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MODELING OF ANTICANCER ACTIVITY OF ANTHRA PYRAZOL-6 (2H)-ONE DERIVATIVES BY QSAR METHOD

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Abstract: In this study the anticancer activity of a series of Anthra (1,9-cd) Pyrazol-6(2H)-one derivatives are studied by two dimentional quantitative structure activity relationship (QSAR) analysis. Multiple regression analysis and cross validation is used as statistical tool. Best model is obtained by considering the value of R^2, R^2cv, R^2adj, F-ratio and Q-value. Strong correlation is obtained between experimental and predicted anticancer activity.

Index Terms - Quantitative Structure-Activity Relationship (QSAR), NCSS, Anticancer activity, Surface tension, indicator parameter, Edge Adjecency indices.

I. INTRODUCTION

Cancer is one of the leading causes of disease and mortality worldwide [1]. Studies conducted over more than 40 years have revealed mounting evidence supporting that extracellular matrix remodelling proteinases, such as matrix metalloproteinases (MMPs), are the principal mediators of the alteration observed in the microenvironment during cancer progression [2,3].

The matrix metalloproteinases (MMPs) are a family of structurally related zinc-dependent endoproteinases that degrade and remodel structural protein in the extracellular matrix [4]. They include more than 20 subtypes, among which MMP-2 is highly involved in the process of tumor invasion and metastasis and has been considered as a promising target for cancer therapy [5,6].

A number of natural and synthetic HDAC inhibitors have been reported, and in recent years the importance of HDAC inhibitors has increased due to their efficacy against many malignant diseases [7]. Several of these HDAC inhibitors inhibit tumor growth and many of them are under clinical trials [8-9]. Quantitative structure-activity relationships (QSAR) studies have been successfully applied for modelling the biological activities of natural and synthetic chemicals [10,11].

To find quantitative relation between Anthra Pyrazol derivatives structure and their Antticancer activity against histone deacetylase (HDAC-8) and metalloproteinases various methods of mathematical modeling have been applied. QSAR/QSPR investigations have opened a new page in the history of computer applications in chemistry and created extensive software dealing with the search for structure activity / property relationship during past 2 decades [12-14]. The major goal of any QSAR / QSPR research is to assign the structure of a number of set which (I) must correlate well with the property (activity) value measured experimentally and if possible (II) should provide some physical insight to the molecular behavior.

Anticancer activity :-

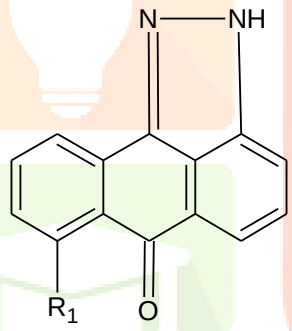
The Anticancer activity of Anthra Pyrazol derivatives against metalloproteinases and histone deacytalase is represented in the form of PIC_{50} and has been expressed in (µM) in this study Anticancer activities of compounds are used as PIC_{50} value.

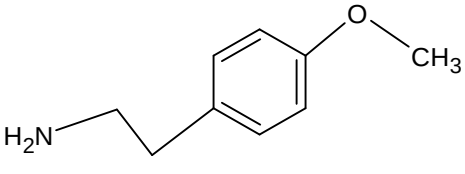
Presentation of data :- In present study Table-1 represent the structure of Anthra Pyrazol derivatives with Anticancer activity, while Table-2 Represents the various calculated descriptors used in the QSAR analysis. Table-3 shows the correlation among various descriptors and Anticancer activity as in the form of correlation matrix. Table-4 represents the cross validation statistical parameters for significant developed models.Table-5 contains the results of regression analysis while Table-6 represents the estimated value of PIC_{50} used in this study figure-1 Is the graph plotted between predicted and observed PIC_{50} value.

II. Material and Methods

In the present study , we chose 32 substitutions of anthra [1,9-cd] pyrazol-6(2H)-one for which their anticancer activities are reported in the literature by Chen et al. [12]. On the other side and for the 2DQSAR study, the reported value of IC_{50} have been converted into PIC_{50} by taking negative logarithm (PIC_{50} = log10 IC_{50}) and subsequently used as the dependent variable for the 3D-QSAR model development. Figure -1 represents the basic structure of the pyrazol and table-1 shows the studied substitution of the compounds and corresponding experimental activities of PIC_{50}.

