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QSAR and Docking Studies on 1,2-benzisoxazole Derivatives for Antipsychotic activity against Dopamine receptor (D2)

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ABSTRACT

With a view to the rational design of a series of selected 48 substituted benzisoxazoles, 3D-QSAR and docking studies have been performed for the prediction of antipsychotic activity. Overall model classification accuracy was 76.00% (q^2 = 0.7600, representing internal validation) in training set and 68.33% (Pred_r^2 = 0.6833, representing external validation) in test set using sphere exclusion and forward–backward as a method of data selection and variable selection, respectively. The docking studies suggest that compound 38 interact with GLU43, THR48, GLN79, GLN147, LEU148, ASN149, ASP150, SER151, ARG178, LYS270, LEU273, THR327, GLU43, GLN79, GLN147, ASN149, ASP150, SER151 and GLU43 amino acid residues. Both QSAR and docking study of such derivatives provide guidance for further lead optimization and designing of more potent antipsychotic agents.

Keywords: kNN-MFA, antipsychotic agents, QSAR, docking, benzisoxazole, narcoleptic.

1. INTRODUCTION

An antipsychotic (or narcoleptic) is a psychiatric medication primarily used to manage psychosis (including delusions or hallucinations, as well as disordered thought), particularly in schizophrenia and bipolar disorder, and is increasingly being used in the management of non-psychotic disorders. A first generation of antipsychotics, known as typical antipsychotics, was discovered in the 1950s. Most of the drugs in the second generation, known as atypical antipsychotics, have been developed more recently, although the first atypical antipsychotic, clozapine, was discovered in the 1950s and introduced clinically in the 1970s. Both generations of medication tend to block receptors in the brain's dopamine pathways, but antipsychotic drugs encompass a wide range of receptor targets[1, 2].

The important limitations of antipsychotic prescription are their critical side effects, such as extra-pyramidal symptoms (EPS), increased plasma prolactin levels and decreasing tardive dyskinesia (TD), which develop in about 70 % of patients[3].

Risperidone and olanzapine, two extremely potent antipsychotics, are included in empirical protocols for the treatment of psychosis with good tolerance in patients. They decrease the negative symptoms by acting on the serotonergic and noradrenergic receptors, while the positive symptoms are reduced by their effects on the dopaminergic pathway with lower side effects[4]. There is currently much interest in the development of new derivatives starting from these antipsychotics.

Unlike classical antipsychotics like haloperidol, which mainly block D2 receptors, clozapine and other atypical antipsychotics are relatively more potent at blocking 5-HT2A receptors than D2 receptors. This binding gave rise to the serotonin-dopamine hypothesis[5], suggesting that blockade of presynaptic 5-HT2A receptors by atypical antipsychotics is a predominant mechanism in the nigrostriatal, mesocortical, and tuberoinfundibular dopaminergic pathways where they increase dopamine release.

Structure activity relationship (QSAR) studies using the classical quantitative structure–activity relationship (2D-QSAR) and a few 3D-QSAR–CoMFA and/or 3D-comparative molecular similarity analysis (3D-CoMSIA) approaches have enhanced knowledge concerning the interactions of antipsychotics with different classes of membrane receptors[6,7].

The aim of this study is to develop predictive 3D-QSAR models and receptor interactions to observe which structural features are responsible for selective 5HT2A antagonism vs. D2 receptor binding.

2. MATERIALS AND METHODS

2.1 Selection of Data set

A data set of 48 molecules of reported series of compounds 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles for antipsychotic activities was taken for QSAR study[8]. Out of 48 molecules, 2 molecules were discarded for which the precise data was not available (Table 1). The biological activity values (IC50 (nM)) reported in literature were converted to their molar units and then further to negative logarithmic scale and subsequently used as the dependent variable for the QSAR analysis.

To the best of our knowledge, this series (Table 1) contains most potent 1,2-benzisoxazoles for antipsychotic activities so far and there is high structural diversity and a sufficient range of the antipsychotic activity in the selected series of these derivatives. It insists us to select this series of compounds for present QSAR studies.

2.2 Ligand Preparation for 3D-QSAR Analysis

The structure of (benzoisoxazol-3-yl)-piperidine was used as the template to build the molecules in the dataset on Vlife 3.5 software9 and their geometries were subsequently optimized by energy minimizations using Merck molecular force field (MMFF) and MMFF charge10 followed by considering distance-dependent dielectric constant of 1.0 and convergence criterion of 0.01 kcal/mol.

2.3 Molecular Alignment

The molecules of the dataset were aligned by template based method11, where a template structure is defined and used as a basis for alignment of a set of molecules and a reference molecule is chosen on which the other molecules of the dataset get aligned considering the chosen template. The most active molecule 47 was selected as a reference molecule for alignment and the alignment of all the molecules is shown in Fig.1.

