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2D QSAR studies of some novel Sulfonamide derivatives as Inhibitors of Histone Deacetylase

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ABSTRACT

In the present study, quantitative structure activity relationship study was performed on a series of novel sulfonamide derivatives as inhibitors of Histone deacetylase using chem. office ultra 7.01. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the production of activity. The best quantitative structure activity relationship model was selected with a correlation coefficient (r^2) of 0.2782. This study indicates that steric descriptors (conolly solvent excluded volume, exact mass, total connectivity) play important role for the activity. The data obtained from this present quantitative structure activity relationship study may be useful in the design of more potent substituted sulfonamide derivatives.

Key words: 2D-QSAR, Sulphonamides, Inhibitors of histone deacetylase.

INTRODUCTION

To carry out gene expression, a cell must control the coiling and uncoiling of DNA around histones. This is performed with the assistance of histone acetylases, which acetylate the lysine residues in core histones leading to a less compact and more transcriptionally active chromatin, and on the converse, the actions of histone deacetylases, removes the acetyl groups from the lysine residues leading to the formation of a condensed and transcriptionally silenced chromatin. Reversible modification of the terminal tails of core histones constitute the

major epigenetic mechanism for remodeling higher-order chromatin structure and controlling gene expression. Histone deacetylase inhibitors (HDAC) block this action and can result in hyperacetylation of histones, thereby affecting gene expression [1,2].

Histones undergo a number of post- translational modifications like methylation, acetylation or phosphorylation. These modifications occur in the N- terminal sequences of histones. Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation. The enzymes that catalyze and regulate the acetylation state of histones are known as histone deacetylases. The study of inhibitors of histone deacetylases indicate that these enzymes play an important role in cell proliferation and differentiation. These enzyme inhibitors are effective in treating solid tumors [3-6]. Histone deacetylase inhibitors are a new class of cytostatic agents that inhibit the proliferation of tumor cells in culture and *in vivo* by inducing cell cycle arrest, differentiation and apoptosis. Several compounds are currently in early phase of clinical development as potential agents for treatment of solid and hematological cancer both as monotherapy and in combination with cytotoxics.

QSAR studies have been widely used to understand the relationship between the structure of the molecule and biological activity [7]. In the present study, QSAR analysis of some substituted sulphonamide derivatives with histone deacetylase inhibition property was performed by using multiple linear regression analysis. No QSAR studies have been performed on these molecules. It was interesting to perform QSAR analysis using Chem Office 7.01 and correlate various physiochemical parameters to the activity for the design of some sulphonamide derivatives [Fig 1].

MATERIALS AND METHODS

Experiments:

A data set of 59 compounds has been taken from published article (Paul W.Finn etal [8]). The various descriptors studied are shown in Table 1. The values of PIC_{50} have been considered for computational work. All structure of these sulfonamide derivatives were constructed using ChemDraw and transferred to Chem 3D to convert them in to 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AMI (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/mol respectively for calculating partial atomic charges and electron density on various atoms. Most stable structure for all the compounds was generated and used for calculating various thermodynamic, steric and electronic descriptors. Values of descriptors, which are significant in equation, are shown in Table-II. All the calculated descriptor values were considered as independent variable and biological activity as dependent variable. INSTAT software was used to generate QSAR models by multiple linear regression analysis. Cross validation was performed using leave-one method. Statistical measures used were: n-number of moles in regression, r^2–correlation-coefficient, F-test (Fischer's value) for statistical significance, S-standard deviation.

