Sanmati and Achal, J Theor Comput Sci 2015, 2:2
DOI:10.4172/2376-130X.1000124

Journal of
Theoretical & Computational Science

Research Article Open Access

3D QSAR Analysis on Isatin Derivatives as Carboxyl Esterase Inhibitors Using *K*-Nearest Neighbor Molecular Field Analysis

Sanmati KJ[1*], Achal M[2]

[1]*SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur-495 009 (C.G.), India*
[2]*Shri Shankaracharya Institute of Pharmaceutical Sciences, Bhilai-490200 (C.G.), India*

Abstract

A three dimensional quantitative structure activity relationship (3D QSAR) using k nearest neighbor molecular field analysis (kNN MFA) method was performed on a series of isatin derivatives as carboxylesterase (CE) inhibitors. This study was performed with 49 compounds (data set) using sphere exclusion (SE) algorithm for the division of the data set into training and test set. SE algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. Between 3.0 to 5.5 dissimilarity levels which comprises of test set size 4 to 10, kNN-MFA methodology with stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) was used for building the QSAR models. Four predictive models were generated with SW-kNN MFA (pred_r2=0.7552 to 0.9376), three predictive models were generated with SA-kNN MFA (pred_r2=0.7019 to 0.9367) and two predictive models were generated with GA-kNN MFA (pred_r2=0.8226 to 0.8497). Most significant model generated by stepwise kNN-MFA showed internal predictivity 82.11% (q2=0.8211) and external predictivity 93.76% (q2=0.9376). In this model hydrophobic and steric interactions dominate the CE inhibitory activity. Hydrophobic field descriptor (H_977) with positive range indicates that positive hydrophobic potential is favorable for increase in activity and hence more hydrophobic substituent group is preferred in that region. Steric field descriptor (S_619) with negative range indicates that negative steric potential is favorable for increase in activity and hence less bulky substituent group is preferred in that region. The kNN-MFA contour plots provided further understanding of the relationship between structural features of substituted isatin derivatives and their activities which should be applicable to design newer potential CE inhibitors.

Keywords: 3D-QSAR; kNN-MFA; Carboxylesterases inhibitors; Isatin derivatives

Introduction

Carboxylesterases (CE) are ubiquitous enzymes which are responsible for the metabolism and detoxification of xenobiotics. Carboxylesterases (CEs) hydrolyze endogenous and exogenous esters to the corresponding alcohol and carboxylic acid [1-4]. In mammals, they tend to be expressed in tissues likely to be exposed to xenobiotics, including the liver, lung, small intestine, kidney, and so on [5]. CEs metabolize a number of useful drugs [6-9] such as Demerol and lidocaine, the anticancer agents capecitabine and CPT-11 [10] (irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin), breast cancer drug tamoxifen [11], antiviral drug oseltamivir, alzheimer's drug tacrine [12], narcotics cocaine and heroin [13], antithrombogenic agent clopidogrel, cholesterol lowering drug mevastatin [11]. Therefore, identification and application of selective CE inhibitors may prove useful in modulating the metabolism of esterified drugs *in-vivo* and for prolonging the bioactivity of agents that are inactivated by CEs or conversely may reduce the toxicity of compounds that are activated by these enzymes.

Benzil, ethane-1,2-dione chemo type (Benzil based compounds [14-17], analogues of isatin [18] reported in literature as CE inhibitors. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate properties (descriptors) of compounds with activities. The QSAR relationship is expressed as a mathematical equation [19-23]. Isatin analogs [18] with varied mode of selectively inhibits the Carboxylesterases (CE) were selected and 3D QSAR studies were performed to generate best predicative and validated QSAR model. In the present study, we have applied k-nearest neighbor molecular field analysis (kNNMFA) [24,25]. 3D-QSAR models permitted an understanding of the steric, electrostatic and hydrophobic requirements for ligand binding.

Materials and Methods

Data set and biological activity

In the present study 49 molecules of Isatin (indole-2,3-dione) derivatives [18] were used which were reported to have carboxylesterase inhibitory activity. Human intestinal carboxylesterase (hiCE) inhibitory data Ki [inhibition constant (μM)] reported have been converted to the logarithmic scale [pKi (moles)] for QSAR study.

Molecular modeling study

Molecular modeling and kNN-MFA studies were performed on HCL computer having genuine Intel Pentium Dual Core Processor and Windows XP operating system using the software Molecular Design Suite (MDS) [26]. Structures were drawn using the 2D draw application and converted to 3D structures. Structures were optimized by energy minimization and geometry optimization was done using Merck Molecular Force Field (MMFF) method with 10000 as maximum number of cycles, 0.01 as convergence criteria (root mean square gradient) and 1.0 as constant (medium's dielectric constant which is 1 for in vacuo) in dielectric properties. The default values of 30.0 and 10.0 Kcal/mol were used for electrostatic and steric energy cutoff.

***Corresponding author:** Sanmati KJ, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur-495 009 (C.G.) India, Tel: +919691054057; Fax: +919691054057; E-mail: sanmatijain72@yahoo.co.in

Received April 08, 2015; **Accepted** May 01, 2015; **Published** May 10, 2015

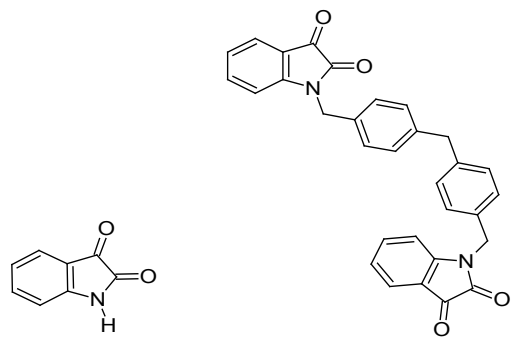
Citation: Sanmati KJ, Achal M (2015) 3D QSAR Analysis on Isatin Derivatives as Carboxyl Esterase Inhibitors Using K-Nearest Neighbor Molecular Field Analysis. J Theor Comput Sci 2: 124. doi:10.4172/2376-130X.1000124

Molecular alignment: The dataset were aligned by template based alignment method using most active molecule (49, Table 1) as a reference molecule **2** and structure **1** as a template (Figure 1) for alignment of the molecules. The alignment of all the molecules on the template (Figure 2). In the template based alignment method, a template structure was defined and used as a basis for alignment of a set of molecules.

