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## D<sub>2</sub> Dopaminergic and 5-HT<sub>1A</sub> Serotonergic Activity of 2-(1-Naphthyl)ethyl- and 2-(2-Naphthyl)ethyl Amines

Several tertiary 2-phenylethyl, 2-(1-naphthyl)ethyl and 2-(2-naphthyl)ethyl amines were synthesized and their binding affinities for dopamine D<sub>1</sub>, D<sub>2</sub> and serotonin 5-HT<sub>1A</sub> receptors evaluated in radioligand binding assays. All compounds were inactive in D<sub>1</sub> dopamine radioligand binding assay. The 2-(1-naphthyl)ethyl analogues expressed a low but significant binding affinity for the D<sub>2</sub> and moderate one for the 5-HT<sub>1A</sub> receptor subtypes. Most of the remaining compounds expressed binding affinity at the 5-HT<sub>1A</sub> receptor subtype but were inactive in D<sub>2</sub> receptor binding assay. Based on these results and considering the chemical characteristics of the compounds synthesized and evaluated for dopaminergic and serotonergic activity throughout the present study it can be concluded that hydrophobic type of interaction (stacking or edge-to-face) plays a significant role in the formation of receptor-ligand complexes of 2-(1-naphthyl)ethyl amines. This structural motive can be applied to design and synthesize new, more potent dopaminergic/serotonergic ligands by slight chemical modifications.

**Keywords:** 2-(1-Naphthyl)ethyl; 2-(2-Naphthyl)ethyl; Dopaminergic; Serotonergic; D<sub>1</sub>; D<sub>2</sub>; 5-HT<sub>1A</sub>

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### Introduction

Recent application of molecular cloning technology revealed a number of dopamine receptor (DAR) subtypes belonging to the two main classes, D<sub>1</sub>-like (D<sub>1</sub>, D<sub>5</sub>) and D<sub>2</sub>-like (D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>) [1]. These receptors have been associated to the pathogenesis of neuropathological diseases such as schizophrenia [2], Parkinson's disease [3], and ADHD (Attention Deficit Hyperactivity Disorder) [4]. The therapeutic benefit of dopaminergic agents in the treatment of psychotic disorders has been fully recognized with the discovery of antipsychotic drugs expressing a high binding affinity at dopamine receptors.

The binding sites of dopamine receptors occur in the cavity formed among their seven, mostly hydrophobic, membrane-spanning segments [5]. The surface of this cavity contains residues that can interact with specific agonists or antagonists and other residues that may affect the steric conformation of the receptor itself, thus indirectly affecting ligand binding.

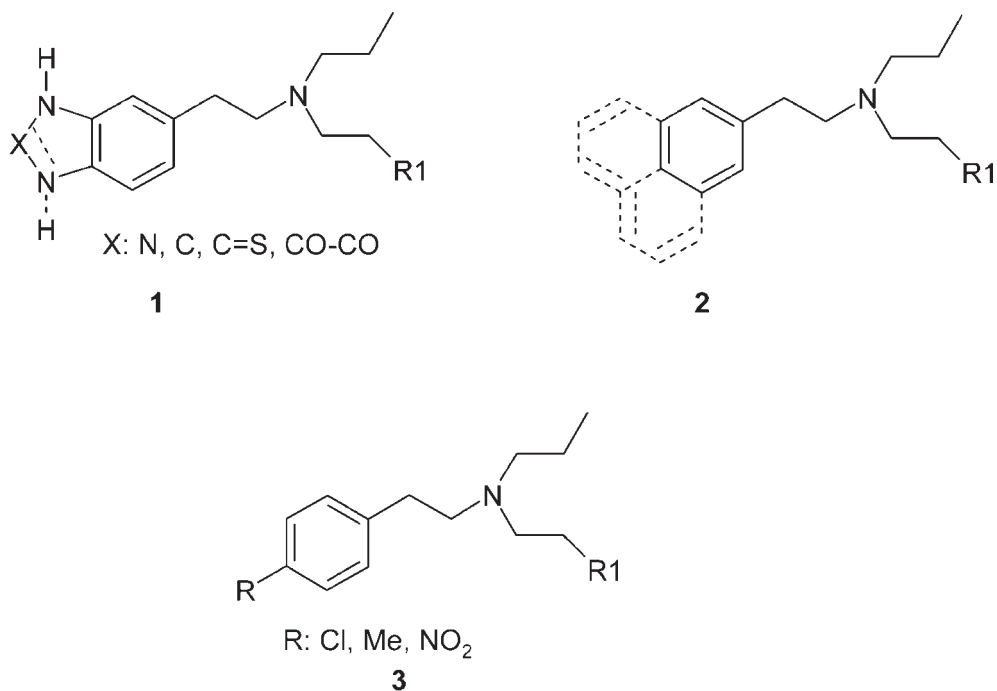
McDermid et al. [6] suggested a model of DA pharmacophore by superpositioning of the pharmacophoric elements of DAR agonists, such as the nitrogen, nitrogen lone pairs, oxygen and aromatic rings. In addition, the

presence of two lipophilic sites which bind the *N*-alkyl groups has been postulated [7]. In our earlier studies we have demonstrated that even the substituents as bulky as 2-(1-naphthyl)ethyl can be accommodated in one of these binding sites [8].

