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IN-SILICO STUDY OF ARYL SULPHONAMIDES AS 5-HT$_6$ SEROTONIN LIGAND: A 2D QSAR STUDY USING TOPOLOGICAL DESCRIPTORS

Pawan Kumar [1], Priti Singh [1], Rajesh Kumar Singh [2] and Mohd. Adil Khan [* 2]

Department of Chemistry [1], K. S. Saket P. G. College, Ayodhya - 224123, Uttar Pradesh, India.
Department of Chemistry [2], M. L. K. P. G. College, Balrampur - 271201, Uttar Pradesh, India.

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Correspondence to Author:
Mohd. Adil Khan

Department of Chemistry,
M. L. K. P. G. College, Balrampur - 271201, Uttar Pradesh, India.

E-mail: madil.khan207@gmail.com

ABSTRACT: Serotonin plays a crucial role in various cognitive and behavioral functions. The serotonin signaling is mediated by binding of serotonin to specific receptors on the cell surface. Serotonin 5-HT$_6$ receptors turned out to be promising biological targets for the modulation of central nervous system dysfunctions. Several classes of serotonin 5-HT$_6$ receptor ligands have been discovered. Among them, many aryl sulphonamides derivatives as 5-HT$_6$ antagonists were reported to have better affinity towards the receptor. In the present study, a quantitative structure-activity relationship (QSAR) study of forty derivatives of aryl sulphonamide and sulfone based 5-HT$_6$antagonists has been made with the help of topological parameters. The descriptors that have been used are valence connectivity indices of order 0, 1 & 2 and shape indices of order 1, 2 & 3. The biological activities of compounds have been taken from the literature. The study indicates that the valence connectivity index (order-0) appears an important descriptor for the QSAR study of aryl sulphonamides which alone gives a QSAR model with reliable predictive power. The best combination of descriptors obtained for this study is valence connectivity index (order-0), shape index (order-1) and shape index (order-2). The predicted activities obtained from this QSAR model are very close to observed activities. This QSAR model can be used to find the activity of any new derivative of aryl sulphonamides.

INTRODUCTION: Serotonin, or 5-hydroxy-tryptamine (5-HT), is an important neurotransmitter [1, 2]. It plays a crucial role in various cognitive and behavioral functions such as learning, mood, stress, pain, sleep, aggression, depression, anxiety, cognition, sexual behavior *etc* [3, 4]. Improper serotonergic signaling leads to mental disorders such as schizophrenia, depression, suicidal behavior, infantile autism, obsessive-compulsive disorder *etc* [5, 6].

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The binding of serotonin to specific receptors on the cell surface mediates serotonin signaling [7-9]. Drugs targeting serotonin receptors are useful in treating various disorders, making drug development involving serotonin receptors an important area of research [10]. In previous decades, serotonin 5-HT$_6$ receptor turned out to be promising biological targets for the modulation of central nervous system dysfunctions.

5-HT$_6$ serotonin receptor is the family member of G-protein coupled receptors (GPCRs) [11, 12] which is present in various brain regions. Blockade of their function enhances the cognitive process, which sufficiently demonstrates the therapeutic usefulness of this receptor for CNS-mediated disorders such as schizophrenia, Alzheimer's disease, obesity, eating disorders *etc*. [13–21]. Worldwide research efforts

have discovered several classes of serotonin 5-HT_6 receptor ligands with good affinity and selectivity. Many aryl sulphonamides as 5-HT_6 antagonists reported better affinity towards the receptor [22]. Literature survey depicts various highly active aryl sulphonamides based 5-HT_6 antagonists [23]. Understanding common structural features of these aryl sulphonamides responsible for affinity is helpful for designing novel entities. In the research work of Velingkar and Chindhe, the pharmacophore generation and atom-based 3D-QSAR analysis of earlier reported aryl sulphonamide and sulfone based 5-HT_6 antagonists were studied using the PHASE program to get insight into their structural requirements responsible for high affinity [24].

Interest has been created in understanding the other structural features of these compounds responsible for their high affinity towards 5-HT_6 receptor, which can help potent design of inhibitors of this receptor. In this paper, Topological descriptors have been used for the development of QSAR models for the forty derivatives of aryl sulphonamide and sulfone based 5-HT_6 antagonists. The descriptors used are valence connectivity indices of order 0, 1 & 2 and shape indices of order 1, 2 & 3. Topological parameters gained much importance in recent years, and QSAR studies of different compounds have been made using these parameters [25-31]. In the present work, the predicted activities obtained from developed QSAR models using these topological parameters were found close to reported observed activities.

