Research Article

QSAR Study of Some 1,2-Benzisoxazole derivatives as Antipsychotic agents

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Abstract

Objective: The Quantitative structure-activity relationship (QSAR) analyses were carried out for a series of some 1,2-benzisoxazole derivatives to find out the structural requirements of their antipsychotic activities. **Materials and Methods**: Multiple linear regression (MLR) methodology coupled with various feature selection methods viz. stepwise (SW), genetic algorithm (GA) and simulated annealing (SA) were applied to develop QSAR models which were further validated for statistical significance and predictive ability by internal and external validation. **Results:** The statistically significant most excellent 2D QSAR model having correlation coefficient $r^2 = 0.7249$ and cross validated squared correlation coefficient $q^2 = 0.6941$with external predictive ability of pred_$r^2 = 0.6091$was developed by SW-PLS with the descriptors like SaaCHE-index, SssOE-index, T_T_S_7, T_N_O_3 and SsssCHcount. **Conclusions**: The results of the present study may be helpful for the designing potent analogues as antipsychotic agents.

***Keywords*:** QSAR, 1,2-benzisoxazole, antipsychotic agents, VLife MDS, MLR

Introduction

Psychoses is the mental disorder, with severe alteration of thought, behaviour, and capacity to identify reality and of awareness (delusions and hallucinations), affecting about 10% of world's population. All clinically effective antipsychotics (except Clozapine like) have effective post synaptic dopaminergic D2 receptor blocking action and antipsychotic strength has shown well connection with their capacity to bind with D2 receptor (Lemke *et al*., 2008). Blockade action of dopamine in corpus striatum is responsible for the extrapyramidal symptoms (EPS) which is associated with antipsychotic drugs. In addition to blockade of dopaminergic receptor, some antipsychotics drugs like resperidone and clozapine also block 5HT system, which helps to lessen EP reactions, those related to their usefulness in improving negative symptoms (Nielsen and Nielsen, 2009). Some of antipsychotic drugs such as chlorpromazine have various adverse drug reactions such as parkinsonism, muscular rigidity, excessive salivation and many of the metabolic disturbances such as gynaecomastia, galactorrhea and aggravation of diabetes. Since epilepsy is very often associated with CNS psychiatric disorders, the drugs with antipsychotic as well as antiepileptic activity will be more beneficial. Further a need for more effective and less toxic antipsychotic drugs still exists. 1,2-benzisoxazole derivatives have reported consistent advances in the design of novel antipsychotic as well as anticonvulsant agents (Strupczewski *et al.* 1995**,** Uno *et al.*, 1979**)**.

Computational chemistry has developed as an important contributor to rational drug design. The Quantitative Structure-Activity Relationship (QSAR) move toward pioneered by Hansch *et al.* (2001) that helps to connect with definite biological actions or physical properties of large compounds with the measured or computed molecular properties, in terms of descriptors. QSAR methodologies save assets and expedite the process of the development of new drug molecules. There have been many QSAR researches related to design of antipsychotic drugs so far but a systematic QSAR study is yet to be carried out for series of 1,2-benzisoxazole derivatives.

The aim of present work is to derive some statistically significant QSAR models for 1,2-benzisoxazole derivatives for their antipsychotic activity and to relate antipsychotic activity to its physicochemical properties. The results obtained may contribute to further

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designing novel antipsychotic agents.

Materials and Methods

Data set

A data set of forty nine molecules from reported series of compounds 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles for antipsychotic activities was taken for QSAR study (Strupczewski *et al*., 1995). Out of all these molecules, two molecules were discarded for which the precise data was not available (Table 1).

All 47 compounds were built on workspace of molecular modeling software VLife MDS 3.5 and then the structure was converted to three-dimensional space for further analysis. All these molecules were batch optimized for the reduction of energies using Merck molecular force field (MMFF) followed by considering distance-dependent dielectric constant of 1.0, convergence criterion or root-mean-square (RMS) gradient at 0.01 kcal/mol Å and the iteration limit to 10,000 (Halgren, 1996). The energy-minimized geometry was used for the calculation of the various 2D descriptors. The preprocessing of the independent variables (i.e., 2D descriptors) was done by removing invariable, which resulted in total 316 descriptors to be used for QSAR analysis. The sphere exclusion (SE) method (Golbraikh and Tropsha, 2003) was adopted for division of training and test data set comprising of 36 and 11 molecules, respectively, with dissimilarity value of 1.9 where the dissimilarity value gives the sphere exclusion radius. The unicolumn statistics of the training and test sets is reported in Table 2.