TABLE-1:-Structure and Anticancer Activity of Anthrax Pyrazol-6 (2H)-One Derivatives used in this Study



Compound	R_1	PIC_{50}(obs)
1	Cl	1.258
2	$NHCH_2CH(CH_3)_2$	1.251
3	$NHCH_2CH_2CH_3$	1.491
4	$NHCH_2CH_2CH_2CH_2CH_2OH$	1
5	$NHCH_2CH_2C_6H_5$	1.340
6	NH-Cyclohexane	1.109
7	NH-Cyclopentane	1.2
8	$NHCH_2$-Cyclohexane	1.302
9	$NHCH_2CH_2CH_2OH$	1.16
12	$NHCH_2CH_2CH_2CH_3$	1.386
11	$NHCH_3$	1.556
12	$NHCH_2C_6H_5$	0.946
13	$NHCH_2CH_2$-Cyclohexane	1.505
14		1.532

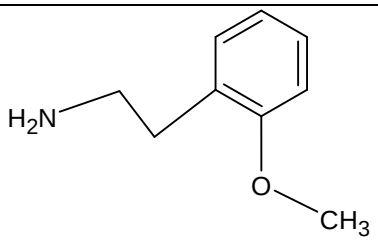
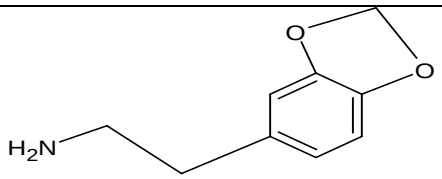
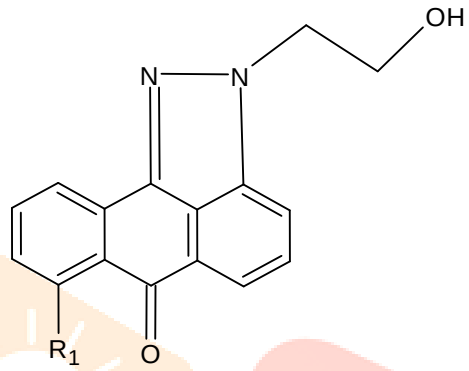
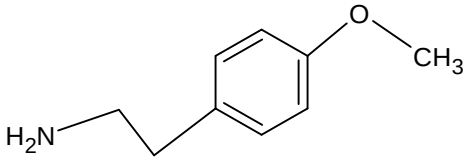
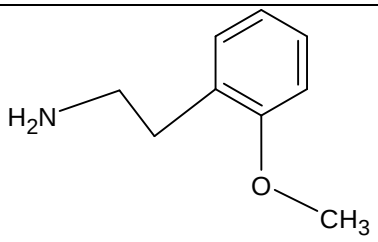
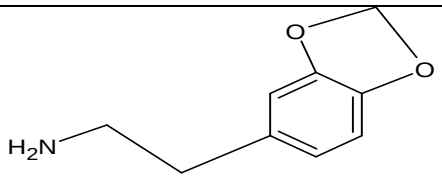
15		0.926
16		0.74

TABLE -1:- Continued



Compound	R_1	PIC_{50}(obs)
17	Cl	1.137
18	$NHCH_2CH(CH_3)_2$	1.455
19	$NHCH_2CH_2CH_3$	1.484
20	$NHCH_2CH_2CH_2CH_2CH_2OH$	1.486
21	$NHCH_2CH_2C_6H_5$	1.489
22	NH-Cyclohexane	1.49
23	NH-Cyclopentane	1.346
24	$NHCH_2$-Cyclohexane	1.254
25	$NHCH_2CH_2CH_2OH$	1.272
26	$NHCH_2CH_2CH_2CH_3$	1.519
27	$NHCH_3$	1.487
28	$NHCH_2C_6H_5$	1.493
29	$NHCH_2CH_2$-Cyclohexane	1.324
30		1.505
31		1.504
32		1.497

III. RESULTS AND DISCUSSION :-

The list of Anthra pyrazol derivatives and value of Anticancer activity in PIC_{50} is taken from literature[15]. In order to understand the experimental Anticancer activity data of 32 novel substituted Anthra Pyrazol derivatives on theoretical besis we established a quantitative structure activity relationship between their Anticancer activity and descriptors coding for Edge Adjecency indices properties of molecules under consideration using described by Hansch, Free & Wilson.

