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Full Paper

The Effect of Carboxamide/Sulfonamide Replacement in Arylpiperazinylalkyl Derivatives on Activity to Serotonin and Dopamine Receptors

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A series of carboxamide and sulfonamide alkyl (*p*-xylyl and benzyl) 1-(2-methoxyphenyl)piperazine (*o*-OMe-PhP) and 1-(2,3-dichlorophenyl)piperazine (2,3-DCPP) analogs were prepared and tested for their affinity to bind to serotonin 5-HT_{1A}/5-HT_6/5-HT_7 and dopamine D_2 receptors. This chemical modification let us explore the impact of the replacement of the carboxamide by the sulfonamide group on the affinity changes. In both the *o*-OMe-PhP and 2,3-DCPP series, the relative activities of the carboxamides versus sulfonamides toward the 5-HT_{1A}/5-HT_6/5-HT_7 and D_2 receptors show similar trends. Varied or similar activities for particular receptors were found for the carboxamides/sulfonamides with *p*-xylyl spacer, while of the two classes of carboxamides and sulfonamides examined, benzyl derivatives of the sulfonamides displayed the highest serotoninergic affinity, in particular to the 5-HT_7 receptors (K_i 8–85 nM). The K_i values revealed that, irrespective of the carboxamide/sulfonamide zone, both *p*-xylyl and benzyl derivatives had the highest affinity for the dopamine D_2 receptor (i.e., 16 out of 24 compounds investigated have an affinity below 100 nM). A molecular modeling study of carboxamide **9a** and sulfonamide **9b** showed that their binding effects to each of 5-HT_{1A}R and D_2R created binding modes interaction with different conserved receptors residues. Structural similarities of carboxamide **9a** in complexes with a 5-HT_{1A}R (**9aI**) and D_2R (**9aII**) are over 83%, while the respective similarities of sulfonamide **9b** structures (**9bI**/**9bII**) are only about 40%.

Keywords: Arylpiperazines / Carboxamides / Serotonin 5-HT_{1A}/5-HT_6/5-HT_7 and D_2 receptor ligands / Structure–activity relationship (SAR) / Sulfonamides

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Introduction

Bioisosterism represents a successful strategy in rational drug design, useful in molecular modification of new therapeutically attractive drug substances of different pharmacological classes [1–4]. Replacement of carboxamide group with sulfonamide isoster is a common modification used in medicinal chemistry. Although both come under the class of amides, replacement of the carboxamide by a sulfonamide strongly modifies physical properties and the spatial orientation of the molecules [5] and the success of this chemical modification was varied in the literature [5–20].

In the case of arylpiperazines **1**, both carboxy (**1a**) and sulfonyl (**1b**) derivatives bond with high affinity to 5-HT_{1A} receptors (K_i values $<$10 nM) [16] (Fig. 1). Similarly, carboxamide **2a** and sulfoamide **2b** have excellent 5-HT_{1A}, D_2, and α_1

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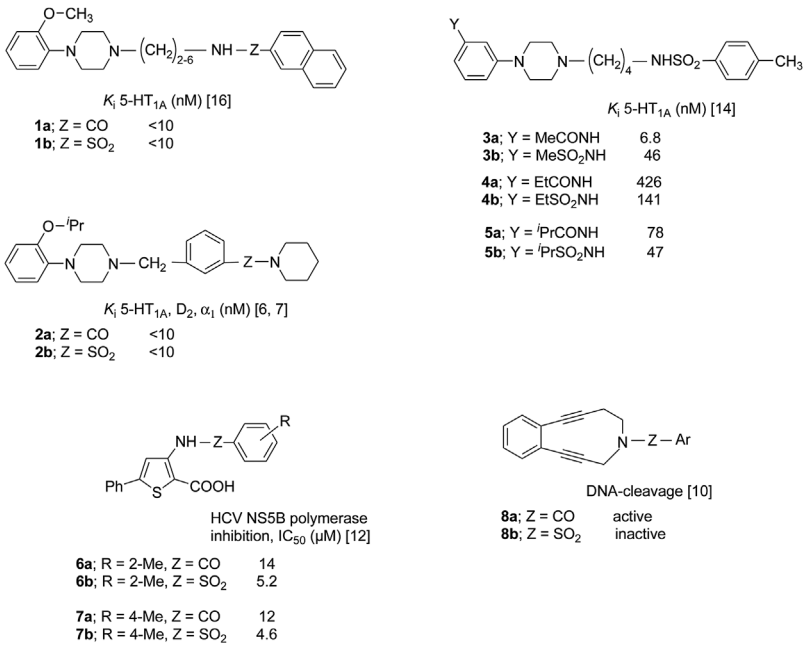


Figure 1. The activities of selected carboxamides versus sulfonamide derivatives.

receptors affinities with K_i's <10 nM [6, 7], but only **2a** had *in vivo* activity in the catalepsy test in rats [7].

The 5-HT_{1A} receptor ligands **3**–**5** [14] (Fig. 1), however, showed varied activity depending on the presence of carboxamide or sulfonamide group at *meta*-position of the phenyl ring attached to piperazine. The best K_i values were obtained for MeCONH in **3a** ($K_i = 6.8$ nM), while $MeSO_2NH$ in **3b** ($K_i = 46$ nM) exhibits seven to eightfold lower 5-HT_{1A} binding affinity. Higher K_i values were measured for ethyl (**4**) and isopropyl (**5**) analogs, but in these cases sulfonyl derivatives **4b** and **5b** showed higher 5-HT_{1A} binding affinity compared to carboxy analog **4a** and **5a**, respectively.

Investigation of 3-arylcarboxyaminothiophene (**6a** and **7a**) and 3-arylsulfonylaminothiophene (**6b** and **7b**) derivatives, as a novel class of HCV NS5B polymerase inhibitors [12], proved that the molecules with sulfonamide moieties (series **b**) had higher activity than their carboxamide (series **a**) analogs (Fig. 1).

Basak et al. [10] studied the DNA-cleavage activity of monocyclic enediynyl carboxamides **8a** versus sulfonamides **8b** (Fig. 1). It was shown that only carboxamides **8a** were able to cleave the plasmid DNA at micromolar concentration. On the contrary, the sulfonamides **8b** did not show any DNA-cleavage activity even at millimolar level.

While continuing the structure-activity studies described in the literature (Fig. 1), in this paper we report the synthesis of four long-chain arylpiperazine (LCAP) sets of the carboxamide (**9a**–**20a**) and sulfonamide (**9b**–**20b**) derivatives, investigated as serotonergic and dopaminergic receptor ligands (Table 1). The first two sets of the investigated compounds contained 1-(2-methoxyphenyl)piperazine (*o*-OMe-PhP) moiety as an amine pharmacophore (compounds **9**–**14**), while the other two sets comprised 1-(2,3-dichlorophenyl)piperazine (2,3-DCPP) isostere (compounds **15**–**20**). In the terminal part of the molecules studied phenyl, 2-naphthyl, or methyl group was introduced. In comparison with the classic LCAP we replaced an alkylene spacer with partly constrained *p*-xylyl (**9**–**11**, **15**–**17**) and benzyl (**12**–**14**, **18**–**20**) fragment, because the effect of the spacer structure in LCAP ligands was the subject of our subsequent research [22, 23].

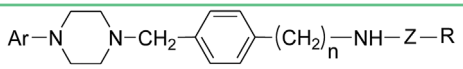
Results and discussion

Chemistry

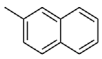
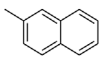
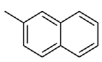
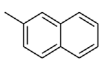
The synthesis of the compounds under study was carried out according to Schemes 1 and 2. All the carboxamides (**9a**–**20a**) and sulfonamides (**9b**–**20b**) were prepared by the reaction of commercially available acyl or sulfonyl chlorides with the amines **24**, **25**, **29**, or **30** in the presence of a base (Schemes 1–2).

The synthesis of *p*-benzylmethylamines **24** and **25** was carried out using *N*-[4-(chlorometyl)benzyl]phthalimide (**21**) as the starting compound (Scheme 1). The intermediate **21** was obtained by reacting phthalimide with α, α′-dichloro-*p*-xylene as described previously [22]. The reaction of **21** with *o*-OMe-PhP or 2,3-DCPP, carried out in DMF in the presence of K_2CO_3 at ambient temperature, afforded *N*-alkylated phthalimides **22** and **23**, respectively. The latter compounds yielded amines **24** and **25** upon cleavage in 40% aqueous solution of methylamine.

Table 1. Structures of the compounds studied and their binding profile to 5-HT$_{1A}$, 5-HT$_6$, 5-HT$_7$, and D$_2$ receptors.