MATERIAL AND METHOD: Forty derivatives of aryl sulphonamide and sulfone based 5-HT_6 antagonists that have been taken from literature, [24] are used as study material. These are listed in **Table 1** along with their observed biological activity in terms of pKi (nM). The geometry optimization of all the compounds has been done with the help of CAChe Pro software developed by Fujitsu Corporation of Japan, using the DFT [32-34] Method. Evaluation of the values of descriptors has been done with the help of the same software. The QSAR models have been developed by multi-linear regression (MLR) analysis with the help of the Project Leader program associated with CAChe Pro. The descriptors that have been used are described below.

Valence Connectivity Indices [35, 36]: It is calculated from the hydrogen-suppressed molecular graph and defined as follows,

$$ {}^{m}\chi^{v} = \sum_{i=1}^{Ns} \prod_{k=1}^{m+1} \left[\frac{1}{\delta_k^v} \right]^{1/2} $$

Where,

$$ \delta_k^v = \frac{(Z_k^v - H_k)}{(Z_k - Z_k^v - 1)} $$

Valence connectivity for the k-th atom in the molecular graph,

Z_k= the total number of electrons in the k-th atom,

Z^v_k= the number of valence electrons in the k-th atom,

H_k= the number of hydrogen atoms directly attached to the k^{th} non-hydrogen atom,

m = 0 - atomic valence connectivity indices (called order-0),

m = 1 - one bond path valence connectivity indices (called order-1),

m = 2 - two bond fragment valence connectivity indices (called order-2).

Shape Indices [37, 38]: The first order shape index (1κ or κ_1) is given by,

$$ {}^{1}K = A\,(A-1)^2 / ({}^{1}P)^2 $$

Where, iP = Length of paths of bond length i in the hydrogen suppressed molecule and A is the number of non-hydrogen atoms in the molecule. The second-order kappa shape index (2κ or κ_2) is given by

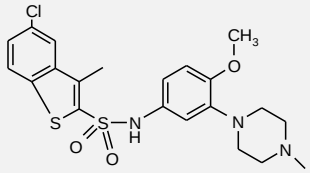
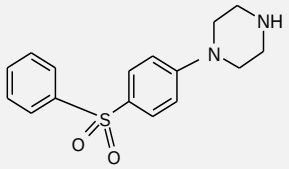
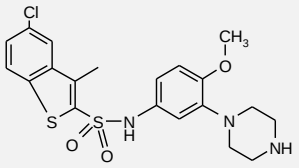
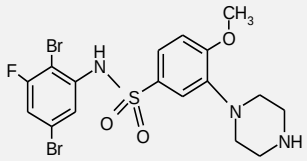
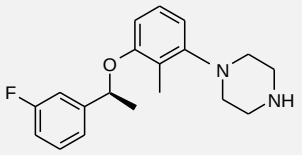
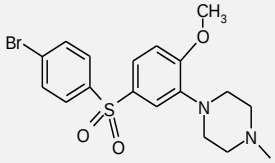
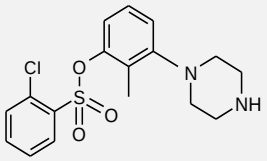
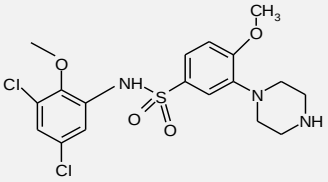
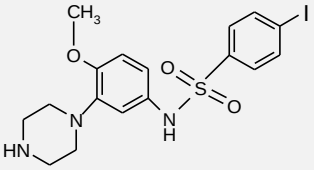
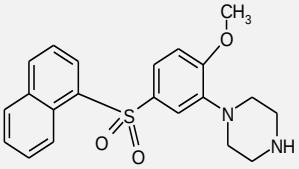
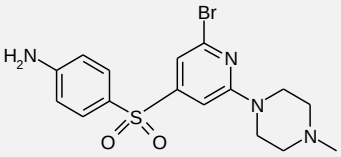
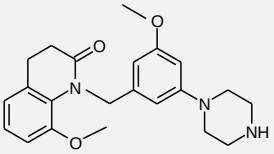
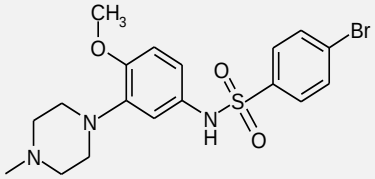
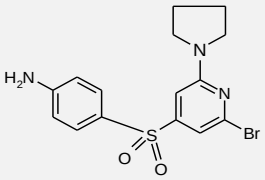
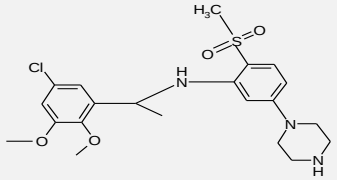
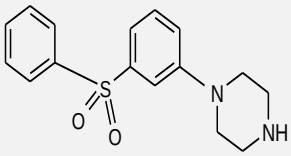
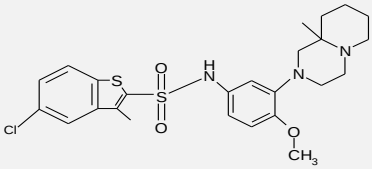
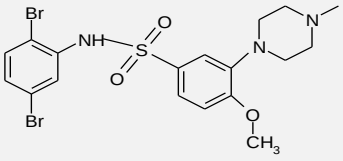
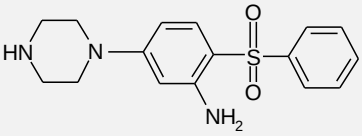
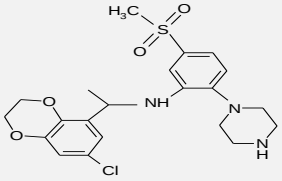
$$ {}^{2}K = (A-1)\,(A-2)^2 / ({}^{2}P)^2 $$

