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Ligand based pharmacophore generation and 3D-QSAR study of serotonin ligands using PHASE

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ABSTRACT

5-HT_6 (serotonin, 5-hydroxytryptamine) antagonism has been proposed on a promising approach for treating cognitive impairment associated with neuropsychiatric disorders (e.g. Alzheimer's disease, Schizophrenia). Using PHASE programme (Schrodinger-USA), pharmacophore generation and atom based 3D-QSAR analysis of earlier reported aryl sulphonamide and sulfone based 5-HT_6 antagonists were studied to get insight into their structural requirements responsible for high affinity. The best pharmacophore model generated consisted of four features AAPR: two hydrogen bond acceptors (A), a positive ionisable group (P) and an aromatic ring (R). Based on model generated, a statistically valid 3D-QSAR with good predictability was developed. Developed QSAR model showed good coefficient of determination (R^2 > 0.90), higher variance ratio (F > 20), significant values for Q^2 = 0.67 and Pearson correlation coefficient (Pearson-R) = 0.83. Statistical results of the generated model are significant and excellent which strongly recommends that this model is acceptable for designing of various novel derivatives with different scaffolds and their biological activity prediction as novel, potent 5-HT_6 antagonists in future.

Keywords: Cognitive impairment, 3D-QSAR, Serotonin, Pharmacophore, PHASE.

INTRODUCTION

The 5-HT_6 receptor is a subtype of 5-HT receptor that binds the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). It is a G protein-coupled receptor (GPCR) that is coupled to G_s/G_o and mediates excitatory neurotransmission.[2] 5-hydroxytryptamine 6 (5-HT_6) receptor was discovered only recently, its almost exclusive distribution in the brain makes it a promising, novel, target CNS mediated diseases such as Alzheimer's disease (cognitive function), schizophrenia, anxiety and obesity. [3] Cognitive impairment (CI) has been recognized as a core features of Alzheimer's disease (AD) and schizophrenia. The 5-HT_6 receptor antagonists have been shown to modulate multiple neurotransmitter systems and therefore enhance cognition in preclinical studies. 5-HT_6 receptor is expressed almost exclusively in the CNS, where blockade of the receptor function increases cholinergic and glutaminergic transmission and *in-vivo* cognitive efficacy in rodent behaviour models. [4, 10-16] This indicates the current progress with 5-HT_6 receptor antagonists as a therapeutic strategy for Alzheimer's disease and Schizophrenia-associated cognitive dysfunction and obesity. [1, 10-16]

Literature survey depicts various highly active aryl sulphonamides based 5-HT_6 antagonists in which many compounds showed several fold higher affinity towards the receptor as compared to standard drugs (Table 1). [4] An interest was created to understand the structural features of these compounds responsible for their high affinity towards 5-HT_6 receptor which can be helpful for designing potent inhibitors of this receptor.

MATERIALS AND METHODS

For pharmacophore generation and atom-based 3D-QSAR analysis, a dataset of 46 compounds was selected which was carried out using PHASE drug design software (Schrodinger, Inc). [5] The computations were done on a Redhat Linux platform with a processor of 2 GHz and memory 512 RAM. Phase supports various ligand-based drug design approaches like pharmacophore perception, structure alignment, 3D-QSAR and database searching. [6] Using Macro model with OPLS 2005 force field, energy minimization of dataset structures was carried out. [7] Structures minimized were imported in PHASE and appropriate protonation states at physiological pH 7.2 ± 2.0 were assigned to them by LigPrep. [8] Using Mixed MCMM/LMOD with OPLS 2005 force field with distance dependent dielectric solvation treatment, various conformations of prepared structures were generated. [9] Defining pharma set, compounds with pKi > 9.2 were considered as active, while those with pKi < 7.14 as inactive. Default pharmacophore features in PHASE include hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (H), negative (N), positive (P) and aromatic ring (R). For development of pharmacophore model, these default definitions were used. Finding common pharmacophore, maximum number of sites was set to 5 and minimum to 5. Box size of pharmacophore was adjusted to 2 Å. Active and inactive molecules were scored for a given pharmacophore using default weights of scoring parameters. Top ranking hypotheses were subjected to 3D-QSAR analysis for which grid spacing was 1 Å and maximum PLS factors 6. 33 molecules to training set and 13 molecules to test set were assigned, based on variation in structure and biological activity.

