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Research Article

SURFACE AREA GRID IN MODELING OF ANTI HIV ACTIVITY OF TIBO DERIVATIVES

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ABSTRACT

Due to their role in the inhibition of non nucleoside reverse transcriptase, 4,5,6,7-Tetrahydro- 5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-ones (TIBO) derivatives present a significant importance as a potent chemotherapeutic agent against the AIDS disease. In this work, we report our attempt to find out the other factors required in quantitative structure-activity relationship for a set of 89 TIBO derivatives.

In vitro Anti HIV activity of TIBO derivatives logIC50 expressed as log1/C values were considered as a biological activity parameter. The QSAR study of the dataset of 89 TIBO derivatives was performed using different parameters namely Topological, physicochemical, hydrophobic descriptors and indicator parameters. Multiple regression analysis performed to obtain QSAR model and to capture the descriptor other than the logP.

The QSAR study highlights the logP, Is and surface area grid (SAG) descriptors, that affect the anti HIV activity of these TIBO derivatives. SAG is found as the cofactor working with hydrophobicity of TIBO derivatives. Eventually, the study provides a strong foundation to design new and more potent inhibitors of HIV-1 RT.

Keywords: TIBO derivatives; Anti HIV activity; QSAR, Topological descriptors, physicochemical descriptors, Surface area Grid.

INTRODUCTION

The NNRTIs plays an important role in current anti-HIV therapy as a part of a successful combination therapy. Different aspects of NNRTIs have recently been reviewed such as; NNRTIs in general 1-7, specific NNRTIs 8-13, resistance issues 14,15, x-ray and binding of NNRTIs 16,17, clinical use of NNRTIs 18-21 and toxicity issues with NNRTIs 22-25. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are potent antiretroviral agents that bind noncompetitively to a hydrophobic pocket in the reverse transcriptase (RT) enzyme close to the active site.26 A potential limitation in using this class of antiretrovirals is that a single mutation in the RT enzyme, NNRTI-binding pocket may confer high-level resistance to one or all of the available NNRTIs.27,28 Despite this low resistance barrier, the NNRTIs have been effective in durably suppressing HIV in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs), in both previously untreated HIV-infected patients29-32and NRTI-experienced patients 29-31 as well as or better than unboosted protease inhibitor-based regimens.29,30,33.

In our previous reports and according to the study of Gupta and Garg (1999),34 the anti-HIV activity of the TIBO derivatives that have been found to elicit their action through the allosteric inhibition of the enzyme viral RT is analyzed in relation to the physicochemical properties of the molecules and significant correlations are obtained between the activity and the hydrophobic constant and some dummy parameters of the substituents. The role of hydrophobic parameters like logP is well established in QSAR studies of

TIBO derivatives. In light of the above findings, an effort has been made to elucidate other cofactors, with hydrophobicity participate in regulating anti HIV activity of the TIBO derivatives. It is worthy to seek other factors, in order to optimize the structural aspects relatively. The general structure of TIBO derivatives is represented in Figure 1.

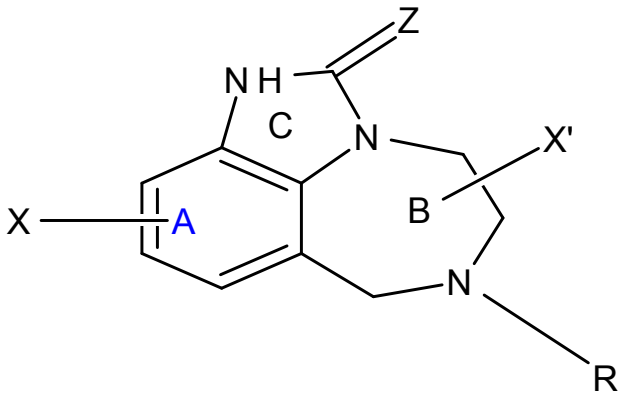


Fig 1. General structure of TIBO derivatives (X, X', Z and R: substituents).

2. MATERIAL & METHOD

2.1 Experimental dataset

In the present study a data set of 89 TIBO derivatives 34 as NNRTI's has been taken from the literature for QSAR study. Activity was measured as log IC50 and expressed as log 1/C, where C (the activity) is represented as the molar concentration of the drug required to achieve 50% protection of MT-4 cells against the cytopathic effect of virus. The activity of different substituted TIBO derivatives is presented in Table 1.

