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RESEARCH PAPER

Investigation on quantitative structure-activity relationships of benzoylamino benzoic acid derivatives as *β-ketoacyl-acyl carrier protein synthase* III (FABH) inhibitors

PP Subramani, SV Khare, SP Choudhari, SP Phalle, SS Kumbhar, VS Kavade, AA Pratavale, PB Choudhari

ABSTRACT

Fatty acid biosynthesis is an important process in the microorganism life cycle. *β-Ketoacyl-acyl Carrier Protein Synthase* III (FABH) catalyzes a critical step in fatty acid biosynthesis via type ii fatty acid biosynthesis. Series of 43 Benzoyl amino benzoic acid derivatives were subjected to 2D and 3D quantitative structure-activity relationships (QSAR) analysis via multiple linear regression and partial least square analysis respectively. Statistically significant four QSAR models were developed with good cross-validated correlation coefficient and external validation values. Developed QSAR model indicated the significance of the lipophilic parameters in an inhibitory potential of benzoyl amino benzoic acid derivatives.

Keywords: QSAR, Benzoyl amino benzoic acid, *FabHβ-Ketoacyl-acyl Carrier Protein Synthase III*, Partial least square (PLS), Multiple linear regression (MLR).

PP Subramani, SV Khare, SP Choudhari, SP Phalle, SS Kumbhar, VS Kavade, PB Choudhari
Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra

AA Pratavale
Department of Chemistry, Shivaji University, Kolhapur

Corresponding Author:
P. B Choudhari
e-mail: prafulla.choudhari@bharatividyapeeth.edu, praffula12@gmail.com

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Introduction:

Tuberculosis (TB) is the most common infectious and lethal disease known to human. In recent decade mortality rate of tuberculosis is increased rapidly in developing countries [1]. In 1993, World Health Organization noted tuberculosis as a global emergency The problem of the tuberculosis is further aggravated by the emergence of the resistant form of tuberculosis like MDR, XDR, and TDR Association of tuberculosis with HIV-1 and 2 infections are major factors in the actual resurgence of tuberculosis. Development of the newer antitubercular agents targeting conservative pathways now becomes need of time in the current scenario [1-5]. One of the important strategies which are currently employed is to develop inhibitors of mycobacterial cell wall biosynthesis. The cell wall of the *M. tuberculosis* contributes significantly towards resistance to most commonly-used antibiotics and chemotherapeutic agents. The cell wall of the mycobacteria is made up of three major components macromolecules, peptidoglycan, arabinogalactan and mycolic acids which were covalent bound with each other [6-8]. Fatty acid biosynthesis is an important step in the cell wall generation in mycobacteria, it has been established that this fatty acid biosynthesis process

may become the source of utilizable molecular targets due its non-homologous nature to mammalian system. Mycobacteria possess both a type I and type II fatty acid synthase in which type I fatty acid synthase is responsible for the formation of 16-24 carbon length fatty acids, which are then elongated to form long chain high molecular mass mycolate. Bacterial *3-Ketoacyl Acyl Carrier Protein Synthase III* (FabH) is a key enzyme plays important role in fatty acid bio synthesis. The enzyme FabH catalyzes the first step of fatty acid biosynthesis via a type II dissociated fatty acid synthase [9-10]. The important role of this enzyme in fatty acid biosynthesis and its conservative nature made it an attractive target for antitubercular drug design and development. Quantitative structure-activity relationships (QSAR) are the important methodologies in chemo metrics in which mathematical equations were generated for correlation of biological activity with structural properties. QSAR studies are of different types like 2D, 3D, 4D and GQSAR. In 2D QSAR analysis physiochemical properties were correlated with the biological potential to identify critical physicochemical parameters for optimization. 3D QSAR is more advanced than 2D where in 3D properties in terms of interactions energies are correlated with bioactivity [11-12]. In this research paper we are focused on development of 2D and 3D-QSAR models for benzoyl amino benzoic acid derivatives as *Ketoacyl-acyl Carrier Protein Synthase III* (FABH) inhibitors.

