EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 9
259-268
Year: 2022

PREDICTING THE ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY OF SOME BENZOTHIAZOLE DERIVATIVES USING 2D AND 3D QSAR ANALYSIS

Mahfoozur Rahman[1]*, Ziyaul Haque[2], Dr. Rashid Akhtar[3], Dr. J. V. Musale[1], D. P. Patil[1], P. P. Nahar[1]

[1]Mahatma Gandhi Vidyamandir's Institute of Pharmacy, Malegaon Camp, Nashik-423105.
[2]Assistant professor Department of Pharmaceutical Chemistry Maulana Azad University Jodhpur.
[3]Associate Professor Department of Pharmacognosy, KES's Royal College of Pharmaceutical Education & Research, Malegaon, Nashik- 423203.

***Corresponding Author: Mahfoozur Rahman**
Mahatma Gandhi Vidyamandir's Institute of Pharmacy, Malegaon Camp, Nashik-423105.

Article Received on 30/06/2022 **Article Revised on 20/07/2022** **Article Accepted on 10/08/2022**

ABSTRACT
A series of 21 molecules of Benzothiazole derivatives reported in literature Ashok kumar *et al* (2010) were used for development of 2D and 3D QSAR models. The data set of 20 molecules were divided into training and test set in the ratio of 70:30, The biological activity was converted to logarithmic scale (pIC_{50}) in mathematical operation mode of the software. The statistically significant 2D-QSAR models for Analgesic activity are r^2 =0.8578 and q^2 = 0.7415 and on Anti inflammatory giving r^2 = 0.9457 and q^2 =0.9476. 3D QSAR results for internal (q^2 = 0.9245, q^2=0.8170) and external (predictive r^2 = 0.6320, q^2 = 0.7773) validation criteria. Thus, 3D QSAR models showed that electrostatic effects dominantly determine the binding affinities. 2D QSAR studies revealed that Saas CE Index descriptors were major contributing descriptor in case of analgesic activity and Xlog P in case of Anti inflammatory activity. By using kNN-MFA method. The results derived may be useful in further designing novel anti-cancer agents. After successful QSAR studies, attempts were made to predict the activities of the newly designed analogues of these reported compounds. In future we can synthesize these designed compounds using the selected scheme and confirm their activity by carrying out *in vivo* evaluation.

KEYWORDS: Benzothiazole derivatives, Anti-inflammatory agents, 2D QSAR, 3D QSAR, kNN-MFA.

INTRODUCTION
Any bacterial infection leads to cause inflammation and pain. In common practice the prescriber prescribes a chemotherapeutic agent i.e. antibiotics along with analgesic or anti-inflammatory drug. Literature survey revealed that benzothiazoles are the class of compound which are having plethora of activities that attracted the huge attention of medicinal chemists to invent newer, safer and better drugs. The reported activities of benzothiazole derivatives are Analgesic, Anti-inflammatory, Anti microbial and antipsychotic **[Ashok kumar *et al* (2010)]**. In present study by using Quantitative Structural Activity Relationship (QSAR), it was envisaged that a drug molecule possessing the above mentioned pharmacophore could be of advantage since it might possess analgesic, anti-inflammatory activity.

Quantitative Structural Activity Relationship is a method of drug design by establishing a mathematical relationship in the form of an equation between biological activity and measurable physicochemical parameters.

OBJECTIVES
To optimize the existing leads so as to improve their biological activities. To predict the biological activities of untested and sometimes yet unavailable compounds. The current approach is to find out the effective and better anti-inflammatory agents from Benzothiazole derivatives reported in literature.

MATERIALS AND METHODS
Software Package
For the present study, the software package QSAR pro and MDS 4.2 were used which were procured from VLife sciences Pvt. Ltd. Pune (www.vlifesciences.com). Simple QSAR studies were done by QSAR pro software and 3D QSAR studies using kNN-MFA method was done using MDS software (version 4.2).

QSAR studies
Calculation of descriptors
Number of descriptors was calculated after optimization or minimization of the energy of the data set molecules viz. physicochemical, alignment independent and atom type count. Various types of physicochemical descriptors were calculated: Individual (Molecular weight, H-

Acceptor count, H-Donor count, XlogP, slogP, SMR, polarisablity, etc.), retention index (Chi), atomic valence connectivity index (ChiV), Path count, Chi chain, ChiV chain, Chain PathCount, Cluster, Pathcluster, Kappa, Element count (H, N, C, S count etc.), and Polar surface area. More than 200 alignment independent descriptors were also calculated using the following attributes.

- Structural descriptors: Topological,
- Range: min- 0 and max-7,
- Selected attributes: 2, T (any), C, N, O, S, Cl.

All the atom type count descriptors were also calculated.

Data selection

For the development of QSAR models all the calculated descriptors were considered as independent variable and biological activity as dependent variable. In order to evaluate the QSAR model, data set was divided into training and test set using random data selection and manual data selection method. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive power of the model which is not included in model generation.

- ***Random data selection method:*** the data was selected randomly entering the percentage of training set molecules to be selected. The percentage value was adjusted subsequently in order to get the different sets of training and test molecule. This is based on trial and error method to get the desired test set molecules.
- ***Manual data selection method:*** Data set is divided manually into training and test sets on the basis of the result obtained in random data selection method.