9–14; Ar = 2-methoxyphenyl
15–20; Ar = 2,3-dichlorophenyl

Comp. no	Set no	R	n	Z	Receptor binding K_i (nM) 5HT$_{1A}$	5-HT$_6$	5-HT$_7$	D$_2$
9a	1		1	CO	52 ± 6	2430 ± 312	178 ± 67	25 ± 3
9b				SO_2	56 ± 5	2779 ± 251	226 ± 36	32 ± 2
10a	1		1	CO	121 ± 9	2521 ± 342	84 ± 6	126[a] ± 14
10b				SO_2	67 ± 7	2018 ± 173	106 ± 9	137 ± 19
11a	1	CH_3	1	CO	196 ± 23	2309 ± 281	33 ± 4	69 ± 8
11b				SO_2	171 ± 19	3827 ± 447	455 ± 52	102 ± 7
12a	2		0	CO	140 ± 12	4704 ± 612	635 ± 48	12 ± 2
12b				SO_2	55 ± 8	1767 ± 249	32 ± 5	10 ± 3
13a	2		0	CO	287 ± 37	3719 ± 232	505 ± 43	68 ± 5
13b				SO_2	59 ± 11	657 ± 85	12 ± 2	98 ± 4
14a	2	CH_3	0	CO	1408 ± 162	7257 ± 618	717 ± 95	116 ± 9
14b				SO_2	275 ± 34	4138 ± 577	13 ± 3	187 ± 27
15a	3		1	CO	1007 ± 71	794 ± 81	188 ± 26	66 ± 7
15b				SO_2	1097 ± 126	680 ± 79	213 ± 18	87 ± 11
16a	3		1	CO	14690 ± 1421	5634 ± 467	208 ± 13	99 ± 8
16b				SO_2	3925 ± 527	1749 ± 248	179 ± 16	232 ± 17
17a	3	CH_3	1	CO	906 ± 139	1954 ± 173	92 ± 7	49 ± 6
17b				SO_2	1610 ± 267	1695 ± 185	311 ± 39	93 ± 16
18a	4		0	CO	2168 ± 316	1602 ± 94	1151 ± 95	76 ± 9
18b				SO^2	1982 ± 164	525 ± 61	85 ± 6	99 ± 6
19a	4		0	CO	36950 ± 2457	5665 ± 429	4496 ± 359	224 ± 34
19b				SO_2	1147 ± 79	939 ± 132	52 ± 4	466 ± 51
20a	4	CH_3	0	CO	1140 ± 183	1675 ± 148	231 ± 41	9 ± 2
20b				SO_2	343 ± 29	627 ± 76	8 ± 2	71 ± 8

[a] $K_i = 200 \pm 14$ nM according to Hackling et al. Ref. [21].

In the synthesis of *p*-benzylamines **29** and **30** commercially available *p*-nitrobenzyl chloride (**26**) was applied (Scheme 2). The reaction of **26** with arylpiperazines led to the nitro-intermediates **27** and **28**. Reduction of the nitro group in **27** to the amine group in **29** was done using activated zinc and ammonium formate [24], while the amine **30** was obtained by reduction of **28** with stannous chloride under acidic conditions [25].

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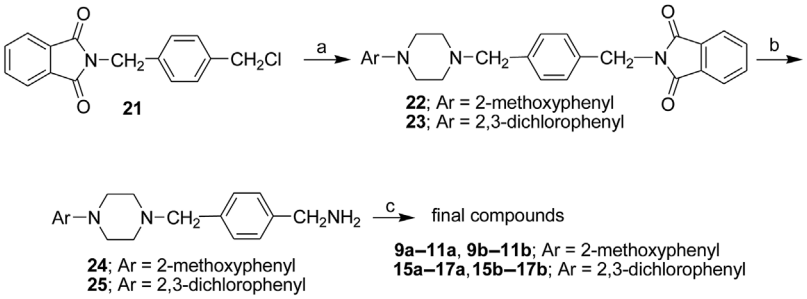


Scheme 1. Preparation of *N*-{[(4-arylpiperazin-1-ylmethyl)phenyl]methyl}carboxamides **9a–11a**, **15a–17a**, and *N*-{[(4-arylpiperazin-1-ylmethyl)-phenyl]methyl}sulfonamides **9b–11b**, **15b–17b**. Reagents and conditions: (a) 1-(2Methoxyphenyl)piperazine hydrochloride or 1-(2,3-dichlorophenyl)piperazine hydrochloride, DMF, K_2CO_3, rt, 48 h, 72–80%; (b) methylamine 40% in H_2O, rt, 24–48 h, 90–93%; (c) acyl chlorides or sulfonyl chlorides, TEA, DCM, rt, 24 h, 45–80%.

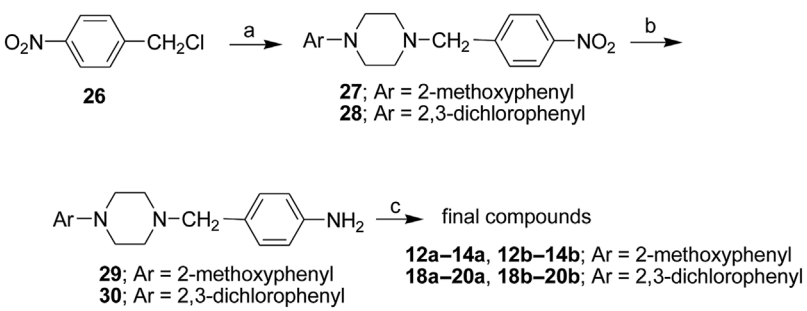
Biological evaluation

The affinity of the compounds studied toward serotonin 5-HT_{1A}, 5-HT_6, 5-HT_7, and dopamine D_2 receptors was evaluated *in vitro* by radioligand binding experiments (Table 1), as described previously [26, 27]. This was accomplished by displacement of radioligands from cloned human receptors, all stably expressed in HEK293 cells: [^{3}H]-8-OH-DPAT for 5-HT_{1A}R, [^{3}H]-LSD for 5-HT_6R, [^{3}H]-5-CT for 5-HT_7R, and [^{3}H]-raclopride for D_2R, respectively (other details are shown in the Experimental part).

Activities of the phenylcarboxamides with *p*-xylyl spacer (**9a**, **15a**) toward all of the investigated serotonin and dopamine receptors are very similar to the activities of the corresponding phenylsulfonamides (**9b**, **15b**). For example, the activities (K_i) of **9a** and **9b** toward 5-HT_{1A}R are 52 and 56 nM, respectively, while those of **15a** and **15b** are 1007 and 1097 nM, respectively. The same applies to the activity of carboxamide **9a** versus sulfonamide **9b**, and **15a** versus **15b** toward 5-HT_6R, 5-HT_7R, and D_2R (Table 1). In the remaining cases, (i.e., the 2-naphthyl and methylcarboxamides with *p*-xylyl spacer **10a**, **11a**, **16a**, and **17a**, and the corresponding sulfonamides **10b**, **11b**, **16b**, and **17b**), the relative activities toward particular receptors vary, so in general it is difficult to discern any universal rules. Different or similar activity of the ligands with *p*-xylyl spacer indicates that their activity is dependent both on the carboxamide/sulfonamide unit, as well as on the nature of arylpiperazine moiety and the type of substituent within the carboxamide/sulfonamide group. Different activity of carboxamides compared to sulfonamides toward receptors 5-HT_{1A} and 5-HT_7 was also found for other compounds with serotonic activity [14, 11], as well for compounds investigated as estrogen receptor ligands [8] or for dispiro-1,2,4-trioxolanes [9] with antimalarial activity.

In the series of benzyl derivatives of *o*-OMe-PhP and 2,3-DCPP, all of the carboxamides **12a–14a** and **18a–20a** bind with lower affinity to serotonin 5-HT_{1A}, 5-HT_6, 5-HT_7 receptors than their sulfonamide analogs **12b–14b** and **18b–20b** (Table 1). This indicates that the activity of compounds with benzyl spacer is strongly affected by the presence of carboxamide/sulfonamide core in the molecule. The structural correlation of the compounds containing benzyl spacer revealed that, for the same substituents within the carboxamide (**12a–14a**, **18a–20a**) and sulfonamide (**12b–14b**, **18b–20b**) series, the sulfonamides show significantly higher serotonin 5-HT_{1A}/5-HT_6/5-HT_7 activity. Moreover, the sulfonamides with benzyl spacer (**12b–14b**, **18b–20b**) exibit outstanding affinity toward 5-HT_7R. Their K_i values in the range 8–85 nM (Table 1) are affected to a lesser extent by the nature of the arylpiperazine moiety and the type of sulfonamide group, which is in contrast to the activity of arylpiperazinylpropylsulfonamides [28] and arenesulfonamides [29, 30] toward the same receptor.

K_i values of the compounds studied, related to serotonin 5-HT_{1A}, 5-HT_6, 5-HT_7, and dopamine D_2 receptors (Table 1), disclose that these compounds bind preferably to dopamine receptor, as the largest number (i.e., 16 out of 24) of the compounds tested showed the affinity below 100 nM, within both the carboxamide (9 compounds) and the sulfonamide (7 compounds) series. Moreover, several of those compounds have comparable D_2R activity, and only amide **20a** (K_i 9 nM) showed explicitly greater activity than its sulfonyl analog **20b** (K_i 71 nM). In the face of the above, the affinity of examined



Scheme 2. Preparation of *N*-[(4-arylpiperazin-1-ylmethyl)phenyl]carboxamides **12a–14a**, **18a–20a**, and *N*-[(4-arylpiperazin-1-ylmethyl)phenyl]sulfonamides **12b–14b**, **18b–20b**. Reagents and conditions: (a) 1-(2-Methoxyphenyl)piperazine hydrochloride or 1-(2,3-dichlorophenyl)piperazine hydrochloride, DMF, K_2CO_3, rt, 48 h, 80–88%; (b) Zn, $HCOONH_4$, THF/MeOH, rt, 30 min or $SnCl_2$, EtOH, HCl, reflux, 2 h, 60–68%; (c) acyl chlorides or sulfonyl chlorides, pyridine, rt, 24 h, 35–60%.

compounds toward D_2R is not dependent on the presence of carboxamide or sulfonamide group.

