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QSAR Studies of N-(2-Aminophenyl)-Benzamide derivatives as Histone deacetylase2 Inhibitors

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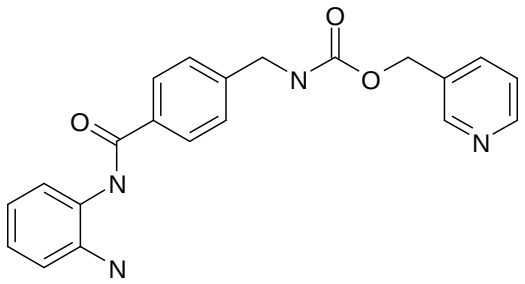
Abstract: Histone deacetylase 2 is a promising target for drug intervention and its inhibitors are useful in treating cancer. QSAR (2D and 3D) studies were performed on a series of N-(2-Aminophenyl)-Benzamide derivatives using Cerius2 software (accelrys). QSAR study performed on 25 analogues of which 21 were used in the training set and the rest 4 considered for the test set. 2D- QSAR study performed using Partial least squares (PLS), Genetic function approximation (GFA), Genetic partial least squares (G/PLS). Among these three methods GFA method came out with good correlation coefficient r^2 0.794, cross-validated coefficient r^2_{CV} 0.634 and r^2_{pred} of 0.6343. 3D-QSAR studies using Molecular field analysis (MFA), Regression analysis were carried out using GFA method. A highly predictive and statistically significant model was generated. The analyzed MFA model demonstrated a good fit, having r^2 value of 0.927, cross-validated coefficient r^2_{CV} value of 0.815 and r^2_{pred} of 0.845.The QSAR models were found to accurately predict the Histone deacetylase2 inhibitory activity of structurally diverse test set compounds and to yield reliable clues for further optimization of the N-(2-Aminophenyl)-Benzamide derivatives in the data set.
Key words: Histone deacetylase 2; Genetic Function Approximation; Molecular field analysis; N-(2-Aminophenyl)-Benzamide derivatives.

1. Introduction:

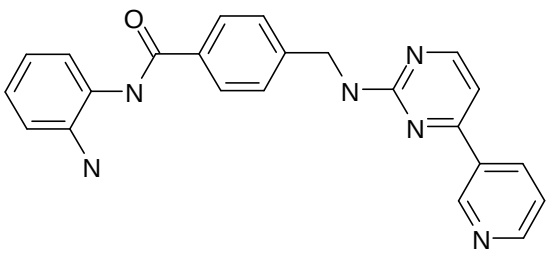
Histone deacetylase (HDACs) represent a family of enzymes that compete with histone acetyltransferases (HATs) to modulate chromatin structure and transcriptional activity via change in acetylation status of nucleosomal histones. HDACs are deacetylating the ε-amino groups of lysine located near the amino termini of core histone proteins [1-2]. Mammalian HDACs have been classified into three classes. Class I (HDACs 1, 2, 3 and 8) are homologs of yeast RPD3 and localize to the nucleus; Class II (HDACs 4, 5, 6, 7, 9 & 10) are homologs of yeast Hda1 and are found in both the nucleus and cytoplasm; Class III (Sirt1 - Sirt7). Class I and II HDACs operate by zinc-dependent mechanisms and Class III by NAD [3]. HDAC2 highly homologous to HDAC1 is a class I HDAC

first identified as a human homolog of the yeast histone deacetylase Rpd3. HDAC2 found, along with HDAC1, in the Sin3, NuRD and CoREST complexes, also can act independently to deacetylate non-histone proteins such as transcription factors. HDAC activities are present in many types of cancers. HDAC have been recognized as attractive therapeutic targets for anticancer [4, 5] and also for antifungal, antiviral and anti-inflammatory treatment. HDAC2 is a potential target for anticancer drug discovery. HDAC2 is a key regulator of genes regulating cell cycle, apoptosis, cell adhesion and migration. HDAC2 is useful to treat various cancer diseases, which are colon, gastric, cervical, prostate carcinoma, Colon cancer, Breast cancer, Prostate cancer, pancreatic cancer, chronic obstructive pulmonary disease and also treating Alzheimer disease [6]. Histone deacetylase inhibitors are more interested because of their anticancer activity. Several class of HDAC inhibitors are under research, which are Hydroxamic acid, Cyclic tetra peptides, Benzamide type derivatives. Different types of hydroxamic acid and Benzamide derivatives are in clinical trials [7]. The Benzamide derivatives are Entinostat (MS-275) IC50 is 0.34 uM [8], Mocetinostat (MGCD0103) IC50 is 0.18 uM [9]. The Quantitative structure activity relationship (QSAR) which has become an accepted tool for establishing quantitative relationship between biological activity and descriptors representing physicochemical properties of the compounds in a series using statistical methods and it helps to predict the biological activities of newly designed analogues contributing to the drug discovery processes. QSAR (2D and 3D) studies of N-(2-Aminophenyl)-Benzamide derivatives have been carried out using different statistical methods. The aim of the research includes finding the clues for further optimization of the N-(2-Aminophenyl)-Benzamide derivatives in the data set.