Computational Methodology

Dataset:

A series of 43 3-phenoxybenzoylamino benzoic acid derivatives as β-*ketoacyl-acyl carrier protein synthase III (FabH)* inhibitors reported by Zhe Nieet. al and Ashek et. Al [14-16] was utilized to perform the QSAR study. Biological activity is expressed in terms of $pMIC_{50}$ (-log MIC_{50}) was utilized as a dependent variable and physicochemical parameters in terms of 2D and 3D descriptors are utilized as independent variables. Table 1 shows the structure of 43 selected derivatives along with their biological activity values.

Selection of Training and Test Sets for Models

Selected 3-phenoxybenzoylamino benzoic acid derivatives were drawn using 2D sketcher of Vlife engine 4.5. Derivatives were further optimized via converting into 3D structures keeping native bond angle and bond length intact. Energy minimization and geometry optimization of all 43 derivatives were carried out using Merck Molecular Force Field. Compounds were sketched using the 2D draw application and converted to 3D structures. Energy minimization and geometry optimization was conducted using Merck molecular force field using batch energy minimization method. Dataset of all 43 molecules was randomly classified into training set (30 molecules) for the development of QSAR model and test set (13 molecules) for validation of developed models.

Calculation of 2D and 3D-QSAR Descriptor:

Molecular descriptors are acting as independent variables were calculated using QSAR module of V life MDS. Total 239 2D molecular descriptors were calculated which are consist of various physicochemical parameters**.** Molecular alignment is critical step to be followed by calculation of the 3D descriptors. Optimized molecules were aligned using template-based alignment. 3D field descriptor, were calculated using Tripos force field steric, electrostatic and hydrophobic field types, having cutoffs of 10.0 and 30.0 kcal/mol using Gasteiger and Marsilli charges. More than 3000 3D descriptors were calculated but the invariable descriptors were eliminated prior to the QSAR model development.

Model Validation:

Generated QSAR models were validated using standard leave one out method**.** The formula for calculation of cross-validated $r^2(q^2)$ value was given in equation 1, where yi and $\hat{y}i$ are the actual and predicted activities of the i^{th} molecule, respectively and ymean is the average activity of all molecules in the training set.

Equation 1:

$$q^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{mean})^2}$$

The predicted r^2 (pred_r^2) value was calculated using equation. 2, where yi and $\hat{y}i$ are the actual and predicted activities of the i^{th} molecule, respectively and y mean is the average activity of all molecules in the training set.

Equation 2:

$$\text{Pred\_}r^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - y_{mean})^2}$$

Result and Discussion:

For developing the 2D and 3D QSAR models for benzoylamino benzoic acid derivatives as *β-ketoacyl-acyl carrier protein synthase* III (FABH) inhibitors partial least square analysis is utilized with stepwise variable selection using forward-backward selection algorithm. Statistically significant two 2D and 3D QSAR models were generated having good internal and external predictive abilities.

Interpretation of 2D QSAR models

2D QSAR model represents the critical physicochemical parameters which are having the influence on the biological activity of the molecules under study; in simple terms, it is the mathematical equation which can be utilized to predict biological activity. Here we are reporting two developed 2D QSAR model selected on basis of various statistical measures obtained from MLR analysis like cross-validated correlation coefficient (q^2), correlation coefficient (r^2) and Fischer statistics (F test) which are indicators of good reliable and predictive QSAR model as shown in table 2 and figure 3.

