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QSAR analysis of substituted phenyl-piperazine analogs as Histamine H1-receptor antagonists

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ABSTRACT

QSAR (Quantitative Structure Activity Relationship) studies were carried out on a set of 26 chalcone, pyrimidine and pyrazole substituted phenyl-piperazines as potent histamine H1-receptor antagonists using multiple regression procedure. The activity contributions of these compounds were determined from regression equation and the validation procedures such as external set cross-validation r^2, ($R^2_{cv,ext}$) and the regression of observed activities against predicted activities and vice versa for validation set were described to analyze the predictive ability of the QSAR model. An accurate and reliable QSAR model involving five descriptors was chosen based on the FIT Kubinyi function which defines the statistical quality of the model. Applicability domain of QSAR model such as training and test set leverages, y-randomization were reported.

Key Words: phenyl-piperazine, QSAR, multiple regression, H1 antagonists.

INTRODUCTION

Heterocyclic systems are one of the most important classes of organic compounds present in nature or synthesized in laboratory. These compounds are known to possess an array of biological activities and are employed in the treatment of commonly occurring diseases. This has been the backbone for medicinal chemists to keep perpetuating interest to synthesize some novel derivatives of possible high biological activity.

Literature survey revealed that chalcones, pyrimidines and pyrazolines possess a broad spectrum of biological activities like, antibacterial [1], anti-inflammatory [2-3], antimalarial [4], antihistamine [5], antitubercular [6], anticancer [7-9] etc. The above classes of compounds are used extensively to elicit varied pharmacological responses. It has also been reported that substituted phenyl-piperazines possess antihistaminic [10-11], antioxidative [12], adrenolytic, hypotensive and CNS depressant activities [13]. As a part of our search for potent H1-receptor antagonists, a novel series of various chalcone, pyrimidine and pyrazole substituted phenyl-piperazines were synthesized [14-16] and considered for structure-activity relationship studies.

Structure activity relationship studies delineate the structural requirements for potency of inhibitors. QSAR studies have been investigated on the basis of the fact that the biological activity of the compound is a function of its physicochemical properties.

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From literature it was observed that several attempts were made to build QSAR models of various histamine H1-receptor antagonists such as benzimidazoles [17-18], thieno[2,3-d]pyrimidin-4(3H)-ones [19], 1,2,3,4-tetra hydronaphthalenes [20], pyrazinopyridoindoles [21] and thiazolidin-4-ones [22]. Moreover, none of the QSAR studies were reported on structures that covered two or more different kinds of ligands. Hence, a QSAR study on ligands with observable structure diversity, would lead to a more universal and robust QSAR model for designing novel histamine H1-receptor antagonists.

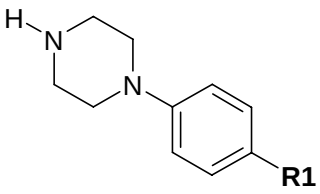
To address such powerful models covering different types of ligands, here, we report QSAR studies on 26 chalcone substituted phenyl-piperazines, pyrimidine and pyrazole substituted phenyl-piperazine compounds, respectively to investigate the influence of molecular structure on biological activity.

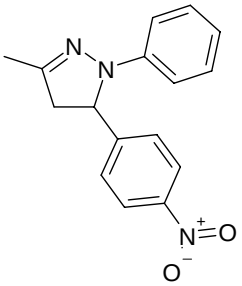
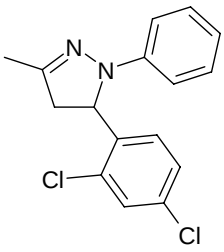
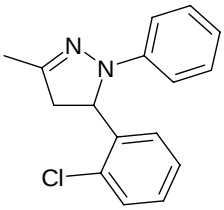
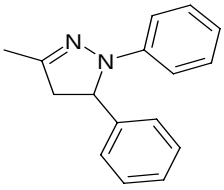
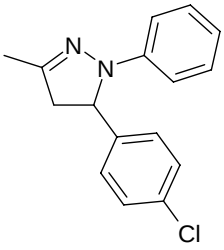
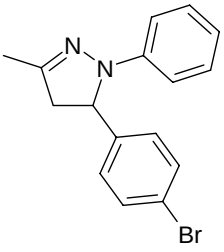
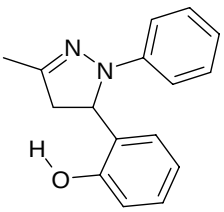
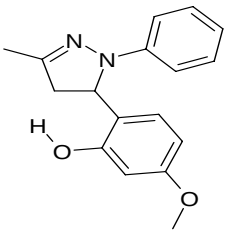
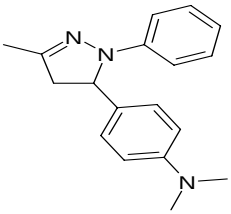
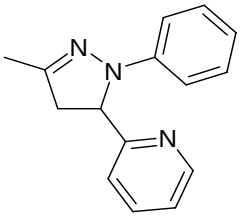
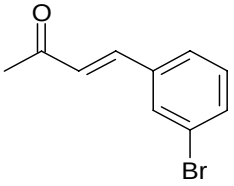
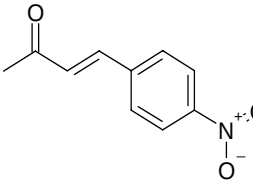
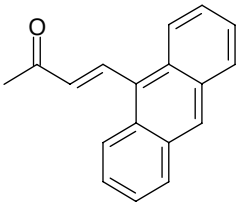
MATERIALS AND METHODS