The virtual construction of the molecules and the geometry optimization has been done using computational software ACD Labs. Separately, for each molecule, the values for topological descriptors like Balaban Index (J) 35 Wiener index (W),36 Electrotopological State (TIE),37 Shultz Molecular Topological Index (SMTI),38 Randic connectivity indices (χ□,1χ, 2χ, 3χ, 4χ, 5χ)39 have been calculated, using the DRAGON software.

2.2 Physicochemical Parameter tested in present investigation

It mainly includes MR (Molecular Refractivity), MV (Molar Volume), Parachor (Pc), Index of refraction (η), Surface Tension (ST), Density (D), Polarizability (Pol), Octanol-water partition coefficient (logP), Approximate Surface Area (ASA) and Surface Area Grid (SAG). The physicochemical parameters have been calculated using chemsketch and Hyperchem. The SAG calculated in the present study is a solvent accessible surface area, calculated at solvent probe radius of 1.4 Ao

The indicator parameters are the user defined variables and indicated by unity i.e. 1 (for the presence) and zero i.e. 0 (for the absence) for substituents. The descriptors found suitable in QSAR Models is presented in Table 2

2.3 MLR (Multiple Linear Regression) Analysis

MLR is a method used for modeling the linear relationship between dependent variable Y (log1/C) and independent variable X (descriptors). MLR is based on the least squares method: the model is fitted such that the sum-of-squares of differences of observed and a predicted value is minimized. MLR estimates values of regression coefficients (r2) by applying least squares curve fitting method. The model creates a relationship in the form of a straight line (linear) that best approximates all the individual data points. In regression analysis, conditional mean of the dependant variable (log1/C) Y depends on (descriptors) X. MLR analysis extends this idea to include more than one independent variable.

Regression equation takes the form

$Y=b1*x1 + b2*x2 + b3*x3 + c$

where Y is dependent variable, 'b's are regression coefficients for corresponding 'x's (independent variable), 'c' is a regression constant or intercept 39,40.

3. Result & Discussion

The molecular backbone of the TIBO derivatives consists a 7-membered diazepine ring (B-ring) fused to a bicyclearomatic moiety (Ring A & C) (Fig. 1). A dimethylallyl moiety is also attached to the B-ring. TIBO derivatives, like the other nonnucleoside inhibitors, share a common butterfly like shape consisting of two wings; a π-electron-containing moiety and a dimethylallyl moiety. The specific conformation of the 7-membered B-ring of the TIBO derivatives is responsible for producing their butterfly like geometry 41-43.

However the role of hydrophobocity in the binding of NNRTI's to the RTase enzyme has been demonstrated earlier in many reports, but the objective of the present study is to identify the other cofactors performing role with hydrophobocity. In order to achieve this objective the stepwise regression analysis has been performed with log

Table 1: Substitutents with their Experimental and Estimated biological activity

R	X'	Obs.	Calc.	Calc.
		log(1/C)	log(1/C) eq(3)	log(1/C) eq(4)
DMAa	5-Me(S)	7.36	6.692	7.136
DMA	5-Me(S)	7.47	6.817	7.336
DMA	5-Me(S)	8.37	7.294	7.826
DMA	5-Me(S)	8.24	6.811	7.272
DMA	5-Me(S)	8.3	7.46	7.983
DMA	5-Me(S)	7.47	6.932	7.375
DMA	5-Me(S)	7.02	7.554	8.068
DMA	5-Me(S)	5.94	5.352	5.41
DMA	5-Me(S)	7.25	6.354	6.917
DMA	5-Me(S)	6.73	6.412	6.784
DMA	5-Me(S)	5.2	4.608	4.527
DMA	5-Me(S)	7.33	6.044	6.237
DMA	5-Me(S)	8.52	7.407	7.958
DMA	5-Me(S)	7.06	6.305	6.531
DMA	5-Me(S)	7.32	7.685	8.271
DMA	5-Me(S)	6.36	5.606	5.706
DMA	5-Me(S)	7.53	7.119	7.603
DMA	5-Me(S)	6	5.123	5.231
DMA	5-Me(S)	7.87	7.162	7.669
CPMb	5-Me(S)	4.48	4.926	4.925
CPM	5-Me(S)	3.07	3.593	3.411
CPM	5-Me(S)	5.18	4.742	4.732
CPM	5-Me(S)	4.22	3.622	3.441
CPM	5-Me(S)	5.18	5.102	5.103
CPM	5-Me(S)	3.8	3.678	3.453
CPM	5-Me(S)	5.61	6.179	6.51
DMA	5-Me(S)	7.6	6.293	6.739
DMA	5-Me(S)	5.23	5.801	6.004
DMA	5-Me(S)	6.31	7.073	-
DEAc	5-Me(S)	6.5	6.58	6.819
DMA	5-Me(S)	5.18	5.384	5.437
DMA	5-Me(S)	5.33	6.841	-
DMA	5-Me(S)	7.6	7.889	8.498
DMA	5-Me(S)	5.97	7.496	-
$CH_2CH=CH2$	5-Me(S)	4.15	4.149	4.087
2-MAd	5-Me(S)	4.33	4.505	4.493
CH_2CO_2Me	5-Me(S)	3.07	3.324	3.155