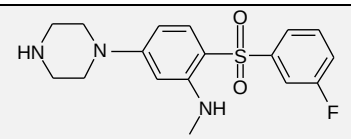
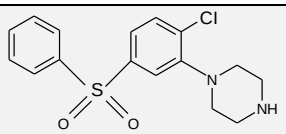
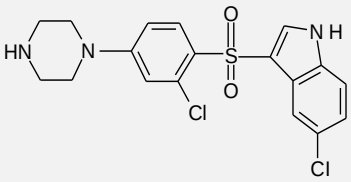
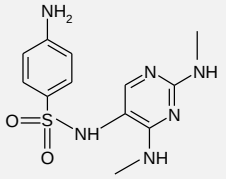
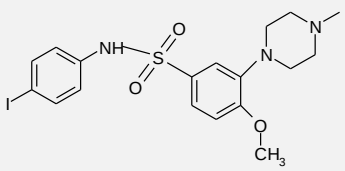
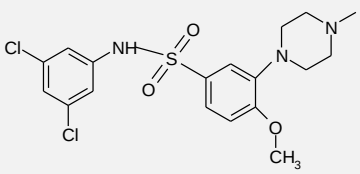
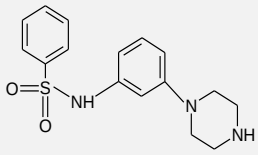
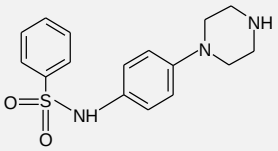
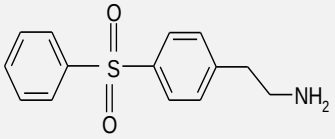
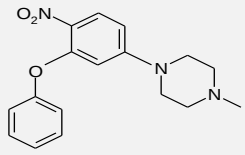
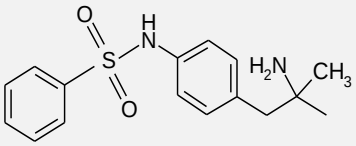
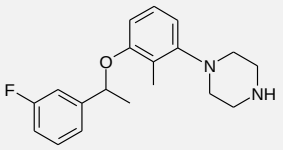
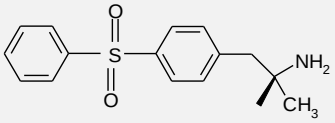
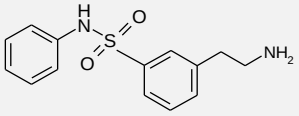
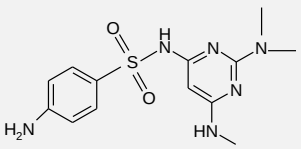
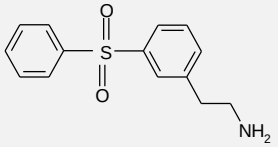
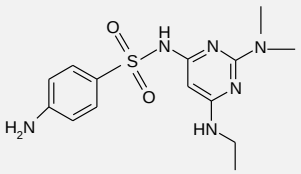
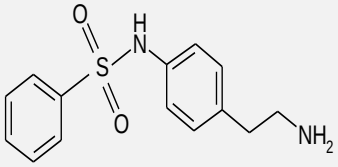
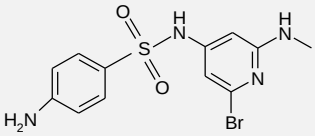
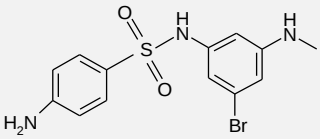
The third-order kappa shape index (3κ or κ_3) is given by