Feature selection and model development

Among several search algorithms, stepwise (SW) forward variable selection method (Darlington, 1990), genetic algorithms (GA) (Hasegawa, 1999) and simulated annealing (SA) (Zeng and Tropsha, 2000) based characteristic selection events are most popular for building QSAR models and can elucidate the situation more effectively.

To the selected equations, a cross-correlation limit was set at 0.5, the number of variables at 10, and the term selection criteria at q^2. An F value was specified to evaluate the significance of a variable. The variance cutoff was set at auto scaling in which the number of random iterations was set at 100.

Model quality and validation

The developed QSAR models were evaluated using the following statistical measures: r2 (the squared correlation coefficient), Fischer's value for statistical significance, q2 (correlation coefficient); pred_r2, r2 for external test set. The regression coefficient r2 is a relative measure of fit by the regression equation. It represents the deviation in the observed data that is explained by the regression. However, QSAR model is considered to be predictive, if the following conditions are satisfied: r2 > 0.6, q2 > 0.6 and pred_r2 > 0.5 (Golbraikh and Tropsha, 2002).

Internal validation was carried out using 'leave-one-out' (q2, LOO) method (Cramer, 1988). The cross-validated coefficient, q2, was calculated using the following equation:

$$q^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{mean})^2}$$

where yi, and ŷi are the actual and predicted activity of the ith molecule in the training set, respectively, and ymean is the average activity of all molecules.

However, a high q2 value does not necessarily give a suitable representation of the real predictive power of the model. So, an external validation was also carried out in the present study. The external predictive power of the model was assessed by predicting pIC50 value of the 9 test set molecules, which were not included in the QSAR model development. The predictive ability of the selected model was also confirmed by pred_r2.

$$\text{pred\_}r^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{mean})^2}$$

where yi, and ŷi are the actual and predicted activity of the ith molecule in the test set, respectively, and ymean is the average activity of all molecules in the training set.

Results and Discussion

The QSAR study of 47 1,2-benzisoxazole derivatives for antipsychotic activity (Table 1) through MLR, PLS methodology, based on various selected methods viz. SW, GA and SA using VLife MDS 3.5 software that resulted following significant models, taking consider the term selection criterion as r2, q2 and pred_r2.

A Uni-Column statistics for training set and test set were generated to check correctness of selection criteria for trainings and test set molecules (Table 2).

This observation showed that test set was interpolative and derived within the minimum–maximum range of training set. The mean and standard deviation of pIC50 values of sets of training and test provide insights to relative difference of mean and point density distribution of two sets. Some statistically significant 2D QSAR models were chosen for discussion (Table 3).

Model 1 (SW-PLS) (Best model)

pIC50 = - 0.0720 (SaaCHE-index) - 0.0413 (SssOE-index) - 0.7863 (T_T_S_7) - 0.3121 (T_N_O_3) - 0.2099 (SsssCHcount) + 8.3330

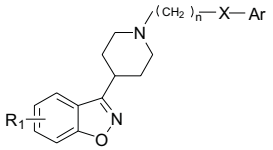
Model 2 (SW-MLR)

pIC50 = 0.3622 (T_T_N_7) + 0.3778 (T_2_F_1) - 0.6015 (SsssCHcount) + 0.2623 (OxygensCount) - 0.0774 (T_C_C_5) + 5.6277

Model 3 (SW-PCR)

pIC50 = 0.1066 (T_T_N_7) + 0.3488 (T_N_O_7) - 0.1437 (SaasCE-index) - 0.2716 (SssOcount) + 6.7358

Table 1. Structures and antipsychotic activities of substituted 1,2- benzisoxazole derivatives



