saturated aqueous $NaHCO_3$ solution (3×100 mL), H_2O (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtrated and concentrated under reduced pressure, which gave the crude amide as a brown oil. Purification by column chromatography (eluent: MeOH/CH_2Cl_2, 1/15 (v/v)) yielded 1.68 g (4.6 mmol) of the pure base of **12a** as a colourless oil, which was converted to the hydrochloride salt.

Method B. The method adopted for the synthesis of 5-methoxy-2-{N-[2-(2,3-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (**12c**) is described: a solution of 2,3-dimethoxybenzoyl chloride (0.72 g, 3.6 mmol) in $CDCl_3$ (10 mL) was added dropwise to a boiling solution of the free base of **11a** (0.375 g, 1.4 mmol) in $CDCl_3$ (15 mL). When addition was complete, the reaction mixture was allowed to cool to room temperature and stirring was continued overnight. The reaction mixture was transferred to a separatory funnel and subsequently washed with saturated $NaHCO_3$ solution (3×20 mL), H_2O (20 mL) and brine (20 mL). After drying (Na_2SO_4) and filtration, the organic layer was concentrated under reduced pressure, which gave the crude amide as a brown oil. Purification by column chromatography (eluent: $MeOH/CH_2Cl_2$, 1/20 (v/v)) yielded 0.28 g (0.7 mmol, 46%) of the pure base of **12c** as a colourless oil, which was converted to the hydrochloride salt.

Method C. The method adopted for the synthesis of 5-methoxy-2-{N-[2-(4-amino-5-chloro-2-methoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (**12k**) is described: ethyl chloroformate (81 mg, 0.7 mmol) was added to a stirred solution of 4-amino-5-chloro-2-methoxybenzoic acid (150 mg, 0.7 mmol) and triethylamine (75 mg, 0.7 mmol) in acetone (5 mL) at 0 °C. Stirring was continued for 1 h at 0 °C, upon which a white solid precipitated. Then **11a** (250 mg, 0.7 mmol) was added, immediately followed by a second amount of triethylamine (100 mg, 1.0 mmol). Stirring was again continued for 1 h at 0 °C, and then the precipitate was removed from the reaction mixture by filtration. The filtrate was concentrated under reduced pressure, the resulting residue was dissolved in CH_2Cl_2 (50 mL) and the organic solution was subsequently washed with saturated aqueous $NaHCO_3$ solution (3×25 mL), H_2O (25 mL) and brine (25 mL). After drying (Na_2SO_4) and filtration, the organic solution was concentrated in vacuo, which yielded the crude amide as a light brown oil. After purification by column chromatography (eluent: $MeOH/CH_2Cl_2$, 1/15 (v/v)), 150 mg (0.3 mmol, 43%) of the pure base of **12k** was obtained as a colourless oil, which was converted to the hydrochloride salt.

5-Methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (12a). Method A. Yield 39%; mp 91–93 °C; IR: cm^{-1} 3267, 2938, 2836, 2611 (b), 2517 (b), 1654, 1588, 1540; 1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.42–1.71 (m, 3H), 1.99–2.08 (m, 1H), 2.45–2.63 (m, 3H), 2.75–2.86 (m, 4H), 2.93–3.07 (m, 2H), 3.45–3.55 (m, 2H), 3.80 (s, 3H), 6.67 (dd, J = 7.4 Hz, 7.4 Hz, 2H), 7.06–7.13 (m, 2H), 7.40–7.52 (m, 3H), 7.78–7.83 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.8, 23.5, 25.3, 31.9, 37.6, 48.3, 51.9, 55.0, 55.6, 106.8, 121.4, 124.9, 126.1, 126.7, 128.4, 131.1, 134.6, 137.3, 157.1, 167.1; MS (CI with NH_3): m/z (rel. intensity) 78 (6), 161 (2), 232 (8), 367 (100, M + 1); Anal. ($C_{23}H_{30}N_2O_2 \cdot HCl \cdot ¼H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(2-methoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12b). Method B. Yield 92%; mp 88–92 °C; IR: cm^{-1} 3335 (b), 2939, 2837, 2593 (b), 2499 (b), 1640, 1597, 1523; 1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.43–1.71 (m, 3H), 2.02–2.12 (m, 1H), 2.46–3.10 (m, 9H), 3.53–3.61 (m, 2H), 3.81 (s, 3H), 3.98 (s, 3H), 6.68 (dd, J = 7.3 Hz, 7.3 Hz, 2H), 6.97–7.14 (m, 3H), 7.41–7.50 (m, 1H), 8.26 (dd, J = 7.9 Hz, 1.9 Hz, 1H), 8.43 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.3, 23.9, 25.5, 32.1, 38.4, 48.7, 52.3, 55.2, 55.7, 56.1, 106.9, 111.2, 121.1, 121.5, 121.8, 125.1, 126.2, 132.2, 132.5, 137.8, 157.2, 157.6, 165.1; MS (CI with NH_3): m/z (rel. intensity) 72 (21), 135 (41), 161 (62), 178 (14), 232 (100), 397 (38, M + 1); Anal. ($C_{24}H_{32}N_2O_3 \cdot HCl \cdot ¼H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(2,3-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12c). Method B. Yield 46%; mp 113–116 °C; IR: cm^{-1} 3420 (b), 2981, 2838, 2667 (b), 2519 (b), 1660, 1611, 1538; 1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, J = 7.3 Hz, 3H), 1.41–1.69 (m, 3H), 2.02–2.12 (m, 1H), 2.43–2.61 (m, 3H), 2.74–3.06 (m, 6H), 3.51–3.59 (m, 2H), 3.80 (s, 3H), 3.91 (s, 6H), 6.67 (dd, J = 8.5 Hz, 8.5 Hz, 2H), 7.01–7.19 (m, 3H), 7.71 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 8.40 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.1, 23.6, 25.3, 31.7, 38.2, 48.7, 52.1, 55.0, 55.8, 56.1, 61.1, 106.7, 114.9, 121.5, 122.7, 124.1, 125.0, 126.0, 126.9, 137.7, 147.5, 152.5, 157.1, 165.0; MS (CI with NH_3): m/z (rel. intensity) 182 (6), 232 (6) 427 (100, M + 1); Anal. ($C_{25}H_{34}N_2O_4 \cdot HCl \cdot H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(2,6-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12d). Method A. Yield 59%; mp 113–116 °C; IR: cm^{-1} 3400 (b), 2939, 2837, 2630 (b), 2519 (b), 1655, 1595, 1524; 1H NMR (base, 200 MHz, $CDCl_3$): δ 0.86 (t, J = 7.3 Hz, 3H), 1.41–1.61 (m, 3H), 1.99–2.05 (m, 1H), 2.43–2.55 (m, 3H), 2.73–2.88 (m, 4H), 2.94–3.05 (m, 2H), 3.49–3.56 (m, 2H), 3.80 (s, 9H), 6.43 (bs, 1H), 6.56 (d, J = 8.6 Hz, 2H), 6.66 (dd, J = 7.1 Hz, 7.1 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.8, 23.6, 25.2, 31.8, 37.6, 48.7, 51.9, 55.0, 55.6, 55.8, 103.7, 106.8, 116.1, 121.4, 124.9, 126.1, 130.3, 137.7, 157.1, 157.3, 165.6; MS (CI with NH_3): m/z (rel. intensity) 232 (6), 427 (100, M + 1); Anal. ($C_{25}H_{34}N_2O_4 \cdot HCl \cdot ½H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(5-bromo-2-methoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12e). Method A. Yield 49%; mp 108–110 °C; IR: cm^{-1} 3328 (b), 2938, 2837, 2596 (b), 2478 (b), 1649, 1590, 1522; 1H NMR

