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QSAR Analysis on 2-(4-(Piperidin-1-yl)piperidin-1-yl)-6-Substituted Thiazolo[4,5-B]Pyridines as H_3 Receptor Antagonists

Sanmati K. Jain*, Lokesh Sahu, Rahul Jain and Arvind K. Yadav

SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh-495009, India

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ABSTRACT

Quantitative structure activity relationship (QSAR) study was performed on a series of 2-(4-(piperidin-1-yl)piperidin-1-yl)-6-substituted thiazolo[4,5-b]pyridines possessing H_3 receptor antagonistic activity for establishing quantitative relationship between biological activity and their physicochemical/ structural properties. Several statistical regression expressions were obtained using partial least squares regression (PLSR) analysis. Three statistical significant models were generated [r^2 = 0.8130, q^2 = 0.6103, pred_r^2 = 0.9818; r^2 = 0.8166, q^2 = 0.6213, pred_r^2 = 0.9421 and r^2 = 0.8164, q^2 = 0.6392, pred_r^2 = 0.9399 for model 1, 2 and 3 respectively] indicating that biological activity is influenced by the descriptors T_C_N_5, T_N_O_2, XKMostHydrophobicHydrophilicDistance and XAHydrophilicArea.

Keywords: 2D-QSAR, H_3 receptor antagonists, thiazolo[4,5-b]pyridines

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INTRODUCTION

Histamine plays a variety of physiological roles in the central nervous system (CNS) and peripheral tissues through the four known G protein-coupled receptors, H_1, H_2, H_3 and H_4 [1]. H_3 receptor is expressed in both the central and peripheral nervous system where it is located presynaptically on both histaminergic neurons, as an autoreceptor, and other neuronal systems, as a heteroreceptor regulating release of other neurotransmitters e.g., dopamine, norepinephrine, acetylcholine, glutamate and serotonin [2-4].

Activation of histamine H_3 receptor (H_3R) by the endogenous ligand, histamine reduces neurotransmitter release [2, 5-8], while antagonism of the H_3R leads to enhanced neurotransmitter release [9-10]. This improved neurotransmitter release by H_3 receptor antagonist offers a promising approach to the treatment of a number of CNS disorders [11-14], including attention deficit hyperactivity disorder [15,16], sleep disorders [17], epilepsy [18] and schizophrenia [19]. Furthermore, given the role of histamine in regulating appetite, H_3 receptor ligands are also active in obesity [20-25].

Thus, H_3 receptor antagonists may be potential therapeutic agents for attention deficit/hyperactivity disorder, Alzheimer's disease, mild cognitive impairment or schizophrenia and obesity.

Imidazole based H_3 antagonists were among the earliest structures investigated [26]. Drug-drug interactions through inhibition of hepatic cytochrome P450 enzymes and also relatively poor CNS penetration [27,28] are the two major drawbacks to this class of compounds.

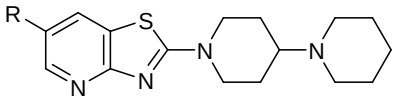
More recently, interest in the field has turned to non-imidazole class of H_3 antagonists as these compounds offer improvements in binding affinity, CNS penetration and reduced potential for CYP inhibition [29]. The majority of the reported non-imidazole H_3 antagonists possess an aromatic ring-linker-basic amine motif. Notable examples include ABT-239 [30-32], GSK-189254 [33], UCL-2190 [34], A-331440 [35] and JNJ-5207852 [36].

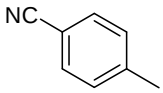
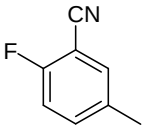
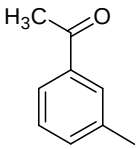
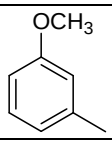
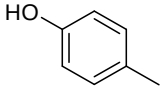
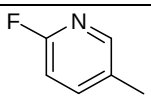
The main objective of the present study is the search of some novel thiazolo[4,5-b]pyridine derivatives that would show a promise to become useful H_3 receptor antagonist. For this purpose, a series of thiazolo[4,5-b]pyridine derivatives [37] as H_3 receptor antagonist were selected, in order to develop quantitative structure activity relationship (QSAR) model(s), which can be used for drug design.