RESULTS

Biological activity predicted by 3D-QSAR for the present dataset is reported in Table 1. The PLS statistics for 3D-QSAR is shown in Table 2. Visual inspection of QSAR model revealed H-bond donor, hydrophobicity and electron-withdrawing effects as structural requirements critical for activity; *H-bond donor*: presence of methyl on nitrogen of piperazine ring and methoxy on aromatic ring capable of acting as hydrogen bond donor seemed to have a favourable effect on activity. However, hydrogen bond donor in the aryl sulphonamide side chain affected activity adversely (Figure 3A); *Hydrophobicity*: hydrophobic group at aromatic ring negatively correlated with activity, whereas as its presence on piperazine nitrogen had a positive influence on activity (Figure 3B); *Electron-withdrawing*: presence of electron-withdrawing sulfonyl group exercised a favourable effect on the activity (Figure 3C). The plot of predicted pKi against experimental is depicted in Figure 2.

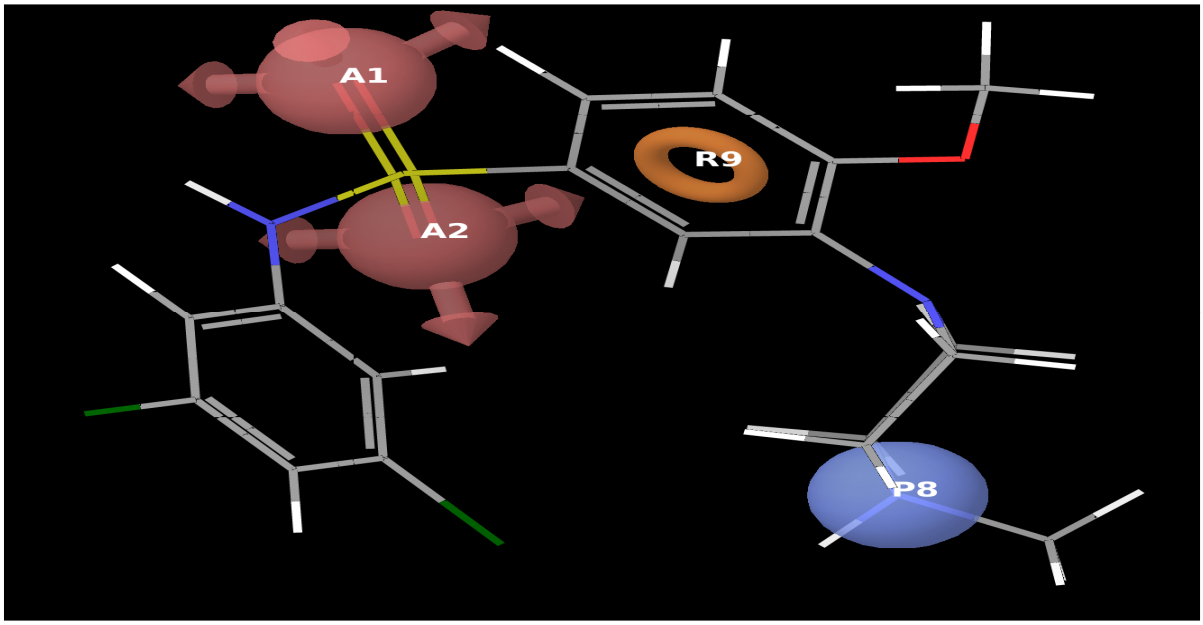


Figure 1. Generated pharmacophore model AAPR: 10 aligned on best fit compound '25'