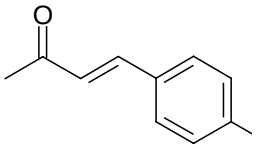
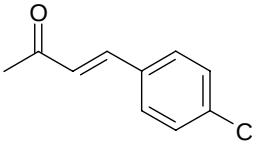
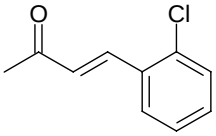
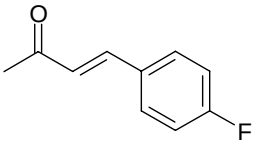
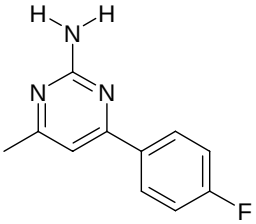
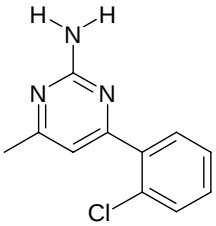
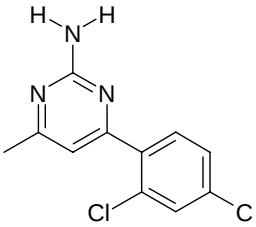
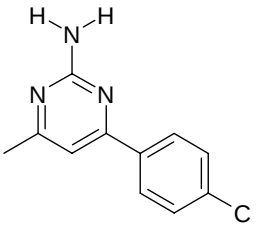
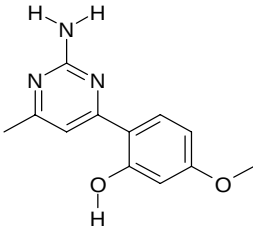
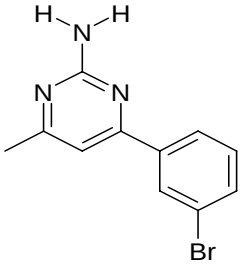
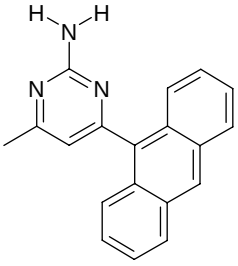
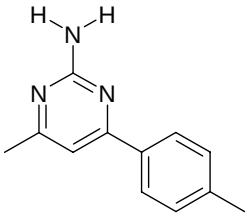
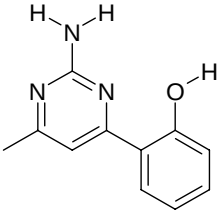
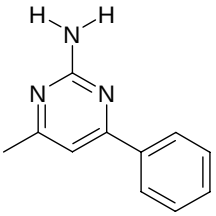
Data Set

The inhibiting activity data of a set of 26 compounds synthesized were utilized to obtain a reliable and robust QSAR model. The inhibitory activities of these derivatives reported in terms of percent inhibition and their structures along with bioactivities are given in Table 1. The structures were sketched using ISIS Draw 2.3 (www.mdli.com) software and the descriptors were calculated using Tsar 3.3 software (www.accelrys.com). Before the calculation of descriptors, three dimensional structures of all molecules were generated using Corina 3D package, charges were derived and the geometries optimized using cosmic module of Tsar.

Table 1: Structures and biological activities of compounds in the data set.