The derivatives of N-(2-Aminophenyl)-Benzamide are Entinostat (MS-275) and Mocetinostat (MGCD0103) are in phase II clinical study for treatment of various cancers Hodgkin lymphoma, lung cancer and breast cancer; follicular lymphoma, Hodgkin lymphoma and acute myeloid leukemia) respectively. The structures of the compounds are as follows-



MS-275 (IC50: 0.34 uM)



MGCD0103 (IC50: 0.18 uM)

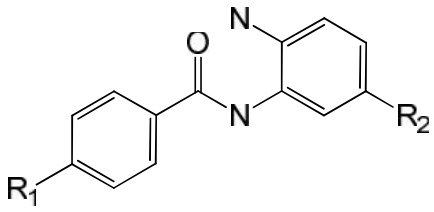
2. Materials & Methods:

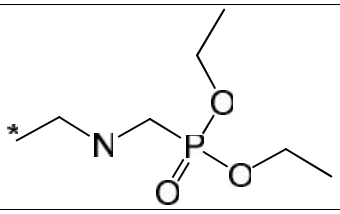
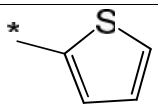
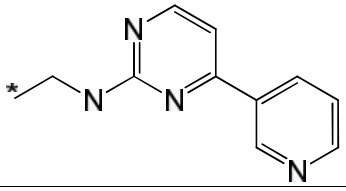
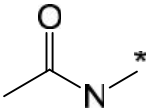
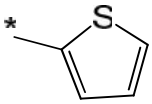
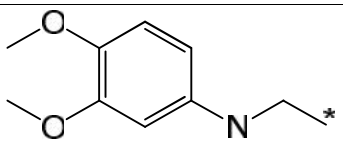
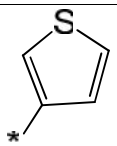
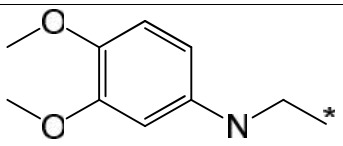
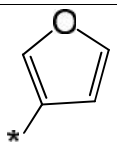
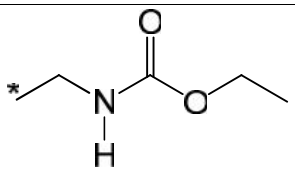
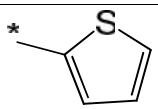
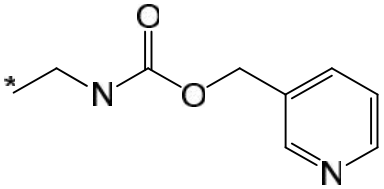
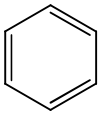
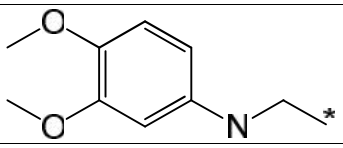
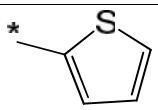
A) Data set:

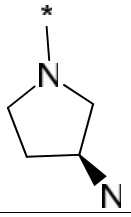
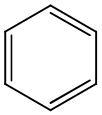
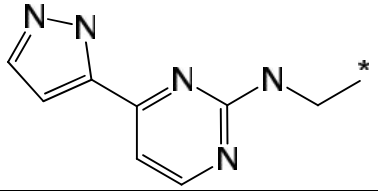
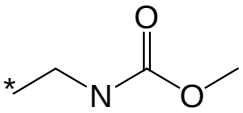
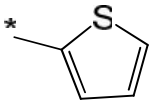
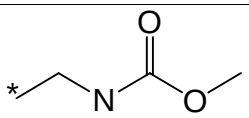
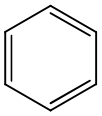
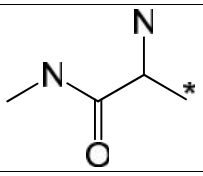
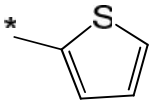
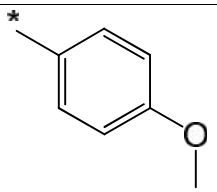
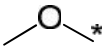
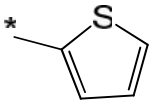
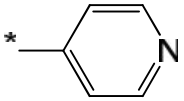
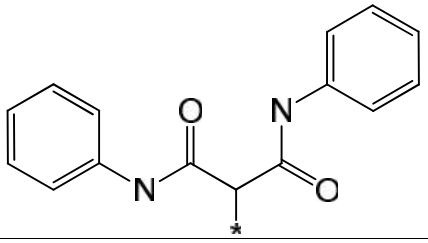
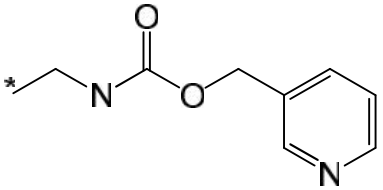
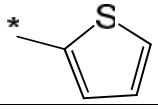
Twenty five molecules belonging to N-(2-Aminophenyl)-Benzamide as Histone deacetylase2 inhibitors were taken from the GOSTAR [10] database and used for QSAR analysis. 2D-QSAR models were generated for this series using Partial least squares (PLS), Genetic function approximation (GFA), Genetic partial least squares (G/PLS) and those which come out with promising results are discussed here. QSAR models were generated by a training set of 21 molecules. Predictive power of the resulting models was evaluated by a test set of 4 molecules with uniformly distributed biological activities. Likewise 3D-QSAR models were generated for this series using Genetic function approximation (GFA). The structures of all the compounds presented in **Table 1** and their experimental and predicted biological activities are presented in **Table 2**.

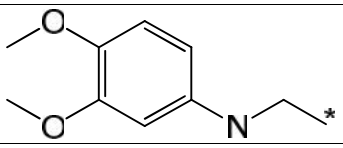
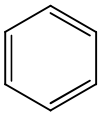
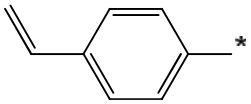
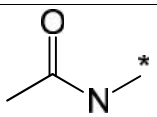
Table 1:

Scaffold: N-(2-Aminophenyl)-Benzamide derivatives:



Compound	R1	R2
1		
2 T		H
3		
4		
5		
6		
7		
8 T		

9		
10		H
11		
12		
13		
14	H	
15		
16	H	
17		H
18 T		H
19	H	

20		H
21	H	
22	H	
23		H
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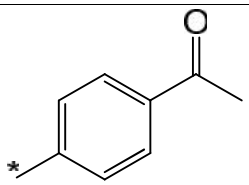
25	H	

Total 25 compounds, 21 are training set compounds and 4 Test set compounds. Here 'T' indicates Test set compound.

B) Biological Activities:

The biological activity data IC50 (inhibitory concentration for 50% in uM) were converted to negative logarithmic dose in moles (pIC50) for QSAR analysis. The pIC50 values of the molecules under study spanned a wide range from 5 to 8.

C) Computational Data:

The dataset used for the QSAR analysis contains 25 molecules belonging to N-(2-Aminophenyl)-Benzamide as Histone deacetylase2 inhibitors. All the structures of the compounds were drawn and the modeling analysis, calculations and visualizations for 2D & 3D QSAR were performed using the Cerius2 4.11 version (Accelrys) [11] on silicon work station running under the Linux operating system. All compounds were then subjected to energy minimization under Open Force field Method (OFF METHOD) using smart minimizer, partial atomic charges were calculated using the charge-equilibrium method and conformational analysis search with optimal search method. Most stable structure for each compound was generated after energy minimization and used for calculating various physico-chemical descriptors.

D) Molecular Descriptors:

The various descriptors selected for 2D QSAR and 3D QSAR were Conformational descriptors, Electronic descriptors, Quantum mechanical descriptors, Topological descriptors, Spatial descriptors, Structural descriptors, Thermodynamic descriptors are used as independent variables and biological activity as dependent variable.