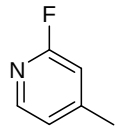
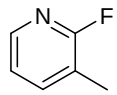
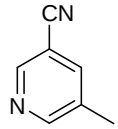
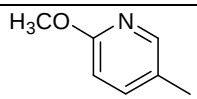
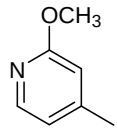
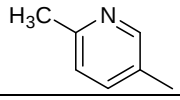
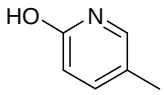
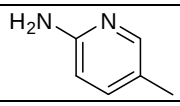
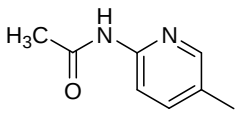
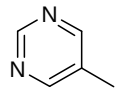
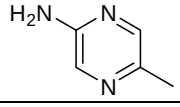
MATERIALS AND METHODS

***Data set*:** A dataset of 22 molecules has been taken from the literature [37]. Selected data set, their biological activity is shown in Table-1. Biological data's represented as human H_3 binding K_i values (nM) were converted into log $(1/K_i)$ $[pK_i]$ for computational work.

Table-1: General structure of 2-[4-(piperidin-1-yl)piperidin-1-yl]-6-substituted thiazolo[4,5-b]pyridines and their biological activities (data set of 22 molecules)



S. No.	Compounds	R	pK_i
1	12a	-H	6.856
2	12b	$-NH_2$	7.102
3	12c	-CN	7.443
4	12d	-Cl	6.903
5	12e	-NHCOMe	7.508
6	12f		7.552
7	12g		7.638
8	12h		7.481
9	12i		6.853
10	12j		7.229
11	12k		7.200

12	12l		7.886
13	12m		7.376
14	12n		7.795
15	12o		7.455
16	12p		8.397
17	12q		6.876
18	12r		7.376
19	12s		7.795
20	12t		8.000
21	12u		7.602
22	12v		7.180

***QSAR Analysis*:** Structure of the compounds of selected series were drawn using 2D Draw application option of QSAR Plus [38] and converted to 3D structure by exporting to QSAR Plus window. Energy minimizations of the compounds were done by using Merck Molecular Force Field (MMFF) method [Charge-Modified Qeq charge; Maximum number of cycles = 10,000; Convergence criteria (root mean square gradient) = 0.01; Gradient type=analytical and 1.0 as constant (medium's dielectric constant which is 1 for in vacuo) in dielectric properties. The default values of 20.0 and 10.0 Kcal/mol were used for electrostatic and steric energy cutoff] followed by batch optimization. After optimization, number of physicochemical (Individual (HAcceptorcount, H-Donor count , X logP, SMR, polarisablity, etc.), retention index (Chi), atomic valence connectivity index (ChiV), Path count, Chi chain, Chiv chain, Chain Path Count, Cluster, Path cluster, Kapa, Element count (H, N, C, S, O, Cl, Br, I), Estate numbers (SsCH3 Count, SdCH2 Count, SssCH2 Count, StCH count etc.), Estate contribution (SsCH3-index., SdCH2- index, SssCH2- index, StCH index) and Polar surface area), alignment (for example, T_2_O_7, T_2_N_5, T_2_2_6, T_C_O_1, T_O_Cl_5 etc.) and atom type (based on MMFF atom types and their count in each molecule. In MMFF, there are 99 atom types and hence 99 descriptors indicating number of times that atom has occurred in a given molecule are generated) independent descriptors were calculated for the data set. Calculated descriptors and

biological activity were taken as independent and dependent variables respectively. Random, manual and sphere exclusion methods were used for creation of training and test data set. Partial least squares regression (PLSR) statistical method was used to generate QSAR models. Following statistical parameters were considered to select the statistical significance QSAR models: squared correlation coefficient (r^2), F-test (F-test for statistical significance of the model), and cross-validated squared correlation coefficient (q^2).

Generation of training and test set of compounds: In order to evaluate the QSAR model, data set was divided into training and test set using Sphere Exclusion, random and manual data selection methods. Training set is used to develop the QSAR model for which biological activity data are known. Test set is not included in model generation, used to assess the predictive power of the model.

Sphere Exclusion method: In this method dissimilarity value provides an idea to handle training and test set size. It needs to be adjusted by trial and error until a desired division of training and test set is achieved. Increase in dissimilarity value results in increase in number of molecules in the test set.

Random selection: In order to construct and validate the QSAR models, both internally and externally, the data sets were divided into training (85% of total data set) set and test sets (15%) in a random manner. Ten trials were run.

