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CoMFA and CoMSIA 3D QSAR analysis on N_1-arylsulfonylindole compounds as 5-HT$_6$ antagonists

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Abstract—Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) three-dimensional quantitative structure–activity relationship (3D-QSAR) studies were conducted on a series of N_1-arylsulfonylindole compounds as 5-HT$_6$ antagonists. Evaluation of 20 compounds served to establish the models. The lowest energy conformer of compound **1** obtained from random search was used as template for alignment. The best predictions were obtained with CoMFA standard model ($q^2 = 0.643$, $r^2 = 0.939$) and with CoMSIA combined steric, electrostatic, hydrophobic, and hydrogen bond acceptor fields ($q^2 = 0.584$, $r^2 = 0.902$). Both the models were validated by an external test set of eight compounds giving satisfactory predictive r^2 values of 0.604 and 0.654, respectively. The information obtained from CoMFA and CoMSIA 3D contour maps can be used for further design of specific 5-HT$_6$ antagonists.
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1. Introduction

The 5-HT$_6$ receptor is one of the most recent additions to the 5-hydroxytryptamine super family of receptors consisting of seven classes (5-HT$_1$–5-HT$_7$) that contain totally 14 human subclasses.[1] It was first isolated from rat striatal mRNA[2] in 1993 and subsequently the human 5-HT$_6$ gene was cloned and characterized by Kohen et al.[3] in 1994. The 5-HT$_6$ receptor is a seven transmembrane 440 amino acid polypeptide, which is positively coupled to the adenylate cyclase secondary messenger system.[4] Evaluation of the expression pattern of 5-HT$_6$ receptor mRNA and protein revealed that it is selectively expressed in the central nervous system, exhibiting wide spread distribution throughout the brain. This intriguing distribution in the brain, together with its high affinity for a wide range of drugs used in the psychiatry[5,6] stimulated significant interest recently. Most atypical antipsychotic drugs, which lack extrapyramidal side effects, bind with very high affinity to the 5-HT$_6$ receptor. In fact, the prototypic atypical antipsychotic agent clozapine, exhibits greater affinity for the 5-HT$_6$ receptor than for any other receptor subtype. Initial in vivo experiments showed that administration of antisense oligonucleotides (AOs), directed at 5-HT$_6$ receptor mRNA, elicited a behavioral syndrome in rats consisting of yawning, stretching, and chewing, which could be dose dependently blocked by the muscarinic antagonist atropine.[7] This study implies that 5-HT$_6$ receptors modulate cholinergic neurotransmission and hence 5-HT$_6$ receptor antagonists may be useful for the treatment of memory dysfunction. In addition, treatment with AOs significantly inhibited the increase in 5-HT release from the prefrontal cortex produced by conditioned fear stress, suggesting that 5-HT$_6$ receptors may be involved in certain anxiety disorders.[8]

Recently, several selective 5-HT$_6$ receptor antagonists have been developed including Ro 04-6790,[9] Ro 63-0563,[9] SB-271046,[10] SB-357134,[11] and N_1-benzenesulfonyl tryptamine[12] (Fig. 1). Several of these agents have been used to investigate 5-HT$_6$ receptor function in vivo. Consistent with the previous studies using AOs, Ro 04-6790 produced a stretching behavior that was selectively blocked by muscarinic antagonists, suggesting that the 5-HT$_6$-receptor is involved in regulation of cholinergic signaling.[13] A role for 5-HT$_6$ in the processes of learning and memory was also supported, as SB-271046 and SB-357134 were efficacious in a spatial memory task in rats[14] and Ro 04-6790 improved

Keywords: CoMFA; CoMSIA; QSAR; 5-HT$_6$ antagonists.
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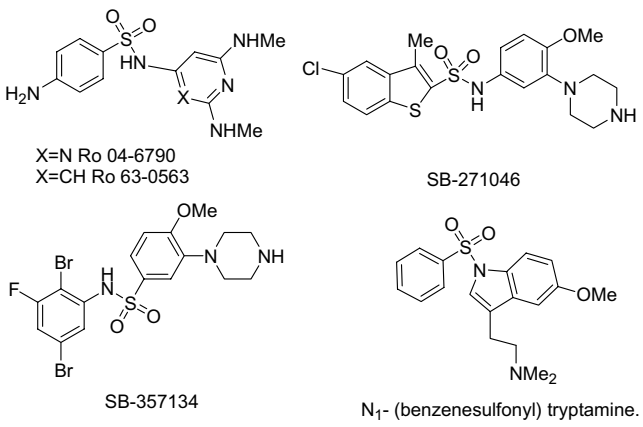


Figure 1. 5-HT_6 antagonists.

learning consolidation in an autoshaping task.[15] In addition, systematic administration of SB-271046 selectively enhanced the levels of excitatory amino acids within the frontal cortex.[16] While several studies suggest that 5-HT_6 receptor antagonists may have utility as cognition enhancers, not all studies have replicated these results.[17] Therefore, the development of additional potent and selective 5-HT_6 receptor antagonists will provide additional tools for delineating the role of the 5-HT_6 receptor in vivo.