Grid size: Once the molecules are aligned, a grid or lattice is established which surrounds the set of compounds in potential receptor surface. Current study uses grid resolution 2 Å.

Descriptor calculation: Once the molecules are aligned, a molecular field is computed on a grid of points in space around the molecule. This field provides a description of how each molecule will tend to bind in the active site. Descriptors representing the steric, electrostatic and hydrophobic interaction energies were computed at the lattice points of the grid using a methyl probe of charge +1.

Generation of training and test set: Sphere exclusion algorithm was used for generation of training and test sets. The whole data set was divided into training and test sets using sphere exclusion algorithm [25]. This algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. The higher the dissimilarity level c is, smaller the training set and larger the test set and *vice versa*. It is expected that the predictive ability of QSAR models generally decrease when the dissimilarity level increases. Once the training and test sets are generated, kNN methodology is applied to descriptors generated over grid.



[1] [2]

Figure 1: Structure of template [1] and reference molecule [2] used in template based alignment.

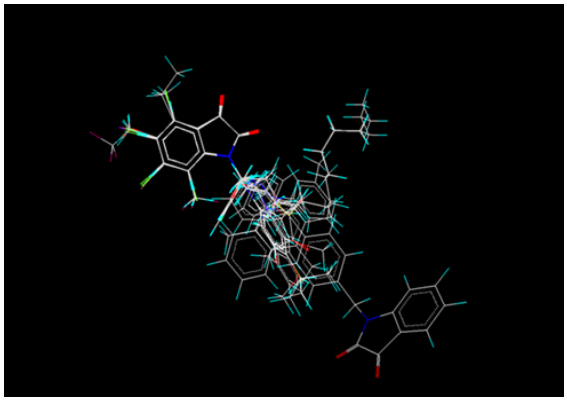


Figure 2: 3D-alignment of molecules (template based).

kNN-MFA methodology for building QSAR models: Models generated by kNN-MFA in conjunction with stepwise (SW) forward-backward, simulated annealing (SA) and genetic algorithm (GA) variable selection methods. The QSAR models were developed using Stepwise forward-backward variable selection method with pK_i activity field as dependent variable and descriptors as independent variable.

The kNN technique is a conceptually simple approach to pattern recognition problems. In this method, an unknown pattern is classified according to the majority of the class memberships of its k nearest neighbors in the training set. The nearness is measured by an appropriate distance metric (e.g., a molecular similarity measure, calculated using field interactions of molecular structures).

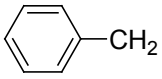
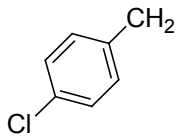
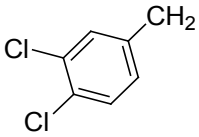
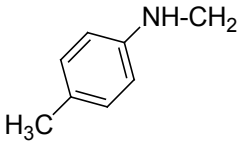
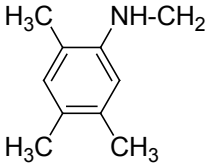
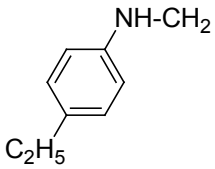
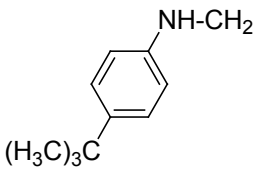
Stepwise forward-backward variable selection method [27] **(SW-kNN MFA):** This method uses stepwise variable selection and k-NN principle to build QSAR model. In each step this method optimize (i) the number of nearest neighbors (k) used to estimate the activity of each compound and (ii) select variables (stepwise) from the original pool of all molecular descriptors that are used to calculate similarities between compounds. It involves a step-by-step search procedure that begins by addition of a single independent variable with optimal k value (optimizing k value from the given range of k values) and highest sum of weighted k-nearest neighbor cross validation (q^2) and external validation ($pred\_r^2$) value amongst all available descriptors to form a model.

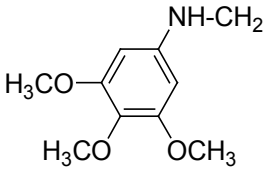
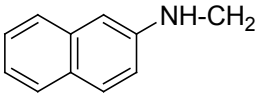
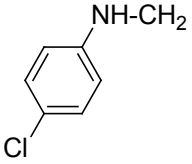
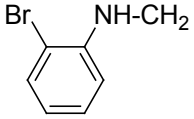
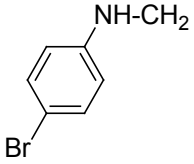
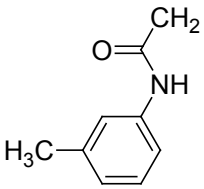
The parameter settings used for SW-kNN MFA are Cross correlation limit as 0.5, maximum number of variable in final equation as n/5 (n is number of compounds in training set), term selection criteria as q^2, Ftest in as 4 and Ftest out as 3.99, variance cut-off as 0 and Scaling as Auto Scaling, number of maximum neighbors as 5, number of minimum neighbors as 2 and distance based weighted average as prediction method.

