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QSAR Study for the treatment and prevention of thrombosis using Mer Specific tyrosine kinase inhibitors.

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Abstract

Anti-platelet compounds are an important drug for cardiovascular diseases and for certain surgical procedures where a risk of stroke or thrombosis. Mer is a member of the TAM (Tyro3, Axl and Mer) receptor tyrosine kinase (RTK) subfamily with growth-arrest-specific-6Gas6) as one of the endogenous ligands. Currently, Mer has been shown to play important roles in regulating macrophage activity and platelet aggregation. The role of Mer kinase in regulating the second phase of platelet activation generates an opportunity to use Mer inhibitors for preventing thrombosis with diminished likelihood for bleeding as compared to current therapies. The QSAR tries to explain the observed variance in the biological effect of certain classes of compounds as a function of molecular changes caused by the substituents. These physiochemical descriptors which included parameters to account for hydrophobicity, electronic properties and steric effect are determined empirically or, more recently, by computational methods. QSAR methodologies save resources and expedite the process of the development of new molecules and drugs. In our works, we calculated many descriptors from the 43 molecular structures in literature1 by the software Dragon, MLR Methods was used to select descriptor and set up linear model. Then we developed a new QSAR model to explore the IC_{50} of anti-thrombosis the compounds with diverse structures. The square of correlation coefficient (R^2) for best model with penta molecular descriptors after deletion of three compound is 0.9326. The best model since the values R = 0.9657, R^2 = 0.9326 , R^2A = 0.9227 , R^2cv = 0.9325 are the best as compared to all the models. The calculated F value is greater than F theoretical value , the value of standard error of estimate is the lowest , SE = 0.5655, PRESS/SSY = 0.06743 confirms that it is statistically significant and excellent model and it has been found to be having outstanding predictive power also. The present finding the based on QSAR are in excellent agreement with the result obtain by Linhao Xu et al.

Key words: QSAR, Anti-platelet compounds, Thrombosis using Mer, tyrosine kinase inhibitors.

Introduction

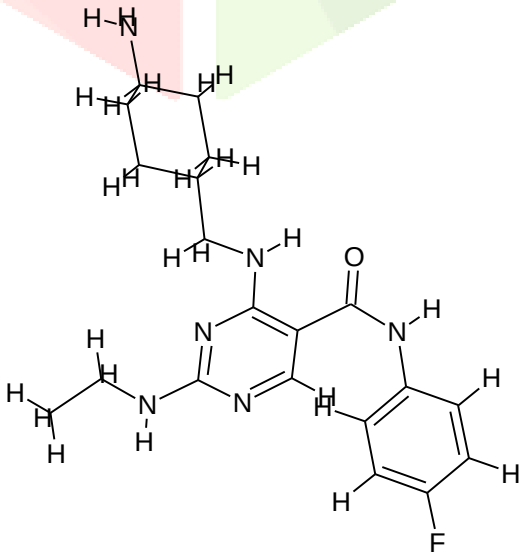
Pathologic thrombus formation cause stroke or heart attack. Therefore, Anti-platelet compounds are an important drug for cardiovascular diseases and for certain surgical procedures where a risk of stroke or thrombosis. Mer is a member of the TAM (Tyro3, Axl and Mer) receptor tyrosine kinase (RTK) subfamily with growth-arrest-specific-6Gas6) as one of the endogenous ligands [1,2]. Currently, Mer has been shown to play important roles in regulating macrophage activity and platelet aggregation. The role of Mer kinase in regulating the second phase of platelet activation generates an opportunity to use Mer inhibitors for preventing thrombosis with diminished likelihood for bleeding as compared to current therapies.

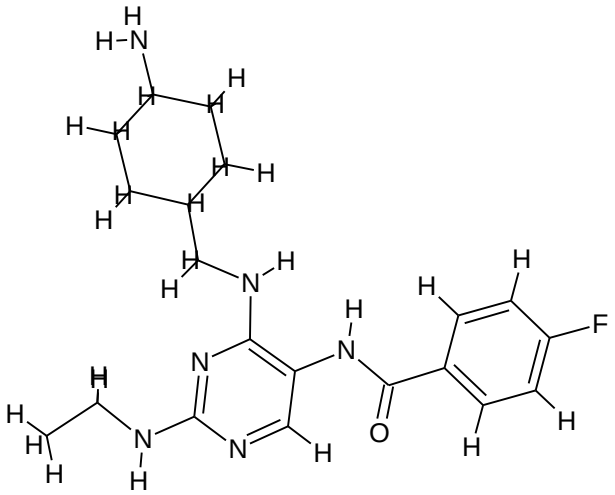
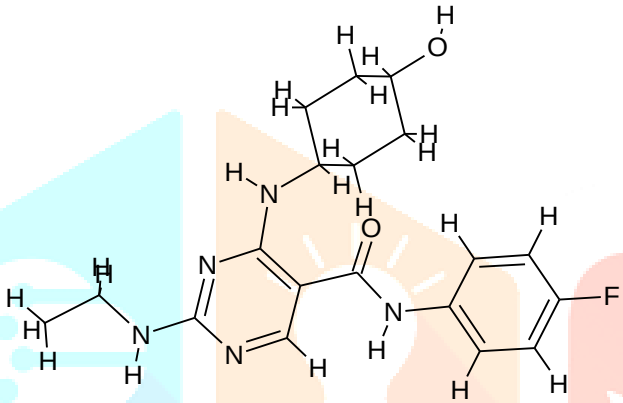
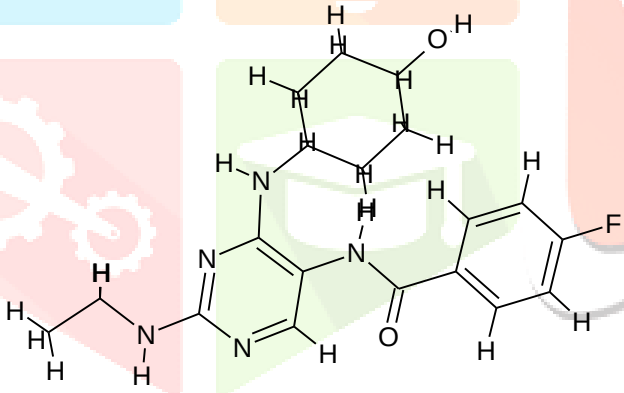
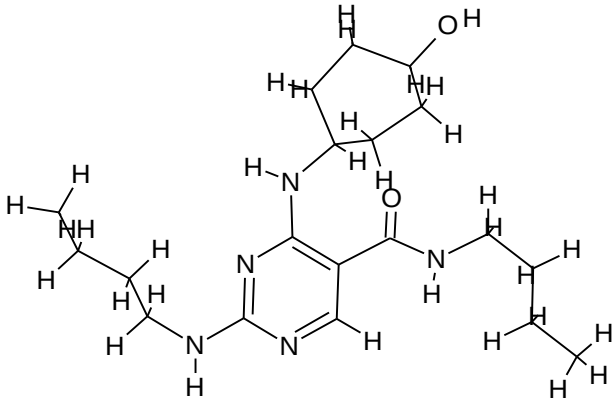
MATERIALS AND METHODS:

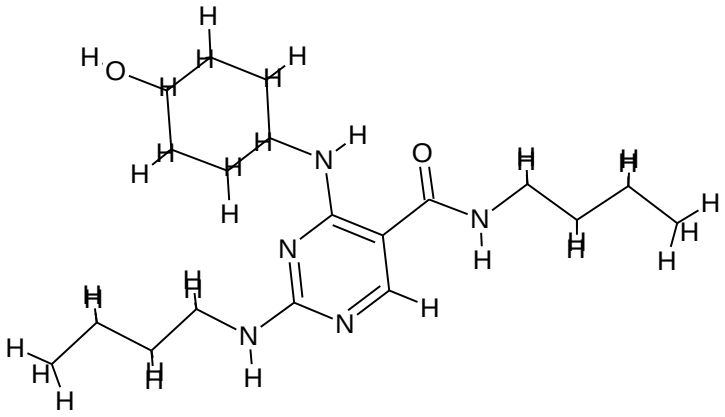
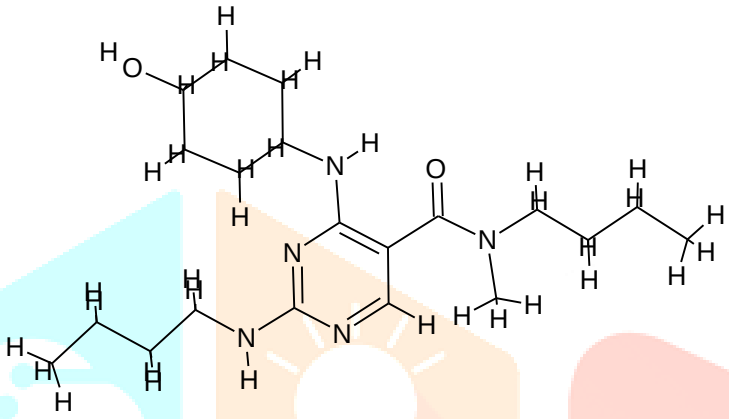
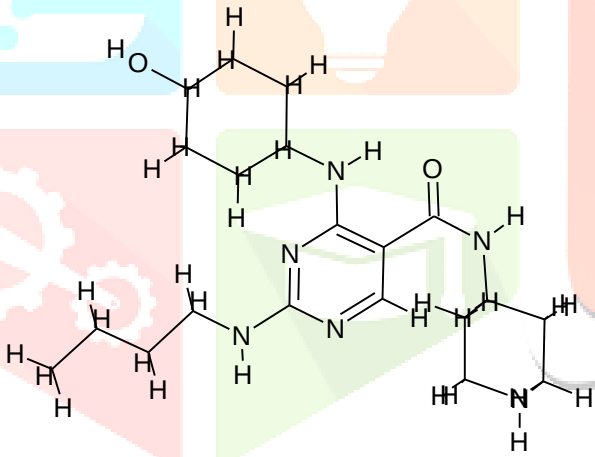
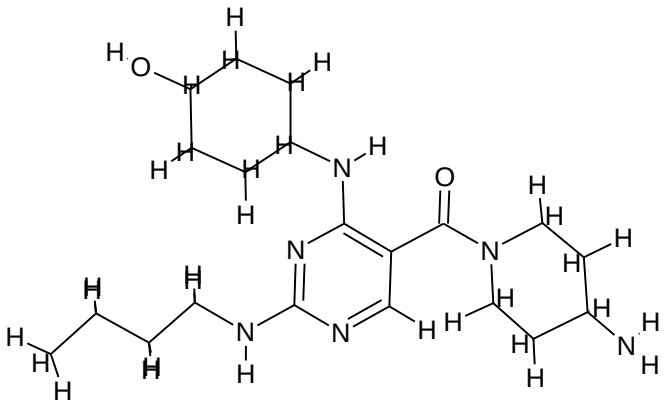
The QSAR (Quantitative structure activity relationship) tries to explain the observed variance in the biological effect of certain classes of compounds as a function of molecular changes caused by the substituents. These physiochemical descriptors which included parameters to account for hydrophobicity, electronic properties and steric effect are determined empirically or, more recently, by computational methods [4]. QSAR methodologies save resources and expedite the process of the development of new molecules and drugs [5-7]. In our works, we calculated many descriptors from the 43 molecular structures in literature1 by the software Dragon, MLR Methods was used to select descriptor and set up linear model. Then we developed a new QSAR model to explore the IC_{50} of anti-thrombosis the compounds with diverse structure.

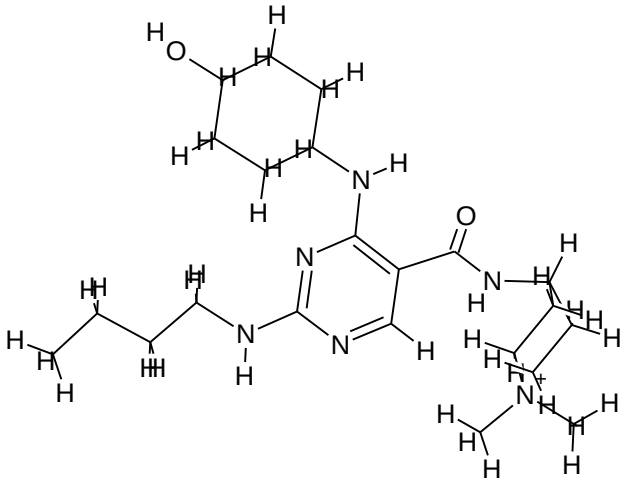
RESULTS AND DISCUSSION :

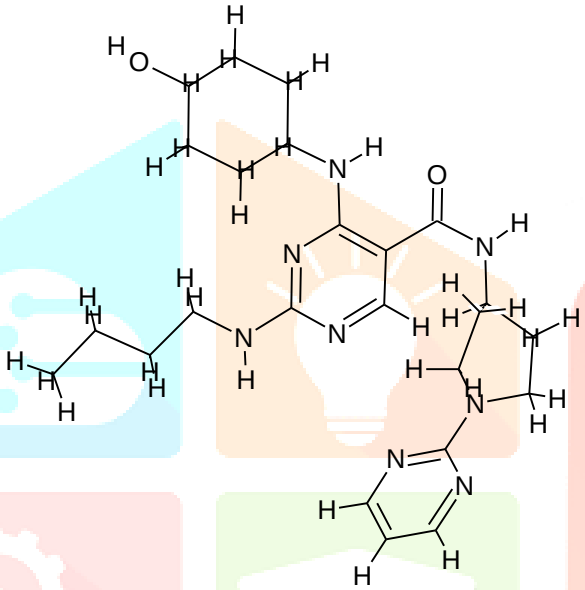
Table- 1: Structural details and their activity use in present study.

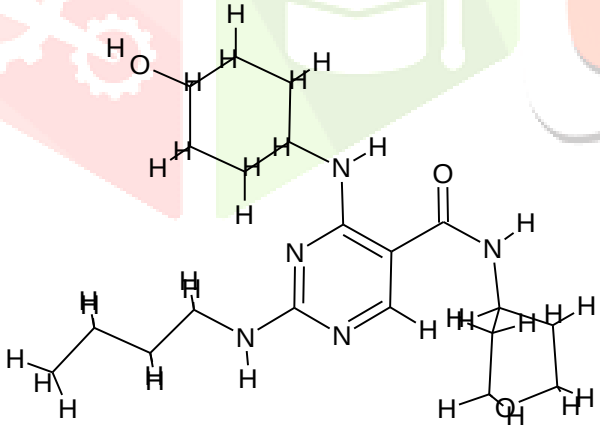
Sr.N.	Structure of The Compounds	IC_{50}(μM) Mer
1		0.04