2D QSAR Model A

pIC_{50} =0.0215+ 0.1743(±0.0911)SaasCcount

+ 0.3141(±0.0867)
XAMostHydrophobicHydrophilicDistance

+ 0.1880(±0.0558)SAMostHydrophobicHydrophilicDistance

-0.0084(±0.0002)XAHydrophilicArea

+ 0.0590(±0.0269)SsOHE-index

-0.1742(±0.1000)SaaNE-index

N = 30 ; r^2 = 0.8116; q^2 = 0.7122; F test = 30.654; pred r^2 = 0.7181

2D QSAR model A revels some interesting facts about the contribution of various descriptors towards FABH inhibition. SaasCcount is nothing but the total number of carbon connected with one single bond along with two aromatic bonds. The positive contribution of SaasCcount indicates substitution of aromatic rings with one single bond will potentiate the antimicrobial activity of the benzoylamino benzoic acid derivatives. XAMost hydrophobic hydrophilic distance and SA most hydrophobic hydrophilic distance these two descriptors are positively contributing towards biological activity, they are signifying distance between most hydrophobic and hydrophilic point on the vdW surface calculated by kellong method and distance between most hydrophobic and hydrophilic point on the vdW surface calculated by audry method using Slogp. The positive contribution of these two descriptors indicates increment in the hydrophobic surface area will lead to increase in antifungal activity.XAHydrophilicArea is another descriptor contributing negatively towards the antifungal activity which signifies vdW surface descriptor showing hydrophilic surface. Reduction in the polar surface area of benzoylamino benzoic acid derivatives will potentiate antimicrobial activity. SsOHE-index is topological descriptor contributing positively toward antimicrobial activity,SsOHE-index is an electron topological state indices for a number of –OH group connected with one single bond. Positive contribution of SsOHE-index indicates substitution of the hydroxyl group on benzoylamino benzoic acid skeletal will potentiate antifungal activity.SaaNE-index is the electrotopological state indices for a number of nitrogen atom connected with two aromatic bonds, negative contribution of this descriptor indicates the reduction in the nitrogen substitution will potentiate antimicrobial activity.

2D QSAR Model B

pIC_{50} = 1.8242+ 0.8670(±0.1440)6ChainCount

+ 0.0776(±0.0182)SsOHE-index

+ 0.1849(±0.0542)SAMostHydrophobicHydrophilicDistance

-0.0401(±0.0013)XAHydrophilicArea

-0.0313(±0.0015) SAHydrophilicArea

-0.0856(±0.0240)SssOE-index

N = 30; r^2 = 0.7421; q^2 = 0:6821; F test = 21.654; pred r^2 = 0.6182

2D QSAR model B is another generated model which indicates the positive contribution of descriptors like 6ChainCount, SsOHE-index and SAMost hydrophobic hydrophilic distance and negative contribution of XAHydrophilicArea, SAHydrophilicArea and SssOE-index. 6ChainCount is a topological descriptor indicating total number six-membered rings in a compound, while SssOE-index is electro-topological descriptor for number of oxygen atom connected with two single bonds.

Interpretation of 3D QSAR models

3D QSAR model represents the critical conformation attributes like electrostatic, steric and hydrophobic which

are affecting the antimicrobial potential of molecules under study. Here we are reporting two developed 3D QSAR model selected on basis of various statistical measures obtained from PLS analysis like cross-validated correlation coefficient (q^2), correlation coefficient (r^2) and Fischer statistics (F test) which are indicators of good reliable and predictive QSAR model as shown in table 2.

3D QSAR Model C

pIC50 = 5.4024+ 0.0470S_989

+0.4348S_141

+0.0487S_614

+0.1804 E_899

+0.0760 E_444

+0.2222 E_853

N = 30; r^2 = 0.8972; q^2 = 0.6296; F test = 28.654; pred r^2 = 0.7362

QSAR Model C explains Electrostatic and steric requirement for 3-phenoxybenzoylamino benzoic acid derivatives to act as FABH inhibitor. Negative contribution of E_899indicates the reduction of electrostatic interactions is favored in that region; the substitution of the electron with drawing groups like nitro will potentiate the antimicrobial activity. The positive contribution of S_989, S_141 and S_614 indicates the increase in the lipophilic nature of the molecules will lead to increase in the antimicrobial activity. Increased lipophilic nature of the molecules may be responsible for permeation through the cell wall of the organisms. Electrostatic interactions at the grid point E_899, E_444and E_853are positively contributing which indicates critical role of substitution of electron releasing groups which will potentiate the delocalization of the electron in the ring system as shown in figure 1 and figure 4

