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QSAR Modeling of Sulfonamide Inhibitors of Histone Deacetylase

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QSAR Modeling of Sulfonamide Inhibitors of Histone Deacetylase

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Abstract

Motivation. Quantitative structure–activity relationships (QSAR) analyses have been performed on a new set of sulfonamide derivatives applying linear free energy related (LFER) approach of Hansch to explain the structural requirements of sulfonamide derivatives for histone deacetylase inhibition.

Method. The lowest energy structures of the compounds in the series were used to calculate electronic, thermodynamic and steric parameters available in the molecular modeling program ChemOffice 2001.

Results. Among the various descriptors studied, energy of highest occupied molecular orbital (HOMO) and torsion energy (TOE) showed good correlation (correlation coefficients R = 0.881) with histone deacetylase inhibitory activity. The best model showed 77.6% explained variance in the activity with low standard deviation value (0.37) and a significant F value (36.369). Leave–one–out (LOO) and leave–25%–out cross–validation was performed to check the predictive power of the equation, which shows good predictive ability of the model (q^2_{LOO} = 0.711 and $q^2_{L25\%O}$ = 0.566).

Conclusions. The results of the QSAR study suggest that electron–withdrawing substituents in the aromatic ring will increase the binding affinity of sulfonamide derivatives towards histone deacetylase while bulky substituents are not tolerable for inhibitory activity. The results obtained from the study can further rationalize the design of new potent anticancer drug belonging to the category of histone deacetylase inhibitory sulfonamides.

Keywords. QSAR; quantitative structure–activity relationships; histone deacetylase; LFER model; sulfonamide analogues.

1 INTRODUCTION

The search for anti–cancer therapies, which target cancer cells specifically and selectively with less toxicity has been a quest in oncology for many years. The chemotherapeutic agents used in most cases produces only regression of the disease and permanent cure is still a distant reality.

Dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday.

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Targeting the enzymes implicated in the etiology of cancer has been useful in cancer chemotherapy. Histones are core proteins of nucleosomes, which can be acetylated and deacetylated. Cell specific pattern of gene expression dependent on histone acetylation result from a balance of the competing activities of two classes of enzymes, the histone acetyl trasferases [1,2] and the histone deacetylase (HDACS) [3,4]. Histone deacetylation is also implicated for cancer and it is characterized of inappropriate cell proliferation or altered pattern of cell death. The development of histone deacetylase inhibitors (HDAIs) has received much attention for treatment of cancer by inducing growth arrest, differentiation and/or apoptotic death of transformed cells. In addition, HDAC inhibitors might lead to activation of the host immune response and inhibition of tumor angiogenesis by multifactorial processes [5].

Despite the significance of histone deacetylase as a potential target for treatment of cancer, only few molecules such as trichostatin A (TSA) [6], suberoylanilide hydroxamic acid (SAHA)[7], Scriptaid analogs, and oxamflatin [8] or 2 amino anilide MS–275 [9] have been reported and some molecules (such as hydroxamate and cyclic peptide) are in II stage of clinical trials (Figure1). Among these inhibitors, US FDA has approved only butyrates as histone deacetylase inhibitors. Natural HDAC inhibitors are considered to be effective in treatment of malignant cancer tumors *in vivo*; however, they are somewhat inefficient in implementation [10]. Therefore synthetic inhibitors, specifically designed to reduce problems with efficiency are needed.

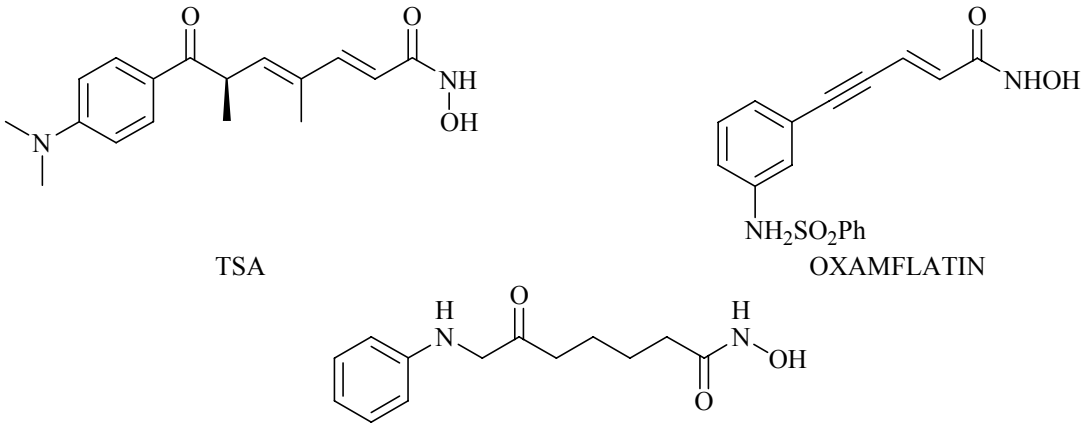


Figure 1. Structures of some histone deacetylase inhibitors.