ID	R1	Ki (%)	log1/Ki
1		26.7	-1.427
2.		52.4	-1.719
3.		47.9	-1.680
4.		21.4	-1.330
5.		49.7	-1.696
6.		44.9	-1.652
7.		33.3	-1.522
8.		28.4	-1.453
9.		32.5	-1.512
10.		32.6	-1.513
11.		54.8	-1.739
12.		18.5	-1.267
13.		25.6	-1.408

14.		31.5	-1.498
15.		47.6	-1.678
16.		53.3	-1.727
17.		39.4	-1.595
18.		38.9	-1.590
19.		29.5	-1.470
20.		30.6	-1.486
21.		49.8	-1.697
22.		52.3	-1.719
23.		46.7	-1.669
24.		27.4	-1.438
25.		29.8	-1.474
26.		51.9	-1.715
27.		14.8	-1.170

Multivariate Regression Analysis

QSAR models were constructed on complete and training sets, respectively. Validation was done internally using leave-one-out (LOO) technique and externally by predicting the activities of validation set. The relationship between dependent variable (log1/Ki) and independent variables was established by linear multiple regression analysis using Tsar. Significant descriptors were chosen based on the statistical data of analysis. Statistical quality of the generated QSAR equation was judged based on the parameters like correlation coefficient (r), standard error of estimate (s), F-value, cross-validation r^2 (q^2) and predictive residual sum of squares (PRESS). Cross-validation was calculated using leave-one-out (LOO) technique over 5 random trials with F to leave and F to enter being 2 in F stepping to include the most significant variables in generating the QSAR model.

Cross-validation

Cross-validation is a popular technique used to test the reliability of QSAR models. In this study, leave-one-

out (LOO) technique was utilized to create a number of modified data sets by deleting the first row and its value predicted using the rest of the data. Likewise, each row is left in turn, so that the value of each row is predicted from all others. The model is judged based on these predictions.

Molecular Descriptors

Thirty molecular descriptors were selected for the study which includes topological, shape and connectivity indices, total dipole and lipole, molecular weight, h-bond donors, h-bond acceptors, logP and rotatable bond counts. A semi-empirical molecular orbital package was used to calculate thermodynamic property like heat of formation and electrostatic properties like HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) and Quadrupole components.

Predictive Ability of QSAR model

Predictive ability of the generated model was estimated externally by predicting the activities of validation set. This criterion may not be sufficient for a QSAR model to be truly predictive [23]. An additional condition for high predictive ability of QSAR model is based on external set cross-validation r^2, ($R^2_{cv,ext}$) and the regression of observed activities against predicted activities and vice versa for validation set, if the following conditions are satisfied [23-24].

$$R^2_{cv,ext} > 0.5 \quad (1)$$

$$R^2 > 0.6 \quad (2)$$

$$(R^2 - R_0^2) / R^2 < 0.1 \text{ or } (R^2 - R_0'^2) / R^2 < 0.1 \quad (3)$$

$$0.85 \leq k \leq 1.15 \text{ or } 0.85 \leq k' \leq 1.15 \quad (4)$$

Calculations relating to $R^2_{cv,ext}$, R_0^2 and the slopes, *k* and *k'* are based on regression of observed values against predicted values and vice versa.

Domain of Applicability

Applicability domain of a QSAR model must be defined if the model is to be used for screening new compounds. Predictive ability of the model may be considered reliable if the data set falls into this domain [24]. One simple approach is based on y-randomization and the calculation of leverages for compounds used in the study.

Y-randomization

This test ensures the robustness of a QSAR model [25] and to assess the multiple linear regression models obtained by descriptor selection [26]. In y-randomization test, the dependent variable or y-data is randomly shuffled and a new QSAR model is developed keeping X-data intact. The new models are expected to have low R^2 and Q^2 values, which determine the statistical significance of the original model. Moreover, if the model development includes F-stepping, then it is necessary to shuffle both dependent and independent variables to indicate that the original model is not because of chance correlation.

Leverage Test

Leverage values refers to the diagonal elements of the hat matrix $H = (X(X'X)^{-1}X')$. A given diagonal element ($h[_{ii}]$) represents the distance between the X value for the i^{th} observation and the means of all X values. Leverages measure the distance of an observation from the centre of a set of X observations [27]. A leverage value, $h_{ii,}$ greater than 3p/n is usually considered large (where p is the number of parameters in the model plus constant and n is the number of observations). If high leverage points fit the model well (i.e. have small residuals), they are called "good high leverage points" or good influence points. Such points stabilize the model and make it more precise. High leverage points, which do not fit the model (i.e. have large residuals) are called "bad high leverage points" or bad influence points [27].