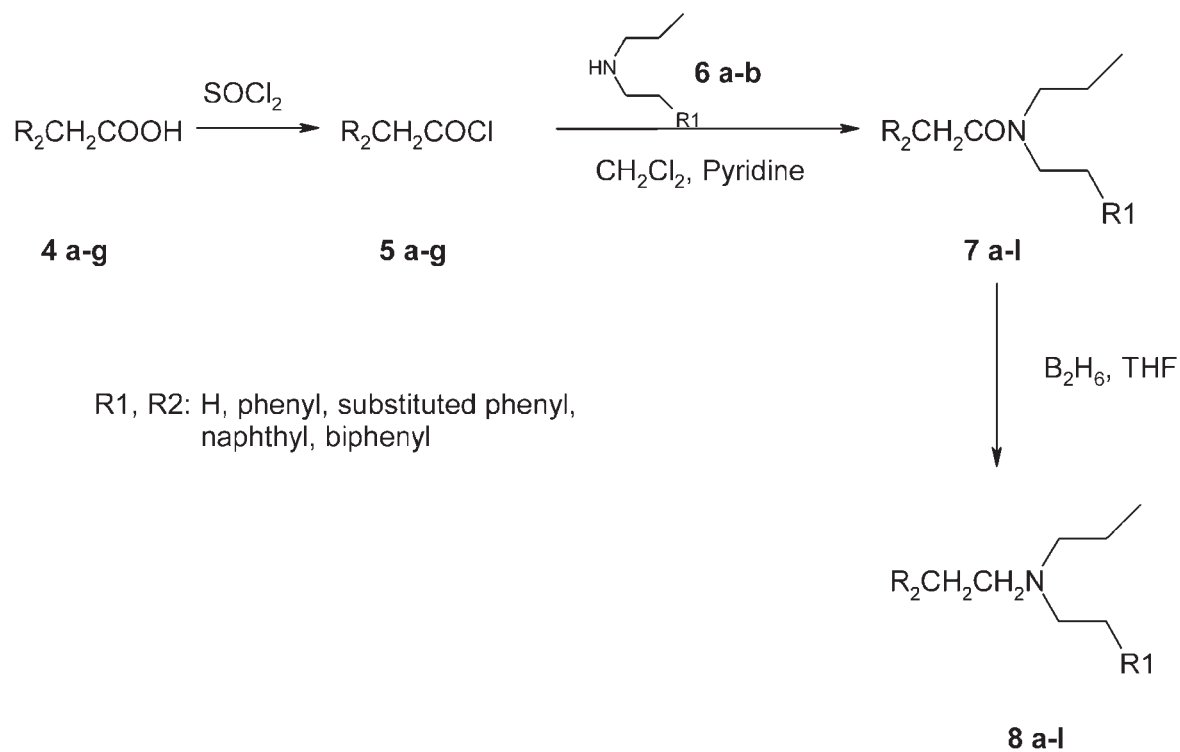
The model of McDermid et al. [6] has been employed as a starting point in most dopamine D<sub>2</sub> drug design strategies [9]. Using a similar approach we have designed and explored the affinities of benzimidazole type ligands for the binding at the D<sub>2</sub> DAR [8]. We have noticed that consideration of only hydrogen and ionic bonds is not sufficient to explain the affinities of these ligands for the binding at this class of DAR. It seems that the interaction of hydrophobic type (e.g. stacking or edge-to-face interaction) play a significant role in the formation of receptor-ligand complexes and that for the better understanding more attention should be paid to this type of interactions.

To examine the contribution of hydrophobic interactions in the formation of receptor-ligand complexes, we have designed compounds (**2** and **3**) that share topological similarities with benzimidazole pharmacophore (**1**), but lack functional groups able to form strong hydrogen bonds with the receptor molecule (Figure 1). This type of interactions between compounds and the receptor should be exclusively dependent on the shape of the ligand molecule and its ability to realize stacking or edge-to-face interactions with aromatic residues in the binding pocket of the receptor [10, 11].

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**Figure 1.** The structure of synthesized and evaluated tertiary 2-arylethyl amines.



**Scheme 1.** Synthesis of tertiary 2-arylethyl amines.

Synthesis and binding properties of a series of such compounds are discussed in the present study. In addition, new ligands have been evaluated for the binding affinity at the 5-HT<sub>1A</sub> receptor since some of benzimidazoles prepared and evaluated previously were shown to be efficient displacers of the specific serotonin 5-HT<sub>1A</sub> receptor radioligand [<sup>3</sup>H]-8-OH-DPAT.

## Chemistry

Chemical structure of the compounds synthesized throughout the present work is depicted in Scheme 1. Different arylacetic acids **4 a–g** were used as a starting material to produce acylchlorides **5 a–g** using thionyl chloride method. All tertiary amines (**8 a–l**) were synthesized by refluxing the appropriate amide (**7 a–l**) with B<sub>2</sub>H<sub>6</sub> in THF for 60 min. The resulting crude products were purified by silica gel column chromatography and further converted to and crystallized as oxalic acid salts.

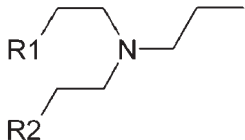
## Results and discussion

### Binding affinity and selectivity of compounds **8 a–l** towards D<sub>1</sub> and D<sub>2</sub> dopamine and 5-HT<sub>1A</sub> serotonin receptors

The final products **8 a–l** were evaluated for the binding affinity at the D<sub>1</sub> and D<sub>2</sub> dopamine and serotonin 5-HT<sub>1A</sub> receptors by *in vitro* competition displacement of the specific radioligands from synaptosomal membranes prepared from fresh bovine caudate nuclei (D<sub>1</sub> and D<sub>2</sub>) and hippocampi (5-HT<sub>1A</sub>). The K<sub>i</sub> values for individual compounds calculated from displacement curves are listed in Table 1. Benzimidazole analogues **9–11** [12] were run simultaneously in the same test systems as references.

As seen from Table 1, none of the compounds synthesized and evaluated for the dopaminergic/serotonergic activity throughout the present study expressed the affinity for the binding at the D<sub>1</sub> dopamine receptor. Compounds **8 f** and **8 l** were completely inactive competitors

**Table 1.** Affinity and selectivity of the new ligands for the binding at the D<sub>1</sub> and D<sub>2</sub> dopamine and 5-HT<sub>1A</sub> serotonin receptors.



