A Three-Dimensional Pharmacophore Model for 5-Hydroxytryptamine$_6$ (5-HT$_6$) Receptor Antagonists

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Abstract: Forty-five structurally diverse 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) antagonists were selected to develop a 3D pharmacophore model with the Catalyst software. The structural features for antagonism at this receptor are a positive ionizable atom interacting with Asp$^{3.32}$, a hydrogen bond acceptor group interacting with Ser$^{5.43}$ and Asn$^{6.55}$, a hydrophobic site interacting with residues in a hydrophobic pocket between transmembranes 3, 4, and 5, and an aromatic-ring hydrophobic site interacting with Phe$^{6.52}$.

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that mediates a wide range of physiological functions[1−3] by interacting with seven serotoninergic receptor families (5-HT$_{1-7}$) subdivided into 14 subpopulations.[4]

The 5-HT$_6$ receptor (5-HT$_6$R) is a G protein coupled receptor (GPCR)[5] and is one of the most recently identified subtypes in the serotonin family.[6] It was first cloned from the rat brain cDNA[7,8] based on its homology to previously cloned GPCRs and is positively coupled to adenylyl cyclase via the G$_s$ protein.[9] Subsequently, the human 5-HT$_6$R has also been isolated, displaying 89% homology with rat receptors.[10] Studies using several methods have shown that the 5-HT$_6$R is almost exclusively localized in the central nervous system (CNS), mainly in the olfactory tubercle, striatum, nucleus accumbens, and hippocampus.[7,8,11,12]

Because of its recent identification, the biological functions of the 5-HT$_6$R are still being investigated, but there is some evidence to suggest that it may be involved in memory impairment, psychosis, convulsive disorders, appetite control, and related CNS diseases.[6,13−15] Although the future of 5-HT$_6$R ligands as potential therapeutic drugs seems quite exciting, selective agents are required to substantiate the proposed therapeutic applications. In the past few years the discovery of ligands with affinity and selectivity for this receptor has become an area of intense research in medicinal chemistry.[6,13,16,17] To date, the efforts in this area have provided a number of selective antagonists, mostly identified by high-throughput screening.

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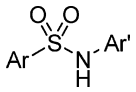
Table 1. Training Set and pK_i Values Used in the Generation of the Pharmacophore for Selective 5-HT$_6$R Antagonists



compd	Ar	Ar′	exptl	est
1 (Ro 04-6790)	4-aminophenyl	2,6-bis-methylamino-pyrimidin-4-yl	7.3[a]	7.3
2 (Ro 63-0563)	4-aminophenyl	2,6-bis-methylamino-pyridin-4-yl	7.8[a]	7.5
3 (SB-271046)	5-chloro-3-methyl-1-benzothien-2-yl	4-methoxy-3-piperazin-1-ylphenyl	9.0[b]	8.3
(*R*)-**4**	5-chloro-3-methyl-1-benzothien-2-yl	3-[(8a*R*)-hexahydro-pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-methoxyphenyl	9.1[c]	8.5
(*S*)-**4**	5-chloro-3-methyl-1-benzothien-2-yl	3-[(8a*S*)-hexahydropyrro-lo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-methoxyphenyl	9.1[c]	9.2
5 (SB-258585)	4-iodophenyl	4-methoxy-3-piperazin-1-ylphenyl	8.6[b]	8.8
6	4-aminophenyl	2-amino-6-methylamino-pyrimidin-4-yl	6.0[a]	6.7
7	4-aminophenyl	2-bromo-6-methylamino-pyridin-4-yl	7.3[a]	7.3
8	4-aminophenyl	3-methoxy-5-methyl-aminophenyl	7.4[a]	7.2
9	4-aminophenyl	3-methylaminophenyl	6.2[a]	7.1
10	4-aminophenyl	1*H*-indol-4-yl	7.2[a]	7.4
11	4-aminophenyl	1*H*-indol-6-yl	5.9[a]	7.2
12	3-iodophenyl	4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl	9.1[b]	9.0
13	3-nitrophenyl	4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl	7.1[b]	7.5
14 (SB-331711)	5-chloro-3-methyl-1-benzothien-2-yl	4-piperazin-1-ylquinolin-6-yl	8.7[d]	8.5
15	5-chloro-3-methyl-1-benzothien-2-yl	3-(4-methylpiperazin-1-yl)quinolin-6-yl	7.1[d]	7.3
16 (SB-357134)	4-methoxy-3-piperazin-1-ylphenyl	2,5-dibromo-3-fluorophenyl	8.5[e]	9.0
17	5-chloro-3-methyl-1-benzothien-2-yl	1-[2-(dimethylamino)-ethyl]-1*H*-indol-4-yl	7.2[f]	7.6
18	6-chloroimidazo-[2,1-*b*][1,3]thiazol-5-yl	1-[2-(dimethylamino)-ethyl]-1*H*-indol-4-yl	8.7[f]	7.8
19	6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl	1-(3-piperidin-1-ylpropyl)-1*H*-indol-5-yl	6.0[f]	7.2
20	6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl	1-(2-pyrrolidin-1-ylethyl)-1*H*-indol-6-yl	7.3[f]	7.6
21	5-chloro-2-naphthyl	3-[2-(dimethylamino)-ethyl]-1*H*-indol-5-yl	9.7[f]	8.9
22[g] (LY485731)	2,6-difluorophenyl	1-methyl-3-(1-methylpip-eridin-4-yl)-1*H*-indol-5-yl	9.0[h]	8.2