$$ {}^{3}K = (A-1)\,(A-3)^3 / ({}^{3}P)^2 \text{ If “A” is odd} $$

$$ {}^{3}K = (A-3)\,(A-2)^2 / ({}^{3}P)^2 \text{ If “A” is even} $$

TABLE 1: ARYL SULPHONAMIDES AS 5-HT$_6$ SEROTONIN LIGAND WITH THEIR EXPERIMENTAL pKi

S. no.	Structure	pKi	S. no.	Structure	pKi
1		9.22	2		8.16
3		8.88	4		8.58
5		8.16	6		8.55
7		8.22	8		9.09
9		8.74	10		10
11*		9.95	12*		9.52
13*		8.3	14		9
15*		8.39	16		8.92
17*		9.09	18		9
19		8.58	20		8.88

21*		8.05	22		7.49
23		8.01	24		7.32
25		8.69	26		9.2
27		7.2	28		7.07
29*		7.43	30*		7.56
31*		7.46	32		7.4
33		7.13	34		7.15
35*		7.3	36		7.3
37		7.39	38		7.42
39		7.3	40		7.69

*Test Set Compounds

RESULT AND DISCUSSION: QSAR models were generated to determine the effect of structural features of aryl sulphonamides on their 5-HT_6 antagonist activity. Forty derivatives of aryl sulphonamides are given in **Table 1** along with their observed activity in terms of pKi. The forty compounds were randomly divided into training set (thirty compounds) and a test set (ten compounds). The values of six descriptors of compounds, which have been calculated, are given in **Table 2.** For developing QSAR models multi-linear regression (MLR) analysis has been performed. Different

combinations of six descriptors were used in the MLR analysis. In the development of QSAR models six descriptors were taken as independent variables and pKi as the dependent variable of the training set (thirty compounds). The validity of QSAR model was judged by statistical parameters such as correlation coefficient, cross-validation coefficient, standard error *etc*.