No	R <sub>2</sub>	R <sub>1</sub>	K <sub>i</sub> ± S.E.M. (nM)		
			D <sub>1</sub>	D <sub>2</sub>	5-HT <sub>1A</sub>
<b>8 a</b>	Phenyl	H	>10 000	>10 000	990 ± 110
<b>8 b</b>	Phenyl	Phenyl	>10 000	>10 000	101 ± 9
<b>8 c</b>	4-nitrophenyl	Phenyl	>10 000	867 ± 94	121 ± 21
<b>8 d</b>	4-chlorophenyl	Phenyl	>10 000	>10 000	98 ± 9
<b>8 e</b>	4-methylphenyl	Phenyl	>10 000	>10 000	110 ± 10
<b>8 f</b>	1-naphthyl	H	>10 000	>10 000	>10 000
<b>8 g</b>	2-naphthyl	H	>10 000	>10 000	532 ± 73
<b>8 h</b>	1-naphthyl	Phenyl	>10 000	988 ± 110	99 ± 6
<b>8 i</b>	2-naphthyl	Phenyl	>10 000	>10 000	233 ± 30
<b>8 j</b>	1-naphthyl	1-naphthyl	>10 000	2730 ± 290	147 ± 18
<b>8 k</b>	1-naphthyl	2-naphthyl	>10 000	>10 000	226 ± 14
<b>8 l</b>	Biphenyl	phenyl	>10 000	>10 000	>10 000
<b>9</b>	5-benzimidazole	H	>10 000	>10 000	465 ± 64
<b>10</b>	5-benzimidazole	phenyl	>10 000	1057 ± 90	126 ± 11
<b>11</b>	5-benzimidazole	1-naphthyl	>10 000	421 ± 32	160 ± 24

Values are the means of three independent experiments done in triplicate performed at eight competing ligand concentrations (10<sup>-4</sup>–10<sup>-9</sup> M). [<sup>3</sup>H]SCH 23390 and [<sup>3</sup>H]Spiperone concentrations were 0.2 nM while [<sup>3</sup>H]-8-OH-DPAT was 0.6 nM per assay.

in both D<sub>2</sub> and 5-HT<sub>1A</sub> binding assays. Besides, compounds **8a**, **b**, **e**, **g**, **i**, **k**, and **8l** were poor competitors of [<sup>3</sup>H]spiperone only.

The remaining novel compounds acted as displacers of [<sup>3</sup>H]spiperone and [<sup>3</sup>H]8-OH-DPAT expressing the binding affinity at the corresponding receptors in a micromolar and nanomolar range of concentrations, respectively. Among the naphthyl derivatives, compound **8h** with a K<sub>i</sub> value of 988 nM and 99 nM was the most potent in displacing [<sup>3</sup>H]spiperone and [<sup>3</sup>H]8-OH-DPAT from the D<sub>2</sub> and 5-HT<sub>1A</sub> serotonin receptors, respectively. Most of the tested compounds **8b–l** expressed a similar affinity with in the range of 100 nM for the binding at the 5-HT<sub>1A</sub> serotonin receptor. The same compounds were more selective with regard to the binding at the D<sub>2</sub> dopamine receptor, 4-nitrophenyl compound **8c** with a K<sub>i</sub> value of 867 nM being the most active.

With the exception of compound **8c**, all synthesized compounds were lacking groups able to build hydrogen bonds attached to the aromatic rings. The only possible stabilizing interaction of these compounds and the receptor can be that of hydrophobic type. According to the generally accepted dopamine receptor model, there is a cluster of aromatic amino acids in TM5 and TM6 of the receptor that interact with the aromatic ring of ligands [5, 13, 14]. Recently, it has emerged that attractive interactions of a different type exist between aromatic moieties devoid of polar substituents. These “edge-to-face” interactions, though modest in energy terms, can play an important role in such diverse areas as protein folding, base pair stacking in DNA, host-guest binding in supramolecular assemblies, crystal engineering, drug-receptor interactions and other molecular recognition processes [10]. This type of interactions can energetically stabilize the system up to −2.7 kcal/mol. Contribution of hydrogen bond to complex stability is often exceeding this value, what can be taken as the explanation for the fact that the benzimidazole derivatives, which can form hydrogen bonds, have higher affinities for the binding at the D<sub>2</sub> dopamine receptor, than the corresponding naphthyl derivatives.

Thus, we hypothesized that affinities of compounds **8h** and **8j** for the binding at the D<sub>2</sub> dopamine receptor are due to edge-to-face interaction of 1-naphthyl group in these ligands and aromatic amino acids in the receptor binding pocket. Hypothetical model of edge-to-face interaction between ligand **8h** and D<sub>2</sub> dopamine receptor is presented in Figure 2.