Multiple linear Regressions

All molecules were subjected to regression analysis using multiple linear regressions, coupled with stepwise forward backward variable selection method. Cross Correlation Limit was set as 0.5, Number of Variable in Final Equation was set as 5, Term Selection Criteria as r^2, F test In as 4 and F test Out as 3.99. In the 'Additional Parameter Settings' dialog box Variance Cut-Off was set as 0, number of random iterations to 10 and the Scaling options was chosen as Auto scaling. After deriving the suitable model, its summary is copied with data fitness plot and contribution chart.

Obtaining conventional 2D QSAR models using VLifeMDS

QSAR Plus module enables evaluation of several molecular descriptors and provides a facility to build the QSAR equation for predicting activity of new molecules. Regression methods are used to build a QSAR model in the form of a mathematical equation. This equation explains variation of one or more dependent variables (usually activity) in terms of independent variables (descriptors). The QSAR model can then be used to predict activities for new molecules, for screening a large set of molecules whose activities are not known.

Obtaining 3D QSAR models by kNN-MFA method using VLifeMDS

VLifeMDS includes a module that facilitates evaluation of three dimensional molecular fields around molecules and generates relationship of these fields' values with the activity. This section illustrates use of the k-nearest neighbor (kNN) method for generating relationship between activity and molecular field and provides interpretation of results thus providing clues for designing new molecules.

3D QSAR studies

k-Nearest neighbour molecular field analysis (kNN-MFA)

The kNN methodology (Ajmani S. *et al*. 2006) relies on a simple distance learning approach whereby an unknown member is classified according to the majority of its kNN in training set. The nearness is measured by an appropriate distance metric. The 3D QSAR studies were performed by kNN-MFA using stepwise forward backward variable selection method. In this method the cross-correlation limit set to 0.5 and term selection criterion as q^2. F-test 'in' was set to 4.0, and F test 'out' to 3.99. As some additional parameters, variance cutoff was set at 0 kcal/mol and scaling to auto scaling; additionally, kNN parameter setting was done within the range of 2-5 and prediction method was selected as the distance-based weighted average.

The model was derived by clicking OK, after all the parameters have been set. Once the significant model is obtained, its fitness plot and contour plot is saved.

Development and validation of QSAR models

Models were generated by using significant statistical methods, namely, multiple linear regression (MLR) and kNN-MFA method. The following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2) i.e. q^2, predicted r^2 (pred_r^2), and Fischer's value (F).

The best way to evaluate quality of regression model is internal validation of QSAR model. Mostly leave-one-out (LOO) cross validation method is used. In this method one object (one biological activity value) is eliminated from training set and training dataset is divided into subsets (number of subsets = number of data points) of equal size. Model is build using these subsets and dependent variable value of the data point that was not included in the subset is determined, which is a predicted value. Mean of predicted will be same as r^2 and LOO q^2 (cross-validated correlation coefficient value) since all the data point will be sequentially considered as predicted in LOO subset. Same procedure is repeated after elimination of another object until all objects have been eliminated once. (Kubyani, 1994). The leave-one-

out (LOO) method indicated the value of q^2 (cross-validated explained variance), which is a measure of the internal predictive ability of the model and pred_r^2 which is a measure of the external predictive ability of the model.

Statistical significance of these models was further supported by 'fitness plot' obtained for each model; this is a plot of actual versus predicted activity of training and test set compounds and provides an idea about how fit the model was trained and how well it predicts activity of external test set. Nearness of experimental to predicted activity is also a tool to determine the statistical validity of models. Another feature for validation of QSAR model is value of F test. If the F value is greater than the tabulated value the equation is statistically significant and has high acceptance criteria.

Activity prediction of newer derivatives

After successful development of 2D and 3D QSAR models of all the reported series, an attempt was made to predict the activity of some newer derivatives which has not yet reported and synthesized.

This was performed using the Molecular Design Suite (VLife MDS software package, version 4.2; from VLife Sciences, Pune, India), on a Lenovo computer with Intel Core i3- processor and a window XP operating system.

The structure entry and optimization was done as stated in previous section 4.8.3. The descriptors were calculated and data was selected by random and manual data selection method. 2D QSAR studies were done by multiple linear regression method by stepwise forward backward variable selection method.

A suitable model was selected for prediction of activity and it was saved by proper name in the software. In the next step open all the new molecules whose activities are to be determined, were opened in the QSAR worksheet. Once all the molecules have appeared in worksheet, go to tools and click on generic prediction. A prediction window is then opened in which the saved model is selected for activity prediction. Once the model is open it is analyzed by clicking on predict button and the activity of all the new molecules is obtained along with the proper contribution of all descriptors.

QSAR studies on Benzothiazole derivatives

A series of 21 molecules of Benzothiazole derivatives reported in literature by Ashok kumar *et al* (2010) were used for development of 2D and 3D QSAR models. The data set of 20 molecules were divided into training and test set in the ratio of 70:30, The biological activity was converted to logarithmic scale (pIC_{50}) in mathematical operation mode of the software. The grid setting for the 3D QSAR shown in the table 01.

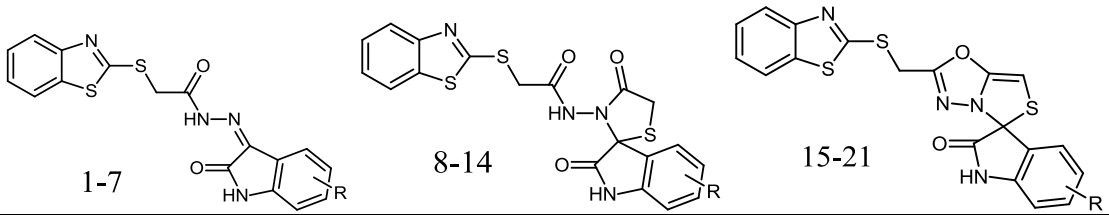
Table 01: Grid settings for benzothiazole derivatives.