(base, 300 MHz, $CDCl_3$): δ 0.91 (t, $J=7.3$ Hz, 3H), 1.56–1.70 (m, 3H), 2.11–2.13 (m, 1H), 2.47–2.66 (m, 3H), 2.82–3.13 (m, 6H), 3.55–3.62 (m, 2H), 3.79 (s, 3H), 3.96 (s, 3H), 6.66 (dd, $J=7.9$ Hz, 3.8 Hz, 2H), 6.87 (d, $J=8.8$ Hz, 1H), 7.08 (t, $J=7.9$ Hz, 1H), 7.52 (dd, $J=8.8$ Hz, 2.9 Hz, 1H), 8.30 (d, $J=2.6$ Hz, 1H), 8.45 (bs, 1H); ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 11.6, 23.5, 38.0, 49.0, 55.1, 56.0, 107.0, 113.1, 113.6, 121.3, 123.3, 124.7, 126.3, 129.2, 134.7, 135.0, 156.6, 157.1, 163.8; MS (CI with NH_3): *m/z* (rel. intensity) 72 (19), 161 (27), 232 (58), 475 (100, M[Br = 79] + 1), 477 (100, M[Br = 81] + 1); Anal. ($C_{24}H_{31}N_2O_3Br{\cdot}HCl{\cdot}H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(5-iodo-2-methoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12f). Method A. Yield 46%; mp 110–112 °C; IR: cm^{-1} 3337 (b), 2937, 2837, 2598 (b), 2502 (b), 1644, 1586, 1523; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, $J=7.3$ Hz, 3H), 1.45–1.68 (m, 3H), 2.03–2.08 (m, 1H), 2.47–2.59 (m, 3H), 2.72–2.83 (m, 4H), 2.97–3.05 (m, 2H), 3.51–3.57 (m, 2H), 3.80 (s, 3H), 3.94 (s, 3H), 6.66 (dd, $J=7.3$ Hz, 7.3 Hz, 2H), 6.75 (d, $J=8.8$ Hz, 1H), 7.08 (t, $J=7.8$ Hz, 1H), 7.70 (dd, $J=8.8$ Hz, 2.6 Hz, 1H), 8.32 (bs, 1H), 8.49 (d, $J=2.6$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.9, 23.7, 25.3, 31.9, 38.2, 48.7, 52.2, 55.1, 55.8, 56.2, 106.9, 107.7, 113.5, 121.4, 123.8, 124.9, 126.1, 128.5, 140.6, 140.8, 157.1, 157.2, 163.5; MS (CI with NH_3): *m/z* (rel. intensity) 161 (4), 232 (10), 523 (100, M + 1); Anal. ($C_{24}H_{31}N_2O_3I{\cdot}HCl{\cdot}H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(5-bromo-2-hydroxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12g). Method B. Yield 15%; mp 106–109 °C; IR: cm^{-1} 3225 (b), 2937, 2837, 2608 (b), 2508 (b), 1638, 1589, 1542; ^{1}H NMR (200 MHz, CD_3OD): δ 1.02 (t, $J=7.3$ Hz, 3H), 1.74–1.95 (m, 3H), 2.31 (bs, 1H), 2.55–2.68 (m, 1H), 3.01–3.42 (m, 9H), 3.49–3.62 (m, 2H), 3.75 (s, 3H), 6.71 (m, 2H), 6.85 (d, $J=8.8$ Hz, 1H), 7.06 (t, $J=7.9$ Hz, 1H), 7.47 (dd, $J=8.8$ Hz, 2.6 Hz, 1H), 7.94 (d, $J=2.2$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.3, 17.7, 22.6, 23.8, 28.6, 35.7, 51.5, 54.5, 55.3, 60.6, 108.0, 110.9, 115.3, 119.9, 121.1, 124.5, 127.3, 130.0, 132.4, 137.2, 157.1, 160.5, 169.8; MS (CI with NH_3): *m/z* (rel. intensity) 72 (24), 91 (10), 161 (76), 232 (100), 461 (17, M[Br = 79] + 1), 463 (17, M[Br = 81] + 1); Anal. ($C_{23}H_{29}N_2O_3Br{\cdot}HCl{\cdot}½H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(2-hydroxy-5-iodo)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12h). Method B. Yield 68%; mp 102–105 °C; IR: cm^{-1} 3414 (b), 3216 (b), 2939, 2836, 2610 (b), 2510 (b), 1637, 1588, 1542; ^{1}H NMR (300 MHz, CD_3OD): δ 1.06 (t, $J=7.1$ Hz, 3H), 1.83–1.95 (m, 3H), 2.33–2.38 (m, 1H), 2.62–2.70 (m, 1H), 3.07–3.43 (m, 7H), 3.61–3.64 (m, 1H), 3.80 (s, 3H), 3.81–3.83 (m, 2H), 6.69–6.77 (m, 3H), 7.11 (t, $J=8.1$ Hz, 1H), 7.68 (dd, $J=8.5$ Hz, 2.2 Hz, 1H), 8.15 (d, $J=2.0$ Hz); ^{13}C NMR (300 MHz, CD_3OD): δ 11.3, 19.5, 23.6, 24.6, 30.6, 37.3, 52.2, 54.4, 55.8, 61.9, 109.0, 119.5, 120.6, 122.3, 124.5, 128.2, 134.5, 138.8, 143.7, 158.5, 159.8, 170.4; MS (CI with NH_3): *m/z* (rel. intensity) 180 (16), 223 (12), 383 (100), 509 (7, M + 1); Anal. ($C_{23}H_{29}N_2O_3I{\cdot}HCl$) C, H, N.

5-Methoxy-2-{N-[2-(2-methoxy-5-sulfamoyl)benzamidoethyl]-N-*n*-propylamino}-tetralin hydrochloride (12i). Method C. Yield 32%; mp 177–178 °C; IR: cm^{-1} 3317, 3188 (b), 3072 (b), 2941, 2841, 2485 (b), 2363, 1632, 1591, 1528; ^{1}H NMR (300 MHz, CD_3OD): δ 1.07 (t, $J=7.6$ Hz, 3H), 1.87–1.96 (m, 3H), 2.34–2.42 (m, 1H), 2.62–2.70 (m, 1H), 3.07–3.45 (m, 6H), 3.63–3.69 (m, 1H), 3.80 (s, 3H), 3.83–3.89 (m, 3H), 4.05 (s, 3H), 6.68–6.77 (m, 2H), 7.11 (t, $J=7.3$ Hz, 1H), 7.31 (d, $J=8.8$ Hz, 1H), 8.04 (dd, $J=8.8$ Hz, 2.4 Hz, 1H), 8.50 (d, $J=2.0$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 10.6, 18.8, 22.9, 23.8, 30.0, 37.3, 52.0, 53.9, 55.1, 56.7, 61.1, 108.3, 112.9, 121.3, 121.6, 123.9, 127.5, 130.1, 132.1, 133.9, 136.9, 157.8, 161.0, 167.8; MS (EI, 70 eV): *m/z* 86 (68), 161 (100), 204 (49), 232 (71), 355 (7), 377 (9), 432 (4), 461 (7), 475 (13, M^+); Anal. ($C_{24}H_{34}N_3O_5S{\cdot}HCl$) C, H, N.