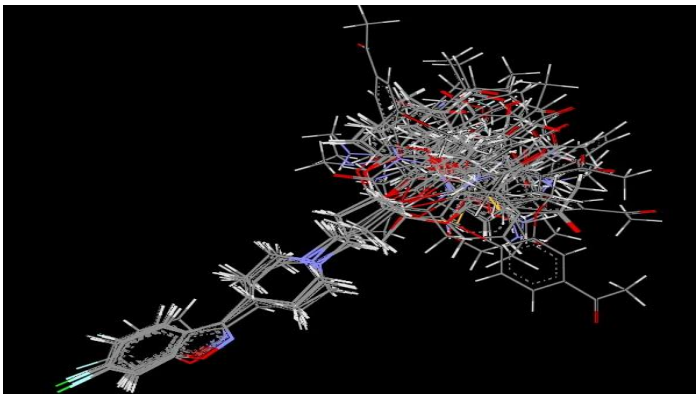

Fig. 1: Superposition of compounds in the training and test sets using the template-based alignment method

2.4 Calculation of Descriptors

The aligned biologically active conformations of 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles are used for the calculation of molecular fields. Molecular fields are the steric and electrostatic interaction energies which are used to formulate a relationship between steric and electrostatic properties together with the biological activities of compounds. Each conformation is taken in turn, and the molecular fields around it are calculated. This is done by generating 3D rectangular grids around the molecule and calculating the interaction energy between the molecule and probe group placed at each grid point. Steric and electrostatic fields are computed at each grid point considering Gasteiger-Marsili' charges12. Methyl probe of charge +1 with 10.0 kcal/mole electrostatic and 30.0 kcal/mole steric cut off were used for fields generation. A value of 1.0 is assigned to the distance-dependent dielectric constant. The software produces more than 6000 descriptors and prior to model development descriptors having zero values or same values are removed.

The sphere exclusion method13,14 was adopted for division of training and test set comprising of 35 and 11 molecules, respectively, with dissimilarity value of 9.0 where the dissimilarity value gives the sphere exclusion radius. Eleven compounds, namely, 40, 48, 61, 62, 65, 66, 68, 69, 70, 73 and 75 were used as

test set while the remaining molecules as the training set. The unicolumn statistics is shown in Table 2.

2.5 Model Development

A relationship between independent and dependent variables (3D fields and biological activities, respectively) was determined using kNN method14-16. The kNN methodology relies on a simple distance learning approach whereby an unknown member is classified according to the majority of its k-nearest neighbors in the training set.

The step-by-step search procedure begins by developing a trial model with a single independent variable and adds independent variables, one step at a time, examining the fit of the model at each step (using weighted kNN cross validation procedure). The method continues until there are no more significant variables remaining outside the model. Once the training and test sets are generating, kNN methodology is applied to the descriptors generated over the grid. The steric, electrostatic & hydrophobic energies are computed at the lattice points of the grid using a methyl probe of charge +1. These interaction energy values are considered for relationship generation and utilized as descriptors to decide the nearness between molecules.

kNN-MFA models were developed using the Forward Stepwise Variable Selection method with cross-correlation limit set of 1.0 and the term selection criteria as r2. F-test 'in' was set to 4.0. As some additional parameters, variance cutoff was set at 0.000 kcal/mol Å and scaling to none; additionally kNN parameter setting was done within the range of 2-5 and the prediction method was selected as the distance-based weighted average.

2.6 Model Quality and Validation

The developed QSAR models were evaluated using the following statistical measures: r2 (the squared correlation coefficient), F test (Fischer's value) for statistical significance, q2 (cross-validated 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 part of the variation in the observed data that is explained by the regression. However, a QSAR model is considered to be predictive, if the following conditions are satisfied: r2 > 0.6, q2 > 0.6 and pred_r2 > 0.517. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. The low standard error of Pred_r2se, q2_se and r2_se shows absolute quality of fitness of the model.

Internal validation was carried out using 'leave-one-out' (q2, LOO) method18. The cross-validated coefficient, q2, was calculated using the following equation:

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

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

However, a high q2 value does not necessarily give a suitable representation of the real predictive power of the model for antipsychotic ligands. 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 11 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.

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

where yi, and ýi i 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.

2.7 Molecular Docking

2.7.1 Retrieval of 3D Structure of Receptor and Ligands

For the docking study, co-crystallized structure of protein (PDB id 2HLB) with co-crystallized ligand GDP355A19 was taken from Protein Data Bank (www.pdb.org) and prepared by removing water molecules, cofactors and ligands present and addition of hydrogen atoms in the crystal structure of protein.