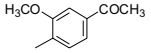
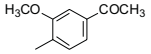
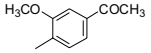
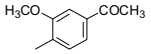
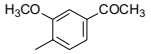
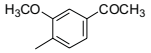
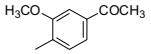
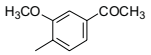
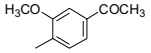
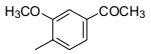
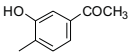
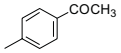
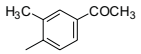
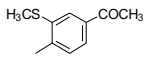
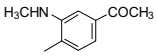
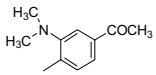
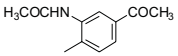
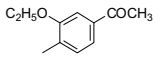
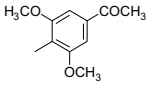
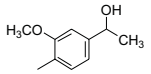
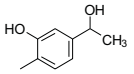
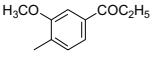
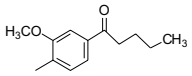
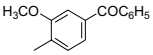
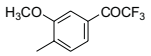
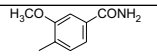
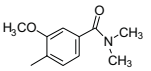
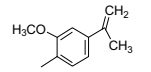
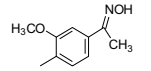
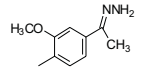
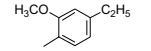
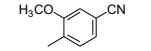
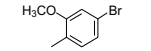
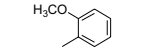
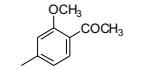
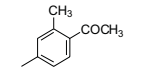
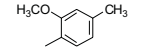
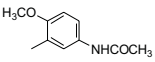
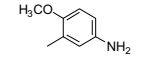
Compounds	R_1	N	X	Ar	IC_{50} (nM)[a]	pIC_{50} (M)[b]
37	H	2	O		969	6.014
38	H	3	O		168	6.775
39	H	4	O		66	7.18
40	6-Cl	2	O		940	6.027
41	6-Cl	3	O		111	6.955
42	6-Cl	4	O		110	6.959
43	5-F	3	O		455	6.342
44	6-F	2	O		427	6.37
45	6-F	3	O		110	6.959
46	6-F	4	O		23	7.638
47	6-F	3	O		8.6	8.066
48	6-F	3	O		16	7.796
49	6-F	3	O		66	7.18
50	6-F	3	O		295	6.53
51	6-F	3	O		250	6.602
52	6-F	3	O		116	6.936
53	6-F	3	O		107	6.971
54	6-F	3	O		127	6.896
55	6-F	3	O		45	7.347
56	6-F	3	O		727	6.138
57	6-F	3	O		>1000	-
58	6-F	3	O		135	6.87
59	6-F	3	O		242	6.616
60	6-F	3	O		460	6.337
61	6-F	3	O		169	6.772

Table 1. Continue

62	6-F	3	O		59	7.229
63	6-F	3	O		127	6.896
64	6-F	3	O		221	6.656
65	6-F	3	O		90	7.046
66	6-F	3	O		107	6.971
67	6-F	3	O		213	6.672
68	6-F	3	O		111	6.955
69	6-F	3	O		262	6.582
70	6-F	3	O		66	7.18
71	6-F	3	O		237	6.625
72	6-F	3	O		182	6.74
73	6-F	3	O		336	6.474
74	6-F	3	O		147	6.833
75	6-F	3	O		112	6.951
76	6-F	3	O		454	6.343
77	6-F	3	O		40	7.398
78	6-F	3	O		246	6.609
79	6-F	3	O		364	6.439
80	6-F	3	S		571	6.243
81	6-F	3	NH		58	7.237
82	6-F	1	CH_2		>1000	-
83	6-F	3	O		97	7.013
84	6-F	3	O		118	6.928
85				Risperidone	37.5	7.426

[a] *In-vitro* antipsychotic activity against Dopamine receptor (D_2)

[b] $pIC_{50}(M) = -\log IC_{50}(M)$

Table 2. Uni-Column statistics of the training and test sets of substituted 1,2-benzisoxazole derivatives in 2D-QSAR

Data Set	Sum	Average	Max	Min	Std Dev
Training	245.8590	6.8294	8.0660	6.0140	0.4260
Test	75.8630	6.8966	7.7960	6.3420	0.4832