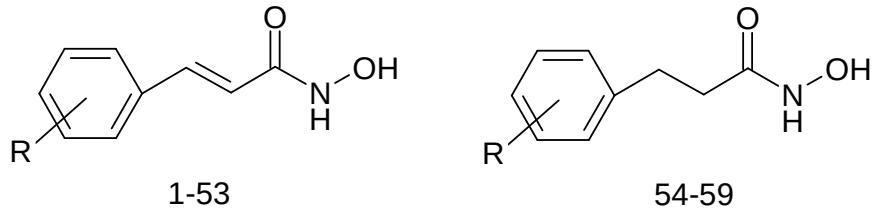
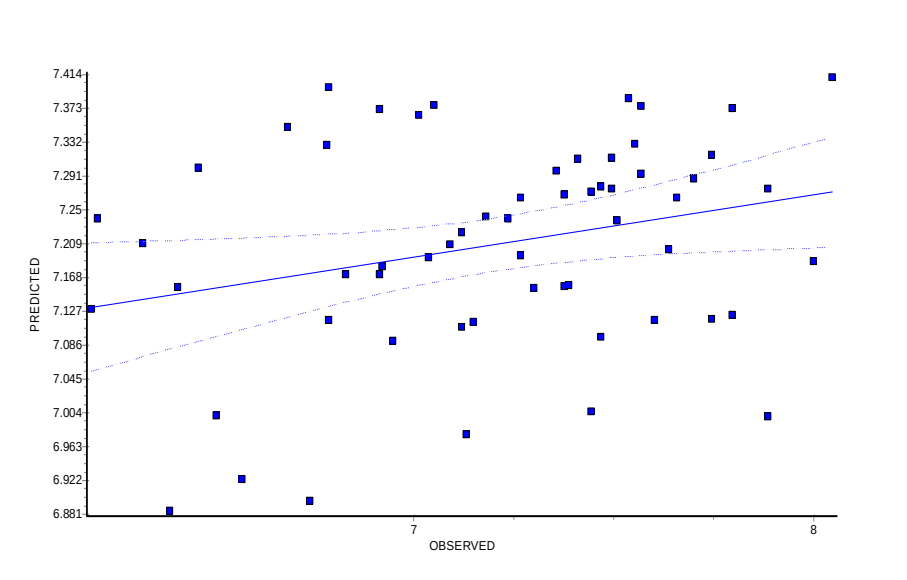


