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QSAR Studies of Uracil-Containing Histone Deacetylase Inhibitors

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Inhibitors of histone deacetylase (HDACs) are a new class of anticancer agents that affect gene regulation and have been shown to induce terminal differentiation of human tumor cell lines and to have antitumor effects *in vivo*. Quantitative structure activity relationship (QSAR) studies have been carried out in a series of new uracil based hydroxamide against maize HD2 inhibitory activities. The 2D QSAR studies activity is negatively influenced by the presence of electron donating substituent at the X-position whereas the contribution of hydrophobicity also shows negative effect. The best QSAR model with good correlation coefficient ($r^2 = 0.775$), of high statistical significance (> 99.9 %) well explained the variance in activity.

Key Words: QSAR, Histone deacetylase inhibitors.

INTRODUCTION

Histone deacetylases (HDACs) have been recently attracted considerable interest for the treatment of cell proliferative diseases like cancer. Histone deacetylase (HDAC) competes with histone acetyl-transferases (HATs) to modulate gene transcriptional activity by changing the acetylation status of lusines of nucleosomal histones[1]. HDAC inhibitors help in histone hyperacetylation and reactivate the suppressed genes and hence inhibit cell cycle. They have important role in apoptosis and hence bear a great potential as a new chemical entity. Consequently, the identification of potent HDAC inhibitors represents a compelling opportunity for the development of therapeutics for treatment of cancer[2].

In order to identify the influence of essential physico-chemical and structural parameter on histone deacetylase inhibitors, QSAR studies have been carried out on a series of 28 inhibitors of histone deacetylase using classical 2D QSAR. The studies of histone deacetylases inhibitors (HDACi) has shown that no work has been carried out on the series of inhibitors for computational studies. Thus the main objective of present studies is to design specific inhibitors in the hope that these molecules may be further proved as powerful anticancer agents.

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EXPERIMENTAL

The QSAR analysis was carried out on 28 compounds containing a uracil moiety as the connection between a phenyl/phenylalkyl portion and a N-hydroxyl polymethylenealkanamide or methylene cinnamylamide group for their antiproliferative activity[3] (IC_{50}) as dependent and different physico-chemical parameters[4] such as hydrophobicity FR; FRR (hydrophobicity for position R), FRX (hydrophobicity for position X), steric (molar refractivity MR); MRR (molar refractivity for position R), MRX (molar refractivity for position X), electronic (field effect F); FR (field effect for position R), FX (field effect for position X), FX2 (square term of field effect for position X) as independent parameter (Table-1). The total of 28 compounds was divided into training and test set of 19 and 9 compounds, respectively. The training set of 19 compounds was analyzed for correlation between the variation in inhibitory activity. The values for physico-chemical parameters were taken from the literature[5]. The multiparameter regression analysis was executed on personal computer using Systat version 7.2[6]. Pearson correlation matrix (Table-2) was constructed to determine the inter-correlation between physico-chemical parameters used in QSAR analysis.

RESULTS AND DISCUSSION

Different combination of physio-chemical parameters (independent) showing some acceptable correlation with the biological activity (dependent) were carried out using stepwise multiple regression analysis in order to develop QSAR equations. The equations are of statistical significance with correlation value > 0.7 and with regression coefficient values significant more than 99.9 %.

$$-\log IC_{50} = -5.594\ (\pm 1.438)\ FX2 - 8.476\ (\pm 1.799)\ FX - 3.324\ (\pm 0.292) \quad (1)$$
$$N = 19,\ r = 0.793,\ r^2 = 0.628,\ s = 0.526,\ F = 13.519$$

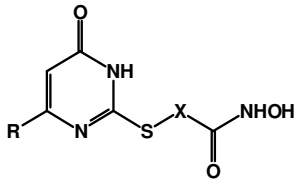
$$-\log IC_{50} = -20.432\ (\pm 4.085)\ FX - 14.770\ (\pm 3.152)\ FX2 - 0.968\ (\pm 0.309)\ FRX - 2.572\ (\pm 0.316) \quad (eq.2)$$
$$N = 19,\ r = 0.880,\ r^2 = 0.775,\ s = 0.423,\ F = 17.229$$