Max., maximum; Min., minimum; Std Dev, standard deviation

Table 3. Statistical results of some 2D-QSAR models generated for 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazole derivative

S. No.	Statistical parameters	Model 1 (Best Model)	Model 2	Model 3
1	r^2	0.7249	0.7253	0.6294
2	q^2	0.6941	0.5941	0.6486
3	pred_r^2	0.6091	0.6530	0.5640
4	r^2_se	0.2327	0.2370	0.2619
5	q^2_se	0.2473	0.2866	0.2415
6	pred_r^2se	0.2669	0.2953	0.3015
7	*F* test	15.1903	20.6393	15.8332
8	*Z*score	5.70240	4.82294	3.10712
9	$n_{training}$	36	36	36

Table 4. Inter-correlation matrix between descriptors used in best 2D-QSAR model 1

	SaaCHE-index	*SssOE-index*	*T_T_S_7*	*T_N_O_3*	*SssCHcount*
SaaCHE-index	1				
SssOE-index	0.094	1			
T_T_S_7	-0.02	-0.239	1		
T_N_O_3	0.087	-0.26	-0.103	1	
SssCHcount	-0.05	0.174	-0.055	-0.127	1

The statistically best 2D-QSAR model (model 1, Eq. 3.9) using the SW-PLS method with r2 = 0.7249 was considered. The equation explains 72% (r2 = 0.72) of the total variance in the training set. It also has an internal (q2) and external (pred-r2) predictive ability of ~69% and ~61% respectively. The F-test = 15.19 shows the statistical significance of 99.99% of the model which means that probability of failure of the model is 1 in 10000.

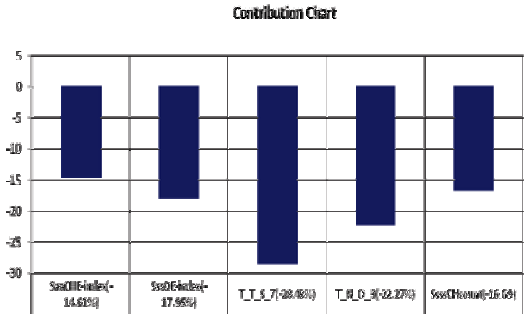


Figure 1. Contribution chart of descriptors used in Best 2D QSAR Model 1

The inter-correlation matrix between five descriptors with the biological activity for the best model 1 is given in Table 4 and contribution charts of models are shown in Figure 1.

The negative contribution of all above descriptors showed that decrease in the values of these descriptors would be beneficial for the antipsychotic activity of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazole derivatives. The residuals (difference between the actual and predicted activities) were found to be minimal and are presented in Table 5. Also the graphs for actual versus predicted activity for the series are shown in Figure 2 which shows good correlations.

Table 5. Comparative observed and predicted activities of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazole derivatives by 2D-QSAR models