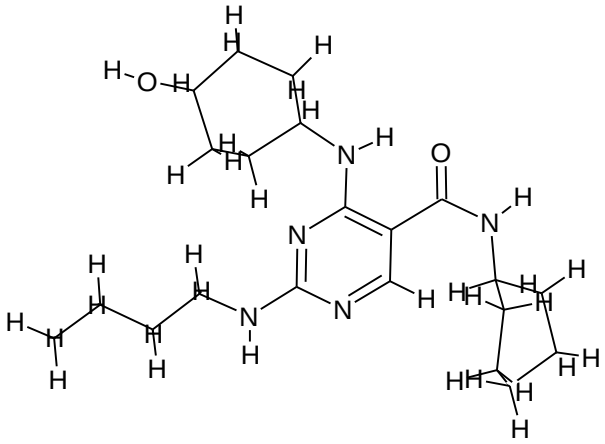
2		12.6
3		0.023
4		32
5		0.067

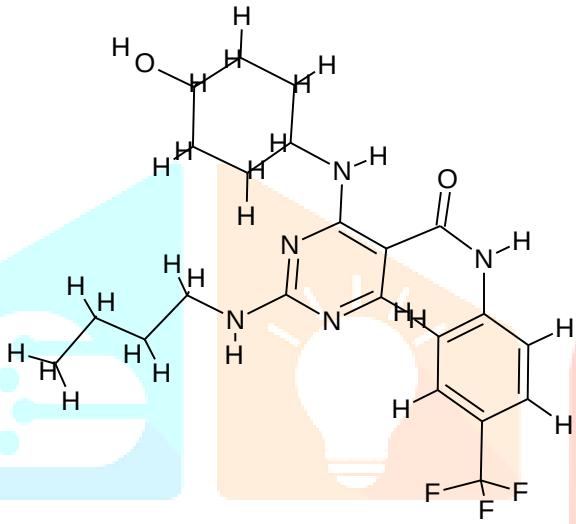
6		5.9
7		0.009
8		2.5
9		0.0084

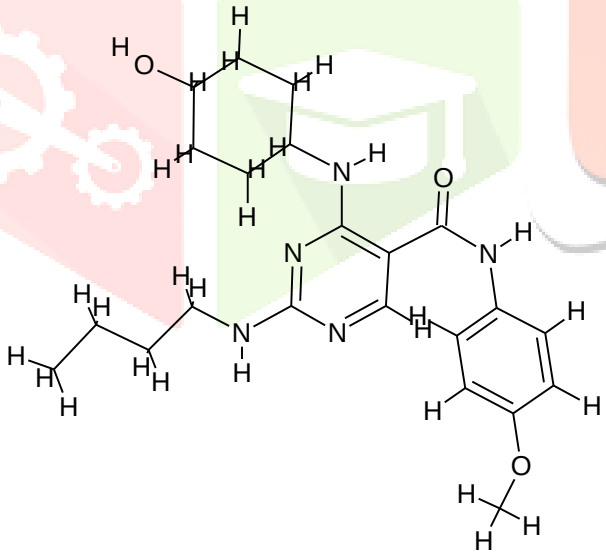
10  0.0041

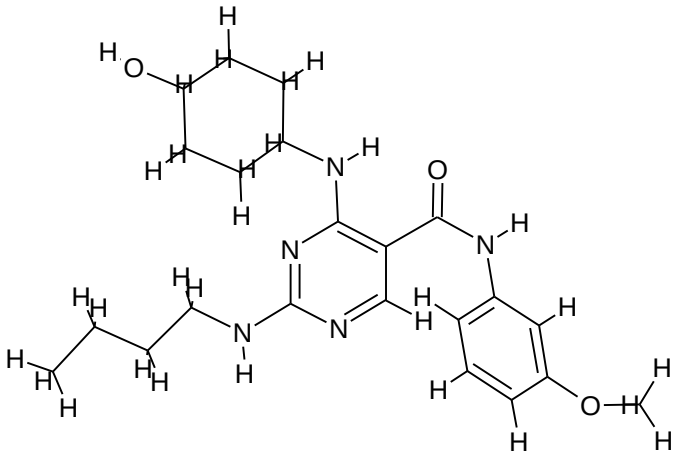
11  0.013

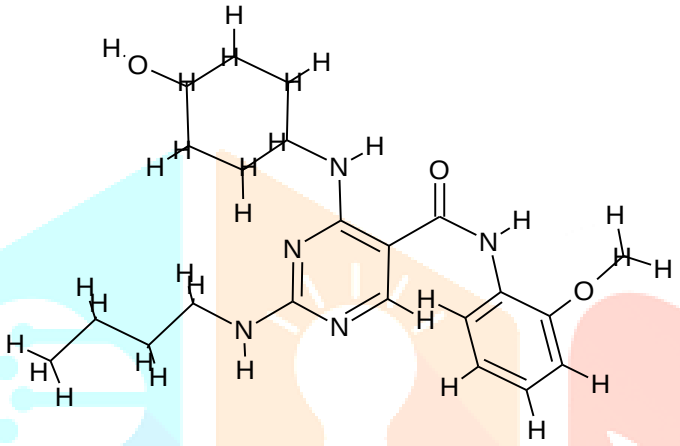
12  0.008

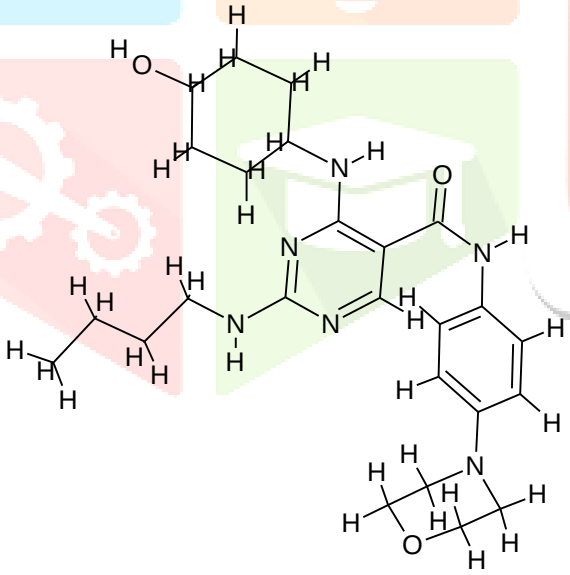
13  0.23

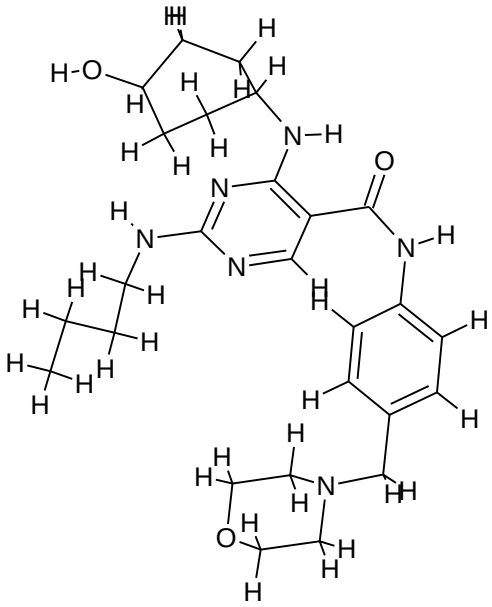
14  0.015

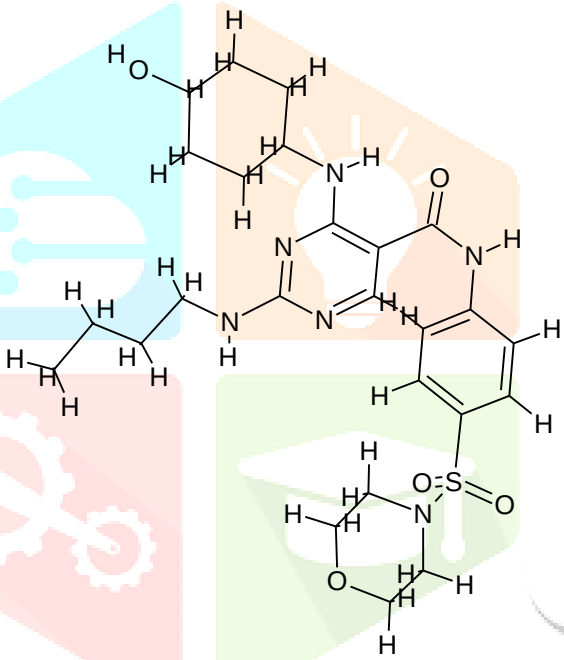
15  0.029

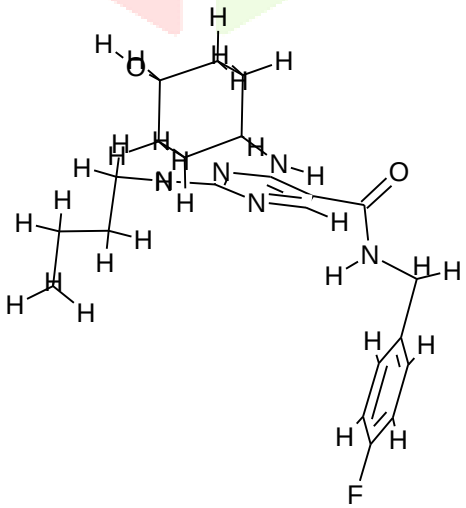
16  0.039

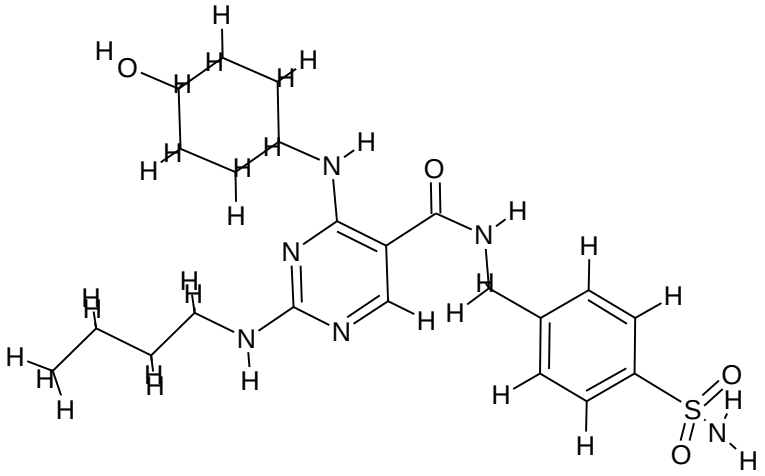
17  0.014

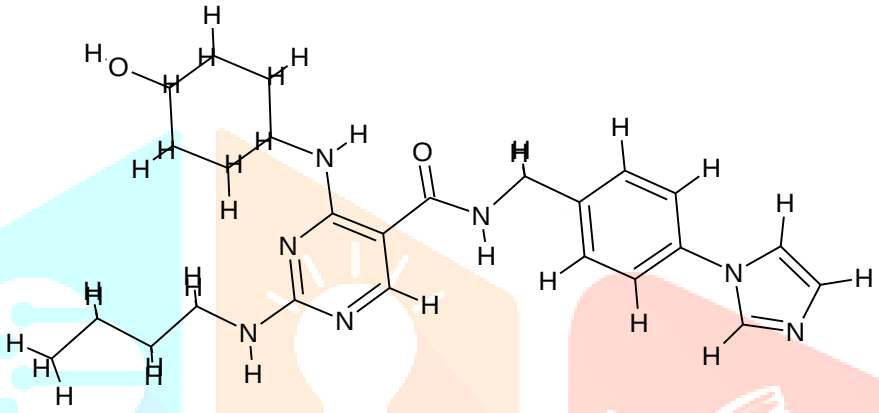
18  0.0067

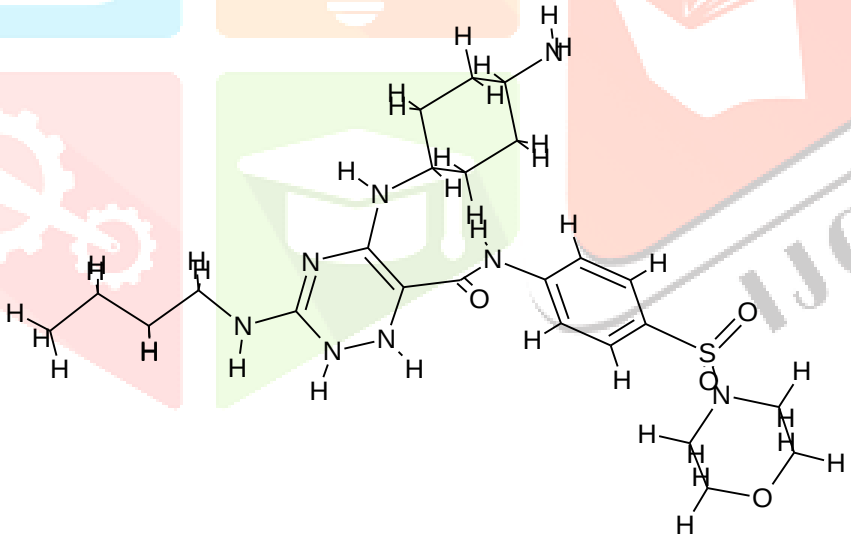
19  0.0063

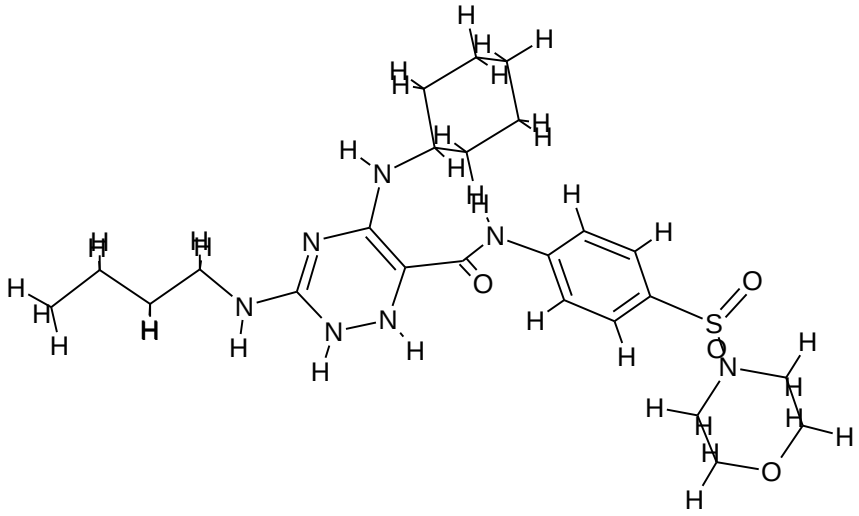
20  0.014

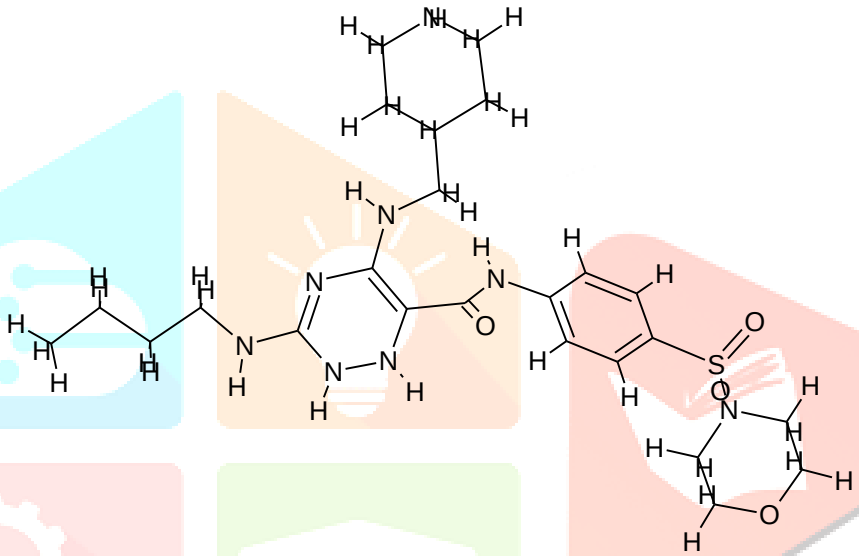
21  0.0052

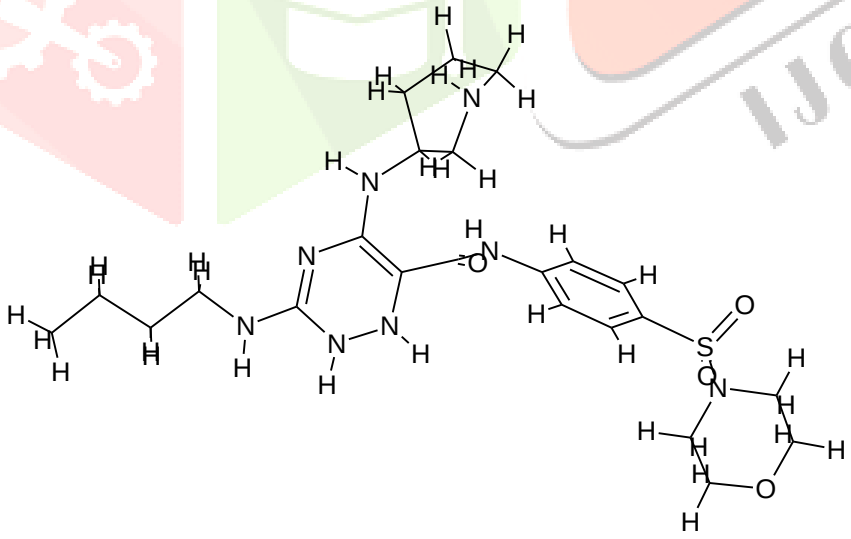
