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Prediction of Bio-Activity of some NNRTIs Derivatives; SAR Study using Molecular Modeling

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Abstract: The work describes QSAR and SAR studies on the TIBO derivatives as non-molecular reserve transcriptase inhibitor of HIV-1using the 2D-topological, physicochemical and hydrophobic parameters along with the indicator parameters.The set of 20compounds. Application of multiple linear regression analysis indicated that the combination of adhoc molecular descriptors and indicator parameters yielded a statically significant model for activity iog1/c (50%of effective concentration for inhabitation of reverse transcriptase of HIV.)
Keywords: LogP QSAR, anti HIV-1 cytotoxic concentration, NNRTI-1, physicochemical descriptors.

I. INTRODUCTION

Many structure-based techniques of drug discovery and development have evolved in the past 20 years during the search for therapeutically useful agents in the treatment of acquired immunodeficiency syndrome (AIDS)[3].
RT catalyses the transcription of the HIV-encoded single-stranded RNA into double-stranded DNA. Many of the currently approved anti-AIDS agents are potent inhibitors of retroviral RT. The NNRTI, as opposed to the nucleoside analogues, constitute a number of different, structurally unrelated, classes of compounds that are highly selective against HIV-1 RT and are targeted at a non-substrate binding site of this enzyme. The TIBO7 were discovered to be active in cell culture before their target was identified. In the present work, a quantitative structure activity study has been performed to develop mathematical relationship between structural descriptors and biological activity log1/C (cytotoxic concentration) of 19 TIBO derivatives. (Shown in Table1.)

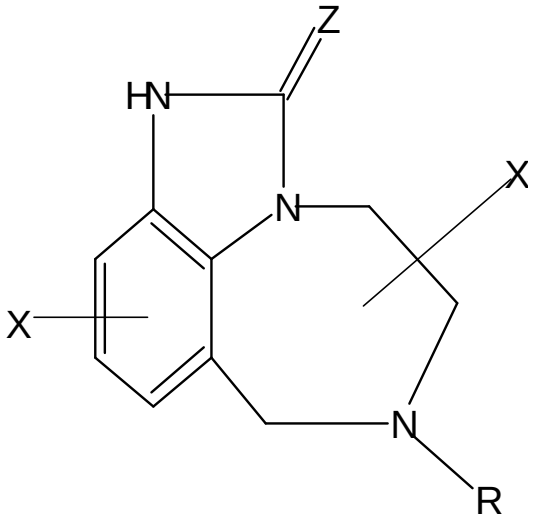

Figure 1 Parent structure of TIBO derivative used in present study

A. Experimental and Methodology

The cytotoxic concentration of the compound leading to 50% effect has been measured and expressed as log1/C in mol/l. Three separate descriptors were used namely, non-conventional physicochemical properties, classical physicochemical properties and hydrophobic parameter logP (Octanol/Water partition coefficient). Non-conventional physicochemical descriptors[7] used in present study are calculated using Hyperchem7 software and presented in Table2. All classical physicochemical properties are calculated using ACD Chemsketch software and presented in Table3. The multiple linear regression analysis is carried out for obtaining QSAR model.
Partition coefficient (logP)[8] is calculated and represented in Table4.

Table 1 Substituents and Biological Activity log1/C(Observed) of TIBO Derivatives used in present study.

S.no.	X	Z	R	X'	Obs.log1/C
1	H	O	$CH_2CH=CH_2$	5-Me	3.21
2	H	O	$CH_2C(Me)=CH_2$	5-Me	3.96
3	H	O	$CH_2CH=CMe_2$	5-Me	3.33
4	9-Cl	O	$CH_2C(Me)=CH_2$	5-Me	4.77
5	9-Me	O	$CH_2CH=(C2H5)_2$	5-Me	4.70
6	9-Cl	O	$CH_2CH=CMe_2$	5-Me	4.66
7	H	S	$CH_2CH=CMe_2$	5-Me	3.26
8	7-Me	S	$CH_2CH=CMe_2$	5-Me	4.13
9	H	S	C_3H_7	5-Me	3.25
10	9-Cl	S	$CH_2CH=CMe_2$	5-Me	4.47
11	9-Cl	S	$CH_2CH_2C_3H_5$	5-Me	4.44
12	9-Cl	S	$CH_2C_1H_7$	5-Me	4.55
13	9-Cl	S	$CH_2CH=C(C_2H_5)2$	5-Me	4.92
14	9-C1	S	$CH_2C_4H_7$	5-Me	4.72
15	9-Cl	S	$CH2CH(Me)=CH_2$	4-Me	4.62
16	9,10-di-Cl	S	$CH_2CH=CMe_2$	5-Me	4.35
17	8-Cl	S	$CH_2CH=CMe_2$	5-Me	3.85
18	8-Cl	S	$CH_2CH=C(C_2H_5)2$	5-Me	4.92
19	8-Br	S	$CH_2C=CMe2$	5-Me	4.28
20	8-Me	S	$CH_2CH=CMe2$	5-Me	4.10