CH_2C=-CH	5-Me(S)	3.24	3.782	3.642
CH_2-2-furanyl	5-Me(S)	3.97	4.335	4.259
S (+)CH_2CH=CH_2	5-Me(S)	4.18	4.149	4.087
CH_2CH_2CH=CH_2	5-Me(S)	4.3	4.618	4.602
$CH_2CH_2CH_3$	5-Me(S)	4.05	4.281	4.234
2-MA[S(+)]	5-Me(S)	4.72	4.505	4.493
CPM	5-Me(S)	4.36	4.25	4.211
CH_2CH=CHMe(E)	5-Me(S)	4.24	4.528	4.512
CH_2CH=CHMe(Z)	5-Me(S)	4.46	4.129	4.102
$CH_2CH_2CH_2$Me	5-Me(S)	4	4.856	4.878
DMA	5-Me(S)	4.9	5.16	5.22
CH_2C(Br)=CH_2	5-Me(S)	4.21	4.761	4.786
CH_2C(Me)=CH Me(E)	5-Me(S)	4.54	4.827	4.86
DMA[R(+)]	5-Me(S)	4.66	5.16	5.22
DMA[S(+)]	5-Me(S)	5.4	5.16	5.2
CH_2 (C_2H_5)=CH_2	5-Me(S)	4.43	4.944	4.981
CH_2 CH=CHC6H5(Z)	5-Me(S)	3.91	3.88	3.969
CH_2C(CH=CH_2)=CH_2	5-Me(S)	4.15	4.797	4.804
DMA	H	7.34	6.759	7.208
DMA	H	6.8	6.82	7.27
2-MA	5,5-di Me	4.64	4.496	4.519
2-MA	4-Me	4.5	4.426	4.38
2-MA	4-Me(S)	6.17	6.246	6.696
CPM	4-Me(R)	5.66	6.47	6.906
C_3H_7	4-CHMe2	4.13	5.051	5.119
2-MA	4-$CHMe_2$	4.9	5.162	5.262
2-MA	4-C_3H_7	4.32	4.979	5.087
DMA	7-Me	4.92	5.087	5.145
DMA	7-Me	6.84	5.875	6.048
DMA	7-Me	6.8	5.88	6.053
C_3H_7	7-Me	5.61	5.766	6.102
DMA	7-Me	7.11	6.623	7.064
DMA	7-Me	7.92	7.177	7.706
DMA	7-Me	7.64	7.282	7.814
DMA	4,5-di-Me(cis)	4.25	5.52	-
DMA	4,5-di-Me(cis)	5.65	7.038	-
CPM	4,5-di-Me(cis)	4.87	6.274	-
DMA	4,5-di-Me(trans)	4.84	7.056	-
DMA	5,7-di-Me(trans)	7.38	7.055	7.562
DMA	5,7-di-Me(cis)	5.94	7.055	-
DMA	5,7-di-Me(R,R-trans)	6.64	6.317	6.554
DMA	5,7-di-Me(R,R-trans)	6.32	7.721	-
DMA	4,7-di-Me(trans)	4.59	7.032	-
DMA	5-Me(S)	6.74	5.955	6.13
CPM	5-Me(S)	7.47	6.439	6.875
CPM	5-Me(S)	7.22	5.764	6.107
C_3H_7	5-Me	4.22	4.281	4.234
C_3H_7	5-Me	5.78	5.821	6.158
2-MA	5-Me	4.46	4.084	4.059
DMA	5-Me	7.01	6.693	7.137
DMA	5-Me (S)	5.48	5.16	5.22
2-MA	5-Me (S)	7.59	6.038	6.41