22  0.0043

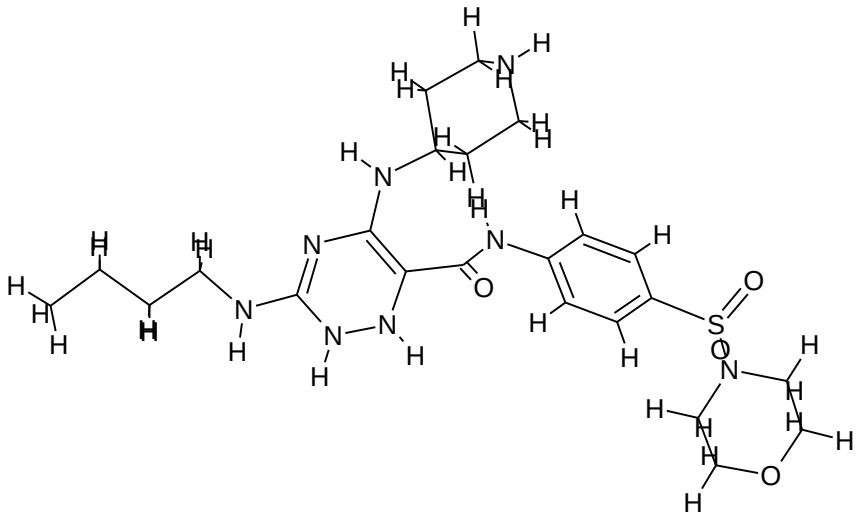
23  0.0021

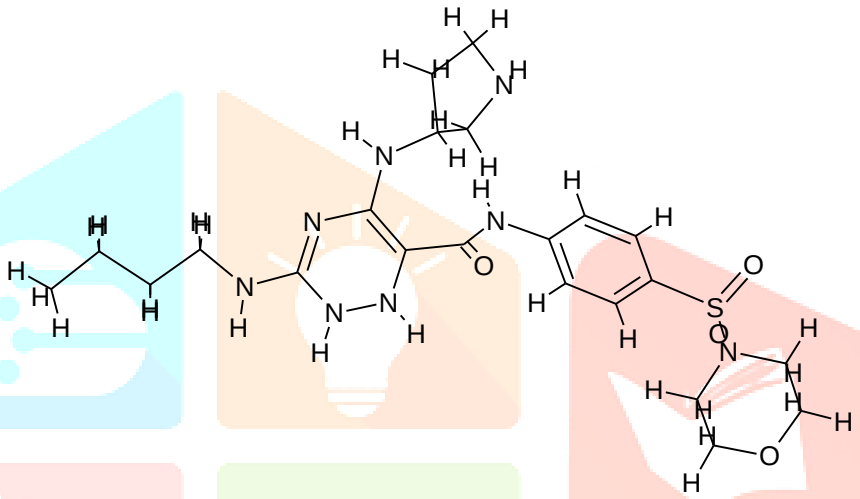
24  0.59

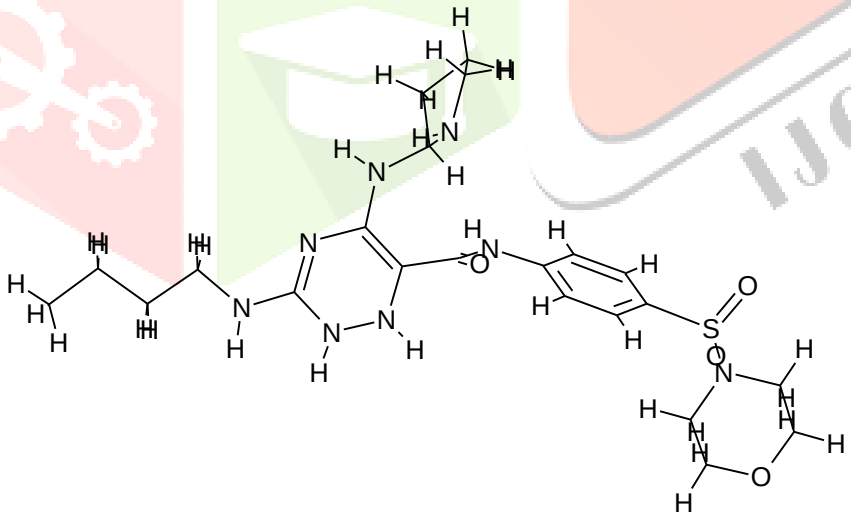
25  0.037

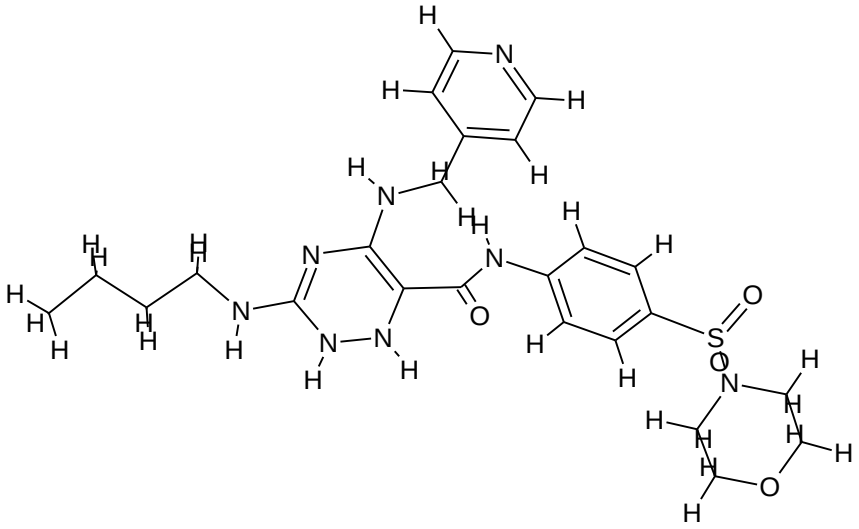
26  0.14

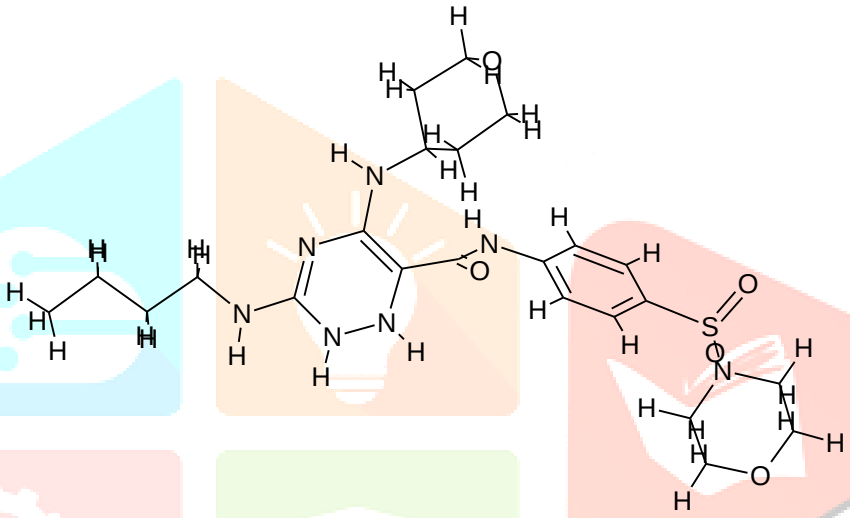
27  0.062

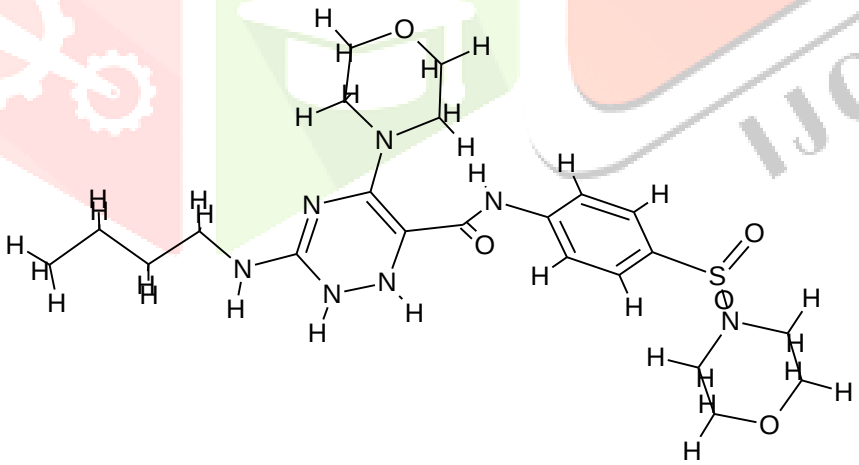
28  1

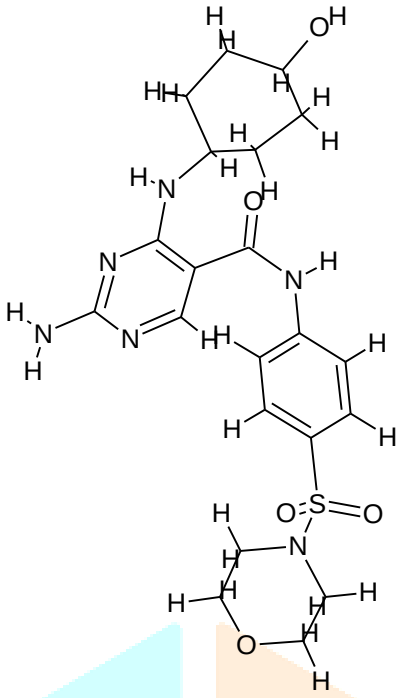
29  0.11

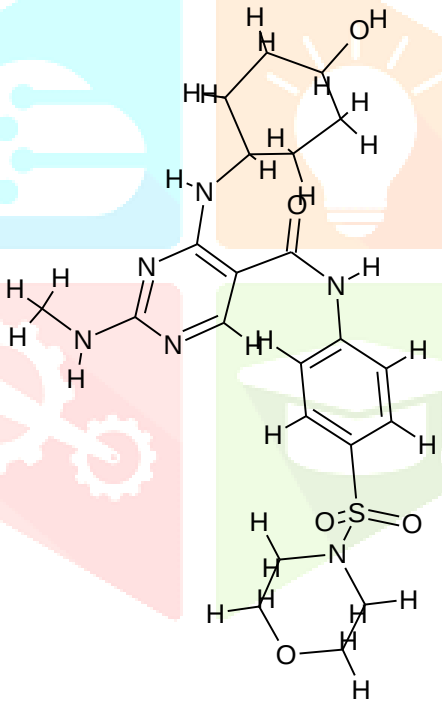
30  0.62

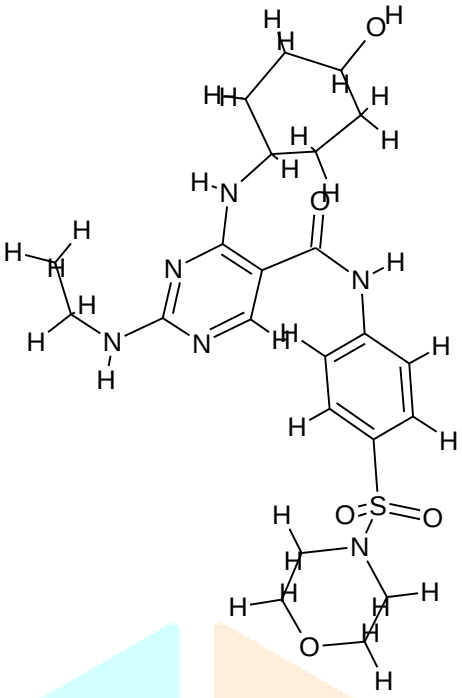
31  0.17

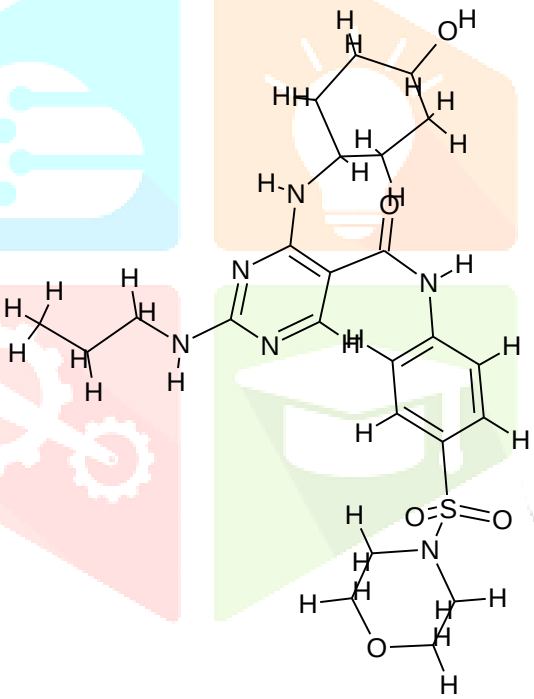
32  9.9

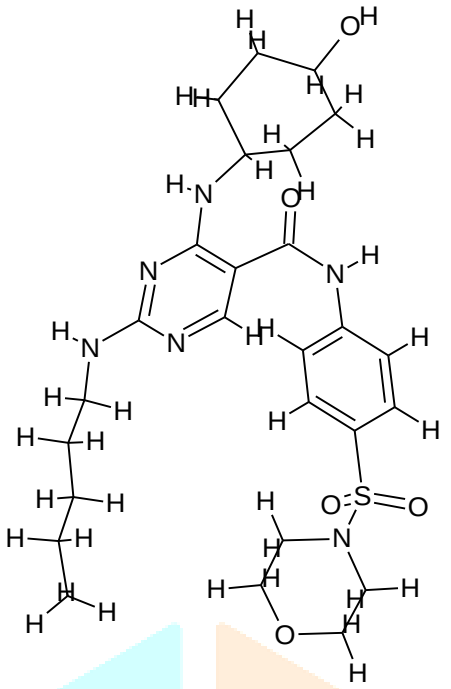
33  2.4

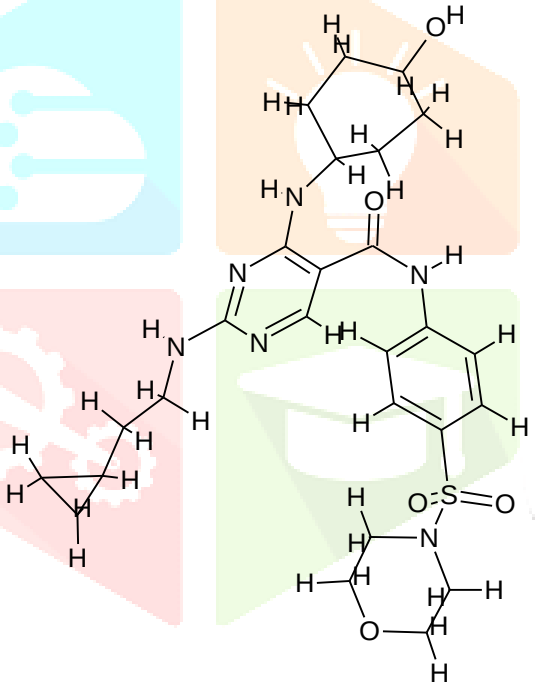
34  0.15

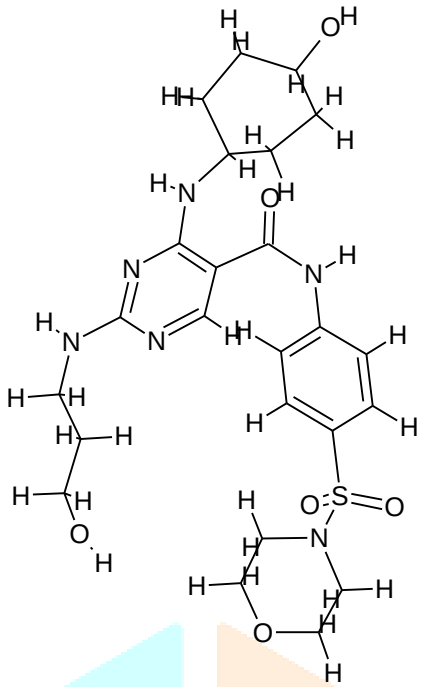
35  0.037

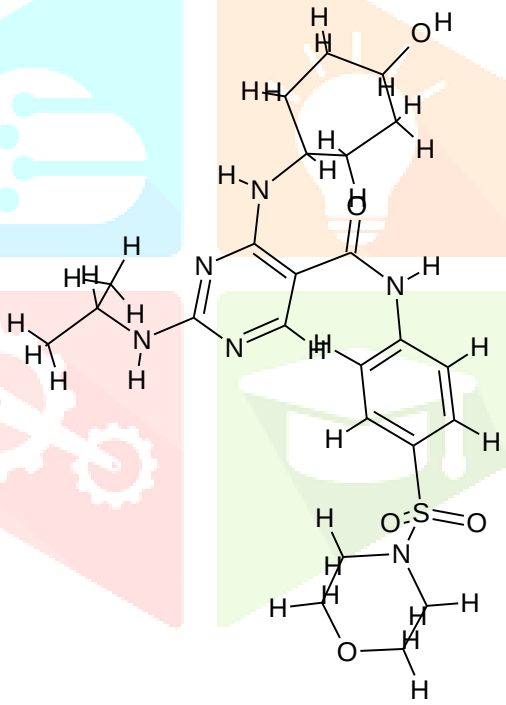
36  0.011

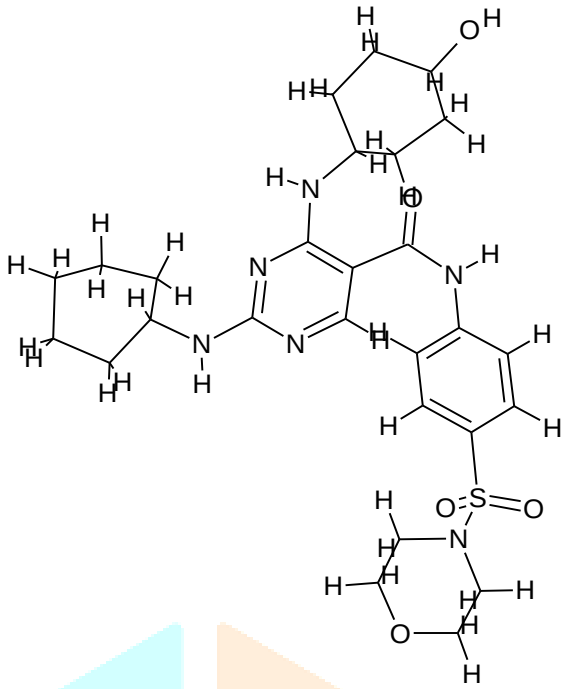
37  0.027

38  0.0073

39  0.059

40  0.024