RESULTS AND DISCUSSION

Multivariate regression analysis with F stepping (F to enter and F to leave being 2) and cross-validation by leaving-out-one row, to test the predictive power, resulted in LUMO, Molecular refractivity, Kappa3 index, H-bond donors and logP as the most significant descriptors. Equation 5 represents the linear QSAR model from a complete set of 26 inhibitors.

$$\begin{aligned}\log(1/Ki) = {} & +0.064 * \text{H-bond Acceptors} \\ & + 0.180 * \text{HOMO} \\ & - 0.014 * \text{Quadpole XZ} \\ & + 0.012 * \text{Quadpole YZ} \\ & - 0.597 * \text{KAlpha3} \\ & + 2.257\end{aligned}$$

$r = 0.849$, $r^2 = 0.721$, $q^2 = 0.631$, F = 10.356, n = 26, PRESS = 0.169, s = 0.092 (5)

Outlier detection

The data set was investigated for outliers, by calculating the standard residuals. Standardized residuals greater than 2 and less than -2 are usually considered large[27]. Outliers should be removed in order to obtain the best statistical result[28]. From Table 2, compound **20** has standardized residual -2.094 respectively and can safely be excluded from the data set.

Extent of extrapolation

Another criterion to detect outliers from data set was done by extrapolating the data using MedCalc software (www.medcalc.be). From the Figure 1, it is evident that all values lie within 95% prediction levels except compound 20 and hence rejected as outlier from the data set.

QSAR Model

A new QSAR model was attempted by dividing the set as a 20 molecule training set and a 5 molecule validation set (Table 2) after rejecting the outlier. More specifically, the selection of molecules in the training set was made according to the biological action and molecular structure, so that representatives of a wide range of structures with different substituents, atoms and

activity were included. The distribution of activity values for the validation set follows the similar distribution of the activity values for the training set [29].

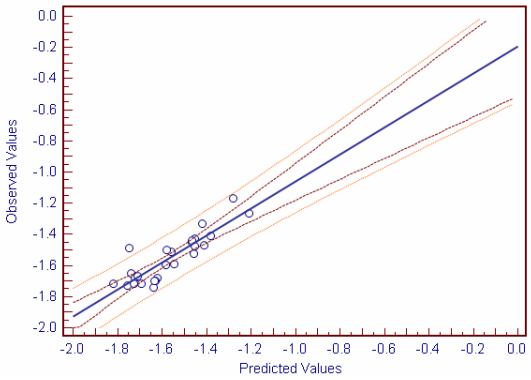


Figure 1: Extent of extrapolation graph displaying compound 20 as outlier.
Middle Dark line: regression line; Dotted lines: 95% confidence level; Solid lines: 95% prediction level

Cross-validation was performed using leave-one-out (LOO) technique over 5 random trials with F to enter and F to leave being 2 in F stepping to include the most significant variables in generating the QSAR model. The equations obtained from the multiple linear regression procedure with varied number of descriptors are given below with their statistics.

log (1/Ki) = -0.113* logP
+ 0.616* HOMO
- 0.004* Quadpole XX
- 0.015* Quadpole XZ
+ 0.011* Quadpole YZ
- 0.582* KAlpha3
+ 6.499
r =0.919, r^2 = 0.844, q^2 =0.658, F = 11.705, n = 20, PRESS = 0.076, s = 0.077 (6)

log (1/Ki) = -0.004* ADME weight
+0.184* 6-membered aromatic rings
+ 0.487* HOMO
- 0.011* Quadpole XZ
+ 0.008* Quadpole YZ
+ 3.618
r =0.869, r^2 = 0.755, q^2 =0.847, F = 8.634, n = 20, PRESS = 0.119, s = 0.093 (7)

log (1/Ki) = -0.113* Kappa2
-0.376* Shape Flexibility
-0.168* logP
+0.002* Heat of Formation
+ 0.625* HOMO
- 0.010* Quadpole XZ
+ 0.010* Quadpole YZ
+ 5.164
r = 0.925, r^2 = 0.855, q^2 =0.609, F = 10.087, n = 20, PRESS = 0.071, s = 0.077 (8)