[a]3,3-Dimethylallyl. [b]Cyclopropylmethyl. [c]3,3-Diethylallyl. [d]2-Methylallyl

Table 2: The parameters participating in the estimation of biological activity (log1/C)

Comp. No.	logP	SAG	I_S
1	3.53	501.08	1
2	4.24	461.14	1
3	4.24	519.44	1
4	3.67	504.67	1
5	4.09	551.49	1
6	3.45	536.63	1
7	3.98	571.53	1
8	3.76	511.73	0
9	2.96	526.06	1
10	2.89	516.52	1
11	2.59	511.62	0
12	4.91	506.98	0
13	4.39	521.7	1
14	5.17	518.68	0
15	4.66	534.72	1
16	4.11	515.55	0
17	3.8	532.34	1
18	4.34	438.51	0
19	4.03	519.61	1
20	3.3	495.31	0
21	1.88	442.59	0
22	3.27	475.12	0
23	1.88	446.2	0
24	3.27	519.16	0
25	1.42	488.89	0
26	2.55	514.48	1
27	3.67	441.28	1
28	5.09	463.19	0
29	4.41	479.15	1
30	5.22	548.37	0
31	3.71	519.5	0
32	3.28	538.67	1
33	4.84	545.59	1
34	4.39	532.51	1
35	2.91	430.61	0
36	3.31	443.04	0
37	2.09	393.41	0
38	2.24	437.81	0
39	2.72	468.13	0
40	2.91	430.61	0
41	3.24	462.35	0
42	3.02	438.23	0
43	3.31	443.04	0
44	3.11	427.43	0
45	3.27	448.96	0
46	3.27	400.11	0
47	3.55	467.37	0
48	3.84	481.98	0
49	3.6	451.87	0
50	3.67	454.45	0
51	3.84	481.98	0
52	3.84	481.98	0
53	3.67	468.8	0
54	4.51	273.16	0
55	3.41	471.05	0
56	3.56	506.93	1
57	3.56	514.33	1
58	3.66	414.75	0
59	3	457.43	0
60	3.72	431.66	1
61	3.52	474.6	1
62	3.95	460.06	0
63	4.24	451.07	0
64	4.37	418.61	0
65	3.84	473.04	0
66	4.76	497.93	0
67	4.76	498.56	0
68	2.72	450.69	1
69	3.53	492.52	1
70	4.24	505.21	1
71	4.24	518.04	1
72	4.36	485.54	0
73	4.05	502.87	1
74	3.32	466.24	1
75	4.05	505.1	1
76	4.05	505.02	1
77	4.05	505.02	1
78	5.28	511.52	0
79	4.77	530.54	1
80	4.05	502.23	1
81	4.76	507.74	0
82	3.52	470.87	1
83	2.8	444.2	1
84	3.02	438.23	0
85	2.72	457.39	1
86	3.31	391.46	0
87	3.53	501.15	1
88	3.84	481.98	0
89	3	462.21	1

Table 3 Correlation matix presenting mutual correlations of the parameters

	Log1/C	MR	MV	Pc	Pol	LogP	Hy	SAG	I_S	I_{DMA}
Log1/C	1.0000									
MR	0.6675	1.0000								
MV	0.5483	0.9115	1.0000							
Pc	0.6290	0.9849	0.9570	1.0000						
Pol	0.6658	0.9765	0.8875	0.9611	1.0000					
LogP	0.4733	0.5322	0.6669	0.5515	0.5056	1.0000				
Hy	0.4582	0.4008	0.1517	0.3301	0.3862	-0.1652	1.0000			
SAG	0.6028	0.5925	0.5639	0.6127	0.5735	0.3218	0.3089	1.0000		
I_S	0.6895	0.5956	0.3786	0.5271	0.5767	0.0883	0.7809	0.4426	1.0000	
I_{DMA}	0.6276	0.6342	0.6637	0.6582	0.6197	0.5508	0.2347	0.6276	0.4007	1.0000