	From	To	Interval
X	-3.69664	21.9125	2.000
Y	-0.200126	20.8187	2.000
Z	-6.9389	12.4315	2.000

RESULTS AND DISCUSSION

A series of substituted Benzothiazole derivatives reported in literature (hemlata kaur*et al* 2010) were chosen for QSAR study in order to establish quantitative relationship between physiochemical properties and biological activities of the compounds using software MDS version 4.2 (VlifeScience). A series of 21 molecules of Benzothiazole derivatives against the analgesic and anti-inflammatory activity were selected to develop models for establishing 2D and 3D QSAR. The structure and biological activity of the selected series is shown in Table 02.

Table 02: Structures of Benzothiazole derivatives with reported activities.



Sr. No.	R	Activity(Analgesic) IC_{50}	Activity(Analgesic) Log IC_{50}	Activity(Anti-inflammatory) IC_{50}	Activity(Anti-inflammatory) Log IC_{50}
1	5-OCH_3	12.6	1.1003	10.8	1.0334
2	5-CH_3	8.8	0.9444	13.5	1.1303
3	7-CH_3	10.8	1.0334	11.5	1.0606
4	5-Cl	14.7	1.1673	17.8	1.2504
5	7-Cl	12.4	1.0934	15.6	1.1931
6	5-Br	12.2	1.086	14.4	1.1583
7	7-Br	11.8	1.0718	12.8	1.1072

8	5-OCH_3	13.2	1.1205	15.9	1.2013
9	5-CH_3	14.5	1.1613	18.4	1.2648
10	7-CH_3	14.8	1.1702	24.6	1.3909
11	5-Cl	16.6	1.2201	27.2	1.4345
12	7-Cl	18.6	1.2695	20.7	1.3159
13	5-Br	18.6	1.2695	26.1	1.4166
14	7-Br	16.3	1.2121	18.6	1.2695
15	5-OCH_3	29.2	1.1014	31.2	1.4941
16	5-CH_3	25.9	1.4132	31.4	1.4969
17	7-CH_3	25.9	1.4698	28.6	1.4563
18	5-Cl	32.2	1.5078	44.8	1.6512
19	7-Cl	43.2	1.6354	36.4	1.5611
20	5-Br	27.6	1.440	32.2	1.5078
21	7-Br	27.3	1.4361	30.8	1.4885

2D QSAR Benzothiazole derivatives

In 2D QSAR analysis, multiple linear regression analysis (MLR) coupled with stepwise forward backward variable selection method was applied to generate 2D models. Selection of training and test set was done by Manual data selection, Random selection method and sphere exclusion method. From these models, the best model was selected having good q^2 and pred_r^2 values. Statistically significant 2D QSAR models are shown in Table 03 and 04.

2D QSAR for Analgesic activity

Table 03: Statistical evaluation of 2D-QSAR models of benzothiazole derivatives.

Trials	r^2	q^2	r^2se	q^2se	Pred_r^2	Pred_r^2se	F test
1(Model-1)	**0.8578**	**0.7415**	**0.0759**	**0.1024**	**0.7015**	**0.1147**	**33.17**
2(Model-2)	0.8369	0.7150	0.071	0.1044	0.6636	0.1173	28.72
3(Model-3)	0.9656	0.9371	0.0350	0.0473	0.5832	0.1393	154

The selection of the best model is based on the values of r^2 (squared correlation coefficient), q^2 (cross-validated correlation coefficient), pred_r^2 (predicted correlation coefficient for the external test set), F (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^2se, q^2se and pred_r^2se are the standard errors terms for r^2, q^2 and pred_r^2 respectively.

Interpretation of the model -1

Model-(Test set: 7, 14, 16, 2, 6, 7, and 9)

***p*IC$_{50}$(column)**= 0.3185 (SaasCE-Index) 0.0174(T_2_C_6) -0.5394 (I)

Statistics

[n= 14; Degree of freedom= 9; r^2 =0.8578; q^2=0.7415; F test=33.1724; r^2se=0.0759; q^2se= 0.0.1024; pred_r^2= 0.7015; pred_r^2se = 0.1147]

From the equation (I), model 1 explains 85.78% (r^2 = 0.8578) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of 74.15% and 70.15% 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 99.9999 (Alpha Rand Pred R^2 = 0.00000) that the generated model is not random and hence chosen as the QSAR model. The F-test=33.17 which is greater than the tabulated value 1.93766 (Bolton 2004). From QSAR model 1,

1. Positive coefficient value of SaasCE-Index [Electrotopological state indices for number of carbon atom connected with one single bond along with two aromatic bonds.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.
2. Positive coefficient value of T_2_C_6 [This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from Carbon atom by 5 bonds.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

Contribution chart Data fitness plot and activity of training and test set for model 1 is represented in Fig. 01, 02, 03 and 04 respectively.