In order to deduce the correlation of observed Anticancer activity in terms of PIC_{50} of the 32 compounds with different structural parameters a systematic QSAR investigation has been carried out. The Anticancer activity is taken as dependent variable to get a linear relationship in the QSAR model. The value of the selected descriptors are given in Table-2, these parameters are calculated by using the software dragon supplied by Vcc lab running in dual core processor at Department of Chemistry, Govt. M.S. Golwalkar College Rewa (M.P.). Using these data (table-2) a correlation matrix is calculated to find the correlation as well as the co linearity between the descriptors. A high interrelationship was observed between IR_1 & SpAD_EA, (0.445), IR_1 and SpAD_EA(dm) (0.167).

The data presented in Table-3 demonstrated the high co linearity between the parameters. ($r>0.82$) except with ST, SpMAD_EA(ri) & IR_1. No significant correlation is obtained between Anticancer activity and descriptors. So multiple correlation is helpful in QSAR analysis.

The mathematical formulation of quantitative structure activity relationship is based on the principle of poly linearity. Multiple linear regression is a common method used in QSAR studies.

The QSAR was obtained by forward stepwise multiple regression technique the multi linear form for example-

Log MIC = $a_o+a_1D_1+a_2D_2+----------+a_nDn$

Where D_1, D_2 and D_n are descriptors, n is the no. of descriptors, The intercept (a_o) and regression coefficient of descriptors are determined by using the least square method.

The statistical equation of the data was performed using NCSS software. To test the quality of regression equations cross validation method is also used.

The result of stepwise regression analysis is given below:

Mono Parametric Model:-

$PIC_{50} = 1.9812 – 0.0098\ ST$ ---------- (1)

n = 32, $R^2 = 0.2973$, $R^2A = 0.2739$, F-ratio = 12.695

The model 1 (eq-1) represents a very poor value of variance with SpMAD_EA(ri), Which is high among all mono parametric correlation. It has no statistical significance so further addition of parameters take place and hence stepwise regression is applied.

Bi Parametric model:-

$PIC_{50} = 1.6935 – 0.0121\ ST – 0.9819\ SpMaxA\_EA(ed)$ ---------- (2)

n = 32, $R^2 = 0.3655$, $R^2A = 0.3218$, F-ratio = 8.354,

For Anthra Pyrazol derivatives eq-(2) is obtained by model no. (2). It can be concluded from above equation that ST exerts negative effect on Anticancer activity, while SpMaxA_EA(ed) exerts positive effect. The point to be noted that there is a sudden rise in the value of variance. It becomes 36.55 % which reveals the significant value of correlation with r=0.6045 for more improvement further addition of descriptors is applied.

Tri Parametric Model:-

$PIC_{50} = 1.2163 + 0.2728\ IR_1 – 0.0129\ ST + 1.5928\ SpMaxA\_EA(ed)$-- (3)

n = 32, $R^2 = 0.4402$, $R^2A = 0.3803$, F-ratio = 7.341

The model no.(3) is described by equation (3). It is obtained by addition of indicator parameter IR. The significance of this is that presence of Amine group decreases the Anticancer activity against matrix metalloproteinases and histone deacetylase. The value of variance is 44.02 % and correlation coefficient is 0.6634. It is significant but it is not best so further addition of descriptors is required to establish a best equation.

Tetra Parametric Model:-

PIC_{50} = 0.2504 + 0.4411 IR_1 – 0.0193 ST + 3.8933 SpMaxA_EA(ed) + 0.0371 SpAD_EA(dm) ---------- (4)

n = 32, R^2 = 0.5301, R^2A = 0.4605, F-ratio = 7.615

The model no. (4) is described by Equation (4). It is obtained from the QSAR analysis shows a better correlation from eq. (3) . Value of variance is increased from 44.02 % to 53.01 % and F-ratio is also increased from 7.341 to 7.615. It is also clear from eq. (4) that presence of Amine group also decrease the Anticancer activity of these Anthra Pyrazol derivatives.