2.1 Method:

The different statistical models were developed using Partial least squares (PLS), Genetic function approximation (GFA), Genetic partial least squares (G/PLS) Regression methods. The equations were found to derive 2D-QSAR model [12]. The Molecular field analysis (MFA) technique was used to derive 3D-QSAR model using Genetic function approximation (GFA) regression method.

A) Statistical Parameters:

Statistical measures used for the evaluation of models were the number of compounds in Regression (n), the correlation coefficient (r), square of correlation coefficient (r^2), sequential Fischer test (F), the cross–validated correlation coefficient r^2_{CV} and the Boot strap r^2. The regression coefficient r^2 is a relative measure of fit by the regression equation. It represents the part of the variation in the observed data that is explained by the regression. The F–test reflects 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. Validation parameter, predictive r^2 (r^2_{pred}) was calculated for evaluating the predictive capacity of the model. The value of r^2_{pred} greater 0.5 indicates the good predictive capacity of the QSAR model [13].

B) Model Validation:

For the validation of QSAR models "Leave-one-out (Loo)" Cross-validation method was used, the best model was selected on the basis of various statistical parameters such as correlation coefficient (r), square of correlation coefficient (r^2), sequential Fischer test (F), quality of the each model was estimated from the cross-validated squared correlation coefficient (r^2_{CV}), PRESS (Predicted sum of squared residuals), Sum of squared deviations from the mean (SD), and boot-strapping square BS correlation coefficient (r^2), which confirm the robustness and applicability of QSAR equation.

A) Alignment of molecules:

Molecular alignment is a crucial step in 3D-QSAR study to obtain meaningful results. This Method is based on moving of molecules in 3D space, which is related to the conformational Flexibility of molecule, the goal is to obtain optimal alignment between the molecular structures necessary for ligand–receptor interactions. All molecules in the data set were aligned by shape reference molecule using higher activity of molecule as shape reference [14]. A highly bioactive energetically stable conformation in this class of compounds is chosen as a reference molecule on which other molecules in the data set are aligned, considering shape reference molecule as a basis for the alignment, in **figure 2**.

B) Computation of steric and electrostatic fields:

The aligned biologically active conformations of N-(2-Aminophenyl)-Benzamide derivatives are used for the calculation of molecular fields. Molecular fields are the steric and electrostatic interaction energies which are used to formulate a relationship between steric and electrostatic properties together with the biological activities of compounds. MFA is a method implemented in the Cerius2 program. Its formalism calculates probe interaction energies on a rectangular grid around a bundle of active molecules. The surface is generated from a "shape field." The atomic coordinates of the contributing models are used to compute field values on each point of a 3D grid. MFA then evaluates the energy between a probe (H^+ and CH3) and a molecular model at a series of points defined by a rectangular grid. Fields of molecules are represented with grids in MFA and corresponding energy associated with an MFA grid point can serve as input for the calculation of a QSAR. These energies are added to the study table to form new columns headed according to the probe type, which are used as independent variable. GFA was applied to obtain a 3D-QSAR model based on steric and electrostatic descriptors [15]. Many of the spatial and structural descriptors such as polarizability, dipole moment, radius of gyration, molecular area, molecular dimensions, density, principal moments of inertia, molecular volume, molecular weight, number of rotatable bonds, hydrogen bond donors and acceptors, log P, molar refractivity and others were also considered along with field values [16]. Only 10% of the total variables whose variance is highest were considered as independent variables. The negative logarithm of the biological activity was chosen as the dependent variable in the generation of QSAR equations using the GFA regression method (with only linear terms involved in the equations) [17].

3. Results and Discussion:

3.1 2D QSAR modeling and its validation:

In QSAR modeling, the first goal was to establish a predictive model with a reasonable number of input features to ensure good generalization performance. While correlating various descriptors, biological activity is the most important means to study structure activity relationships. PLS, GFA and G/PLS techniques were used in the present study for selecting a significant set of descriptors in order to build the significant models. In this section, the prediction performances of the method proposed by three different models (PLS, GFA and G/PLS) were evaluated. The PLS, GFA and G/PLS models predicted the training data with an r^2 of 0.696, 0.794 and0.751 together with r^2_{CV} estimating to 0.312, 0.634 and 0.588, respectively. The graph of experimental versus predicted pIC_{50} values are shown in **Figure 1.** The experimental and predicted activities of the training set and test set molecules are given in **Table 2**. In the case of all three models equation (I) appears to be the best QSAR model obtained by the GFA analysis. Equation (II) and (III) for PLS and G/PLS respectively