Manual data selection: Whole range of activities was sorted on the basis of results obtained in sphere exclusion and random methods.

After the creation of training and test set, Min and Max value of the test and training set is checked, using the QSAR tool, if the values are not following the Min – Max, then the training / test set is again set and procedure is repeated. If the Min – Max is following, then Partial Least Squares Regression (PLSR) used for model building (Cross correlation Limit – < 0.5; No. of variables – 1/5th of total training set; Term selection – r2; F test: In – 4.00, Out – 3.99; Model building criteria – Cross validation).

Partial least square regression (PLSR): PLSR was used for model generation. PLSR is an expansion of the multiple linear regression (MLR). PLSR is probably the least restrictive of the various multivariate extensions of the multiple linear regression models. PLSR can be used as an exploratory analysis tool to select suitable predictor variables and to identify outliers before classical linear regression. All the calculated descriptors were considered as independent variable and biological activity as dependent variable.

RESULTS AND DISCUSSION

When all the 22 molecules of the selected series were subjected to partial least squares regression (PLSR) analysis, the following significant QSAR models with equations were obtained for H_3 receptor antagonistic activity (Table-2).

In the above QSAR models, n is the number of molecules (Training set) used to derive the QSAR model, r^2 is the squared correlation coefficient, q2 is the cross-validated correlation coefficient, pred_r^2 is the predicted correlation coefficient for the external test set, *F* is the Fisher ratio, 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. r^2 se, q2 se and pred_r^2se are the standard errors terms for r^2, q^2 and pred_r^2 (smaller is better). R^2 is the correlation coefficient for observed vs. predicted biological activity.

From this table, the equation of Model-01 explains 82% (r2=0.8163) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predicative ability of 61 % and 99% respectively. Model-02 explains 81% (r2= 0.81) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predicative ability of 62% and 94% respectively. Model-03 explains 82% (r2= 0.8164) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predicative ability of 64 % and 94 % respectively.

Table-2: List of predictive QSAR models with equation generated from PLSR

Model	Method	Test set	Equation
1	Manual selection method/ trial 27/ PLS	12a 12h 12k	pK_i= 0.2714 T_C_N_5 + 0.4399 T_N_O_2 - 0.0723 XKMostHydrophobicHydrophilicDistance - 0.0058 XAHydrophilicArea + 5.3094 Optimum Components = 3 n = 19 Degree of freedom = 15 F test = 21.737 r^2 = 0.8130 q^2 = 0.6103 pred_r^2 = 0.9818 r^2 se = 0.1911 q^2 se = 0.2759 pred_r^2se = 0.0643 Alpha Rand R^2 = 0.000 Alpha Rand Q^2 = 0.001 Alpha Rand Pred R^2 = 0.05
2	Manual selection method/ trial 32/ PLS	12a 12g 12h 12j	pK_i = 0.2782 T _C_N_5 + 0.4285 T_N_O_2 -0.0717 XKMostHydrophobicHydrophilicDistance -0.0061 XAHydrophilicArea + 5.2529 Optimum Components = 3 n = 18 Degree of freedom = 14 F test = 20.7769 r^2 = 0.8166 q^2 = 0.6213 pred_r^2 = 0.9421 r^2 se = 0.1954 q^2 se = 0.2808 pred_r^2se = 0.0934 Alpha Rand R^2 = 0.000 Alpha Rand Q^2 = 0.05 Alpha Rand Pred R^2 = 0.1
3	Manual selection method/ trial 31/ PLS	12a 12g 12h 12k	pK_i = 0.2790 T_C_N_5 + 0.4326 T_N_O_2 - 0.0724 XKMostHydrophobicHydrophilicDistance – 0.0061XAHydrophilicArea + 5.2480 Optimum Components = 3 n = 18 Degree of freedom = 14 F test = 20.7460 r^2 = 0.8164 q^2 = 0.6392 pred_r^2 = 0.9399 r^2 se = 0.1950 q^2 se = 0.2734 pred_r^2se = 0.0968 Alpha Rand R^2 = 0.001 Alpha Rand Q^2 = 0.001 Alpha Rand Pred R^2 = 0.05

Table-03 represents the predicted biological activity by the model for training and test set. The plot of observed vs. predicted activity provides an idea about how well the model was trained and how well it predicts the activity of the external test set. From the plot (Figure-01 to 3) it can be seen that the model is able to predict the activity of the training set quiet well as well as external test set, providing confidence of the model.