As a part of ongoing work in our lab aimed at the discovery of new 5-HT_6 antagonists, we studied three-dimensional structure–activity relationship of N_1-arylsulfonylindole derivatives reported by Russell et al.[12] to gain insight into steric, electrostatic, hydrophobic, and hydrogen bonding properties influencing the activity.

In this paper, two 3D-QSAR methods, CoMFA and CoMSIA, were applied to investigate the local physicochemical properties involved in the interaction between ligand and receptor. The widely used CoMFA (comparative molecular field analysis) calculates steric and electrostatic properties according to Lennard-Jones and Coulomb potentials.[18] The more recently reported CoMSIA approach (comparative molecular similarity indices analysis) calculates similarity indices in the space surrounding each of the aligned molecules in the dataset.[19–21] CoMSIA is believed to be less affected by changes in molecular alignment and provides smooth and interpretable contour maps as result of employing Gaussian type distance dependence with the molecular similarity indices it uses.[19] Furthermore, in addition to steric and electrostatic fields of CoMFA, CoMSIA defines explicit hydrophobic and hydrogen bond donor and acceptor descriptor fields.

The contour maps derived from both the CoMFA and CoMSIA models permitted an understanding of the steric, electrostatic, lipophilic, and hydrogen bonding requirements for ligand binding. As a consequence, the structural variations in the training set that gives rise to variations in the molecular fields at particular regions of the space are correlated to biological activities serving as a guide to the design of novel inhibitors.

2. Materials and methods

2.1. Data set

The training set used for the analysis comprises of N_1-arylsulfonylindole derivatives obtained from a report published by Russell et al.[12] This report contains about 33 compounds with K_i values ranging from 1.3 to 1700 nM (Table 1). From these 33 compounds, only 20 compounds (compounds **1**–**20**) were selected as training set based on the criteria of selectivity, partial agonistic activity and outliers. Compounds **21**–**26** were removed from training set as their representatives **21**, **22**, and **23** showed good affinity for the other subtypes such as 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}, 5-HT_2, and dopamine receptors (Table 2[12]). Furthermore both **21** and **23** behaved as partial agonists, giving 59% and 49%, of the response seen with 5-hydroxytryptamine and the remaining compounds deleted (not shown in the table) were detected as outliers. The K_i values of the training set are converted to pK_i ($-\log K_i$) and used as dependent variables in the CoMFA and CoMSIA QSAR analyses. The predictiveness of the derived model was evaluated using an external test set of eight compounds (Table 3) obtained from a report by Glennon and co-workers.[22]

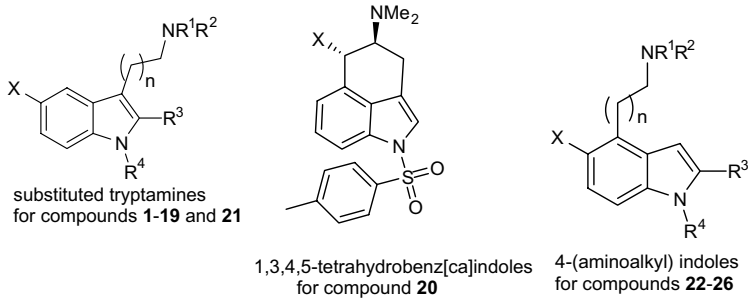
2.2. Molecular modeling and alignment

All molecular modeling calculations were performed using SYBYL[23] program, package version 6.9.1 on silicon graphics origin300 workstation with IRIX 6.5 operating system. Energy minimizations were performed using Tripos force field[24] and Gasteiger Huckel charge with distance dependent dielectric and conjugate gradient method with convergence criterion of 0.01 kcal/mol. The most important requirement for CoMFA and CoMSIA studies is that the 3D structures to be analyzed were aligned according to a suitable conformational template, which is assumed to be a 'bioactive' conformation.[18] As no structural information is available about ligand–receptor complexes, the lowest energy conformer of compound **1**, obtained from random search option given in SYBYL, was used as template structure for the alignment. All the molecules of the training set were aligned on template molecule **1** by using simple 'align database' (rigid fit) option given in SYBYL. Alignment and atoms used for superimposition were shown in Figure 2.