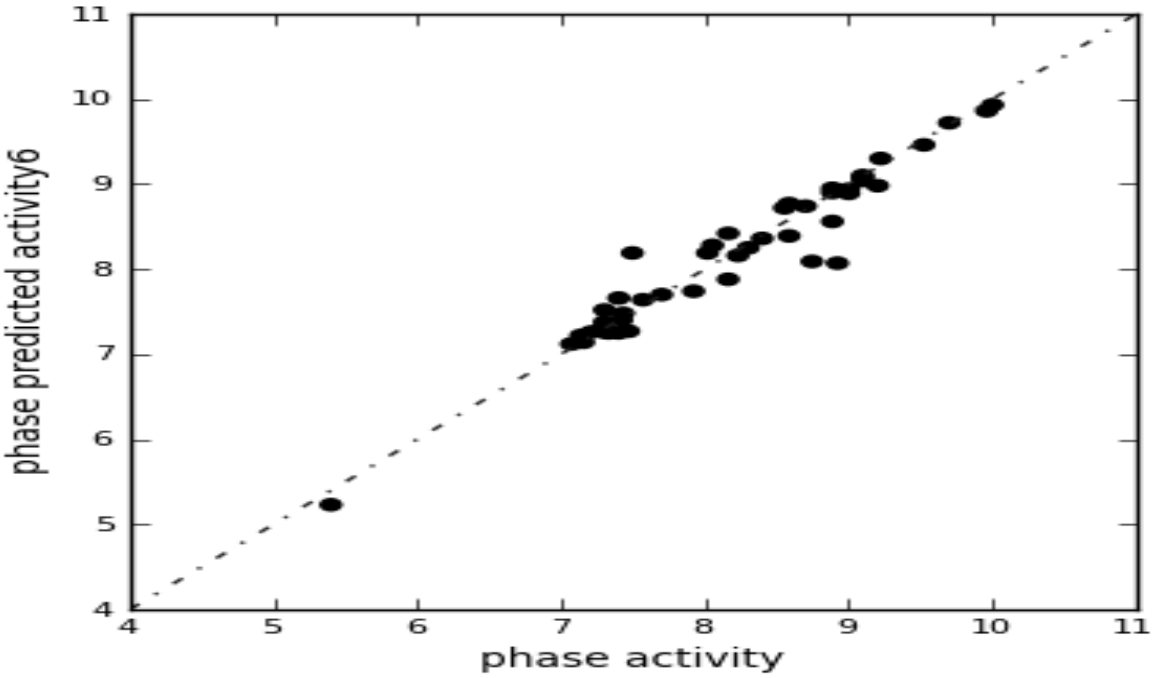
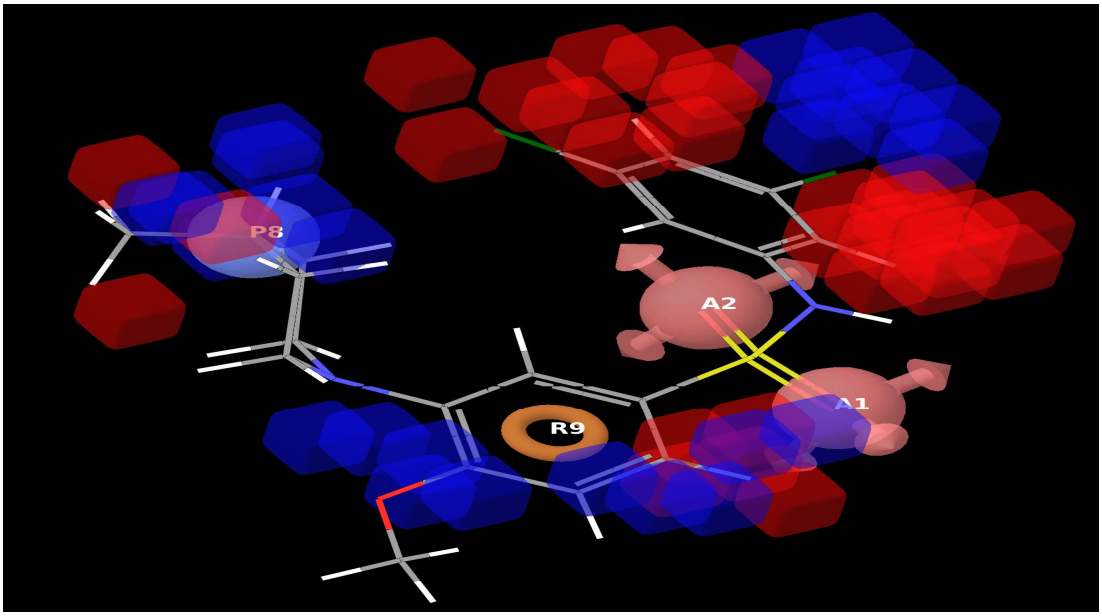


Figure 2. Scatter plot of predicted pKi against experimental pKi for training and test set compounds