Simulated annealing k-NN QSAR algorithm [24] **(SA-kNN MFA):** Simulated annealing is to simulate a physical process called annealing, in which a system is heated to a high temperature and then is gradually lowered to a preset temperature value (e.g. room temperature). During this process, the system samples possible configurations according to Boltzmann distribution. At equilibrium, low energy states wil be mostly populated.

k-NN MFA method employs the kNN classification principle combined with the variable selection procedure. For each predefined number of variables (nvar) it seeks to optimize using stochastic sampling and simulated annealing as an optimization tool. The parameter settings used for simulated annealing in the present study are Maximum temperature as 100, minimum temperature as 0.01, cross correlation limit as 0.5, terms in model as n/5 (n is number of compounds in training set), iteration at given temperature as 5, decrease temperature by as 10, seed as 0, perturbation limit as 1, term selection criteria as q^2, variance cut-off as 0 and Scaling as Auto Scaling, number of maximum neighbors as 5, number of minimum neighbors as 2 and distance based weighted average as prediction method.

Genetic algorithm k-NN QSAR algorithm (GA-kNN MFA): The genetic function approximation (GFA) algorithm (Rogers and Hopfinger) offers a new approach in building quantitative structure-activity relationship (QSAR) and quantitative structure-property relationship (QSPR) models. Replacing regression analysis with the GFA algorithm allows the construction of models competitive with or superior to those produced by standard techniques and makes available additional information not provided by other techniques [28].

S. No.	ID	R_1	R_2	R_3	R_4	R_5	Ki (hiCE) [μM]	log (1/Ki) or pK_i [M]
1	2	CH_3					38.2	4.417
2	3	CH_2OH					34.5	4.4621
3	4	Cl					29.2	4.5346
4	5	C_2H_4I					1.58	5.8013
5	6	C_2H_4I					0.74	6.1307
6	10	COC_3H_7					68.2	4.1662
7	13						0.95	6.0222
8	14						0.87	6.0604
9	15						0.032	7.4948
10	16						0.067	7.1739
11	17						1.08	5.9665
12	18						2.88	5.5406
13	19						0.41	6.3872
14	20						0.61	6.2146

15	21						2.69	5.5702
16	22						0.11	6.9586
17	23						0.2	6.6989
18	24						0.047	7.3279
19	25						0.17	5.7695
20	27						5.51	5.2588
21	28		C_2H_5				37.9	4.4213
22	29		Cl				7.77	5.1095
23	33			Cl			14.9	4.8268
24	34			Br			13.3	4.8761
25	35			I			22.8	4.6420
26	36			CF_3O			7.49	5.0990
27	38	$CH_2(C=CH_2)CH_3Cl$		Br			0.28	6.5528
28	40				Cl		29.7	4.5361
29	43					Cl	9.55	5.0199
30	45					CH_3	33.4	4.4762
31	47		CH_3			CH_3	30.8	4.5114
32	48			CH_3		CH_3	84.6	4.0736
33	49		Cl	Cl			2.56	5.5917
34	50		Cl		Cl		0.62	6.2076

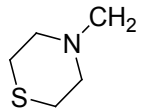
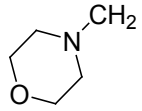
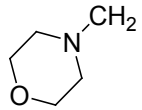
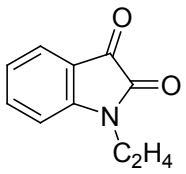
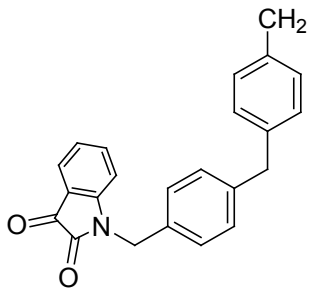
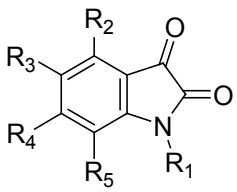
35	51					Cl	0.65	6.1870
36	52			Cl	Cl		16.6	4.7798
37	53			Cl		Cl	4.08	5.3893
38	54				Cl	Cl	21.8	4.6615
39	55		CH_3			CH_3	17.2	4.7520
40	56			CH_3		CH_3	21.8	4.6615
41	57				Cl	CH_3	53.5	4.2716
42	58			CH_3	Br		7.41	5.1301
43	59						22.2	4.6536
44	60						27.4	4.5622
45	61						22.5	4.478
46	62	$C_{12}H_{25}$					0.008	8.0969
47	63	$C_{16}H_{33}$					0.011	7.9586
48	64						1.54	5.8124
49	65						0.01	8.0000

Table 1: General structure of Isatin derivatives and their biological activities (data set of 49 molecules).



*Compounds having Ki>100 (μM) in the selected series were excluded and the resulting total data set of 49 molecules for hiCE were used for the present study.

The GFA algorithm used to perform a search over the space of possible QSAR/QSPR models using the fitness score (LOO q^2/cross terms) to estimate the fitness of each model. Such evolution of a population of randomly constructed models leads to the discovery of highly predictive QSARs/QSPRs.

The parameter settings used for genetic algorithm in the present study are Cross correlation limit as 0.5, chromosome length as n/5 (n is number of compounds in training set), cross over probability as 0.95, mutation probability as 0.05, population as 10, number of generations as 1000, convergence criteria as 0.01, seed as 0, term selection criteria as q^2, variance cut-off as 0 and Scaling as Auto Scaling, number of maximum neighbors as 5, number of minimum neighbors as 2 and distance based weighted average as prediction method.

Cross-validation (q^2) using weighted k-nearest neighbor [25]**:** In cross validation, a compound is eliminated in the training set and its biological activity is predicted on the basis of the k-NN principle, i.e., as the weighted average activity of k most similar molecules (k is set to 1 initially). The similarities are evaluated as Euclidean distances between compounds using only the subset of descriptors that corresponds to the current model. This step is repeated until every compound in the training set has been eliminated and its activity is predicted once.

Cross-validated r^2 (q^2) value can be calculated by using following equation, where y_i and y_* are the actual and predicted activities of the i^{th} compound, respectively, and y_{mean} is the average activity of all compounds in the training set. Both summations are over all compounds in the training set. The obtained q^2 value is indicative of the predictive power of the current k-NN QSAR model in predicting compounds in training set.

$$q^2 = 1 - \sum (y_i - y_*)^2 / \sum (y_i - y_{mean})^2$$

Above procedure is repeated for k=2, 3, 4, etc. Formally, the upper limit of k is the total
number of compounds in the data set. The k value that leads to the highest q^2 value is
chosen for the current k-NN QSAR model.