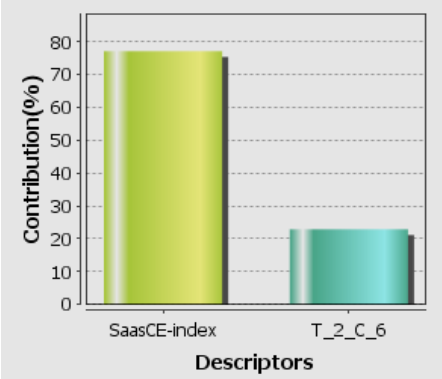


Figure 1: Contribution plot for model 1.

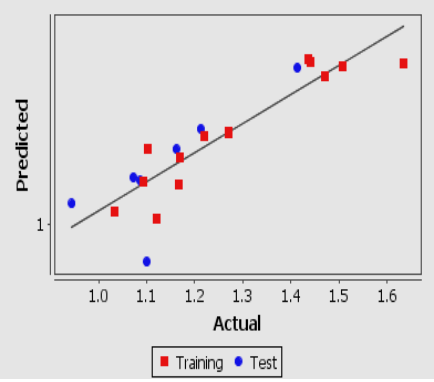


Figure 2: Contribution plot for model 1.

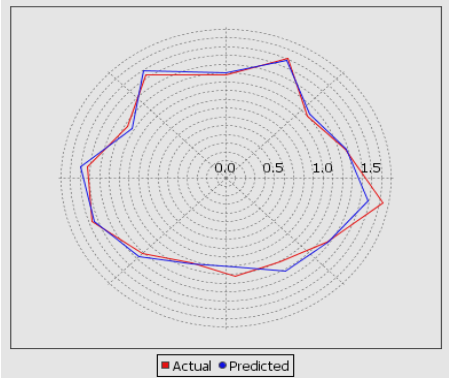


Figure 3: Test set for model 1.

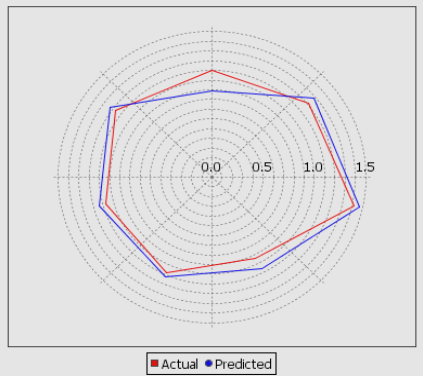


Figure 4: Training set for model 1.

2D QSAR for Anti inflammatory activity

Table 04: Statistical evaluation of 2D-QSAR models of Benzothiazole derivatives.

Trials	r^2	q^2	r^2se	q^2se	Pred_r^2	Pred_r^2se	F test
1(Model-4)	**0.9457**	**0.9189**	**0.0463**	**0.0565**	**0.9476**	**0.04**	**58.037**
2(Model-5)	0.9870	0.9791	0.0222	0.0282	0.8921	0.07	253.14
3(Model-6)	0.9732	0.9459	0.0340	0.483	0.8890	0.014	120.89

Interpretation of Model-4 (Test set: 15, 16, 2, 20, 21, 3, and 8)

***p*IC$_{50}$ (column)** = 0.1113(XlogP) 0.0952 (T_C_Cl_5) - 0.0799 (T_N_Br_3) 0.7355 (II)

Statistics: [n= 14; Degree of freedom=9 r^2 =0.9457; q^2=0.9189; F test=58.037; r^2se=0.0463; q^2se = 0.0565; pred_r^2= 0.9476; pred_r^2se = 0.04.

From equation (II), model 1 explains 94.57% (r^2 = 0.9457) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of 91.89% and 94.76% 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 99.9999 (Alpha Rand Pred R^2 = 0.00000) that the generated model is not random and hence chosen as the QSAR model. The F-test=58.037 which is greater than the tabulated value 2.14 (Bolton 2004). From QSAR model 1,

1. Positive coefficient value of XlogP [This descriptor signifies ratio of solute concentration in octanol & water and generally termed as Octanol Water partition Coefficient. This is atom based evaluation of logP as described in Wang et al.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.
2. Positive coefficient value of T_C_Cl_5 [This is the count of number of Carbon atoms (single double or triple bonded) separated from any Chlorine atom (single double or triple bonded) by 5 bonds in a molecule.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.
3. Negative coefficient value of T_N_Br_3 [This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any Bromine atom (single or double bonded) by 3 bonds distance in a molecule.] On the biological activity indicated that lower values leads to good inhibitory activity while higher value leads to reduced inhibitory activity. Contribution chart Data fitness plot and activity of training and test set for model 1 is represented in Fig. 05, 06, 07 and 08 respectively.

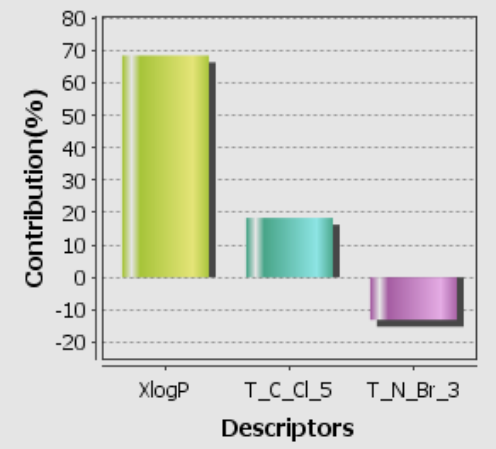


Fig. 05 Contribution Plot.

