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Rationalization of Physicochemical Properties of Alkanoic Acid Derivatives towards Histone Deacetylase Inhibition

Divya Jaiswal, Chandrabose Karthikeyan, and Piyush Trivedi

Drug Design Laboratory, Department of Pharmacy, SGSITS, Indore, India

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Rationalization of Physicochemical Properties of Alkanoic Acid Derivatives towards Histone Deacetylase Inhibition

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Abstract

Motivation. Quantitative Structure–Activity Relationships (QSAR) analyses have been attempted on a new set of (2–amino–phenyl)–amides of ω substituted alkanoic acids derivatives using linear free energy related (LFER) model of Hansch to explain the structural requirements of derivatives for histone deacetylase inhibition.

Method. The lowest energy structures of the compounds in the series were used to calculate electronic, thermodynamic, and topological parameters employing software package ChemOffice 2001.

Results. Out of various descriptors studied, torsion energy (TOE), and sum of valence degrees (SOVD) showed good correlation with histone deacetylase inhibitory activity (R = 0.851, %EV = 72.4, q^2 = 0.654) while dipole moment (DM) and ovality (O) showed good correlation with activity for induction of histone acetylation in human bladder T24 cancer cells (R = 0.893, %EV=79.7, q^2 = 0.728). Sum of valence degrees (SOVD) and radius (R) contribute to the antiproliferative activity against HCT116 cells (R = 0.880, %EV = 77.4, q^2 = 0.646).

Conclusions. The present study suggests that bulky substituents in the aromatic ring will decrease the binding affinity of alkanoic acid derivatives towards histone deacetylase as indicated by the negative contribution of the torsion energy. The positive contribution of SOVD illustrates that increase in branching and presence of heteroatoms is conducive for antiproliferative activity. The positive correlation of dipole moment indicates non–covalent, electronic interactions between the enzyme and inhibitor molecules whereas the positive correlation of ovality suggests that bulky substituents are significant for the induction of histone acetylation. Our study supplements the previous SAR studies and provides the necessary physico–chemical requirements at the substituents position for better HDAC inhibitory activity.

Keywords. Quantitative Structure–Activity Relationships; QSAR; histone deacetylase; ω–substituted alkanoic acids derivatives.

1 INTRODUCTION

Chemotherapy has been the corner stone of cancer treatment for several decades. Chemotherapeutic agents have considerable nonspecific toxicities, which limit the dosage that can be given. Moreover, development of resistance to treatment is common. Targeting the enzymes implicated in the etiology of cancer has been useful in cancer chemotherapy.

Dedicated on the occasion of the 65th birthday to Danail Bonchev.

* Correspondence author; phone: +91–0731–2368582; fax: +91–0731–2368582; E–mail: drtrivedislab@yahoo.co.in.

Chromatin is a nuclear macromolecular complex containing DNA, histones and nonhistone proteins [1]. One of the key steps in the regulation of expression of target genes is the posttranslational modification of the N– terminal tails of core histones by acetylation [2–4]. Histone deacetylase (HDACS) and histone acetyltrasferase (HAT) enzymes are involved in determining the acetylation status of histones. Such reversible acetylation reactions play an important role in modulation of chromatin topology and regulation of gene expression [5]. Aberrant acetylation of histone tails emerging from HAT mutations or abnormal recruitment of HDAC has been clearly linked to carcinogenesis. Rubinstein–Taybi syndrome [6–7], acute promyelocytic leukemia (APL) [8–9], acute myelogenous leukemia (AML) involving AML1–ETO fusion proteins [10], non–Hodgkin's lymphoma with over expression of the BCL–6 oncogene repressor [11], colorectal and gastric carcinomas [12] are examples of cancer diseases associated with an upset of biological HAT/HDAC balance.

In addition, HDAC inhibitors might lead [13] to activation of the host immune response and inhibition of tumor angiogenesis by multifactorial processes. Despite the significance of histone deacetylase as a target for treatment of cancer, very few molecules have been reported for of histone deacetylase inhibitory activity. Some good examples of this class of inhibitors are trichostatin A (TSA) [14], suberoylanilide hydroxamic acid (SAHA) [15], Scriptaid or its analogues, oxamflatin [16] & 2–amino anilide MS–275 [17]. Some molecules (such as hydroxamate and cyclic peptide) are in II stage of clinical trials [18]. These inhibitors, while effective in vivo, are inefficient due to instability, low retention, or nonspecific toxicity.