The cavities in the receptor were mapped to assign an appropriate active site, the basic feature used to map the cavities were the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics. Considering the dimensions and hydrophobic surface area, Cavity-1 was found to be the best void as an active site.

2.7.2 Docking Methodology

Piecewise linear pairwise potential (PLP)-based molecular docking of imidazopyradazine derivatives has been performed using the biopredicta module of VLife MDS 3.5, which involves the use of the PLP function summed over energy interactions between all pairs of protein and ligand atoms. The PLP function is

incorporated in the GRIP docking method that calculates the ligand–receptor binding affinity in terms of the PLP score. The PLP score is designed to enable flexible docking of ligands to perform a full conformational and positional search within a rigid binding site20,21.

All the optimized ligand were docked into active binding sites of protein 2HLB and co-crystallized ligand GDP355A was considered as the reference to define the active binding sites in the present investigation. A rotation angle of 30° was set so that ligand would be rotated inside the receptor cavity to generate different ligand poses inside the receptor cavity. After completion of the docking process, the minimum interaction energy between each ligand and 2HLB protein for the best ligand pose inside the receptor cavity was obtained as the PLP score.

3. RESULTS AND DISCUSSION

3.1 3D-QSAR Study

The kNN-MFA technique was used to derive 3D-QSAR model for 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazoles. The *in vitro* inhibitory activity (IC_{50} values) in μM, were converted to pIC_{50}, was used as dependant variable. Relative alignment of all the energy minimized molecules was then carried out by using template based technique for better results.

The training (35 compounds) and test sets (11 compounds) were selected using sphere exclusion method and the electrostatic and steric descriptors were selected using default settings. 3D-QSAR models were generated by kNN-MFA and MLR in conjunction with SA, GA & SW Forward-Backward selection methods[22,23]. From these models, two of them were having good q^2 & pred_r^2 values, one of which was selected having good internal and external predictivity (Table 3).

The q^2, pred_r^2, k value of kNN-MFA with SW, SA & GA were (0.6370, 0.6188, 4) (0.6136, 0.6020, 4) and (0.7600, 0.6833, 5) although there are no common descriptors among these three methods, GA kNN-MFA method have better q^2 (0.7600) and pred_r^2 (0.6833) than other two methods, model validation correctly predicts activity 86.7% and 73.9% for the training and test set respectively. It uses 2 steric (S_1775, S_1682) and 2 electrostatic (E_2276, E_1767) descriptors with 4 k-nearest neighbor to evaluate activity of new molecule hence, model generated by GA kNN-MFA is the best model. The points which contribute to the kNN-MFA models in best model (model C) are displayed in Fig. 2.

The green-coloured balls specify the positions of the steric descriptors and the descriptors with positive or negative coefficients show a region where bulky substituent is favored or disfavored, respectively. Electrostatic field descriptors (blue-coloured balls) with positive coefficients represent regions where electropositive (electron-withdrawing) groups are favorable, whereas negative coefficient indicates that electronegative (electron-rich or electron-donating) groups are favorable in this region[15].

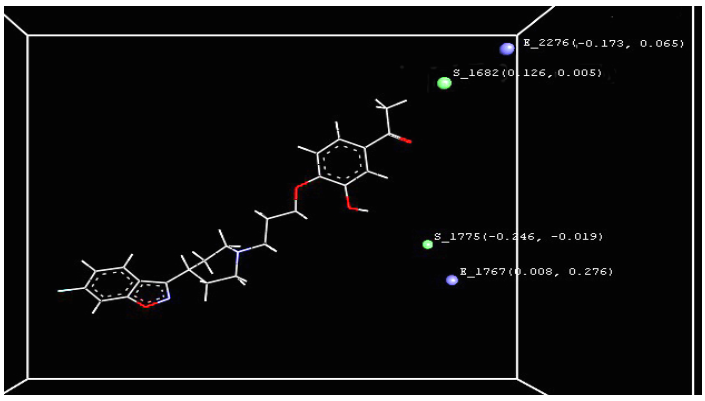

Fig. 2: Distribution of chosen points in the GA kNN-MFA method (Best Model C)

Negative values of electrostatic field descriptors (blue) indicates that negative electronic potential is required to increase activity and more electronegative substituent group is preferred in that position, positive range indicates that group that imparting positive electrostatic potential is favorable for activity so less electronegative group is preferred in that region.

Steric descriptors (green), negative range indicates that negative steric potential is favorable for activity and less bulky substituents group is preferred in that region, Positive value of steric descriptors reveals that positive steric potential is favorable for increase in activity and more bulky group is preferred in that region.