The availability of X–ray structure from *Aquifex aeolicus* for histone deacetylase–like protein (HDLP) facilitates structure–based design of HDAIs [11]. X–ray crystallographic studies of TSA bound to HDLP (an archaebacterial homologue of human HDAC) pointed out that the hydroxamic acid coordinates the zinc ion through its keto and hydroxyl groups, resulting in a penta coordinate Zn^{2+} ion complex. Three additional hydrogen bonds exist between the CO, NH and OH groups of SAHA and Tyr 297, His 132, His 131 of HDLP, respectively. Therefore, by comparing the structures of known HDAC inhibitors like TSA, SAHA and TPX, it clearly appears at this stage that

all these HDAC inhibitors possess a metal–binding functionality, linked by a hydrocarbon chain to a cap substructure that interacts with amino–acids at the entrance of the N–acetyl lysine binding channel.

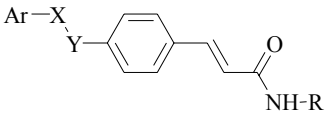


Figure 2. General structure of sulfonamide analogues.

Table 1. Substituents and HDAC–1 Inhibition Data

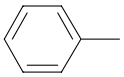
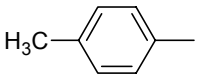
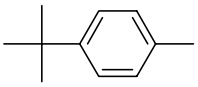
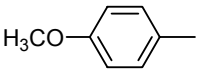
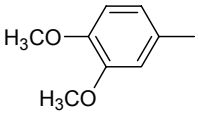
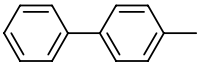
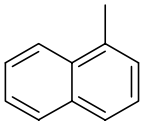
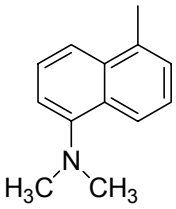
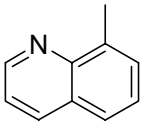
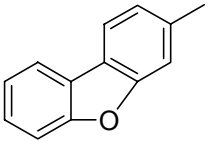
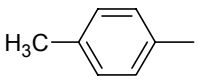
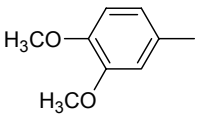
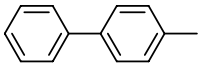
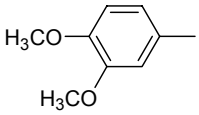
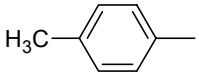
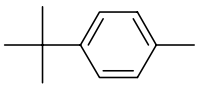
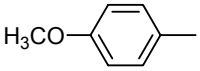
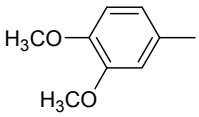
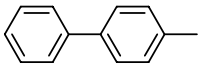
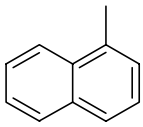
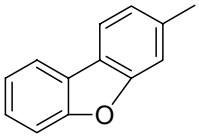
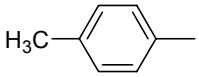
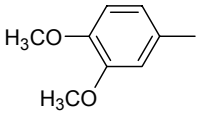
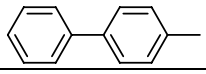
Compd. No.	Ar	X–Y	R	IC_{50} (μM)	–log IC_{50}
1		SO_2NH	OH	0.20	6.699
2		SO_2NH	OH	0.30	6.523
3		SO_2NH	OH	0.10	7.000
4		SO_2NH	OH	0.06	7.222
5		SO_2NH	OH	0.09	7.046
6		SO_2NH	OH	0.01	8.000
7		SO_2NH	OH	0.05	7.301
8		SO_2NH	OH	0.20	6.699
9		SO_2NH	OH	0.50	6.301
10		SO_2NH	OH	0.04	7.398
11		$NHSO_2$	OH	0.20	6.699
12		$NHSO_2$	OH	0.05	7.301