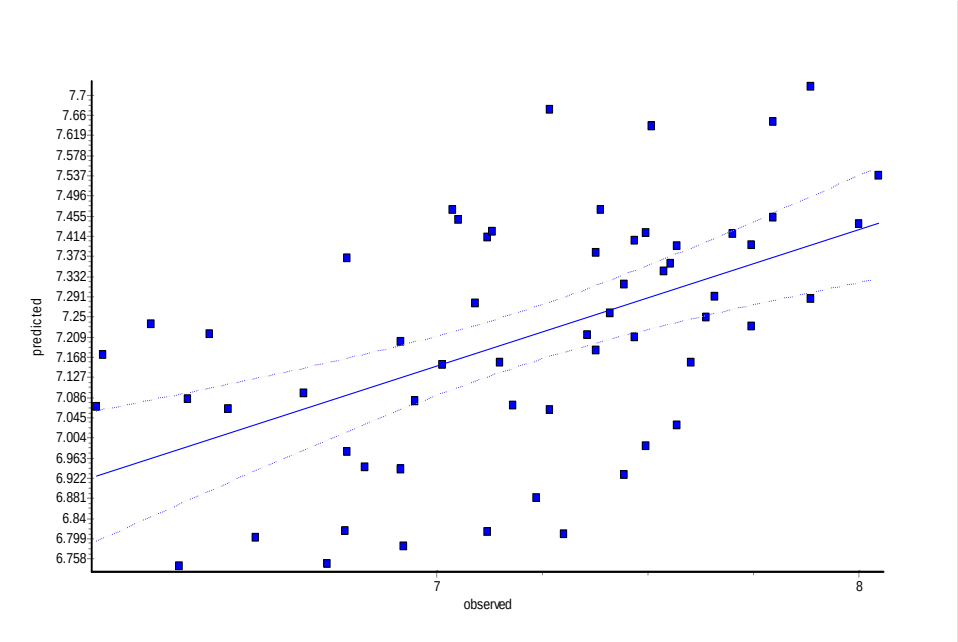
Fig.1

Table 1: Descriptors considered for the QSAR study

S.No	Descriptor	Type
1	Heat of formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
6	Henry's Law constant (HLC)	Thermodynamic
7	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
8	LogP	Thermodynamic
9	Melting Point (MP)	Thermodynamic
10	Molar Refractivity (MR)	Thermodynamic
11	Standard Gibbs Free Energy (SGFE)	Thermodynamic
12	Connolly Accessible Area (SAS)	Steric
13	Connolly Molecular Area (CMA)	Steric
14	Connolly Solvent-Excluded Volume (SEV)	Steric
15	Ovality (OVA)	Steric
16	Principal Moment of Inertia – X (PMI-X)	Steric
17	Principal Moment of Inertia – Y (PMI-Y)	Steric
18	Principal Moment of Inertia – Z(PMI-Z)	Steric
19	Dipole Moment (D)	Electronic
20	Dipole Moment – X Axis (DX)	Electronic
21	Dipole Moment – Y Axis (DY)	Electronic
22	Dipole Moment – Z Axis (DZ)	Electronic
23	Electronic Energy (EE)	Electronic
24	HOMO Energy (HOMO)	Electronic
25	LUMO Energy (LUMO)	Electronic
26	Repulsion Energy (RE)	Electronic
27	Bend Energy (E_b)	Thermodynamic
28	Charge - Charge Energy (CCE)	Thermodynamic
29	Charge - Dipole Energy (CDE)	Thermodynamic
30	Dipole - Dipole Energy (DDE)	Thermodynamic
31	Non-1,4 VDW Energy (E_v)	Thermodynamic
32	Stretch Energy (SE)	Thermodynamic
33	Stretch-Bend Energy (SEE)	Thermodynamic
34	Torsion Energy (E_t)	Thermodynamic
35	Total Energy (E)	Thermodynamic
36	Van der Waals 1,4 Energy (VDWE)	Thermodynamic



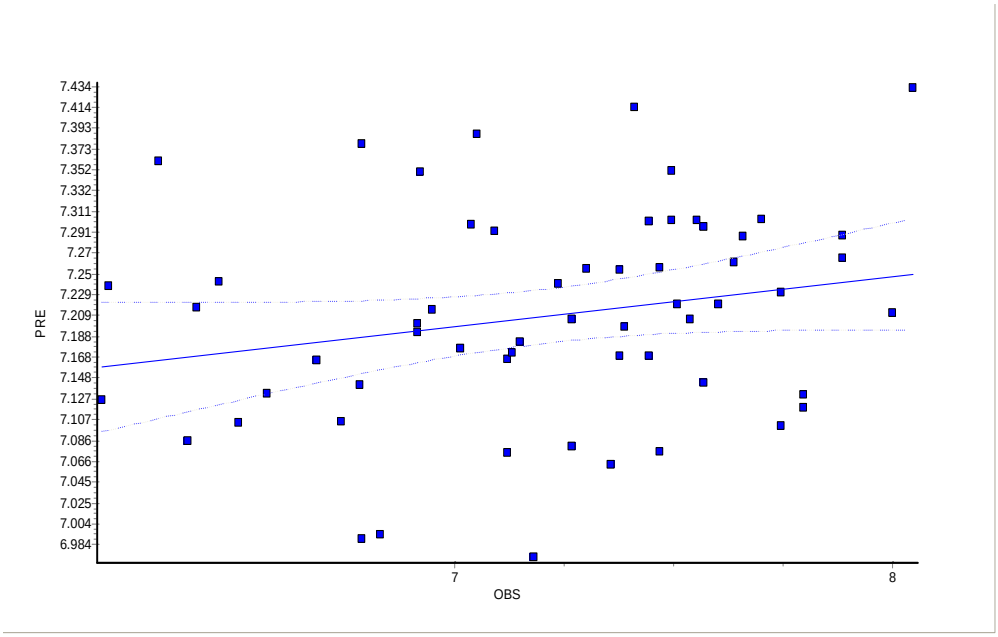
Model I: [A:IC_{50}] = 7.987-0.06199*[B:log]-0.03992*[C:cc]+0.03559*[D:dm] - 0.02389*[E:dp]
SEM : 0.03484, Standard deviation : 0.1239, Correlation co-efficient (r) : 0.2735,
R squared : 0.07480, P value : 0.0361, F : 4.608.