2.3. PLS calculations and validations

Partial least squares (PLS)[25,26] methodology was used for all 3D-QSAR analyses. The CoMFA and CoMSIA descriptors were used as independent variables, and pK_i values were used as dependent variables in partial least squares (PLS) regression analyses to derive 3D-QSAR models. The predictive value of the models was first evaluated by leave-one-out (LOO)[27,28] cross-validation.

Table 1. 5-HT_6 binding affinity of substituted tryptamines, 1,3,4,5-tetrahydrobenz[*ca*] indoles and 4-(aminoalkyl)indoles (Russell et al.[12])



Compd	X	*n*	NR^1R^2	R^3	R^4	K_i (nM) h5-HT_6[a]
1	MeO	1	NMe_2	H	$PhSO_2$	2.3 (1.7, 3.2)
2	MeO	1	NMe_2	H	2-$ClC_6H_4SO_2$	11 (7.8, 15)
3	MeO	1	NMe_2	H	3-$ClC_6H_4SO_2$	7.9 (6.2, 10)
4	MeO	1	NMe_2	H	4-$ClC_6H_4SO_2$	17 (19, 21)
5	MeO	1	NMe_2	H	4-$MeOC_6H_4SO_2$	26 (23, 30)
6	MeO	1	NMe_2	H	2-Naphthyl-SO_2	9.8 (7.8, 12)
7	MeO	1	NMe_2	H	2-Thienyl-SO_2	8.3 (7.1, 9.8)
8	MeO	1	NMe_2	H	PhCO	25 (22, 27)
9	MeO	1	Pyrrolidinyl	H	$PhSO_2$	44 (40, 48)
10	MeO	1	Piperidinyl	H	$PhSO_2$	350 (280, 430)
11	MeO	1	4-Methylpiperazinyl	H	$PhSO_2$	490 (410, 590)
12	MeO	1	Morpholinyl	H	$PhSO_2$	1700 (1400, 2100)
13	H	1	NMe_2	H	$MeSO_2$	620 (420, 910)
14	HO	1	NMe_2	H	$PhSO_2$	19 (18, 21)
15	HO	1	NMe_2	H	PhCO	54 (37, 78)
16	HO	1	NMe_2	H	*t*-BuOCO	370 (300, 470)
17	NC	1	NMe_2	H	$PhSO_2$	33 (13, 45)
18	MeO	1	NMe_2	Me	$PhSO_2$	12 (10, 13)
19	MeO	1	NMe_2	Me	H	89 (69, 110)
20	HO					7.2 (6.0, 8.7)
21	H	1	NMe_2	H	$PhSO_2$	2.9 (2.1, 3.9)
22	H	1	NH_2	H	$PhSO_2$	2.4 (1.7, 3.4)
23	H	1	NMe_2	H	$PhSO_2$	1.5 (1.0, 2.3)
24	H	2	NMe_2	H	$PhSO_2$	7.9 (6.3, 11)
25	H	1	NMe_2	COPh	$PhSO_2$	3.0 (2.0, 4.5)
26	H	1	NMe_2	COPh	H	260 (240, 290)

Compounds **1**–**20** were used as training set, compounds **21**–**26** were deleted from training set because of nonselectivity and partial agonistic activity.
[a] Displacement of [^{3}H]-5-HT binding to cloned h5-HT_6 receptors stably expressed in HeLa cells. The figures are the geometric mean of at least three independent determinations performed in duplicate. The values in parentheses are the upper and lower limits derived as a result of the SEM. In each case the radioligand concentration used was approximately at the K_D for the receptor. Clozapine was used as a control [K_i 13 (11,15) nM].

Table 2. Binding affinity at other serotonin and dopamine receptors (Russell et al.[12])

Compd	h5HT_{1A}	h5HT_{1B}	h5HT_{1D}	h5HT_{1F}	5HT_2	r5HT_{5A}	h5HT_7	hD_2	hD_3	hD_4
1	1100	2200	720	2500	65	>5000	1900	210	80	>3200
21	520	2300	510	770	84	4000	3700	62	23	>3200
22	140	6.5	4.5	47	4.8	1200	29	>1700	940	>3200
23	170	11	9.3	3.9	18	3400	460	1600	300	>3200
25	480	190	98	570	6.6	1600	1300	750	66	>3200