GFA:

Activity (pIC50) = 7.30 - 2.79 * "LogP" + 0.214 * "MW" - 6.75 * "Hbond acceptor" - 0.0035 * "Apol" + 0.285 * "Rotlbonds" (I)

Mean Activity: 6.72; Sum of squared deviations from the mean (SD): 8.30; LOF: 0.190; r^2: 0.794; r^2adj: 0.740; F-test: 14.629; LSE: 0.069; r: 0.891; C (p): -12.740; XV r^2: 0.634; Boot strap (BS) r^2: 0.795; BS r^2err: 0.008; N obs: 25.000; N vas: 6.000; Press: 3.037; Dep SD: 8.306; Dep mean: 6.729

PLS:

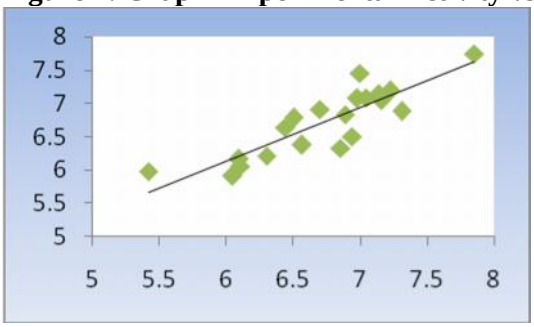
Activity = 0.00088 * "MW" + 0.0046 * "Rotlbonds" + 0.0415 * "Hbond acceptor" - 0.029 * "AlogP" + 0.0029 * "MolRef" - 0.0472 * "LogP" (II)

G/PLS:

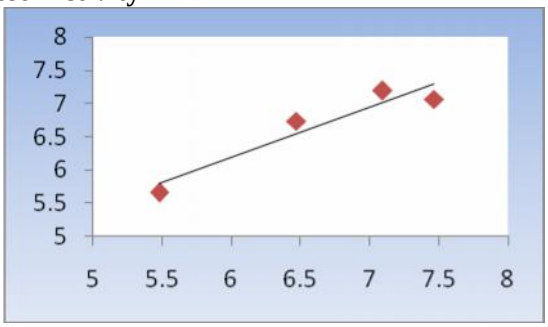
Activity = 4.43 + 0.0149 * "MW" - 0.155 * "LogP" - 0.0049 * "Vm" - 0.136 * "Rotlbonds" - 0.0307 * "Dipole-mag" (III)

This QSAR study has shown that the descriptors - Log of the partition coefficient (LogP), Molecular weight (MW), Number of hydrogen-bond acceptors (H-bond acceptor), Sum of atomic polarizabilities (Apol), Number of rotatable bonds (Rotlbonds) play a vital role in imparting the biological activity. This study has also shown that the biological activity is governed by various thermodynamic, electronic and Structural descriptors. The models provide a brief insight into the mechanism of action of these compounds. All these parameters considered for further designing of newer molecules for histone deacetylase2 inhibitor activity.

Figure 1: Graph- Experimental Activity vs. Predicted Activity



Training Set of compounds



Test Set of Compounds

3.1.2 Randomization Test:

To evaluate the statistical significance of the QSAR model for an actual data set, we have employed a one-tail hypothesis testing. The robustness of the QSAR models for experimental training sets was examined by comparing these models to those derived for random data sets. Random sets were generated by rearranging biological activities of the training set molecules.

Randomization test results: Test results from 19 trails, r from non-random: 0.8909, Confidence level: 90%, Mean value of r from random trails: 0.706, Standard deviation of random trails: 0.0785, Standard deviation from non-random r to mean: 2.35, r^2: 0.691, r: 0.831, LSE: 0.103, LOF: 0.285.

3.1.3 Cross-validation:

The cross-validation process repeats your regression many times on subsets of your data. Usually each molecule is left out in turn, and the r^2 is computed using the predicted values of the missing molecules (the cross-validated r^2). Cross-validation is often used to determine how large a model (number of terms) can be used for a given dataset.

Leave-one out cross-validation test results -PRESS: 2.136, Sum of Squared deviation: 8.305, Trails: 1, r^2_{CV}: 0.743, r^2: 0.789, F-test: 13.496.