Molecular modeling

Intrigued by the same activity of both phenylcarboxamide **9a** and phenylsulfonamide **9b** toward each of the serotonin 5-HT_{1A}, 5-HT_6, 5-HT_7, and dopamine D_2 receptors (Table 1), we became interested in investigation of the effects of swapping carboxamide with sulfonamide in these molecules. In order to realize that goal, we performed molecular modeling studies of **9a** and **9b** docked to the models of 5-HT_{1A} and D_2 receptors, to which the compounds **9a** and **9b** displayed strongest bonding affinity (Table 1).

The molecular modeling study was performed by ONIOM procedure (details are shown in Experimental part).

The postulated binding sites of monoaminergic 5-HT_{1A} and D_2 receptors to LCAPs are divided into two pockets that extend to both sides of the main ligand-anchoring residue, which is Asp3.32 [29, 31, 32]. The first pocket is situated between TMHs 4 and 6, which consist of the conserved aromatic amino acid residues, capable for binding ligands via hydrophobic/aromatic interactions. The second pocket is formed between TMHs 7 and 3, with the contribution of residues that ensure both aromatic and H-bond interactions. The ONIOM calculations showed that the anchoring points of **9a** and **9b** to both receptors involved a salt-bridge with Asp3.32 and a weak H-bonding with Tyr7.41 in 5-HT_{1A}R, or with Tyr7.42 in D_2R. The aromatic moiety (A) of the arylpiperazine fragment of **9a** and **9b** interacts with the aromatic residues of TMH6 and with nonpolar residue of TMH3 (Val3.33) in both receptors, showing very similar poses. (Fig. 2, Tables 2 and 3).

The carboxamide/sulfonamide moieties of **9a** and **9b** are placed in the second pocket, and their arrangement in the ligand-receptor (L-R) complexes limits the diversity of amino acid sequence between the 5-HT_{1A} and D_2 receptors. The carboxamide moiety of **9a** occupies the pocket located between TMHs 7 and 2 for both the serotonin and the dopamine receptors (Fig. 2). Despite, the orientation of the amide moiety of **9a** in 5-HT_{1A}R, compared to that in D_2R, is determined by different interactions (Table 2; columns D and E), similarity of **9aI** and **9aII** conformations in L-R complexes is clearly higher (over 83%, see Fig. 3). In the case of **9b**, the sulfonamide moiety orientation in 5-HT_{1A}R is determined by strong two hydrogen bonds with Asp185 and Lys101, which are not present in D_2R (Table 3; columns C and E). Because of the latter, as well as the absence of participation of the sulfonamide unit in L-R complex stabilization, binding of **9b** to D_2R is associated with a conformational change of 60% compared to that in 5-HT_{1A}R (see **9bI** and **9bII** in Fig. 3).

Analysis of the complexes between 5-HT_{1A} receptor and the carboxamide **9a (9aI)** or sulfonamide **9b (9bI)** ligands indicates that their same binding effect (K_i for **9a** and **9b** to 5-HT_{1A}R are 52 and 56 nM, respectively, Table 1) allows formation of different attractive hydrogen bonds with three polar residues Tyr7.41, Asp185, and Asn7.39 in the case of carboxamide **9a**

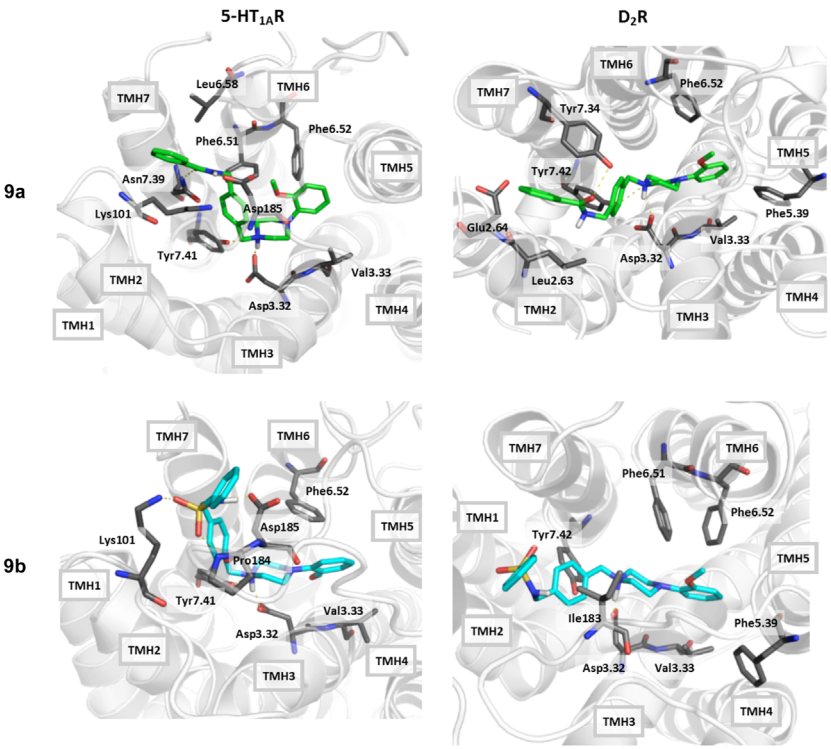
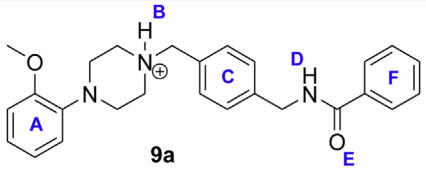


Figure 2. Binding mode of the compounds **9a** and **9b** to 5-HT_{1A}R and D_2R, respectively. Key residues in the binding site are presented as thick sticks. Distances between key amino acid moieties and ligand structural elements are shown in Tables 2 and 3. Dotted yellow lines represent H-bonds with polar residues.

Table 2. Distances (in Å)[a] between key amino acid residue and the structural elements of carboxamide 9a, measured in ONIOM-optimized ligand-receptor (L-R) complexes; 9aI-5-HT$_{1A}$R and 9aII-D$_2$R.



9a

Receptor	Structure 9a in L-R complexe	A	B	C	D	E	F
5-HT$_{1A}$	**9aI**	Phe6.52 (CH-p) 2.89 Val3.33 (CH-p) 3.43	Asp3.32 (H-bond) 1.41 Tyr7.41 (H-bond) 2.78	Phe6.51 (CH-p) 3.18	Asp185 (H-bond) 1.79	Asn7.39 (H-bond) 1.81	Leu6.58 (CH-p) 2.65
D$_2$	**9aII**	Phe5.39 (CH-p) 3.82 Phe6.52 (CH-p) 4.12 Val3.33 (CH-p) 3.09	Asp3.32 (H-bond) 1.64 Tyr7.42 (H-bond) 2.60	–	–	Tyr7.34 (H-bond) 1.66	Tyr7.34 (CH-p) 3.13 Leu2.63 (CH-p) 3.24 Glu2.64 (CH-p) 3.83

[a] H-bond distance measured between HBA (hydrogen bond acceptor) and the hydrogen. CH-π distances measured between hydrogen and the center of aromatic ring.

(**9aI**) (Table 2), and Tyr7.41, Asp185, and Lys101, respectively, for sulfonamide **9b** (**9bI**) (Table 3). The same binding interactions of **9a** and **9b** with D$_2$R (K_i of **9a** and **9b** to D$_2$R are 25 and 32 nM, respectively, Table 1) balances hydrogen bonds of both ligands with Tyr7.42 and Tyr7.34 of carboxamide **9a**. Moreover, it is important to note that the sulfonamide unit in **9b** does not affect the L-D$_2$R complex stabilization (Tables 2 and 3).

Conclusions

In conclusion, new *o*-OMe-PhP and 2,3-DCPP ligands have been prepared to explore the effect of replacement of carboxamide by a sulfonamide moiety in LCAP's on their binding affinity to serotonin 5-HT$_{1A}$/5-HT$_6$/5-HT$_7$ and dopamine D$_2$ receptors. In both *o*-OMe-PhP and 2,3-DCPP series the relative activities of the carboxamides versus sulfonamides toward 5-HT$_{1A}$/5-HT$_6$/5-HT$_7$ and D$_2$ receptors show similar trends. The carboxamides/sulfonamides with *p*-xylyl spacer show varied or similar activities toward particular receptors, while of the two classes of the amides examined, the sulfonamides with benzyl spacer exhibit the highest serotoninergic affinity, in particular toward the 5-HT$_7$ receptor. On the other hand, where receptor type is concerned, regardless of the carboxamide/sulfonamide zone, and the *p*-xylyl or benzyl spacer, the derivatives studied have the highest affinity toward the dopamine D$_2$ receptor.