41  0.047

42  0.18

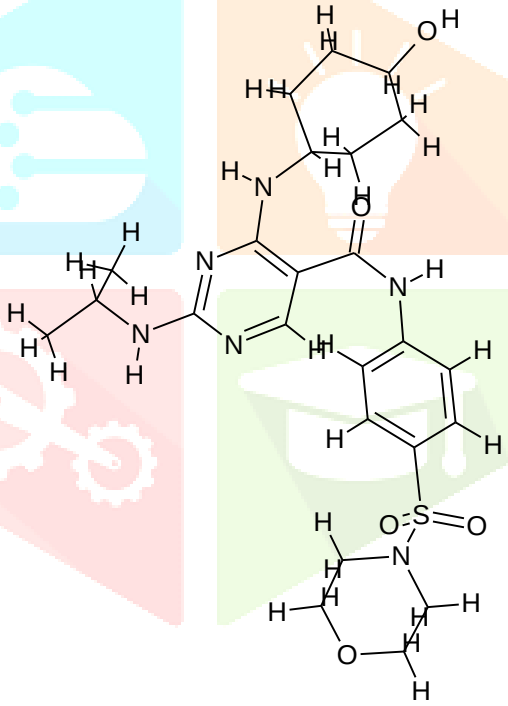
43  0.12

Table 2: Structural Details of Compounds with their activities and topological parameters used in the present study.

Comp No	IC50(μM)	IP1	Jhetm	J	X2A	IP2
1	0.04	1	1.869	1.517	0.298	0
2	12.6	0	1.862	1.507	0.298	0
3	0.023	1	1.953	1.558	0.297	1
4	32	0	1.945	1.548	0.297	1
5	0.067	1	2.275	1.886	0.307	1
6	5.9	1	2.345	1.946	0.304	1
7	0.009	1	1.858	1.552	0.299	1
8	2.5	1	1.908	1.588	0.296	1

9	0.0084	1	1.842	1.551	0.302	1
10	0.0041	1	1.522	1.273	0.293	1
11	0.013	1	1.861	1.552	0.299	1
12	0.008	1	1.854	1.552	0.299	1
13	0.23	1	1.923	1.539	0.303	1
14	0.015	1	1.921	1.538	0.297	1
15	0.029	1	1.946	1.561	0.297	1
16	0.039	1	1.972	1.587	0.295	1
17	0.014	1	1.585	1.273	0.293	1
18	0.0067	1	1.54	1.247	0.296	1
19	0.0063	1	1.711	1.285	0.292	1