[a] Value reported in ref 22. [b] Value reported in ref 23. [c] Value reported in ref 24. [d] Value reported in ref 25. [e] Value reported in ref 26. [f] Value reported in ref 27. [g] SO_2O instead of SO_2NH. [h] Value reported in ref 28.

The structural requirements for the 5-HT$_6$R ligands are at present unknown, hampering a rational development of new specific compounds acting at this receptor. A pharmacophore definition is known as the first essential step toward understanding the interaction between a receptor and a ligand and is clearly established as one of the successful computational tools in rational drug design.[18,19]

The purpose of this communication is to report the structural features for 5-HT$_6$R antagonism. Using Catalyst,[20] we have developed a three-dimensional pharmacophore model from a set of 45 structurally diverse 5-HT$_6$R antagonists selected from the literature (Tables 1−3). The best output hypothesis (Figure 1), with a positive ionizable atom (PI), a hydrogen bond acceptor group (HBA), a hydrophobic site (HYD), and an aromatic-ring hydrophobic site (AR), presents good statistical values (see Supporting Information). The Fixed, Null, and Total Costs are 167, 263, and 197 bits, respectively. The Configuration Cost is 14.4. The difference of >60

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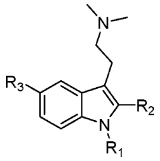
Table 2. Training Set and pK_i Values Used in the Generation of the Pharmacophore for Selective 5-HT$_6$R Antagonists

compd	Ar	Ar′	exptl	est
23	phenyl	(4*E*)-4-imino-2-(methylthio)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	8.4[a]	7.3
24	4-aminophenyl	2,6-dibromopyridin-4-yl	7.3[b]	6.9
25	1-naphthyl	4-methoxy-3-piperazin-1-ylphenyl	9.9[c]	9.7
26	phenyl	4-piperazin-1-yl-1*H*-indol-2-yl	9.9[d]	10.0
27	phenyl	3-[2-(dimethylamino)ethyl]-5-methoxy-1*H*-indol-1-yl	8.6[e]	9.1
28	1-naphthyl	3-[2-(dimethylamino)ethyl]-5-methoxy-1*H*-indol-1-yl	9.1[e]	9.4
29	2-naphthyl	3-[2-(dimethylamino)ethyl]-7-methoxy-1*H*-indol-1-yl	8.3[e]	8.5
30	1-naphthyl	6-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl-1*H*-indol-1-yl	9.7[f]	9.1
31	1-naphthyl	6-(1,2,3,5,8,8a-hexahydroindolizin-7-yl)-1*H*-indol-1-yl	8.9[f]	8.9
32	1-naphthyl	6-octahydroindolizin-7-yl-1*H*-indol-1-yl	9.1[f]	9.1
33	phenyl	3-[2-(dimethylamino)ethyl]-1*H*-indol-1-yl	8.5[g]	9.2
34	4-methylphenyl	(4*S*,5*S*)-4-(dimethylamino)-5-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indol-1-yl	8.1[g]	7.6
35	phenyl	3-[(dimethylamino)methyl]-1*H*-indol-1-yl	8.5[h]	8.5
36	4-aminophenyl	3-[(dimethylamino)methyl]-1*H*-indol-1-yl	8.2[h]	7.7
37	4-aminophenyl	3-methyl-1*H*-indol-1-yl	7.9[h]	7.3
38	4-acetamidophenyl	3-[2-(diethylamino)ethyl]-5-methoxy-1*H*-indol-1-yl	6.6[h]	7.5
39	4-methoxy-3-piperazin-1-ylphenyl	6-iodoindolin-1-yl	9.5[i]	9.2
40	4-aminophenyl	1,2,3,4-tetrahydro-9*H*-carbazol-9-yl	7.5[j]	7.3

[a] pIC_{50} value reported in ref 29. [b] Value reported in ref 30. [c] Value reported in ref 31. [d] Value reported in ref 32. [e] Value reported in ref 33. [f] Value reported in ref 34. [g] Value reported in ref 35. [h] Value reported in ref 36. [i] Value reported in ref 26. [j] Value reported in ref 37.