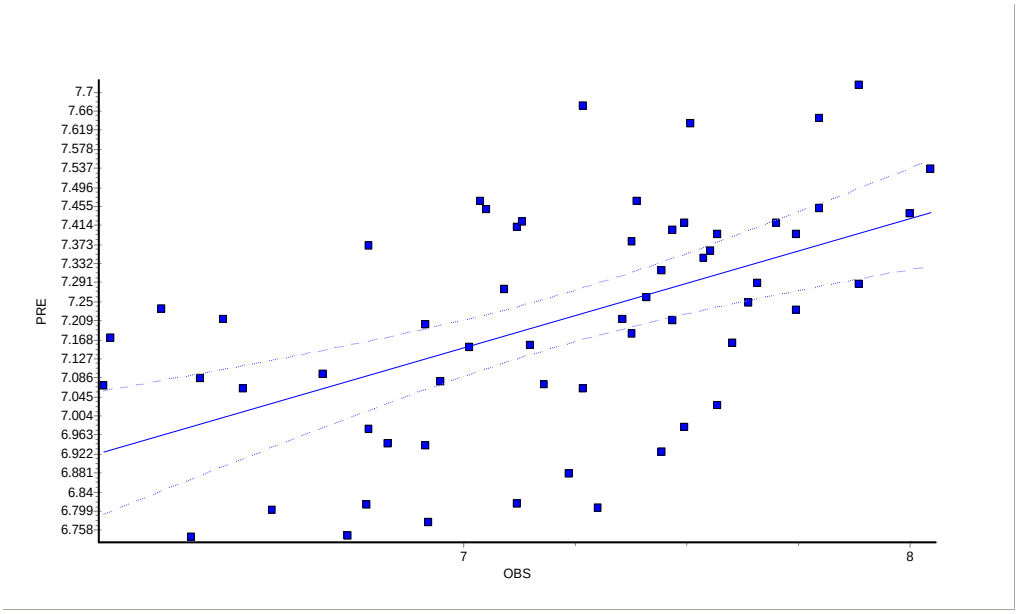
Model II: [A:IC_{50}] = 7.712 - 0.07789*[B:log p] - 0.01190*[C:sev]+ 0.007851*[D:em]
SEM : 0.05934, Standard deviation : 0.2111, Correlation co-efficient (r) : 0.5275,
R squared : 0.2782, P value : <0.0001, F : 21.974.

Table II: Model II:

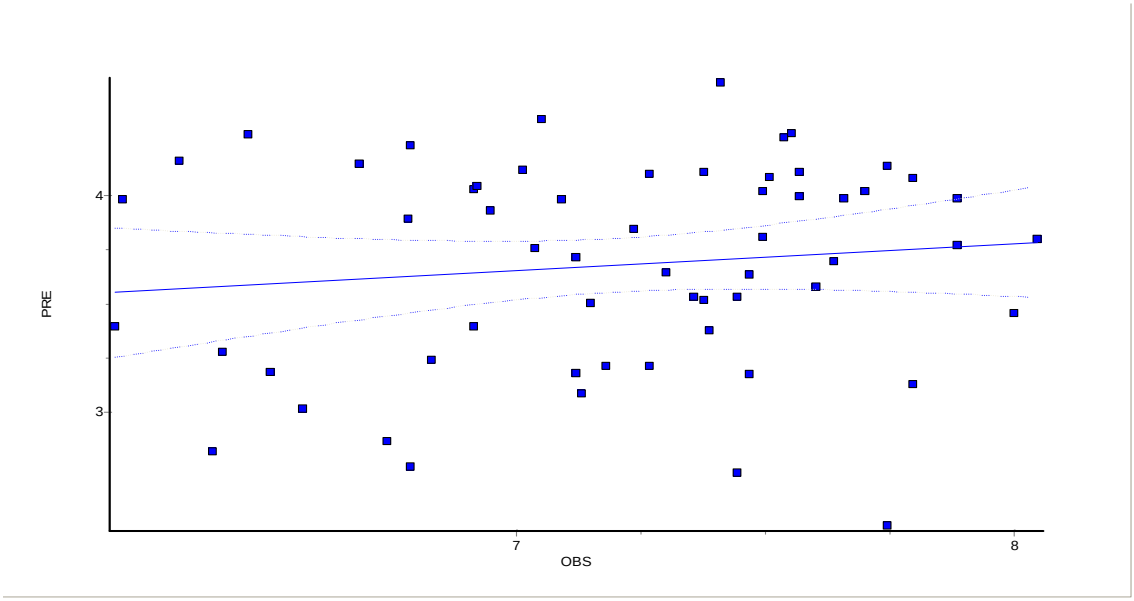
PIc 50	log P	SEV	Em	Obs activity	Pred activity
7.5528000	1.8550	227.397	318.067	7.5528000	7.358633767
7.7447000	2.3421	244.287	332.083	7.7447000	7.229742164
7.2676000	2.6839	247.138	395.978	7.2676000	7.670832107
7.3767500	2.4132	244.348	352.028	7.3767500	7.380066480
7.0915000	1.7286	254.881	348.078	7.0915000	7.277035824
7.6576000	1.7286	253.750	348.078	7.6576000	7.290494724
7.5086400	2.6839	250.043	395.978	7.5086400	7.636262607
7.7958800	3.3818	265.028	402.050	7.7958800	7.451252948
7.4948500	2.0131	233.053	336.058	7.4948500	7.420260299
7.6989700	2.0131	233.192	336.058	7.6989700	7.418606199
8.0000000	2.4375	260.354	384.059	8.0000000	7.439177734
7.0362000	2.1712	239.943	354.049	7.0362000	7.467202231
7.1307680	2.6497	281.449	416.065	7.1307680	7.422898082
7.3872000	2.7761	257.082	386.055	7.3872000	7.467411576
7.4685000	3.9478	275.759	418.027	7.4685000	7.404903735
7.1191860	3.9478	275.254	418.027	7.1191860	7.410913235
6.9469200	2.8292	262.967	346.099	6.9469200	7.079549561
7.8860600	2.1712	284.856	454.042	7.8860600	7.717782574
7.7447270	3.6972	235.994	354.049	7.7447270	7.395335191
7.8860600	1.7286	254.093	348.078	7.8860600	7.286413024
7.6382700	1.6022	277.952	378.089	7.6382700	7.247952581
7.1487420	2.8522	270.791	368.083	7.1487420	7.157248875
7.3767500	2.8522	268.768	368.083	7.3767500	7.181322575
6.5072396	3.5302	291.388	394.099	6.5072396	7.063586771
7.2676060	3.5302	291.663	394.099	7.2676060	7.060314271
8.0457575	0.6318	246.902	358.074	8.0457575	7.535894272
7.4436975	3.0228	333.180	435.125	7.4436975	6.927878483
6.9208190	2.4430	310.283	376.146	6.9208190	6.782469276
7.4685200	2.1616	247.264	332.083	7.4685200	7.208375009
7.4436970	1.9410	268.767	376.073	7.4436970	7.315037333
6.7878120	0.8245	243.135	333.078	6.7878120	7.369468573
6.4100500	1.7824	319.596	422.115	6.4100500	7.084001329
6.1938200	3.1588	285.561	382.099	6.1938200	7.067644417
7.6020600	1.9088	292.784	392.104	7.6020600	7.157602472
7.0506100	0.7773	229.713	322.062	7.0506100	7.446380165
7.5686360	2.1670	271.523	346.099	7.5686360	7.029311919
6.9136400	2.4260	316.860	406.120	6.9136400	6.940852980
7.2365700	2.6230	290.245	360.114	7.2365700	6.881034044
7.4948500	1.7710	286.994	360.094	7.4948500	6.985926204
7.1191860	3.0790	302.185	374.130	7.1191860	6.813469820
6.5718650	3.8745	320.329	408.114	6.5718650	6.802403109
6.7399290	4.1542	332.277	422.130	6.7399290	6.748475692
7.3010300	3.0960	302.559	374.130	7.3010300	6.807695090
7.4089350	0.8040	271.763	362.094	7.4089350	7.258196734