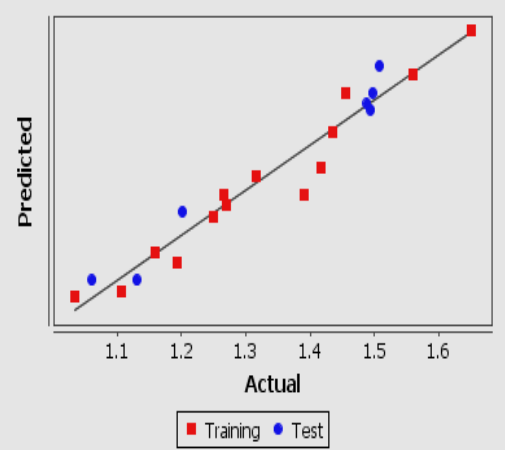


Fig. 06 Fitness plot.

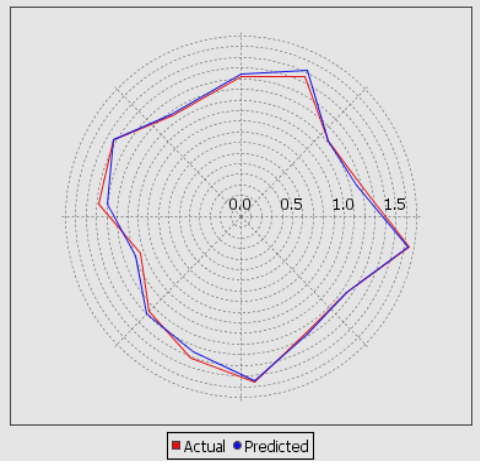


Fig. 07 Training Set.

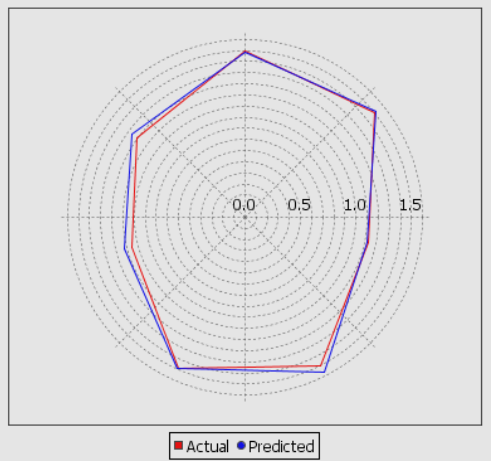


Fig. 08 Test Set.

3D QSAR Benzothiazole derivatives

kNN-MFA samples the steric and electrostatic fields surrounding a set of ligands and constructs 3D-QSAR models by correlating these 3D fields with the corresponding biological activities. Molecular alignment was used to visualize the structural diversity in the given set of molecules. The template structure i.e Benzothiazole derivatives was used for alignment by considering the common elements of the series as shown in Fig. 09 and 10.

Fig. 09 Template molecule.

Fig. 10 Stereo view of aligned molecules.

3D QSAR for Analgesic activity

Table 05: Statistical evaluation of 3D-QSAR models of Benzothiazole derivatives.

Trials	kNN	DOF	q^2	q^2_se	pred_r^2	pred_r^2se
1(Model-1)	**2**	**12**	**0.9245**	**0.0415**	**0.6320**	**0.1505**
2(Model-2)	2	12	0.8555	0.0717	0.6197	0.1133
3(Model-3)	2	12	0.8153	0.0782	0.4614	0.1624

Model-1(Test set: 18, 19, 2, 4, 7, 8, and 9)
***p*IC$_{50}$**= E_160 0.8499 - 0.8514 and S_1158 -0.0635 - 0.0626 (III)

Statistics
[kNN= 2; n = 14; DOF= 12; q^2= 0.9245; q^2_se = 0.0415; pred_r^2 = 0.6320; pred_r^2se = 0.1505]
The model 1 explains values of k (2), q^2 (0.9245), pred_r^2 (0.6320), q^2_se (0.0415), and pred_r^2 se (0.1505) prove that QSAR equation so obtained is statistically significant and shows the predictive power of the model is 92.45% (internal validation). Table 05 represents the predicted inhibitory activity by the model-1 for training and test set.

The data for Plot of contribution chart, fitness plot, training set and test set for model 1 are shown in Fig.11, 12, 13 and 14. 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.

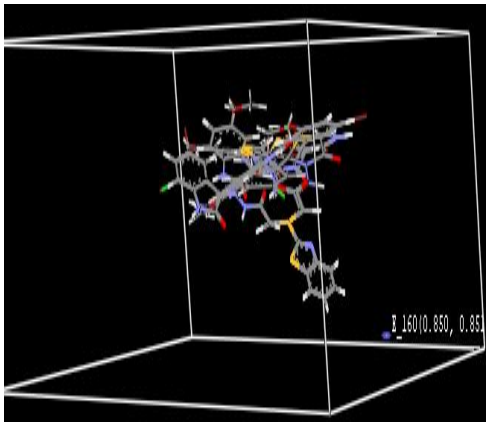


Figure 11: Plot of Contribution Chart.

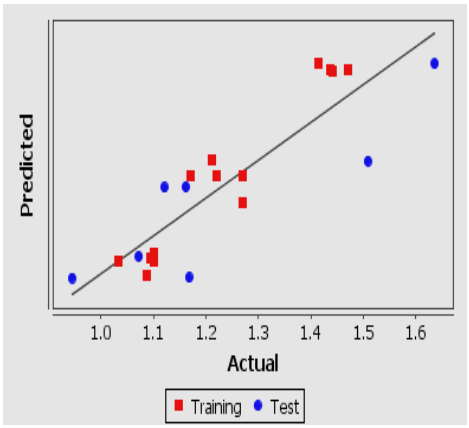


Figure 12: Fitness Plot.