The same K_i binding effect of carboxamide **9a** and sulfonamide **9b** to each of the 5-HT$_{1A}$R and D$_2$R receptors created interaction binding modes with different conserved receptors residues. Structural similarity of carboxamide **9a** in the complexes with 5-HT$_{1A}$R (**9aI**) and D$_2$R (**9aII**) is over 83%, while the corresponding similarity of sulfonamide structures (**9bI/9bII**) is only about 40%.

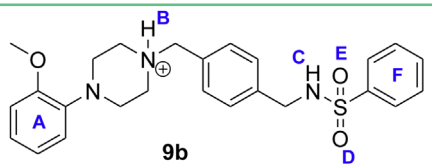
Experimental

Chemistry

General

Melting points were determined on a Böethius melting point apparatus and are uncorrected. Elemental analyses were performed on PerkinElmer 2400 analyzer and the results are within ±0.4% of the calculated values. Infrared spectra were recorded in pressed KBr discs on a Bio-Rad FTS 175B spectrometer. ^{1}H NMR spectra were taken on a Varian 300 MHz Mercury-VX spectrometer in $CDCl_3$, using TMS as an internal standard; the chemical shifts are given in ppm (δ). The mass spectra were recorded on an Esquire 3000 mass spectrometer (Bruker Daltonik, Bremen, Germany) equipped with an electrospray source. ESI-MS spectra were registered in a positive-ion mode. The reactions and

Table 3. Distances (in Å)[a] between key amino acid residue and the structural elements of sulfonamide 9b, measured in ONIOM-optimized ligand-receptor complexes; 9bI-5-HT$_{1A}$R and 9bII-D$_2$R.



9b

Receptor	Structure 9b in L-R complexe	A	B	C	D	E	F
5-HT$_{1A}$	**9bI**	Phe6.51 (CH-p) 2.98 Val3.33 (CH-p) 4.30	Asp3.32 (H-bond) 1.59 Tyr7.41 (H-bond) 2.85	Asp185 (H-bond) 1.09	Pro184 (polar contact) 3.00	Lys101 (H-bond) 1.70	–
D_2	**9bII**	Phe5.39 (CH-p) 3.16 Phe6.52 (CH-p) 4.63 Val3.33 (CH-p) 2.78	Asp3.32 (H-bond) 1.14 Tyr7.42 (H-bond) 3.08	–	–	–	Ile183 (CH-p) 3.37

[a] H-bond distance measured between HBA (hydrogen bond acceptor) and the hydrogen. CH-π distances measured between hydrogen and the center of aromatic ring.

purifications were monitored by TLC (UV detection) on aluminum plates coated with silica gel 60 F254 (Merck), using chloroform/methanol 9:1 mixture as eluent. All starting materials were purchased from commercial sources (Sigma–Aldrich and Merck) and were used without further purification.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*General procedure for the synthesis of **22** and **23***

A mixture of 0.01 mol of the *N*-[4-(chlorometyl)benzyl]-phthalimide (**21**), 0.01 mol of the 1-(2-methoxyphenyl)-piperazine (*o*-OMe-PhP), or 1-(2,3-dichlorophenyl)arylpiperazine (2,3-DCPP) in the hydrochloride forms, 0.03 mol of anhydrous potassium carbonate, and a few crystals (∼0.01 g) of potassium iodide in 20 mL of dimethylformamide, were stirred with a magnetic stirrer at a room

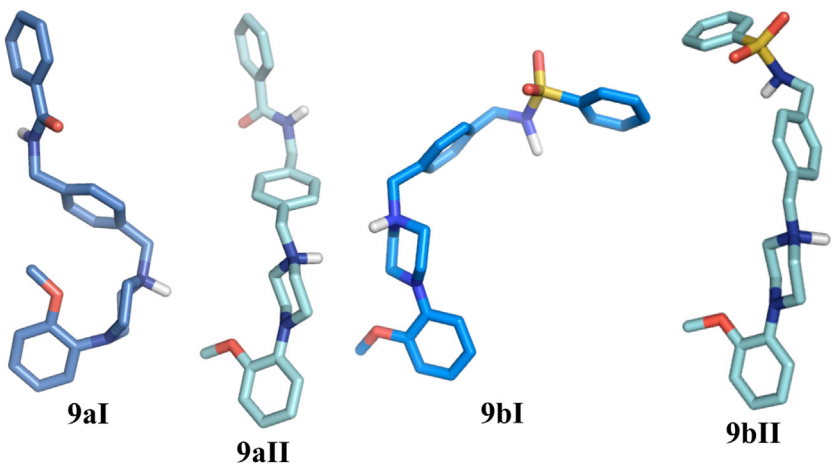


Figure 3. ONIOM optimized structures of the carboxamide derivative **9a** bound to 5-HT$_{1A}$R (**9aI**) and D$_2$R (**9aII**) and the sulfonamide derivative **9b** bound to 5-HT$_{1A}$R (**9bI**) and D$_2$R (**9bII**) receptors. For clarity, nonpolar hydrogens have been removed. The calculated overlay similarity **9aI/9aII** is 0.837, and **9bI/9bII** is 0.395.

temperature for 48 h. Then, the reaction mixture was poured into 100–150 mL of water, and the precipitate was collected by filtration. The solid products were purified by crystallization.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-phthalimide (**22**)*
m.p.: 124–126°C (DMF/methanol); (Ref. [22]; m.p.: 124–126°C); yield 62%. ^{1}H NMR, IR and MS-ESI+ spectra are consistent with the original sample [22].

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}phthalimide (**23**)*
m.p.: 164–166°C (DMF/methanol); yield 70%; ^{1}H NMR (δ): 2.55–2.65 (4H, m, 2xCH_2), 2.99–3.09 (4H, m, 2xCH_2), 3.53 (2H, s, CH_2-N_{piper}), 4.84 (2H, s, CH_2-N_{imide}), 7.10–7.46 (7H, m, H-Ar), 7.55–7.67 (2H, m, H-Ar), 7.75–7.81 (2H, m, H-Ar); IR (cm^{-1}): 2936, 2816, 1767, 1714, 1450, 1392, 1245, 808, 743; ESI-MS+: *m/z* 480 $(MH)^+$.

*General procedure for the synthesis of amines **24** and **25** by removal of the phthalimide group*
A mixture of 6 mmol of **22** or **23** and 30 mL of 40% aqueous solution of methylamine was stirred at room temperature for 2 days. To the resulting solution 30 mL of 20% aqueous sodium hydroxide was added and the mixture was stirred for 1.5 h. Then 4 g of sodium chloride was added and the solution was extracted with methylene chloride (2 × 30 mL). Organic layer was washed with water (30 mL), and then dried over anhydrous magnesium sulfate. The product was obtained by evaporation of methylene chloride. Where necessary, the product was purified on silica gel column, using chloroform/methanol 9:1 as eluent.

*4-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}-benzylamine (**24**)*
Oil; yield 90%; ^{1}H NMR spectrum is consistent with the original sample [21]; IR (cm^{-1}): 3358, 3276, 2935, 2817, 1499, 1237, 1115, 1021, 755; ESI-MS+: *m/z* 312 $(MH)^+$.

*4-{[4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl}-benzylamine (**25**)*
m.p.: 88–91°C (ethanol/*n*-hexane); yield 93%; ^{1}H NMR (δ): 1.80 (2H, s, NH_2), 2.57–2.68 (4H, m, 2xCH_2), 2.99–3.12 (4H, m, 2xCH_2), 3.57 (2H, s, CH_2-N_{piper}), 3.86 (2H, s, $\underline{CH_2}$-NH_2), 7.10–7.46 (7H, m, H-Ar); IR (cm^{-1}): 3353, 3288, 2957, 2816, 1446, 1236, 798, 772; ESI-MS+: *m/z* 350 $(MH)^+$.