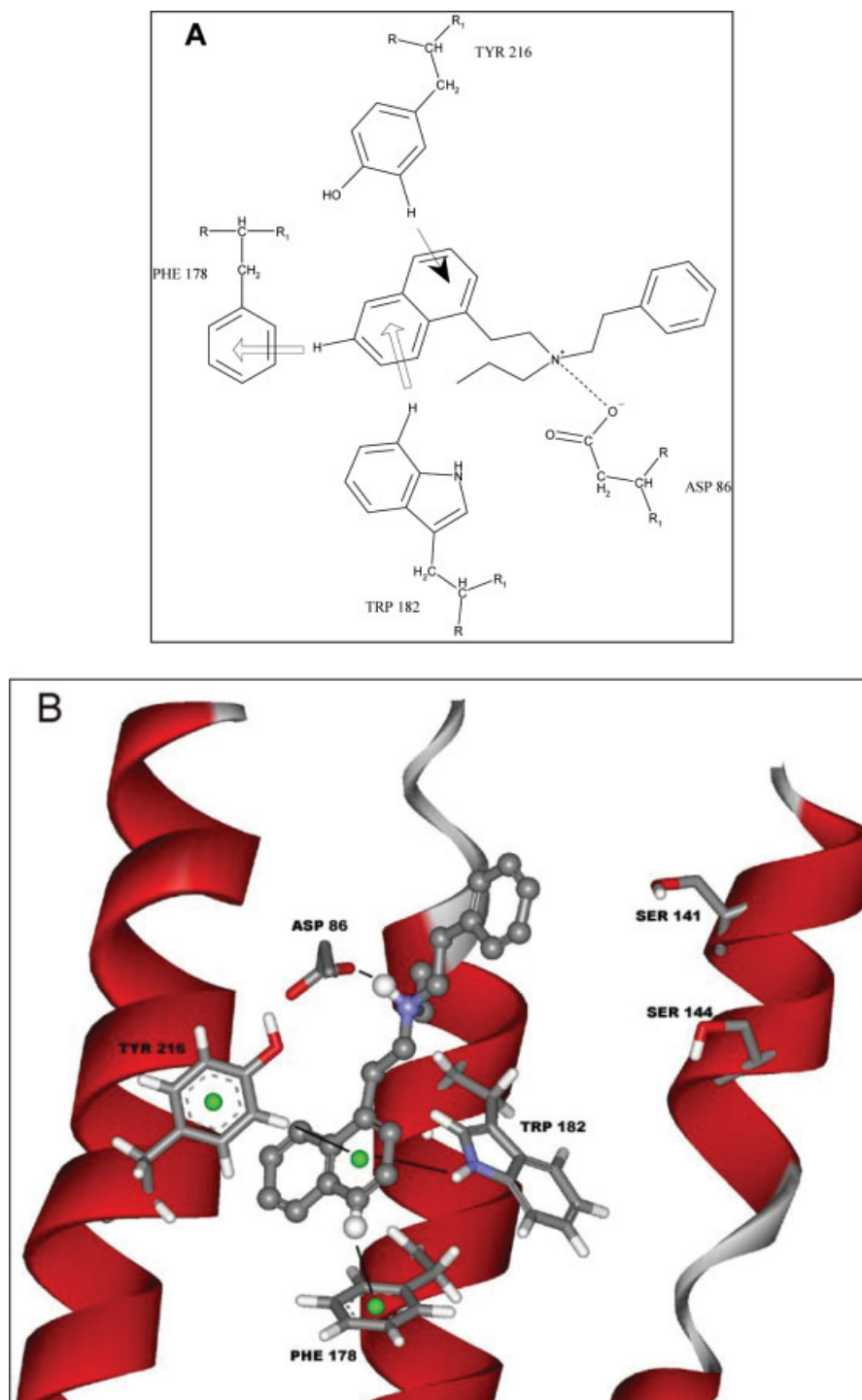
Inactivity of 2-naphthyl derivatives **8g** and **8i**, as well as of biphenyl compound **8l** can be interpreted in terms of steric hindrance. According to the proposed model unfavourable steric interactions occurs between 2-naphthyl group of the compounds **8g** and **8i** as well as biphenyl

group of the ligand **8l** with Phe 178 of D<sub>2</sub> dopamine receptor. Ligands with phenyl groups (**8a**, **8b**, **8d** and **8e**) were inactive in spiperone binding assay, with the only exception of compound **8c**. Since a phenyl group is much less voluminous compared to a naphthyl group, edge-to-face interactions are probably less likely to take place. A significantly higher affinity of compound **8c** for the binding at the D<sub>2</sub> dopamine receptor can be explained by possible hydrogen bond formation between the nitro group of the ligand and hydrogen bond donor in the D<sub>2</sub> receptor binding pocket.

Binding constants of naphthyl compounds **8c** and **8e** obtained in tritiated spiperone assay were similar to those of thienylethylamines (compounds 3 and 4) described by Dijkstra et al. [15]. These authors suggested that the thiophene and the phenol ring utilize the same interaction points and that the sulfur atom in the thienylethyl substituents forms a hydrogen bond with the hydroxyl moiety of a Ser residue in the D<sub>2</sub> receptor. Although this is a “pleasurable” explanation, additional (or even exclusive) edge-to-face interactions of the thienyl moiety of the ligands and aromatic residues in the binding pocket of the receptor molecule cannot be excluded.

It would be very interesting to introduce a naphthalene structure in semirigid 2-aminotetralin-like structure in a similar way as done with the thiophene ring and to evaluate the binding affinity of thus obtained compounds. Research in that direction is under way and we hope to produce the ligands of higher binding affinity than observed for the compounds described in the present study. This type of dopaminergic compounds would confirm our hypothesis that edge-to-face interactions of ligands and the receptor could be sufficient to create a high affinity ligand. From a practical point of view, clinical utility of catechol- and phenol-containing drugs has been limited due to their low oral bioavailability and short duration of action. Thus, for many years, emphasis has been focused on the identification of bioisosteric replacements of both catechols and phenols. The idea that neither catecholic nor phenolic hydroxyl groups are an absolute requirement for potent dopaminergic activity is not new [16] and we believe that our results contribute somewhat to collective efforts to find more efficient dopaminergic drugs.

The model of McDermid et al. [6] of the D<sub>2</sub> dopamine receptor postulated the presence of two lipophilic sites which bind the *N*-alkyl groups. One of these sites is large enough to accommodate rather bulky groups. Introduction of different 2-arylethyl groups as substituents in this position, lead to a significant increase in the affinity of benzimidazole (**1**) [6] or phenylethylamine (R: *m*- or *p*-OH) (**3**) [7] type of ligands in comparison with the parental ones. Similar pattern of behaviour has been observed



**Figure 2.** Schematic representation of edge-to-face interaction between ligand **8h** and D<sub>2</sub> dopamine receptor.