Currently, USFDA has approved only butyrates as histone deacetylase inhibitors. During the past several years there have been extensive efforts in the identification and optimization of histone deacetylase inhibitors (HDAICS) as novel anticancer drugs due to the ability of this therapeutic class to promote apoptosis and differentiation by targeting key components of tumor proliferation [19]. HDAC inhibitors have the potential to occupy an indomitable position in the fast–moving cytostatic market as they are able to improve the efficacy of existing cytostatics (such as the retinoids) and moreover, they are able to target the transcription of specific disease–causing genes, conferring unprecedented therapeutic windows to cancer therapy.

In 1999, the X–ray structure of the catalytic core of an archaebacterial HDAC homologue [histone deacetylase–like protein (HDLP)] was reported by Finnin *et al*. [20]. From the X–ray crystal he pointed out that the hydroxamic acid coordinates the zinc ion through its CO and OH groups, resulting in a penta–coordinate Zn^{2+} ion. Three additional hydrogen bonds exist between the CO, the NH and the OH groups of SAHA and Tyr 297, His 132, His 131 of HDLP, respectively. Therefore, from comparing the structures of known HDAC inhibitors like TSA, SAHA and TPX, it

clearly appeared 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.

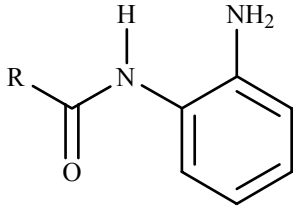
Wang *et al*. have performed recently docking studies on HDAICS [21] while three–dimensional structure based drug design and conformational analyses reported by Massa *et al*. [22]. Since QSAR studies provide deeper insight into the mechanism of action of compounds that ultimately becomes of great importance in modification of the structure of compounds and predict the activity of compounds even before their synthesis there is urge for QSAR studies on these compounds [23]. Wang *et al*. [24] have reported QSAR studies on these inhibitors. Urged by the need to develop novel histone deacetylase inhibitors, we performed QSAR studies on ω–substituted alkanoic acids analogues to rationalize the physicochemical properties before designing and developing new potent molecules.

2 MATERIALS AND METHODS

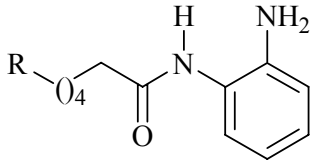
Twenty–five compounds belonging to (2–amino–phenyl)–amides of ω–substituted alkanoic acids derivatives were taken from literature [25]. The compounds were shown to inhibit recombinant human HDAC–1 with IC_{50} value in the low micro molar range. To confirm the ability of compounds to inhibit HDACS in whole cells the compounds were also evaluated for induction of histone acetylation in human bladder T24 cancer cells. The *in vitro* antiproliferative activity of compounds using the 3–[4,5–dimethylthiazol–2yl–2,5–diphenyltetrazolium] bromide (MTT) assay against HCT116 (human colon cancer) showed a range from 1 to 50 μM. The structures of series of compounds along with their biological activities are given in Table 1.

2.1 Biological Data

All biological activities used in present study were expressed as: $pIC_{50}= -\log_{10} IC_{50}$, where IC_{50} is the micro molar concentration of the inhibitor producing 50% inhibition. The conversion was done in order to linearly relate free energy of the interaction of compounds with receptor and to reduce the skewness of the data set.



(**1**–**16**)



(**17**–**25**)

Figure 1. 8–Oxo–8–aryl–octanoic acid (2 amino–phenyl)–amides and 6–Heteroaryl–hexanoic acid (2 amino–phenyl)–amides.