Table 2: Activity data of complete, training and validation sets and descriptor values of the proposed QSAR model (Eq. 6)

ID	Activity log (1/Ki)	Complete Set [b] log (1/Ki)	Standard Residuals	Training Set [c] Log (1/Ki)	Validation Set [d] log (1/Ki)	Log P	HUMO	Quadpole XX	Quadpole XY	Quadpole YZ	Kalpha3 index
1	-1.427	-1.356		-1.451		5.167	-8.314	-0.549	-41.491	-19.571	4.549
2	-1.719	-1.720		-1.819		6.249	-8.146	5.657	-2.236	4.071	4.550
3	-1.680	-1.588		-1.620		5.731	-8.069	8.282	6.021	7.256	4.222
4	-1.330	-1.482		-1.418		5.213	-8.036	7.859	-5.177	-7.820	4.018
5	-1.696	-1.586		-1.629		5.731	-8.117	10.678	-7.223	-0.539	4.359
6[a]	-1.652	-1.639		-	-1.739	6.005	-8.106	16.853	-3.380	2.920	4.430
7	-1.522	-1.447		-1.456		4.929	-8.153	0.274	4.270	7.023	4.103
8	-1.453	-1.468		-1.464		4.676	-7.947	16.053	-10.617	1.382	4.543
9[a]	-1.512	-1.592		-	-1.557	5.005	-7.961	30.914	-17.734	1.358	4.697
10	-1.739	-1.597		-1.638		3.700	-8.669	9.549	-15.105	-1.303	4.378
11[a]	-1.267	-1.317		-	-1.207	2.862	-8.812	-43.805	-36.442	-7.784	4.448

12	-1.408	-1.407		-1.382		4.912	-8.141	13.676	-3.649	-8.602	3.809
13	-1.498	-1.556		-1.580		3.375	-8.616	20.418	-12.846	-7.363	4.153
14	-1.678	-1.728		-1.721		3.426	-8.674	2.665	-3.146	-2.867	4.288
15	-1.727	-1.669		-1.755		3.426	-8.663	19.908	11.669	8.761	4.077
16[a]	-1.595	-1.655		-	-1.585	3.047	-8.674	-3.668	-0.351	-1.831	4.121
17	-1.590	-1.537		-1.546		3.349	-8.511	13.174	-9.742	-10.961	4.118
18	-1.715	-1.661		-1.692		2.925	-8.527	7.777	11.723	-8.854	3.970
19	-1.470	-1.370		-1.410		3.727	-8.443	15.708	-12.536	-1.980	4.100
20#	-1.486	-1.658	2.094	-	-	4.245	-8.494	6.780	-5.127	0.582	4.446
21	-1.697	-1.653		-1.632		3.727	-8.508	-6.212	-3.485	-6.099	4.264
22	-1.719	-1.741		-1.724		2.672	-8.363	-0.246	21.280	10.851	4.427
23	-1.669	-1.697		-1.711		4.001	-8.499	-4.979	-1.072	-3.178	4.342
24[a]	-1.438	-1.460		-	-1.466	5.214	-8.112	2.628	-6.404	-11.598	4.019
25	-1.474	-1.428		-1.451		3.677	-8.452	8.727	-4.804	4.662	4.146
26	-1.170	-1.316		-1.282		3.209	-8.465	4.360	-0.970	6.403	3.899

Notes**:** [a] Validation set molecules. [#] Outliers, [b] Calculated values from Equation 5, [c] Calculated values from Equation 6, [d] Predicted values from Equation 6

FIT Kubinyi function

To define the statistical quality of activity prediction, the number of variables that enter in a QSAR model are compared by using FIT Kubinyi function (Eq. 9), a criteria closely related to F value was proven to be useful[30].

$$FIT = R^2 (n - k - 1) / (n + k^2) (1 - R^2) \quad (9)$$

where *n* is the number of compounds in training set and *k* is the number of variables in the QSAR equation.

The main feature of the F value is its sensitivity to changes in k, if k is small sensitivity is high and vice versa if k is large. The FIT criterion has a low sensitivity towards changes in k values, as long as they are small numbers, and a substantial increase in sensitivity for large k values [30-31]. The best model will be the one that possess a high value of this function. Hence, QSAR models with five, six and seven variables are generated (Table 3) to choose the best among them.

According to the statistical values of the models reported in Table 3, we chose the model with five variables since this showed high FIT than others. The observed, calculated and predicted values of the statistically significant five parameter QSAR model (Eq. 6) are presented in Table 2.