20	0.014	1	1.851	1.51	0.301	1
21	0.0052	1	1.892	1.494	0.304	1
22	0.0043	1	1.541	1.24	0.293	1
23	0.0021	1	1.71	1.285	0.292	0
24	0.59	1	1.71	1.285	0.292	0
25	0.037	1	1.681	1.267	0.292	0
26	0.14	1	1.722	1.279	0.291	0
27	0.062	1	1.718	1.279	0.291	0
28	1	1	1.721	1.271	0.29	0
29	0.11	1	1.725	1.271	0.29	0
30	0.62	1	1.719	1.267	0.292	0
31	0.17	1	1.72	1.279	0.291	0
32	9.9	1	1.756	1.289	0.288	0
33	2.4	1	1.704	1.264	0.29	1
34	0.15	1	1.722	1.277	0.288	1
35	0.037	1	1.727	1.285	0.289	1
36	0.011	1	1.723	1.287	0.291	1
37	0.027	1	1.692	1.279	0.293	1
38	0.0073	1	1.476	1.116	0.287	1
39	0.059	1	1.713	1.285	0.292	1
40	0.024	1	1.737	1.295	0.294	1
41	0.047	1	1.505	1.137	0.288	1
42	0.18	1	1.737	1.295	0.294	1
43	0.12	1	1.499	1.121	0.29	1

Table 3: Correlation Matrix showing inter- correlation among all the parameters with the activity.