Best equation of this analysis is obtained by model no. (8)

PIC_{50} = -

6.7068 – 0.0142 ST + 0.1340 SpAD_EA + 9.0674 SpMaxA_EA(ed) + 45.8726 SpMaxA_EA(dm) – 1.4425 SpDiam_EA(dm) + 0.0853 SpAD_EA(dm) ---------- (5)

n = 29, R^2 = 0.8270, R^2A = 0.7798, F-ratio = 17.526

Equation (5) obtained from the model no (8) is the best model of this study which represents 82.70 value of variance with significant value of correlation cofficientic 0.9093, ST, SpAD_EA, SpMaxA_EA(ed), SpMaxA_EA(dm), SpDiam_EA(dm) and SpAD_EA(dm) are used in this equation maximum value of Fischer projection 17.526 and minimum value of mean square error 0.0102 also supports the superiority of this model .cross validation result (Table –4) also supports it as a best model .

TABLE-2:- Calculated Descriptor with Activity of Anticancer Derivatives used in this Study

No.	PIC_{50} (obs)	IR_1	ST	SpAD_EA	SpMaxA_EA(ed)	SpMaxA_EA(dm)	SpDiam_EA(dm)	SpAD_EA(dm)	SpMAD_EA(ri)
1	1.258	0	81.8	32.736	0.599	0.064	2.679	4.035	1.516
2	1.251	1	70	38.556	0.505	0.036	1.814	4.185	1.527
3	1.491	1	75.4	36.543	0.526	0.033	1.575	2.931	1.507
4	1		78.6	40.323	0.467	0.029	1.575	2.931	1.473
5	1.340	1	76.8	45.427	0.421	0.077	3.45	7.531	1.502
6	1.109	1	76.1	42.845	0.451	0.061	2.871	6.214	1.516
7	1.2	1	82.3	41.473	0.468	0.064	2.871	6.214	1.521
8	1.302	1	68.7	44.32	0.435	0.082	3.772	7.935	1.515
9	1.16	1	88.6	37.777	0.505	0.031	1.575	2.931	1.489
10	1.386	1	71.4	37.777	0.505	0.031	1.575	2.931	1.496
11	1.556	1	86.2	33.997	0.574	0.036	1.575	2.931	1.53
12	0.946	1	80.9	44.32	0.435	0.082	3.772	7.935	1.515
13	1.505	1	66.1	45.427	0.421	0.077	3.45	7.531	1.502
14	1.532	1	72.2	48.295	0.394	0.072	3.644	12.519	1.482
15	0.926	1	72.2	48.296	0.394	0.041	2.63	7.861	1.482
16	0.74	1	82.9	52.091	0.371	0.075	4.471	14.591	1.502

17	1.137	0	61.2	37.008	0.532	0.056	2.679	2.679	1.489
18	1.455	1	50.9	42.828	0.457	0.032	1.814	2.828	1.503
19	1.484	1	54.1	40.816	0.474	0.029	1.575	1.575	1.484
20	1.486	1	56.6	44.595	0.427	0.026	1.575	1.575	1.456
21	1.489	1	54.9	49.701	0.388	0.07	3.45	6.175	1.484
22	1.49	1	58.1	47.119	0.413	0.056	2.871	4.857	1.495
23	1.346	1	60.1	45.744	0.427	0.057	2.871	4.857	1.499
24	1.254	1	56.4	48.593	0.4	0.074	3.772	6.579	1.495
25	1.272	1	60.5	42.049	0.457	0.028	1.575	1.575	1.469
26	1.519	1	58	38.27	0.512	0.031	1.575	1.575	1.503
27	1.487	1	52.5	42.049	0.457	0.028	1.575	1.575	1.475
28	1.493	1	56.4	48.593	0.4	0.074	3.772	6.579	1.495
29	1.324	1	54.9	49.701	0.388	0.07	3.45	6.175	1.484
30	1.505	1	52.7	52.569	0.366	0.066	3.644	11.162	1.467
31	1.504	1	52.7	52.57	0.366	0.038	2.63	6.504	1.467
32	1.497	1	60.9	56.365	0.346	0.069	4.471	13.235	1.486

ST = Surface tension.