Table 3: Statistical parameters of the regression models obtained for five, six and seven variables.

Eq No.	r^2	*s*	*F*	FIT	Var [a]
6	0.844	0.077	11.705	1.256	6
7	0.755	0.093	8.634	0.959	5
8	0.855	0.077	10.087	0.986	7

Notes: [a] number of significant variables

Equation 6 accounts for the significant correlation of descriptors with biological activity and displayed good internal predictivity as shown by q^2 value of 0.658 and was able to explain 84.4 % variance of inhibitory activities of the compounds under study. The predictive residual sum of squares and the standard error of estimate are 0.076 and 0.077, respectively. Observed verses predicted values of molecules in training and validation set are shown graphically in Figure 2. The proposed QSAR model Eq. 6 illustrated the predictive ability of Eqs. 1-4 and depicted graphically in Figures 3 and 4.

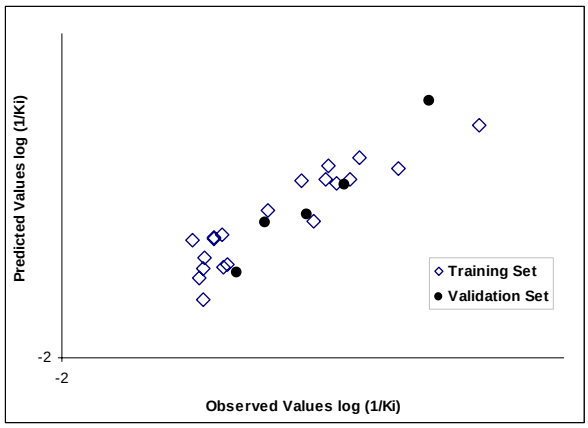


Figure 2: Observed and predicted values of molecules in training and validation set

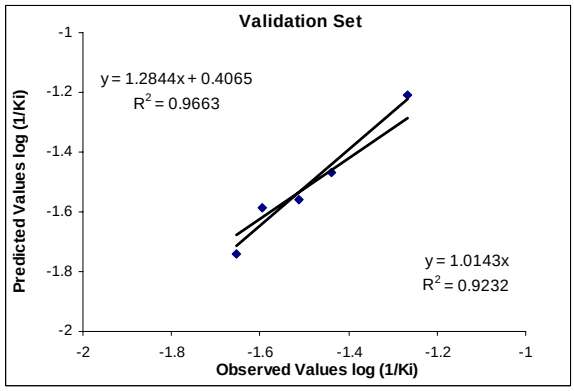


Figure 3: Regression plot between observed vs. predicted values of compounds from validation set justifying the predictive ability of QSAR model Eq.6

The low R^2 and Q^2 values indicate that the variables obtained in our original model (Eq. 6) are not due to chance correlation. Alternatively, Table 5 given below represents the leverage values of training and validation sets. From the leverages computed, it is observed that all compounds are within the domain of the model.

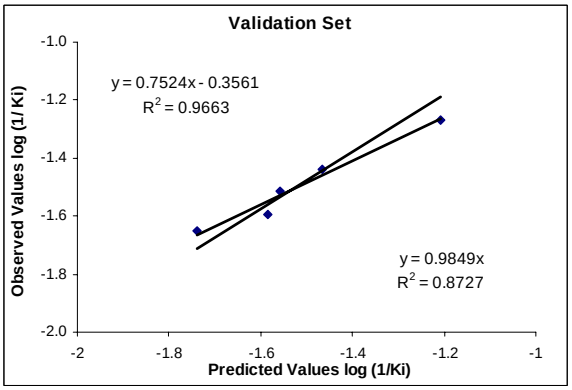


Figure 4: Regression plot between predicted vs. observed values of compounds from validation set justifying the predictive ability of QSAR model Eq.6

Interpretation of Descriptors

A brief explanation of the descriptors that were utilized to generate the statistical QSAR model:

Molecular Orbital (MO) surfaces represent the various stable electronic distributions of a molecule. According to Frontier Orbital theory, the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) are crucial in predicting the reactivity of a species. HOMO is the outermost orbital containing the electron and LUMO is the first orbital that does not contain an electron. The energy of the highest occupied molecular orbital (HOMO) measures the electron donating character of a compound and the energy of the lowest unoccupied molecular orbital (LUMO) measures its electron accepting character [32]. The generated QSAR model (Eq. 6) indicates that a high value of HOMO energy contributes positively to the activity.

