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Research Article

QSAR STUDY ON 2, 5-DISUBSTITUTED 1,3,4-OXADIAZOLES AS ANTIFUNGAL AGENTS

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ABSTRACT

QSAR study were performed on novel 2,5 disubstituted 1,3,4-oxadiazoles analogues. Stepwise multiple linear regression analysis was performed to derive QSAR models for better activity and lesser side effects. The best QSAR model was selected, having correlation coefficient (r) = 0.91 and cross validated squared correlation coefficient (q2) = 0.70. The predictive ability of the selected model was also confirmed by leave one out cross validation. The QSAR model indicate that the thermodynamic descriptors (Molar refractivity) and principal moment inertia, play an important role for antifungal activities. The data obtained from this present quantitative structure activity relationship study may be useful in the design of more potent substituted oxadiazole derivatives as antifungal agents.

Keywords: Quantitative structure-activity relationship, Oxadiazole, Antifungal activity.

INTRODUCTION

There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant.[1]The increasing recognition and importance of fungal infections, the difficulties encountered in their treatment and the increase in resistance to antifungals have stimulated the search for therapeutic alternatives.[2] The conception that there exists a close relationship between bulk properties of compounds and their molecular structure is quite rooted in chemistry. Therefore, it is the basic tenet of chemistry to identify these assumed relationships between the molecular structure and physico-chemical properties and then to quantify them. QSAR approach is beneficial in developing new therapeutically active compounds. This method represents an attempt to correlate biological activities of compounds with structural or molecular descriptors including physico-chemical, electronic, geometrical, topological or thermodynamic parameters.[3-9] Only a few substances have been discovered that exert an inhibitory effect on the fungi pathogenic in man and most of these are relatively toxic.[10-12] The central objective of the study was to select a mathematical model which correlates the best inhibitory activity against *F.oxysporium*.

With the aim to obtain new potent antifungal agents, we performed QSAR studies on a series of 2-substituted phenyl-5-(1-(substituted piperidin-4-yl)-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives. The objective of QSAR study is to develop a relationship between the structure of a set of compounds and the biological activity (BA) of interest.[13]

The relationship can be defined as

BA = f (molecular structure) = f (descriptors)

The ultimate objective of QSAR is prediction of either hypothesis on the mechanism of action for new analogs with high potency[14]. The nature of descriptors used and the extent to which they encode the structural feature of the molecules that are related to biological activity of drugs, depend on the types and magnitude

of reaction between the receptor and drug molecules.

The descriptors may be physicochemical parameters (hydrophobic, steric or electronic), structural descriptors, topological indices geometric parameters (calculated from quantum mechanical method[15]) and are the determining factors regulating the interactions[16].

A QSAR enables the investigators to establish a reliable quantitative structure-activity and structure-property relationship to derive an *in-silico* QSAR model to predict the activity of novel molecules prior to their synthesis. The overall process of QSAR model development can be divided into three stages namely, the data preparation, data analysis, and model validation, representing a standard practice of any QSAR modeling. In this research, an attempt has been made to describe and deduce a correlation between structure and antifungal activity of substituted 2-substituted phenyl-5-(1-(substituted piperidin-4-yl)-1H-1,2,3–triazol-4–yl)-1,3,4-oxadiazole derivatives.

MATERIALS AND METHODS

A set of 17 substituted 2-substituted phenyl-5-(1-(substituted piperidin-4-yl)-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives exhibiting potent antifungal activity was taken from the reported work of Shinde D. B *et al*.[17] The biological activity was converted to -log (biological activity) to decrease the variance and to convert the data into free energy changes related value used as the response variable for the QSAR analysis. The -log values of MIC along with the structure of compounds in the series are presented in **Table 1**.