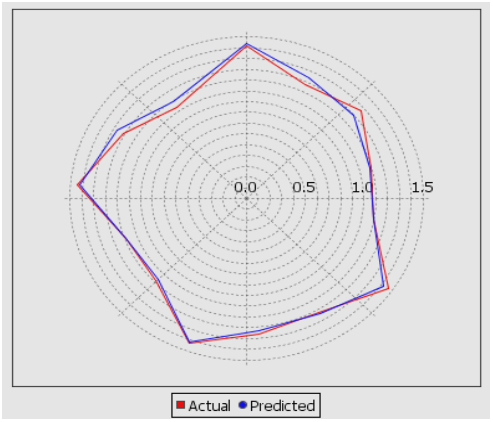


Figure 13: Plot of training Set.

Figure 14: Plot of Test Set.

Steric field, S_1158 (-0.065-0.0626) negative steric potential is favourable for increase in the activity and hence less bulky substituent group is preferred in that region.

Electrostatic field, E_160 (0.8499, 0.8514) positive Electrostatic potential is favourable for increase in the activity and hence more bulky substituent group is preferred in that region.

3D QSAR for Anti inflammatory activity
Table 06: Statistical evaluation of 3D-QSAR models of Benzothiazole derivatives.

Trials	kNN	DOF	q^2	q^2_se	pred_r^2	pred_r^2se
1(Model-4)	**3**	**22**	**0.8170**	**0.2667**	**0.7773**	**0.2815**
2(Model-5)	2	23	0.7121	0.2951	0.67541	0.3759
3(Model-6)	2	22	0.7979	0.2638	0.5119	0.4780

Interpretation of Model-4(Test set:12,14,22,26,28,29,34,5,6,7,8,9)
***p*IC$_{50}$**= -E_499 (-4.6902-2.8921) (IV)

Statistics
[kNN= 2; n = 26; DOF= 23; q^2= 0.8170; q^2_se = 0.2667; pred_r^2 = 0.7773; pred_r^2se = 0.2815]
The model 6 explains values of k (2), q^2 (0.8170), pred_r^2 (0.7773), q^2_se (0.2667), and pred_r^2 se (0.2815)

prove that QSAR equation so obtained is statistically significant and shows the predictive power of the model is 80.03% (internal validation). Table 06 represents the predicted inhibitory activity by the model-1 for training and test set. The data fitness plot for model 1 is shown in Fig.16. 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.

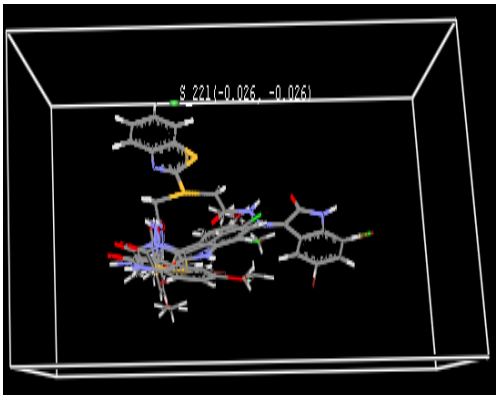


Figure 15: Plot of contribution chart.

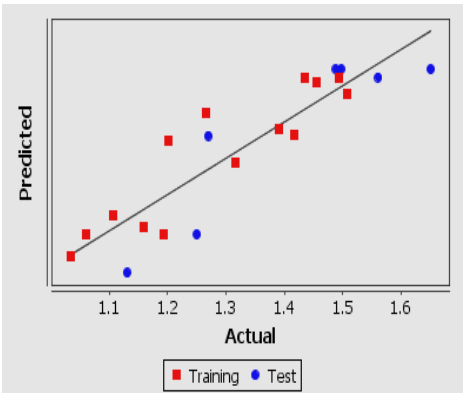


Figure 16: Data fitness plot.

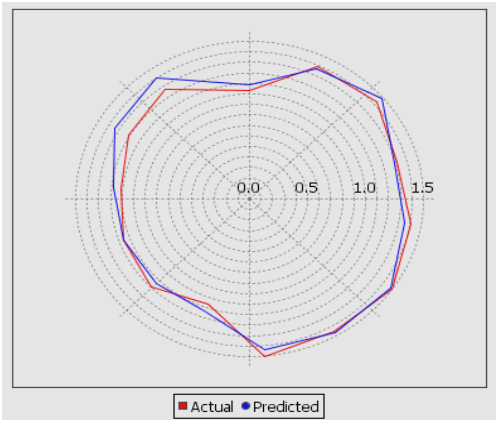


Figure 17: Training Set.

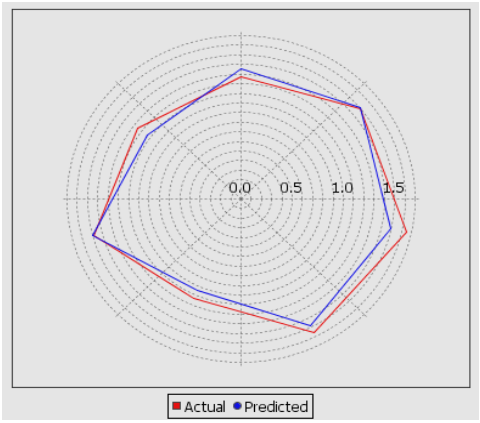


Figure 18: Test Set.