IR_1 = indicator parameter value of it is 1 if NH_2 is present In place of R_1 otherwise it is zero

SpMaxA_EA(ed) = normalized leading eigenvalue from edge adjacency matrix

SpMaxA_EA(dm) = normalized leading eigenvalue from edge adjacency matrix

SpDiam_EA(dm) = spectral diameter from edge adjacency matrix

SpAD_EA(dm) = spectral absolute deviation from edge adjacency matrix

SpMAD_EA(ri) = spectral mean absolute deviation from edge adjacency matrix

Table -3:- Correlation Matrix

	PIC50 (obs)	IR_1	ST	SpAD_EA	SpMaxA_EA(ed)	SpMaxA_EA(dm)	SpDiam_EA(dm)	SpAD_EA(dm)	SpMAD_EA(ri)
PIC50(obs)	1								
IR_1	0.1541	1							
ST	-0.5272	-0.1031	1						
SpAD_EA	-0.0675	0.4453	-0.4195	1					
SpMaxA_EA(ed)	0.0817	-0.5314	0.4107	-0.9836	1				
SpMaxA_EA(dm)	-0.2415	-0.1066	0.1610	0.4524	-0.4050	1			
SpDiam_EA(dm)	-0.3056	-0.0118	0.0522	0.6672	-0.6095	0.9505	1		
SpAD_EA(dm)	-0.3242	0.1672	0.2047	0.6921	-0.6425	0.7557	0.8763	1	
SpMAD_EA(ri)	-0.1576	-0.1327	0.5721	-0.4295	0.4649	0.3715	0.1871	0.0876	1

TABLE -4:- Results of Cross Validation

Model	N	PRESS	SSY	PRESS/SSY	R^2cv	R^2	R^2adj
1	32	1.1156	1.3627	0.8159	0.1813	0.2973	0.2739
6	32	1.1306	1.3627	0.8296	0.1703	0.3655	0.3218
21	32	1.0179	1.3627	0.7469	0.2530	0.5752	0.4935
31	29	0.4383	1.2978	0.3377	0.6622	0.8270	0.7798

Table -5 Result of Regression

Model no.	Parameter	Ai, i=1,2,3....	Intercept	MSE	AR^2	R^2	R	F-Ratio	Q-Value
1	ST	A1=-0.0098	1.9812	0.0319	0.2739	0.2973	0.5452	12.695	17.0925
2	ST SpMAXA_EA(ed)	A1=-0.0121 A2=0.9819	1.6935	0.0298	0.3218	0.3655	0.6045	8.354	20.2874
3	IR_1 ST SpMaxA_EA(ed)	A1=0.2728 A2=-0.0129 A3=1.5928	1.2163	0.0272	0.3803	0.4402	0.6634	7.341	24.3924
4	IR_1 ST SpMaxA_EA(ed) SpAD_EA(dm)	A1=0.4411 A2=-0.0193 A3=3.8933 A4=0.0371	0.2504	0.0237	0.4605	0.5301	0.7280	7.615	30.7206
5	ST SpAD_EA SpMaxA_EA(ed) SpMaxA_EA(dm)	A1=-0.0063 A2=0.1638 A3=11.0397 A4=28.6995	-9.6598	0.0222	0.4935	0.5752	0.7584	7.042	34.1630

	SpDiam_EA(dm)	A5=-0.8331							
6	ST SpAD_EA SpMaxA_EA(ed) SpMaxA_EA(dm) SpDiam_EA(dm) SpAD_EA(dm)	A1=-0.0125 A2=0.1501 A3=10.7161 A4=35.0293 A5=-1.0968 A6=0.0583	-8.4448	0.0185	0.5786	0.6602	0.8125	8.095	43.9203
7	IR_1 ST SpAD_EA SpMaxA_EA(ed) SpMaxA_EA(dm) SpDiam_EA(dm)	A1=0.3751 A2=-0.0097 A3=0.1543 A4=12.5862 A5=23.5394 A6=-0.6288	-103342	0.0189	0.5683	0.6519	0807 4	7.803	42.7197
After Deletion of Compound No. 2,28 & 32									
8	ST SpAD_EA SpMaxA_EA(ed) SpMaxA_EA(dm) SpDiam_EA(dm) SpAD_EA(dm)	A1=-0.0142 A2=0.1340 A3=9.0674 A4=45.8726 A5=-1.4425 A6=0.0853	-6.7068	0.0102	0.7798	0.8270	0.9093	17.526	89.1564