TABLE 2: VALUES OF DESCRIPTORS AND EXPERIMENTAL pKi OF ARYL SULPHONAMIDES

Compound No.	$^0\chi$	$^1\chi$	$^2\chi$	κ_1	κ_2	κ_3	pKi
1	19.495	12.291	10.804	23.168	9.469	5.010	9.22
2	12.513	8.520	6.997	15.879	7.051	3.673	8.16
3	18.548	11.918	10.250	22.203	9.240	4.769	8.88
4	18.418	11.196	9.316	21.703	9.212	5.136	8.58
5	13.681	8.123	5.952	17.811	8.393	4.545	8.16
6	16.678	10.314	8.947	19.753	8.347	4.466	8.55
7	14.900	9.518	7.527	18.781	8.131	4.411	8.22
8	17.788	10.789	8.671	22.680	9.871	5.389	9.09
9	16.802	10.477	8.611	19.753	8.792	5.042	8.74
10	15.999	10.460	8.470	20.280	8.789	4.160	10.00
11*	15.717	9.854	8.609	18.781	7.709	4.411	9.95
12*	16.533	9.792	7.224	21.240	9.871	4.855	9.52
13*	17.178	10.564	8.834	20.727	9.000	5.299	8.30
14	14.270	9.275	8.013	16.844	6.857	3.753	9.00
15*	19.231	11.989	9.707	24.639	10.745	6.081	8.39
16	12.513	8.520	7.001	15.879	7.051	3.673	8.92
17*	22.116	14.274	12.876	25.641	10.045	5.086	9.09
18	19.064	11.463	9.806	21.703	9.212	5.331	9.00
19	13.013	8.725	7.194	16.844	7.266	3.753	8.58
20	18.646	12.250	10.026	23.168	9.868	5.507	8.88
21*	14.236	9.286	7.546	18.781	8.131	4.233	8.05
22	13.570	9.004	7.524	16.844	7.266	3.753	7.49
23	16.126	10.475	8.928	19.322	7.788	3.806	8.01
24	12.400	7.552	5.813	17.355	7.513	4.488	7.32
25	17.749	10.850	9.164	20.727	9.000	5.299	8.69
26	17.404	10.627	8.943	21.703	9.212	5.538	9.20
27	13.013	8.770	6.888	16.844	7.713	4.521	7.20
28	13.013	8.770	6.885	16.844	7.713	4.521	7.07
29*	10.729	7.219	5.949	14.410	6.438	3.526	7.43
30*	13.014	7.581	5.615	17.811	8.393	4.759	7.56
31*	13.022	8.203	7.463	17.355	7.051	5.606	7.46
32	13.681	8.123	5.952	17.811	8.393	4.545	7.40
33	12.522	7.953	7.575	16.372	6.406	4.496	7.13
34	11.229	7.469	5.840	15.390	7.136	4.500	7.15
35*	13.347	7.925	6.440	18.340	7.713	4.997	7.30
36	10.729	7.219	5.952	14.410	6.438	3.526	7.30
37	14.054	8.485	6.720	19.326	8.393	5.500	7.39
38	11.229	7.469	5.837	15.390	7.136	4.500	7.42
39	12.994	7.919	6.483	16.372	6.840	4.496	7.30
40	13.124	8.049	6.751	16.372	6.840	4.496	7.69

*Test Set Compounds

Where; $^0\chi$ = Valence connectivity index (order-0), $^1\chi$ = Valence connectivity index (order-1), $^2\chi$ = Valence connectivity index (order-2), κ_1 = Shape index (order-1), κ_2 = Shape index (order-2), κ_3 = Shape index (order-3).

From MLR analysis a QSAR model with good predictive power was obtained by using only one descriptor. It means the activity of 5-HT_6 serotonin ligand can be predicted by a mono-parametric regression equation using descriptor valence connectivity index (order-0). This QSAR model is given by following regression equation.

$$PA1 = 0.199639 \times {}^0\chi + 5.03626$$

$r^2 = 0.81227$, $rCV^2 = 0.765826$, Std. Error = 0.0909, P Value = 0,

r^2_{test}= 0.676373, $N_{training\ set}$ = 30, $N_{test\ set}$ = 10, VC = 1

In the above regression equation, r^2 is the correlation coefficient, rCV^2 is the cross-validation coefficient, Std. Error is the standard error, $N_{training\ set}$ is the number of compounds of the training set used to develop QSAR model, $N_{test\ set}$is the number of compounds of test set and VC is variable count. In the above regression equation, the value of r^2 is sufficiently higher than 0.5 which is the essential condition for the validity of a QSAR model. From the higher correlation coefficient (r^2) and cross-validation coefficient (rCV^2) for the above QSAR model, it is clear that the model has high predictive power. Also, the low standard error and P value for this regression support the predictive capacity of this QSAR model. External validation (r^2_{test}) for test set compounds also confirmed the predictive power. QSAR models with improved predictive power were obtained by combining two descriptors. The best bi-parametric QSAR model is obtained by using descriptors valence connectivity index (order-0) and shape index (order-3). This QSAR model is given by following regression equation.

$$PA2 = 0.224281 \times {}^0\chi - 0.189884 \times \kappa_3 + 5.55946$$

r^2 = 0.832759, rCV^2 = 0.73415, Std. Error = 0.0847, P Value = 0

r^2_{test}= 0.901906, $N_{trainingset}$ = 30, $N_{testset}$ = 10, VC = 2

From the higher values of correlation coefficient (r^2) and cross-validation coefficient (rCV^2) and lower standard error value and P value for the above QSAR model, it is clear that the model has higher predictive power. External validation (r^2_{test}) for test set compounds also confirmed the predictive power.