Table 4: Selected compounds of minimum residual values

Compd. No.	**X**	**Z**	**R**	**X'**	**Obs. log(1/C)**	**Calc. log(1/C) eq(3)**	**Residual[a]**
24	9-NMe2	O	CPM	5-Me(S)	5.18	5.102	0.078
30	9-Me	O	DEAc	5-Me(S)	6.5	6.58	-0.08
40	H	O	$CH_2CH{=}CH_2$ [S(+)]	5-Me(S)	4.18	4.149	0.031
44	H	O	CPM	5-Me(S)	4.36	4.25	0.11
52	H	O	DMA[S(+)]	5-Me(S)	5.4	5.16	0.24
54	H	O	$CH_2CH{=}CHC_6H_5$(Z)	5-Me(S)	3.91	3.88	0.03
57	9-Cl	S	DMA	H	6.8	6.82	-0.02
58	H	O	2-MA	5,5-di Me	4.64	4.496	0.144
59	H	O	2-MA	4-Me	4.5	4.426	0.074
60	9-Cl	S	2-MA	4-Me(S)	6.17	6.246	-0.076
63	H	O	2-MA	4-CHMe2	4.9	5.162	-0.262
65	H	O	DMA	7-Me	4.92	5.087	-0.167
68	H	S	C_3H_7	7-Me	5.61	5.766	-0.156
84	H	O	C_3H_7	5-Me	4.22	4.281	-0.061
85	H	S	C_3H_7	5-Me	5.78	5.821	-0.041

[a]**residual** = Observed log (1/C) – Calculated log (1/C)

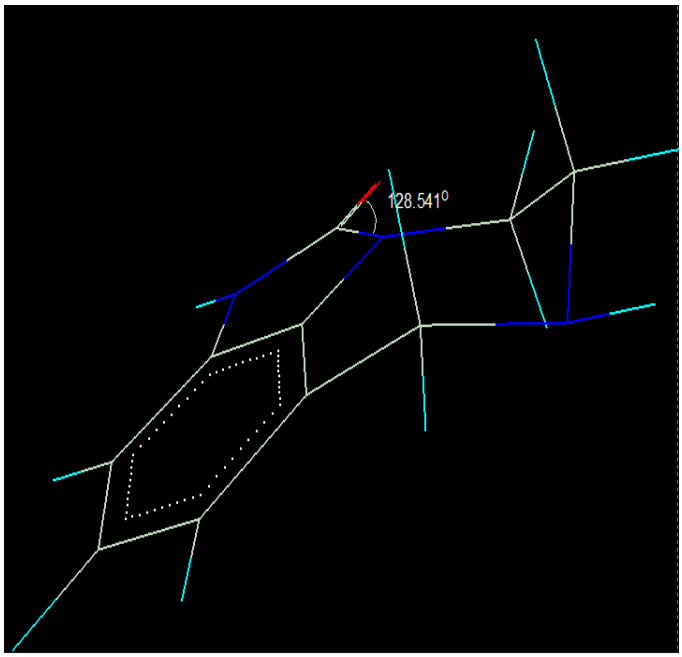


Fig 2a : 3D geometry of Oxygen containing unsubstituted TIBO, showing a bond angle.

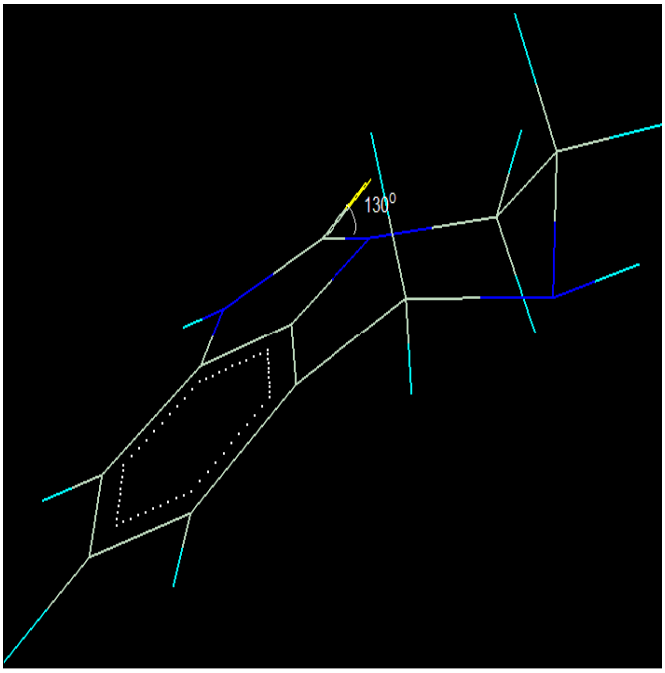


Fig 2b : 3D geometry of Sulphur containing unsubstituted TIBO, showing a bond angle.