The calculated and predicted activities of the training and test set of compounds by selected models generated through all three methods are shown in Table 4. Graph between actual Vs predicted activities of the training and test set molecules of best 3D-QSAR model is shown in Fig. 3.

Good correlation between the activity predicted by the 3D-QSAR model and the observed biological activity (Table 4) indicates that each of the selected 3D descriptors has appropriate weightage in the selected QSAR equation representing the correlation of these descriptors with biological activity.

3.2 Molecular Docking Study

Docking study was performed on the high resolution crystal structures of enzymes (PDB: 2HLB) using Biopredicta module of VLife MDS 3.5 software to study the binding modes of quality and quantum interactions between differently substituted benzisoxazole derivatives with the target enzyme (PDB 2HLB). Table 5 shows PLP scores (Dock score) of 30 best docked ligands of selected series on receptor (2HLB).

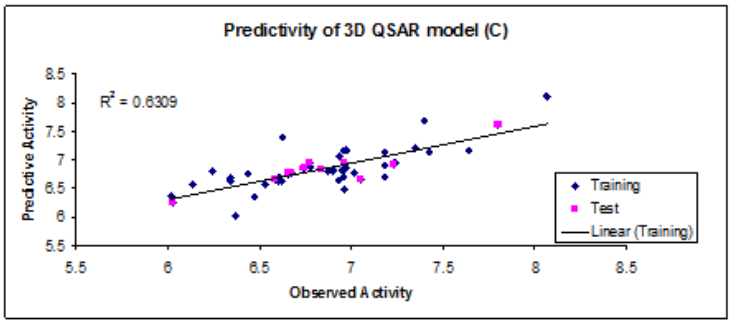

Fig. 3: Graph of actual vs predicted activities of the training and test set of selected series obtained by best 3D-QSAR model

The reliability of the docking results were first checked by comparing the best docking poses obtained for the co-crystallized inhibitors with its bound conformations. This was done by removing each co-crystallized ligands from their active site and subjecting again to docking into the binding pocket in the conformations found in the crystal structures. Comparison of docked complexes provides an insight into the activity patterns of various 3-(1-substituted-4-piperidinyl)-1,2-benzisoxazole derivatives in terms of hydrogen-bond (green dotted line), VDW interactions (purple dotted line), hydrophobic interactions (light blue dotted line) and ionic charge interaction. Figs. 4-5 represent the interaction patterns of a most docked compound 38 P7 and co-ligand GDP355A, respectively, with receptor for a clear understanding of prediction of binding site.

In the binding pocket of receptor 2HLB, co-crystallized ligand GDP 355A showed hydrogen bonding with GLU43A (1.882 Å), GLY45A (2.244 Å), LYS46A (2.083 Å), SER47A (2.178 Å), ARG178A (1.987 Å), ASN269A (2.563 Å), LYS270A (2.513 Å), ALA326A (2.137 Å) and best docked compound 38 P7 showed hydrogen bonding with GLN79A (2.522 Å) and interact with GLU43, THR48, GLN79, GLN147, LEU148, ASN149, ASP150, SER151, ARG178, LYS270, LEU273, THR327, GLU43, GLN79, GLN147, ASN149, ASP150, SER151, GLU43 amino acid residues.

In the docking study with protein (pdb: 2HLB), it was observed that compound 38 had higher PLPScore with one hydrogen bonding. A close comparison of the binding modes of benzoisoxazole derivatives and GDP 355A with receptor 2 HLB helped to understand at the molecular level, the strategy of fusing benzoisoxazole ring with the chalcone ring at hydroxylphenyl position to generate active compounds. Thus docking study suggests that chalcone moiety at hydroxylphenyl position provides medium bulky group to fit in hydrophobic pocket.

4. CONCLUSION

The present work reveals how the antipsychotic activities of various benzoisoxazole may be treated statistically to uncover the molecular characteristics which are essential for high activity. 3D-QSAR and docking studies have been carried out on a series of benzoisoxazole with antipsychotic activity against D2 receptor. Among various combinations, GA-based kNN method provides the best results in 3D-QSAR study. From the molecular docking studies, it is evident that the benzoisoxazole and chalcone rings play a crucial role for producing biological activity. Thus, the results obtained from QSAR study gives a hypothetical image to design new potent antipsychotic agents and these results should prove to be an essential guide for the future work.