5-Methoxy-2-{N-[2-(5-bromo-2,6-dimethoxy)benzamidoethyl]-N-*n*-propylamino}-tetralin hydrochloride (12j). Method B. Yield 36%; mp 193–195 °C; IR: cm^{-1} 3183, 2940, 2835, 2575 (b), 1661, 1587, 1541; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.85 (t, $J=7.3$ Hz, 3H), 1.40–1.64 (m, 3H), 1.96–2.05 (m, 1H), 2.24–3.04 (m, 9H), 3.47–3.57 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 6.45 (bs, 1H), 6.58–6.70 (m, 3H), 7.10 (t, $J=7.8$ Hz, 1H), 7.49 (d, $J=8.8$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 21.6, 23.5, 25.1, 31.7, 37.8, 48.5, 52.0, 55.0, 55.8, 62.2, 106.8, 108.0, 108.2, 121.4, 123.0, 124.9, 126.1, 133.7, 137.5, 154.6, 156.5, 157.1, 164.4; MS (CI with AcOH): *m/z* (rel. intensity) 506 (94, M[Br = 79] + 1), 508 (100, M[Br = 81] + 1); Anal. ($C_{25}H_{33}N_2O_4Br{\cdot}HCl{\cdot}¼H_2O$) C, H, N.

5-Methoxy-2-{N-[2-(4-amino-5-chloro-2-methoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (12k). Method C. Yield 43%; mp 135–137 °C; IR: cm^{-1} 3394, 3319, 3204, 2940, 2835, 2434 (b), 1637, 1589, 1534; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, $J=7.3$ Hz, 3H), 1.40–1.68 (m, 3H), 2.02–2.11 (m, 1H), 2.42–2.58 (m, 3H), 2.66–2.81 (m, 4H), 2.94–3.05 (m, 2H), 3.46–3.52 (m, 2H), 3.79 (s, 3H), 3.87 (s, 3H), 4.48 (bs, 2H), 6.32 (s, 1H), 6.66 (dd, $J=6.7$ Hz, 6.7 Hz, 2H), 7.07 (t, $J=7.8$ Hz, 1H), 8.11 (s, 1H), 8.24 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 21.8, 23.6, 25.1, 31.7, 38.0, 48.6, 52.1, 55.0, 55.7, 55.9, 97.6, 106.8, 111.2, 112.4, 121.4, 124.9, 126.1, 132.9, 137.5, 146.5, 157.1, 157.5, 164.4; MS (CI with NH_3): *m/z* (rel. intensity) 72

(17), 161 (18), 201 (14), 220 (21), 232 (15), 446 (100, M + 1); Anal. ($C_{24}H_{31}N_3O_3$·HCl) C, H, N.

5-Methoxy-2-[N-(2-thiophen-2-carboxamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (12l). Method A. Yield 62%; mp 102–105 °C; IR: cm^{-1} 3238 (b), 2938, 2836, 2608 (b), 2497 (b), 1640, 1588, 1543; ^1H NMR (300 MHz, CD_3OD): δ 1.00 (m, 3H), 1.84–2.18 (m, 3H), 2.52–2.65 (m, 2H), 2.96–3.04 (m, 2H), 3.08–3.47 (m, 4H), 3.61–3.70 (m, 2H), 3.79 (s, 3H), 3.89–3.99 (m, 2H), 6.62 (dd, J = 33.5 Hz, 7.5 Hz, 1H), 6.75 (dd, J = 8.1 Hz, 2.20 Hz, 1H), 7.04–7.18 (m, 2H), 7.66–7.70 (m, 1H), 8.18 (dd, J = 7.3 Hz, 3.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.0, 17.4, 22.4, 28.4, 30.0, 35.8, 51.5, 54.4, 55.0, 60.6, 107.7, 121.0, 123.1, 127.0, 128.1, 129.4, 130.5, 132.6, 138.3, 156.9, 162.7; MS (CI with NH_3): m/z (rel. intensity) 161 (3), 232 (6), 373 (100, M + 1); Anal. ($C_{21}H_{28}N_2O_2S$·HCl·¼H_2O) C, H, N.

5-Methoxy-2-[N-(2-thiophen-3-carboxamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (12m). Method B. Yield 20%; mp 93–95 °C; IR: cm^{-1} 3232 (b), 3061, 2938, 2835, 2479 (b), 1653, 1588, 1543; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.46–1.66 (m, 3H), 2.00–2.05 (m, 1H), 2.55 (dd, J = 7.4 Hz, 7.4 Hz, 3H), 2.74–2.83 (m, 4H), 2.94–3.06 (m, 2H), 3.44–3.52 (m, 2H), 3.81 (s, 3H), 6.68 (dd, J = 6.7 Hz, 6.7 Hz, 2H), 6.94 (bs, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.32–7.41 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.6, 23.4, 25.2, 31.9, 37.3, 48.3, 51.9, 55.0, 55.7, 106.9, 121.4, 124.8, 125.8, 126.2, 126.3, 127.8, 137.2, 157.1, 162.8; MS (CI with AcOH): m/z 373 (M + 1); Anal. ($C_{21}H_{28}N_2O_2S$·HCl·¼H_2O) C, H, N.

5-Methoxy-2-[N-(2-naphthalen-1-carboxamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (12n). Method B. Yield 45%; mp 152–153 °C; IR: cm^{-1} 3232 (b), 2939, 2835, 2512 (b), 1655, 1588, 1522; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.43–1.62 (m, 3H), 1.98–2.06 (m, 1H), 2.54 (dd, J = 7.3 Hz, 7.3 Hz, 3H), 2.75–2.79 (m, 4H), 2.89–3.08 (m, 2H), 3.50–3.61 (m, 2H), 3.81 (s, 3H), 6.65 (dd, J = 7.8 Hz, 4.2 Hz, 2H), 6.91 (bs, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.42–7.64 (m, 4H), 7.89 (dd, J = 7.8 Hz, 7.8 Hz, 2H), 8.39–8.44 (m, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.7, 21.9, 23.6, 25.2, 31.9, 38.0, 48.5, 52.1, 55.0, 55.8, 106.9, 121.5, 124.7, 124.8, 124.9, 125.5, 126.2, 126.8, 128.2, 130.1, 130.3, 133.6, 134.7, 137.5, 157.1, 169.4; MS (CI with AcOH): m/z 417 (M + 1); Anal. ($C_{27}H_{32}N_2O_2$·HCl·½H_2O) C, H, N.

2-[N-(2-Naphthalen-2-carboxamidoethyl)-N-*n*-propylamino]-5-methoxytetralin hydrochloride (12o). Method B. Yield 35%; mp 117–119 °C; IR: cm^{-1} 3246, 2938, 2835, 2479 (b), 1653, 1588, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): 0.92 (t, J = 7.3 Hz, 3H), 1.44–1.69 (m, 3H), 2.04–2.09 (m, 1H), 2.58 (dd, J = 7.3 Hz, 7.3 Hz, 3H), 2.79–2.83 (m, 4H), 2.95–3.05 (m, 2H), 3.51–3.61 (m, 2H), 3.78 (s, 3H), 6.65 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.8 Hz, 1H), 7.32 (bs, 1H), 7.49–7.59 (m, 2H), 7.82–7.94 (m, 4H), 8.34 (s, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.6, 23.5, 25.1, 31.8, 37.7, 48.4, 52.1, 55.0, 55.9, 106.9, 121.4, 123.4, 124.8, 126.2, 126.5, 127.3, 127.4, 127.6, 128.3, 128.9, 131.8, 132.6, 134.5, 137.1, 157.1, 167.2; MS (CI with AcOH): m/z 417 (M + 1); Anal. ($C_{27}H_{32}N_2O_2$·HCl·H_2O) C, H, N.