Table 1. (2–Amino–Phenyl)–amides of ω substituted alkanoic acids derivatives and their biological activities

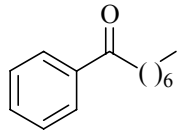
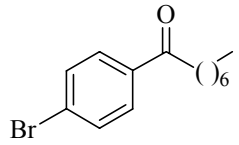
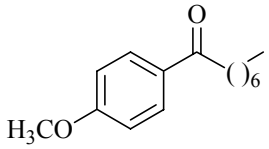
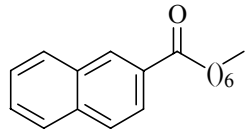
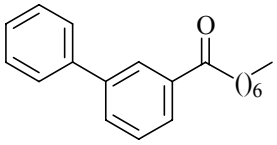
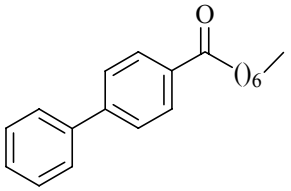
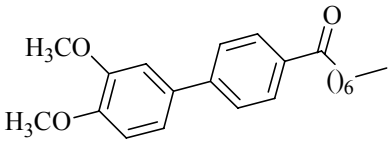
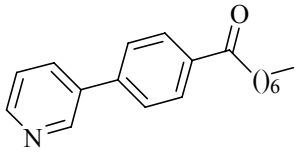
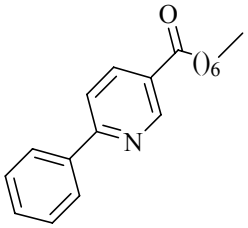
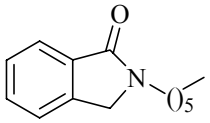
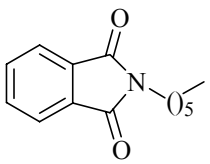
No	R	pIC_{50} (HDAC)	pIC_{50} (MTT)	pIC_{50} (H4AC)
1		5.046	ND	4.602
2		5.222	4.699	4.824
3		5.301	4.678	5.301
4		5.699	5.046	4.602
5		6.000	4.921	4.602
6		5.699	5.155	5.000
7		5.398	5.398	5.523
8		5.000	4.721	4.699
9		5.522	5.301	5.301
10		5.398	4.824	4.004
11		5.699	4.619	5.301

Table 1. (Continued)

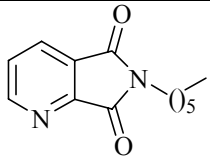
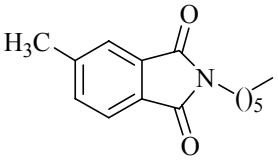
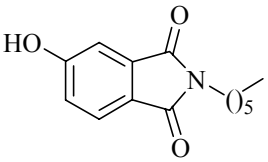
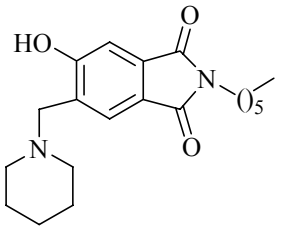
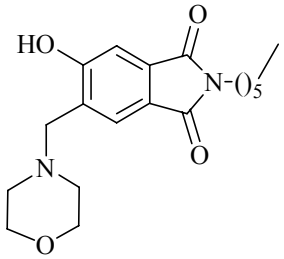
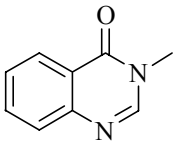
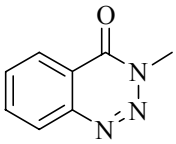
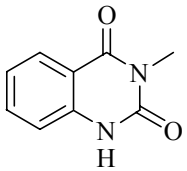
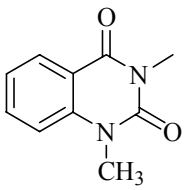
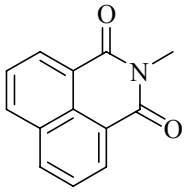
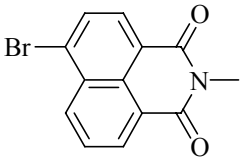
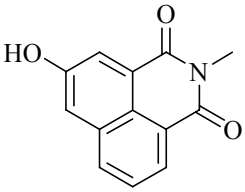
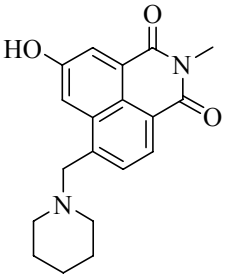
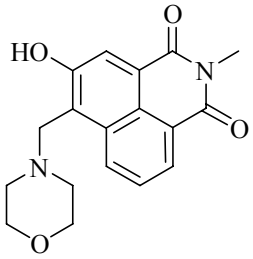
No	R	pIC_{50} (HDAC)	pIC_{50} (MTT)	pIC_{50} (H4AC)
12		5.301	ND	ND
13		5.522	5.221	5.221
14		5.522	4.958	5
15		5.522	4.508	ND
16		5.398	4.921	ND
17		4.921	5.000	5.301
18		5.097	5.000	5.000
19		5.398	5.301	5.000
20		5.398	5.301	ND