Table-03: Actual and predicted activity for Training set and test set

S. No.	Compounds	Actual	Model-1	Model-2	Model-3
			Predicted	Predicted	Predicted
1	12a	6.856	6.790*	6.781*	6.777*
2	12b	7.102	6.878	6.871	6.867
3	12c	7.443	7.280	7.282	7.281
4	12d	6.903	6.974	6.968	6.966
5	12e	7.508	7.436	7.416	7.417
6	12f	7.552	7.406	7.432	7.427
7	12g	7.638	7.747	7.778*	7.775*
8	12h	7.481	7.503*	7.508*	7.507*
9	12i	6.853	7.262	7.279	7.275
10	12j	7.229	7.202	7.221*	7.216
11	12k	7.200	7.142*	7.156	7.151*
12	12l	7.886	7.782	7.811	7.808
13	12m	7.376	7.177	7.190	7.186
14	12n	7.795	7.644	7.668	7.665
15	12o	7.455	7.494	7.497	7.495
16	12p	8.397	8.145	8.162	8.163
17	12q	6.876	7.093	7.107	7.102
18	12r	7.376	7.551	7.554	7.553
19	12s	7.795	7.930	7.944	7.945
20	12t	8.000	8.146	8.142	8.146
21	12u	7.602	7.578	7.582	7.582
22	12v	7.180	7.240	7.239	7.235

**indicates compounds are in the test set for the corresponding model and rest are in the training set.*

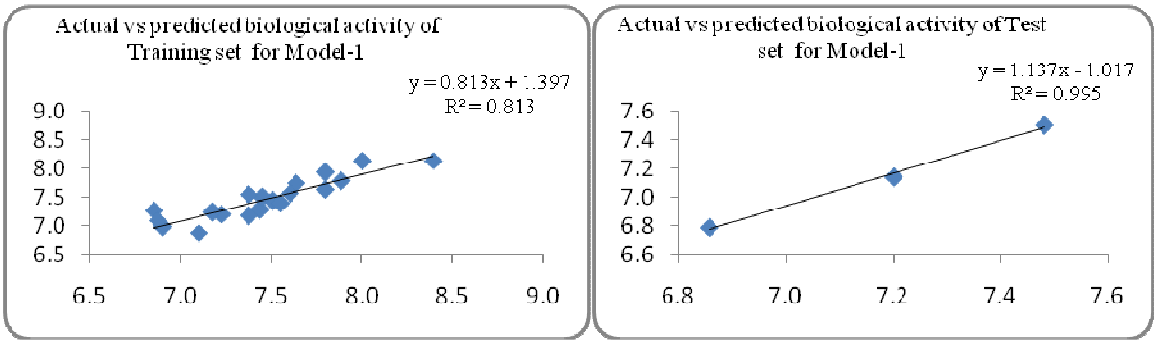


Figure-01: Graph between actual and predicted biological activity of training and test set for Model-1.

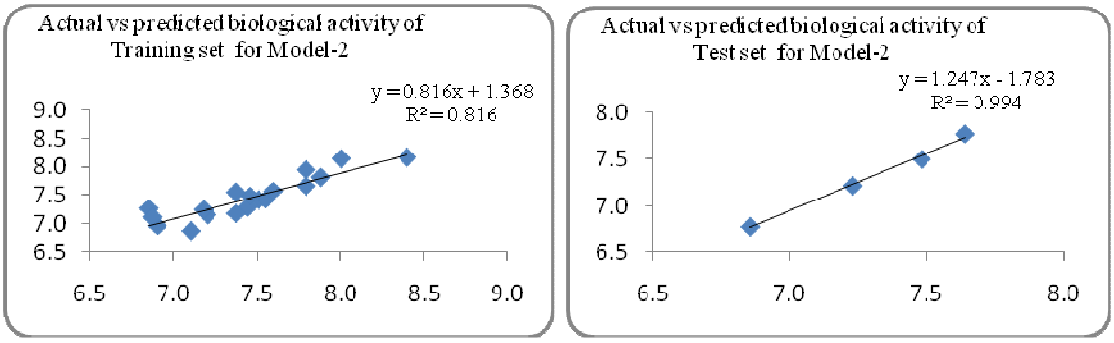


Figure-02: Graph between actual and predicted biological activity of training and test set for Model-2.