5. ACKNOWLEDGMENTS

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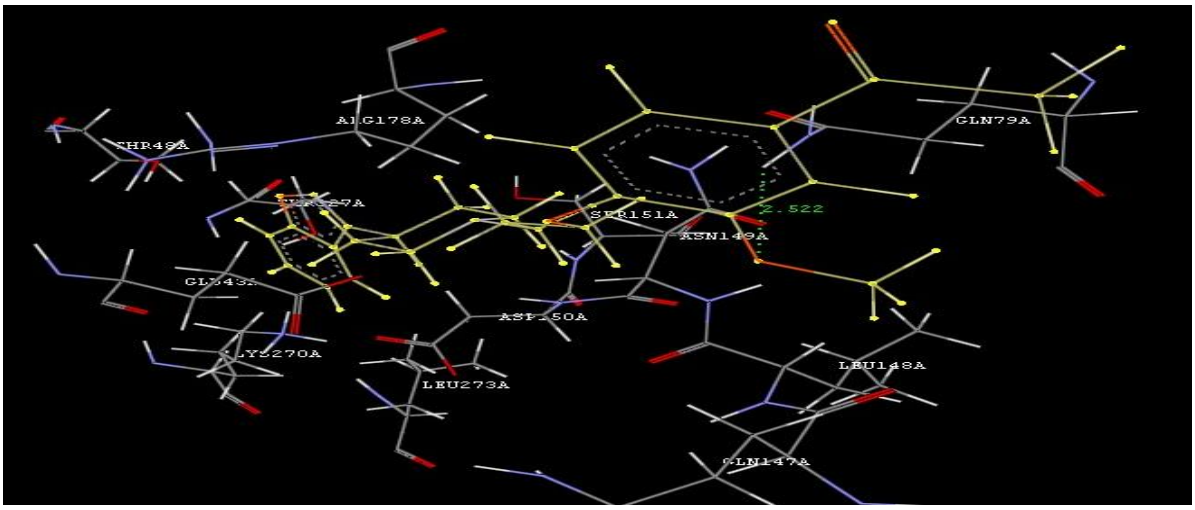


Fig. 4: Most active ligand 38 P7 bound with the active binding sites of receptor 2HLB; the bound ligand is represented as stick model (yellow color). The residue within 5Å of the inhibitor are displayed. Dotted line represents interactions