Table 1. (Continued)

No	R	pIC_{50} (HDAC)	pIC_{50} (MTT)	pIC_{50} (H4AC)
21		5.522	5.699	5.522
22		6.000	5.222	5.000
23		6.000	6.046	5.301
24		5.699	6.000	6.000
25		6.301	6.000	5.699

2.2 Computer Software

Molecular Modeling studies and Quantum mechanical calculations were performed using CS ChemOffice Software version 6.0 (Cambridge software) running on a P–IV processor [26]. All molecules were built using Chemdraw Ultra ver 6.0 and subjected to energy minimization using Allinger's MM_2 force field. 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 [27] Austin model–1 (AM–1) method and RHF (restricted Hartee–Fork: closed shell) wave function was adopted for re–optimization until the root mean square (RMS) gradient attains a value smaller than 0.001 kcal/mol. Å by the use of MOPAC module.

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.

Table 2. Descriptors contributing to the HDAC inhibitory and antiproliferative activity of (2–Amino–Phenyl)–amides of ω substituted alkanoic acids derivatives

No	TOE	SOVD	R	DM	O
1	–8.979	78	8	1.828	1.612
2	–10.517	80	9	2.433	1.633
3	–9.107	86	9	3.119	1.649
4	–20.086	92	9	2.169	1.673
5	–22.201	98	10	2.015	1.704
6	–22.191	98	10	1.783	1.703
7	0.700	114	11	2.258	1.756
8	5.766	100	10	1.889	1.695
9	–12.237	100	10	3.203	1.701
10	–9.930	84	8	1.129	1.611
11	–7.873	92	8	3.588	1.612
12	–0.398	94	8	4.332	1.606
13	–8.594	94	8	3.788	1.639
14	–7.857	98	8	3.865	1.619
15	–5.463	116	10	2.856	1.685
16	–5.996	120	10	4.886	1.679
17	–8.244	90	8	4.481	1.614
18	–7.334	92	8	4.349	1.613
19	–7.112	96	8	3.375	1.616
20	–7.164	98	8	3.333	1.631
21	–15.16	106	8	4.727	1.645
22	–14.315	108	9	3.381	1.657
23	–15.382	112	8	3.589	1.651
24	–0.401	124	10	1.326	1.691
25	–12.196	134	11	5.296	1.699

The 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. The topological descriptors calculated were Balaban index (BI), cluster count (CC), diameter (D), molecular topological index (MTI), radius (R), shape attributes (SA), shape coefficient (SC), sum of degree (SOD), sum of valence degree (SOVD), sum of total connectivity (TC), total valence connectivity (TVC), and the Wiener index (WI).

Different combination of descriptors were subjected to stepwise multiple linear regression analysis employing SYSTAT 10.2 software [28]. In stepwise multiple linear regression analysis the independent variables are individually added or deleted from the model at each step of the regression depending on the fisher ratio value selected to enter and to remove until the 'best' model is obtained. The descriptors found in the best models for HDAC inhibitory and antiproliferative activity of (2–amino–phenyl) amides of ω substituted alkanoic acids derivatives are summarized in Table 2.

Statistical qualities of the models were gauged by parameters like: correlation coefficient (*R*), standard error of estimate (*SEE*), variance ratio *F* (ratio between the described part and non–described part of the variance) explained variance (*%EV*), probability factor (*p*), and adjusted squared correlation coefficient (R^2a). To ascertain the predictivity of models, cross validation was done by mean of leave–one–out (LOO) procedure/Jack–Knife validation test [29] using in–house program VALSTAT [30]. Each compound is eliminated once and a model is derived from the remaining compounds and the eliminated compound is predicted from this model. The same procedure is repeated after elimination of another compound, until all the compounds have been eliminated once. The predictivity of the QSAR models was given by parameters cross–validated correlation coefficient (R^2cv or q^2), standard error of predictions (S_{DEP}), and standard deviation of prediction (S_{PRESS}). A compound was considered as an outlier for deriving a particular model when the residual value exceeded twice the standard error of estimate of the model.