Table 3. Training Set and pK_i Values Used in the Generation of the Pharmacophore for Selective 5-HT$_6$R Antagonists



compd	R_1	R_2	R_3	exptl	est
41	H	Ph	OMe	7.3[a]	7.2
42	COPh	H	OMe	7.6[b]	7.7
43	H	COOEt	H	7.7[b]	7.7
44	H	3-(3-methoxybenzyl)-1,2,4-oxadiazol-5-yl	H	8.9[b]	9.1

[a] Value reported in ref 38. [b] Value reported in ref 35.

bits between Fixed and Null Costs indicates >90% chance of obtaining a predictive hypothesis. This model was further evaluated for statistical significance using the Fisher method as implemented in the CatScramble module. The pK_i values were scrambled randomly 19 times, and new hypotheses were generated (not shown). None of the outcome hypotheses had a cost lower than the reported hypothesis. Thus, there is at least 95% probability that this hypothesis represents true correlation in the data. There is also a significant correlation ($r^2 = 0.75$, $s = 0.5$, $p < 0.001$) between measured and estimated activities. In detail, compound **30** (Table 2) fulfills the PI feature through the protonated bridgehead nitrogen, the HBA with the sulfonyl group, the HYD with the naphthalene ring, and the AR with the indole ring (see Supporting Information).

The PI feature is a common pharmacophoric element of most of the ligands that interact with biogenic amine

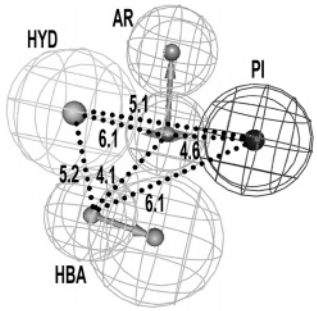


Figure 1. Pharmacophore model for **1**−**44** created with the HypoGen algorithm as implemented in Catalyst.[20] The procedure employed in the calculation is similar to the recently described pharmacophore model of the 5-HT$_7$R.[21] The structural features are a positive ionizable atom (PI), a hydrogen bond acceptor group (HBA), a hydrophobic site (HYD), and an aromatic-ring hydrophobic site (AR) at the shown interatomic distances (top). The HYD and PI features are drawn as globes, whereas HBA and AR features are shown as two globes because of the directional nature of these chemical functions.

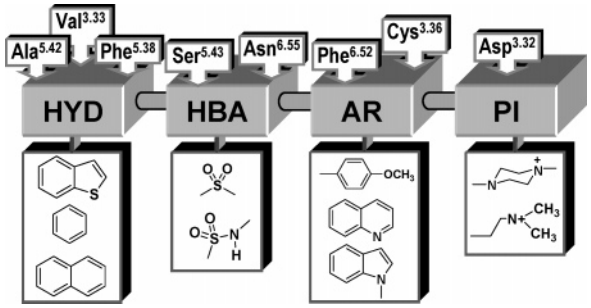


Figure 2. Schematic representation of the pharmacophore model, the most common functional groups observed in compounds with pK_i > 8, and the predicted amino acids in the transmembrane domain of the 5-HT$_6$R involved in the interaction with the ligands.

GPCRs.[39] This pharmacophoric element is accomplished, in a selected set of 5-HT$_6$R ligands with pK_i > 8, mostly through the piperazine (**3**−**5**, **12**, **14**, **16**, **25**, **26**, **30**, **39**) or (dimethylamino)ethyl (**18**, **21**, **27**−**29**, **33**, **44**) moieties (Figure 2). Figure 3 depicts **12** and **30** in the binding pocket of a computational model of the 5-HT$_6$R. The protonated piperazine moiety of the ligand interacts with Asp$^{3.32}$ (standarized nomenclature[40]) in transmembrane (TM) 3. The AR feature is created in most cases by the 4-methoxyphenyl (**3**−**5**, **12**, **16**, **25**, **39**), quinoline (**14**), or differently substituted indole rings (**18**, **21, 22**, **26**−**36**, **39**) (Figure 2). These aromatic rings interact mainly with Phe$^{6.52}$ in TM 6 and partly with Phe$^{5.47}$ in TM 5 (shown in Figure 3a for compound **30**). Compounds that contain at this AR element an aromatic ring with additional hydrogen bond donor/acceptor capabilities (i.e., the methoxy group of **3**−**5**, **12**, **16**, **25**, **39**; the quinoline system of **14**; or the NH of the indole ring of **21**) can form a hydrogen bond interaction with Cys$^{3.36}$ (Figure 3b). The HBA feature is formed by a sulfonyl group (Figure 2). The oxygen atoms of the sulfonyl group act as hydrogen bond acceptors in the hydrogen bond interaction with Ser$^{5.43}$ in TM 5 and Asn$^{6.55}$ in TM 6 (Figure 3), whereas the NH of the sulfonamide group in **3**−**5**, **12**, **14**, **16**, **18**, **21** forms an additional interaction with Ser$^{5.43}$ in TM 5 (Figure 3b). The interaction between a series of conserved Ser/Thr residues at positions 5.42 and 5.43 in TM 5 and ligands