*General procedure for the preparation of carboxamides **9a–11a, 15a–17a**, and sulfonamides **9b–11b, 15b–17b***
A mixture of the amine **24** or **25** (1 mmol), 1 mL of triethylamine, and 10 mL of methylene chloride was stirred for 5 min. Then the corresponding acyl chloride or sulfonyl chloride (1.1 mmol) in 2 mL of methylene chloride was added at 10°C. The reaction mixture was left at room temperature for 24 h. The solvent and excess of triethylamine were evaporated. The residue was dissolved in 10 mL of methylene chloride and washed subsequently with 5% solution of sodium hydrogen carbonate (2 × 10 mL) and water (10 mL). Organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. Crude amides were purified by crystallization, and some of them by silica gel column chromatography, using chloroform/methanol 9:1 as eluent. For biological experiments, free bases of carboxamides **9a–11a**, **15a–17a**, and sulfonamides **9b–11b**, **15b–17b** were converted into hydrochloride salts, using ethanol saturated with HCl, and their molecular weights were established on the basis of elemental analysis.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-benzamide (**9a**)*
Base: m.p.: 125–126°C (acetone); yield 59%; ^{1}H NMR (δ): 2.59–2.70 (4H, m, 2xCH_2), 3.03–3.15 (4H, m, 2xCH_2), 3.58 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 4.63 (2H, d, J = 5.60 Hz, $\underline{CH_2}$NH), 6.48 (1H, br s, NHCO), 6.90–6.95 (4H, m, H-Ar), 7.26–7.52 (7H, m, H-Ar), 7.74–7.86 (2H, m, H-Ar); IR (cm^{-1}): 3279, 3050, 2941, 2805, 1624, 1549, 1499, 1239, 1181, 1029, 701; ESI-MS+: *m/z* 416 $(MH)^+$.
Hydrochloride: m.p.: 221–223°C; Anal. calcd. for $C_{26}H_{29}N_3O_2 \cdot HCl$ (451.99): C, 69.09; H, 6.69; N, 9.30. Found: C, 69.17; H, 6.79; N, 9.22.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-2-naphthalenecarboxamide (**10a**)*
Base: m.p.: 193–195°C ($CHCl_3$/*n*-hexane); yield 75%; ^{1}H NMR (δ): 2.63–2.70 (4H, m, 2xCH_2), 3.04–3.13 (4H, m, 2xCH_2), 3.59 (2H, s, CH_2-N_{piper}), 3.85 (3H, s, OCH_3), 4.70 (2H, d, J = 5.61 Hz, $\underline{CH_2}$NH), 6.58 (1H, br s, NHCO), 6.83–6.95 (3H, m, H-Ar), 7.34–7.37 (4H, m, H-Ar), 7.53–7.57 (3H, m, H-Ar), 7.85–7.90 (4H, m, H-Ar), 8.31–8.32 (1H, m, H-Ar); IR (cm^{-1}): 3279, 3055, 2940, 2803, 1622, 1498, 1238, 1142, 1024, 751; ESI-MS+: *m/z* 466 $(MH)^+$.
Hydrochloride: m.p.: 225–229°C; Anal. calcd. for $C_{30}H_{31}N_3O_2 \cdot 2HCl \cdot H_2O$ (556.52): C, 64.75; H, 6.34; N, 7.55. Found: C, 64.86; H, 6.19; N, 7.32.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-acetamide (**11a**)*
Base: oil; yield 47%; ^{1}H NMR (δ): 2.02 (3H, s, $COCH_3$), 2.57–2.64 (4H, m, 2xCH_2), 3.00–3.11 (4H, m, 2xCH_2), 3.59 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 4.41 (2H, d, J = 5.60 Hz, $\underline{CH_2}$NH), 6.83–7.02 (4H, m, H-Ar), 7.23–7.26 (2H, m, H-Ar), 7.32–7.34 (2H, m, H-Ar), invisible NHCO; IR (cm^{-1}): 3288, 3060, 2933, 2818, 1652, 1500, 1241, 1141, 1027, 732; ESI-MS+: *m/z* 354 $(MH)^+$.
Hydrochloride: m.p.: 218–221°C; Anal. calcd. for $C_{21}H_{27}N_3O_2 \cdot HCl$ (389.92): C, 64.69; H, 7.24; N, 10.78. Found: C, 64.70; H, 7.01; N, 10.59.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-benzenesulfonamide (**9b**)*
Base: m.p.: 61–63°C (methanol); yield 52%; ^{1}H NMR (δ): 2.55–2.67 (4H, m, 2xCH_2), 3.02–3.14 (4H, m, 2xCH_2), 3.54 (2H, s, CH_2-N_{piper}), 3.85 (3H, s, OCH_3), 4.15 (2H, d, J = 5.85 Hz, $\underline{CH_2}$NH),

4.71 (1H, t, $J = 5.95$ Hz, $NHSO_2$), 6.90–7.08 (4H, m, H-Ar), 7.18–7.33 (4H, m, H-Ar), 7.48–7.60 (3H, m, H-Ar), 7.83–7.93 (2H, m, H-Ar); IR (cm^{-1}): 3284, 3058, 2936, 2818, 1499, 1325, 1236, 1140, 1022, 748; ESI-MS+: *m/z* 452 $(MH)^+$.

Hydrochloride: m.p.: 246–248°C; Anal. calcd. for $C_{25}H_{29}N_3O_3S \cdot 2HCl \cdot H_2O$ (542.52): C, 55.35; H, 6.13; N, 7.75. Found: C, 55.59; H, 6.00; N, 7.82.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-2-naphthalenesulfonamide (**10b**)*

Base: m.p.: 120–122°C (methanol); yield 80%; ^1H NMR (δ): 2.50–2.62 (4H, m, $2xCH_2$), 3.00–3.11 (4H, m, $2xCH_2$), 3.46 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 4.16 (2H, d, $J = 6.16$ Hz, $\underline{CH_2}NH$), 4.79 (1H, t, $J = 6.10$ Hz, $NHSO_2$), 6.80–6.98 (4H, m, H-Ar), 7.18–7.31 (4H, m, H-Ar), 7.57–7.74 (2H, m, H-Ar), 7.85–8.03 (4H, m, H-Ar), 8.44 (1H, s, H-Ar); IR (cm^{-1}): 3289, 3053, 2854, 1497, 1333, 1235, 1156, 1062, 740; ESI-MS+: *m/z* 502 $(MH)^+$.

Hydrochloride: m.p.: 182–185°C; Anal. calcd. for $C_{29}H_{31}N_3O_3S \cdot 2HCl$ (574.56): C, 60.62; H, 5.79; N, 7.31. Found: C, 60.80; H, 5.59; N, 7.54.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)benzyl}-methanesulfonamide (**11b**)*

Base oil; yield 45%; ^1H NMR (δ): 2.61–2.68 (4H, m, $2xCH_2$)), 2.88 (3H, s, SO_2CH_3), 2.95–3.12 (4H, m, $2xCH_2$), 3.58 (2H, s, CH_2-N_{piper}), 3.85 (3H, s, OCH_3), 4.31 (2H, d, $J = 5.68$ Hz, $\underline{CH_2}NH$), 6.83–7.01 (4H, m, Ar-H) 7.28–7.34 (4H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3288, 2934, 2820, 1500, 1451, 1320, 1241, 1146, 1010, 913, 750; ESI-MS+: *m/z* 390 $(MH)^+$.

Hydrochloride: m.p.: 214–216°C; Anal. calcd. for $C_{20}H_{27}N_3O_3S \cdot 2HCl$ (462.43): C, 51.95; H, 6.32; N, 9.09. Found: C, 52.12; H, 6.39; N, 9.21.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}benzamide (**15a**)*

Base: m.p.: 162–164°C (methanol/H_2O); yield 63%; ^1H NMR (δ): 2.57–2.68 (4H, m, $2xCH_2$), 3.00–3.12 (4H, m, $2xCH_2$), 3.57 (2H, s, CH_2-N_{piper}), 4.63 (2H, d, $J = 5.66$ Hz, $\underline{CH_2}NH$), 6.49 (1H, br s, NHCO), 6.92–7.17 (2H, m, H-Ar), 7.26–7.38 (5H, m, H-Ar), 7.38–7.48 (3H, m, H-Ar), 7.74–7.86 (2H, m, H-Ar); IR (cm^{-1}): 3291, 3057, 2942, 2817, 1633, 1451, 1245, 970, 696; ESI-MS+: *m/z* 454 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{25}H_{25}Cl_2N_3O \cdot 2HCl \cdot H_2O$ (545.33): C, 55.06; H, 5.36; N, 7.71. Found: C, 55.09; H, 5.39; N, 7.89.

*N-{4-([4-(2,3-dichlorophenyl)piperazin-1-yl]methyl)-benzyl}2-naphthalenecarboxamide (**16a**)*

Base: m.p.: 172–173°C ($CHCl_3$/*n*-hexane); yield 79%; ^1H NMR (δ): 2.61–2.67 (4H, m, $2xCH_2$), 3.03–3.08 (4H, m, $2xCH_2$), 3.58 (2H, s, CH_2-N_{piper}), 4.70 (2H, d, $J = 5.67$ Hz, $\underline{CH_2}NH$), 6.54 (1H, br s, NHCO), 6.92–7.14 (3H, m, H-Ar), 7.34–7.38 (4H, m, H-Ar), 7.50–7.58 (2H, m, H-Ar), 7.82–7.95 (4H, m, H-Ar), 8.30–8.32 (1H, m, H-Ar); IR (cm^{-1}): 3260, 3057, 2942, 2817, 1615, 1448, 1300, 772; ESI-MS+: *m/z* 504 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{29}H_{27}Cl_2N_3O \cdot 2HCl$ (577.37): C, 60.33; H, 5.06; N, 7.28. Found: C, 60.60; H, 5.31; N, 7.01.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}acetamide (**17a**)*

Base: oil; yield 49%; ^1H NMR (δ): 2.02 (3H, s, $COCH_3$), 2.60–2.67 (4H, m, $2xCH_2$), 3.03–3.09 (4H, m, $2xCH_2$), 3.58 (2H, s, CH_2-N_{piper}), 4.41 (2H, d, $J = 5.62$ Hz, $\underline{CH_2}NH$), 6.90–6.97 (1H, m, H-Ar), 7.11–7.15 (2H, m, H-Ar), 7.22–7.35 (4H, m, H-Ar), invisible NHCO; IR (cm^{-1}): 3288, 3064, 2932, 2820, 1652, 1577, 1448, 1370, 1246, 957, 733; ESI-MS+: *m/z* 392 $(MH)^+$.