	IC50(µM)	*IP1*	*Jhetm*	*J*	*X2A*	*IP2*
IC50(µM)	1					
IP1	-0.85858	1				
Jhetm	0.238235	-0.15881	1			
J	0.210039	-0.16793	0.952375	1		
X2A	0.088171	-0.13495	0.762843	0.869459	1	
IP2	-0.05797	0.108787	0.119253	0.246989	0.3143	1

Table- 4: Regression Model

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/se
1	IP1	-21.6993 (±2.0236)	22.3000	2.7944	0.8586	0.7372	0.7308	114.9903	0.3073
41	IP1 JHETM	-21.2798(±2.0326) 3.1516 (±2.4251)	16.3010	2.7712	0.8648	0.7478	0.7352	59.3057	0.3121
47	IP1 JHETM J	-21.4239(±2.0191) 12.6952 (±7.7880) -9.7215 (±7.5453)	12.9842	2.7486	0.8707	0.7581	0.7395	40.7429	0.3168
52	IP1 JHETM X2A J	-21.3343(±1.9741) 6.5452 (±8.4447) -318.8828 (±189.6345) -318.8828 (±10.7088)	99.6132	2.6864	0.8803	0.7749	0.7512	32.6961	0.3277
55	IP1 JHETM J X2A IP2	-21.6965(±2.0009) 9.8653 (±9.0005) -0.2654 (±11.2247) -0.2654 (±189.5203) 9.8653 (±1.0398)	100.7374	2.6824	0.8840	**0.7814**	0.7519	26.4570	0.3296

The Models are as follows-

Mono Parametric

iC50= -21.6993(±2.0236) IP1 +22.3000,

N=43 , SE = (2.7944), R = (0.8586) , R2 = (0.7372) , R2A = (0.7308), F RATIO = (114.9903), Q = (0.3073)

Bi Parametric

iC50= -21.2798(±2.0326) IP1 3.1516 (±2.4251) JHETM +16.3010,

N=43 , SE = (2.7712), R = (0.8648) , R2 = (0.7478) , R2A = (0.7352), F RATIO = (59.3057), Q = (0.3121)

Tri Parametric

iC50= -21.4239(±2.0191) IP1 12.6952 (±7.7880) JHETM -9.7215 (±7.5453) J +12.9842,

N=43 , SE = (2.7486), R = (0.8707) , R2 = (0.7581) , R2A = (0.7395), F RATIO = (40.7429), Q = (0.3168)

Tetra Parametric

iC50= -21.3343(±1.9741) IP1 6.5452 (±8.4447) JHETM -318.8828 (±189.6345) J -318.8828 (±10.7088) X2A +99.6132,

N=43 , SE = (2.6864), R = (0.8803) , R2 = (0.7749) , R2A = (0.7512), F RATIO = (32.6961), Q = (0.3277)

Penta Parametric

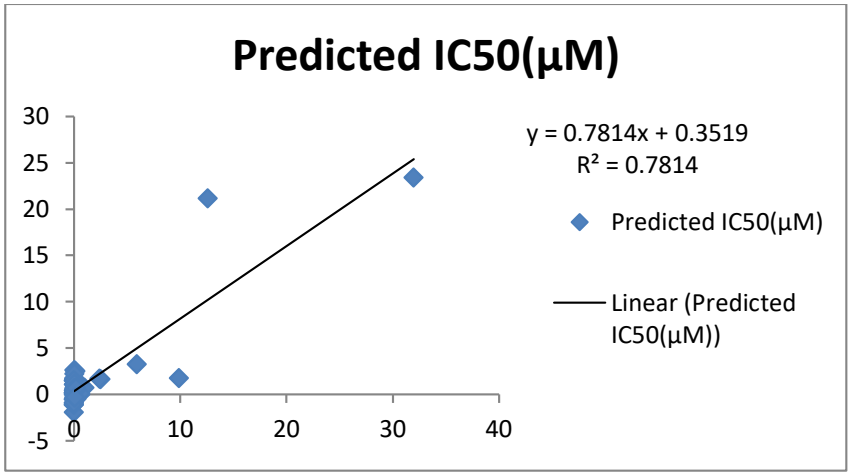
iC50= -21.6965(±2.0009) IP1 9.8653 (±9.0005) JHETM -0.2654 (±11.2247) J -0.2654 (±189.5203) X2A 9.8653 (±1.0398) IP2 +100.7374,

N=43 , SE = (2.6824), R = (0.8840) , R2 = (0.7814) , R2A = (0.7519), F RATIO = (26.4570), Q = (0.3296)

Table- 5: Observed and Estimated Model -55 Topological Indices

CompNo	Observed IC50(μM)	Predicted IC50(μM)	Residuals
1	0.04	-0.446145615	0.486145615
2	12.6	21.18399885	-8.583998853
3	0.023	1.795722029	-1.772722029
4	32	23.41600115	8.583998853
5	0.067	1.612746724	-1.545746724
6	5.9	3.269171979	2.630828021
7	0.009	0.205590762	-0.196590762
8	2.5	1.671077899	0.828922101
9	0.0084	-0.93376243	0.94216243
10	0.0041	-1.07158255	1.07568255
11	0.013	0.23518681	-0.22218681
12	0.008	0.166129366	-0.158129366
13	0.23	-0.458742379	0.688742379
14	0.015	1.485338244	-1.470338244
15	0.029	1.725868478	-1.696868478
16	0.039	2.62998327	-2.59098327
17	0.014	-0.450065556	0.464065556
18	0.0067	-1.86887964	1.87557964
19	0.0063	1.117041659	-1.110741659
20	0.014	-0.506836488	0.520836488
21	0.0052	-1.079884241	1.085084241
22	0.0043	-0.87538373	0.87968373
23	0.0021	0.010375508	-0.008275508
24	0.59	0.010375508	0.579624492
25	0.037	-0.270942968	0.307942968
26	0.14	0.457609572	-0.317609572
27	0.062	0.418148176	-0.356148176
28	1	0.777124836	0.222875164
29	0.11	0.816586233	-0.706586233
30	0.62	0.103940298	0.516059702
31	0.17	0.437878874	-0.267878874
32	9.9	1.772150725	8.127849275
33	2.4	1.708072288	0.691927712
34	0.15	2.536714088	-2.386714088
35	0.037	2.256660221	-2.219660221
36	0.011	1.562152768	-1.551152768
37	0.027	0.603934583	-0.576934583
38	0.0073	0.479820324	-0.472520324
39	0.059	1.136772357	-1.077772357
40	0.024	0.716371726	-0.692371726
41	0.047	0.433085034	-0.386085034
42	0.18	0.716371726	-0.536371726
43	0.12	-0.276376469	0.396376469

Figure- 1



The cross validated parameters have been calculated for these models and recorded in table 7 on the basis of cross validated parameters The penta parametric model discussed above has been formed to be the best model.

Table-6: Cross validation of Topological Indices

Model No	Parameter Used	press	Ssy	Press/SSY	R^2CV	PSE	Spress
1	IP1	320.1539	1218.07	0.2628	0.7372	2.7286	2.7944
41	IP1 JHETM	307.1837	1218.07	0.2522	0.7478	2.6728	2.7712
47	IP1 JHETM J	294.6422	1218.07	0.2419	0.7581	2.6177	2.7486
52	IP1 JHETM X2A J	274.2358	1218.07	0.2251	0.7749	2.5254	2.6864
55	IP1 JHETM J X2A IP2	266.2293	1218.07	0.2186	0.7814	2.4882	2.6824

Among all the penta parametric models listed in table 5 models 1, 41, 47, 52 and 55 gave quite improved results. The significance and quality of these models was checked on the basis of the values of '' R '', '' R2'', ''R2A '', quality factor "Q", standard error of estimate "SE", " R2 C2V", "PSE", and PRESS/SSY ratio of these equations. The squared correlation coefficient (R2) is a measure of the fit of the regression model correspondingly, it represents the part of variation in the observed data explained by the model .Study of these models shows that while carrying out the tetra parametric regression analysis, R2A goes on increasing while SE goes on decreasing and it means that statistically the quality of models goes on increasing. All the equations have higher Q value . Q is the quality factor estimated to determine the predictive value of the model.