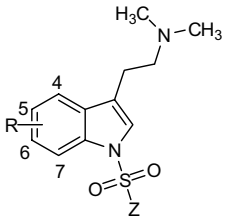
Receptors and radioligands used in the binding assays were as follows: 5-HT_{1A} (human cloned receptors in HeLa cells, [^{3}H]-5-HT); 5-HT_{1B} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_{1D} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_{1F} (human cloned receptors in CHO cells, [^{3}H]-5-HT); 5-HT_2 (rat cortical membranes, [^{3}H]DOB); 5-HT_{5A} (rat cloned 5-HT_{5A} receptors in HEK 293 cells); [^{3}H]LSD; 5-HT_7 (human cloned 5-HT_7 receptors in CHO cells, [^{3}H]-5-HT); dopamine D_2 (human cloned dopamine D_2 receptors in CHO cells, [^{3}H]spiperone); dopamine D_3 (human cloned dopamine D_3 receptors in HEK 293 cells, [^{3}H]spiperone); dopamine D_4 (human cloned dopamine D_4 receptors in HEK 293 cells, [^{3}H]spiperone). For the 5-HT assays, nonspecific binding was defined with 10 μM 5-HT, and for the dopamine assays, with 10 μM apomorphine.

To maintain the optimum number of PLS components and minimize the tendency to over fit the data, the number of components corresponding to the lowest PRESS value was used for deriving the final PLS regression models.[28]

2.4. Predictive *R* squared (r^2_{pred})

To validate the derived CoMFA and CoMSIA models, biological activities of an external test set of eight

Table 3. Binding affinity of test compounds (Glennon and co-workers)[22]

Compd[a]	Structure	R	Z	K_i (nM) (±SEM)[b]	K_i[c]	K_i[d]
27		5-OMe	2,5-DiOMePh	1.3 (±0.2)	—	3.9
28		5-OMe	1-Naphthyl	0.9 (±0.2)	—	2.7
29		4-OMe	2,5-DiOMePh	7.4 (±0.2)	—	22.2
30		6-OMe	2,5-DiOMePh	9.5 (±0.6)	—	28.5
31		7-OMe	4-ClPh	45 (±7)	—	135
32		7-OMe	4-OMePh	93 (±7)	—	279
33		7-OMe	2,5-DiOMePh	183 (±32)	—	549
34		7-OMe	2-Naphthyl	5.0 (±0.6)	—	15
35(1)		5-OMe	Ph	2.3 (±0.5)	2.3	6.9
36(4)		5-OMe	4-ClPh	3.1 (±0.1)	17	9.3
37(5)		5-OMe	4-OMePh	8.0 (±0.4)	26	24
38(6)		5-OMe	2-Naphthyl	1.6 (±0.3)	9.8	4.8

[a] Compounds **27**–**34** were used as test set, (numbers in the parenthesis indicates corresponding numbers in Table 1 Russell et al.[12]).
[b] K_i values were determined in triplicate. Clozapine ($K_i = 4.8 \pm 0.6$ nM) was employed as control.
[c] Corresponding K_i values in Russell et al.
[d] Approximately corrected values (3 times) based on Russell et al.'s data [clozapine as control $K_i = 13(11, 15)$ nM].[12]

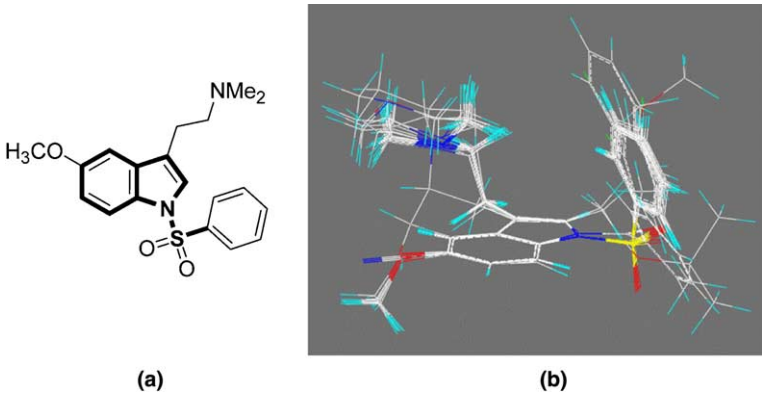


Figure 2. (a) Template used for alignment (reference atoms are shown in bold). (b) Training set aligned on minimum energy conformation of compound **1**.

compounds (Table 3) were predicted using models derived from the training set. The predictive ability of the models is expressed by predictive r^2 value, which is analogous to cross-validated r^2 (q^2) and is calculated by using the formula.

$$r^2_{\text{pred}} = \frac{\text{SD} - \text{PRESS}}{\text{SD}}$$

where SD is the sum of squared deviation between the biological activities of the test set molecule and the mean activity of the training set molecules and PRESS is the sum of squared deviations between the observed and the predicted activities of the test molecules.