External validation (pred_r^2) using weighted k-nearest neighbor [26]: Following procedure was applied for external validation.

(1) Predict biological activity of a compound in the test set on the basis of the k-NN principle, i.e., as the weighted average activity of k (that correspond k value for highest q^2 value) most similar molecules in the training set. The similarities are evaluated as Euclidean distances between compounds using only the subset of descriptors that corresponds to the current model (for highest q^2 value).

(1) Repeat step 1 for every compound in the test set.

(2) Calculate the predicted r^2 (pred_r^2) value using following equation, where y_i and y_* are the actual and predicted activities of the i^{th} compound in test set, respectively, and y_{mean} is the average activity of all compounds in the training set. Both summations are over all compounds in the test set. The obtained pred_r^2 value is indicative of the predictive power of the current k-NN QSAR model for external test set.

$$pred\_r^2 = 1 - \sum (y_i - y_*)^2 / \sum (y_i - y_{mean})^2$$

Results and Discussion

Different training and test set of isatin (1-H-indole-2,3-dione) derivatives were constructed using sphere exclusion data selection method at different dissimilarity levels (3.0 to 5.5). Training and test set were selected using sphere exclusion method at different dissimilarity level if they follow the Uni column statistics, i.e., maximum of the test is less than maximum of training set and minimum of the test set is greater than of training set, which is prerequisite for further QSAR analysis (Table 2). This result shows that the test is interpolative i.e., derived from the min-max range of training set. The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution of the two sets. k-Nearest neighbor molecular field analysis (kNN-MFA) was applied using stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) approace QSAR models. Results of models developed by SW-kNN MFA, SA-kNN MFA and GA-kNN MFA are shown in Table 3. Best three significant models generated on the basis of predicted correlation coefficient are shown in Table 4. Following statistical measure was used to correlate biological activity and molecular descriptors: n=number of molecules, Vn=number of descriptors, k=number of nearest neighbor, df=degree of freedom, r2=squared correlation coefficient, q2=cross validated correlation coefficient (by the leave-one out method), pred_r2=predictive correlation coefficient for external test set, pred_r2se=coefficient of correlation of predicted data set, Z score=the Z score calculated by q2 in the randomization test, and α=the statistical significance parameter obtained by the randomization test. Data fitness plot for models 1-3 are shown in Figures 2-4. Result of the observed and predicted biological activity for the training and test compounds in the models 1-3 are shown in Table-5. The plot of observed vs. predicted activity of training and test sets for models 1 to 3 is shown in Figures 5-7**.** From the plot it can be seen that kNN-MFA model is able to predict the activity of training set quite well (all points are close to regression line) as well as external. Sphere exclusion (SE) algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. Between 3.0 to 5.5 dissimilarity levels which comprises of test set size 4 to 10, kNN-MFA methodology with stepwise (SW), simulated annealing (SA) and genetic algorithm (GA) was used for building the QSAR models. Four predictive models were generated with SW-kNN MFA (pred_r2=0.7552 to 0.9376), three predictive models were generated with SA-kNN MFA (pred_r2=0.7019 to 0.9367) and two predictive models were generated with GA-kNN MFA (pred_r2=0.8226 to 0.8497). The kNN-MFA contour plots (Figures 8) provided further understanding of the relationship between structural features of substituted isatin derivatives and their activities which should be applicable to design newer potential CE inhibitors. Further increase in dissimilarity value has produced decrease in model quality.

Interpretation of model 1

It is produced by using stepwise kNN-MFA method having internal predictivity 82.11% (q2=0.8211) and external predictivity 93.76% (pred_r2=0.9376). kNN-MFA plot shown in Figure 8. This model showed that hydrophobic (H_977) and steric (S_619) interactions play important role in determining carboxyl esterase inhibitory activity. Hydrophobic field descriptor (H_977) has positive range (0.3552 to 0.7596) indicates that positive hydrophobic potential is favorable for increase in activity and hence more hydrophobic substituent group

Column Name	Average	Max	Min	Std Dev	Sum
Training set (pK_i)	5.5896	8.0969	4.0726	1.1302	245.9431
Test set (pK_i)	5.3106	6.6990	4.5346	0.9228	26.5531

Table 2: Uni-Column Statistics for model 1 for training and test set activity.

		SW-KNN MFA		SA-KNN MFA		GA-KNN MFA	
Dissimilarity Value	**Test set mol**	**q^2**	**pred_r^2**	**q^2**	**pred_r^2**	**q^2**	**pred_r^2**
3.0	23;34;35;5	0.8272	0.8528	0.7679	0.6081	0.7131	0.8226
4.0	23;34;35;4;5	0.8211	0.9376	0.7348	0.7200	0.7673	0.8497
4.5	23;33;35;40;43;5;55	0.8221	0.8906	0.7522	0.7019	0.6585	0.6785
5.0	17;23;33;34;43;6;40;55; 47	0.8346	0.7552	0.8038	0.5230	0.6228	0.7101
5.5	17;23;33;34;43;5;6;40;55;47	0.9012	-0.1341	0.6662	0.0375	0.7961	0.3852

Table 3: Result of kNN-MFA study using various variable selection methods.

Parameters	**Model-1 (Diss val=4.00) SW-kNN MFA**	**Best Model-2 (Diss val=3.00) SA-kNN MFA**
Training Set Size (n)	44	42
Test set size	5	7
k nearest neighbour	3	3
q^2	0.8211	0.8221
q^2se	0.4780	0.4830
pred_r^2	0.9376	0.8906
pred_r^2se	0.2433	0.3048

Table 4: Statistical significant models generated using kNN-MFA method on the basis of predictive correlation coefficient (Best three model).