6-Methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (13a). Method A. Yield 77%; mp 76–78 °C; IR: cm^{-1} 3245 (b), 2938, 2835, 2479 (b), 1654, 1610, 1578, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.45–1.63 (m, 3H), 1.95–2.18 (m, 1H), 2.54 (dd, J = 7.3 Hz, 7.3 Hz, 2H), 2.70–3.09 (m, 7H), 3.47–3.58 (m, 2H), 3.75 (s, 3H), 6.61–6.71 (m, 2H), 6.95–7.15 (m, 2H), 7.38–7.49 (m, 3H), 7.79–7.83 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.7, 25.5, 29.7, 31.0, 37.7, 48.4, 52.0, 55.0, 56.3, 111.9, 113.0, 126.7, 130.1, 131.2, 134.6, 137.1, 157.6, 167.1; MS (EI, 70 eV): m/z (rel. intensity) 77 (28), 105 (36), 161 (100), 232 (83), 366 (2, M +); Anal. ($C_{23}H_{30}N_2O_2$·HCl·¼H_2O) C, H, N.

6-Methoxy-2-{N-[2-(2,3-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (13b). Method A. Yield 37%; mp 83–85 °C; IR: cm^{-1} 3353 (b), 2937, 2835, 2465 (b), 1647, 1611, 1578, 1505; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.40–1.72 (m, 3H), 1.98–2.16 (m, 1H), 2.49–2.60 (m, 2H), 2.68–3.04 (m, 7H), 3.50–3.58 (m, 2H), 3.74 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 6.59–6.69 (m, 2H), 6.94–7.17 (m, 3H), 7.70 (dd, J = 7.0 Hz, 1.7 Hz, 1H), 8.38 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.1, 25.6, 29.9, 30.8, 38.3, 48.8, 52.2, 55.0, 55.8, 56.7, 61.1, 111.8, 113.0, 114.9, 122.6, 124.1, 126.9, 128.2, 130.1, 137.3, 147.5, 152.5, 157.5, 165.0; MS (EI, 70 eV): m/z (rel. intensity) 91 (12), 122 (9), 161 (100), 202 (7), 232 (98), 383 (2), 426 (2, M^+); Anal. ($C_{25}H_{34}N_2O_4$·HCl·¼H_2O) C, H, N.

6-Methoxy-2-{N-[2-(2,6-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (13c). Method A. Yield 76%; mp 83–85 °C; IR: cm^{-1} 3240 (b), 2939, 2838, 2606 (b), 2499 (b), 1655, 1596, 1503; ^1H NMR (300 MHz, CD_3OD): δ 1.10 (t, J = 7.3 Hz, 3H), 1.88–2.00 (m, 3H), 2.35–2.37 (m, 1H), 2.98–3.27 (m, 5H), 3.36–3.44 (m, 2H), 3.60–3.65 (m 1H), 3.75 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.88–3.91 (m, 1H), 6.69–6.76 (m, 4H), 7.08 (d, J = 8.3 Hz, 1H), 7.35–7.39 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 11.3, 19.7, 24.5, 29.5, 37.9, 53.7, 54.3, 55.7, 56.4, 61.9, 105.1, 114.1, 115.1, 125.3, 131.2, 132.8, 137.1, 158.6, 159.9, 172.1; MS (EI, 70 eV): m/z (rel. intensity) 91 (18), 161 (100), 232 (98), 267 (10), 383 (5), 426 (3, M^+); Anal. ($C_{25}H_{34}N_2O_4$·HCl·½H_2O) C, H, N.

6-Methoxy-2-[N-(2-thiophen-2-carboxamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (13d). Method B. Yield 36%; mp 88–90 °C; IR: cm^{-1} 3244 (b), 3059, 2937, 2837, 2609 (b), 2486 (b), 1640, 1611, 1543; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, $J=7.3$ Hz, 3H), 1.42–1.74 (m, 3H), 1.96–2.03 (m, 1H), 2.54 (dd, $J=8.2$ Hz, 6.5 Hz, 2H), 2.63–3.09 (m, 7H), 3.39–3.51 (m, 2H), 3.76 (s, 3H), 6.60–6.71 (m, 2H), 6.95–7.10 (m, 3H), 7.43–7.53 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.6, 25.4, 29.7, 30.9, 37.4, 48.2, 52.0, 55.0, 56.2, 111.9, 113.0, 127.5, 127.7, 127.8, 129.4, 130.1, 137.1, 139.2, 157.6, 161.7; MS (EI, 70 eV): *m/z* (rel. intensity) 72 (24), 111 (27), 161 (100), 202 (14), 232 (63), 372 (3, M^+); Anal. ($C_{21}H_{28}N_2O_2S{\cdot}HCl{\cdot}¼H_2O$) C, H, N.

7-Methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (14a). Method A. Yield 45%; mp 70–72 °C; IR: cm^{-1} 3252 (b), 2937, 2836, 2590 (b), 2486 (b), 1655, 1611, 1578, 1533; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.93 (t, $J=7.5$ Hz, 3H), 1.44–1.76 (m, 3H), 1.97–2.07 (m, 1H), 2.57 (dd, $J=8.1$ Hz, 6.4 Hz, 2H), 2.77–2.83 (m, 6H), 3.00–3.11 (m, 1H), 3.46–3.58 (m, 2H), 3.77 (s, 3H), 6.61 (d, $J=2.6$ Hz, 1H), 6.70 (dd, $J=8.4$ Hz, 2.6 Hz, 1H), 7.00 (d, $J=8.4$ Hz, 1H), 7.04 (bs, 1H), 7.41–7.52 (m, 3H), 7.79–7.84 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.0, 26.0, 28.9, 32.3, 37.8, 48.6, 52.2, 55.2, 56.3, 112.2, 113.9, 126.8, 128.3, 128.5, 129.5, 131.3, 134.8, 137.3, 157.6, 167.2; MS (CI with NH_3): *m/z* 367 (M + 1); Anal. ($C_{23}H_{30}N_2O_2{\cdot}HCl$ $\cdot ½H_2O$) C, H, N.

7-Methoxy-2-{N-[2-(2,3-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (14b). Method A. Yield 37%; mp 88–90 °C; IR: cm^{-1} 3345 (b), 2938, 2835, 2461 (b), 1649, 1587, 1516; ^1H NMR (200 MHz, CD_3OD): δ 1.07 (t, $J=7.3$ Hz, 3H), 1.85–2.03 (m, 3H), 2.27–2.47 (m, 1H), 2.56–2.77 (m, 1H), 3.03–3.70 (m, 8H), 3.80 (s, 3H), 3.85–3.88 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 6.68–6.79 (m, 2H), 7.09–7.26 (m, 3H), 7.37–7.45 (m, 1H); ^{13}C NMR (50 MHz, CD_3OD): δ 11.0, 19.1, 23.2, 24.0, 30.5, 37.7, 52.8, 54.3, 55.3, 56.2, 61.3, 61.6, 108.7, 117.2, 122.0, 122.2, 124.4, 125.1, 127.9, 134.5, 158.3; MS (CI with NH_3): *m/z* (rel. intensity) 232 (6), 392 (4), 427 (100, M + 1); Anal. ($C_{25}H_{34}N_2O_4{\cdot}HCl$ $\cdot ½H_2O$) C, H, N.