3D QSAR Model D

pIC50 = 5.7340 +0.1882S_149

+0.0433S_989

-0.0306S_710

-0.0411E_917

-0.0411S_452

+0.0698E_902

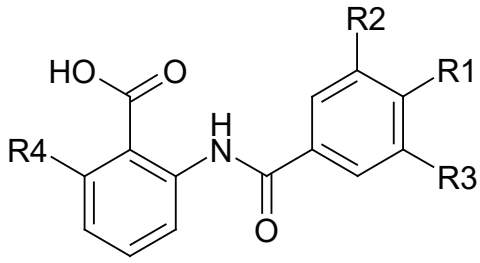
N = 30; r^2 = 0.8114; q^2 = 0.6161; F test = 26.882; pred r^2 = 0.4184

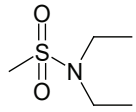
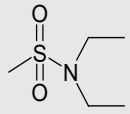
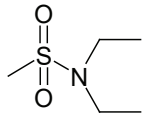
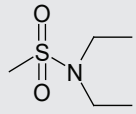
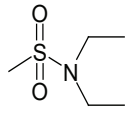
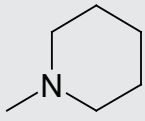
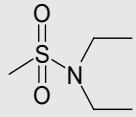
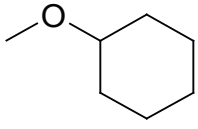
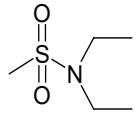
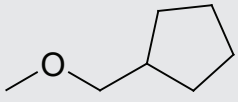
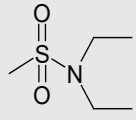
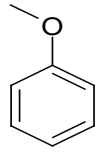
QSAR D is another generated 3D QSAR model for prediction of antimicrobial potential of selected 3-phenoxybenzoylamino benzoic acid derivatives to act as FABH inhibitor. Applicability of this QSAR model is limited due lower correlation coefficient and other statistical measures in compares with 3D QSAR model C. QSAR model D signifies positive contribution of S_149, S_989 and E_902, while negative contribution of S_710, E_917 and S_452 as shown in figure 2

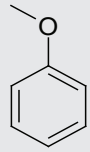
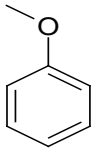
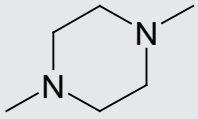
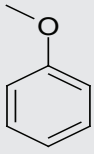
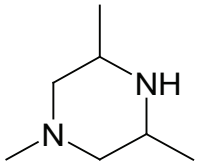
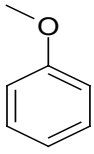
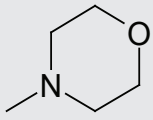
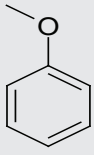
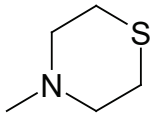
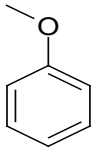
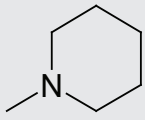
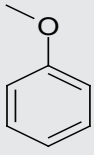
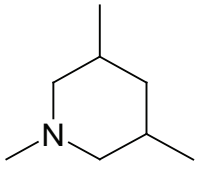
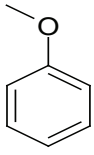
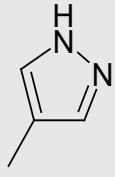
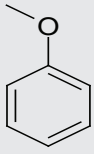
Conclusion

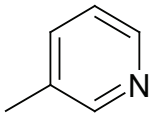
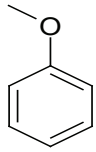
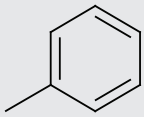
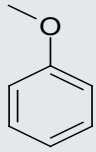
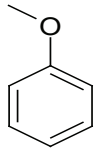
In this communication, we have successfully employed 2D and 3DQSAR models forbenzoylamino benzoic acid derivatives as *β-Ketoacyl-acyl Carrier Protein Synthase III* (FABH) inhibitors. The results revealed that generated QSAR model are having high degree of predictivity, which indicates these models can be successfully employed for the development of FABH inhibitors. Generated QSAR model indicated the importance of lipophilic parameters in FABH inhibition by benzoylamino benzoic acid derivatives. Furthermore, in the presence of electronegative groups are also having the critical influence on the antimicrobial activity. Furthermore, this theoretical study will give valuable inputs for development for novel FABH inhibitors**.**