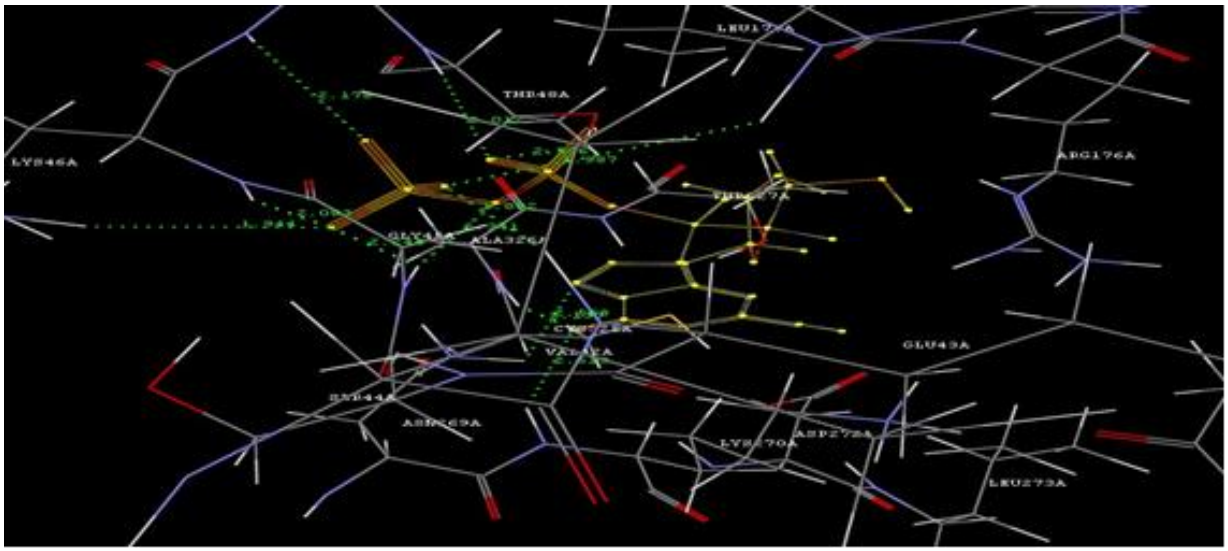
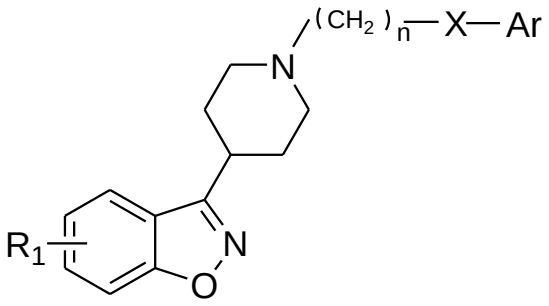
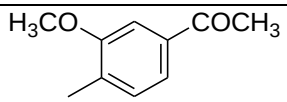
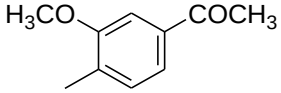
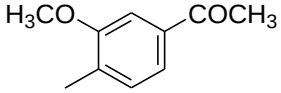
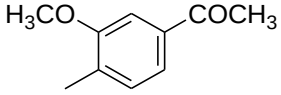
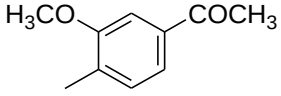
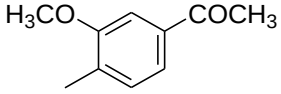
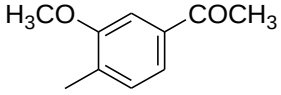
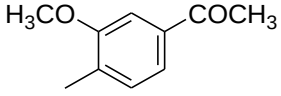
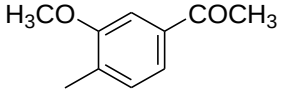
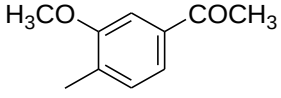
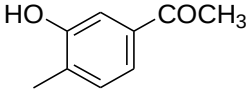
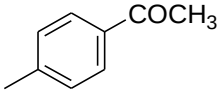
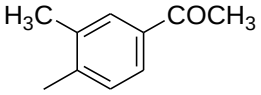
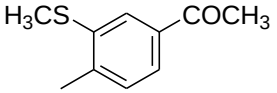
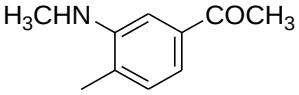
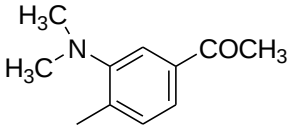
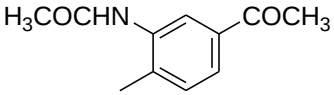
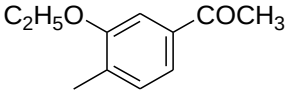
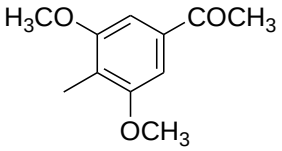
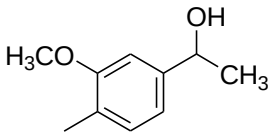
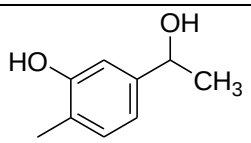
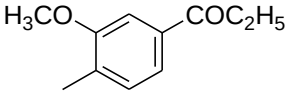
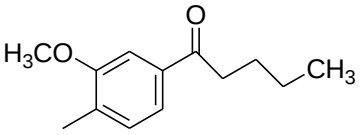
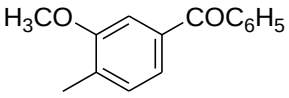
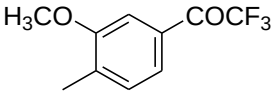
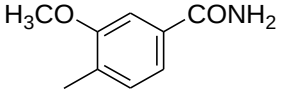


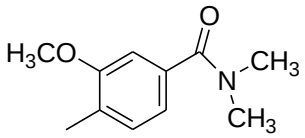
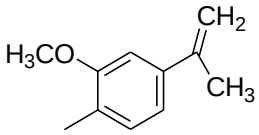
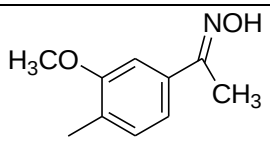
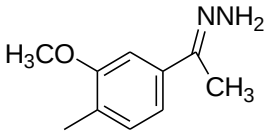
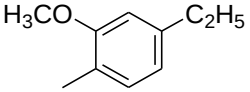
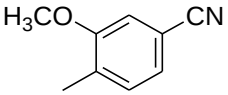
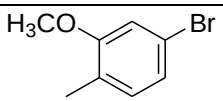
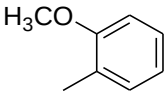
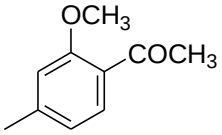
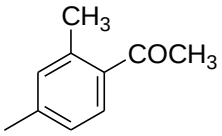
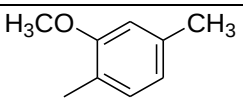
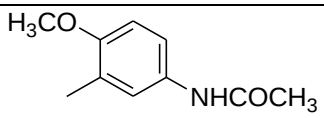
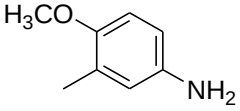
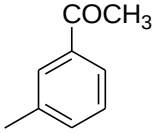
Fig. 5: Interaction of co-ligand GDP 355A with receptor 2HLB