Schematic model of the proposed interaction of the studied compound **8h** with the D<sub>2</sub> receptors. **A:** Cartoon describes possible edge-to-face interaction between **8h** and the aromatic residue in the binding pocket of the receptor. **B:** 3D presentation of the same interaction using a theoretical dopamine D<sub>2</sub> receptor model on bacteriorhodopsin (PDB identification code: 1115, Protein Data Bank, Brookhaven) and ligand **8h**.



in 1-naphthyl derivatives **8f**, **8h** and **8j**, while compound **8k** was inactive due to the incompatibility of the 2-naphthyl group geometry with this receptor system.

The profile of activity detected in [ $^3\text{H}$ ]-8-OH-DPAT competition binding assay revealed a rather high affinity but relatively low structural selectivity of most of the ligands discussed here. Lower structural selectivity for 5-HT<sub>1A</sub> receptor compared to the D<sub>2</sub> dopamine receptor can be due to its more spacious and flexible ligand binding site. This can be a plausible explanation for lower but are still significant activities of 2-naphthyl ligands **8g** and **8i**. Compounds **8f** and **8l** behaving as inactive competitors of the specific radioligand were the only exception, while compounds **8a** and **8g** had a rather low binding affinity. As in the case of the D<sub>2</sub> dopamine receptor, linking of the 2-arylethyl group to the basic nitrogen, significantly increased the affinity of the ligands to bind at the 5-HT<sub>1A</sub> receptor. The receptor binding pocket is large enough to accommodate as bulky substituents as 2-(1-naphthyl)-ethyl and 2-(2-naphthyl)ethyl, but not so voluminous substituent as 2-(biphenyl)ethyl [17]. On the other hand, due to chemical properties of the ligands examined in this study, hydrophobic edge-to-face interactions represent the principal driving force in ligand-receptor complex formation.

In conclusion, these data demonstrate the affinity of tertiary 2-(1-naphthyl)ethyl and 2-(2-naphthyl)ethyl amines for the binding at the D<sub>2</sub> dopamine and 5-HT<sub>1A</sub> serotonin receptors. The lack of heteroatoms in the ligands which could build strong hydrogen bonds with the receptor molecules clearly point to a pronounced role of stabilizing aromatic stacking or edge-to-face interactions in the formation of ligand-receptor complexes.

Further elaboration of the chemical structure of the ligands described in the present report, which focused on the improvement of their dopaminergic/serotonergic properties, and on providing a more precise map of the receptor site interacting with naphthyl derivatives is in progress.

## Acknowledgement

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## Experimental

### General

Melting points of the novel ligands determined on a Boetius PHMK apparatus (VEB Analytic, Dresden, Germany) are presented as uncorrected. The results of microanalyses were with-

in 0.4 % of the calculated values. 200 MHz  $^1\text{H}$ -NMR spectra recorded on a Gemini 2000 spectrometer (Varian, Palo Alto, CA, USA) with  $\text{CDCl}_3$  as a solvent unless otherwise stated are reported in ppm ( $\delta$ ) downfield from the internal standard tetramethylsilane. The IR spectra were run on a Perkin Elmer 457 Grating Infrared Spectrophotometer (Perkin Elmer, Beaconsfield, England). The mass spectra were determined on a Bruker Biflex MALDI TOF mass spectrometer (Bruker, Bremen, Germany). For analytical thin-layer chromatography, E. Merck (Darmstadt, Germany) F-256 plastic-backed thin-layer silica gel plates were used. Chromatographic purifications were performed on Merck-60 silica gel columns, 230–400 mesh ASTM under medium pressure (MPLC). Solutions were routinely dried over anhydrous  $\text{Na}_2\text{SO}_4$  prior to evaporation.

### Chemistry

#### General procedure for the synthesis of acyl chlorides (**5a–g**)

Synthesis of acyl chlorides (**5a–g**) was performed according to the modified general procedure starting from the corresponding acid and thionyl chloride [17]. Shortly, to the solution of 25 mmol arylacetic acids in 10 mL dichloromethane, 0.5 mL DMF and 0.030 mol thionyl chloride were added. The mixture was incubated at room temperature overnight. The solvent was removed *in vacuo* and obtained acyl chlorides were used without further purification for amides preparation.

#### General procedure for the synthesis of secondary amines **6a–d**

The details on the synthesis of secondary amines **6a–d** were given previously [12].

#### General procedure for the synthesis of arylacetamides **7a–l**

To the solution of each secondary amine **6a–d** (15 mmol) in 50 mL of dry dichloromethane and 15 mmol pyridine cooled in an ice bath, 15 mmol solution of either acyl chloride (**5a–g**) in 10 mL dichloromethane was added dropwise. After overnight stirring at ambient temperature, the reaction mixture was extracted first with 5 % NaOH followed by 5 % HCl and water. After drying over  $\text{Na}_2\text{SO}_4$  organic phase was evaporated *in vacuo* to dryness and the crude product purified by MPLC or crystallized from ethanol.

#### *N,N*-dipropyl-2-phenylacetamide (**7a**):

Yield 3.00 g (92 %); oil – IR (KBr): ( $\text{cm}^{-1}$ ) 2962, 1641, 1089, 793. –  $^1\text{H}$ -NMR:  $\delta$  0.92 (t,  $J$  = 8 Hz, 6 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 1.45 (tq,  $J$  = 8 Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.1–3.2 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.62 (s, 2 H,  $\text{PhCH}_2\text{CON}$ ); 7.21 (s broad, 5 H,  $\text{PhH}$ ). – Anal. ( $\text{C}_{14}\text{H}_{21}\text{NO}$ ), C, H, N. [18]

#### *N*-propyl-*N*-(2-phenylethyl)-2-phenylacetamide (**7b**):

Yield 3.75 g (89 %); mp 62 °C. – IR (KBr): ( $\text{cm}^{-1}$ ) 2960, 1659, 1061, 792. –  $^1\text{H}$ -NMR:  $\delta$  0.93 (t,  $J$  = 8 Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 1.40–1.70 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 2.70 (t,  $J$  = 8 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.0–3.25 (m, 4 H,  $\text{PhCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.46–3.60 (m, 2 H,  $\text{PhCH}_2\text{CH}_2\text{N}$ ); 3.64 (s, 2 H,  $\text{PhCH}_2\text{CON}$ ); 7.22 (m, 10 H,  $\text{PhH}$ ). – Anal. ( $\text{C}_{19}\text{H}_{23}\text{NO}$ ), C, H, N.