3.2 3D QSAR modeling and its validation:

3.2.1 Molecular field analysis (MFA):

The MFA model of 25 N-(2-Aminophenyl)-Benzamide derivatives (21 compounds in a training set; 4 compounds in a test set) was developed using field fit alignment. The most active compound,diethyl(((4-((2-amino-5-(thiophen-2-yl)phenyl)carbamoyl)benzyl)amino)methyl)phosphonate **(1)** was used as a shape reference to which all the structures of compounds in the study were aligned through pair-wise super positioning. The method used for performing the alignment was maximum common subgroup [MCSG]. Superimposition of the aligned molecules is shown in **Figure2**. The molecular field was created using as probes, the methyl group and a proton for steric and electrostatic interactions respectively. The steric (CH3) and electrostatic (H+) descriptors in the MFA-QSAR equations specify the regions where variations in the structural features (steric or electrostatic) of different compounds in the training set shows. The numbers accompanying descriptors in the equations represent their positions in the three-dimensional MFA grid (**Figure 3**). The MFA-QSAR equation is expressed as follow-

Activity (pIC50) = 4.58 + 0.0141 * "H^+/419" + 0.014 * "CH3/395" + 0.011 * "H+/408" + 0.276 * "Hbond acceptor" - 0.0044 * "H+/509" (IV)

Mean Activity: 6.72; Sum of squared deviations from the mean (SD): 8.30; Lack of fit (LOF): 0.067; r^2: 0.927; r^2adj: 0.908; F-test: 48.164; Least square error (LSE): 0.024; r: 0.963; C(p): -12.921; XV r^2: 0.815; Boot strap (BS) r^2: 0.894; BS r^2err: 0.003; N obs: 25.000; N vas: 6.000; Press: 1.053; Dep SD: 8.306; Dep mean: 6.729.

A QSAR equation is generally acceptable if the squared correlation coefficient (r^2) is approximately 0.7 or higher. The r^2 value is a relative measure of the quality of fit of the model. Its value depends on the overall variance of the data. An r^2_{CV}, a squared correlation coefficient generated during a cross-validation procedure, is used as a diagnostic tool to evaluate the predictive power of an equation. Cross-validation is often used to determine how large a model (number of terms) can be used for a given data set. The predictive power of the model was calculated by using the following equation-

$$r^2_{pred} = (SD - PRESS)/SD \quad (V)$$

Where SD is the sum of the squared deviations between the biological activities of each molecules and the mean activity of the training set of

molecules and PRESS is the sum of squared deviations between the predicted and experimental activity values for every molecule in the test set.

The predicted activity obtained from equation (IV) and experimental activity of the training set and test set molecules are summarized in Table 2. The graph of experimental versus predicted pIC_{50} values are shown in Figure 5. MFA- 3D QSAR model shows good statistical results with r^2_{CV}: 0.815, r^2: 0.927 and r^2_{pred} = 0.845.

Figure 2 Superimposition of the aligned molecules in the training set

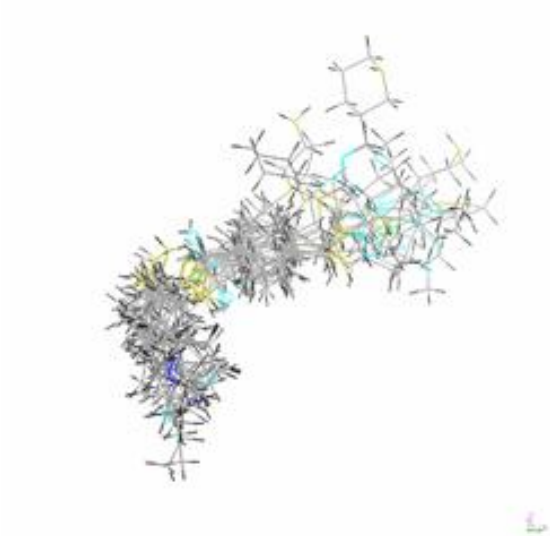


Figure 3& 4. Mapping of the best MFA model and the interaction points. The most active compound, diethyl (((4-((2-amino-5-(thiophen-2-yl) phenyl) carbamoyl) benzyl) amino) methyl) phosphonate **(1)**, is displayed in background as reference.