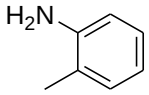
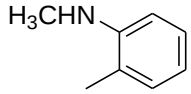
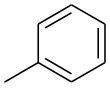
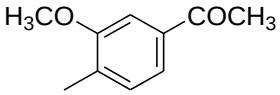
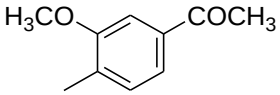
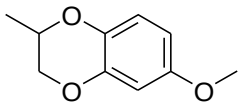
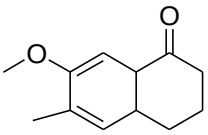
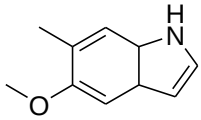
Table 1: Structures and antipsychotic activities of substituted1,2- benzisoxazole derivatives



Compd	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[c]	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[c]	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[c]	6-F	3	O		169	6.772
62[c]	6-F	3	O		59	7.229

63	6-F	3	O		127	6.896
64	6-F	3	O		221	6.656
65[c]	6-F	3	O		90	7.046
66[c]	6-F	3	O		107	6.971
67	6-F	3	O		213	6.672
68[c]	6-F	3	O		111	6.955
69[c]	6-F	3	O		262	6.582
70[c]	6-F	3	O		66	7.18
71	6-F	3	O		237	6.625
72	6-F	3	O		182	6.74
73[c]	6-F	3	O		336	6.474
74	6-F	3	O		147	6.833
75[c]	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)

[c]Indicates the compounds considered in the test set for 3D QSAR study.

Table 2: Unicolumn statistics of the training and test sets (3D-QSAR) of selected series of compounds for antipsychotic activity

Data Set	Average	Max.	Min.	SD	Sum
Training	6.8193	8.0660	6.0140	0.4339	245.4960
Test	6.9075	7.7960	6.0270	0.4563	75.9830

Max., maximum; Min., minimum; SD, standard deviation

Table 3: Model summary of 3D-QSAR models of selected series

kNN-MFA Method	Descriptors	Statistical Parameters
Model-A kNN- Stepwise (SW)	S_1656 (30.0000 30.0000) S_376 (-0.0038 -0.0037) S_1660 (0.1479 0.0109) S_1621(-0.2203 -0.0325) E_1777 (0.1952 0.8275)	k Nearest Neighbour= 4 n = 36 Df = 30 q^2 = 0.6370 q^2_se = 0.3041 $Predr^2$ = 0.6188 pred_r^2se = 0.3158
Model-B Simulated Annealing (SA)	E_1078 (-0.1208 0.2260) E_2129 (-0.0724 0.1221) S_1453 (-0.0034 -0.0027) E_1613 (0.0646 0.3705) S_1116 (-0.2522 -0.0105)	k Nearest Neighbour= 4 n = 36 Df = 30 q^2 = 0.6136 q^2_se = 0.2612 $Predr^2$ = 0.6020 pred_r^2se = 0.2638
Model-C (Best Model) kNN-Genetic Algorithm (GA)	E_2276 (-0.1733 0.0653) E_1767 (0.0082 0.2762) S_1775(-0.2462 -0.0190) S_1682 (0.1258 0.0052)	k Nearest Neighbour= 5 n = 36 Df = 31 q^2 = 0.7600 q^2_se = 0.2342 $Predr^2$ = 0.6833 pred_r^2se = 0.2504

Table 4: Comparison of predicted activities of compounds of selected series by various 3D-QSAR models