Table 4: R2 and Q2 values after several y-randomization tests

Iteration	R^2	Q^2	Iteration	R^2	Q^2
1	0.47	0.30	11	0.10	0.32
2	0.15	0.14	12	0.12	0.24
3	0.36	0.30	13	0.11	0.27
4	0.49	0.16	14	0.35	0.37
5	0.19	0.02	15	0.39	0.32
6	0.17	0.19	16	0.16	0.20
7	0.38	0.37	17	0.28	0.13
8	0.44	0.44	18	0.34	0.19
9	0.34	0.21	19	0.44	0.18
10	0.24	0.04	20	0.30	0.43

Table 5: Leverage values of all compounds in training and test set.

Training Set		**Training Set**		**Test Set**	
Compounds	Leverages	Compounds	Leverages	Compounds	Leverages
1	0.412	14	0.137	6	0.199
2	0.332	15	0.318	9	0.482
3	0.213	17	0.179	1	0.739
4	0.211	18	0.362	16	0.115
5	0.122	19	0.170	24	0.247

7	0.222	21	0.129
8	0.352	22	0.583
10	0.197	23	0.141
12	0.284	25	0.145
13	0.232	26	0.355

(Warning leverage limit: 1.05)

An electron-donating substituent, such as hydroxy, or methoxy group, on the ring increases the energy of the HOMO orbital. For instance, a lone pair of electrons on oxygen atom of methoxy group delocalizes into the π space of benzene ring, thereby increasing the energy of HOMO. Electron-withdrawing substituents, such as halogens, lower the energy of HOMO. An electronegative halogen removes electron density from the σ space of benzene ring thereby decreasing the energy of HOMO [33]. Thus, designing analogs with electron-donating substituents should improve activity.

Log P is a measure of hydrophobicity/lipophilicity and describes the distribution of a compound between organic (usually octanol) and water phase. A value of Log P > 0 indicates greater solubility in the organic phase whereas Log P < 0 indicates greater solubility in the aqueous phase. On the other hand, from equation 6, a high value of Log P represents a negative contribution to the activity. Log P is known to be an important parameter for absorption, permeability and *in vivo* distribution of organic compounds [34-35]. Therefore, according to Eq. 6, decrease in logP value on molecules favors better binding and activity at the molecular level.

A high value of KAlpha3 index represents a negative contribution to the activity. The basic Kappa indices were derived assuming that all atoms are equivalent. Hall and Kier also defined a group of modified indices, the Kappa Alpha indices. The contribution of each atom to the overall shape of a molecule is based on a comparison with a Carbon sp3 atom. An alpha value is calculated for each atom type using the ratio of covalent radii of C(sp3) and the atom according to the equation,

$$\alpha_x = ((r_x / r_{(Csp3)})-1)$$

An elementary quadrupole can be represented as two dipoles oriented antiparallel. Quadrupole properties are a measure of molecular electric quadrupole moments of interactions which represents the binding of compounds through electrostatic interactions with active site residues [36]. Quadrupole moment is a description of the molecular charge distribution and as such has considerable importance in modeling the origin of the electrical forces which exist between molecules, particularly, in modeling how the observable bulk physical properties of the condensed phase may be related to the properties of individual molecules [37].

Moreover, the energy of interactions between an acceptor group and a donor group of an enzyme and inhibitor, vice-versa, depends on the separation and relative orientation of the groups of atoms [38]. Hence, designing or screening compound libraries for new analogues with electron donating substituents on aromatic ring, decrease in logP and KAlpha3 index with a reduced quadpole XX, XZ and increase in quadpole YZ would enhance inhibitory activity of these compounds as histamine H1-receptor antagonists.

CONCLUSION

The generated QSAR model on the data set with reasonable chemical diversity and biological activity demonstrated a promising method and the six descriptors [logP, HOMO, Quadpole XX, XZ and YZ, KAlpha3] were found to be important in describing the histamine H1-receptor inhibition. The predictive ability of the model and the internal and external validation procedures illustrated the accuracy on one hand and offered a useful alternative to the time consuming experiments, on the other. This work emphasizes the use of various tests in QSAR analysis such as applicability domain of the model, predictive ability of validation set and FIT Kubinyi function as important parameters to obtain a reliable and robust QSAR model and thus help in designing more potent histamine H1-receptor antagonists.

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