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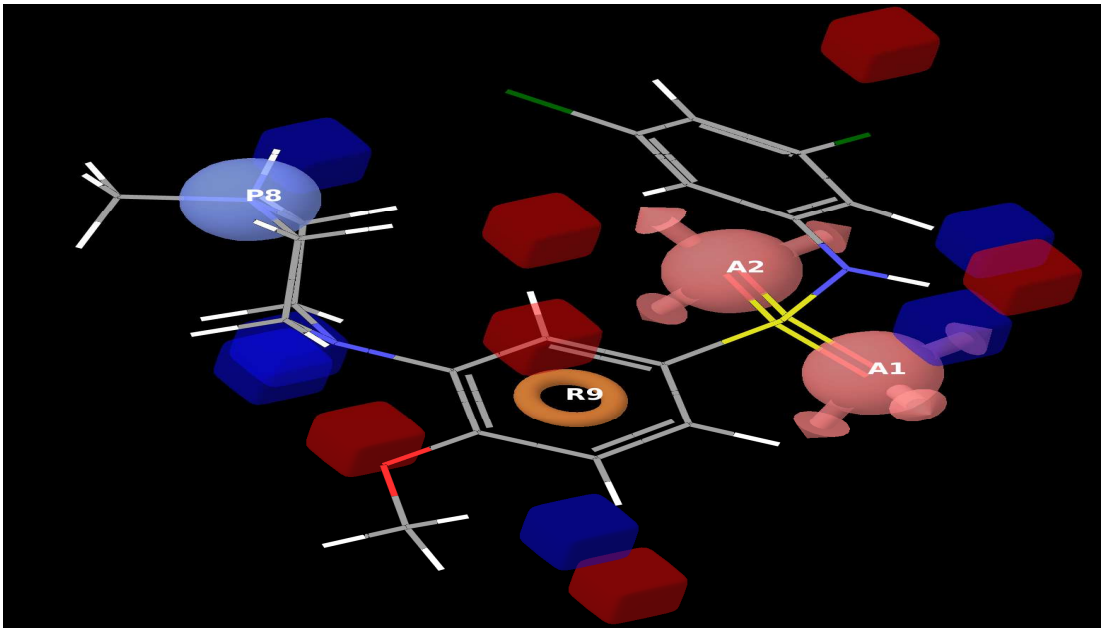

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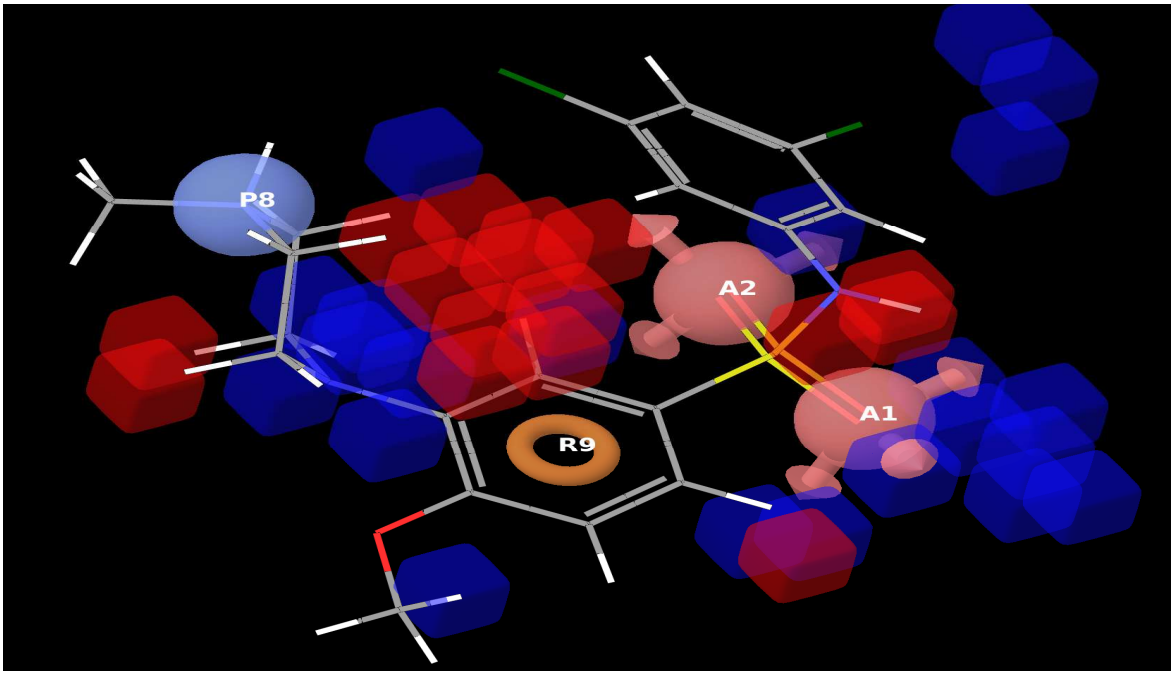