All the computations in the present study were performed on PIV workstation. The molecular structures of the training set were sketched using Chem. Draw Ultra module of CS Chem. Office 2004 molecular modeling software ver. 6.0[18], supplied by Cambridge Software Company. The sketched structures were exported to Chem3D module in order to create its 3D model. Each model was “cleaned up” and energy minimization was performed using Allinger’s MM2 force field by fixing Root Mean Square Gradient (RMS) to 0.1 Kcal/mol Aº. Further geometry optimization was done using semiemperical AM1 (Austin Model) Hamiltonian method, closed shell restricted wave function available in the MOPAC module until the RMS value becomes smaller than 0.001 Kcal/mol Aº.

The low energy conformers obtained from the aforementioned procedure were used for the calculation of the ChemSAR descriptors. The ChemSAR descriptors include physicochemical, thermodynamic, electronic and spatial descriptors available in the ‘Analyze’ option of the Chem3D package (**Table 2**). The descriptors calculated for the present study accounts four important properties of the molecules: physicochemical, thermodynamic, electronic and steric, as they represent the possible molecular interactions between the receptor and indole (value of only those descriptors occurring in different equation is given in **Table 3**).

To establish the correlation between physicochemical parameters as independent variable and antifungal activity as dependent variable, the data were transferred to statistical program VALSTAT.[19] Sequential multiple linear regression analysis method (in sequential multiple regression, the program searches for all permutations and combinations sequentially for the data set) was applied for the same. The best model was selected on the basis of statistical parameters viz., observed squared correlation coefficient (r^2), standard error of estimate (s), and sequential Fischer test (F). Z score (absolute difference between values of model and activity field, divided by the square root of mean square error of data set) was taken as a measure of outlier detection. To assess the self-consistency of derived models, they were validated using leave one out (LOO) and the predictive ability was checked using cross-validated squared correlation coefficient (r^2_{cv} or q^2), bootstrapping squared correlation coefficient (r^2_{bs}), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation), and outliers (on the basis of Z-score value). The ±data within parentheses are the standard deviation, associated with the coefficient of descriptors in regression equations. Each of the statistical parameters mentioned above were used for assessing the statistical significance of QSAR.

The generated QSAR models were validated for predictive ability inside the model (leave one out method) by using VALSTAT. The statistical program which is tailored specifically for QSAR statistics estimates the predictive potential of model by calculating the validation parameters squared cross-correlation coefficient (q^2), standard deviation of sum of square of difference between predicted and observed values (S_{PRESS}) and standard deviation of error of prediction (S_{DEP}).

RESULTS AND DISCUSSION

Biological activity data and various physicochemical parameters were taken as dependent and independent variables, respectively and correlation's were established using sequential multiple regression analysis.

Among the many correlations generated, two best quadratic and triparametric models were selected on the basis of statistical significance. The best models obtained are given below along with their statistical measures.

Model-I:

BA = 5.617(± 0.854)-0.00406(± 0.00159) MR+0.00014(± 3.955) PMIY -0.03714(± 0.0373) DM

n=17, r=0.912, r^2=0.833, STD=0.09, F=21.5806

Model-II:

BA= 5.041(± 0.663)-0.0055(±0.002) CAA +0.00013(±3.829) PMI-0.0304(±0.0385) DM

n=17, r=0.909, r^2=0.826, STD=0.1, F=20.5985

Model–I show good correlation (r = 0.912) between descriptors (MR, PMIY, DM) and the biological activity. Molar refractivity, thermodynamic descriptors is a corrected from of the molar volume, it reflects the effect of size, polarizability and steric bulk of molecules, as indicate in model-I, suggesting that MR plays a significant role towards the expressed biological activities, which is probably due to steric interaction occurring in the polar spaces. It has generally been assumed that a negative coefficient with an MR term in a correlation equation suggests the conformational are detrimental. Such; however, if the binding could produce a concomitant conformational change in a macromolecular binding site, a positive coefficient could result for the MR term. Moment of inertia is a steric parameter. The value of PMI depends on the total mass of the molecule, the distribution within the molecule and position of axis rotation of the molecule. Principal moment of inertia (PMI-Y) is a spatial descriptor which explains the significance of orientation and conformational rigidity of biological activity. The positive coefficient of PMI-Y suggests the presence of less bulky substituents oriented towards Z-axis of the molecule will give better activity. Dipole moment indicates the strength and orientation behavior of a molecule in an electrostatic field. It is a vector quantity with both additive and constitutive properties. The contribution of dipole moment illustrates the non–covalent, electronic interactions between the microtubule enzymes and inhibitor molecules. Thus, model-I suggests that molar refractivity is of significance having high value of t-test indicating statistical significance of calculated regression coefficient.[20,21]