Table 1. (Continued)

Compd. No.	Ar	X–Y	R	IC_{50} (μM)	–log IC_{50}
13		$NHSO_2$	OH	0.04	7.398
14		NHCONH	OH	1.00	6.000
15		SO_2NH	$–C_6H_4–$ (2–NH_2)	3.00	5.523
16		SO_2NH	$–C_6H_4–$ (2–NH_2)	1.00	6.000
17		SO_2NH	$–C_6H_4–$ (2–NH_2)	1.00	6.000
18		SO_2NH	$–C_6H_4–$ (2–NH_2)	4.00	5.398
19		SO_2NH	$–C_6H_4–$ (2–NH_2)	1.00	6.000
20		SO_2NH	$–C_6H_4–$ (2–NH_2)	3.00	5.228
21		SO_2NH	$–C_6H_4–$ (2–NH_2)	0.40	6.398
22		$NHSO_2$	$–C_6H_4–$ (2–NH_2)	2.00	5.698
23		$NHSO_2$	$–C_6H_4–$ (2–NH_2)	3.00	5.523
24		$NHSO_2$	$–C_6H_4–$ (2–NH_2)	1.00	6.000

Wang *et al*. have performed recently docking studies on HDAIs [12] while three–dimensional structure based drug design and conformational analyses were reported by Massa *et al*. [13]. QSAR studies provide deeper insight into the mechanism of action of compounds that ultimately becomes of great importance in modification of the structure of compounds. In addition, QSAR also provides quantitative models, which permits prediction of activity of compounds prior to the synthesis [14]. Wang *et al*. have reported QSAR studies on this class of inhibitors [15].

Recently, Bouchain *et al*. studied sulfonamide analogues as a new class of potent histone deacetylase inhibitors (HDAIs) [16]. Urged by the need to develop novel histone deacetylase inhibitors, we applied the linear free energy related (LFER) approach of Hansch on sulfonamide analogues to rationalize the physicochemical properties before designing and developing new effective inhibitors.

2 MATERIALS AND METHODS

Bouchain *et al*. reported a series of 24 sulfonamide derivatives [16] as inhibitors of Histone Deacetylase (Table1 & Figure 2). The biological activity data reported in the literature [16] (IC_{50} in μm) was converted to negative logarithmic molar dose (pIC_{50}) in order to linearly relate free energy of the interaction of compounds with receptor and to reduce the skewness of the data set.

2.1 Computer Software

Molecular Modeling studies were performed using CS ChemOffice Software version 6.0 (Cambridge software) running on a P–IV processor [17]. All molecules were built using Chemdraw module and subjected to energy minimization using molecular mechanics (MM2). The minimization is continued until the root mean square (RMS) gradient value reaches a value smaller than 0.1 kcal/mol Å. The Hamiltonian approximations Austin model–1 (AM–1) method [18] and RHF (restricted Hartree–Fock: closed shell) wave function available in the MOPAC module of Chem3D is adopted for re–optimization until the root mean square (RMS) gradient attains a value smaller than 0.001 kcal/mol Å. The lowest energy structure of the compounds in the series was used to calculate physicochemical properties using the 'Analyze' option of the Chem3D package.

The physicochemical properties calculated include thermodynamic, steric and electronic descriptors. Molar refractivity, torsion energy (TOE), stretch bend energy (SBE), logP and bend energy (BE) are descriptors of thermodynamic property.

Steric descriptors calculated were Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded volume (CSEV), molecular weight, principal moments of inertia–x component (PMI–X), principal moments of inertia–y component (PMI–Y), principal moments of inertia–z component (PMI–Z) and ovality.

Electronic descriptors such as dipole moment (DM), electronic energy (EE), highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), repulsion energy (RE), and total energy (TE) were also calculated.

Sequential multiple linear regression analysis [19] method was used to generate QSAR models employing VALSTAT software [20]. In this technique the program search for all permutation and combination sequentially for the given data set and provides best model based on squared correlation coefficient. To check predictive power of the models, cross validation was done by leave–one–out (LOO) procedure [21]. Following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (*R*), explained variance (*%EV*), Standard deviation (*Std*), F–test (ratio between the described part and non–described part of the Y variance.), and internal predictive power discerned by cross–validated coefficient (q^2).