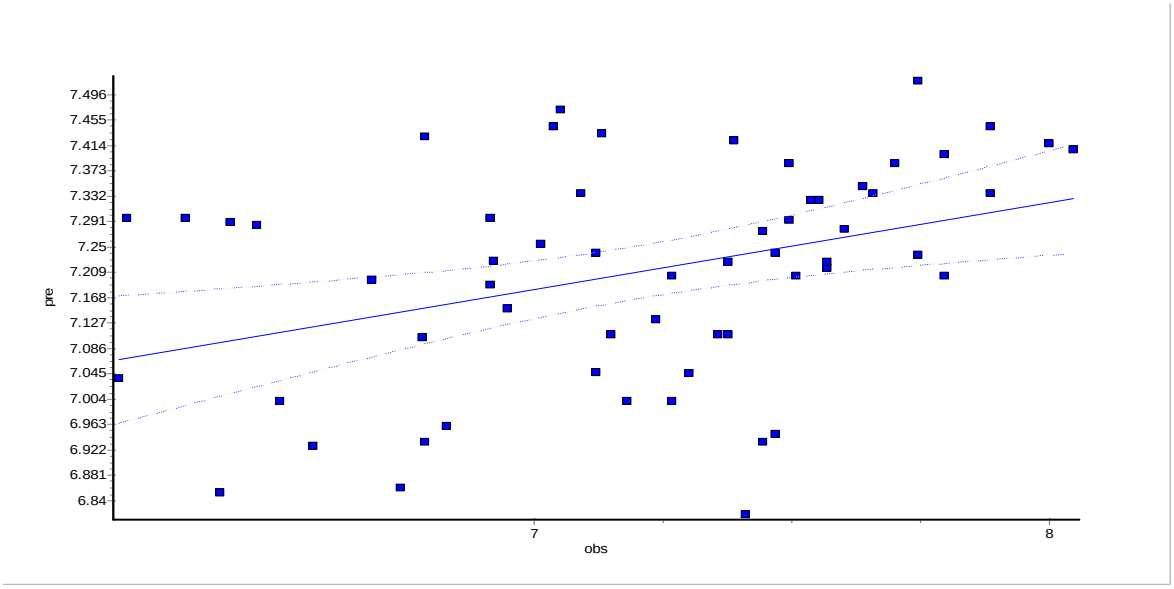
Model III: [A:IC $_{50}$] = 8.706 - 0.08601*[B:log p] - 0.02480*[C:hlc]- 0.7834*[D:ov]
SEM : 0.02865, Standard deviation : 0.1019, Correlation co-efficient (r) : 0.2218,
R squared : 0.0492, P value :0.0913, F : 2.950.