3. Results and discussion

CoMFA and CoMSIA 3D-QSAR models were derived for a set of 20 structurally similar compounds acting as 5-HT_6 antagonists with K_i values ranging from 2.3 to 1700 nM. All the compounds of the training set were aligned on a minimum energy conformation of compound **1**, obtained by using random search option given in SYBYL. The best predictions were obtained with CoMFA standard model ($q^2 = 0.643$, $r^2 = 0.939$) and CoMSIA combined steric, electrostatic, hydrophobic, and hydrogen bond acceptor fields ($q^2 = 0.584$, $r^2 = 0.902$) (Table 4).

In addition, C log*P* along with steric and electrostatic fields of CoMFA and CoMSIA were also analyzed as a hydrophobic parameter influencing the activity. The results in Table 5 show that C log*P* did not have significant effect on activity, showing a contribution of less than 6% in both the models. Furthermore q^2 and r^2 values decreased from 0.643 and 0.939 to 0.549 and 0.909, respectively, in the case of CoMFA model and from 0.447 and 0.910 to 0.383 and 0.867, respectively, in the case of CoMSIA model.

Figure 3 shows the graph of observed activities versus predicted activities of training set for both CoMFA std and CoMSIA combined models (Table 6). It is striking to see that both models predicted less activity for compound **1** indicating inconsistency in the data or in the models itself. According to the report,[12] compound **1** is one of the most important compounds of the series with high affinity for 5-HT_6, good selectivity over other

Table 4. CoMFA and CoMSIA results

	q^2	N	r^2	SEE	F	SEP	q^2bs	SD
CoMFA std	0.643	3	0.939	0.210	82.139	0.508	0.943	0.023
CoMSIA (steric+electro)	0.447	3	0.910	0.255	53.916	0.632	0.910	0.025
CoMSIA (steric+electro+ hydrophobic)	0.552	3	0.908	0.257	52.945	0.569	0.924	0.023
CoMSIA (steric+ electro+hydro+donor)	0.505	4	0.860	0.329	23.007	0.618	0.919	0.036
CoMSIA (steric+ electro+hydro+acceptor)	0.584	3	0.902	0.267	48.906	0.548	0.917	0.047
CoMSIA (all descriptors)	0.517	5	0.913	0.268	29.283	0.632	0.951	0.053

q^2—Leave one out (LOO) cross-validated correlation coefficient, N—optimum number of components, r^2—noncross-validated correlation coefficient, SEE—standard error of estimate, F—F-test value, SEP—standard error of prediction, q^2bs—mean r^2 of boot strapping analysis (10 runs), SD—standard deviation.

Table 5. CoMFA and CoMSIA steric and electrostatic fields along with C log$P$ as hydrophobic parameter influencing the activity

	CoMFA[a]+C log$P$	CoMSIA[b]+C log$P$
q^2	0.549	0.383
N	3	10
r^2	0.909	0.867
SEE	0.256	0.310
F	53.37	34.67
SEP	0.571	0.759
q^2bs	0.930	0.906
SD	0.031	0.043
Contributions		
Steric	57.7	40.5
Electrostatic	37	54
C log$P$	5.3	5.6

[a] CoMFA steric and electrostatic fields.
[b] CoMSIA steric and electrostatic fields.

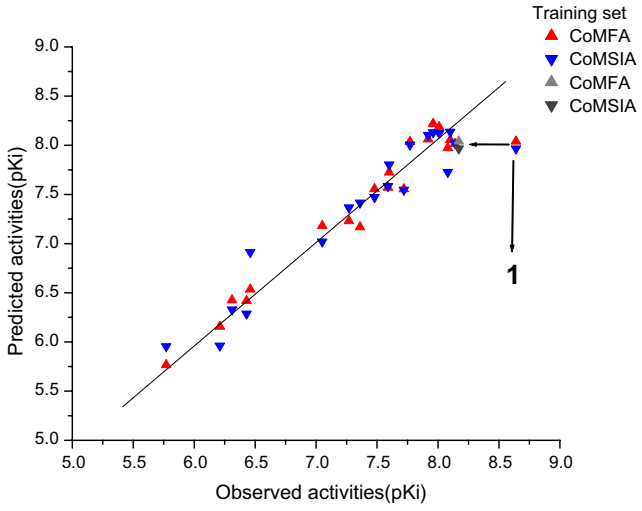


Figure 3. Plot of observed versus predicted activities of training set. Red triangles show the predictions of CoMFA std model and blue triangles show predictions of CoMSIA combined model. Grey triangles show the corresponding corrected positions of compound **1**.