S. No.	**Compound**	**Actual pK_i**	**Predicted pK_i**	
			Model 1	**Model 2**
1	2	4.4179	4.2856	4.42142
2	3	4.4622	4.4775	4.57359
3	4	4.5346	4.9248*	4.80192
4	5	5.8013	6.1564*	5.22974*
5	6	6.1308	6.1973	5.03719
6	10	4.1662	4.5053	4.68625
7	13	6.0223	5.366	5.96055
8	14	6.0605	6.2589	5.9456
9	15	7.4949	6.8866	7.42994
10	16	7.1739	7.0584	7.49075
11	17	5.9666	6.3036	5.74261
12	18	5.5406	4.6004	6.64539
13	19	6.3872	6.0876	5.76312
14	20	6.2147	6.6778	6.42331
15	21	5.5702	6.1764	5.61473
16	22	6.9586	6.4886	6.7688
17	23	6.699	6.8574*	6.83228*
18	24	7.3279	6.5834	6.58432
19	25	6.7696	6.7559	6.77363

20	27	5.2588	4.5878	6.0899
21	28	4.4214	5.4597	4.84025
22	29	5.1096	4.6401	5.14193
23	33	4.8268	4.5935	4.61013*
24	34	4.8761	4.7465*	5.21946
25	35	4.6421	4.6747*	4.61006*
26	36	5.1255	4.399	5.13725
27	38	6.5528	6.8635	5.783
28	40	4.5272	4.9229	4.6101*
29	43	5.0200	4.6755	5.02772*
30	45	4.4763	5.0249	4.49826
31	47	4.5114	4.9379	4.91948
32	48	4.0726	5.0253	4.53604
33	49	5.5918	6.1975	5.92876
34	50	6.2076	5.8884	5.72282
35	51	6.1871	5.9035	5.73006
36	52	4.7799	5.0287	5.0603
37	53	5.3893	4.7203	5.21589
38	54	4.6615	5.0894	5.45793
39	55	4.7645	4.8172	4.36713*
40	56	4.6615	4.6952	4.51981
41	57	4.2716	4.8949	4.65049
42	58	5.1302	4.3986	4.94322
43	59	4.6536	4.6057	4.33347
44	60	4.5622	5.3129	4.28558
45	61	4.6478	5.3305	4.51014
46	62	8.0969	7.9786	7.55117
47	63	7.9586	8.051	7.76452
48	64	5.8125	4.8107	5.19885
49	65	8.0000	7.1532	6.89096

*Indicates that the compounds are in the test set.

Table 5: Actual and predicted biological activity for models 1-3.

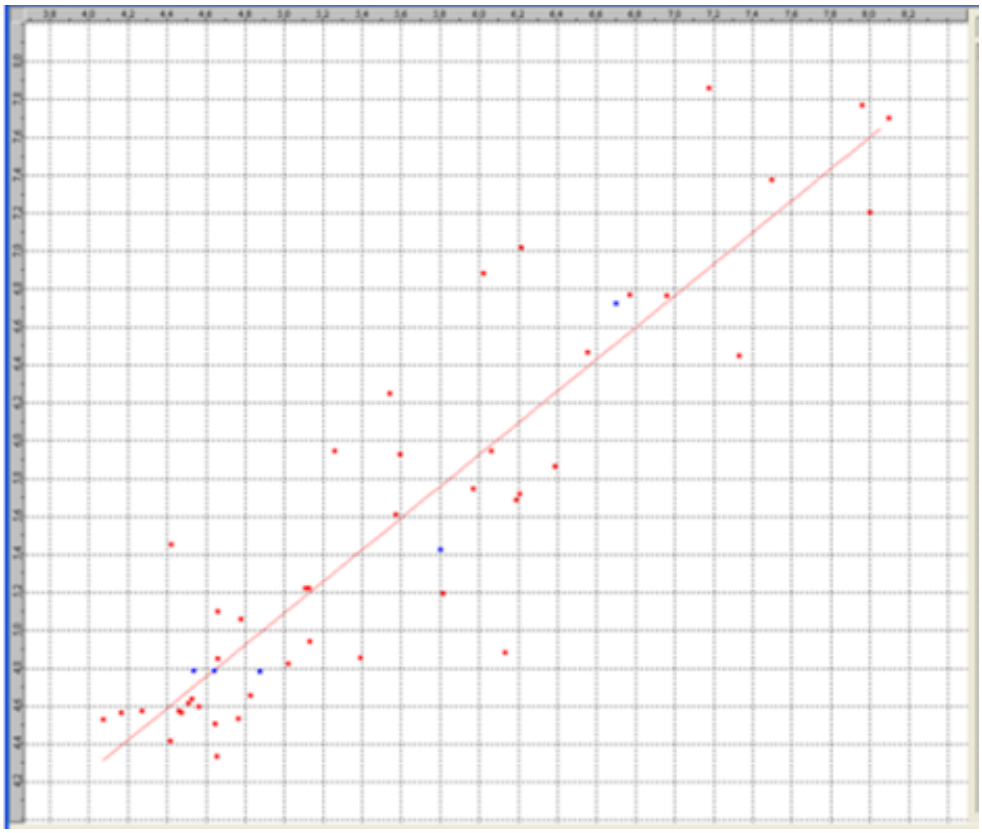


Figure 3: Data fitness plot for Model 1.