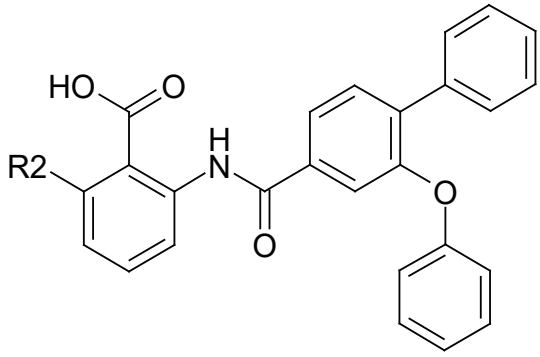
Table 1. Table showing Molecules under study



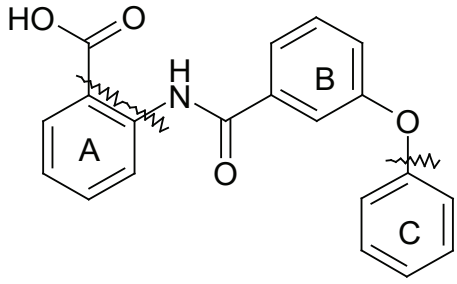
Sr. No.	R1	R2	R3	R4	Observed activity
1.	F	H		H	5.08
2.	Br	H		H	5.8
3.	Ph	H		H	5.8
4.	Br	Me		H	3.8
5.	OMe	H		H	4.94
6.		H		H	5.66
7.		H		H	5.21
8.		H		H	5.68
9.	H	H		H	5.57

10.	F	H		H	5.42
11.	Br	H		H	4.96
12.		H		H	4.6
13.		H		H	4.42
14.		H		H	5.49
15.		H		H	5.92
16.		H		H	6.54
17.		H		H	6.57
18.		H		H	4.66

19.		H		H	6.96
20.		H		H	7.25
21.	Br	H		OH	7.21



Sr. no	R1	R2	Observed activity
22.	CF_3	H	7.02
23.	Me	H	6.8
24.	CO_2H	H	5.68
25.	OH	H	6.39
26.	OEt	H	6.66
27.	SO_2Me	H	7.55
28.	OCF_3	H	6.33
29.	iPr	H	6.1
30.	3-Me-4-F	H	6.62
31.	2,4-di-F	H	6.8
32.	3,4-di-F	H	6.48
33.	3-Me-4-Cl	H	6.6
34.	3-Cl-4-F	H	6.24
35.	H	OH	8.4



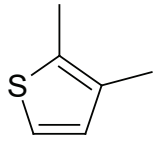
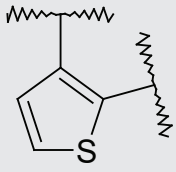
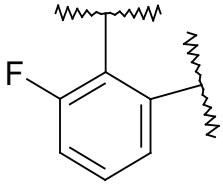
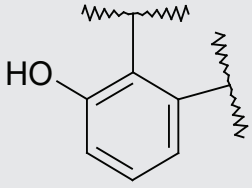
Sr. No.	A	C	Observed activity
36.		Ph	5
37.		Ph	4.37
38.		Ph	5.22
39.		Ph	6.39
40.	Ph	4-Pyr	5
41.	Ph	3-CO_2H-Ph	5.43
42.	Ph	4-CO_2H-Ph	5.36
43.	Ph	4-F-Ph	5.3