Table 2 Non-conventional physicochemical parameters and indicator parameters for subset of TIBO derivatives used in present study.

Comp. No.	ASA	SAG	HE	I_Z	I_R	I_X
1	399.2	400.48	-2.33	0	0	0
2	353.44	410.80	-2.32	0	0	0
3	398.62	440.76	-2.31	0	1	0
4	369.17	445.58	-2.30	0	0	1
5	440.99	502.38	-2.24	0	0	0
6	414.71	473.92	-2.29	0	1	1
7	414.37	462.16	-3.56	1	1	0
8	377.52	488.58	-3.63	1	1	0
9	413.56	425.96	-3.66	1	0	0
10	431.35	494.73	-3.66	1	1	1
11	533.42	509.10	-3.71	1	0	1
12	583.53	533.59	-3.70	1	0	1
13	511.35	529.34	-3.64	1	0	1
14	437.45	501.93	-5.14	1	0	1
15	444.17	521.73	-3.43	1	1	1
16	424.35	488.89	-3.56	1	1	1
17	507.81	522.29	-3.54	1	0	1
18	456.76	456.65	-3.53	1	0	1
19	432.99	498.51	-3.55	1	1	1
20	373.35	483.57	-3.53	1	1	0

*ASA = Approximate surface area, SAG = Surface area grid, HE = Hydration energy
I_Z = 1 if S atom at Z position, I_R = 1 if Acyclic structure at R position
I_X = 1 if halogens present at X position

Table 3 Classical physicochemical properties for estimation of log1/C of TIBO derivatives.

Comp. No.	MR	MV	Pc	η	ST	D	Pol
1	70.97	196.6	534.7	1.641	54.6	1.23	28.13
2	75.37	212.7	571.1	1.626	51.8	1.20	29.88
3	80.14	227.0	609.6	1.623	51.9	1.19	31.77
4	80.20	223.7	608.2	1.635	54.6	1.30	31.79
5	94.03	275.3	728.0	1.598	48.9	1.13	37.27
6	84.97	238.0	646.7	1.632	54.5	1.28	33.68
7	86.73	234.4	638.4	1.657	55.7	1.34	33.89
8	87.14	235.2	651.1	1.662	58.7	1.22	34.54
9	91.75	252.0	689.1	1.648	55.8	1.19	36.37
10	78.20	209.5	587.1	1.669	61.6	1.24	31.00
11	91.97	246.1	688.2	1.670	61.1	1.30	36.46
12	92.20	246.3	692.0	1.671	62.3	1.30	36.55
13	92.20	246.3	692.0	1.671	62.3	1.30	36.55
14	101.23	278.5	768.4	1.646	57.8	1.25	40.13
15	87.20	231.8	649.7	1.675	61.6	1.32	34.56
16	96.79	257.0	725.4	1.676	63.4	1.38	38.37
17	91.97	246.1	688.2	1.670	61.1	1.30	36.46
18	101.23	278.5	768.4	1.646	57.8	1.25	40.13
19	94.86	248.0	702.1	1.690	64.2	1.47	37.60
20	91.76	251.0	689.4	1.651	56.8	1.20	36.37

*

MR = Molar Refractivity, ST = Surface Tension, D = Density, Pol = Polarizability

Table 4 logP values of subset of TIBO derivatives for calculation of log1/C used in present study.