3 RESULTS AND DISCUSSION

The correlation between different physicochemical and topological descriptors as independent variable and HDAC inhibitory activity as response variable was found out. Statistical processing by Stepwise regression method gave many QSAR models. Only those parameters having intercorrelation below 0.6 and confidence interval limit >95% were considered to select the best model [31]. The best model along with its statistical measures is given below.

$$\begin{gathered} pIC_{50}\,(HDAC) = 3.592\ (\pm 0.290) - 0.031\ (\pm 0.006)\ TOE + 0.016\ (\pm 0.003)\ SOVD \\ n = 25\ R = 0.851\ \%EV = 72.4\ R^2_A = 0.769\ F_{(3,21)} = 28.788\ p<0.001\ SEE = 0.185 \\ Spress = 0.206\ S_{DEP} = 0.194\ R^2cv = 0.655 \end{gathered} \quad (1)$$

where *n* is the number of data points, *R* is correlation coefficient, *%EV* is explained variance, *SEE* is standard error of estimate, and values given in the parentheses are standard error of the coefficients.

The model has a correlation coefficient of 0.851 with 72.4 % 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 $F_{(3,21)} = 4.874$. Since p–value from analysis of variance (ANOVA) table is less than 0.01, there exists statistically significant relationship between the descriptors TOE, and SOVD and biological activity. The t–values of –5.511, and 5.877 for TOE and SOVD respectively exceed the critical value (1.71), making the model reliable. The model also exhibits good predictivity as established by the cross validation of the model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table 3).

Table 3. Observed, Calculated, Residual, Predicted and Predicted residual activities of compounds for HDAC inhibitory activities

No	Observed activity	Calculated activity	Residual	Predicted activity	Predicted residual
1	5.046	5.135	–0.088	5.150	–0.104
2	5.222	5.215	0.007	5.215	0.008
3	5.301	5.268	0.033	5.265	0.036
4	5.699	5.706	–0.007	5.707	–0.008
5	6.000	5.869	0.131	5.838	0.162
6	5.699	5.869	–0.169	5.909	–0.210
7	5.398	5.418	–0.019	5.421	–0.023
8	5.000	5.034	–0.034	5.045	–0.045
9	5.522	5.592	–0.070	5.596	–0.074
10	5.398	5.261	0.136	5.246	0.151
11	5.699	5.327	0.372	5.304	0.395
12	5.301	5.128	0.173	5.102	0.198
13	5.522	5.382	0.141	5.375	0.147
14	5.522	5.424	0.098	5.419	0.102
15	5.522	5.641	–0.119	5.655	–0.133
16	5.398	5.723	–0.325	5.771	–0.373
17	4.921	5.306	–0.385	5.333	–0.412
18	5.097	5.310	–0.213	5.324	–0.227
19	5.398	5.368	0.029	5.366	0.031
20	5.398	5.402	–0.004	5.402	–0.005
21	5.522	5.780	–0.258	5.804	–0.282
22	6.000	5.786	0.214	5.767	0.233
23	6.000	5.884	0.116	5.869	0.131
24	5.699	5.614	0.085	5.590	0.108
25	6.301	6.142	0.156	6.069	–0.023

The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table 4) and the descriptors TOE, and SOVD were orthogonal.

Table 4. Correlation matrix for model–1

	HDAC	TOE	SOVD
HDAC	1.000		
TOE	–0.538	1.000	
SOVD	0.585	0.128	1.000

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 alkanoic acids derivatives. The positive contribution of SOVD illustrates that increase in branching and presence of heteroatoms is favourable for inhibitory activity.

The *in vitro* antiproliferative activities of 23 compounds evaluated using the MTT assay against HCT116 (human colon cancer). Stepwise regression by taking antiproliferative activity as response and afore–mentioned descriptors as predictor variable resulted in a biparametric model.