7-Methoxy-2-{N-[2-(2,6-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (14c). Method A. Yield 41%; mp 114–116 °C; IR: cm^{-1} 3252 (b), 2939, 2837, 2490 (b), 1657, 1595, 1505; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.85 (t, $J=7.3$ Hz, 3H), 1.41–1.65 (m, 3H), 1.93–2.00 (m, 1H), 2.51 (dd, $J=7.4$ Hz, 7.4 Hz, 2H), 2.73–3.01 (m, 7H), 3.44–3.58 (m, 2H), 3.75 (s, 3H), 3.78 (s, 6H), 6.43 (bs, 1H), 6.54–6.69 (m, 4H), 6.97 (d, $J=8.3$ Hz, 1H), 7.26 (t, $J=8.4$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 21.7, 25.6, 28.7, 31.9, 37.6, 48.9, 52.0, 55.0, 55.6, 56.3, 103.7, 111.9, 113.8, 116.0, 128.2, 129.3, 130.3, 137.2, 157.3, 157.4, 165.7; MS (CI with NH_3): *m/z* (rel. intensity) 161 (14), 182 (27), 232 (26), 267 (14), 427 (100, M + 1); Anal. ($C_{25}H_{34}N_2O_4$ $\cdot HCl{\cdot}¾H_2O$) C, H, N.

7-Methoxy-2-[N-(2-thiophen-2-carboxamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (14d). Method A. Yield 27%; mp 80–83 °C; IR: cm^{-1} 3238 (b), 2937, 2837, 2606 (b), 2499 (b), 1638, 1611, 1543; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.94 (t, $J=7.3$ Hz, 3H), 1.43–1.75 (m, 3H), 1.96–2.08 (m, 1H), 2.54 (dd, $J=8.1$ Hz, 6.4 Hz, 2H), 2.69–2.86 (m, 6H), 2.94–3.05 (m, 1H), 3.42–3.52 (m, 2H), 3.77 (s, 3H), 6.62 (d, $J=2.6$ Hz, 1H), 6.70 (dd, $J=8.1$ Hz, 2.6 Hz, 1H), 6.89 (bs, 1H), 7.00 (d, $J=8.1$ Hz), 7.08–7.12 (m, 1H), 7.45–7.52 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.1, 26.0, 28.9, 32.4, 37.7, 48.4, 52.0, 55.2, 56.1, 112.1, 113.9, 127.6, 127.9, 128.3, 129.5, 137.2, 157.6, 161.8; MS (CI with NH_3): *m/z* 373 (M + 1); Anal. ($C_{21}H_{28}N_2O_2S{\cdot}HCl$ $\cdot ½H_2O$) C, H, N.

8-Methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (15a). Method A. Yield 48%; mp 107–109 °C; IR: cm^{-1} 3276 (b), 2981, 2840, 2480 (b), 1659, 1596, 1542; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.92 (t, $J=7.3$ Hz, 3H), 1.43–1.73 (m, 3H), 1.95–2.02 (m, 1H), 2.42–2.62 (m, 3H), 2.73–3.08 (m, 6H), 3.40–3.62 (m, 2H), 3.81 (s, 3H), 6.70 (dd, $J=10.1$ Hz, 7.9 Hz, 2H), 7.07–7.14 (m, 2H), 7.41–7.56 (m, 3H), 7.82–7.88 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 22.0, 25.2, 25.7, 29.9, 37.6, 48.2, 52.0, 55.0, 55.9, 106.7, 120.7, 124.7, 126.0, 126.8, 128.4, 131.1, 134.7, 137.5, 157.4, 167.1; MS (CI with AcOH): *m/z* 367 (M + 1); Anal. ($C_{23}H_{30}N_2O_2{\cdot}HCl{\cdot}1½H_2O$) C, H, N.

8-Methoxy-2-{N-[2-(2,3-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (15b). Method A. Yield 66%; mp 88–92 °C; IR: cm^{-1} 3345 (b), 2936, 2837, 2585 (b), 2461 (b), 1647, 1578, 1514; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, $J=7.3$ Hz, 3H), 1.44–1.67 (m, 3H), 1.97–2.06 (m, 1H), 2.52–2.60 (m, 3H), 2.77–3.01 (m, 6H), 3.41–3.58 (m, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 6.68 (dd, $J=9.8$ Hz, 8.1 Hz, 2H), 7.02–7.19 (m, 3H), 7.73 (dd, $J=7.9$ Hz, 2.9 Hz, 1H), 8.18 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.4, 25.5, 25.7, 30.2, 38.5, 48.9, 52.4, 55.1, 56.0, 56.6, 61.3, 106.7, 115.0, 120.7, 122.8, 124.1, 125.1, 126.0, 126.9, 129.2, 137.7, 152.6, 157.7, 165.0; MS (CI with NH_3): *m/z* (rel. intensity) 161 (47), 182 (97), 220 (24), 232 (50), 267 (12), 385 (8), 427 (100, M + 1); Anal. ($C_{25}H_{34}N_2O_4$ $\cdot HCl{\cdot}¾H_2O$) C, H, N.

8-Methoxy-2-{N-[2-(2,6-dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (15c). Method A. Yield 41%; mp 121–123 °C; IR: cm^{-1} 3391 (b), 2938,

2838, 2605 (b), 2512 (b), 1654, 1596, 1524; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H), 1.40–1.69 (m, 3H), 1.89–1.96 (m, 1H), 2.33–2.60 (m, 3H), 2.73–2.98 (m, 6H), 3.47–3.56 (m, 2H), 3.78 (s, 9H); 6.46 (bs, 1H), 6.55 (d, J = 8.3 Hz, 2H), 6.66 (dd, J = 8.6 Hz, 8.6 Hz, 2H), 7.07 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.6 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.9, 25.3, 30.0, 37.7, 48.8, 51.8, 54.9, 55.6, 56.1, 103.7, 106.6, 116.0, 120.7, 124.9, 125.9, 130.2, 137.5, 157.3, 165.7; MS (CI with NH_3): m/z (rel. intensity) 60 (31), 139 (17), 161 (30), 182 (100), 220 (23), 267 (15), 427 (19, M + 1); Anal. ($C_{25}H_{34}N_2O_4$·HCl·½H_2O) C, H. N.

8-Methoxy-2-[N-(2-thiophen-2-carboxamidoethyl)-N-*n*-propylamino]tetralin oxalate (15d). Method A. Yield 66%; mp 135–137 °C; IR: cm^{-1} 3257 (b), 2968, 2833, 2787 (b), 2662 (b), 1718, 1642, 1588, 1541; ^{1}H NMR (200 MHz, CD_3OD): δ 1.03 (t, J = 7.3 Hz, 3H), 1.79–1.90 (m, 3H), 2.14–2.26 (m, 1H), 2.67–2.94 (m, 3H), 3.19–3.34 (m, 4H), 3.45–3.56 (m, 2H), 3.71–3.93 (m, 6H), 6.68–6.75 (m, 2H), 7.07–7.17 (m, 2H), 7.69–7.78 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 9.6, 17.8, 22.7, 23.1, 27.7, 36.0, 50.8, 53.1, 54.1, 60.5, 106.9, 120.1, 120.5, 126.8, 127.6, 129.3, 131.2, 135.7, 137.3, 157.1, 164.7; MS (CI with AcOH): m/z 373 (M + 1); Anal. ($C_{21}H_{28}N_2O_2S$·$C_2H_2O_4$) C, H, N.