To confirm these results, the value of -Log MIC was estimated using leave one-out and correlated with observed value of -Log MIC. The value of r^2_{bs}, chance and q^2 in randomized biological activity indicates the statistical significance of the model as given below.

r^2_{bs} = 0.846, Chance = < 0.001, q^2 = 0. 724, S_{PRESS} = 0. 140, S_{DEP} = 0. 123

The predicted activity data of model-I is shown in **Table 4**. A plot of observed versus predicted -Log MIC for antifungal activity using model-I is shown in **Figure 1**.

Model-II shows good correlation (r =0.909) between descriptor (CAA, PMI-Y, D) and the biological activity. Connolly's solvent accessible area, a steric descriptor, represents the surface area that is in contact with the solvent. The descriptor bears negative coefficient in the model, suggesting increase in the bulkiness of the substituents and molecular solvent accessible surface area is not conducive to the activity. The descriptor Ovality in the second model bears a negative coefficient thereby it represent the steric hindrance associated with the bulk of the substituents. The observation only reaffirms the conclusion drawn from the descriptor CAA in the model II. The positive coefficient of PMI-Y suggests the presence of less bulky substituents oriented towards Z-axis of the molecule will give better activity. The dipole moment (D) shows positive contribution as explained in Model I. [20, 21]

To confirm these results, the value of -Log MIC was estimated using leave one-out and correlated with observed value of -Log MIC. The value of r^2_{bs}, chance and q^2 in randomized biological activity indicates the statistical significance of the model as follows.

r^2_{bs} = 0.837, Chance= 0.001, q^2 = 0.620, S_{PRESS} = 0.139, S_{DEP} = 0.121

The predicted activity data of model-II is shown in **Table 5**. A plot of observed versus predicted -Log MIC for antifungal activity using model-II is shown in **Figure 2**.

Although the intercorrelation between the two descriptors is within the acceptable range (< 0.8).

Comparison of model-I and model-II revels that model-I shows better correlation (r = 0.912) between descriptors and biological activity than model-II (0.909). The bootstrapping r^2 (r^2_{bs} = 0.846) results reflect the significance of the model-I when compared to model-II. The cross validate (q^2) values reflect predictive power of the model-I. Low standard error of estimation (<0.4) suggests a

high degree of confidence in the analysis. Moreover, the descriptors used to construct the model are not correlated with each other as suggested by their correlation matrix values, respectively (**Table 6** and **Table 7**). However, the model manifests moderate predictive potential as indicated by cross-validated correlation coefficient values.

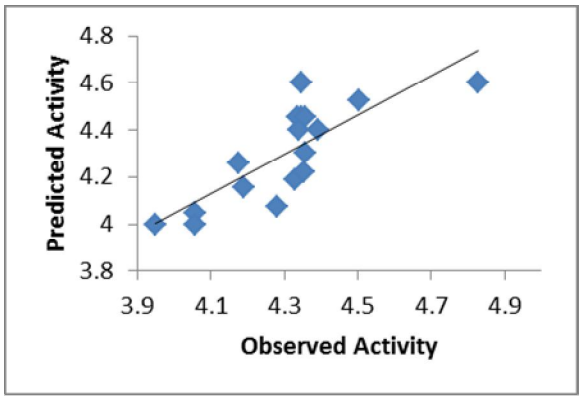

Fig. 1: Observed versus predicted (LOO) pIC50 for anti-fungal activity using model-I