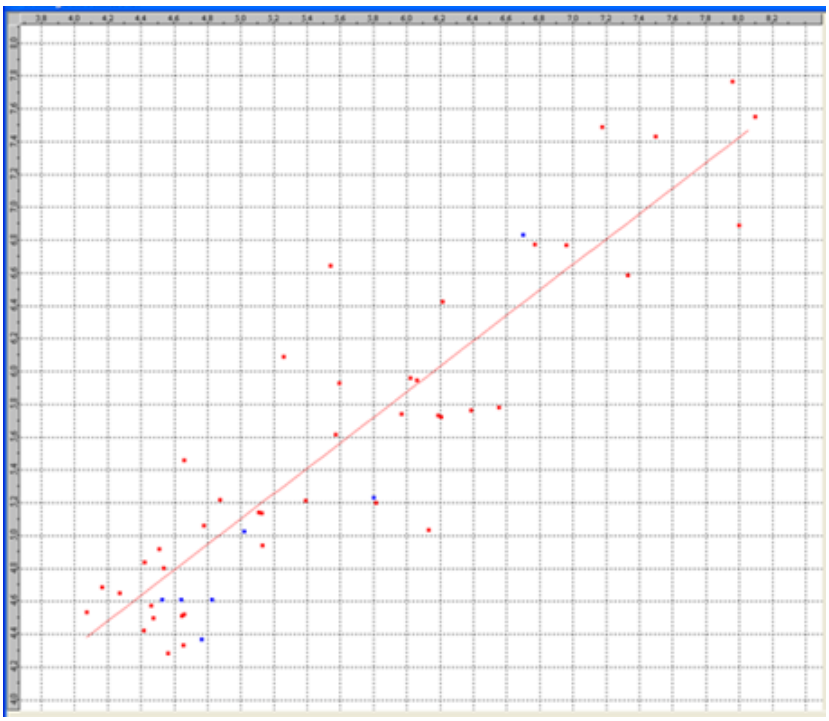


Figure 4: Data fitness plot for Model 2.

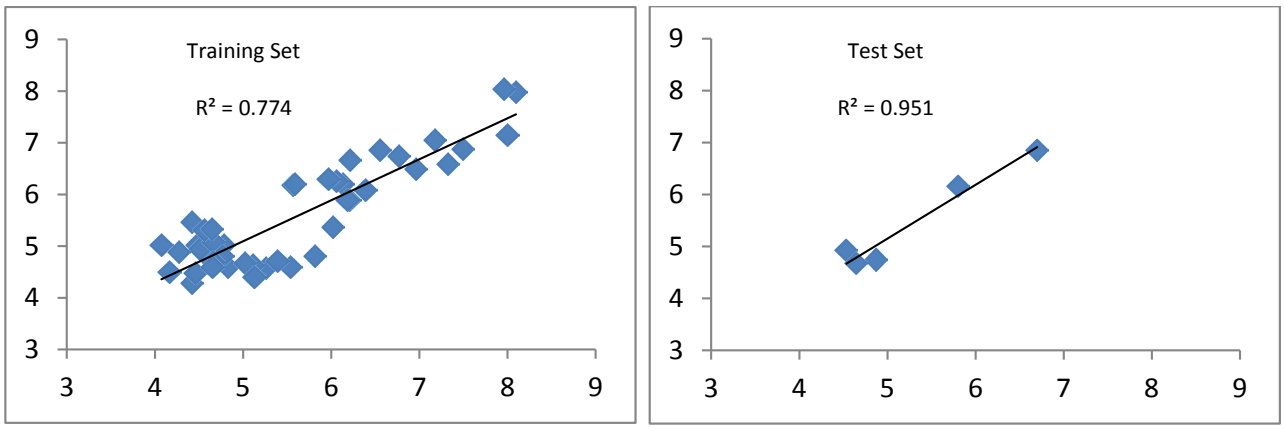


Figure 5: Graph between actual and predicted activity for training and test set (Model 1).

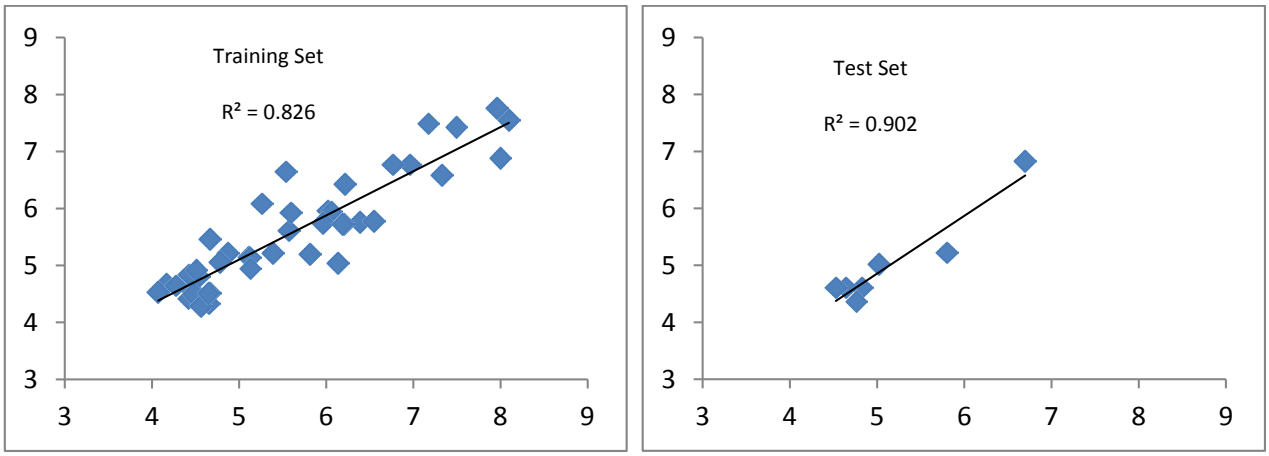


Figure 6: Graph between actual and predicted activity for training and test set (Model 2).