Comp. No.	logP
1.	0.456
2.	1.033
3.	1.753
4.	1.157
5.	2.986
6.	2.400
7.	1.738
8.	2.111
9.	0.876
10.	2.430
11.	2.260
12.	2.260
13.	3.244
14.	1.916
15.	3.655
16.	2.430
17.	3.244
18	2.434
19.	2.692
20.	2.202

Table 5 Correlation matrix of non-conventional physicochemical properties, indicator parameter and biological activity of TIBO derivatives.

	log 1/C	ASA	SAG	HE	I_Z	I_R	I_X
log1/C	1.00000						
ASA	0.44911	1.00000					
SAG	0.71339	.72380	1.00000				
HE	-0.16775	-.39684	-.54584	1.00000			
I_Z	0.11294	.45007	.61578	-.88533	1.00000		
I_R	- 0.25432	- .36340	.07098	-.01476	.19096	1.00000	
I_X	0.69191	.55973	.63682	-.36765	.33796	-.04495	1.00000

Table 6 Correlation matrix of classical physicochemical properties and biological activity of TIBO derivatives.

	MR	MV	Pc	η	ST	D	Pol	I_Z	I_R	I_X	log1/C
MR	1.000										
MV	0.952	1.000									
Pc	0.993	0.978	1.000								
η	0.287	-0.016	0.185	1.000							
ST	0.390	0.098	0.299	0.979	1.000						
D	0.271	0.035	0.196	0.770	0.780	1.000					
Pol	1.000	0.952	0.993	0.287	0.390	0.271	1.000				
I_Z	0.637	0.412	0.564	0.808	0.825	0.399	0.637	1.000			
I_R	0.174	0.104	0.134	0.226	0.148	0.193	0.174	0.190	1.000		
I_X	0.517	0.379	0.486	0.487	0.580	0.748	0.517	0.337	-0.044	1.000	
log1/C	0.641	0.681	0.668	-0.046	0.067	0.256	0.641	0.112	-0.254	0.691	1.000

Table 7 Correlation matrix of logP, indicator parameter and biological activity of TIBO derivatives.

	logP	I_Z	I_R	I_X	log1/C
logP	1.00000				
I_Z	0.42597	1.00000			
I_R	0.26299	0.19096	1.00000		
I_X	0.52076	0.33796	-0.04495	1.00000	
log1/C	0.63858	0.11294	-0.25432	0.69191	1.00000

Table 8 Observed and calculated log1/C (from Eq.1) of subset of TIBO derivatives used in present study.

Comp.No.	log1/C(Obs.)	log1/C(Calc.)	Residual
1	3.21	3.58	- 0.37
2	3.96	3.85	0.10
3	3.33	3.67	- 0.34
4	3.66	4.12	-0.32
5	4.77	4.46	0.30
6	4.70	4.76	- 0.06
7	4.66	4.28	0.37
8	3.26	3.57	-0.31
9	4.13	3.87	0.25
10	3.25	3.24	0.01
11	4.47	4.19	0.27
12	4.44	4.50	- 0.06
13	4.55	4.50	0.04
14	4.92	5.01	- 0.09
15	4.62	4.37	0.24
16	4.35	4.80	- 0.45
17	3.85	4.19	- 0.34
18	4.92	5.01	- 0.09
19	4.28	3.97	0.30
20	4.10	3.84	0.25

Table 9 Observed and calculated log1/C (from Eq.2) of subset of TIBO derivatives used in present study.

Comp.No.	log1/C(Obs.)	log1/C(Calc.)	Residual
1	3.21	3.33	-0.12
2	3.96	3.66	0.29
3	3.33	3.82	-0.49
4	4.77	4.55	0.21
5	4.70	4.61	0.08
6	4.66	4.71	- 0.05
7	3.26	3.53	- 0.27
8	4.13	3.87	0.25
9	3.25	3.13	0.11
10	4.47	4.42	0.04
11	4.44	4.35	0.08
12	4.55	4.35	0.19
13	4.92	4.93	- 0.01
14	4.62	4.25	0.36
15	4.35	4.39	- 0.04
16	3.85	4.42	- 0.57
17	4.92	4.93	-0.01
18	4.28	4.27	0.01
19	4.10	3.80	0.30
20	4.16	3.82	0.31

Table 10 Observed and calculated log1/C (from Eq.3) of subset of TIBO derivatives used in present study.