IC50 (as log1/C) as dependent variable and physicochemical descriptors as independent variables. From the statistical analysis, significant equations (models) were developed. In order to observe the relationship of log 1/C with the tested descriptors, correlation matrix is presented in Table 3.

The correlation matrix shows that there is significant correlation between log1/C and indicator parameter Is, for the presence and absence of Sulfur atom at the place of =Z of a parent structure (Figure 1).

The statistically significant monoparametric model obtained with Is is:

log 1/C= 1.9837(±0.2234) IS + 4.8568 Eq (1)

N= 89 r= 0.6896 SEE=1.0456 F= 78.870

The positive coefficient of Is indicate presence of Sulfur predominates over the Oxygen, i.e., there is an increase in log1/C in the presence of sulfur, which eventually reduces the value of IC50. (as IC50 is reciprocal of 1/C)

To pursue another parameter affecting the binding of TIBO derivatives, biparameteric model has been developed, which include hydrophobic parameter i.e., logP (octanol/water partition coefficient) in Eq 1. and presented below in the form of Eq (2).

log 1/C= 1.8780(±0.1851) IS +0.7694 (±0.1191) logP + 2.0810 Eq (2)

N= 89 r= 0.8043 SEE=0.8628 F= 78.787

Eq 2 demonstrates the positive role of hydrophobicity (log P) on the inhibitory action of the TIBO derivative, this observation has been emphasized in many reports. It is worthy to mention that the TIBO derivative binds to the hydrophobic pocket of RTase enzyme, therefore the appearance of logP in Eq 2 is an apparent feature.

Furthermore in order to identify the cofactor effective with the hydrophobicity, triparametric equation has been developed and among the tri parametric models the best one was found to be the following :

log1/C = 1.5734(±0.1930) IS +0.6355 (±0.1176) logP + 0.0082(±0.0023) SAG -1.2184 Eq (3)

N= 89 r= 0.8328 SEE=0.8086 F= 64.104

Eq.3 shows the relative role of the surface area grid, presence of Sulfur atom and hydrophobicity (log P) towards inhibitory activity of TIBO derivatives. With increase in surface area grid, there is an increase in inhibitory action.

3.1 Structure activity relationship

On the basis of statistical relationship, presence of the S atom predominates over the O atom at Z. Secondly, the substitution, which increases hydrophobicity of the compound,

is favorable for the inhibitory action, as the binding site on RTase is hydrophobic in nature. SAG is a cofactor, working with hydrophobicity on regulating inhibitory action of TIBO derivatives. The positive coefficient of SAG and logP collectively indicate that larger surface area is needed, but a substitution for larger surface area should be hydrophobic in nature.

3.2 Interpretation of SAR of TIBO Derivative

The binding of TIBO derivatives on hydrophobic grooves of the RTase, is expected due to the participation of logP. The hydrophobic interaction between TIBO derivatives and RTase indicate towards the Vander Waal interactions between drug (TIBO derivative) and a target (RTase).

The role of Is shows the positive presence of S. This shows that the larger atomic radii of S atom than O, lead to the sterically repulsive surface expansion of 5-membered and 7-membered ring, this consequently increases the field distance between 5 & 7-membered ring. This sterically influenced broadening of the compound, increases exposure of TIBO derivative to the surface of an active site. The bond angle between the Z atoms and the atom fused in both the ring, has been taken into account to represent repulsive broadening in a compound. The increase in bond angle from 128.54° to 130° by the replacement of the O atom by S atom is clearly observed from Figure 2a & b.

Since the Surface area grid is a solvent accessible surface area, it strictly represents the size related features & an active molecular surface area. The role of such surface area, indicate that the inhibition of RTase activity by TIBO derivative is an adsorption phenomenon, involving interfacial interaction between the surface of the active site of an enzyme and the molecular surface of the TIBO derivatives. It is worthy to mention, that any substitution on TIBO derivatives, which leads to increase in SAG is favorable, irrespective to the site of substitution i.e., X, Z, R & X`.

In order to observe above finding deeply the set of 16 compounds with minimum residue (Difference of Obs. & Calc. log 1/C) (from Eq 3, Table 1) has been selected. These compounds are presented in Table 4.