Steric field, S_221 (-0.0264, -0.0263) negative steric potential is favourable for increase in the activity and hence less bulky substituent group is preferred in that region.

Table 07: Actual vs. predicted activity of Benzothiazole derivatives.

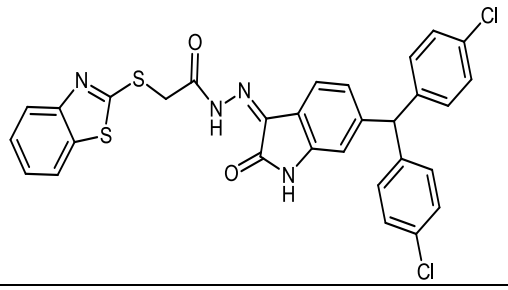
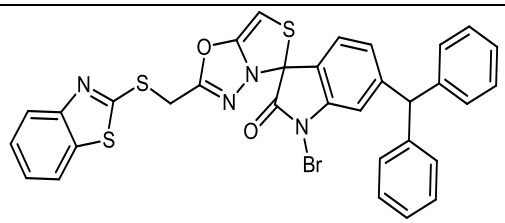
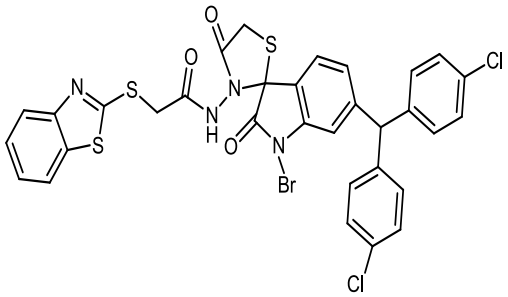
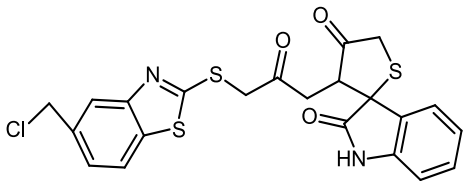
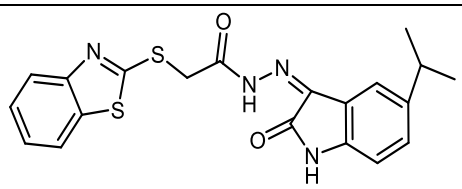
Sr. No.	Analgesic actual activity	Predicted		Anti-inflammatory Actual activity	Predicted activity	
		2D	3D		2D	3D
1	1.1003	0.888	1.02	1.0334	1.086	1.084
2	0.9444	1.063	1.059	1.1303	1.121	1.047
3	1.0334	1.038	1.09	1.0606	1.121	1.133
4	1.1673	1.121	1.06	1.2504	1.254	1.133
5	1.0934	1.128	1.094	1.1931	1.159	1.133
6	1.086	1.132	1.063	1.1583	1.178	1.15
7	1.0718	1.141	1.097	1.1072	1.098	1.176
8	1.1205	1.016	1.219	1.2013	1.266	1.341
9	1.1613	1.226	1.22	1.2648	1.301	1.404
10	1.1702	1.201	1.241	1.3909	1.301	1.366
11	1.2201	1.266	1.241	1.4345	1.434	1.482
12	1.2695	1.274	1.191	1.3159	1.339	1.292
13	1.2695	1.277	1.241	1.4166	1.358	1.353
14	1.2121	1.287	1.27	1.2695	1.278	1.352
15	1.1014	1.266	1.09	1.4941	1.48	1.482
16	1.4132	1.47	1.439	1.4969	1.516	1.5
17	1.4698	1.445	1.427	1.4563	1.516	1.471

18	1.5078	1.476	1.266	1.6512	1.649	1.5
19	1.6354	1.483	1.439	1.5611	1.553	1.482
20	1.440	1.487	1.425	1.5078	1.573	1.445
21	1.4361	1.496	1.427	1.4885	1.493	1.5

CONCLUSION

The data set of 21 molecules were divided into training and test set in the ratio of 70:30, The biological activity was converted to logarithmic scale (pIC_{50}) in mathematical operation mode of the software. The statistically significant 2D-QSAR models for Analgesic activity are r^2 =0.8578 and q^2 = 0.7415 and on Anti inflammatory giving r^2 = 0.9457 and q^2 =0.9476. 3D QSAR results for internal (q^2 = 0.9245, q^2=0.8170) and external (predictive r^2 = 0.6320, q^2 = 0.7773) validation criteria. Thus, 3D QSAR models showed that electrostatic effects dominantly determine the binding affinities. 2D QSAR studies revealed that Saas CE Index descriptors were major contributing descriptor in case of analgesic activity and Xlog P in case of Anti inflammatory activity. By using kNN-MFA method. The results derived may be useful in further designing of novel therapeutic agents as follows.

Table 08: Newly Designed Benzothiazole molecules with predicted activity.

Sr.No.	Newly Designed Molecules	Anti- inflammatory Predicted activity	Analgesic Predicted activity
1		38.58	199.89
2		38.59	229.08
3		72.44	575.43
4		41.68	512.86
5		57.54	426.57

ACKNOWLEDGEMENT

The author wishes to express gratitude to V-life Science Technologies Pvt. Ltd. for providing the software for the study. Also the author is thankful to The Principal of Mahatma Gandhi Vidyamandir's Institute of Pharmacy for providing the necessary facilities to carry out the research work.