Table 2. Observed and predicted activity

Molecule No	Observed Activity	Predicted Activity			
		2D QSAR A	2D QSAR B	3D QSAR C	3D QSAR D
1.	5.0	5.2	5.1	5.3	4.8
2.	5.8	5.6	4.6	5.	5.0
3.	5.8	5.7	5.1	6.7	6.8
4.	3.8	3.5	4.5	4.8	3.8
5.	4.9	4.9	4.9	6.3	4.7
6.	5.6	5.8	5.7	5.8	5.9
7.*	5.2	5.2	5.3	5.9	5.2
8.*	5.6	5.6	5.7	5.4	5.8
9.	5.5	5.7	5.5	5.4	5.3
10.*	5.4	5.3	5.5	6.5	5.5
11.*	4.9	5.8	5.5	5.3	5.4
12.	4.6	4.9	4.7	6.6	4.6
13.	4.4	4.3	4.5	7.3	5.4
14.	5.4	5.6	5.9	6.9	5.3
15.	5.9	6.0	6.2	6.4	5.1
16.	6.5	6.8	6.4	6.2	6.4
17.	6.5	6.7	6.2	6.5	6.0
18.*	4.6	5.2	4.6	6.6	4.8
19.*	6.9	6.5	6.4	7.5	6.2
20.*	7.2	6.9	6.4	6.5	6.2
21.	7.2	7.1	6.2	6.1	6.6
22.	7.0	6.6	6.7	5.3	6.1
23.	6.8	6.6	6.6	6.3	6.7
24.	5.6	5.5	6.6	6.1	6.5
25.	6.3	6.2	6.2	6.1	6.3
26.*	6.6	6.5	6.2	6.5	6.2
27.	7.5	7.6	5.7	6.2	6.4
28.	6.3	6.5	6.4	9.4	5.8
29.	6.1	6.9	6.5	5.2	6.2
30.	6.6	6.7	6.7	4.5	6.6
31.*	6.8	6.3	6.5	5.6	7.4
32.*	6.4	6.2	6.4	5.7	6.6
33.	6.6	6.5	6.6	5.9	6.4
34.	6.2	6.7	6.9	5.1	6.5
35.*	8.4	7.8	7.1	5.1	8.6
36.*	5	5.2	4.6	5.5	5.4
37.*	4.3	4.3	5.0	5.6	5.7
38.	5.2	5.1	5.3	3.8	5.5
39.	6.3	6.2	6.1	4.7	5.7
40.	5	5.4	5.7	5.8	5.0
41.	5.4	5.2	5.4	6.1	5.2
42.	5.3	4.9	5.6	5.5	5.3
43.	5.3	5.8	5.8	4.8	5.5

*: test set molecules

Table 3. Correlation Matrix for 2D QSAR Model A

	Saas Ccount	XAMost Hydrophobic Hydrophilic Distance	SAMost hydrophobic Hydrophilic Distance	XA Hydrophilic Area	SsOHE-index	SaaNE-index
SaasCcount	1	0.442	0.524	-0.253	0.042	0.097
XAMost Hydrophobic HydrophilicDistance	0.442	1	0.042	0.403	-0.159	-0.066
SAMost Hydrophobic HydrophilicDistance	0.524	0.042	1	-0.64	0.197	-0.096
XA HydrophilicArea	-0.253	0.403	-0.64	1	-0.179	-0.054
SsOHE-index	0.042	-0.159	0.197	-0.179	1	-0.116
SaaNE-index	0.097	-0.066	-0.096	-0.054	-0.116	1

Table 4. Correlation Matrix for 2D QSAR Model B

	6Chain Count	SsOHE-index	SAMost Hydrophobic Hydrophilic Distance	XAHydrophilic Area	SAHydrophilic Area	SssOE-index
6ChainCount	1	0.442	0.524	-0.253	0.042	0.097
SsOHE-index	0.442	1	0.042	0.403	-0.159	-0.066
SAMostHydrophobic HydrophilicDistance	0.524	0.042	1	-0.64	0.197	-0.096
XA HydrophilicArea	-0.253	0.403	-0.64	1	-0.179	-0.054
SA HydrophilicArea	0.042	-0.159	0.197	-0.179	1	-0.116
SssOE-index	0.097	-0.066	-0.096	-0.054	-0.116	1