Comp.No.	log1/C(Obs.)	log1/C(Calc.)	Residual
1	3.21	3.52	- 0.31
2	3.96	3.73	0.22
3	3.33	3.57	-0.24
4	4.77	4.23	0.53
5	4.70	4.43	0.26
6	4.66	4.25	0.40
7	3.26	3.56	- 0.30
8	4.13	3.69	0.43
9	3.25	3.67	- 0.42
10	4.47	4.26	0.20
11	4.44	4.62	- 0.18
12	4.55	4.62	- 0.07
13	4.92	4.98	- 0.06
14	4.62	4.50	0.11
15	4.35	4.70	-0.35
16	3.85	4.26	- 0.41
17	4.92	4.98	- 0.06
18	4.28	4.36	- 0.08
19	4.10	3.73	0.36
20	4.17	4.23	0.32

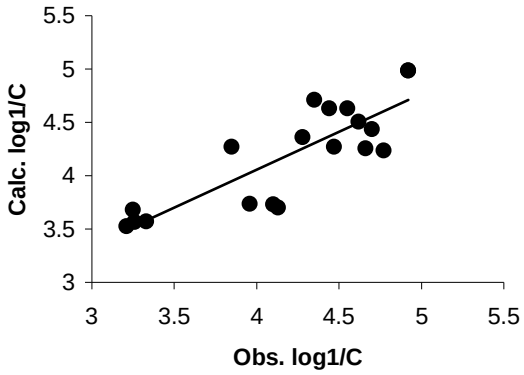

Figure 2 Graph obtained between Obs. log1/C and Calc. log1/C from eq. 2

II.RESULTS AND DISCUSSION

As mentioned in introduction, this set of TIBO derivatives contains 19 compounds. The non-conventional physicochemical properties, Classical physicochemical properties and logP are chosen as previously for the prediction of log1/C (Cytotoxicity).

Table5 in form of correlation matrix[9] shows the correlation between the Approximate Surface Area (ASA), Surface Area Grid (SAG), Hydration energy (HE) and log1/C but individually they are poorly correlated with the biological activity (log1/C)[10]. Similarly, the classical physicochemical properties are poorly correlated with observed biological activity individually, but good correlation exist between MR, MV, Pc and Pol shown in form of correlation matrix in Table6. Table7 in form of correlation matrix shows that the good correlation (r = 0.6385) exist between logP and biological activity (log1/C) individually. All those correlations resulting in low value of R (<0.50) are not considered being statistically insignificant. Not a single univariate correlation of non-conventional physicochemical descriptors/ classical physicochemical properties[11] is able to describe the structure activity relationship in quantitative manner.

In case of non-conventional physicochemical descriptors bivariate correlation of 16 combinations are tested and the regression coefficient is little higher but not sufficient to explain structure activity relationship quantitatively.

The best model obtained from above variables is:

log1/C = 0.0115(±0.0029)SAG - 0.5981(±0.1970)IZ + 0.4036(±0.1895)IX – 1.1528 (1)

n = 19, Se = 0.3133, R = 0.8687, R^2_A = 0.7056, F = 15.379

In order to confirms our finding we have estimated the log1/C values from the best suited model and compared them with the observed values. Both, observed and calculated biological activities are presented in TableV-8 and such correlations are graphically presented in Figure V-2. The best model obtained from above variables is:

log1/C = 0.0646(±0.017)MV – 0.0197(±0.0063)Pc + 0.9094(±0.1757)IX + 1.1712 (2)

n = 19, Se = 0.2772, R = 0.8988, R2A = 0.7695, F = 21.028

In order to confirms our finding we have estimated the log1/C values from the best suited model and compared them with the observed values. Both, observed and calculated biological activities (log1/C) are presented in Table9.

Both, observed and calculated biological activities are presented in Table 5-10.

The equations suggest that the indicator parameter IZS and IX have positive correlation coefficient and indicator parameter IR shows the negative correlation coefficient. Comparison of the magnitude of various indicator parameters shows the domination of presence of sulpher atom at X position. Positive coefficient of indicator parameter IX also exhibits the increase in cytotoxicity with the presence of Sulpher atom at X position.

III. CONCLUSION

The study shows that the mathematical model obtained from classical physicochemical properties is best suitable for the theoretical prediction of Cytotoxic concentration of TIBO derivatives[12] and it better correlates with biological activity log1/C in comparison to non-conventional physicochemical descriptors and logP. Study shows that the biological activity log1/C is structurally specific in nature for the particular series of TIBO derivatives[13]. Equations suggest that the presence of S atom at Z position and presence of Halogen atoms at X position have positive impact on the biological activity i.e., quantitatively increases biological activity. The presence of acyclic structure at R position bears negative impact on biological activity (log1/C) in quantitative manner.