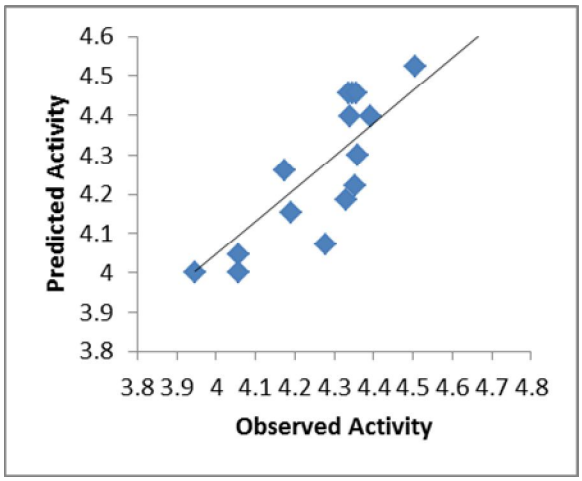

Fig. 2: Observed versus predicted (LOO) pIC50 for anti-fungal activity using model-II

CONCLUSION

QSAR analysis was performed on a series of antifungal 2-substituted phenyl-5-(1-(substituted piperidin-4-yl)-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives using molecular modeling program Chemoffice 2004. QSAR models were proposed for antifungal activity of the oxadiazole using ChemSAR descriptors employing sequential multiple regression analysis method. The selected models were checked for multicolinearity and autocorrelation. The predictive power of each model was estimated with bootstrapping r^2 method and leaves one out cross validation method. The result of the study suggests involvement of molar refractivity and dipole moment in antifungal activity of oxadiazole increases in molar volume responsible for antifungal activity. Thus, the discussed models could be explored further to design potent antifungal agents.

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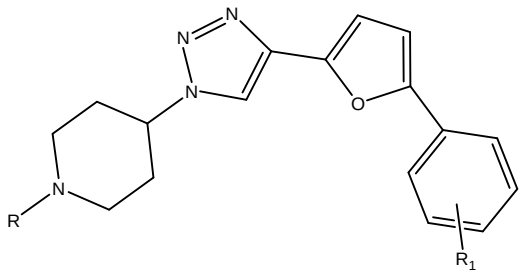
Table 1: **Antifungal Activity of Compounds 8a-8s against *F.Oxysporium.***



S. No.	R	R_1	Compound	-Log MIC
1	–H	–H	8b	4.071
2	$–CH_3$	–H	8c	4.155
3	$–CH_2CH_3$	–H	8d	4.259
4	$–SO_2CH_3$	–H	8e	4.398
5	$–COC_6H_5$	–H	8f	4
6	$–COC_6H_5$, 4 Cl	–H	8g	4.046
7	$–CH_3$	–Cl	8h	4.303
8	$–CH_2CH_3$	–Cl	8i	4.456
9	$–COCH_3$	–Cl	8j	4.523
10	$–SO_2CH_3$	–Cl	8k	4.602
11	$–CH_3$	–OH	8l	4.456
12	$–CH_2CH_3$	–OH	8m	4.456
13	$–SO_2CH_3$	–OH	8n	4.602
14	$–CH_3$	$–OCH_3$	8o	4.187
15	$–CH_2CH_3$	$–OCH_3$	8p	4.259
16	$–COCH_3$	$–CH_3$	8r	4.398
17	COC_6H_5	$–CH_3$	8s	4