By the combination of three descriptors, QSAR models with more improved predictive power were obtained. The best QSAR model obtained using a combination of three descriptors is given by following the regression equation.

$$PA3 = 0.378442 \times {}^0\chi - 0.350304 \times \kappa_1 + 0.44247 \times \kappa_2 + 5.37878$$

r^2 = 0.874764, rCV^2 = 0.844204, Std. Error = 0.0715, P Value = 0

r^2_{test}= 0.737303, $N_{trainingset}$ = 30, $N_{test\ set}$ = 10, VC = 3

This QSAR model involves the valence connectivity index (order-0) as the first descriptor, the shape index (order-1) as second descriptor, and shape index (order-2) as third descriptor. The values of correlation coefficient (r^2), cross-validation coefficient (rCV^2) and other statistical parameters for the above QSAR model confirm that this QSAR model has excellent predictive power. External validation (r^2_{test}) for test set compounds also confirmed the predictive power.

The predicted activities obtained from the above three QSAR models for the training set and test set of compounds are listed in **Table 3** with their observed activity.

TABLE 3: EXPERIMENTAL AND PREDICTED ACTIVITIES (pKi) OF FORTY ARYL SULPHONAMIDES

S. no.	Observed Activity	Predicted Activity					
		PA1	Residual	PA2	Residual	PA3	Residual
1	9.22	8.928	0.292	8.981	0.239	8.830	0.390
2	8.16	7.534	0.626	7.668	0.492	7.672	0.488
3	8.88	8.739	0.141	8.814	0.066	8.709	0.171
4	8.58	8.713	-0.133	8.715	-0.135	8.822	-0.242
5	8.16	7.768	0.392	7.765	0.395	8.031	0.129
6	8.55	8.366	0.184	8.452	0.098	8.464	0.086
7	8.22	8.011	0.209	8.064	0.156	8.036	0.184
8	9.09	8.587	0.503	8.526	0.564	8.533	0.557
9	8.74	8.391	0.349	8.370	0.370	8.708	0.032
10	8.30	8.466	-0.166	8.406	-0.106	8.601	-0.301
11*	10.00	9.328	0.672	10.216	-0.216	9.369	0.631
12*	9.95	9.206	0.744	9.574	0.376	9.731	0.219
13*	9.52	9.560	-0.040	9.483	0.037	8.815	0.705
14	8.39	8.876	-0.486	8.718	-0.328	8.780	-0.390
15*	9.00	8.577	0.423	9.520	-0.520	9.214	-0.214

16	9.09	9.451	-0.361	9.554	-0.464	9.211	-0.121
17*	8.92	7.814	1.106	8.259	0.661	7.901	1.019
18	9.00	8.842	0.158	8.823	0.177	9.067	-0.067
19	8.88	8.759	0.121	8.696	0.184	8.686	0.194
20	8.05	7.878	0.172	7.949	0.101	7.785	0.265
21*	8.58	8.032	0.548	8.523	0.057	8.321	0.259
22	7.49	7.745	-0.255	7.890	-0.400	7.829	-0.339
23	8.01	8.256	-0.246	8.454	-0.444	8.159	-0.149
24	7.32	7.512	-0.192	7.488	-0.168	7.316	0.004
25	8.69	8.580	0.110	8.534	0.156	8.817	-0.127
26	7.43	7.178	0.252	7.296	0.134	7.240	0.190
27	7.56	7.634	-0.074	7.575	-0.015	7.778	-0.218
28	7.46	7.636	-0.176	7.416	0.044	7.347	0.113
29*	9.20	9.938	-0.738	9.039	0.161	10.096	-0.896
30*	7.20	8.032	-0.832	7.245	-0.045	7.814	-0.614
31*	7.07	8.032	-0.962	7.245	-0.175	7.814	-0.744
32	7.13	7.536	-0.406	7.514	-0.384	7.217	-0.087
33	7.15	7.278	-0.128	7.223	-0.073	7.395	-0.245
34	7.30	7.701	-0.401	7.604	-0.304	7.418	-0.118
35*	7.40	8.322	-0.922	7.735	-0.335	7.765	-0.365
36	7.30	7.178	0.122	7.296	0.004	7.24	0.060
37	7.39	7.842	-0.452	7.667	-0.277	7.641	-0.251
38	7.42	7.278	0.142	7.223	0.197	7.395	0.025
39	7.30	7.630	-0.330	7.620	-0.320	7.588	-0.288
40	7.69	7.656	0.034	7.649	0.041	7.637	0.053