Comd.	[a]Exp. pIC_{50} (M)	Model 1 (Best Model)		Model 2		Model 3	
		Pred. pIC_{50} (M)	[a]Res.	Pred. pIC_{50} (M)	[a]Res.	Pred. pIC_{50} (M)	[a]Res.
37	6.014	6.383	-0.37	6.339	-0.33	6.299	-0.28
38	6.775	6.693	0.082	6.546	0.228	6.748	0.027
39#	7.18	6.79	0.39	6.952	0.228	6.688	0.492
40	6.027	6.495	-0.47	6.339	-0.31	6.1	-0.07
41	6.955	6.806	0.149	6.546	0.408	6.549	0.406
42#	6.959	6.804	0.155	6.952	0.007	6.488	0.471
43#	6.342	6.755	-0.41	6.824	-0.48	6.83	-0.49
44	6.37	6.64	-0.27	6.717	-0.35	6.378	-0.01
45	6.959	6.95	0.009	6.924	0.034	6.825	0.134
46#	7.638	7.247	0.391	7.23	0.408	7.363	0.275
47	8.066	7.62	0.445	7.856	0.209	7.642	0.424
48#	7.796	7.427	0.369	7.532	0.264	7.288	0.508
49	7.18	7.144	0.036	6.739	0.441	6.644	0.537
50	6.53	6.33	0.201	6.662	-0.13	6.57	-0.04
51	6.602	6.839	-0.24	7.024	-0.42	6.792	-0.19
52#	6.936	6.827	0.108	6.792	0.143	6.4	0.536
53	6.971	6.873	0.098	7.132	-0.16	6.894	0.077
54	6.896	6.93	-0.03	6.77	0.127	6.816	0.081
55	7.347	6.958	0.388	7.317	0.03	6.988	0.359
56#	6.138	6.517	-0.38	6.323	-0.18	6.581	-0.44
58	6.87	6.94	-0.07	6.77	0.1	6.817	0.052
59	6.616	6.928	-0.31	6.537	0.079	6.81	-0.19
60	6.337	6.273	0.064	6.228	0.109	6.746	-0.41
61	6.772	7.11	-0.34	6.924	-0.15	7.125	-0.35
62	7.229	6.979	0.251	7.364	-0.13	6.985	0.244
63	6.896	6.945	-0.05	7.054	-0.16	6.943	-0.05
64	6.656	6.891	-0.24	6.585	0.071	6.718	-0.06
65	7.046	6.703	0.342	6.685	0.361	6.867	0.179
66	6.971	6.684	0.287	7.147	-0.18	7.395	-0.42
67	6.672	6.876	-0.2	6.662	0.01	6.674	-0
68	6.955	6.958	-0	7.102	-0.15	6.939	0.015
69	6.582	6.873	-0.29	6.817	-0.24	6.652	-0.07
70	7.18	6.772	0.408	6.817	0.364	6.86	0.32
71#	6.625	6.95	-0.32	6.639	-0.01	6.375	0.25
72#	6.74	7.143	-0.4	6.455	0.285	6.543	0.197
73#	6.474	6.535	-0.06	6.662	-0.19	6.67	-0.2
74	6.833	6.941	-0.11	7.209	-0.38	6.919	-0.09
75	6.951	6.94	0.011	7.179	-0.23	6.901	0.05
76#	6.343	6.424	-0.08	6.455	-0.11	6.7	-0.36
77	7.398	6.993	0.405	7.071	0.327	6.908	0.49
78	6.609	6.655	-0.05	6.917	-0.31	6.836	-0.23
79	6.439	6.834	-0.39	6.347	0.092	6.764	-0.32
80	6.243	6.345	-0.1	6.662	-0.42	6.725	-0.48
81	7.237	6.859	0.378	7.024	0.212	7.143	0.094
83	7.013	7.04	-0.03	6.77	0.244	6.63	0.384
84	6.928	6.996	-0.07	6.947	-0.02	6.937	-0.01
85	7.426	7.79	-0.36	7.254	0.172	7.603	-0.18

Conclusion

The present work shows about a set of compounds with antipsychotic activities of 1,2-benzisoxazoles treated

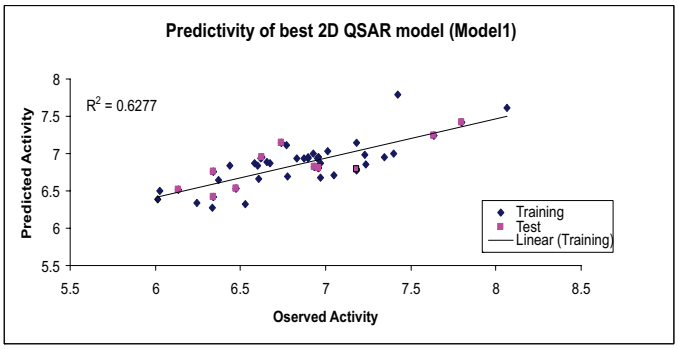


Figure 2. Graph between observed and predicted activities of compounds in selected series obtained by 2D-QSAR best model 1

statistically to uncover the molecular characteristics which are important to high activity. The developed models were analyzed and validated for their statistical significance and external prediction power. The awareness and understanding of the descriptors involved in the activity of these compounds could provide a great opportunity for the ligand structures design with appropriate features. These theories, by which these features affect the biological activity, by binding to the respective receptor target. The results derived may be useful in further designing more novel antipsychotic agents in series.

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