#### *N*-propyl-*N*-(2-phenylethyl)-2-(4-nitrophenyl)acetamide (**7c**):

Yield 3.86 g (79 %); mp 115 °C. – IR (KBr): ( $\text{cm}^{-1}$ ) 2939, 1654, 1553, 1490, 1065, 781. –  $^1\text{H}$ -NMR:  $\delta$  0.91 (t,  $J$  = 8 Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 1.40–1.70 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 2.70 (t,  $J$  = 8 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.0–3.35 (m, 4 H,  $\text{PhCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ); 3.55–3.69 (m, 2 H,  $\text{PhCH}_2\text{CH}_2\text{N}$ ); 3.91 (s, 2 H,  $\text{PhCH}_2\text{CON}$ ); 7.24 (s broad, 5 H,  $\text{PhH}$ ); 7.63 (d,  $J$  = 8 Hz, 2 H,  $\text{ArH}$ ); 8.22 (d,  $J$  = 8 Hz, 2 H,  $\text{ArH}$ ). – Anal. ( $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ ), C, H, N.

***N*-propyl-*N*-(2-phenylethyl)-2-(4-chlorophenyl)acetamide (7 d):**

Yield 4.25 g (90 %); mp 95 °C. – IR (KBr): (cm<sup>-1</sup>) 2961, 1659, 798. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.40–1.70 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.0–3.25 (m, 4 H, PhCH<sub>2</sub>CH<sub>2</sub>N, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.46–3.60 (m, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 3.69 (s, 2 H, PhCH<sub>2</sub>CON); 7.20–7.40 (m, 9 H, ArH). – Anal. (C<sub>19</sub>H<sub>22</sub>ClNO), C, H, N.

***N*-propyl-*N*-(2-phenylethyl)-2-(4-methylphenyl)acetamide (7 e):**

Yield 3.93 g (89 %); mp 61 °C. – IR (KBr): (cm<sup>-1</sup>) 2963, 1649, 1068, 792. – <sup>1</sup>H-NMR: δ 0.93 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.40–1.70 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.33 (s, 3 H, Ar-CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.0–3.25 (m, 4 H, PhCH<sub>2</sub>CH<sub>2</sub>N, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.46–3.60 (m, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 3.64 (s, 2 H, PhCH<sub>2</sub>CON); 7.20–7.40 (m, 9 H, ArH). – Anal. (C<sub>20</sub>H<sub>25</sub>NO), C, H, N.

***N*,*N*-dipropyl-2-(1-naphthyl)acetamide (7 f):**

Yield 3.02 g (75 %); mp 71 °C. – IR (KBr): (cm<sup>-1</sup>) 2959, 1663, 1061, 800. – <sup>1</sup>H-NMR: δ 0.92 (t, J = 8 Hz, 6 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.48 (tq, J = 8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.2–3.3 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 4.16 (s, 2 H, PhCH<sub>2</sub>CON); 7.2–7.9 (m broad, 7 H, ArH). – Anal. (C<sub>18</sub>H<sub>23</sub>NO), C, H, N.

***N*,*N*-dipropyl-2-(2-naphthyl)acetamide (7 g):**

Yield 3.40 g (89 %); mp 82 °C. – IR (KBr): (cm<sup>-1</sup>) 2983, 1659, 1059, 789. – <sup>1</sup>H-NMR: δ 0.92 (t, J = 8 Hz, 6 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.43 (tq, J = 8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.1–3.2 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.98 (s, 2 H, PhCH<sub>2</sub>CON); 7.2–7.9 (m broad, 7 H, ArH). – Anal. (C<sub>18</sub>H<sub>23</sub>NO), C, H, N.

***N*-propyl-*N*-(2-phenylethyl)-2-(1-naphthyl)acetamide (7 h):**

Yield 3.72 g (75 %); mp 125 °C. – IR (KBr): (cm<sup>-1</sup>) 2988, 1648, 1119, 801. – <sup>1</sup>H-NMR: δ 0.92 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.45 (tq, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.05 (s broad, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 3.05–3.6 (m broad, 4 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 4.15 (s, 2 H, PhCH<sub>2</sub>CON); 7.1–7.8 (m broad, 12 H, ArH). – Anal. (C<sub>23</sub>H<sub>25</sub>NO), C, H, N.

***N*-propyl-*N*-(2-phenylethyl)-2-(2-naphthyl)acetamide (7 i):**

Yield 4.12 g (83 %); mp 129 °C. – IR (KBr): (cm<sup>-1</sup>) 2966, 1663, 1065, 791. – <sup>1</sup>H-NMR: δ 0.91 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.43 (tq, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.90 (s broad, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 2.95–3.5 (m broad, 4 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 3.92 (s, 2 H, PhCH<sub>2</sub>CON); 7.1–7.8 (m broad, 12 H, ArH). – Anal. (C<sub>23</sub>H<sub>25</sub>NO), C, H, N.

***N*-propyl-*N*-[2-(1-naphthyl)ethyl]-2-(1-naphthyl)acetamide (7 j):**

Yield 3.94 g (69 %); mp 135 °C. – IR (KBr): (cm<sup>-1</sup>) 2995, 1633, 1044, 781. – <sup>1</sup>H-NMR: δ 0.94 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.49 (tq, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.2–3.3 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.35–3.8 (m, 4 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 4.16 (s, 2 H, PhCH<sub>2</sub>CON); 7.2–7.9 (m broad, 14 H, ArH). – Anal. (C<sub>27</sub>H<sub>27</sub>NO), C, H, N.