Using model no 55 that is best penta parametric model [table -6] we have estimated pIC50 values. The residual values that is difference between estimated and observed pIC50 values of the compounds no 4, 6,and 32 is much higher than other compounds. These compounds have been taken as outlier. Their fore the entire exercise was repeated and new models have been obtain which are reported in table 8. Again pIc50 value of the compound have been estimated using model no 55, of table 8.

Table-7: Topological Indices - Regression of After Deletion of Compound no - [4, 6, 32]

Model No	Parameter Used	AI	B	SE	R	R2	R2A	F Ratio	Q=r/se
1	IP1	-12.3736 (±0.5679)	12.6000	0.5608	0.9622	0.9259	0.9239	474.6829	1.7158
41	IP1 JHTEM	-12.3528(±0.5779) 0.1966 (±0.5779)	12.2340	0.5674	0.9623	0.9261	0.9221	231.8759	1.6960
47	IP1 JHTEM J	-12.3879(±0.5848) 1.2483 (±1.6908) -1.0693 (±1.6140)	11.8872	0.5718	0.9628	0.9270	0.9209	152.3863	1.6838
52	IP1 JHTEM J X2A	-12.3901(±0.5700) 0.1457 (±1.7711) 1.6556 (±2.2458) 1.6556 (±41.2344)	30.7254	0.5573	0.9657	0.9326	0.9249	121.0146	1.7328
55	IP1 JHTEM J X2A IP2	-12.3877(±0.6146) 0.1375 (±1.9354) 1.6643 (±2.4036) 1.6643 (±41.8588) 0.1375 (±0.2343)	30.7229	0.5655	0.9657	**0.9326**	0.9227	94.0460	1.7077

The Model of training is as follow

Mono Parametric

iC50= -12.3736(±0.5679) IP1 +12.6000,

N=40 , SE = (0.5608), R = (0.9622) , R2 = (0.9259) , R2A = (0.9239), F RATIO = (474.6829), Q = (1.7158)

Bi Parametric

iC50= -12.3528(±0.5779) IP1 0.1966 (±0.5779) JHETM +12.2340,

N=40 , SE = (0.5674), R = (0.9623) , R2 = (0.9261) , R2A = (0.9221), F RATIO = (231.8759), Q = (1.6960)

Tri Parametric

iC50= -12.3879(±0.5848) IP1 1.2483 (±1.6908) JHETM -1.0693 (±1.6140) J +11.8872,

N=40 , SE = (0.5718), R = (0.9628) , R2 = (0.9270) , R2A = (0.9209), F RATIO = (152.3863), Q = (1.6838)

Tetra Parametric

iC50= -12.3901(±0.5700) IP1 0.1457 (±1.7711) JHETM 1.6556 (±2.2458) J 1.6556 (±41.2344) X2A +30.7254,

N=40 , SE = (0.5573), R = (0.9657) , R2 = (0.9326) , R2A = (0.9249), F RATIO = (121.0146), Q = (1.7328)

Penta Parametric

iC50= -12.3877(±0.6146) IP1 0.1375 (±1.9354) JHETM 1.6643 (±2.4036) J 1.6643 (±41.8588) X2A 0.1375 (±0.2343) IP2 +30.7229,

N=40 , SE = (0.5655), R = (0.9657) , R2 = (0.9326) , R2A = (0.9227), F RATIO = (94.0460), Q = (1.7077)

Table-8 Topological Indices- Observed and Estimated of After Deletion of Compound no.[4, 6, 32]

Sn	Observed IC50(µM)	*Predicted IC50(µM)*	*Residuals*
1	0.04	0.229887	-0.18989
2	12.6	12.6	-1.4E-14
3	0.023	0.377106	-0.35411
4	0.067	0.266361	-0.19936
5	0.009	0.213874	-0.20487
6	2.5	0.490936	2.009064
7	0.0084	-0.00026	0.008662
8	0.0041	0.12388	-0.11978
9	0.013	0.214287	-0.20129
10	0.008	0.213324	-0.20532
11	0.23	-0.07918	0.309185
12	0.015	0.33942	-0.32442
13	0.029	0.381136	-0.35214
14	0.039	0.568164	-0.52916
15	0.014	0.132544	-0.11854
16	0.0067	-0.12719	0.133887
17	0.0063	0.239934	-0.23363
18	0.014	0.002831	0.011169
19	0.0052	-0.22843	0.23363
20	0.0043	0.071572	-0.06727
21	0.0021	0.242455	-0.24036
22	0.59	0.242455	0.347545
23	0.037	0.20851	-0.17151
24	0.14	0.304211	-0.16421
25	0.062	0.303661	-0.24166
26	1	0.36085	0.63915
27	0.11	0.3614	-0.2514
28	0.62	0.213736	0.406264
29	0.17	0.303936	-0.13394
30	2.4	0.344204	2.055796
31	0.15	0.508496	-0.3585
32	0.037	0.452407	-0.41541
33	0.011	0.315004	-0.304
34	0.027	0.157245	-0.13025
35	0.0073	0.276809	-0.26951

36	0.059	0.240209	-0.18121
37	0.024	0.119971	-0.09597
38	0.047	0.245656	-0.19866
39	0.18	0.119971	0.060029
40	0.12	0.078021	0.041979

Figure 2

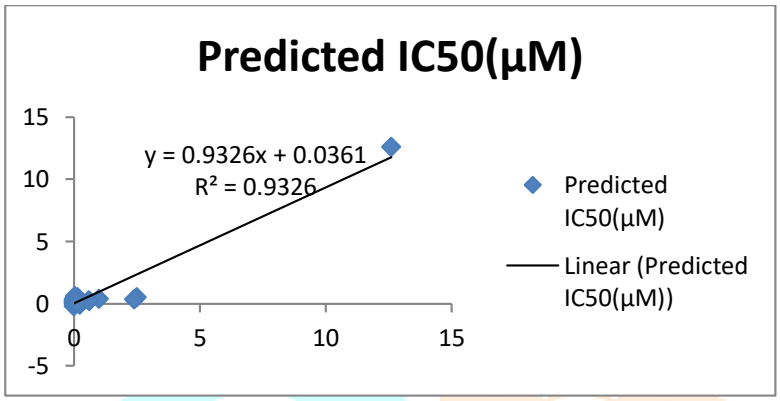


Table-9: Topological Indices- Crossed validation

Model No	Parameter Used	Press	SSY	Press/SSY	R^2CV	PSE	Spress
1	IP1	11.95025	161.2287	0.07412	0.92588	0.546586	0.560785
41	IP1 JHTEM	11.91301	161.2287	0.073889	0.926111	0.545734	0.567427
48	IP1 JHTEM J	11.7695	161.2287	0.072999	0.927001	0.542437	0.571778
53	IP1 JHEM J X2A	10.87162	161.2287	0.06743	0.93257	0.521335	0.557331
56	IP1 JHETM J X2A IP2	10.87157	161.2287	0.06743	0.93257	0.521334	0.565466

PRESS (predicted residual sum of squares) appears to be the most important cross validation parameters accounting for good estimate of the real predictive error of the models. In case its value is less than SSY(sum of the square of all response value), it will mean that the predictive power of the model is good and is not based upon chance therefore, can be considered statistically significant

To be a reasonable QSAR model , PRESS/SSY should be smaller than 0.400. In our case, the ratio PRESS/SSY ranges between 0.0741-0.0674 indicating that all proposed models (equations 1, 41, 47, 52 and 55) are reliable. The PSE and SPRESS are good parameters to discuss the uncertainty in prediction. The lower the value of these parameters, the better will be the predictive ability of the model. The indication of the performance of the model is obtained from R2 CV (the overall predictive ability) higher R2 CV shows that the model is good. In order to examine the relative potential of models , predictive correlation coefficient (R2 pred) were estimated by plotting graphs between observed and calculated ic50 values obtained with the help of eqn 55. The comparison between observed and predicted activities is listed in Table- 9. Such correlations are shown in figure 2. From the fig 2, R2 pred values obtained for equation 55 is 0.9326 is fairly high indicating the good quality of models.

Amongst all these statistically significant five models discussed above model 55 is the best model since the values R = 0.9657, R2 = 0.9326 , R2A = 0.9227 , R2cv = 0.9325 are the best as compared to all the models. The calculated F value is greater than F theoretical value , the value of standard error of estimate is the lowest , SE = 0.5655, PRESS/SSY = 0.06743 confirms that it is statistically significant and excellent model and it has been found to be having outstanding predictive power also.

The generated QSAR model was employed to predicted ic50 activities of the test (Prediction) molecules and the outcome is displayed in table 8 - 10 the predictive power is also shown in the figure 3.

Conclusion

On the basis of data and subsequent discussion presented in this section it may be suggested that in future designing of this class of drug with reference to their activity IC50 the following points may be kept in mind.

(1) Jhet M, J, X2, and IP2 has positive coefficient and IP1 has positive coefficient. The high value of Jhet M, J, X2, and IP2 and low value of IP1 suggesting that these topological parameters are suitable for the modeling of IC50.

(2) The compound no 2 found to be most potent drug. It is an excellent agreement with observed iC50 (observed and predicated and ic50 values are both 12.6)

(3) IP1 favor increases the potency of the drug.

(4) The present finding the based on QSAR are in excellent agreement with the result obtain by Linhao Xu et al

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