TABLE-6:- ESTIMATED PIC_{50} WITH RESIDUAL FROM MODEL NO. 26 and 31

Compound	Obs PIC_{50}	From Model no. 26		From Model no. 31	
		Est PIC_{50}	Residual	Est PIC_{50}	Residual
1	1.258	1.400	-0.142	1.369	-0.111
2	1.251	1.391	-0.140	----	-----
3	1.491	1.330	0.161	1.384	0.107
4	1	1.085	-0.085	1.127	-0.127
5	1.340	1.274	0.066	1.309	0.031
6	1.109	1.214	-0.105	1.234	-0.125
7	1.2	1.218	-0.018	1.254	-0.054
8	1.302	1.205	0.097	1.202	0.100
9	1.16	1.055	0.105	1.080	0.080
10	1.386	1.270	0.116	1.324	0.062
11	1.556	1.432	0.124	1.463	0.093
12	0.946	1.052	-0.106	1.029	-0.083
13	1.505	1.408	0.097	1.461	0.044
14	1.532	1.376	0.156	1.430	0.102

15	0.926	1.130	-0.204	1.074	-0.148
16	0.74	0.884	-0.144	0.700	0.040
17	1.137	1.222	-0.085	1.143	-0.006
18	1.455	1.538	-0.083	1.549	-0.094
19	1.484	1.462	0.022	1.488	-0.004
20	1.486	1.389	0.097	1.396	0.090
21	1.489	1.512	-0.023	1.457	0.032
22	1.49	1.420	0.070	1.372	0.118
23	1.346	1.374	-0.028	1.333	0.013
24	1.254	1.266	-0.012	1.149	0.105
25	1.272	1.350	-0.078	1.363	-0.091
26	1.519	1.508	0.011	1.528	-0.009
27	1.487	1.450	0.037	1.476	0.011
28	1.493	1.266	0.227	-----	-----
29	1.324	1.512	-0.188	1.457	-0.133
30	1.505	1.672	-0.167	1.635	-0.130
31	1.504	1.532	-0.028	1.416	0.088
32	1.497	1.244	0.253	-----	------