Table 2. Descriptors contributing to the HDAC inhibitory activity

Compd. No.	HOMO	TOE
1	–9.005	–12.953
2	–9.027	–11.871
3	–9.068	–12.678
4	–8.975	–12.105
5	–9.181	–15.015
6	–9.115	–26.085
7	–9.083	–20.424
8	–8.940	0.240
9	–8.949	–12.979
10	–8.952	–22.951
11	–8.992	–15.934
12	–8.744	–11.129
13	–8.976	–20.776
14	–8.394	–11.722
15	–8.404	–4.826
16	–8.405	–5.094
17	–8.407	–4.287
18	–8.384	–2.290
19	–7.943	–29.374
20	–7.999	–30.391
21	–8.327	–16.360
22	–8.144	–8.144
23	–8.122	–21.123
24	–8.143	–32.482

3 RESULTS AND DISCUSSION

The correlation between calculated descriptors as independent variable and HDAC inhibitory activity as response variable was found out by sequential linear regression analysis. Only those parameters having intercorrelation below 0.5 and significant at 95% were considered to select the best model. The best model obtained is given below along with its statistical measures.

$$\begin{gathered} pIC_{50} = -8.377\ (\pm 3.635) - 1.668\ (\pm 0.409)\ HOMO - 0.0263\ (\pm 0.0186)\ TOE \\ n = 24\ R = 0.881\ \%EV = 77.6\ variance = 0.138\ Std = 0.372431\ F_{(3,20)} = 36.369 \\ Chance < 0.01\ S_{PRESS} = 0.422\ S_{DEP} = 0.395\ q^2_{LOO} = 0.711 \end{gathered} \quad (1)$$

The model has a correlation coefficient of 0.881 with 77.6% explained variance in the HDAC inhibitory activity. F statistics indicate statistical significance at 99% level as the calculated F value exceeds the tabulated F value, which is $F_{(3,20\ \alpha\ 0.01)}$ 4.938. Since chance is less than 0.01, there exists statistically significant relationship between the descriptors HOMO, TOE and biological activity. The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix which shows that the descriptors HOMO and TOE not intercorrelated, r(HOMO,TOE) = 0.263.

The model also exhibits good internal predictivity as established by the cross validation R^2 value (q^2_{LOO} = 0.711) of the model. Predicted activity values were calculated using the correlation

developed and a comparison was made with the observed values (Table 3 and Figure 3). Since it is realized now that q^2 is no more a sufficient criterion for the predictive ability of the QSAR models [22], the predictive potential of the selected model was further assessed by leave–25%–out method. The model exhibits good predictivity, as $q^2_{L25\%O}$ value is 0.566. The correlation between observed and predictive activity for leave–25%–out method is given in Table 3 and Figure 4.

Table 4. Experimental, calculated, residual calculated, predicted and residual predicted activities

Compd No.	Experimental activities	Calculated activities	Residual	Predicted activities (LOO)	Predicted residual (LOO)	Predicted activities (L25%O)	Predicted residual (L25%O)
1	6.699	6.988	–0.289	7.011	–0.312	7.041	–0.342
2	6.523	6.996	–0.473	7.037	–0.514	7.054	–0.531
3	7.000	7.086	–0.086	7.094	–0.094	7.143	–0.143
4	7.222	6.915	0.307	6.892	0.330	6.969	0.253
5	7.046	7.336	–0.29	7.375	–0.329	7.390	–0.344
6	8.000	7.517	0.483	7.400	0.600	7.530	0.470
7	7.301	7.315	–0.014	7.317	–0.016	7.337	–0.036
8	6.699	6.531	0.168	6.494	0.205	6.488	0.211
9	6.301	6.895	–0.594	6.937	–0.636	6.890	–0.589
10	7.398	7.163	0.235	7.133	0.265	7.186	0.212
11	6.699	7.045	–0.346	7.073	–0.374	7.050	–0.351
12	7.301	6.503	0.798	6.459	0.842	6.484	0.817
13	7.398	7.145	0.253	7.118	0.280	7.105	0.293
14	6.000	5.936	0.064	5.931	0.069	5.964	0.036
15	5.523	5.771	–0.248	5.812	–0.289	5.822	–0.299
16	6.000	5.779	0.221	5.742	0.258	5.829	0.171
17	6.000	5.761	0.239	5.719	0.281	5.815	0.185
18	5.398	5.670	–0.272	5.733	–0.335	5.732	–0.334
19	6.000	5.649	0.351	5.547	0.453	6.373	–0.373
20	5.228	5.769	–0.541	5.923	–0.695	6.488	–1.260
21	6.398	5.947	0.451	5.913	0.485	6.255	0.143
22	5.698	5.831	–0.133	5.849	–0.151	6.356	–0.658
23	5.523	5.730	–0.207	5.758	–0.235	6.219	–0.696
24	6.000	6.065	–0.065	6.084	–0.084	6.760	–0.760