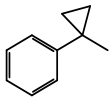
$$-\log IC_{50} = -18.887\ (\pm 8.068)\ FX2 - 25.000\ (\pm 10.474)\ FX - 2.412\ (\pm 3.050)\ FRX + 0.132\ (\pm 0.277)\ MRX - 2.440\ (\pm 0.427) \quad (3)$$
$$N = 19,\ r = 0.882,\ r^2 = 0.779,\ s = 0.434,\ F = 12.312$$

$$-\log IC_{50} = -15.021\ (\pm 3.202)\ FX2 - 20.798\ (\pm 4.156)\ FX - 0.991\ (\pm 0.314)\ FRX + 0.009\ (\pm 0.011)\ MRR - 2.826\ (\pm 0.446) \quad (4)$$
$$N = 19,\ r = 0.886,\ r^2 = 0.785,\ s = 0.428,\ F = 12.79$$

From above equation, it is clear that substituent at position X effects the biological activity of the parent compound significantly. In the pool of descriptors, taken for study, hydrophobicity and field affect the biological activity.

TABLE-1
HISTONE DEACETYLASE INHIBITORY ACTIVITY AND
PHYSIO-CHEMICAL PARAMETERS OF THE COMPOUNDS



Compd. no.	Substitution		Values of the Hansch parameters used			log IC_{50}	
	R	X	FRX	FX	FX^2	Obs.	Calcd.
1	Ph	$(CH_2)_4$	2.16	-1.16	1.35	-0.90	-0.89671
2	$PhCH(CH_3)$	$(CH_2)_5$	2.70	-0.20	0.04	-0.95	-1.68974
3*	Ph	$(CH_2)_5$	2.70	-0.20	0.04	-1.08	-1.68974
4	$PhCH_2$	$(CH_2)_5$	2.70	-0.20	0.04	-1.26	-1.68974
5	Ph	$(CH_2)_3$	1.74	-0.12	0.01	-1.43	-1.87895
6*	$PhCH(C_2H_5)$	$(CH_2)_5$	2.70	-0.20	0.04	-1.51	-1.68974
7	$PhCH_2CH_2$	$(CH_2)_5$	2.70	-0.20	0.04	-1.54	-1.68974
8	$PhCH_2$	$(CH_2)_6$	3.24	-0.24	0.06	-1.57	-1.71910
9*	$PhCH_2CH_2$	$(CH_2)_2$	1.20	-0.08	0.01	-1.57	-2.11961
10	Ph	$(CH_2)_6$	3.24	-0.24	0.06	-1.58	-1.71910
11	$PhCH_2$	$(CH_2)_2$	1.20	-0.08	0.01	-1.58	-2.11961
12*	$PhCH_2CH_2$	$(CH_2)_4$	2.16	-0.16	0.03	-1.60	-1.79539
13	Ph	$(CH_2)_7$	3.78	-0.28	0.08	-1.62	-1.74846
14	PhCH(Ph)	$(CH_2)_5$	2.70	-0.20	0.04	-1.72	-1.68974
15*		$(CH_2)_5$	2.70	-0.20	0.04	-1.79	-1.68974
16	$PhCH_2$	$(CH_2)_7$	3.78	-0.28	0.08	-1.79	-1.74846
17	$PhCH(OCH_3)$	$(CH_2)_5$	2.70	-0.20	0.04	-1.91	-1.68974
18*	$PhCH_2CH_2$	$(CH_2)_6$	3.24	-0.24	0.06	-1.92	-1.71910
19	$PhCH_2CH_2$	$(CH_2)_7$	3.78	-0.28	0.08	-1.95	-1.74846
20	Me	$(CH_2)_5$	2.70	-0.20	0.04	-2.04	-1.68974
21*	$PhCH_2$	$(CH_2)_4$	2.16	-0.16	0.03	-2.10	-1.79539
22	*n*-Pr	$(CH_2)_5$	2.70	-0.20	0.04	-2.13	-1.68974
23	$PhCH_2CH_2$	$(CH_2)_3$	1.74	-0.12	0.01	-2.31	-1.87895
24*	H	$(CH_2)_5$	2.70	-0.20	0.04	-2.33	-1.68974
25	$PhCH_2$	$(CH_2)_3$	1.74	-0.12	0.01	-2.36	-1.87895
26	Ph	$(CH_2)_2$	1.20	-0.08	0.01	-2.91	-2.11961
27*	$PhCH_2$	CH=CH	0.65	0.07	0	-3.95	-4.27505
28	$PhCH_2CH_2$	CH=CH	0.65	0.07	0	-4.61	-4.27505