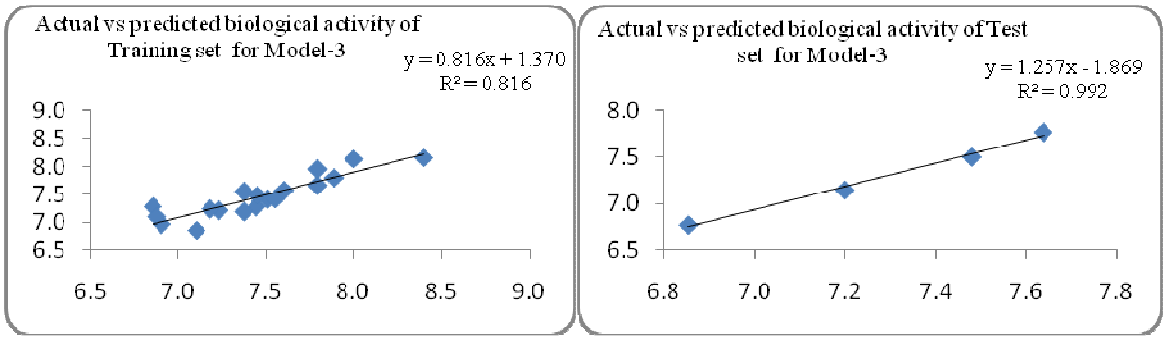
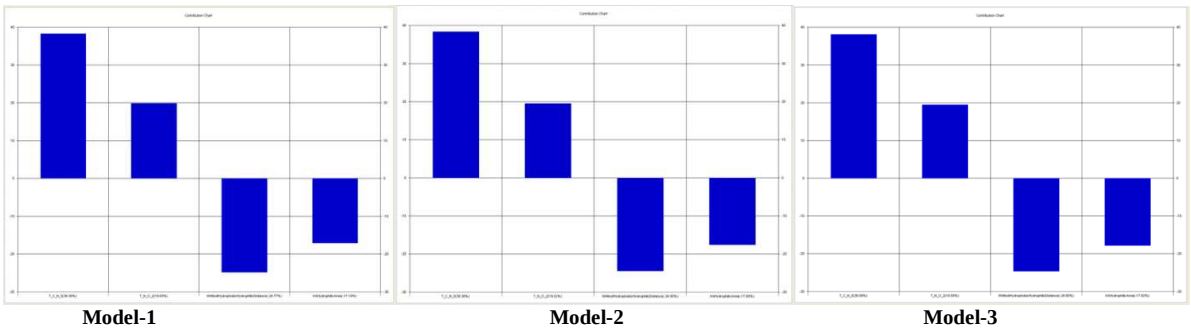
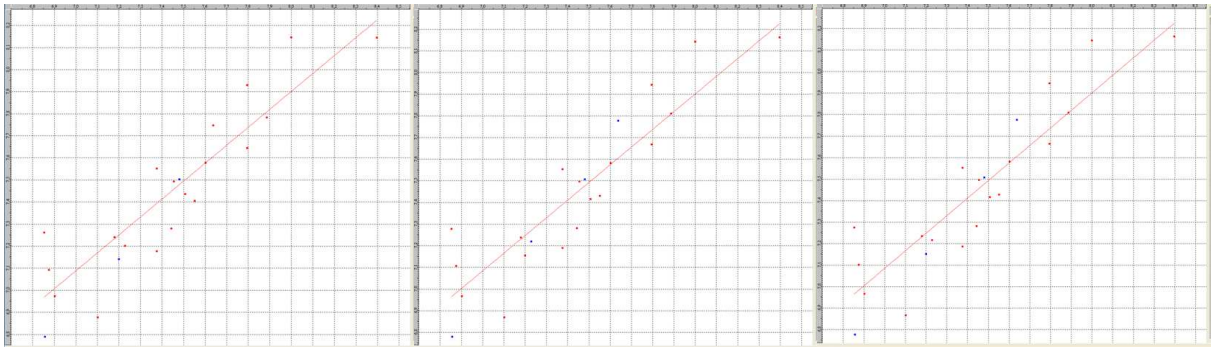


Figure-03: Graph between actual and predicted biological activity of training and test set for Model-3.



Model-1 **Model-2** **Model-3**

Figure-04: Contribution plot for Model 1-3.



Model-1 **Model-2** **Model-3**

Figure-05: Data fitness plot for Model 1-3.