2-[N-(2-Benzamidoethyl)-N-*n*-propylamino)tetralin hydrochloride (16a). Method A. Yield 62%; mp 83–86 °C; IR: cm^{-1} 3436 (b), 3250 (b), 3060, 2936, 2610 (b), 2512 (b), 1654, 1577, 1541; ^{1}H NMR (300 MHz, CD_3OD): δ 1.06 (t, J = 7.3 Hz, 3H), 1.82–1.99 (m, 3H), 2.31–2.42 (m, 1H), 2.95–3.01 (m, 2H), 3.12–3.42 (m, 5H), 3.60–3.65 (m, 1H), 3.77–3.96 (m, 3H), 7.07–7.18 (m, 4H), 7.49 (dd, J = 6.9 Hz, 6.9 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.92 (d, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 10.6, 18.9, 24.2, 28.5, 29.7, 37.0, 52.2, 53.8, 61.1, 126.7, 127.1, 127.9, 128.9, 129.1, 129.6, 132.7, 133.4, 135.3, 171.1; MS (CI with NH_3): m/z (rel. intensity) 202 (14), 337 (100, M + 1); Anal. ($C_{22}H_{28}N_2O$·HCl·¼H_2O) C, H, N.

2-{N-[2-(2,3-Dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin oxalate (16b). Method A. Yield 25%; mp 70–72 °C; IR: cm^{-1} 3360 (b), 2936, 2835, 2619 (b), 2520 (b), 1719, 1649, 1577, 1524; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, J = 7.3 Hz, 3H), 1.45–1.71 (m, 3H), 1.98–2.10 (m, 1H), 2.55 (dd, J = 7.5 Hz, 7.5 Hz, 2H), 2.76–3.04 (m, 7H), 3.52–3.60 (m, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 7.02–7.09 (m, 5H), 7.16 (t, J = 7.9 Hz, 1H), 7.73 (dd, J = 7.2 Hz, 1.8 Hz, 1H), 8.39 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.3, 25.9, 29.9, 31.9, 38.5, 49.0, 52.4, 56.1, 56.7, 61.3, 115.1, 122.8, 124.2, 125.6, 125.7, 127.1, 128.6, 129.4, 136.3, 147.7, 152.5, 165.1; MS (CI with NH_3): m/z 190 (16), 202 (6), 397 (100, M + 1); Anal. ($C_{24}H_{32}N_2O_3$·$C_2H_2O_4$·¼H_2O) C, H, N.

2-{N-[2-(2,6-Dimethoxy)benzamidoethyl]-N-*n*-propylamino}tetralin hydrochloride (16c). Method A. Yield 75%; mp 107–110 °C; IR: cm^{-1} 3241 (b), 2938, 2837, 2473 (b), 1656, 1596, 1522; ^{1}H NMR (300 MHz, CD_3OD): δ 1.13 (t, J = 7.3 Hz, 3H), 1.92–2.04 (m, 3H), 2.38–2.42 (m, 1H), 2.98–3.09 (m, 2H), 3.16–3.35 (m, H), 3.48–3.57 (m, 1H), 3.73–3.79 (m, 2H), 3.83 (s, 6H), 3.88–3.97 (m, 1H), 6.75 (d, J = 8.6 Hz, 2H), 7.16–7.24 (m, 4H), 7.41 (t, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 11.4, 19.9, 24.8, 29.3, 30.6, 38.2, 53.8, 54.4, 56.4, 61.6, 105.1, 115.3, 127.4, 127.7, 129.6, 130.3, 132.7, 133.8, 136.1, 158.6, 171.8; MS (CI with NH_3): m/z (rel. intensity) 202 (14), 397 (100, M + 1); Anal. ($C_{24}H_{32}N_2O_3$·HCl·½H_2O) C, H, N.

2-[N-(2-Thiophen-2-carboxamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (16d). Method A. Yield 62%; mp 93–94 °C; IR: cm^{-1} 3232 (b), 3059, 2937, 2609 (b), 2480 (b), 1639, 1543; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.94 (t, J = 7.3 Hz, 3H), 1.44–1.76 (m, 3H), 1.98–2.07 (m, 1H), 2.56 (dd, J = 8.1 Hz, 6.5 Hz, 2H), 2.71–3.12 (m, 7H), 3.39–3.57 (m, 2H), 7.04–7.14 (m, 6H), 7.45 (dd, J = 5.0 Hz, 1.1 Hz, 1H), 7.55 (dd, J = 3.7 Hz, 1.0 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.7, 21.7, 25.5, 29.5, 31.8, 37.6, 48.3, 52.0, 56.1, 125.6, 125.7, 127.6, 127.8, 128.5, 129.3, 129.5, 135.8, 136.1, 139.2, 161.7; MS (CI with AcOH): m/z 343 (M + 1); Anal. ($C_{20}H_{26}N_2OS$·HCl·¼H_2O) C, H, N.

General procedure for the preparation of compounds 12p, 13e, 14e, and 15e

The method adopted for the synthesis of 5-hydroxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]tetralin hydrochloride (**12p**) is described: under a nitrogen atmosphere, a 1 M solution of BBr_3 in CH_2Cl_2 (2 mL, 4 mmol) was added dropwise to a solution of the free base of **12a** (0.25 g, 0.7 mmol) in CH_2Cl_2 which was cooled at −50 °C. Stirring was continued at −50 °C for 1 h, and then the reaction mixture was allowed to gradually warm to room temperature. After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution. The organic solution was dried (Na_2SO_4), filtered and evaporated to dryness, which gave the crude phenol as a brown oil. Purification by column chromatography yielded 0.21 g (0.6 mmol) of the pure base of **12p** as a colourless oil, which was converted to the hydrochloride salt.

5-Hydroxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (12p). Yield 87%; mp 116–118 °C; IR: cm^{-1} 3231 (b), 2966, 2623 (b), 1654, 1588, 1534; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.47–1.60 (m, 3H), 1.99–2.05 (m, 1H),

2.48–2.60 (m, 3H), 2.78–3.02 (m, 6H), 3.47–3.58 (m, 2H), 6.64 (dd, $J = 19.2$ Hz, 7.7 Hz, 2H), 6.94 (t, $J = 7.6$ Hz, 1H), 7.40–7.52 (m, 3H), 7.79–7.83 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.6, 23.4, 25.2, 31.8, 37.8, 48.2, 52.1, 55.9, 112.0, 120.8, 123.1, 126.2, 126.8, 128.5, 131.4, 134.2, 137.4, 154.1, 167.7; MS (CI with AcOH): m/z 353 (M + 1); Anal. ($C_{22}H_{28}N_2O_2 \cdot HCl \cdot H_2O$) C, H, N.

6-Hydroxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (13e). Yield 89%; mp 108–110 °C; IR: cm^{-1} 3244 (b), 2939, 2629 (b), 1654, 1577, 1534; ^{1}H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.37–1.61 (m, 3H), 1.90–1.95 (m, 1H), 2.52–2.98 (m, 9H), 3.45–3.55 (m, 2H), 6.59–6.66 (m, 2H), 6.82–6.86 (m, 1H), 7.31 (bs, 1H), 7.40–7.52 (m, 3H), 7.82 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.6, 21.4, 25.4, 29.4, 30.7, 37.7, 48.4, 52.2, 56.5, 113.3, 114.8, 126.6, 126.8, 128.5, 130.1, 131.4, 134.1, 137.0, 154.5, 167.6; MS (CI with NH_3): m/z 353 (M + 1); Anal. ($C_{22}H_{28}N_2O_2 \cdot HCl \cdot ¾H_2O$) C, H, N.