serotonin receptors tested and has good brain penetrability as evidenced from centrally mediated mescaline induced head twitch assay, and this compound was predicted to have less activity than the observed, by our models. Fortunately for us, the same compound was also synthesized and assayed by Glennon and co-workers[22] (Table 3), the remaining compounds of which were used as test set in our analysis. In both cases clozapine was used as control, but the K_i values are different, 4.8 ± 0.6 nM in case of Glennon and co-workers, where as it is 13 nM (11,15) in case of Russell et al. Even though the control inhibitory values are almost 3-fold different, the K_i values of compound **1** are same that is 2.3 nM in both cases (compound **35** in case of Glennon and co-workers). Whereas K_i values of compounds **4**, **5**, and **6** (Russell et al.), which were also assayed by Glennon and co-workers are 3–6 times higher than K_i values of same compounds **36** (5.5 times), **37** (3.3 times), and **38** (6.1 times), respectively (Table 3), indicating that the K_i value of compound **1** might be minimum 3 times more than 2.3 nM. In fact when the K_i value of compound **1** was increased 3 times to 6.9 nM, q^2 and r^2 values increased from 0.643 and 0.939 to 0.659 and 0.965, respectively, in case of CoMFA standard model, whereas from 0.584 and 0.902 to 0.605 and 0.928, respectively, in case of CoMSIA combined steric, electrostatic, hydrophobic, and hydrogen bond acceptor fields. Both Glennon and co-workers data and our models show a possibility of small experimental error in the activity value of compound **1**. The corrected positions of compound **1** were also shown in the graph (Fig. 3).

Both CoMFA standard and CoMSIA combined (steric, electrostatic, hydrophobic, and hydrogen bonding acceptor fields) models were validated by using an external test set of eight compounds with K_i values ranging from 2.7 to 549 nM (compounds **27**–**34**, Table 3), which is with in the activity range of training set.

The predictive r^2 values of test set for both CoMFA and CoMSIA models were 0.605 and 0.654, respectively. Figure 4 shows the comparative plot of predictions of the test set by both models and it also contain predictions of compounds **21**, **22**, **23**, **24**, **25**, and **26**, which are nonselective and show partial agonistic activity. Both models predicted far less activity than the observed for these compounds, which are different from others in that they do not contain 5-hydroxy or methoxy substituent, this is accounted for the less predictions by the models and in turn may be the reason for both the nonselectivity and partial agonistic activity in case of 5-HT$_6$ antagonists.

Table 6. Observed versus predicted activities of CoMFA std and CoMSIA combined models

Compd	Obsrvd pK_i	CoMFA[a] predicted	CoMSIA[b] predicted	CoMFA residuals	CoMSIA residuals
Training					
1	8.64	8.04	7.966	0.600	0.674
2	7.96	8.219	8.131	−0.259	−0.171
3	8.1	8.054	8.136	0.046	−0.036
4	7.77	8.035	8.005	−0.265	−0.235
5	7.59	7.57	7.584	0.020	0.006
6	8.01	8.185	8.123	−0.175	−0.113
7	8.08	7.972	7.727	0.108	0.353
8	7.6	7.725	7.803	−0.125	−0.203
9	7.36	7.168	7.416	0.192	−0.056
10	6.46	6.535	6.912	−0.075	−0.452
11	6.31	6.425	6.329	−0.115	−0.019
12	5.77	5.766	5.955	0.004	−0.185
13	6.21	6.157	5.962	0.053	0.248
14	7.72	7.554	7.546	0.166	0.174
15	7.27	7.23	7.367	0.040	−0.097
16	6.43	6.419	6.287	0.011	0.143
17	7.48	7.555	7.471	−0.075	0.009
18	7.92	8.061	8.103	−0.141	−0.183
19	7.05	7.18	7.02	−0.130	0.030
20	8.14	8.014	8.023	0.126	0.117
Test					
27	8.41	8.1	7.752	0.310	0.658
28	8.57	8.256	8.289	0.314	0.281
29	7.66	7.649	7.325	0.011	0.335
30	7.54	7.553	7.205	−0.013	0.335
31	6.87	7.366	7.34	−0.496	−0.470
32	6.56	7.123	6.909	−0.563	−0.349
33	6.26	7.313	6.95	−1.053	−0.690
34	7.83	7.531	7.433	0.299	0.397

[a] CoMFA std model.
[b] CoMSIA combined (steric, electrostatic, hydrophobic, and acceptor fields) model.