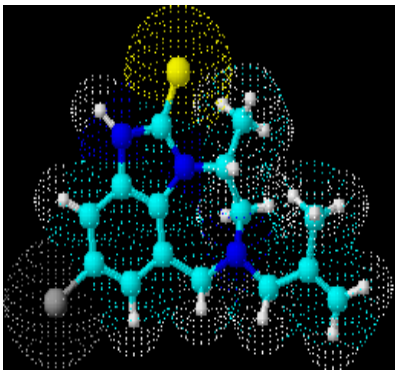

Figure 4. Opt. Structure of Comp. 17

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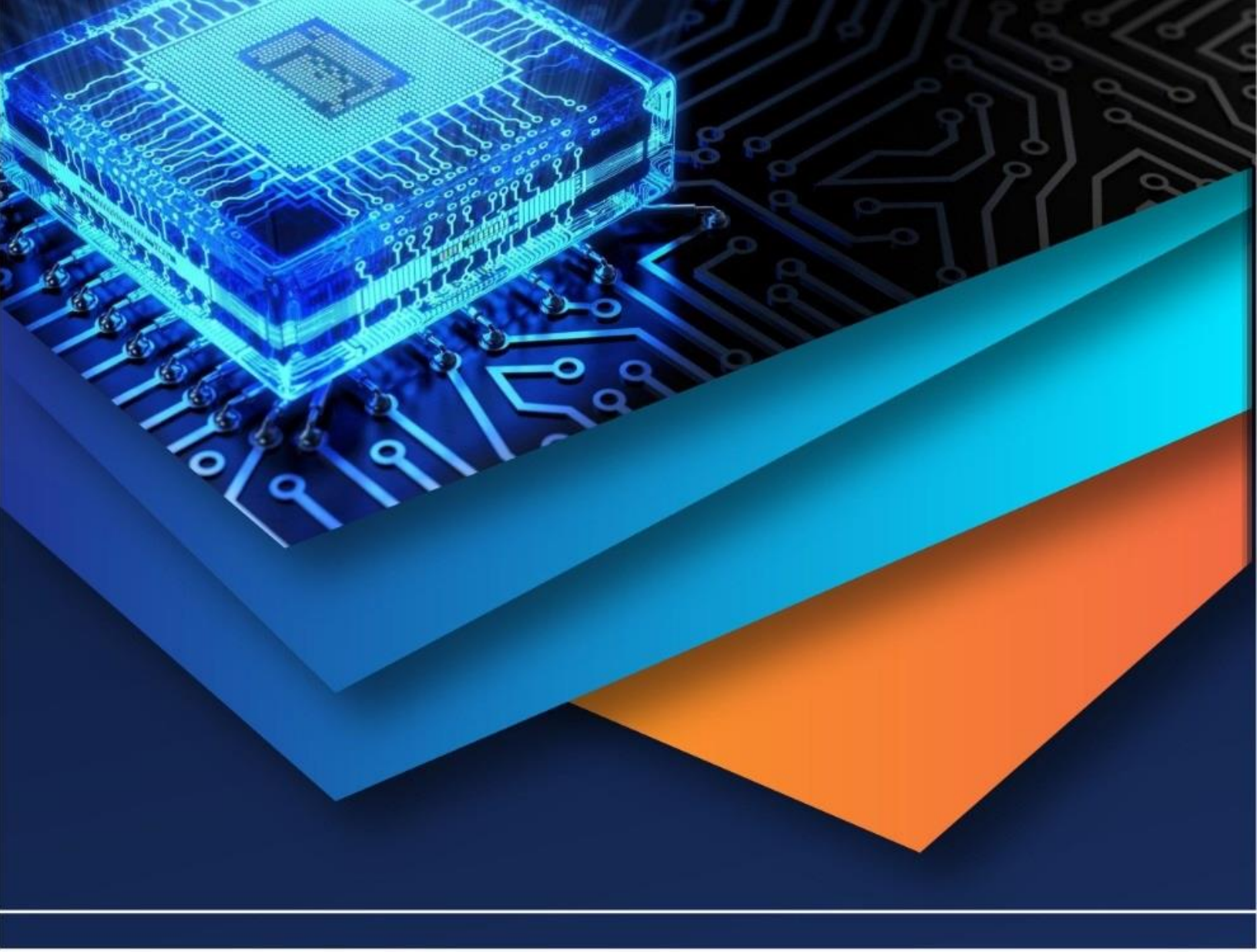

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