C

Figure 3. 3D-QSAR visualization for compound 25; (A) H-bond donor, (B) Hydrophobic, (C) Electron-withdrawing (blue cubes: favourable influence on activity; red cubes: unfavourable influence on activity)

Table 1. Dataset of various 5-HT$_6$ antagonists included in study reported with experimental and predicted activities using developed 3D-QSAR model

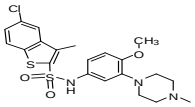
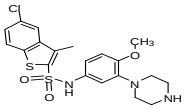
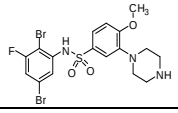
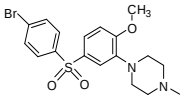
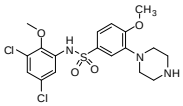
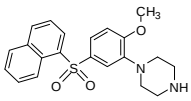
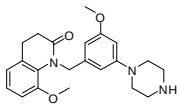
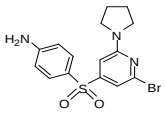
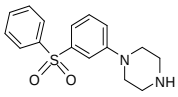
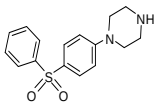
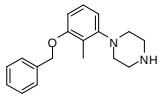
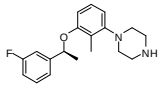
No.	Structure	Ki (nM)	pKi		Fitness Score
			Experimental	Predicted	
1		0.6	9.22	9.30	2.41
2		1.3	8.88	8.95	2.23
3		2.6	8.58	8.39	1.69
4		2.8	8.55	8.72	2.65
5		0.8	9.09	9.04	2.87
6		0.1	10.00	9.93	2.66
7		0.3	9.52	9.46	1.83
8		1.0	9.00	8.89	2.94
9		1.2	8.92	8.07	2.29
10		6.9	8.16	7.88	1.60
11		1.3	8.88	8.56	1.64
12		6.9	8.16	8.42	1.63

Table 1. Continued...

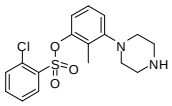
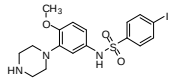
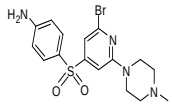
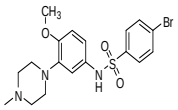
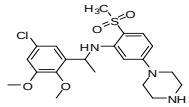
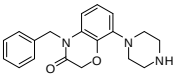
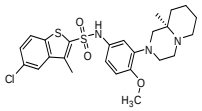
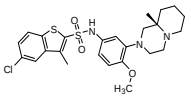
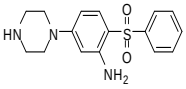
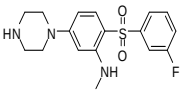
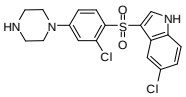
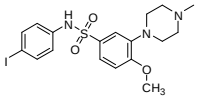
No.	Structure	Ki (nM)	pKi		Fitness Score
			Experimental	Predicted	
13		5.9	8.22	8.16	1.78
14		1.8	8.74	8.09	2.40
15		0.1	9.95	9.86	2.38
16		5.0	8.30	8.25	2.38
17		4.0	8.39	8.36	1.75
18		0.2	9.69	9.72	1.64
19		0.8	9.09	9.08	2.33
20		0.8	9.09	9.10	2.22
21		2.6	8.58	8.77	2.92
22		8.8	8.05	8.28	1.71
23		9.6	8.01	8.19	1.67
24		2.0	8.69	8.74	2.70

Table 1. Continued...

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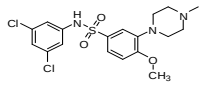
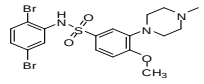
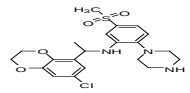
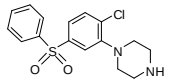
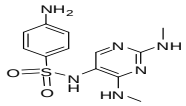
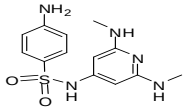
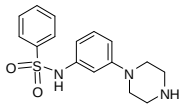
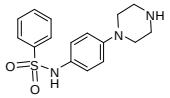
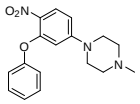
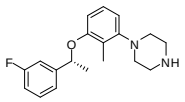
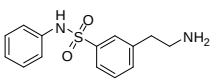
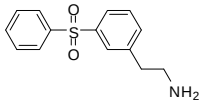
25		0.6	9.20	8.98	3
26		1.0	9.00	8.94	2.03
27		1.3	8.88	8.90	1.47
28		< 32.0	7.49	8.19	2.50
29		46.8	7.32	7.25	2.11
30		12.0	7.92	7.74	2.16
31		62.0	7.20	7.26	2.49
32		85.0	7.07	7.12	1.64
33		27.0	7.56	7.64	1.76
34		39.8	7.40	7.66	1.77
35		70.0	7.15	7.14	2.33
36		50.0	7.30	7.52	2.18

Table 1. Continued...