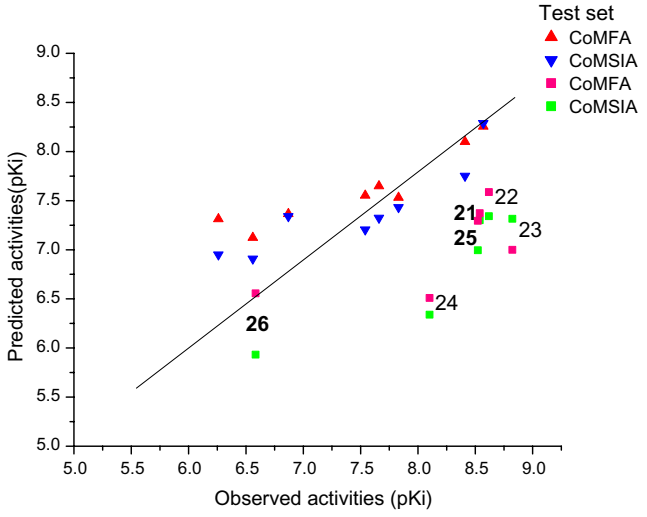


Figure 4. Plot of observed versus predicted activities of test set. Red triangles show the predictions of CoMFA std model and blue triangles show predictions of CoMSIA combined model. The predictions of compounds **21**, **22**, **23**, **24**, **25**, and **26**, which are nonspecific and have partial agonistic activity were also shown. Pink squares show the predictions of CoMFA std model and green squares show the predictions of CoMSIA combined model.

Figure 5 shows steric contour maps of CoMFA standard and CoMSIA combined (steric, electrostatic, hydrophobic, and acceptor fields). Sterically favored green regions were found on phenyl ring of arylsulfonyl group where naphthyl ring was well tolerated (compound **6**), whereas sterically unfavored yellow region is found near amine side chain where larger substituents like pyrrolidinyl, piperidinyl, 4-methylpiperazinyl, and morpholinyl groups (compounds **9**, **10**, **11**, and **12**) decreased the activity.

Figure 6 depicts electrostatic contour maps of CoMFA std and CoMSIA combined (steric, electrostatic, hydrophobic, and acceptor fields). Negative charge favored red region was found near 5-methoxy or hydroxyl group of indole ring, which is a common moiety in most of the 5-HT receptor antagonists and positive charge favored or negative charge unfavored blue region was found near amine side chain, where negatively charged ring systems like morpholinyl drastically decreased the activity (compound **12**). In addition to these, CoMFA std electrostatic map (Fig. 6a) contains an additional negative charge favored red region over phenyl ring of arylsulfonyl group where halide substitution was well tolerated (compounds **2**, **3**, and **4**). In CoMSIA model the corresponding region was occupied by hydrophobic favored yellow region in hydrophobic contour map (Fig. 7), whereas hydrophobic unfavored white region was found around 5-position of the indole ring where most compounds contain oxygen atom.

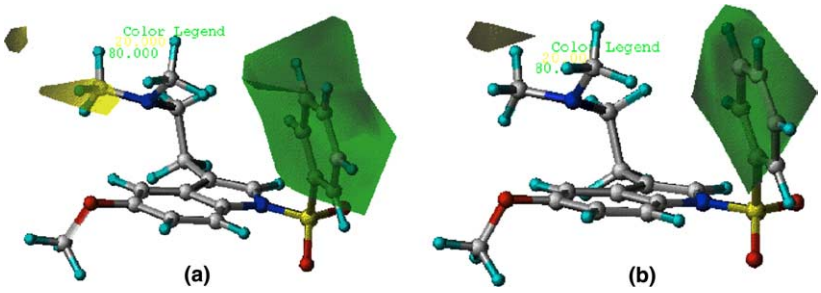


Figure 5. (a) CoMFA std (b) CoMSIA combined stdev * coeff steric contour plots; green contours indicate regions where bulky groups increase activity, whereas yellow contours indicate regions where bulky groups decrease activity.

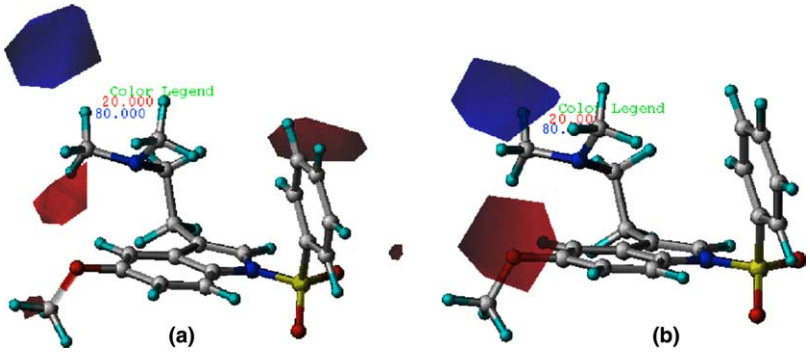


Figure 6. (a) CoMFA std (b) CoMSIA combined stdev * coeff electrostatic contour plots; red contour indicate regions where negative groups increase activity, whereas blue contours indicate regions where negative charge decreases activity.