Table 2: Descriptors Calculated For QSAR Study

Sr. No.	Descriptor	Type
1	Heat of Formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
7	Henry's Law Constant (HLC)	Thermodynamic
8	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
9	Log P	Thermodynamic
10	Melting Point (MP)	Thermodynamic
11	Molar Refractivity (MR)	Thermodynamic
12	Standard Gibbs Free Energy (SGFE)	Thermodynamic
13	Connolly Accessible Area (CAA)	Steric
14	Connolly Molecular Area (CMA)	Steric
15	Connolly Solvent–Excluded Volume (CSEV)	Steric
16	Ovality (OVA)	Steric
17	Principal Moment of Inertia – X (PMI–X)	Steric
18	Principal Moment of Inertia – Y (PMI–Y)	Steric
19	Principal Moment of Inertia – Z (PMI–Z)	Steric
20	Dipole Moment (D)	Electronic
21	Dipole Moment –X Axis (DX)	Electronic
22	Dipole Moment –Y Axis (DY)	Electronic
23	Dipole Moment –Y Axis (DZ)	Electronic
24	Electronic Energy (EE)	Electronic
25	HOMO Energy (HOMO)	Electronic
26	LUMO Energy (LUMO)	Electronic
27	Repulsion Energy (RE)	Electronic
28	Bend Energy (E_b)	Thermodynamic
29	Charge–Charge Energy (CCE)	Thermodynamic
30	Charge–Dipole Energy (CDE)	Thermodynamic
31	Dipole–Dipole Energy (DDE)	Thermodynamic
32	Non–1, 4 VDW Energy (E_v)	Thermodynamic
33	Stretch Energy (SE)	Thermodynamic
34	Stretch–Bend Energy (SBE)	Thermodynamic
35	Torsion Energy (E_t)	Thermodynamic
36	Total Energy (E)	Thermodynamic
37	Van der Waals e 1,4 Energy (VDWE)	Thermodynamic
38	VDW 1,4 Energy (VDWE)	Thermodynamic
39	Partition coefficient	Thermodynamic

Table 3: Calculated Descriptor Values For The Given Series Of Compounds

Comp. No.	MR	PMI-Y	DM	CAA
1	86.5887	6008.89	5.3948	546.509
2	91.8834	6865.25	5.3613	576.905
3	96.6314	7765.31	5.3527	605.912
4	99.9017	10442.4	9.7872	631.065
5	116.327	8170.56	7.9036	671.931
6	121.132	8312.34	8.0232	698.131
7	96.6882	8257.05	3.8774	601.181
8	101.436	9168.23	3.9609	629.196
9	100.959	10220.5	6.5412	634.001
10	104.707	13825	7.087	648.625
11	93.5775	8039.41	5.901	585.456
12	98.3255	9016.98	5.924	614.518
13	101.596	11816.5	8.4127	630.004
14	98.3466	9097.11	5.4274	624.977
15	103.095	10204.8	4.8725	653.325
16	101.196	9895.34	8.3111	641.885
17	121.369	9620	8.1002	698.067

Table 4: Predicted Activity Data of Model-I

S. No.	Observed –Log MIC	Predicted –Log MIC	Calculated –Log MIC
1	4.071	4.280	4.186
2	4.155	4.191	4.183
3	4.260	4.175	4.185
4	4.398	4.391	4.392
5	4	3.948	3.965
6	4.046	4.057	4.054
7	4.301	4.359	4.352
8	4.456	4.347	4.359
9	4.523	4.505	4.509
10	4.602	4.829	4.709
11	4.456	4.336	4.354
12	4.456	4.356	4.369
13	4.602	4.347	4.479
14	4.187	4.329	4.318
15	4.222	4.354	4.332
16	4.398	4.341	4.036
17	4	4.056	4.346

Table 5: Predicted Activity Data of Model –II

S. No.	Observed –Log MIC	Predicted –Log MIC	Calculated –Log MIC
1	4.071	4.272	4.182
2	4.155	4.192	4.183
3	4.260	4.189	4.196
4	4.398	4.407	4.406
5	4	3.946	3.965
6	4.046	4.054	4.051
7	4.301	4.348	4.343
8	4.456	4.346	4.359
9	4.523	4.488	4.497
10	4.602	4.809	4.702
11	4.456	4.319	4.339
12	4.456	4.350	4.364
13	4.602	4.349	4.482
14	4.187	4.337	4.326
15	4.222	4.373	4.351
16	4.398	4.353	4.357
17	4	4.046	4.029

Table 6: Correlation Matrix for Parameters in Model-I

Parameters	MR	PMI-Y	DM
MR	1.000		
PMI-Y	0.601	1.000	
DM	0.441	0.582	1.000

Table 7: Correlation Matrix for Parameters in Model II

Parameters	CAA	PMI-Y	DM
CAA	1.000		
PMI-Y	0.535	1.000	
DM	0.456	0.582	1.000

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