*Compounds included in the test set.

TABLE-2
PEARSON CORRELATION MATRIX

	LA	FRX	FX	FX2
LA	1.000			
FRX	0.535	1.000		
FX	-0.526	-0.264	1.000	
FX2	0.335	-0.004	-0.958	1.000

Conclusion

Among these equations, the eqn. 2 was considered to be the best model with correlation coefficient (r = 0.880) explaining 77.5 % variance in activity. The low standard error of estimate(s), a high F value and one-third value of coefficients suggests that the model is statistically highly significant. The data showed overall statistical significance > 99.9 % with F = 17.229 against tabulated value for Fischer's test at 99.9 % significance [$F_{3,15\alpha0.001}$ = 9.73]. The above model (eqn. 2) also predicted well the inhibitory activity of the molecules of the test set as shown in Fig. 1, where the comparable correlation coefficient value (r = 0.880) was observed.

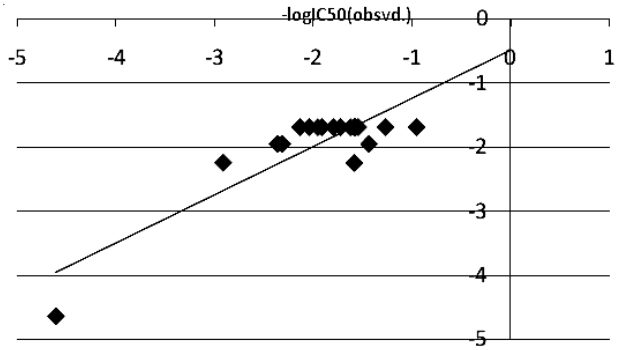


Fig. 1. Plot between observed *vs.* calculated activity (IC_{50}) for the training set of 19 compounds

The above studies indicate that due to the negative contribution by FX, FX2 and FRX, the molecules with the least bulk and electron donating group at X position should be preferred.

External validation: The validation of the best model (eqn. 2) has been done on a test set of 9 compounds, where good correlation (r^2 = 0.76) was observed between the predicted and the observed activity. The eqn. 5 describes the correlation between observed (y) and predicted (x) activities of test set (Fig. 2).

$$y = 1.021x - 0.086 \qquad r^2 = 0.760 \qquad (5)$$

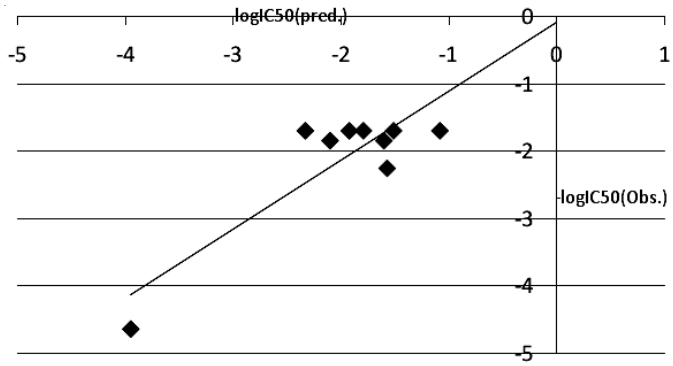


Fig. 2. Plot between observed *vs.* calculated activity (IC_{50}) for the test set of 9 compounds

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