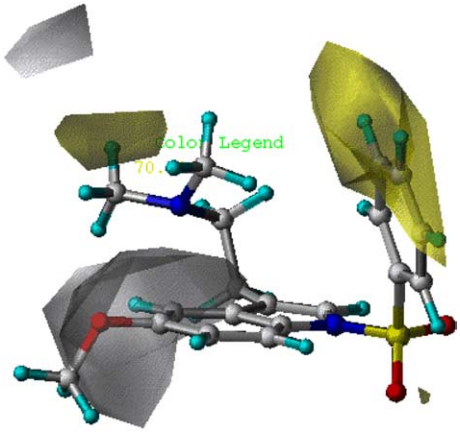


Figure 7. CoMSIA combined stdev * coeff hydrophobic contour plots; yellow contours indicate regions where hydrophobic groups increases activity, whereas white contours indicates regions where hydrophobic group decreases activity.

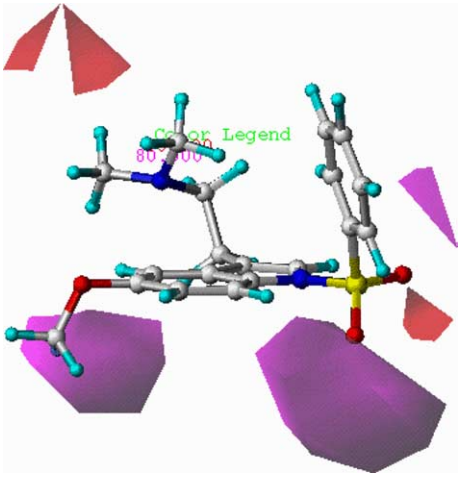


Figure 8. CoMSIA combined stdev * coeff H-bond acceptor plots; magenta contours indicate regions where H-bond acceptor group increases activity, whereas red contours indicate regions where H-bond acceptor group decreases activity.

Figure 8 shows hydrogen bond acceptor contour map of CoMSIA combined (steric, electrostatic, hydrophobic, and acceptor fields). Hydrogen bond acceptor favored magenta regions were found near sulfonyl oxygen moiety and near 5-hydroxy or methoxy group, where as hydrogen bond acceptor unfavored red region is seen near amine side chain where presence of acceptor group (e.g., comp **12**) decreased the activity.

Figure 9 shows compounds **21**, **22**, **23**, **24**, **25**, and **26**, which are nonselective and show partial agonistic activity superimposed on CoMSIA electrostatic contour map. All of these compounds lack methoxy or hydroxyl substituent to fill the negative charge favored red region near 5-position of the indole ring system. This may be accounting for the nonselectivity and partial agonistic activity in case of N_1-arylsulfonylindole derivatives acting as 5-HT_6 antagonists.

The information obtained from contour maps can be used in designing new antagonists. Compounds with

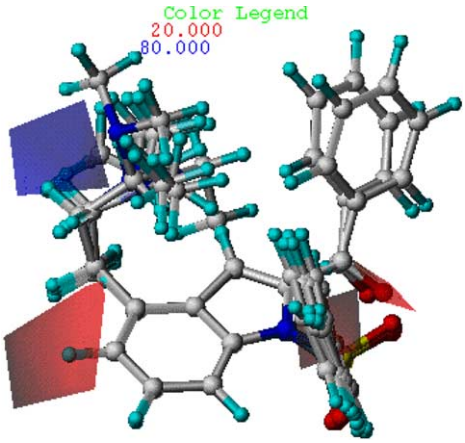


Figure 9. Compounds **21**, **22**, **23**, **24**, **25**, and **26** lacking methoxy or hydroxyl substituent to fill the negative charge favored red region.

more hydrophobic substituents on aryl sulfonyl ring may increase the activity. For example, dihalide or even trihalide substitution can be tried for this purpose. Sterically bulky groups like halogen substituted naphthyl ring systems in place of phenyl ring of arylsulfonyl group may show favorable effect. On amine side chain, small groups preferably with positive charge can be tried to enhance the activity. Different substitutions like thiol or thiomethyl in place of 5-hydroxy or 5-methoxy groups may also show positive effect on the activity.

4. Conclusions

CoMFA and CoMSIA methods were successfully used in our study to build 3D-QSAR models that define accurately the molecular basis for 5-HT_6 antagonism. The information obtained from CoMFA and CoMSIA 3D maps can be used for further design of specific 5-HT_6 antagonists.

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