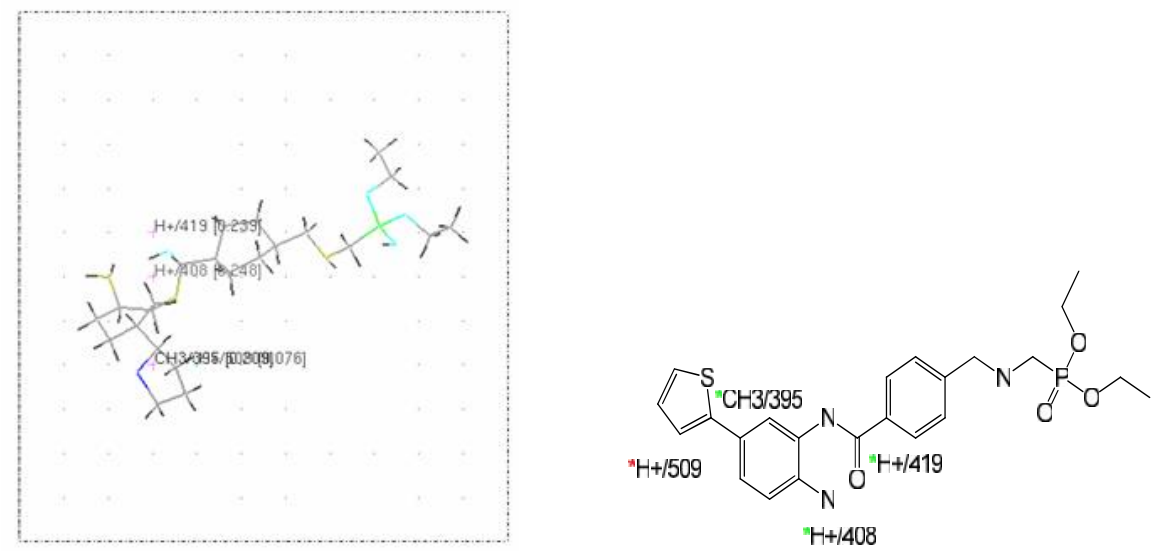
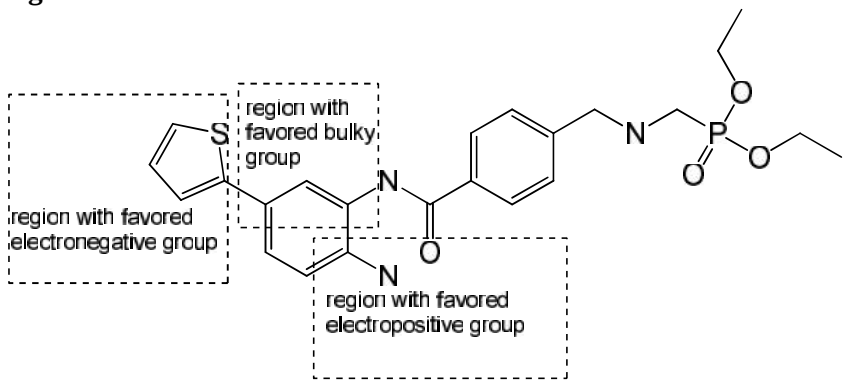


Figure 4:



From these analysis N-(2-Aminophenyl)-Benzamide derivatives shows the following results. The presence of steric descriptors (+CH_3/395) on ring with positive coefficients indicates the importance of steric interactions, bulky groups can substitute and the presence of electrostatic descriptor (+H^+/419) and (+H^+/408) with a positive coefficient near to amide and phenyl group, while (-H^+/509) with negative coefficients substituted aromatic ring indicates that electronegative groups should be substituted on aromatic ring and the appearances of descriptor H-bond acceptors with a positive coefficient suggest that an increased activity of the compound. These are significant in developing novel N-(2-Aminophenyl)-Benzamide derivatives.