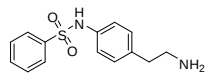
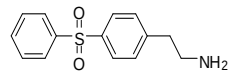
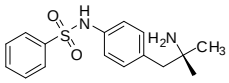
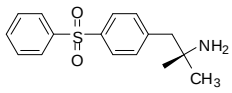
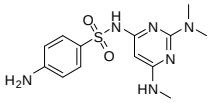
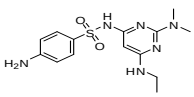
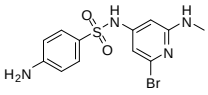
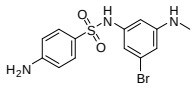
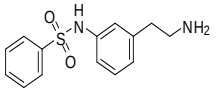
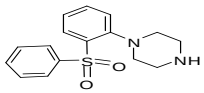
No.	Structure	Ki (nM)	pKi		Fitness Score
			Experimental	Predicted	
37		38.0	7.42	7.40	1.45
38		37.0	7.43	7.48	1.38
39		34.0	7.46	7.27	1.58
40		73.0	7.13	7.22	1.54
41		50.0	7.30	7.26	2.07
42		40.0	7.39	7.25	2.09
43		50.0	7.30	7.38	2.17
44		20.0	7.69	7.70	2.17
45		52.0	7.28	7.30	2.31
46		4000	5.39	5.23	2.19

Table 2. Statistical values for 3D-QSAR model generated by PLS.

Training set	Test set
m = 6	-
n = 33	-
R^2 = 0.98	n_T = 13
SD = 0.14	Q^2 = 0.67
F = 281.50	RMSE = 0.38
P = 2.28e-22	Pearson-R = 0.83

m = number of PLS factors in the model; n = number of molecules in the training set; nT = number of molecules in test set; R2 = coefficient of determination; Q2 = R2 for test set; SD = standard deviation of regression; RMSE = root-mean squared error; F = variance ratio; P = statistical significance; Pearson-R = Pearson correlation coefficient.

DISCUSSION

On the basis of 'Survival' and 'Survival-inactive' scores, the generated pharmacophore hypotheses were evaluated. [5] Top scoring hypothesis AAPR: 10 was selected as the best pharmacophore model for the present dataset of 5-HT_6 receptor antagonists. AAPR: 10 consisted of four features: two hydrogen bond acceptors (A), a positive

ionisable group (P) and an aromatic ring (R) (Fig. 1). Atom-based 3D-QSAR analysis was performed by PLS based on the alignment of pharmacophore features. Training set comprised of 33 compounds and test set of 13 compounds. Atom-based 3D-QSAR analysis yielded a statistically significant model which predicted activity of test compounds.

CONCLUSION

To conclude, the present research work has been carried out for pharmacophore modelling and 3D-QSAR studies of some aryl sulphonamide and sulfone based 5-HT_6 receptor antagonists. The developed pharmacophore model AAPR: 10 implicated the role of two hydrogen bond acceptors (A), a positive ionisable group (P) and an aromatic ring (R) in biological activity as 5-HT_6 receptor antagonists. The best statistical results generated were Q^2 = 0.67, coefficient of determination (R^2) = 0.98, root-mean squared error (RMSE) = 0.38, Pearson correlation coefficient (Pearson-R) = 0.83 which shown the robustness of the model generated. The 3D-QSAR visualisation shown favourable or unfavourable regions and substitutions required at respective places for potent biological activity which will help in designing selective and potent 5-HT_6 receptor antagonists in future. Thus pharmacophore model and 3D-QSAR studies presented in this paper is hoped to be a primer towards the development of various novel 5-HT_6 receptor antagonists with different chemical scaffolds and further its biological activity predictions to invent novel, potent, selective and safe 5-HT_6 receptor antagonists for the treatment of cognitive impairment. Moreover, further use of contemporary experimental and computational techniques to data presented here may widen its scope and applicability.

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