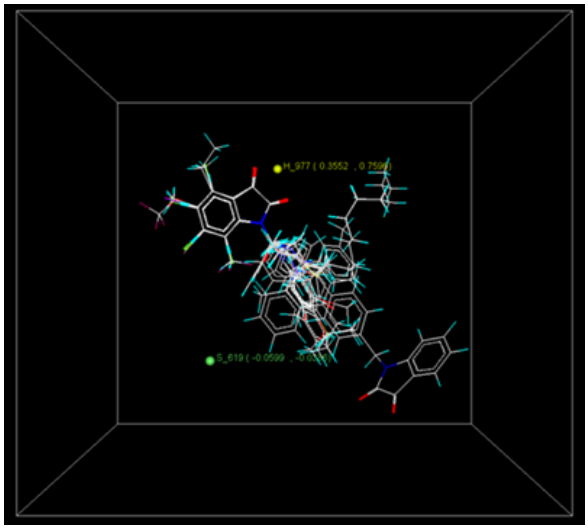


Figure 7: kNN-MFA result plot: 3D-alignment of molecules with the important steric and hydrophobic points contributing with ranges of values shown in parenthesis for model 1.

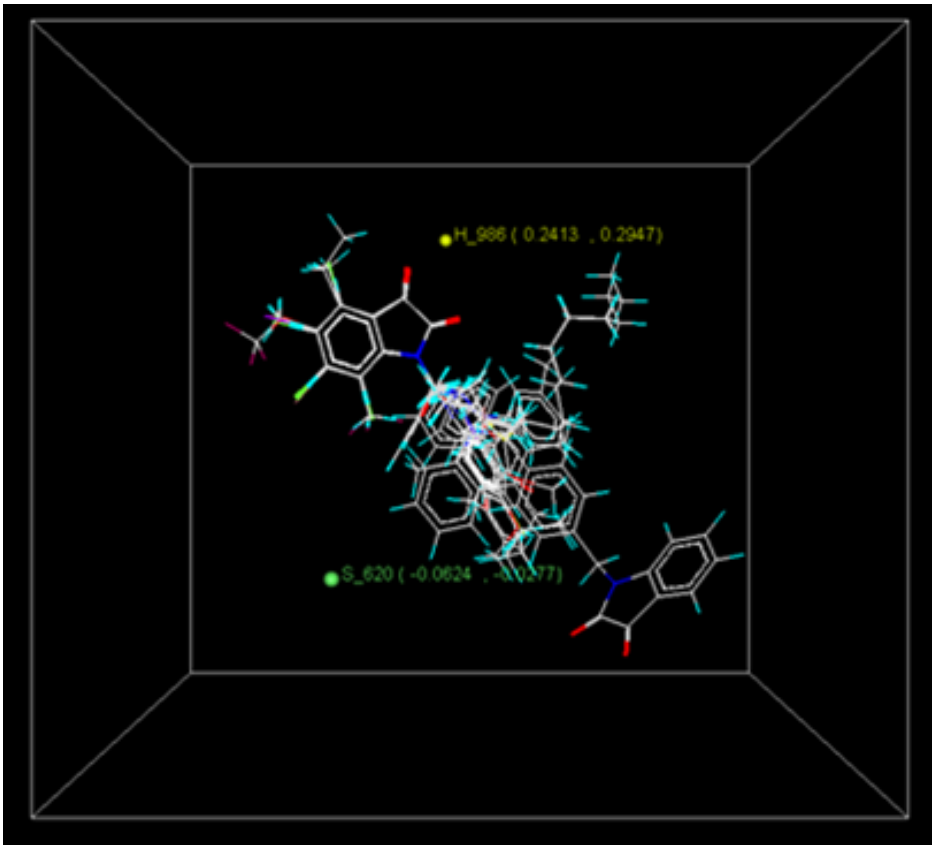


Figure 8: kNN-MFA result plot: 3D-alignment of molecules with the important steric and hydrophobic points contributing with ranges of values shown in parenthesis for model 2.

is preferred in that region. Compounds having lesser hydrophobic substituent group are not favorable for biological activity. Steric field descriptor (S_619) has negative range (-0.0599 to -0.0386) indicates that negative steric potential is favorable for increase in activity and hence less bulky substituent group is preferred in that region. Compounds having more bulky substituent group is not favorable for biological activity.

Interpretation of model 2

It is produced by using stepwise kNN-MFA method having internal predictivity 82.11% (q2=0.8211) and external predictiviy 89.0% (pred_r2=0.89). kNN-MFA plot shown in Figure 4. This model showed that hydrophobic (H_986) and steric (S_620) interactions play important role in determining carboxyl esterase inhibitory activity. Hydrophobic field descriptor (H_986) has positive range (0.2413 to 0.2947) indicates that positive hydrophobic potential is favorable for increase in activity and hence more hydrophobic substituent group is preferred in that region. Compounds having lesser hydrophobic substituent group are not favorable for biological activity. Steric field descriptor (S_620) has negative range (-0.0624 to -0.0277) indicates that negative steric potential is favorable for increase in activity and hence less bulky substituent group is preferred in that region. Compounds having more bulky substituent group is not favorable for biological activity.

Conclusions

In conclusion, the model developed to predict the structural features of Isatins (Indole-2,3-diones) to inhibit carboxylesterases reveals useful information about the structural features requirement for the molecule. In optimized models, Model 1 is giving very significant results. The master grid obtained for the various kNN-MFA models show that negative value in electrostatic field descriptors indicates the negative electronic potential is required to increase activity and more electronegative substituents group is preferred in that position, positive range indicates that the group which imparts positive electrostatic potential is favorable for activity so less electronegative group is preferred in that region. Negative range in steric descriptors indicates that negative steric potential is favorable for activity and less bulky substituents group is preferred in that region. Positive value of steric descriptors reveals that positive steric potential is favorable for increase in activity and more bulky group is preferred in that region. On the basis of the spatial arrangement of the various shapes, electrostatic and steric potential contributions model proposed in this work is useful in describing QSAR of Isatins, Indole-2,3-diones derivatives as carboxylesterase inhibitors and can be employed to design new derivatives with more potent inhibitory activity.

Acknowledgement

We are thankful to the Head, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur (CG) for providing necessary facilities.

References

1. Ollis DL, Cheah E, Cygler M, Dijkstra B, Frolow F, et al. (1992) The alpha/beta hydrolase fold. Protein Eng 5: 197-211.