*Test set compounds

CONCLUSION: From the above study, it is clear that the valence connectivity index (order-0) appears as an important descriptor for the QSAR study of aryl sulphonamides which gives a QSAR model with reliable predictive ability. The best combination of descriptors obtained for this study is the valence connectivity index (order-0), shape index (order-1), and shape index (order-2). This QSAR model can be used to find the activity of any new derivative of aryl sulphonamides. The best QSAR model obtained indicates the positive contribution of valence connectivity index (order-0) and shape index (order-2), whereas the negative contribution of shape index (order-1). The positive contribution of these descriptors shows that an increase in the values of these parameters increases the value of pKi whereas the negative contribution decreases the value of pKi.

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REFERENCES:

1. Berger M, Gray JA and Roth BL: The expanded biology of Serotonin: Annual Review of Medicine 2009; 60: 355-366.
2. Mohammad-Zadeh LF, Moses L and Gwaltney-Brant SM: Serotonin a Review: Journal of Veterinary Pharmacology and Therapeutics 2008; 31: 187-199.
3. Sodhi MSK and Sanders-Bush E: Serotonin and brain development: International Review of Neurobiology 2004; 59: 111-174.
4. Olivier B: Serotonin, a never ending story: European Journal of Pharmacology 2015; 753: 2-18.
5. Heisler LK, Chu HM, Brennan TJ, Danao JA, Bajwa P, Parsons LH and Tecott LH: Elevated anxiety and antidepressant- like responses in serotonin 5-HT1A receptor mutant mice: Proceedings of National Academy of Science 1998; 95: 15049-15054.
6. McCorvy JD and Roth BL: Structure and function of Serotonin G protein coupled receptors: Pharmacology and Therapeutics 2015; 150: 129-142.
7. Peroutka SJ: 5-Hydroxytriptamine receptors: Journal of Neurochemistry 1993; 60: 408-416.
8. Sarkar P, Kumar GA, Pal S and Chattopadhyay A: Biophysics of Serotonin and the Serotonin1a Receptor: Fluorescence and Dynamics. In Serotonin: The Mediator that Spans Evolution; Pilowsky, P., Ed.; Elsevier: Amsterdam, The Netherlands 2018; 3-22.
9. Sarkar P, Mozumder S, Bej A, Mukherjee S, Sengupta J and Chattopadhyay A: Structure, dynamics and lipid interactions of serotonin receptors: excitements and challenges: Biophysical Reviews 2021; 13: 101-122.
10. Fiorino F, Severino B, Magli E, Ciano A, Caliendo G, Santagada V, Frecentese F and Perissuti E: 5-HT1A receptor: an old target as a new attractive tool in drug discovery from central nervous system to cancer: Journal of Medicinal Chemistry 2014; 57: 4407-4426.
11. Hoyer D, Clarke DE, Fozard JR, Harting PR, Martin GR, Mylecharane EJ, Saxena PR and Humphrey PP: International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin): Pharmacological Reviews 1994; 46(2): 157-203.