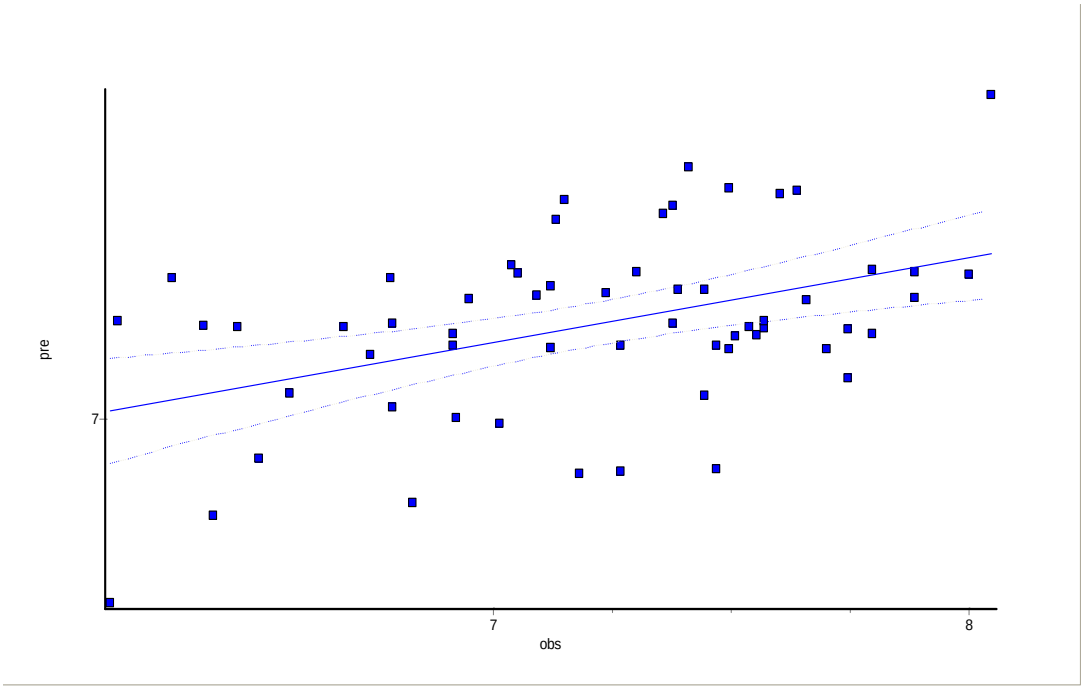
Model IV: [A:IC$_{50}$] = 7.696 - 0.07760*[B:log p] + 0.0001214*[C:sas] - 0.01206*[D:sev] + 0.007814*[E:em]
SEM : 0.05937, Standard deviation : 0.2112, Correlation co-efficient (r) : 0.5275, R squared : 0.2783, P value :<0.000, F: 21.975.