In order to re-examine the role of parameters participating in the eq (3), above compounds has been arranged in decreasing order of their log 1/C value as 57>30>60>85>68>52>24>65>63>58>59>44>84>40>54

3.3 Pharmacophore Study

It has been clearly examined from the compound 57 of Table 4, that the compound with the maximum log 1/C value has no substitution on X' i.e., on the 7- membered ring, in fact this can also seen in Table 1, that almost all the compounds are X` substituted, this shows that the absence of substitution on X' having no significant impact on inhibition activity.

Compound No 57, 60, 85 & 68 are the compound with highest log 1/C values, this is due to the presence of the S atom at Z. However compound 30 is on the second highest place of log 1/C, due to the presence of the 9-Me group and dimethyl allyl group at X and R positions, respectively. This result in the tremendous increase in hydrophobicity and SAG, and eventually compensate the effect of presence O atom or absence of S in the compound 30.

After compound no 68 (except compd. 30) in the descending series, all the compounds are O containing compound, therefore compound no 52>24>65>63>58>59>44>84>40>54 are free from effect of S. By taking examples of these compounds effect of X & R substitution has been investigated.

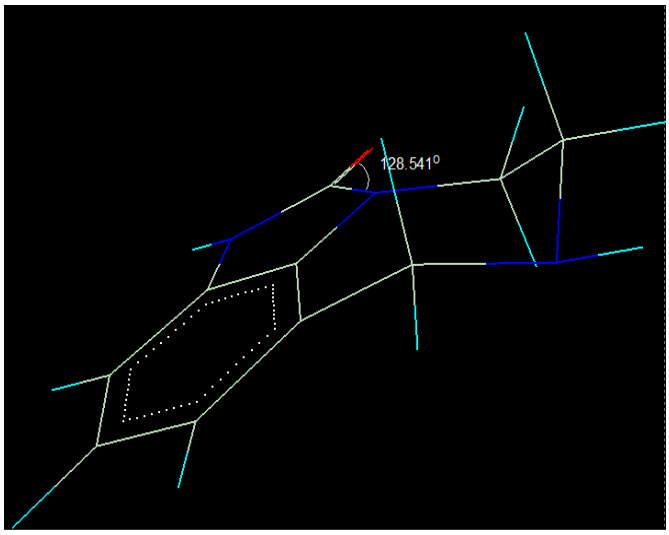
In compound 52 & 65 presence of dimethyl allyl on R is responsible for optimizing hydrophobicity and the surface area grid, therefore showing higher value of log1/C. In compound 24 absence of dimethyl allyl is compensated by 9-NMe2 group at X by increasing its SAG. In compound 63 & 58 presence of methyl allyl at R largely reduces SAG, and therefore its log1/C value is also reduced. In compound 59 lowering of logP, lowers the value of log1/C, in compound 44, 84, 40 there is a regular fall in SAG due to CPM, C3H7 and allyl group substitution at R, respectively. In compound 54 there is an extreme lowering of SAG, due to present of flat C6H5 moity at allyl group, which raises its logP (hydrophobicity), but largely reduces its SAG.

4. Conclusion

The derived QSAR models have shown that hydrophobicity in terms of logP, approximate surface area grid, and presence of sulfur on =Z hold promise for rationalizing the inhibitory actions of titled compounds. The values of parameters, r, Se and F-ratio, ensures that the predictions are reliable and acceptable.

It was also observed in this investigation, that solvent accessible surface area is a cofactor working with hydrophobicity of the compounds for the inhibitory activity of TIBO derivatives. The presence of the S atom on =Z is also seems to justify over O, because of the larger surface area and low electronegativity of Sulfur. This clearly points towards the larger solvent accessible surface area i.e., SAG, is favorable but substitution should preferably nonpolar or hydrophobic in nature.

Out of the present group of pharmacophore, it is relevant to conclude, that dimethyl allyl on R is a group that reasonably increases SAG, with subsequent increase in hydrophobicity. However if smaller group is present on this site, it must be compensated by making a suitable substitution (i.e., larger and hydrophobic) on 6-membered ring.



Graphical Abstract

In this work, quantitative structure-activity relationship (QSAR) for a set of 89 TIBO derivatives has been developed, with an aim to determine the role of Surface area grid in modeling of Anti-HIV activity. The role of hydrophobicity has been already described in many studies, therefore efforts has been made to illustrate the other features contributing in the biological activity of TIBO derivatives.

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