7-Hydroxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (14e). Yield 94%; mp 111–113 °C; IR: cm^{-1} 3236 (b), 2938, 2627 (b), 2513 (b), 1647, 1577, 1536; ^{1}H NMR (200 MHz, CD_3OD): δ 0.98 (t, $J = 7.3$ Hz, 3H), 1.87–2.13 (m, 3H), 2.52–2.60 (m, 1H), 2.76–2.85 (m, 3H), 3.03–3.16 (m, 1H), 3.24–3.42 (m, 4H), 3.62–4.00 (m, 4H), 6.50–6.65 (m, 2H), 6.88 (d, $J = 8.1$ Hz, 1H), 7.43–7.57 (m, 3H), 8.14–8.19 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 11.3, 18.8, 24.0, 24.8, 28.1, 36.5, 52.5, 54.7, 61.4, 114.9, 116.0, 126.3, 128.4, 129.1, 130.2, 132.2, 134.5, 134.8, 156.4, 167.2; MS (CI with NH_3): m/z 353 (M + 1); Anal. ($C_{22}H_{28}N_2O_2 \cdot HCl \cdot ½H_2O$) C, H, N.

8-Hydroxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]-tetralin hydrochloride (15e). Yield 74%; mp 116–119 °C; IR: cm^{-1} 3215 (b), 2968, 2937, 2615 (b), 2515 (b), 1654, 1588, 1635; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92–0.96 (m, 3H), 1.71–1.93 (m, 2H), 2.20–2.30 (m, 3H), 2.47–2.77 (m, 3H), 3.12–3.54 (m, 7H), 3.78–3.94 (m, 2H), 6.43–6.45 (m, 1H), 6.78–6.89 (m, 2H), 7.38–7.53 (m, 3H), 8.01–8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 18.0, 24.1, 28.1, 36.4, 51.5, 53.9, 55.2, 61.6, 112.7, 118.7, 119.7, 127.2, 127.6, 128.6, 132.0, 132.6, 135.6, 154.5, 168.7; MS (CI with NH_3): m/z 353 (M + 1); Anal. ($C_{22}H_{28}N_2O_2 \cdot HCl \cdot ¾H_2O$) C, H; N: calcd, 6.96; found, 6.42.

Pharmacology

[^{3}H]-Raclopride binding to cloned dopamine D_{2A} and D_3 receptors. Mouse fibroblast (Ltk$^-$) cells expressing human dopamine D_{2A} receptors (obtained from Dr. O. Civelli, Vollum Institute for Advanced Biomedical Research, Oregon Health Sciences University, Portland, OR) and Chinese hamster ovary (CHO) cells expressing human dopamine D_3 receptors (obtained from INSERM Institute, Paris, France) were grown and the cell membranes were prepared essentially as described by Malmberg et al.[48] Briefly, the Ltk$^-$ cells were cultured in DMEM (Dulbecco's Modified Eagles Medium) supplemented with 10 mM HEPES, 10% fetal calf serum (FCS, heat-inactivated) and selected with G-418 (Geneticin 0.7 mg/ml). CHO cells were grown in DMEM supplemented as above, except that the FCS was dialyzed and MEM Amino Acids solution (50×) without L-glutamine was added. The cells were detached with 0.05% trypsin and 0.02% EDTA, centrifuged (300×g, for 10 min), washed twice with DMEM and homogenized in 10 mM Tris-HCl and 5 mM $MgSO_4$ (pH 7.4). The homogenate was washed (43,500×g, for 10 min) in binding buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$, 4 mM $MgCl_2$, 1 mM EDTA, pH 7.4) and stored at −70 °C until further use. On the day of the experiment the frozen homogenate was thawed, homogenized with a Branson 450 sonifier and suspended in binding buffer. The binding assays were performed in a total volume of 0.5 mL with a receptor concentration of about 100 pM (~30 μg protein/0.5 mL). 1 nM [^{3}H]-Raclopride (K_d's for dopamine D_{2A} and D_3 1.20 and 1.60 nM, respectively; specific activity 80 Ci/mmol, Du Pont New England Nuclear, Boston, MA, or 41 Ci/mmol, Astra Arcus AB, Södertälje, Sweden) was incubated with the test compound (10–12 concentrations) at 22 °C for 1 h. Binding in the presence of 1 μM (+)-butaclamol (Research Biochemicals Inc., Natick, MA) was defined as nonspecific. The incubation was terminated by rapid filtration through Whatman GF/B glassfiber filters and subsequent washing with ice-cold buffer, using a Brandel cell harvester. Scintillation cocktail (Packard Ultima Gold, 4 mL) was added and the radioactivity was determined with a Liquid Scintillation Counter (Packard 2200CA or 2500TR) at about 50% efficiency. Alternatively, the incubation was terminated by rapid filtration through Wallac Printed Filtermat B and washed with cold buffer using a Tomtec harvester, and the radioactivity was determined in 205 Beta Plate (Wallac), with about 30% efficiency. Protein concentration was measured by the method of Markwell et al.[50]

[^{3}H]-8-OH-DPAT Binding to serotonin 5-HT_{1A} receptors. This assay was performed essentially as previously described by Hedberg et al.[51] Briefly, 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 at 0 °C using an Ultra-Turrax, in 50 mM Tris-HCl buffer containing 10 mM EDTA (pH 7.4). The homogenate was centrifuged at 4 °C for 10 min at

17,000×*g*, the pellet was resuspended in 50 mM Tris-HCl with 10 mM EDTA and recentrifuged. The final pellet was frozen in 0.32 M sucrose and stored at −70 °C until further use. On the day of the experiment the frozen homogenate was thawed and suspended in binding buffer containing 50 mM Tris-HCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 1 mM $MnCl_2$ (pH 7.4), to a final concentration of 2.0 mg original wet weight per 0.5 mL. In order to remove endogenous serotonin the membranes were preincubated for 10 min at 37 °C and subsequently 10 μM pargyline was added. Competition experiments with 1 nM [^{3}H]-8-OH-DPAT (K_d = 1.00 nM; specific activity 136, 149 or 163 Ci/mmol, Du Pont New England Nuclear, Boston, MA) and test compounds (10–12 concentrations) were performed at 37 °C for 45 min. Nonspecific binding was defined with 100 μM 5-HT (Sigma Chemical Co., St. Louis, MO). The incubations were terminated and the radioactivity was determined as described for the dopamine receptor binding assay.

Data analysis

The K_i values (inhibition constants) of the test compounds were determined from inhibition curves using the iterative non-linear curve-fitting program LIGAND.[52] One- and two-site curve fitting was tested in all experiments. The one-site model gave a better fit ($p > 0.05$; *F* test) unless otherwise stated. The K_d values (dissociation constants) of the various radioligands used to calculate the K_i values were determined by saturation studies.

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References

1. Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *Psychopharmacol. Bull.* **1989**, *25*, 390.

2. Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238.

3. Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685.

4. Saller, C. F.; Salama, A. I. *Psychopharmacology Berl.* **1993**, *112*, 285.

5. Hyttel, J.; Arnt, J.; Costall, B.; Domeney, A.; Dragsted, N.; Lembol, H. L.; Meier, E.; Naylor, R. J.; Nowak, G.; Sanchez, C. *Clin. Neuropharmacol.* **1992**, *15 Suppl*, 267A.

6. Gupta, S.; Black, D. W.; Smith, D. A. *Ann. Clin. Psychiatry* **1994**, *6*, 173.

7. Broekkamp, C. L. E.; Oosterloo, S. K.; Berendsen, H. H. G.; van Delft, A. M. L. *Naunyn Schmiedebergs Arch. Pharmacol.* **1988**, *338*, 191.