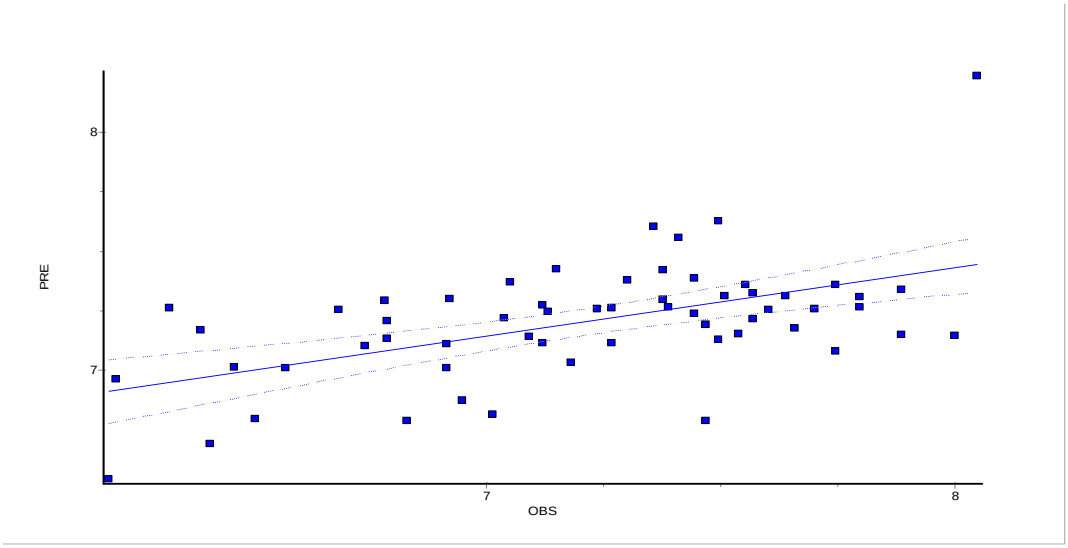
Model V: [A:ic 50] = 6.725 - 0.09405*[B:log p] + 0.8306*[C:ov]-0.04380*[D:sod] + 0.01893*[E:sovd]
SEM : 0.1336, Standard deviation : 0.4751, Correlation co-efficient (r) : 0.1241, R squared : 0.0153, P value :0.3492, F: 0.8909.



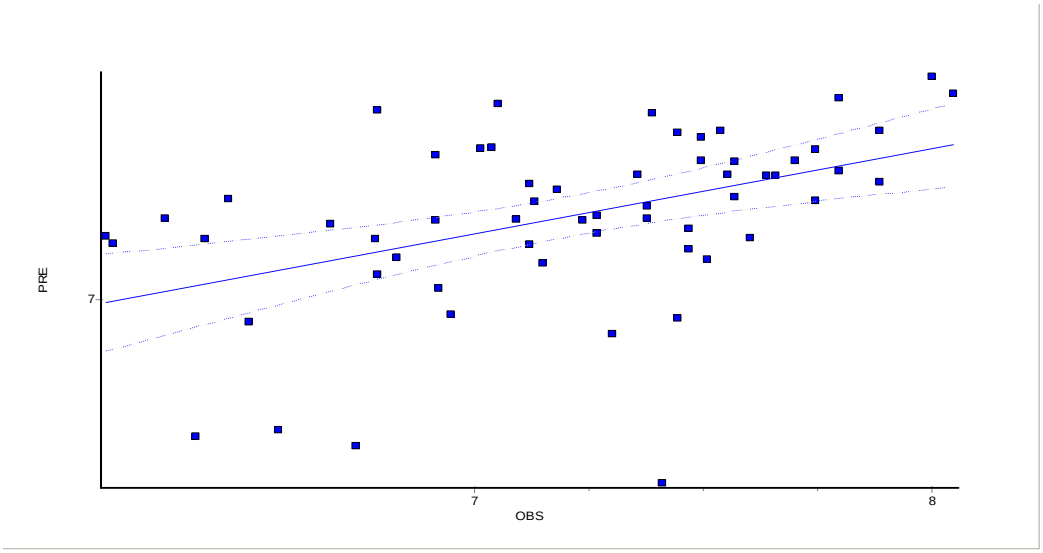
Model VI: [A:ic 50] = 7.737 - 0.1001*[B:log p] - 0.03841*[C:sod] + 0.01908*[D:sovd]
SEM : 0.0459, Standard deviation : 0.1635, Correlation co-efficient (r) : 0.3743,
R squared : 0.1401, P value :0.0035, F: 9.289.



Model VII: [A:ic 50] = 9.450 - 0.1244*[B:log p] - 0.9302*[C:ov]-0.03113*[D:sc]- 0.08490*[E:tc]-0.03920*[F:tvc]
SEM : 0.5178, Standard deviation : 0.1842, Correlation co-efficient (r) : 0.4338, R squared : 0.1882, P value :0.0006, F: 13.217.