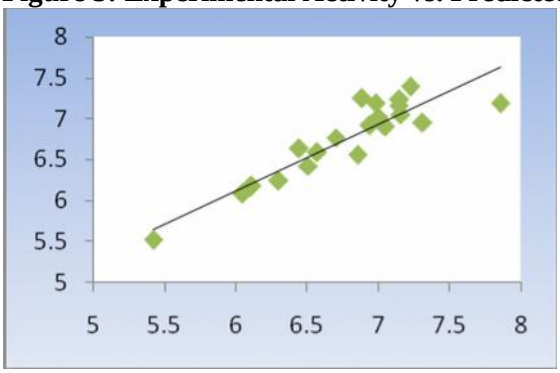
3.2.1 Randomization Test:

Randomization test results: Test results from 19 trails, r from non-random: 0.927, Confidence level: 95%, Mean value of r from random trails: 0.813, Standard deviation of random trails: 0.0995, Standard deviation from non-random r to mean: 1.147, r^2: 0.836, r: 0.919, LSE: 0.055, LOF: 0.151.

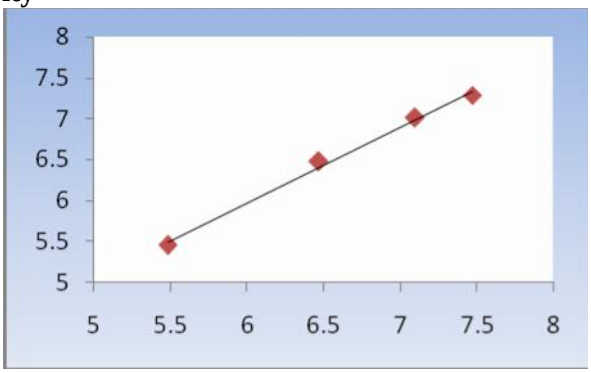
3.2.2 Cross-validation:

Leave-one out cross-validation test results -PRESS: 1.440, Sum of Squared deviation: 8.305, Trails: 1, CV r^2: 0.827, r^2: 0.919, F-test: 41.075.

Figure 5: Experimental Activity vs. Predicted Activity



Training Set of Compounds



Test Set of Compounds

Table 2: The Experimental activity and Predicted activity of the training set and test set molecules are summarized here.

Compound	Experimental pIC50	GFA Predicted	Residue	MFA Predicted	Residue
1	7.853	7.743	0.110	7.185	0.668
2 T	7.468	7.067	0.401	7.287	0.181
3	7.309	6.886	0.423	6.948	0.361
4	7.221	7.191	0.030	7.394	-0.173
5	7.154	7.048	0.106	7.051	0.103
6	7.148	7.093	0.055	7.239	-0.091
7	7.142	7.133	0.009	7.157	-0.015
8 T	7.096	7.191	-0.095	7.018	0.078
9	7.045	7.083	-0.038	6.907	0.138
10	7.000	7.456	-0.456	7.023	-0.023
11	6.978	7.079	-0.101	7.183	-0.025
12	6.939	6.500	0.439	6.923	0.016
13	6.886	6.831	0.055	7.248	-0.362
14	6.853	6.329	0.524	6.560	0.293
15	6.698	6.908	-0.210	6.772	-0.024
16	6.568	6.372	0.196	6.586	-0.018
17	6.504	6.784	-0.280	6.425	0.079
18 T	6.468	6.736	-0.268	6.480	-0.012
19	6.443	6.637	-0.194	6.633	-0.190
20	6.301	6.215	0.086	6.245	0.056
21	6.107	6.058	0.049	6.183	-0.076
22	6.096	6.165	-0.069	6.168	-0.072
23	6.045	5.910	0.135	6.082	-0.037
24 T	5.481	5.661	-0.180	5.458	0.023
25	5.420	5.980	-0.560	5.519	-0.099

4. Conclusions:

In the present 2D QSAR investigation, all proposed QSAR models were statistically significant. However Model by Genetic function approximation (GFA) Regression analysis could be considered as best one in terms of excellent predictive abilities. According to this LogP, Molecular weight, H-bond acceptor, Sum of atomic polarizabilities, Number of rotatable bonds play a vital role in imparting the biological activity and designing novel N-(2-Aminophenyl)-Benzamide derivatives. MFA-3DQSAR studies were performed on a series of N-(2-Aminophenyl)-Benzamide derivatives using field fit alignment with high predictive ability, high cross-validated, conventional and predictive r^2. The MFA equation suggested that electropositive group near to amide group and the electronegative group on substituted aromatic ring. These electronegative and electropositive substituents might help in increasing the activity of N-(2-Aminophenyl)-Benzamide derivatives. The steric descriptors indicated that the bulky substituent's near phenyl group increase the activity. These are important in further lead optimization of the N-(2-Aminophenyl)-Benzamide derivatives.

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