FIG-1 :- GRAPH BETWEEN Obs & Est PIC_{50} FROM MODEL NO. 26

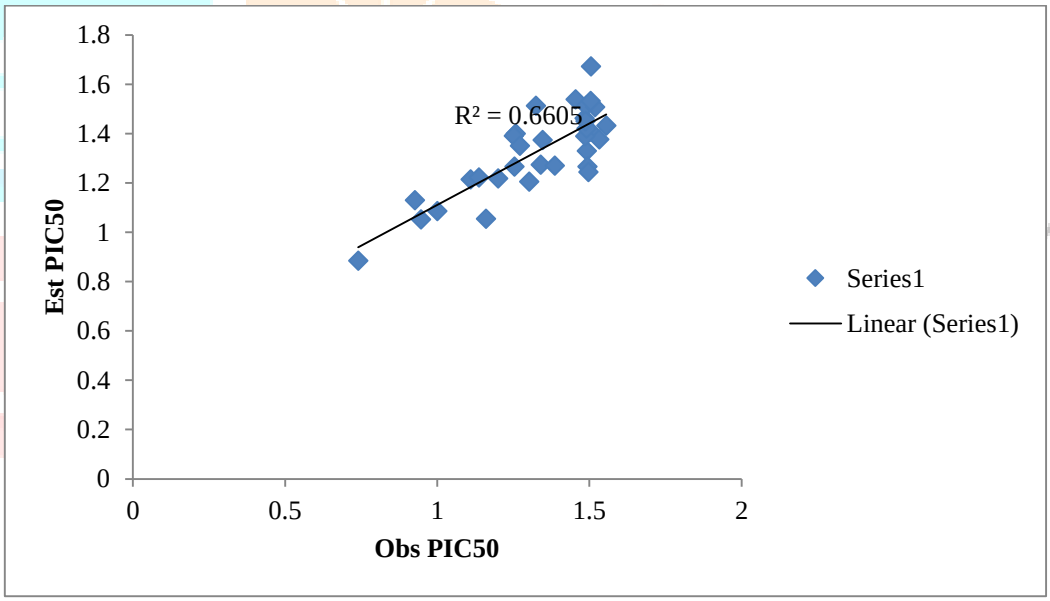


FIG-2 :- GRAPH BETWEEN Obs & Residual PI_{C50} FROM MODEL NO. 26

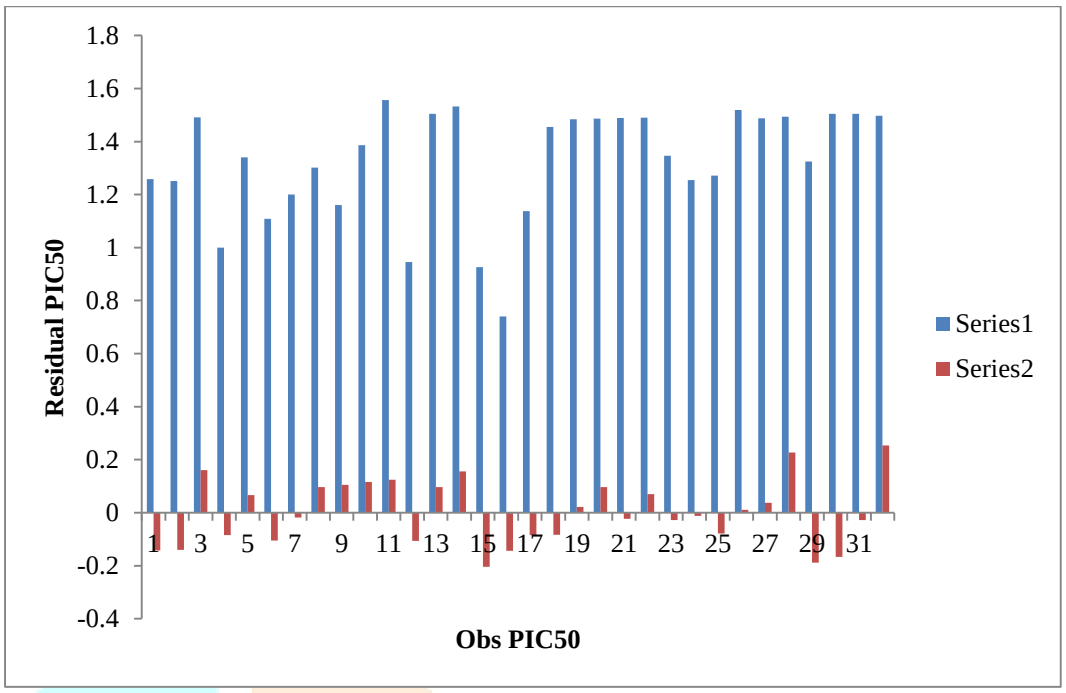


FIG-3 :- GRAPH BETWEEEN Obs & Est PIC_{50} FROM MODEL NO. 31

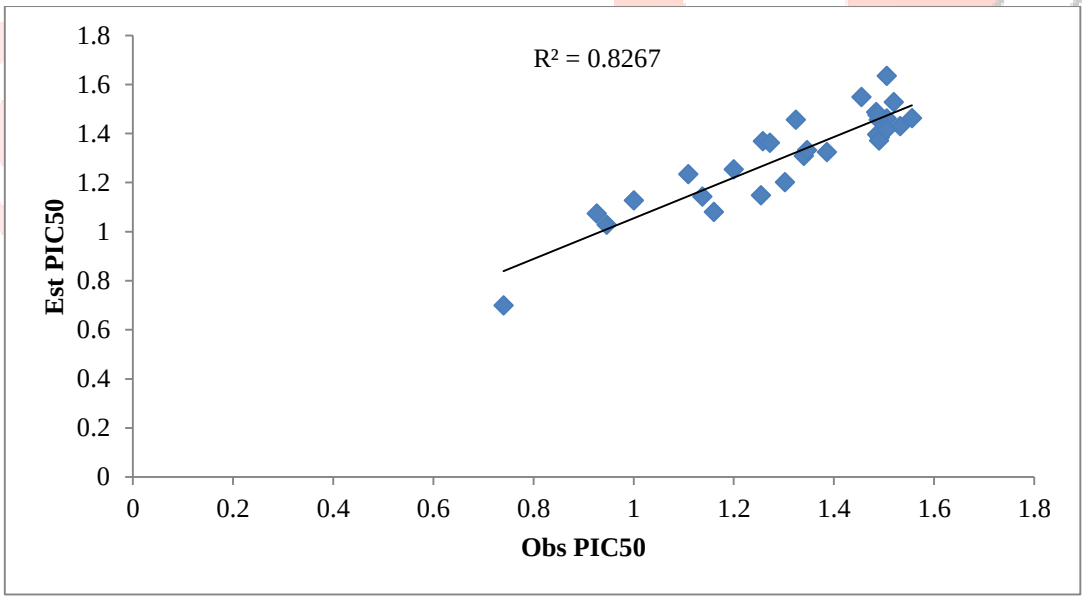
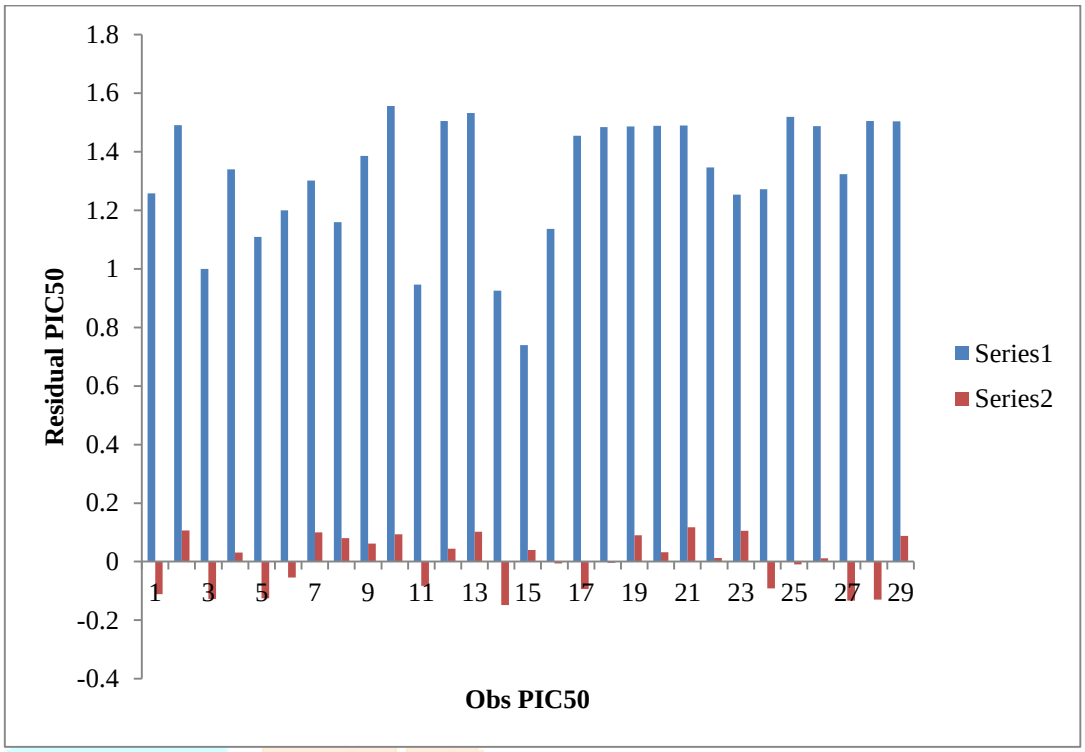


FIG-4 :- GRAPH BETWEEN Obs & Residual PIC_{50} FROM MODEL NO. 31



IV. CONCLUSION

From the results and discussion presented above are conclude that the Anthra pyrazol derivatives are effective against matrix metalloproteinase and histone deacetylase which are progressive target of cancer therapy. The presence of Toluene and sulphonyl group decreases the Anticancer activity. From the established QSAR model it is calculated that Anticancer activity of Anthra pyrazol derivatives and close agreement between experimental and predicted values is obtained. The low residual activity and high cross validated R^2 values (R^2cv) observed indicated and predictive ability of the developed QSAR model.

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