Comd.	*Exp. pIC_{50} (M)	Model A		Model B		Model C (Best model)	
		Pred. pIC_{50} (M)	[a]Res.	Pred. pIC_{50} (M)	[a]Res.	Pred. pIC_{50} (M)	[a]Res.
37	6.014	6.37	-0.36	6.405	-0.39	6.37	-0.36
38	6.775	7.026	-0.25	6.444	0.331	6.879	-0.1
39	7.18	6.9	0.28	6.959	0.222	7.127	0.054
40#	6.027	6.306	-0.28	6.481	-0.45	6.246	-0.22
41	6.955	6.448	0.507	6.422	0.533	6.48	0.475
42	6.959	6.958	9E-04	7.18	-0.22	7.157	-0.2
43	6.342	6.514	-0.17	6.656	-0.31	6.62	-0.28
44	6.37	6.014	0.355	6.185	0.184	6.014	0.355
45	6.959	6.62	0.339	6.496	0.463	6.703	0.256
46	7.638	7.129	0.51	7.27	0.369	7.169	0.469
47	8.066	7.539	0.527	7.879	0.187	8.12	-0.05
48#	7.796	7.455	0.341	7.963	-0.17	7.604	0.192
49	7.18	6.69	0.491	7.117	0.064	6.897	0.283
50	6.53	6.59	-0.06	6.773	-0.24	6.572	-0.04
51	6.602	6.86	-0.26	6.488	0.115	6.636	-0.03
52	6.936	7.108	-0.17	7.145	-0.21	7.063	-0.13
53	6.971	6.801	0.17	6.913	0.057	7.161	-0.19
54	6.896	6.642	0.254	6.899	-0	6.797	0.099
55	7.347	7.127	0.22	7.024	0.323	7.201	0.146
56	6.138	6.602	-0.46	6.529	-0.39	6.558	-0.42
58	6.87	6.496	0.374	6.817	0.053	6.791	0.079
59	6.616	6.841	-0.22	6.739	-0.12	6.638	-0.02
60	6.337	6.085	0.252	6.842	-0.5	6.674	-0.34
61#	6.772	6.562	0.21	6.804	-0.03	6.946	-0.17
62#	7.229	6.683	0.546	6.779	0.451	6.915	0.314
63	7.426	6.843	0.583	6.825	0.601	7.15	0.276
64	6.896	6.968	-0.07	6.835	0.061	6.836	0.061
65#	6.656	6.971	-0.32	7.04	-0.38	6.764	-0.11
66#	7.046	6.668	0.378	6.805	0.241	6.654	0.392
67	6.971	6.726	0.245	6.772	0.198	6.849	0.121
68#	6.672	6.913	-0.24	6.993	-0.32	6.771	-0.1
69#	6.955	6.566	0.389	6.709	0.245	6.942	0.013
70#	6.582	6.729	-0.15	6.707	-0.13	6.66	-0.08
71	7.18	7.082	0.098	6.984	0.197	6.702	0.479
72	6.625	6.99	-0.37	7.02	-0.39	7.397	-0.77
73#	6.74	6.831	-0.09	6.912	-0.17	6.852	-0.11
74	6.474	6.316	0.157	7.116	-0.64	6.361	0.112
75#	6.833	6.949	-0.12	6.895	-0.06	6.842	-0.01
76	6.951	6.664	0.287	6.938	0.012	6.809	0.141
77	6.343	6.79	-0.45	6.821	-0.48	6.693	-0.35
78	7.398	7.287	0.111	6.796	0.602	7.691	-0.29
79	6.609	6.827	-0.22	7	-0.39	6.697	-0.09
80	6.439	6.675	-0.24	6.824	-0.39	6.754	-0.31

81	6.243	6.58	-0.34	6.613	-0.37	6.803	-0.56
82	7.237	6.837	0.399	6.775	0.462	6.955	0.282
83	7.013	6.896	0.117	7.179	-0.17	6.769	0.244
84	6.928	6.994	-0.07	6.7	0.228	6.636	0.292
85	7.426	6.843	0.583	6.825	0.601	7.15	0.276

*Experimental antipsychoic activity (pIC_{50}) in molar concentration

[a]Res. = Exp. pIC_{50} – Pred. pIC_{50}

[#]Compounds belong to test set

Tables 5: PLP scores (Dock score) of 30 best docked ligand of selected series on receptor (2HLB)

S. No.	Ligand	PLP Score
1	38_ opt_P7	-75.352296
2	65_ opt_P24	-74.170063
3	50_ opt_P2	-67.834513
4	58_ opt_P16	-66.565509
5	38_ opt_P4	-62.437417
6	57_opt_P26	-61.002024
7	65_opt_P8	-60.020005
8	65_opt_P11	-59.962476
9	62_opt_P27	-59.910373
10	76_opt_P17	-58.575976
11	80_opt_P10	-54.017628
12	80_opt_P21	-53.601675
13	81_opt_P14	-53.291475
14	64_opt_P12	-53.016358
15	64_opt_P3	-52.906007
16	58_opt_P29	-52.782578
17	80_opt_P23	-51.771625
18	54_opt_P9	-51.605211
19	74_opt_P20	-51.326832
20	57_opt_P1	-48.210030
21	37_opt_P18	-47.642050
22	83_opt_P19	-47.456971
23	62_opt_P13	-47.279884
24	85_opt_P28	-47.222306
25	84_opt_P6	-45.980748
26	79_opt_P30	-45.677832
27	79_opt_P15	-45.622190
28	77_opt_P25	-45.504502
29	61_opt_P22	-45.448088
30	72_opt_P5	-44.310952
31	Co-ligand GDP355A	-14.389273

Minimum Score:

Molecule Name = 38_ opt_P7,

Score = -60.017179

Original Ligand Score = -14.389273

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