8. Invernizzi, R. W.; Cervo, L.; Samanin, R. *Neuropharmacology* **1988**, *27*, 515.

9. McMillen, B. A.; Scott, S. M.; Davano, E. A. *J. Pharm. Pharmacol.* **1988**, *40*, 885.

10. Hicks, P. B. *Life. Sci.* **1990**, *47*, 1609.

11. Neal-Beliveau, B. S.; Joyce, J. N.; Lucki, I. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 207.

12. Wadenberg, M. L.; Ahlenius, S. *J. Neural Transm. Gen. Sect.* **1991**, *83*, 43.

13. Wadenberg, M. L.; Ahlenius, S. *J. Neural. Transm.* **1988**, *74*, 195.

14. Ahlenius, S. *Pharmacol. Toxicol.* **1989**, *64*, 3.

15. Norman, M. H.; Navas III, F.; Thompson, J. B.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 4692.

16. Scott, M. K.; Baxter, E. W.; Bennett, D. J.; Boyd, R. E.; Blum, P. S.; Codd, E. E.; Kukla, M. J.; Malloy, E.; Maryanoff, B. E.; Maryanoff, C. A.; Ortegon, M. E.; Rasmussen, C. R.; Reitz, A. B.; Renzi, M. J.; Schwender, C. F.; Shank, R. P.; Sherrill, R. G.; Vaught, J. L.; Villani, F. J.; Yim, N. *J. Med. Chem.* **1995**, *38*, 4198.

17. Reitz, A. B.; Baxter, E. W.; Bennett, D. J.; Codd, E. E.; Jordan, A.; Malloy, E. A.; Maryanoff, B. E.; McDonell, M. E.; Ortegon, M. E.; Renzi, M. J.; Scott, M. K.; Shank, R. P.; Sherrill, R. G.; Vaught, J. L.; Wustrow, D. J. *J. Med. Chem.* **1995**, *38*, 4211.

18. 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.

19. Högberg, T.; Rämsby, S.; Ögren, S.-O.; Norinder, U. *Acta Pharm. Suec.* **1987**, *24*, 289.

20. Högberg, T. *Drugs Fut.* **1991**, *16*, 333.

21. Högberg, T. *Drug Des. Discov.* **1993**, *9*, 333.

22. Horn, A. S.; Tepper, P.; Van der Weide, J.; Watanabe, M.; Grigoriadis, D.; Seeman, P. *Pharm. Weekbl. Sci.* **1985**, *7*, 208.

23. Arvidsson, L. E.; Hacksell, U.; Nilsson, J. L.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921.

24. Cannon, J. G.; Brubaker, A. N.; Long, J. P.; Flynn, J. R.; Verimer, T.; Harnirattisai, P.; Costall, B.; Naylor, R. J.; Nohria, V. *J. Med. Chem.* **1981**, *24*, 149.

25. Cecchi, R.; Croci, T.; Boigegrain, R.; Boveri, S.; Baroni, M.; Boccardi, G.; Guimbard, J. P.; Guzzi, U. *Eur. J. Med. Chem.* **1994**, *29*, 259.

26. Copinga, S.; Tepper, P. G.; Grol, C. J.; Dubocovich, M. L. *J. Med. Chem.* **1993**, *36*, 2891.

27. Feenstra, M. G.; Rollema, H.; Dijkstra, D.; Grol, C. J.; Horn, A. S.; Westerink, B. H. *Naunyn Schmiedebergs Arch. Pharmacol.* **1980**, *313*, 213.

28. Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1984**, *26*, 452.

29. Beart, P. M.; Cook, C. J.; Cincotta, M.; de Vries, D. J.; Tepper, P.; Dijkstra, D.; Horn, A. S. *Naunyn Schmiedebergs Arch. Pharmacol.* **1987**, *336*, 487.

30. Sonesson, C.; Boije, M.; Svensson, K.; Ekman, A.; Carlsson, A.; Romero, A. G.; Martin, I. J.; Duncan, J. N.; King, L. J.; Wikström, H. *J. Med. Chem.* **1993**, *36*, 3409.

31. Yu, H.; Liu, Y.; Malmberg, Å.; Mohell, N.; Hacksell, U.; Lewander, T. *Eur. J. Pharmacol.* **1996**, *303*, 151.

32. Cymerman Craig, J.; Moore, B.; Ritchie, E. *Aust. J. Chem.* **1959**, *12*, 447.

33. Ames, D. E.; Evans, D.; Grey, T. F.; Islip, P. J.; Richards, K. E. *J. Chem. Soc.* **1965**, 2636.

34. Kanao, M.; Hashizume, T.; Ichikawa, Y.; Irie, K.; Isoda, S. *J. Med. Chem.* **1982**, *25*, 1358.

35. de Paulis, T.; Hall, H.; Kumar, Y.; Rämsby, S.; Ögren, S.-O.; Högberg, T. *Eur. J. Med. Chem.* **1990**, *25*, 507.

36. Harrold, M. W.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1989**, *32*, 874.

37. McOmie, J. W. F.; Watts, M. L.; Wets, D. E. *Tetrahedron* **1968**, *24*, 2289.

38. Högberg, T.; Bengtsson, S.; de Paulis, T.; Johansson, L.; Ström, P.; Hall, H.; Ögren, S.-O. *J. Med. Chem.* **1990**, *33*, 1155.

39. Högberg, T.; Ström, P.; Hall, H.; Ögren, S.-O. *Helv. Chim. Acta* **1990**, *73*, 417.

40. Högberg, T.; Ström, P.; de Paulis, T.; Stensland, B.; Csöregh, I.; Lundin, K.; Hall, H.; Ögren, S.-O. *J. Med. Chem.* **1991**, *34*, 948.

41. Norinder, U.; Högberg, T. *QSAR* **1991**, *10*, 1.

42. Norinder, U.; Högberg, T. *Acta Pharm. Nord.* **1992**, *4*, 73.

43. Naiman, N.; Lyon, R. A.; Bullock, A. E.; Rydelek, L. T.; Titeler, M.; Glennon, R. A. *J. Med. Chem.* **1989**, 32, *253*.

44. Hacksell, U.; Svensson, U.; Nilsson, J. L.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindenberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.

45. Arvidsson, L. E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L.; Lindberg, P.; Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 45.

46. Seiler, M. P.; Stoll, A. P.; Closse, A.; Frick, W.; Jaton, A.; Vigouret, J. M. *J. Med. Chem.* **1986**, *29*, 912.

47. Björk, L.; Höök, B. B.; Nelson, D. L.; Andén, N.-E.; Hacksell, U. *J. Med. Chem.* **1989**, *32*, 779.

48. Malmberg, Å.; Nordvall, G.; Johansson, A. M.; Mohell, N.; Hacksell, U. *Mol. Pharmacol.* **1994**, *46*, 299.

49. van Vliet, L. A.; Tepper, P. G.; Dijkstra, D.; Damsma, G.; Wikström, H.; Puglsey, T. A.; Akunne, H. C.; Heffner, T. G.; Glase, S. A.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 4233.

50. Markwell, M. A. K.; Haas, S. M.; Bieber, L. L.; Tolbert, N. E. *Anal. Biochem.* **1978**, *87*, 206.

51. Hedberg, M. H.; Johansson, A. M.; Nordvall, G.; Yliniemelä, A.; Li, H. B.; Martin, A. R.; Hjorth, S.; Unelius, L.; Sundell, S.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 647.

52. Munson, P. J.; Rodbard, D. *Anal. Biochem.* **1980**, *107*, 220.