Interpretation of the Model 01 (Most significant)

Among the three significant models generated (Table-02), model 1 is the most significant one as it is having the highest predicted correlation coefficient value.

The equation 1 explains 82% (r2 = 0.8163) of the total variance in the training set and has an internal (q2) and external (pred_r2) predictive ability of ~61% and ~99% respectively. The F test shows the statistical significance of 99.99 % of the model which means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows confidence of 95 (Alpha Rand Pred R^2 = 0.05) that the generated model is not random and hence may be chosen as the QSAR model.

In the QSAR model 1, the positive coefficient value of T_C_N_5 [This is the count of number of Carbon atoms (single, double or triple bonded) separated from any Nitrogen atom (single, double or triple bonded) by 5 bond distance in a molecule] and T_N_O_2 [this is the count of number of Nitrogen atoms (single, double or triple bonded) separated from any Oxygen atom (single or double bonded) by 2 bonds in a molecule] on the biological activity indicated that higher value leads to better H_3 receptor antagonistic activity (compound 12p, 12t, 12l, 12s, etc.) whereas lower value leads to decrease activity (compound 12b, 12d, 12q, 12i, etc.). Negative coefficient value of XKMostHydrophobicHydrophilicDistance [this descriptor signifies distance between most hydrophobic and hydrophilic point on the vdW surface] and XAHydrophilicArea [vdW surface descriptor showing hydrophilic area] on the biological activity indicated that lower values leads to good H_3 receptor antagonistic activity (compound 12e, 12s, 12t, 12u, etc.) while higher value leads to reduced activity (compound 12i, 12q, etc.).

Figure-04 represents the contribution chart showing contribution of the various descriptors playing important role in determining the histamine H_3 receptor antagonistic activity and Figure-05 represents the data fitness plot for model 01-03. Contribution chart for model 1 reveals that the descriptors T_C_N_5, T_N_O_2, XKMostHydrophobicHydrophilicDistance and XAHydrophilicArea contributing 38%, 20%, 25% and 17 % respectively.

The observed vs. predicted activity provides an idea about how well the model was trained and how well it predicts the activity of the external test set. From the plot it can be seen that model is able to predict the activity of training set quite well (all points are close to the regression line) as well as external test set providing confidence in the predictive ability of the model. From Figure 1-3, it is seen that the plots of observed vs. predicated activity for different models provide an idea about how well the models were trained and how well they predict the activity of the external test set.

CONCLUSION

A quantitative structure activity relationship study was performed on a series of 2-(4-(piperidin-1-yl)piperidin-1-yl)-6-substituted thiazolo[4,5-b]pyridines possessing H_3 receptor antagonistic activity for establishing quantitative relationship between biological activity and their physicochemical / structural properties.

Two dimensional quantitative structure activity relationship (2D QSAR) study by means of partial least square regression (PLSR) method was performed on a series of 2-(4-(piperidin-1-yl)piperidin-1-yl)-6-substituted

thiazolo[4,5-b]pyridines possessing H_3 receptor antagonistic activity using molecular design suite (VLifeMDS). This study was performed with 22 compounds (data set) using sphere exclusion (SE) algorithm, random and manual selection methods for the division of the data set into training and test set. PLSR methodology with stepwise (SW) forward-backward variable selection method was used for building the QSAR models. Statistically significant QSAR models were generated. Among them most significant model has squared correlation coefficient (r2), cross validated correlation coefficient (q2) and predictive correlation coefficient (pred_r2) 0.813, 0.6103 and 0.9818 respectively. The QSAR model indicates that the descriptors T_C_N_5, T_N_O_2, XKMostHydrophobicHydrophilicDistance and XAHydrophilicArea contributing 38%, 20%, 25% and 17 % respectively to biological activity. The positive coefficient value of T_C_N_5 and T_N_O_2 on the biological activity indicated that higher value leads to better H_3 receptor antagonistic activity whereas lower value leads to decrease activity. Negative coefficient value of XKMostHydrophobicHydrophilicDistance and XAHydrophilicArea indicates that lower value leads to better H_3 receptor antagonistic activity whereas higher value leads to decrease activity.

In present study an attempt has been made to identify the necessary structural and substituent requirements. From the present QSAR analysis, three best models were generated among which any one can be used for predicting the activity of the newly designed compounds in finding some more potent molecules. Finally, it is concluded that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable substituent for active compounds with maximum potency.

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