2. Cygler M, Schrag JD, Sussman JL, Harel M, Silman I, et al. (1993) Relationship between sequence conservation and three-dimensional structure in a large family of esterases, lipases, and related proteins. Protein Sci 2: 366-382.
3. Heikinheimo P, Goldman A, Jeffries C, Ollis DL (1999) Of barn owls and bankers: a lush variety of alpha/beta hydrolases. Structure 7: R141- 146.
4. Cashman JR, Perotti BY, Berkman CE, Lin J (1996) Pharmacokinetics and molecular detoxication. Environ Health Perspect 1: 23-40.
5. Satoh T, Hosokawa M (1998) The mammalian carboxylesterases: from molecules to functions. Annu Rev Pharmacol Toxicol 38: 257-288.
6. Kamendulis LM, Brzezinski MR, Pindel EV, Bosron WF, Dean RA (1996) Metabolism of cocaine and heroin is catalyzed by the same human liver carboxylesterases. J Pharmacol Exp Ther 279: 713- 717.
7. Khanna R, Morton CL, Danks MK, Potter PM (2000) Proficient metabolism of irinotecan by a human intestinal carboxylesterase. Cancer Res 60: 4725- 4728.
8. Redinbo MR, Bencharit S, Potter PM (2003) Human carboxylesterase 1: from drug metabolism to drug discovery. Biochem Soc Trans 31: 620-624.
9. Brodbeck U, Schweikert K, Gentinetta R, Rottenberg M (1979) Fluorinated aldehydes and ketones acting as quasi-substrate inhibitors of acetylcholinesterase. Biochim Biophys Acta 567: 357- 369.
10. Bencharit S, Morton CL, Howard-Williams EL, Danks MK, Potter PM, et al. (2002) Structural insights into CPT-11 activation by mammalian carboxylesterases. Nat Struct Biol 9: 337- 342.
11. Fleming CD, Bencharit S, Edwards CC, Hyatt JL, Tsurkan L, et al. (2005) Structural insights into drug processing by human carboxylesterase 1: tamoxifen, mevastatin, and inhibition by benzil. J Mol Biol 352: 165- 177.
12. Bencharit S, Morton CL, Hyatt JL, Kuhn P, Danks MK, et al. (2003) Crystal structure of human carboxylesterase 1 complexed with the Alzheimer's drug tacrine: from binding promiscuity to selective inhibition. Chem Biol 10: 341- 349.
13. Bencharit S, Morton CL, Xue Y, Potter PM, Redinbo MR (2003) Structural basis of heroin and cocaine metabolism by a promiscuous human drug-processing enzyme. Nat Struct Biol 10: 349- 356.
14. Wadkins RM, Hyatt JL, Wei X, Yoon KJ, Wierdl M, et al. (2005) Identification and characterization of novel benzil (diphenylethane-,2-dione) analogues as inhibitors of mammalian carboxylesterases. J Med Chem 48: 2906- 2915.
15. Hyatt JL, Stacy V, Wadkins RM, Yoon KJ, Wierdl M, et al. (2005) Inhibition of carboxylesterases by benzil (diphenylethane-,2-dione) and heterocyclic analogues is dependent upon the aromaticity of the ring and the flexibility of the dione moiety. J Med Chem 48: 5543- 5550.
16. Hyatt JL, Wadkins RM, Tsurkan L, Hicks LD, Hatfield MJ, et al. (2007) Planarity and constraint of the carbonyl groups in 2-diones are determinants for selective inhibition of human carboxylesterase 1. J Med Chem 50: 5727- 5734.
17. Hicks LD, Hyatt JL, Moak T, Edwards CC, Tsurkan L, et al. (2007) Analysis of the inhibition of mammalian carboxylesterases by novel fluorobenzoins and fluorobenzils. Bioorg Med Chem 15: 3801- 3817.
18. Hyatt JL, Moak T, Hatfield MJ, Tsurkan L, Edwards CC, et al. (2007) Selective inhibition of carboxylesterases by isatins, indole-2,3-diones. J Med Chem 50: 1876- 1885.
19. Corwin H (1969) Quantitative approach to biochemical structure-activity relationships. Accounts of Chem 2:232- 239.
20. Topliss JG (1983) Quantitative Structure-Activity Relationships of Drugs. Academic Press, New York.
21. Franke R (1984) Theoretical Drug Design Methods. Elsevier Amsterdam.
22. Seydel JK (1985) QSAR and Strategies in the Design of Bioactive Compounds. VCH Weinheim.
23. Hansch C, Klein TE, Martin YC (1986) Molecular graphics and QSAR in the study of enzyme-ligand interactions. On the definition of bioreceptors. Accounts of Chem Res 19: 392- 400.
24. Zheng W, Tropsha A (2000) Novel variable selection quantitative structure-property relationship approach based on the *k*-nearest-neighbor principle. J Chem Inf Comput Sci 40:185- 194.
25. Shen M, LeTiran A, Xiao Y, Golbraikh A, Kohn H, et al. (2002) Quantitative structure-activity relationship analysis of functionalized amino acid anticonvulsant agents using k nearest neighbor and simulated annealing PLS methods. J Med Chem 45: 2811-2823.
26. Molecular Design Suite (2004) Vlife Sciences Technologies Pvt. Ltd, Pune, India.
27. Ajmani S, Jadhav K, Kulkarni SA (2006) Three-dimensional QSAR using the k-nearest neighbor method and its interpretation. J Chem Inf Model 46: 24-31.
28. Rogers D, Hopfinger AJ (1994) Application of Genetic Function Approximation to Quantitative Structure-Activity Relationships and Quantitative Structure-Property Relationships. J Chem Inf Comp Sci 34: 854- 866.

Citation: Sanmati KJ, Achal M (2015) 3D QSAR Analysis on Isatin Derivatives as Carboxyl Esterase Inhibitors Using K-Nearest Neighbor Molecular Field Analysis. J Theor Comput Sci 2: 124. doi:10.4172/2376-130X.1000124