Hydrochloride: m.p.: >250°C (>225°C sublim.); Anal. calcd. for $C_{20}H_{23}Cl_2N_3O \cdot HCl$ (428.78): C, 56.02; H, 5.64; N, 9.80. Found: C, 56.18; H, 5.56; N, 9.70.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}benzenesulfonamide (**15b**)*

Base: oil; yield 80%; ^1H NMR (δ): 2.50–2.68 (4H, m, $2xCH_2$), 2.96–3.08 (4H, m, $2xCH_2$), 3.46 (2H, s, CH_2-N_{piper}), 4.07 (2H, s, $\underline{CH_2}NH$), 5.29 (1H, s, $NHSO_2$), 6.85–7.28 (5H, m, H-Ar), 7.50–7.74 (3H, m, H-Ar), 7.88–8.72 (4H, m, H-Ar); IR (cm^{-1}): 3272, 3059, 2938, 2819, 1576, 1447, 1324, 1156, 977, 733; ESI-MS+: *m/z* 490 $(MH)^+$.

Hydrochloride: m.p.: 215–218°C (at >150°C a change of crystalline form); Anal. calcd. for $C_{24}H_{25}Cl_2N_3O_2S \cdot 2HCl \cdot H_2O$ (581.38): C, 49.58; H, 5.03; N, 7.23. Found: C, 49.88; H, 5.31; N, 7.20.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}2-naphthalenesulfonamide (**16b**)*

Base: oil; yield 51%; ^1H NMR (δ): 2.48–2.66 (4H, m, $2xCH_2$), 2.95–3.06 (4H, m, $2xCH_2$), 3.46 (2H, s, CH_2-N_{piper}), 4.16 (2H, s, $\underline{CH_2}NH$), 5.28 (1H, s, $NHSO_2$), 6.91–7.27 (7H, m, H-Ar), 7.55–7.66 (2H, m, H-Ar), 7.83–8.00 (4H, m, H-Ar), 8.41 (1H, s, H-Ar); IR (cm^{-1}): 3272, 3055, 2963, 2818, 1576, 1447, 1346, 1199, 1154, 961, 735; ESI-MS+: *m/z* 540 $(MH)^+$.

Hydrochloride: m.p.: >250°C (at >190°C a change of crystalline form); Anal. calcd. for $C_{28}H_{27}Cl_2N_3O_2S \cdot 2HCl \cdot H_2O$ (631.44): C, 53.26; H, 4.95; N, 6.65. Found: C, 53.56; H, 5.11; N, 6.51.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-benzyl}methanesulfonamide (**17b**)*

Base: oil; yield 51%; ^1H NMR (δ): 2.60–2.66 (4H, m, $2xCH_2$), 2.89 (3H, s, SO_2CH_3), 3.05–3.09 (4H, m, $2xCH_2$), 3.60 (2H, s, CH_2-N_{piper}), 4.32 (2H, d, $J = 5.71$ Hz, $\underline{CH_2}NH$), 6.93–6.96 (1H, m, Ar-H), 7.13–7.16 (2H, m, Ar-H), 7.29–7.39 (4H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3285, 2930, 2822, 1578, 1449, 1320, 1150, 958, 735; ESI-MS+: *m/z* 428 $(MH)^+$.

Hydrochloride: m.p.: >250°C; Anal. calcd. for $C_{19}H_{23}Cl_2N_3O_2S \cdot 2HCl \cdot H_2O$ (519.31): C, 43.94; H, 5.24; N, 8.09. Found: C, 43.71; H, 5.01; N, 8.05.

*General procedure for the synthesis of **27** and **28***
A mixture of 0.01 mol of the 4-nitrobenzyl chloride (**26**), 0.01 mol of the 1-(2-methoxyphenyl)piperazine (*o*-OMe-PhP) or 1-(2,3-dichlorophenyl)arylpiperazine (2,3-DCPP) in the hydrochloride forms, 0.03 mol of anhydrous potassium carbonate, and a few crystals (~0.01 g) of potassium iodide in 20 mL of dimethylformamide, were stirred with a magnetic stirrer at a room temperature for 48 h. Then, the reaction mixture was poured into 100–150 mL of water, and the precipitate was collected by filtration. The solid products **27** and **28** were purified by crystallization.

*1-(4-Nitrobenzyl)-4-(2-methoxyphenyl)piperazine (**27**)*
m.p.: 110–111°C (DMF/methanol); yield 88%; ^{1}H NMR (δ): 2.60–2.73 (4H, m, 2xCH_2), 3.04–3.17 (4H, m, 2xCH_2), 3.67 (2H, s, CH_2-N_{piper}), 3.86 (3H, s, OCH_3), 6.91–7.00 (4H, m, H-Ar), 7.54 (2H, d, $J = 8.80$ Hz, H-Ar), 8.20 (2H, d, $J = 8.82$ Hz, H-Ar); IR (cm^{-1}): 3071, 2808, 1517, 1453, 1346, 1230, 1014, 740; ESI-MS+: *m/z* 328 $(MH)^+$.

*1-(4-Nitrobenzyl)-4-(2,3-dichlorophenyl)piperazine (**28**)*
m.p.: 135–136°C (petroleum ether); yield 80%; ^{1}H NMR (δ): 2.55–2.72 (4H, m, 2xCH_2), 2.97–3.14 (4H, m, 2xCH_2), 3.67 (2H, s, CH_2-N_{piper}), 6.89–7.00 (1H, m, Ar-H), 7.09–7.22 (2H, m, Ar-H), 7.51–7.61 (2H, m, Ar-H), 8.15–8.24 (2H, m, Ar-H); IR (cm^{-1}): 3070, 2823, 1517, 1448, 1341, 1231, 954, 781; ESI-MS+: *m/z* 366 $(MH)^+$.

*Procedure for the preparation of 4-{[4-(2-methoxyphenyl)-piperazin-1-yl]methyl}aniline (**29**)*
1-(4-Nitrobenzyl)-4-(2-methoxyphenyl)piperazine (**27**) (1.64 g, 5 mmol) was dissolved in a mixture of THF (10 mL) and methanol (10 mL), containing 1.63 g (25 mmol) of zinc powder (activated by stirring with 15 mL 5% ag. HCl for 5 min, then washed well with water and finally with 20 mL of methanol). To the stirred mixture, at ambient temperature 1.58 g (25 mmol) of ammonium formate was added in one portion. After 3 min the mixture became warm, and after the following 30 min the reaction was over, as indicated by TLC. The mixture was filtered and the solvents were evaporated. The residue was extracted with 20 mL of ethyl acetate. The extract was washed twice with 15 mL of saturated sodium chloride solution and then with 10 mL of water. The organic layer was dried over sodium sulfate and then concentrated to obtain the crude amine **29**, which was purified by silica gel column chromatography, using chloroform/methanol 9:1 as eluent.

*4-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}aniline (**29**)*
Oil; yield 60%; ^{1}H NMR (δ): 2.58–2.70 (4H, m, 2xCH_2), 3.04–3.16 (4H, m, 2xCH_2), 3.48 (2H, s, CH_2-N_{piper}), 3.56 (2H, br s, NH_2), 3.85 (3H, s, OCH_3), 6.65 (2H, d, $J = 8.32$ Hz, H-Ar), 6.89–6.99 (4H, m, H-Ar), 7.14 (2H, d, $J = 8.24$ Hz, H-Ar); IR (cm^{-1}): 3444, 3350, 3049, 2815, 1451, 1238, 1128, 1030, 758; ESI-MS+: *m/z* 298 $(MH)^+$.

*Procedure for the preparation of 4-{[4-(2,3-dichlorophenyl)piperazin-1-yl]methyl}aniline (**30**)*
The mixture of 2.7 g (12 mmol) of tin(II) chloride dihydrate, 8 mL of ethanol, and 1.6 mL of concentrated HCl was stirred at 70°C until it became clear (about 2 h). To this hot solution 1.1 g (3 mmol) of 1-(4-nitrobenzyl)-4-(2,3-dichlorophenyl)piperazine (**28**) was added portionwise for 30 min. Next, the mixture was gently refluxed until the reaction was complete, as indicated by TLC analysis (about 1 h). After addition of water (20 mL), the resulting solution was alkalized with KOH and allowed to cool to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic extracts were washed with brine (2 × 25 mL) and water (3 × 50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude amine **30** was purified on a silica gel column, using chloroform/methanol 9:1 as eluent.

*4-{[4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl}aniline (**30**)*
Oil; yield 68%; ^{1}H NMR (δ): 2.60–2.67 (4H, m, 2x$CH_{2)}$), 3.00–3.10 (4H, m, 2xCH_2), 3.48 (2H, s, CH_2-N_{piper}), 3.58–3.71 (2H, br. s, NH_2), 6.59–6.70 (2H, m, Ar-H), 6.84–6.99 (1H, m, Ar-H), 7.06–7.22 (4H, m, Ar-H); IR (cm^{-1}): 3447, 3358, 3001, 2814, 1619, 1447, 1245, 1133, 955, 777; ESI-MS+: *m/z* 336 $(MH)^+$.