Compound 13 and14 found successively to be outliers as their residual value exceeded twice the standard error of estimate of the model (Studentized residual = –3.540 and –3.702). The reason for

the outlying behavior of these two compounds may probably due to the bulky substituents (piperidinyl and morpholinyl moieties) at the para position of the phenyl ring. Exclusion of compound 13 and 14 from data set as outliers resulted in model 2.

$$\begin{gathered} pIC_{50}\,(MTT) = -3.009\ (\pm 0.424) - 0.140\ (\pm 0.052)\ R + 0.035\ (\pm 0.004)\ SOVD \\ n = 21\ R = 0.893\ \%EV = 79.7\ R^2_A = 0.774\ F_{(2,18)} = 35.253\ p<0.001\ SEE = 0.207 \\ Spress = 0.238\ S_{DEP} = 0.221\ R^2_{CV} = 0.729 \end{gathered} \quad (2)$$

Table 5. Observed, Calculated, Residual, Predicted and Predicted residual activities of compounds for MTT assay against HCT116 inhibitory activities

No	Observed Activity	Calculated activity	Residual	Predicted activity	Predicted residual
1	4.699	4.503	0.196	4.447	0.252
2	4.678	4.711	–0.033	4.716	–0.038
3	5.046	4.918	0.128	4.908	0.138
4	4.921	4.986	–0.065	4.996	–0.075
5	5.155	4.986	0.169	4.962	0.193
6	5.398	5.401	–0.003	5.402	–0.004
7	4.721	5.056	–0.335	5.099	–0.378
8	5.301	5.056	0.245	5.024	0.277
9	4.824	4.781	0.043	4.775	0.049
10	4.619	5.058	–0.439	5.101	–0.482
11	5.221	5.127	0.094	5.119	0.102
12	4.958	5.266	–0.308	5.299	–0.341
13	4.508	*	*	*	*
14	4.921	*	*	*	*
15	5.000	4.989	0.011	4.988	0.012
16	5.000	5.058	–0.058	5.064	–0.064
17	5.301	5.197	0.104	5.186	0.115
18	5.301	5.266	0.035	5.262	0.039
19	5.699	5.543	0.156	5.515	0.184
20	5.222	5.473	–0.251	5.493	–0.271
21	6.046	5.751	0.295	5.662	0.384
22	6.000	5.887	0.113	5.855	0.145
23	6.000	6.094	–0.094	6.159	–0.159

* Compounds removed as outliers

The model is statistically significant, as it has a correlation coefficient of 0.893 with 79.7% explained variance in the activity. F statistics indicate statistical significance at 99% level as the calculated F value exceeds the tabulated F value, which is $F_{(2,18)}$ = 6.01. Since p–value from analysis of variance (ANOVA) table is less than 0.01, there exists statistically significant relationship between the descriptors and antiproliferative activity. The t–values of –2.698 and 8.120 for R and SOVD respectively exceed the critical value (1.729), making the model reliable. The model also exhibits good predictivity as established by the cross validation of the model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table 5).

The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table 6) and the descriptors R and SOVD were reasonably orthogonal.

Table 6. Correlation matrix for model–2

	MTT	R	SOVD
MTT	1.000		
R	0.227	1.000	
SOVD	0.845	0.552	1.000

The contribution of topological descriptors SOVD and radius (R) revealed that topology of the molecules play important role in HDAC inhibitory activity. SOVD shows positively contribution whereas radius negatively contributes to biological activity. Radius (R) is defined as the smallest vertex eccentricity in the graph [32]. SOVD is most significant descriptor, which is justified by its high value of t–test (8.120). The positive contribution of SOVD illustrates that increase in branching and presence of heteroatoms is favorable for antiproliferative activity.