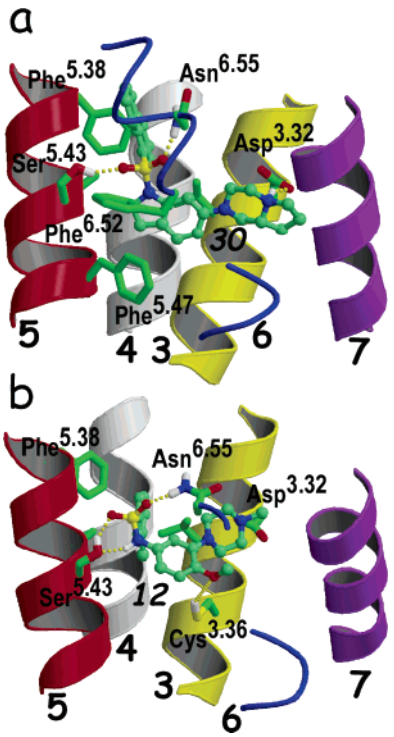


Figure 3. Computational model of the complexes between the transmembrane domain of the 5-HT$_6$R and **30** (a) and **12** (b). The TM 7 model was constructed by homology modeling using the crystal structure of bovine rhodopsin (PDB code 1GZM)[41] as template. The residues considered to be most conserved in the class A of GPCRs were aligned in both sequences (see Supporting Information). SCWRL-3.0 was employed to add the side chains of the nonconserved residues based on a backbone-dependent rotamer library.[44] TM 3 is slightly bent toward TM 5, at position 3.37, as has been suggested for the neurotransmitter family of GPCRs.[42,43] The ligand−receptor systems were energy-minimized with a dielectric constant of 4 and a 13 Å cutoff for nonbonded interactions with AMBER, version 8.[45] Parameters for the systems were obtained from the ff99 force field, and the "general Amber force field" was obtained for **12** and **30** using RESP point charges.

that interact with biogenic amine GPCRs is usually accomplished by −O−, C=O, or −OH groups.[39] The absence of Ser/Thr$^{5.42}$ and the presence of Ser$^{5.43}$ and Asn$^{6.55}$ in the 5-HT$_6$R make the sulfone or sulfonamide groups structurally and electronically optimal for bridging TMs 5 and 6 through hydrogen bonds (Figure 3). The HYD feature is created in this selected set of 5-HT$_6$R ligands by the benzothiene (**3**, **4**, **14**), benzene (**5**, **12**, **16**, **26**, **27**, **33**−**36**), or naphthalene (**21**, **25**, **28**−**32**) systems (Figure 2). This moiety is accommodated between the hydrophobic (Val$^{3.33}$ in TM 3 and Ala$^{5.42}$ in TM 5) and the aromatic (Phe$^{5.38}$ in TM 5) residues (Figure 3). The hydrophobic nature of the residues forming this locus allows different halogen substitution at this aromatic site (**3**−**5**, **12**, **14**, **16**, **18**, **21**, **22**, **39**). It is important to note that the aromatic rings of the AR and HYD features form an angle of approximately 90°. This change of orientation of the molecules is feasible because of the tetrahedral conformation of the sulfonyl group (HBA).

Remarkably, the independent generation of a pharmacophore model and a 3D model of the TM 7 domain of the 5-HT$_6$R complexed with ligands **12** and **30** have provided similar conclusions. These models aid the rational design of new agents acting at this recently identified 5-HT$_6$ serotonin receptor. Design and synthesis of new derivatives that fulfill these models are currently in progress, and the results will be reported in due course.

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Supporting Information Available: Description of the methodology employed in the generation of the pharmacophore model, Tables 1 and 2 containing 2D chemical structures of antagonists **1**−**40**, Figure 4 showing **30** mapped onto the pharmacophore hypothesis, and Figure 5 containing the alignment of the transmembrane sequences of rhodopsin and human 5-HT$_6$R. This material is available free of charge via the Internet at http://pubs.acs.org.

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