***N*-propyl-*N*-[2-(1-naphthyl)ethyl]-2-(2-naphthyl)acetamide (7 k):**

Yield 4.41 g (77 %); mp 141 °C. – IR (KBr): (cm<sup>-1</sup>) 2991, 1643, 1088, 788. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.96 (m broad, 6 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 3.21 (m broad, 2 H, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 14 H, ArH). – Anal. (C<sub>27</sub>H<sub>27</sub>NO), C, H, N.

***N*-propyl-*N*-(2-phenylethyl)-2-(4-biphenyl)acetamide (7 l):**

Yield 3.48 g (87 %); mp 103 °C. – IR (KBr): (cm<sup>-1</sup>) 2987, 1652, 1073, 777. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.40–1.70 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.0–3.25 (m, 4 H, PhCH<sub>2</sub>CH<sub>2</sub>N, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 3.46–3.60 (m, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 3.67 (s, 2 H, PhCH<sub>2</sub>CON); 7.1–7.8 (m, 14 H, ArH). – Anal. (C<sub>25</sub>H<sub>27</sub>NO), C, H, N.

**General procedure for the synthesis of tertiary amines (8 a–l)**

A solution of each arylacetamide **7 a–l** (10 mmol) in 30 ml of dry tetrahydrofuran cooled in an ice bath was bubbled with gaseous diborane generated from 1.1 g NaBH<sub>4</sub> and 5.0 mL BF<sub>3</sub> · Et<sub>2</sub>O. After diborane generation was ceased, the mixture was refluxed for 60 min, cooled to ambient temperature, made alkaline with 20 % NaOH, and extracted with diethyl ether. The extract was evaporated *in vacuo* to dryness, the crude product purified by MPLC and converted to oxalate by neutralization of the amine with oxalic acid solution in 90 % ethanol. The resulting oxalates were subjected to recrystallization from ethanol.

***N*-(2-phenylethyl)-*N*,*N*-dipropyl amine (8 a):**

Yield 1.86 g (91 %); mp 132 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2962, 1643, 1089. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 6 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.90 (s broad, 4 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 7.21 (s broad, 5 H, PhH); mass spectrum m/e 205, 185 (M<sup>+</sup>). – Anal. (C<sub>14</sub>H<sub>23</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N. [18]

***N*,*N*-di(2-phenylethyl)-*N*-propyl amine (8 b):**

Yield 2.35 g (88 %); mp 147 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2962, 1641, 1061. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.91 (s broad, 8 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 7.22 (s broad, 10 H, PhH); mass spectrum m/e 267, 202 (M<sup>+</sup>). – Anal. (C<sub>19</sub>H<sub>25</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N. [19]

***N*-(2-phenylethyl)-*N*-[2-(4-nitrophenyl)ethyl]-*N*-propyl amine (8 c):**

Yield 2.25 g (72 %); mp 174 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2956, 1633, 1555, 1497, 1065. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.92 (s broad, 2 H, PhCH<sub>2</sub>CH<sub>2</sub>N); 3.05 (s broad, 6 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 7.24 (s broad, 5 H, PhH); 7.63 (d, J = 8 Hz, 2 H, ArH); 8.22 (d, J = 8 Hz, 2 H, ArH); mass spectrum m/e 312, 187 (M<sup>+</sup>). – Anal. (C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-(2-phenylethyl)-*N*-[2-(4-chlorophenyl)ethyl]-*N*-propyl amine (8 d):**

Yield 2.55 g (85 %); mp 158 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2957, 1639, 1075, 795. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.92 (s broad, 8 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 7.24 (s broad, 9 H, ArH); mass spectrum m/e 301, 163 (M<sup>+</sup>). – Anal. (C<sub>19</sub>H<sub>24</sub>ClN · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-(2-phenylethyl)-*N*-[2-(4-methylphenyl)ethyl]-*N*-propyl amine (8 e):**

Yield 2.61 g (93 %); mp 149 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2976, 1653, 1077. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.33 (s, 3 H, Ar-CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.90 (s broad, 8 H, ArCH<sub>2</sub>CH<sub>2</sub>N); 7.18 (s broad, 9 H, ArH); mass spectrum m/e 281, 216 (M<sup>+</sup>). – Anal. (C<sub>20</sub>H<sub>27</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(1-naphthyl)ethyl]-*N,N*-dipropyl amine (8f):**

Yield 2.26 g (89 %); mp 143 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2956, 1633, 1065. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 6H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.96 (m broad, 2H, ArCH<sub>2</sub>CH<sub>2</sub>N); 3.21 (m broad, 2H, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 7H, ArH); mass spectrum m/e 255, 195 (M<sup>+</sup>). – Anal. (C<sub>18</sub>H<sub>25</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(2-naphthyl)ethyl]-*N,N*-dipropyl amine (8g):**

Yield 2.11 g (86 %); mp 148 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2993, 1654, 1059. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 6H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.95 (s broad, 4H, 2-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 7H, ArH); mass spectrum m/e 255, 195 (M<sup>+</sup>). – Anal. (C<sub>18</sub>H<sub>25</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(1-naphthyl)ethyl]-*N*-(2-phenylethyl)-*N*-propyl amine (8h):**

Yield 2.50 g (79 %); mp 163 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2978, 1658, 1101. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.94 (m broad, 6H, PhCH<sub>2</sub>CH<sub>2</sub>N, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 3.21 (m broad, 2H, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 12H, ArH); mass spectrum m/e 317, 214 (M<sup>+</sup>). – Anal. (C<sub>23</sub>H<sub>27</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(2-naphthyl)ethyl]-*N*-(2-phenylethyl)-*N*-propyl amine (8i):**