Table 7. Observed, Calculated, Residual, Predicted and Predicted residual activities of compounds for induction of histone acetylation in human bladder T24 Cancer cells

No	Observed activity	Calculated activity	Residual	Predicted activity	Predicted residual
1	4.602	4.457	0.145	4.418	0.184
2	4.824	4.733	0.091	4.724	0.1
3	5.301	5.013	0.288	4.998	0.303
4	4.602	4.831	–0.229	4.853	–0.251
5	4.602	4.921	–0.319	4.977	–0.375
6	5	4.845	0.155	4.814	0.186
7	5.523	5.226	0.297	5.062	0.461
8	4.699	4.844	–0.145	4.868	–0.169
9	5.301	5.269	0.032	5.266	0.035
10	4.004	4.238	–0.234	4.352	–0.348
11	5.301	4.994	0.307	4.957	0.344
12	5.221	5.176	0.045	5.173	0.048
13	5	5.111	–0.111	5.123	–0.123
14	5.301	5.276	0.025	5.273	0.028
15	5	5.232	–0.232	5.271	–0.271
16	5	4.948	0.052	4.942	0.058
17	5.522	5.486	0.036	5.480	0.042
18	5	5.130	–0.13	5.138	–0.138
19	5.301	5.166	0.135	5.158	0.143
20	6	*	*	*	*
21	5.699	5.902	–0.203	6.019	–0.32

* Compound removed as outlier

To confirm the ability of compounds to inhibit HDACS in whole cells, 21 compounds were also evaluated for induction of histone acetylation in human bladder T24 Cancer cells. So correlations were established between H4AC activity as response variable and various physicochemical and topological descriptors as predictor variable and processed by stepwise regression method, which resulted in a biparametric model. Compound **20** is an outlier as the residual value exceeded twice the standard error of estimate of the model (Studentized residual = 5.632). The reason for the outlying behavior is not immediately apparent. Excluding compound **20** from data set as outlier derives model 3.

$$\begin{gathered} pIC_{50}\,(H4AC) = -3.252\ (\pm 1.916) + 0.305\ (\pm 0.042)\ DM + 4.437\ (\pm 1.137)\ O \\ n = 20\ R = 0.880\ \%EV = 77.4\ R^2_A = 0.747\ F_{(2,17)} = 29.094\ p<0.001\ SEE = 0.203 \\ Spress = 0.253\ S_{DEP} = 0.233\ R^2_{CV} = 0.646 \end{gathered} \quad (3)$$

Model 3 explains 77.4% variation in antiproliferative activity. The overall high *R*–value and low standard error of estimate prove it to be the best model describing the activity. The high value of Q^2 (0.646) is fairly high making it to be the best predictive model. Predicted activity values were calculated using the correlation developed and a comparison was made with the observed values (Table 7).

The absence of any serious multicollinearity between the descriptors present in the model was confirmed by the calculation of correlation matrix (Table 8).

Table 8. Correlation matrix for model–3

	H4AC	DM	O
H4AC	1.000		
DM	0.473	1.000	
O	0.323	–0.270	1.000

Dipole moment indicates the strength and orientation behavior of a molecule in an electrostatic field. It is a vector quantity with both additive and constitutive properties. The contribution of dipole moment illustrates the non–covalent, electronic interactions between the HDAC enzyme and inhibitor molecules. The molecular shape is an attribute of a molecule dealing with spatial extension, form, framework, or geometry. It is often described by molecular descriptors such as principal axes, ovality, or connectivity indices. The positive contribution of ovality suggests that bulky groups are favorable for H4AC induction.

4 CONCLUSIONS

The present study provides important structural insights in designing better histone deacetylase inhibitors. The analysis also revealed that thermodynamic and topological descriptors (*i.e.*, torsion energy) play an important role in HDAC inhibitory activity ($R = 0.851$, $\%EV = 72.4$, $q^2 = 0.654$). Bulky substituents in the aromatic ring will decrease the binding affinity of alkanoic acid derivatives towards histone deacetylase indicated by negative contribution of Torsion energy. The positive contribution of SOVD illustrates that increase in branching and presence of heteroatoms is favorable for antiproliferative activity ($R = 0.893$, $\%EV = 79.7$, $q^2 = 0.728$). Positive correlation of dipole moment indicates non–covalent, electronic interactions between the enzyme and inhibitor molecules whereas positive correlation of ovality suggests bulky substituents are favorable for induction of histone acetylation ($R = 0.880$, $\%EV = 77.4$, $q^2 = 0.646$). Our study supplements the previous SAR studies and provides the necessary physico–chemical requirements at the substituents position for better HDAC inhibitory activity.

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