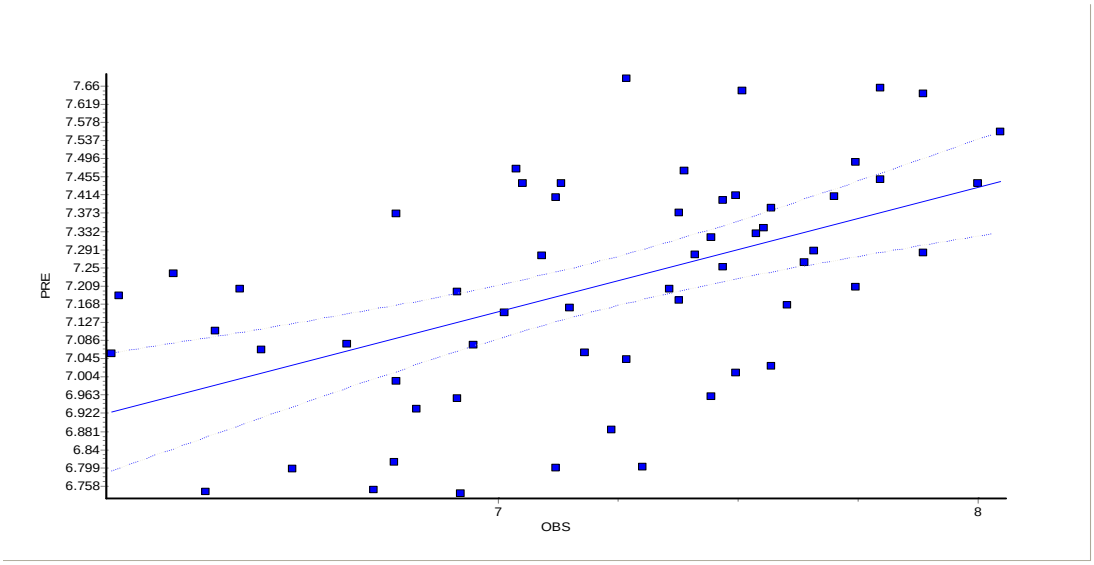


Model VIII: [A:ic 50] = 10.560 - 0.2615*[B:log p] - 608.72*[C:dp]+ 608.65*[D:dl] - 0.03865*[E:hlc] - 1.323*[F:ov]+ 0.1567*[G:pc] - 0.07378*[H:tc] - 0.05099*[I:tvc]
SEM : 0.0600, Standard deviation : 0.2137, Correlation co-efficient (r) : 0.5357,
R squared : 0.2870, P value :<0.0001, F: 22.946.



Model IX: [A:ic 50] = 7.136 - 0.1101*[B:log p] - 0.2331*[C:SA]+ 0.04429*[D:SoD] + 0.02858*[E:SoVD] – 0.03282*[F:CC]+ 0.1100*[G:Dm]

SEM : 0.0541, Standard deviation : 0.1925, Correlation co-efficient (r) : 0.4602,
R squared : 0.2118, P value :0.0002, F: 15.314.



Model X: [A:ic 50] = 7.713 - 0.09473*[B:log p] - 0.001504*[C:SAS] - 0.01190*[D:SEV] + 0.008374*[E:Em] + 0.002316*[F:CMA]

SEM : 0.0594, Standard deviation : 0.2115, Correlation co-efficient (r) : 0.5294,
R squared : 0.2803, P value :<0.0001, F: 22.196.

RESULTS AND DISCUSSION

The QSAR model was performed on ten different models and the results have been verified. Out of all the models studied the Models II,IV and VIII comprising of log P, SEV and Em has been found to be extremely significant showing the importance of these descriptors in the designing of novel sulfonamide analogs for histone deacetylase inhibitor property, while the Models IV and X have been found to be very significant.

CONCLUSION

This QSAR study has shown that the descriptors logP, Conolly Accessible Area (SAS), Exact Mass (Em), Conolly Solvent Excluded Volume (SEV), Conolly Molecular Area (CMA) play a vital role in imparting the biological activity. This study has also shown that the biological activity is governed by various thermodynamic, steric and electronic descriptors. The models provide a brief insight in to the mechanism of action of these compounds. All these parameters can be considered for further designing of newer molecules for histone deacetylase inhibitor activity.

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