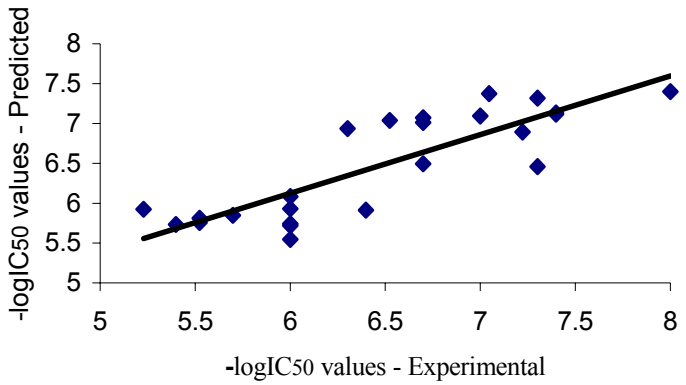


Figure 3. Predicted versus experimental activity values of compounds for model 1 (by leave–one–out method).

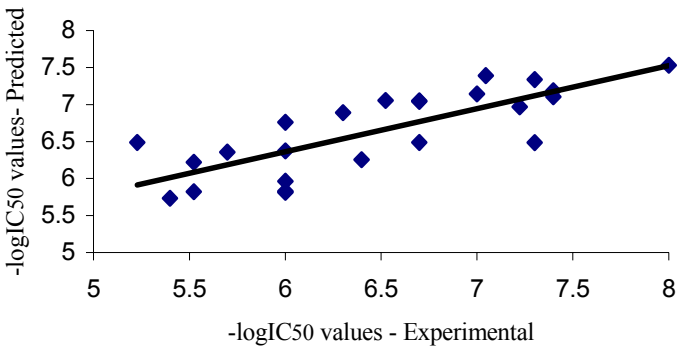


Figure 4. Predicted versus experimental activity values of compounds for model 1 (by leave–25%–out method).

The descriptors in the best model include electronic descriptor energy of highest occupied molecular orbital and thermodynamic descriptor torsion energy. HOMO is the highest energy level in the molecule that contains electrons [23]. It is crucially important in governing molecular reactivity and properties. When a molecule acts as a Lewis base (an electron–pair donor) in bond formation, the electrons are supplied from the molecule's HOMO. How readily this occurs is reflected in the energy of the HOMO. Molecules with high HOMO are having better ability to donate their electrons and are hence relatively reactive compared to molecules with low–lying HOMO; thus the HOMO descriptor measures the nucleophilicity of a molecule.

The descriptor HOMO bears a negative coefficient in the model, which suggests that decrease in HOMO energy will favor histone deacetylase inhibitory activity of sulfonamide derivatives. HOMO energy can be lowered by electron withdrawing substituents. Therefore electron–withdrawing substituents will increase the affinity of sulfonamide derivatives towards histone deacetylase.

TOE is thermodynamic parameter, which represents the energy associated with deforming torsion angles in the molecule from their ideal value. The negative coefficient of descriptor suggests bulky substituents are not tolerable for HDAC inhibitory activity of the sulfonamide derivatives.

4 CONCLUSIONS

The present study provides important structural insights in designing better histone deacetylase inhibitors. The results obtained for the set of 24 sulfonamide derivatives showed that electronic and thermodynamic properties (energy of highest occupied molecular orbital and torsion energy) have good correlation (R = 0.881) with HDAC inhibitory activity. The best model explains 77.6% variance in the activity. The prediction power of the QSAR models tested by leave–one–out (LOO) method which gave a good predictive model of q^2_{LOO} = 0.771.The predictive ability of the model was further assessed by leave–25%–out method and resulted in a good predictivity as $q^2_{L25\%O}$ value is 0.566. The results of the study suggest that electron–withdrawing substituents in the aromatic ring

will increase the binding affinity of sulfonamide derivatives towards histone deacetylase and bulky substituents are not tolerable for HDAC inhibitory activity of the sulfonamide derivatives.

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