12. Glennon RA: Higher end serotonin receptors: 5HT(5), 5HT(6) and 5HT(7): Journal of Medicinal Chemistry 2003; 46(14): 2795-2812.
13. Sebben M, Ansanay H, Bockaert J and Dumuis A: 5-HT6 receptors positively coupled to adenylyl cyclase in striatal neurons in culture: Neuroreport 1994; 5(18): 2553-57.
14. Holenz J, Pauwels PJ, Diaz JL, Merce R, Codony X and Buschmann H: Medicinal chemistry strategies to 5-HT(6) receptor ligands as potential cognitive enhancers and anti obesity agents: Drug Discovery Today 2006; 11(7-8): 283-99.
15. Davies S, Silvestre J and Guitart X: Drug discovery targets, 5HT6 receptor: Drugs Future 2005; 30(5): 479-95.
16. Fisas A, Codony X and Romero G: Chronic 5-HT6 receptor modulation by E-6837 induces hypophagia and sustained weight loss in diet induced obese rats: British Journal of Pharmacology 2006; 148(7): 973-83.
17. Roth BL, Craigo SC, Choudhary MS, Uluer A, Monsma FJ, Shen Y, Meltzer HY and Sibley DR: Binding of typical and atypical antipsychotic agents to 5-HT6 and 5-HT7 receptors: Journal of Pharmacology and Experimental Therapeutics 1994; 268(3): 1403-10.
18. Geldenhuys WJ and Van der Schyf CJ: Serotonin 5-HT6 receptor antagonists for the treatment of Alzheimer's desease: Current Topics in Medicinal Chemistry 2008; 8(12): 1035-48.
19. Reavill C and Rogers DC: The therapeutic potential of 5-HT6 receptor antagonists: Current Opinion in Investigational Drugs 2001; 2(1): 104-109.
20. Johnson CN, Ahmed M, Miller ND: 5-HT6 receptor antagonists, prospects for the treatment of cognitive disorders including dementia: Current Opinion in Drug Discovery and Development 2008; 11(5): 642-54.
21. Geldenhuys WJ and Van der Schyf CJ: The serotonin 5-HT6 receptor, a viable drug target for treating cognitive deficits in Alzheimer's disease: Expert Review of Neurotherapeutics 2009; 9(7): 1073-85.
22. Liu KG and Robichaud AJ: 5-HT6 antagonists as potential treatment for cognitive dysfunction: Journal of Drug Development Research 2009; 70: 145-68.
23. Kevin G and Albert L: 5-HT6 medicinal chemistry: International Review of Neurobiology 2010; 94: 1-34.
24. Velingkar VS and Chindhe AK: Ligand based pharmacophore generation and 3D-QSAR study of serotonin ligands using PHASE: Journal of Computational Methods in Molecular Design 2014; 4(3): 1-9.
25. Singh RK and Khan Mohd. Adil: Valence connectivity indices and shape indices based study of testosterone derivatives as SHBG ligand: Research Journal of Chemical Sciences 2013; 3(5): 47-56.
26. Singh D and Khan Mohd. Adil: Topological descriptor based study of testosterone derivatives: Journal of Chemical and Pharmaceutical Research 2011; 3(5): 1-14.
27. Verma V, Singh K, Kumar D and Narsimhan B: QSAR studies of antimicrobial activity of 1,3-disubstituted-1H-naphtho[1,2-e][1,3] oxazines using topological descriptors: Arabian Journal Of Chemistry 2017; 10(1): 747-756.
28. Rudrapal M and Chetia D: QSAR study of trioxane derivatives as antimalarial agents: Current Trends in Pharmaceutical Research 2016; 3(1): 1-17.
29. Sadr PF, Ebrahimi M, Nekoei M and Chahkandi B: QSAR study of novel indole derivatives in hepatitis treatment by stepwise-multiple linear regression and support vector machine: Archives in Pharmacy Practice 2020; 11(1): 27-37.
30. Yadav R and Nandi S: QSAR and anticancer drug design of β-Carboline compounds utilizing computed molecular descriptors: Journal of Computational Methods in Molecular Design 2014; 4(3): 92-105.
31. Fereidoonnezhad M, Faghih Z, Mojaddami A, Rezaei Z and Sakhteman A: A comparative QSAR analysis, molecular docking and PLIF studies of some N-arylphenyl-2, 2-dichloroacetamide analogues as anticancer agents: Iranian Journal of Pharmaceutical Research 2017; 16(3): 981-998.
32. Kohn W and Sham LJ: Self-consistent equations including exchange and correlation effects: Physical Review 1965; 140(4): 1133-1138.
33. Parr RG and Yang W: Density Functional Theory Of Atoms And Molecules. Oxford University Press 1994, ISBN 978-0-19-509276-9.
34. Becke AD: Perspective: Fifty years of density-functional theory in chemical physics: The Journal of Chemical Physics 2014; 140: 18A301.
35. Balaban AT: Graph theory and theoretical chemistry: Journal of Molecular Structure: THEOCHEM 1985; 120: 117-142.
36. Petitjean M: Applications of the radius-diameter diagram to the classification of topological and geometrical shapes of the chemical compounds. J of Chemical Informations and Computer Sciences 1992; 32(4): 331-337.
37. Kier LB: Shape indices of orders one and three from molecular graphs: Quantitative Structure-Activity Relationship 1986; 5(1): 1-7.
38. Kier LB: Indices of molecular shape from chemical graphs: Medicinal Research Reviews 1987; 7(4): 417-440.

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