Table 5. Table showing Correlation Matrix For 3D QSAR Model C

	S_989	S_141	S-614	E_899	E_444	E_853
S_989	1	0.324	0.125	0.003	0.233	0.017
S_141	0.234	1	0.126	-0.009	-0.083	-0.05
S-614	0.156	0.089	1	-0.10	0.1	-0.003
E_899	0.082	-0.005	-0.349	1	-0.005	0.083
E_444	0.156	-0.073	0.1	-0.075	1	0.214
E_853	0.009	-0.13	-0.033	0.093	0.034	1

Table 6. Correlation Matrix For 3D QSAR Model D

	E_917	E_902	S_149	S_710	S_452	S_989
E_917	1	0.086	-0.228	-0.496	-0.277	0.136
E_902	0.086	1	-0.094	-0.153	-0.232	0.053
S_149	-0.228	-0.094	1	0.256	0.307	0.051
S_710	-0.496	-0.153	0.256	1	0.385	0.189
S_452	-0.277	-0.232	0.307	0.385	1	-0.018
S_989	0.136	0.053	0.051	0.189	-0.018	1

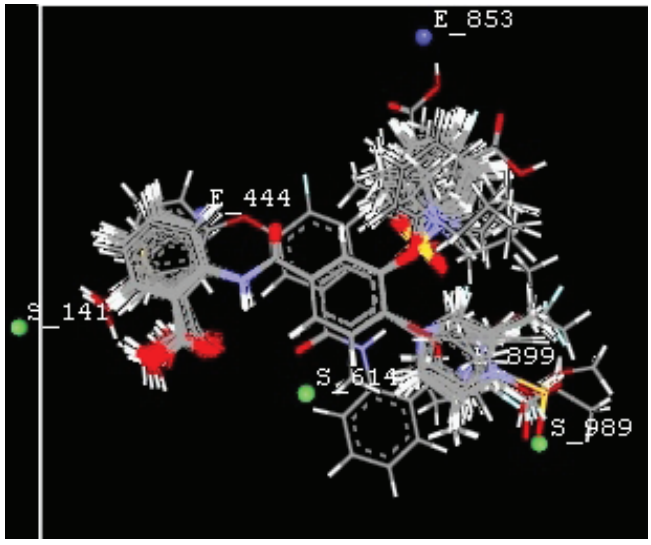


Figure 1. Field point of QSAR model C

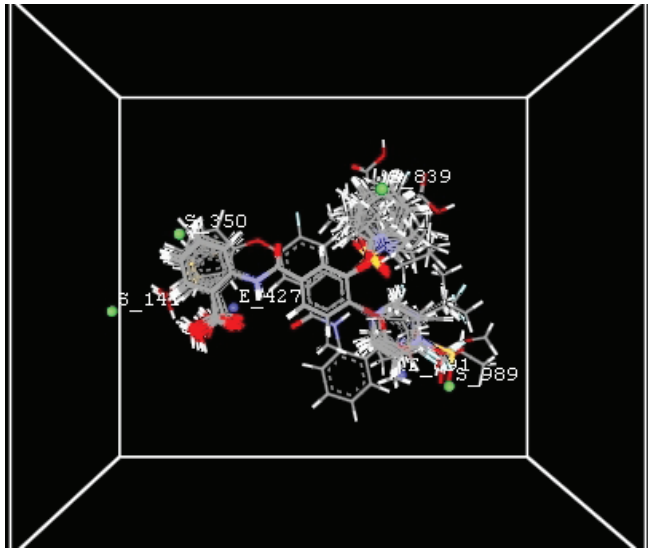


Figure 2. Field point of QSAR model D

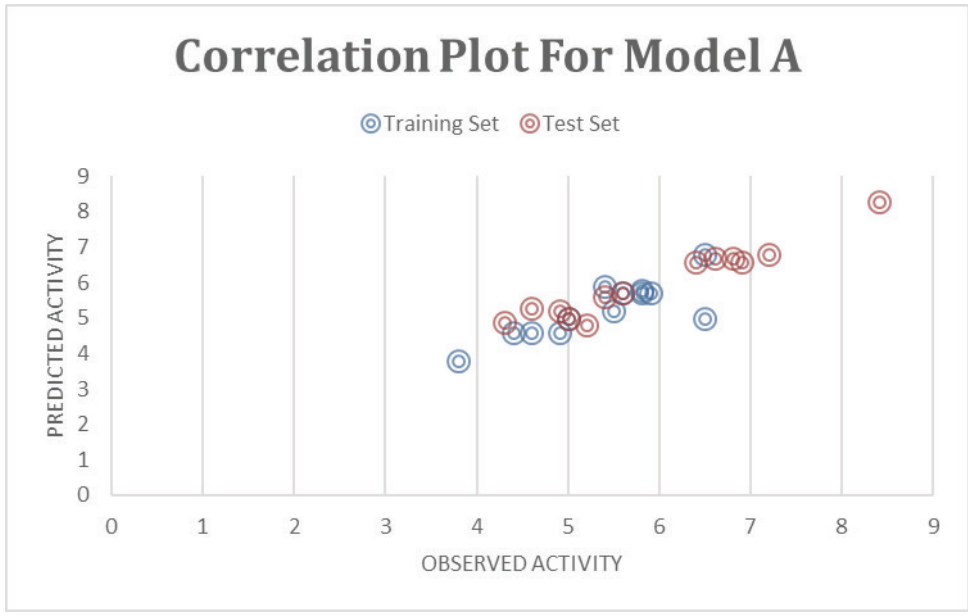


Figure 3. Correlation plot for QSAR model A

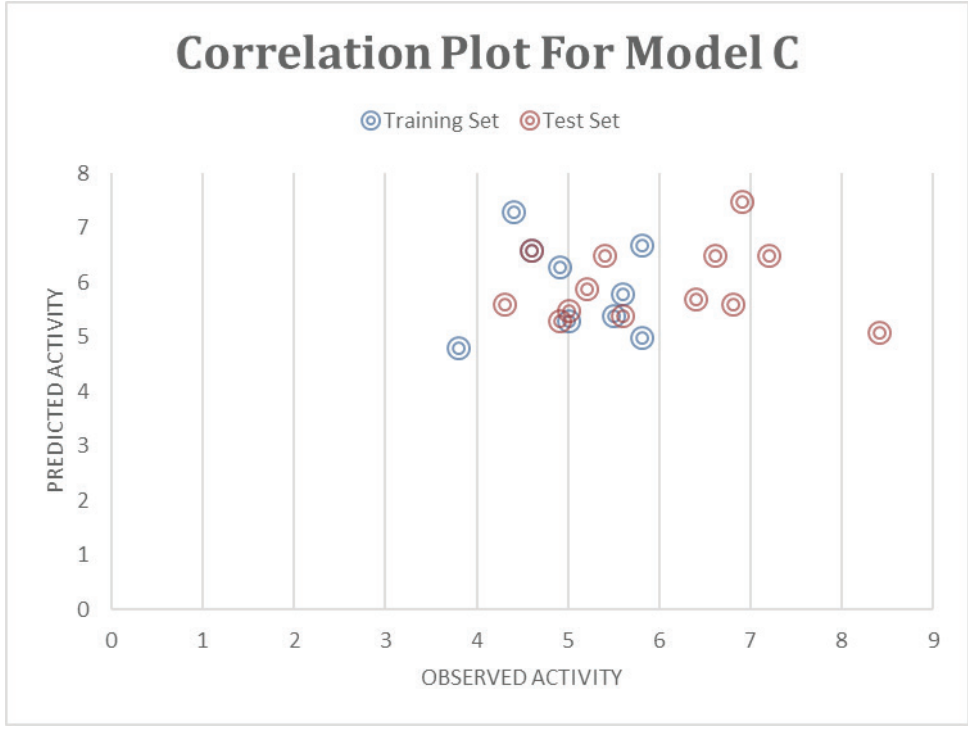


Figure 4. Correlation plot for QSAR model C

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