Yield 2.54 g (80 %); mp 168 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2973, 1651, 1071. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.90 (s broad, 4H, PhCH<sub>2</sub>CH<sub>2</sub>N, 2-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 2.95 (m broad, 4H, PhCH<sub>2</sub>CH<sub>2</sub>N, 2-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.1–7.8 (m broad, 14H, ArH); mass spectrum m/e 317, 217 (M<sup>+</sup>). – Anal. (C<sub>23</sub>H<sub>27</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N,N*-di[2-(1-naphthyl)ethyl]-*N*-propyl amine (8j):**

Yield 2.38 g (65 %); mp 148 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2990, 1649, 1047. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 4H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.96 (m broad, 4H, ArCH<sub>2</sub>CH<sub>2</sub>N); 3.21 (m broad, 4H, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 14H, ArH); mass spectrum m/e 367, 236 (M<sup>+</sup>). – Anal. (C<sub>27</sub>H<sub>29</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(1-naphthyl)ethyl]-*N*-[2-(2-naphthyl)ethyl]-*N*-propyl amine (8k):**

Yield 2.60 g (71 %); mp 154 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2983, 1637, 1085. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.96 (m broad, 6H, PhCH<sub>2</sub>CH<sub>2</sub>N, 2-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 3.21 (m broad, 2H, 1-naphthyl-CH<sub>2</sub>CH<sub>2</sub>N); 7.2–7.9 (m broad, 14H, ArH); mass spectrum m/e 367, 231 (M<sup>+</sup>). – Anal. (C<sub>27</sub>H<sub>29</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

***N*-[2-(4-biphenyl)ethyl]-*N*-(2-phenylethyl)-*N*-propyl amine (8l):**

Yield 2.11 g (83 %); mp 173 °C (oxalate). – IR (KBr): (cm<sup>-1</sup>) 2991, 1673, 1066. – <sup>1</sup>H-NMR: δ 0.90 (t, J = 8 Hz, 3H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.70–1.40 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.70 (t, J = 8 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 2.95 (m broad, 8H, ArCH<sub>2</sub>CH<sub>2</sub>N); 7.1–7.8 (m broad, 14H, ArH); mass spectrum m/e 343, 239 (M<sup>+</sup>). – Anal. (C<sub>25</sub>H<sub>29</sub>N · C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> · H<sub>2</sub>O), C, H, N.

**Radioligand binding studies**

Synaptosomal membranes of fresh bovine caudate nuclei and hippocampi used in radioligand binding assays as sources of the dopamine and serotonin receptors, respectively, were prepared as described previously [20, 21]. [<sup>3</sup>H]SCH 23390 (spec. act. 80 Ci mmol<sup>-1</sup>), [<sup>3</sup>H]spiperone (spec. act. 70.5 Ci mmol<sup>-1</sup>) and [<sup>3</sup>H]-8-OH-DPAT (spec. act. 223 Ci mmol<sup>-1</sup>) used to label D<sub>1</sub>, D<sub>2</sub> and 5-HT<sub>1A</sub> receptors, respectively, were purchased from Amersham Buchler GmbH (Braunschweig, Germany). Competition binding assays in which the novel ligands served as competitors and data analyses were performed exactly as reported previously [19].

**Receptor-binding assay using [<sup>3</sup>H]Spiperone**

[<sup>3</sup>H]Spiperone binding was assayed at membrane protein concentration of 0.7 mg/mL in a solution consisting of (in mM): EDTA 1.0, MgCl<sub>2</sub> 4.0, CaCl<sub>2</sub> 1.5, KCl 5.0, NaCl 120, Tris-HCl 25, pH 7.4, at 37 °C for 20 min in a total volume of incubation mixture of 1.0 mL. Binding of the radioligand to 5-HT<sub>2</sub> receptors was prevented by 50 nM ketanserin. IC<sub>50</sub> values were determined by competition binding at 0.2 nM of the radioligand and eight to ten concentrations of each novel compound (0.1 nM – 0.1 mM). Nonspecific binding was measured in the presence of 1.0 μM (+)-butaclamol. The reaction was terminated by a rapid filtration through Whatman GF/C filters, which were further washed three times with 5.0 mL of ice-cold incubation buffer. Each point was determined in triplicate. Retained radioactivity was measured by introducing dry filters into 10 ml of toluene-based scintillation liquid and counting in a 1219 Rackbeta Wallac scintillation counter at an efficiency of 51–55 % for tritium.

**Receptor-binding assay using [<sup>3</sup>H]SCH 23390**

Binding of [<sup>3</sup>H]SCH 23390 was examined by the same rapid filtration assay discussed for [<sup>3</sup>H]spiperone in the absence of ketanserin.

**Receptor-binding assay using [<sup>3</sup>H]-8-OH-DPAT**

To achieve a final volume of 0.5 mL, a solution containing (in mM) EDTA 1.0, MgCl<sub>2</sub> 4.0, CaCl<sub>2</sub> 1.5, KCl 5.0, NaCl 120, Tris-HCl 25, pH 7.4, 10 μM nialamide and 0.1 % ascorbic acid, at membrane protein concentration of 0.7 mg/mL, 0.6 nM [<sup>3</sup>H]-8-OH-DPAT and various concentrations (0.1 nM – 0.1 mM) of the tested compounds were introduced into each tube. The incubation, termination of the reaction and handling of the filters were done as described in the [<sup>3</sup>H]spiperone binding assay. Specific binding at the 5-HT<sub>1A</sub> receptor was defined as the difference between the binding in the absence and in the presence of 10 μM 5-hydroxytryptamine.

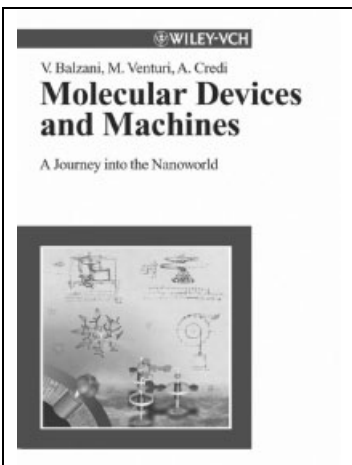
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