*General procedure for the preparation of carboxamides **12a–14a, 18a–20a,** and sulfonamides **12b–14b, 18b–20b***
A mixture of the amine **29** or **30** (1 mmol) and 10 mL of pyridine was stirred for 5 min. Then, the corresponding acyl chloride or sulfonyl chloride (1.1 mmol) in 2 mL of pyridine was added at 10°C. The reaction mixture was left at room temperature for 24 h. Next, the pyridine was evaporated, and the resulting solid was dissolved in 10 mL of methylene chloride and washed subsequently with 5% solution of sodium hydrogen carbonate (2 × 10 mL) and water (10 mL). Organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. Crude amides were purified by crystallization, or by chromatography on a silica gel column, using chloroform/methanol 9:1 as eluent. For biological experiments, free bases of amides **12a–14a**, **18a–20a**, and sulfonamides **12b–14b**, **18b–20b** were converted into hydrochlorides, using ethanol saturated with HCl, and their molecular weights were established on the basis of an elemental analysis.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-benzamide (**12a**)*
Base: m.p.: 146–148°C (propan-2-ol); yield 51%; ^{1}H NMR (δ): 2.66 (4H, br s, 2xCH_2), 3.08 (4H, br s, 2xCH_2), 3.57 (2H, s, CH_2-N_{piper}), 3.86 (3H, s, OCH_3), 6.83–7.02 (4H, m, H-Ar), 7.34–7.40 (2H, m, H-Ar), 7.46–7.63 (5H, m, H-Ar), 7.29 (1H, br s, NHCO), 7.85–7.90 (2H, m, H-Ar); IR (cm^{-1}): 3344, 3056, 2939, 2813, 1654, 1525, 1501, 1243, 746; ESI-MS+: *m/z* 402 $(MH)^+$.

Hydrochloride: m.p.: 215–218°C (decomp.); Anal. calcd. for $C_{25}H_{27}N_3O_2 \cdot 2HCl$ (474.42): C, 63.29; H, 6.16; N, 8.86. Found: C, 63.51; H, 6.01; N, 8.75.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-2-naphthalenecarboxamide (**13a**)*
Base: m.p.: 153–155°C (propan-2-ol); yield 55%; ^{1}H NMR (δ): 2.63–2.71 (4H, m, 2xCH_2), 3.10 (4H, br s, 2xCH_2), 3.58 (2H, s, CH_2-N_{piper}), 3.86 (3H, s, OCH_3), 6.84–7.02 (4H, m, Ar-H), 7.35–7.42 (2H, m, Ar-H), 7.55–7.68 (4H, m, Ar-H), 7.87–7.96 (4H, m, Ar-H), 7.99 (1H, br s, NHCO), 8.36–8.39 (1H, m, Ar-H); IR (cm^{-1}): 3325, 3055, 2952, 2804, 1653, 1501, 1452, 1315, 1243, 746; ESI-MS+: *m/z* 452 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{29}H_{29}N_3O_2 \cdot 2HCl$ (524.48): C, 66.41; H, 5.96; N, 8.01. Found: C, 66.67; H, 6.11; N, 8.25.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-acetamide (**14a**)*
Base: oil; yield 35%; ^{1}H NMR (δ): 2.17 (3H, s, $COCH_3$), 2.59–2.68 (4H, m, 2xCH_2), 3.02–3.12 (4H, m, 2xCH_2), 3.53 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 6.82–7.03 (4H, m, Ar-H), 7.27–7.34 (3H, m, Ar-H + NHCO), 7.41–7.50 (m, 2H, Ar-H); IR (cm^{-1}): 3307, 3058, 2940, 2810, 1659, 1499, 1367, 1312, 1240, 747; ESI-MS+: *m/z* 340 $(MH)^+$.

Hydrochloride: m.p.: 244–248°C (decomp., at >190°C a change of crystalline form); Anal. calcd. for $C_{20}H_{25}N_3O_2 \cdot 2HCl \cdot H_2O$ (430.37): C, 55.82; H, 6.79; N, 9.76. Found: C, 55.88; H, 6.59; N, 9.65.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-benzenesulfonamide (**12b**)*
Base: m.p.: 68–71°C (methanol/H_2O); yield 37%; ^{1}H NMR (δ): 2.52–2.64 (4H, m, 2xCH_2), 3.00–3.12 (4H, m, 2xCH_2), 3.48 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 6.88–6.98 (4H, m, H-Ar), 7.06–7.28 (4H, m, H-Ar), 7.39–7.56 (3H, m, H-Ar), 7.71–7.84 (2H, m, H-Ar), invisible $NHSO_2$; IR (cm^{-1}): 3276, 3056, 2809, 1499, 1452, 1333, 1237, 1153, 1127, 752; ESI-MS+: *m/z* 438 $(MH)^+$.

Hydrochloride: m.p.: 158–160°C; Anal. calcd. for $C_{24}H_{27}N_3O_3S \cdot 2HCl \cdot 0.5H_2O$ (519.48): C, 55.49; H, 5.82; N, 8.09. Found: C, 55.27; H, 5.98; N, 8.00.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-2-naphthalenesulfonamide (**13b**)*
Base: m.p.: 153–155°C (methanol/H_2O); yield 60%; ^{1}H NMR (δ): 2.50–2.62 (4H, m, 2xCH_2), 2.98–3.10 (4H, m, 2xCH_2), 3.47 (2H, s, CH_2-N_{piper}), 3.84 (3H, s, OCH_3), 6.88–6.97 (4H, m, H-Ar), 7.08–7.26 (4H, m, H-Ar), 7.50 (1H, br s, $NHSO_2$), 7.58–7.98 (6H, m, H-Ar), 8.34–8.37 (1H, m, H-Ar); IR (cm^{-1}): 3274, 3058, 2804, 1499, 1447, 1328, 1235, 1153, 1130, 753; ESI-MS+: *m/z* 488 $(MH)^+$.

Hydrochloride: m.p.: 208–210°C; Anal. calcd. for $C_{28}H_{29}N_3O_3S \cdot 2HCl$ (560.54): C, 60.00; H, 5.57; N, 7.50. Found: C, 60.09; H, 5.35; N, 7.67.

*N-{4-([4-(2-Methoxyphenyl)piperazin-1-yl]methyl)phenyl}-methanesulfonamide (**14b**)*
Base: oil; yield 45%; ^{1}H NMR (δ): 2.60–2.67 (4H, m, 2xCH_2), 3.02 (3H, s, SO_2CH_3), 2.97–3.14 (4H, m, 2xCH_2), 3.56 (2H, s, CH_2-N_{piper}), 3.85 (3H, s, OCH_3), 6.80–7.02 (4H, m, Ar-H), 7.16–7.23 (2H, m, Ar-H), 7.30–7.38 (2H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3252, 2936, 2818, 1499, 1452, 1323, 1239, 1148, 1024, 748; ESI-MS+: *m/z* 376 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{19}H_{25}N_3O_3S \cdot 2HCl$ (448.41): C, 50.89; H, 6.07; N, 9.37. Found: C, 50.69; H, 5.95; N, 9.61.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}benzamide (**18a**)*
Base: m.p.: 176–178°C (ethanol); yield 59%; ^{1}H NMR (δ): 2.61–2.68 (4H, m, 2xCH_2), 3.03–3.10 (4H, m, 2xCH_2), 3.57 (2H, s, CH_2-N_{piper}), 6.91–6.99 (1H, m, Ar-H), 7.10–7.17 (2H, m, Ar-H), 7.33–7.39 (2H, m, Ar-H), 7.46–7.63 (5H, m, Ar-H), 7.82 (1H, br s, NHCO), 7.85–7.90 (2H, m, Ar-H); IR (cm^{-1}): 3310, 2946, 2808, 1647, 1595, 1510, 1488, 1448, 1312, 1246, 957, 775; ESI-MS+: *m/z* 440 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{24}H_{23}Cl_2N_3O \cdot 2HCl$ (513.29): C, 56.16; H, 4.91; N, 8.19. Found: C, 56.36; H, 4.92; N, 8.21.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}2-naphthalenecarboxamide (**19a**)*
Base: m.p.: 173–174°C (methanol); yield 56%; ^{1}H NMR (δ): 2.62–2.70 (4H, m, 2xCH_2), 3.04–3.11 (4H, m, 2xCH_2), 3.60 (2H, s, CH_2-N_{piper}), 6.93–7.16 (3H, m, Ar-H), 7.36–7.41 (2H, m, Ar-H), 7.54–7.70 (4H, m, Ar-H), 7.89 (1H, br s, NHCO), 7.90–8.00 (4H, m, Ar-H), 8.37–8.40 (1H, m, Ar-H); IR (cm^{-1}): 3361, 3054, 2965, 1655, 1578, 1451, 963, 761; MS+: *m/z* 490 $(MH)^+$.