REFERENCES

1. Ajmani S, Jadhav K, Kulkarni S. Three-dimensional QSAR using the k-nearest neighbour method and its interpretation. J Chem Info and Model, 2006; 46: 24-31.
2. Balbi A, Anzaldi M. Synthesis and biological evaluation of novel pyrazole derivatives with anticancer Activity. Euro J of Med Chem, 2011; 46: 5293-5309.
3. Chen CL, Chang D, Chen T. Structure-based design, synthesis and evaluation of novel anthra[1,2-d]imidazole- 6,11-dione derivatives as telomerase inhibitors and potential for cancer Polypharmacology. Euro J of Med Chem, 2013; 60: 29-41.
4. Di-Liang Guo, Xing-Jie Zhang, Rui-Rui Wang et al. Structural modifications of 5,6-dihydroxypyrimidines with anti-HIV activity. Bioorg & Med Chem Lett, 2012; 22: 7114–7118.
5. Golbraikh A, And Tropsha A. Predictive QSAR modeling based on diversity sampling of experimental datasets for the training and test set selection. Jour of Comp-Aid Mole Des, 2002; 16(5): 357-369.
6. Kaur H, Kumar S, Singh I, Saxena K.K., Kumar A, Synthesis, characterization and biological activity of various substituted benzothiazole derivatives. Dig J Nano & Biostruct, 2010; 5(1): 67 – 76.
7. Kubinyi, H, Folkers, G And Martin Y. C. 3D QSAR in Drug Design. 3rd ed. Dordrecht, Netherlands: Kluwer Academic Publishers, 2003; 136-145.
8. *MDS (Molecular Design Suite)*. VLife Sciences Technologies, Pvt. Ltd. Pune, India. Available from: http://www.vlifesciences.com.
9. Metwally MA, Gouda MA, Ammar HN, Khalil AM. Synthesis, antitumor, cytotoxic and antioxidant evaluation of some new pyrazolotriazines attached to antipyrine moiety. Euro J Med Chem, 2012; 56: 254-262.
10. Pawel M. Lukasik et al. Synthesis and biological evaluation of imidazo[4,5-b]pyridine and 4-heteroarylpyrimidin derivatives as anti-cancer agents. Euro J Med Chem, 2012; 57: 311-322.
11. Yaseen A. Al-Soud et al. Nitroimidazoles. V. Synthesis and anti-HIV evaluation of new 5-substituted piperazinyl-4-nitroimidazole derivatives. Acta Pharm, 2007; 57: 379–393.
12. Daniel BC, et al. Non-steroidal Anti-inflammatory Agents – Benefits and New Developments for Cancer Pain. Suppor Onco, 2008; 1: 18-22.
13. Fadeyi OO, et al. Antipyretic, analgesic, anti-inflammatory and cytotoxic effects of four derivatives of salicylic acid and anthranilic acid in mice and rats. Afr J Biotech, 2004; 3(8): 426-431.
14. Doucet JP, et al. Nonlinear SVM approaches to QSPR/QSAR studies and drug design. Curr Comp Aid Drug Design, 2007; 3: 263–289.
15. Fabio B., Silvia C. And Renzo R. Synthesis and biological activity of vicinal diaryl-substituted 1H-imidazole., Tetrahedron, 2007; 63: 4571–4624.
16. Hudson BD et al. Parameter Based Methods for Compound Selection from Chemical Databases. Quant Stru-Act Relation, 1996; 15(4): 285-289.
17. Keche AP, Hatnapure GD, Tale RH, Rodge AH And Kamble VM. Synthesis, anti-inflammatory and antimicrobial evaluation of novel 1-acetyl-3,5-diaryl-4,5-dihydro (1H) pyrazole derivatives bearing urea, thiourea and sulfonamide moieties. Bioorg & Med Chem Lett, 2012; 22: 6611–6615.
18. Klebe G. And Mietzner T. A fast and efficient method to generate biologically relevant conformations. J Comp Aid Mole Des, 1994; 8(5): 583-606.
19. Kubiny H. Variable Selection in QSAR Studies. I. An Evolutionary Algorithm. QSAR, 1994; 13(3): 285-294.
20. Kubinyi H, Hamprecht, F.A, And Mietzner T. Three-dimensional quantitative similarity−activity relationships (3D QSAR) from SEAL similarity matrices. J Med Chem, 1998; 41: 2553-2564.
21. Norinder U. Single and domain mode variable selection in 3D QSAR applications. J Chemomet, 1996; 10(2): 95-105.
22. Plummer E. Hansch, C. And Fujita, T. Successful application of the QSAR paradigm in discovery programs. In: Classical and Three-Dimensional QSAR in Agrochemistry, ACS Symposium Series 606, Washington, DC: American Chemical Society, 1995.
23. Bajaj K, Srivastava VK, Lata SR. Chandra AK, Kumar A. Ind J Chem, 2003; 42B: 1723-1728.
24. Harib NJ, Jurcak JF, Bregna DE, Burqher KL, Hartman HB, Kafka S, Kerman LL, SK, Ongsamut J. E. Roehr, M. R. Szewczak, K. A. T. Woods, R., Corbett. Med Chem, 1996; 39(20): 4044-4057.
25. Hadjipavlou-Litina DJ, Geronikari AA. Drug design and discovery, 1998; 15(3): 199.
26. Mruthyunjayaswami BHM., Shanthaveerapa BK. Ind J of Chem, 2000; 39B: 433-439.