Hydrochloride: m.p.:>250°C (decomp.); Anal. calcd. for $C_{28}H_{25}Cl_2N_3O \cdot 2HCl$ (563.35): C, 59.70; H, 4.83; N, 7.46. Found: C, 59.92; H, 4.94; N, 7.33.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}acetamide (**20a**)*
Base: m.p.: 202–204°C (methanol); yield 58%; ^{1}H NMR (δ): 2.17 (3H, s, $COCH_3$), 2.58–2.65 (4H, m, 2xCH_2), 3.02–3.08 (4H, m, 2xCH_2), 3.54 (2H, s, CH_2-N_{piper}), 6.91–6.98 (1H, m, Ar-H), 7.09–7.17 (3H, m, Ar-H + NHCO), 7.27–7.33 (2H, m, Ar-H), 7.42–7.48 (2H, m, Ar-H); IR (cm^{-1}): 3292, 3125, 2812, 1662, 1600, 1510, 1447, 1367, 1314, 1247, 954, 805; MS+: *m/z* 378 $(MH)^+$.

Hydrochloride: m.p.: >250°C (>230°C sublim.); Anal. calcd. for $C_{19}H_{21}Cl_2N_3O \cdot 2HCl$ (451.22): C, 50.58; H, 5.14; N, 9.31. Found: C, 50.59; H, 4.92; N, 9.13.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}benzenesulfonamide (**18b**)*
Base: m.p.: 150–152°C (methanol); yield 49%; ^{1}H NMR (δ): 2.60–2.67 (4H, m, 2xCH_2), 3.04–3.10 (4H, m, 2xCH_2), 3.53 (2H, s, CH_2-N_{piper}), 6.90–6.95 (1H, m, Ar-H), 7.00–7.07 (2H, m, Ar-H), 7.09–7.18 (2H, m, Ar-H), 7.20–7.30 (2H, m, Ar-H), 7.40–7.48 (2H, m, Ar-H), 7.50–7.57 (1H, m, Ar-H), 7.75–7.80 (2H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3384, 3049, 2834, 1581, 1455, 1336, 1156, 1090, 924, 688; MS+: *m/z* 476 $(MH)^+$.

Hydrochloride: m.p.: 161–163°C; Anal. calcd. for $C_{23}H_{23}Cl_2N_3O_2S \cdot 2HCl \cdot 0.5H_2O$ (558.35): C, 49.48; H, 4.69; N, 7.53. Found: C, 49.65; H, 4.49; N, 7.62.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}-2-naphthalenesulfonamide (**19b**)*
Base: m.p.: 194–196°C (methanol/H_2O); yield 60%; ^{1}H NMR (δ): 2.50–2.56 (4H, m, 2xCH_2), 2.97–3.04 (4H, m, 2xCH_2), 3.47 (2H, s, CH_2-N_{piper}), 6.89–6.96 (1H, m, Ar-H), 7.01–7.07 (2H, m, Ar-H), 7.09–7.23 (4H, m, Ar-H), 7.56–7.65 (2H, m, Ar-H), 7.71–7.77 (1H, m, Ar-H), 7.84–7.92 (3H, m, Ar-H), 8.32–8.35 (1H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3224, 3055, 2811, 1507, 1439, 1334, 1156, 1133, 953, 692; MS+: *m/z* 526 $(MH)^+$.

Hydrochloride: m.p.: 225–228°C (decomp.); Anal. calcd. for $C_{27}H_{25}Cl_2N_3O_2S \cdot 2HCl$ (599.40): C, 54.10, 4.54; N, 7.01. Found: C, 54.22; H, 4.41; N, 7.33.

*N-{4-([4-(2,3-Dichlorophenyl)piperazin-1-yl]methyl)-phenyl}methanesulfonamide (**20b**)*
Base: m.p.: 180–182°C (methanol); yield 50%; ^{1}H NMR (δ): 2.59–2.67 (4H, m, 2xCH_2), 3.02 (3H, s, SO_2CH_3), 3.01–3.10 (4H, m, 2xCH_2), 3.56 (2H, s, CH_2-N_{piper}), 6.91–6.98 (1H, m, Ar-H), 7.10–7.21 (4H, m, Ar-H), 7.31–7.38 (2H, m, Ar-H), invisible $NHSO_2$; IR (cm^{-1}): 3287, 3093, 2933, 1615, 1515, 1423, 1333, 1315, 1147, 922, 783; MS+: *m/z* 414 $(MH)^+$.

Hydrochloride: m.p.: >250°C (decomp.); Anal. calcd. for $C_{18}H_{21}Cl_2N_3O_2S \cdot 2HCl$ (487.27): C, 44.37, 4.76; N, 8.62. Found: C, 44.29; H, 4.94; N, 8.88.

In vitro pharmacology

Cell culture
All receptor cDNAs were obtained from the Missouri S&T cDNA Resource Center (www.cdna.org). HEK293 cells with stable expression of human serotonin 5-HT_{1A}R, 5-HT_6R, 5-HT_{7b}R, or dopamine D_{2L}R were obtained with the use of Lipofectamine 2000 (Invitrogen). Cells were maintained at 37°C in a humidified atmosphere with 5% CO_2 and were grown in Dulbecco's modified Eagle's Medium containing 10% dialyzed fetal bovine serum under selective conditions (500 μg/mL G418). For membranes preparations, cells were subcultured into 150 cm^2 cell culture flasks, grown to 90% confluence, washed twice with pre-warmed to 37°C phosphate buffered saline (PBS) and were pelleted by centrifugation (200 × *g*) in PBS containing 0.1 mM EDTA and 1 mM dithiothreitol, and stored at −80°C.

5-HT_{1A}/5-HT_6/5-HT_7/D_2 receptors radioligand binding assays
Membrane preparation and general assay procedures for cloned receptors were adjusted to 96-microwell format based on protocols was described by us previously [26, 27]. Cell pellets were thawed and homogenized in 20 volumes of assay buffer using an Ultra Turrax tissue homogenizer and centrifuged twice at 35000 g for 20 min at 4°C, with incubation for 15 min at 37°C in between. The composition of the assay buffers was as follows: for 5-HT_{1A}R: 50 mM Tris-HCl, 0.1 mM EDTA, 4 mM $MgCl_2$, 10 μM pargyline, and 0.1% ascorbate; for 5-HT_6R: 50 mM Tris-HCl, 0.5 mM EDTA and 4 mM $MgCl_2$, for 5-HT_{7b}R: 50 mM Tris-HCl, 4 mM $MgCl_2$, 10 μM pargyline and 0.1% ascorbate; for dopamine D_{2L}R: 50 mM Tris-HCl, 1 mM EDTA, 4 mM $MgCl_2$, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$ and 0.1% ascorbate. All assays were incubated in a total volume of 200 μL in 96-well microtitre plates for 1 h at 37°C, except for 5-HT_{1A}R which were incubated at room temperature for 1 h. The process of equilibration was terminated by rapid filtration through Unifilter plates with a 96-well cell harvester and radioactivity retained on the filters was quantified on a Microbeta plate reader (PerkinElmer, USA). For displacement studies the assay samples contained as radioligands (PerkinElmer, USA): 2.5 nM [^{3}H]-8-OH-DPAT (135.2 Ci/mmol) for 5-HT_{1A}R; 2 nM [^{3}H]-LSD (83.6 Ci/mmol) for 5-HT_6R; 0.6 nM [^{3}H]-5-CT (39.2 Ci/mmol) for 5-HT_7R or [^{3}H]-raclopride (76.0 Ci/mmol) for D_{2L}R. Non-specific binding was defined with 10 μM of 5-HT in 5-HT_{1A}R and 5-HT_7R binding experiments, whereas 10 μM of methiothepine or 1 mM of (+)butaclamol were used in 5-HT_6R and D_{2L} assays, respectively. Each compound was tested in triplicate at 7–8 concentrations (10^{-11}–10^{-4} M). The inhibition constants (K_i) were calculated from the Cheng–Prusoff equation [33]. Results were expressed as means of atleast three separate experiments.

Computational details

Molecular docking
The 3-dimensional structures of the compounds studied were prepared using LigPrep ver. 3.7 [34], while the appropriate ionization states at pH = 7.4 were assigned using Epik version 3.5 [35]. The Protein Preparation Wizard was used to assign the bond orders, appropriate amino acid ionization states and to check the steric clashes. The receptor grids were generated (the OPLS_2005 force field) by centering the grid box of the size of 15 Å on the Asp3.32. Automated docking was performed by using Glide version 7.0 at SP level with the flexible docking option turned on [36]. The spatial constrain was imposed on creation of an ionic interaction between the protonated amine group of the ligand and Asp3.32 side chain.

ONIOM optimization protocol
Full optimization of the systems studied (4618–4387 atoms depending on the receptor) was performed using QM/MM: ONIOM protocol, implemented in the Gaussian09 [37] software. The high level QM, including ligands and all amino acid residues, whose atoms were less than 4 Å from the ligand was applied. A dividing boundary was established at the C_{sp3}–C_{sp3} bonds, which gave 242–271 atoms for the QM level. The remaining parts of the receptor were assigned to the MM region, described by the AMBER [38] force field. The optimization of the binding site was performed using DFT and B3LYP methods [39, 40], in combination with split-valence basis set 6-31G* [41–46]. For each structure, MM fragment was removed and replaced by hydrogen, and then harmonic vibrational frequencies were calculated to confirm the potential energy minimum (T = 298.15 K, p = 1 atm).

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