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Research Paper

QSAR study of some TIBO derivatives: A non conventional topological parameter approach

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Abstract *- Human Immunodeficiency Virus type 1 (HIV-1) reverse transcriptase is an important target for chemotherapeutic agents against the AIDS disease. 4,5,6,7-Tetrahydro- 5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-ones (TIBO) derivatives are potent non-nucleoside reverse transcriptase inhibitors (NNRTIs). In the present study the aim of the author is to use some non conventional topological parameter in order to find the binding affinity of the TIBO derivatives in the set of compound. The Multiple Linear Regression (MLR) is used to find the best model in order to get the better binding affinity of the drug. The role of constitutional parameter, RBF (Rotatable Bond Friction), information indices, Yindex (Balaben Yindex) along with the indicator parameter shows the higher correlation with the inhibitory concentration (pIC50) of the drug.*

Keywords: QSAR, TIBO, HIV, MLR, Topological parameter etc.

Introduction

The human immunodeficiency virus-1 (HIV-1), the causative agent for acquired immunodeficiency syndrome (AIDS), is the most interesting virus in the history of biomedical research [1–3]. At present, chemotherapy seems to be the main weapon in dealing with the dreaded disease caused by HIV-1 retro-virus. As a retrovirus, HIV has an envelop of lipid bi-layer membrane containing two copies of a single stranded RNA genome that codes for the structural proteins, surface glycoproteins, regulatory factors, and the enzymes reverse transcriptase (RT), protease, and integrase.

There are three types of viral enzymes related to HIV namely: HIVprotease, HIV-integrase and HIV-reverse transcriptase. [4-6]The reverse transcriptase enzyme is an important target for the development of selective inhibitors. The HIV reverse transcriptase inhibitors are of two types: nucleoside reverse transcriptase inhibitors (NRTIs) and non nucleoside reverse transcriptase inhibitors (NNRTIs). The safety, selectivity and high potency of NNRTIs have made them more important in the field of drug research as compared to NRTIs [7]

The investigation of the quantitative structure activity/property relationships (*QSAR/QSPR*) of substances is an important aspect of modern chemistry, biochemistry, medicinal chemistry, and drug discovery [8–13]. The information obtained is composed of mathematical equations relating the chemical structure of the compounds to a wide variety of their physical, chemical, biological and technological properties. Once a correlation between structure and activity/property is found, any number of compounds, including those not synthesized yet, can readily be screened *in silico* for selection of structures with desired properties. Hence, it is possible to select the most promising compounds for synthesis and testing in the laboratory.

TIBO and its derivatives are a class of NNRTIs that have demonstrated good activity towards RT inhibition. One (Tivirapine) of them has moved onto the clinical development cycle.[14]

The crystal structures of several TIBOs/RT complexes are currently available [15-16]. These complexes provide some insight into the binding and interactions of TIBOs in RT. However the inhibition model of TIBOs still needs to be elucidated in order to find and design new and more potent inhibitors that remain effective to HIV-1 RT mutants due to the presence of NNRTIs.

Experimental Methodology

Data set

The parent structure of the TIBO is given in the fig 1. Table 1 shows the all 16 derivatives of TIBO used in the present study. Experimental anti-HIV activity (pIC50) complied from references [17-25]

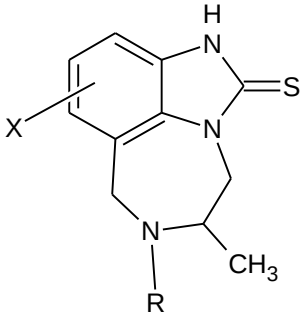

Figure 1: Parent Structure of TIBO derivatives

Calculation of non conventional topological descriptor:

All the topological indices were calculated from the hydrogen suppressed molecular graphs using computer program "Dragon 5.0".

Regression analysis:

Regression analyses were made using maximum R^2 method (Chaterjee et al., 2000) adopting step-wise regression. Univariate, bivariate to multivariate regression has been performed for finding out the best correlation. All those correlation having value of R below 0.50 are considered to be insignificant and discarded from the study. Regression analysis have been made using in- house developed computer program "ANALYSIS"

Results & Discussion

The theoretical basis of QSAR analysis is the presumed existence of a linear free energy relationship between topological descriptors of a molecule and its affinity for a receptor. MLR was performed tp get the best mathematical model and the importance of topological parameter as well as indicator parameter in the binding affinity of the drug. The correlation matrix shows the importance of indicator parameter i.e presence of halogen atom at X position. Only that descriptor is taken in to account in uniparamatric combination, which shows the >0.5 correlation with the pIC 50 and hence only indicator parameter IX shows the >0.5 correlation with the pIC50. So the model obtained from the correlation matrix by uniparametric parameter is given below-

pIC50= 1.5034(± .5336) IX + 6.4886 **Eq(1)**

N= 16, r= .6015, Se= 1.0588, F=7.938

the model shows the dominance role of indicator parameter over other parameter. In order to get best model we were tasted various biparametric combination and the best models are given below-

pIC50= 1.4111(± .5090) IX + 20.0676(± 12.4865) RBF + 4.9358 **Eq(2)**

N= 16, r= .6838, Se= 1.0036, F=5.709

The increment in the value of r shows the model is best biparametric model. In Eq (2) the constitutional parameter, RBF (Rotatable Bond Friction) along with indicator parameter are very much responsible for the binding affinity of the drug. But at the same time lower the value of F ratio and higher the value of standard error is showing that there is some of problem with this model. But the statistical analysis shows that this model is best biparametric model and in order to find the best result we were tested several triparametic combinations and we got the following results-

pIC50= 1.6601(± .5355) IX + 22.6684(± 12.3841) RBF + 3.7816 (± 2.9967) Yindex + 0.6449 **Eq(3)**

N= 16, r= .7280, Se= .9815, F=4.511

Now, again the increased value of r shows that this one is the best model as far as high correlation with the pIC50 is concern. But the higher value of Se= .9815 and lower value of F= 4.511 is not well enough for the study of the drug receptor binding in particular sets of compound.

So, from here, we started the outlier i.e the compound shows the minimum residue between observed and calculated activity. There are three compounds are observed which shows the minimum residue and is misfit in the model. The table given below shows that the step by step outlier of the compound along with there F and Se. Table 6.

On the basis of above table, we can tell that the entire outlier compound is not best fit in the model. As we move from equation 4 to equation 6 each time there is an increment in the value of r as well as F at the same time lower the value of se shows that the equation 6 is the best mathematical model for the particular sets of TIBO derivatives. From the discussion above made, it is concluded that the importance of indicator parameter (IX= Presence of halogen at X position) is very important to enhance the biological activity of the drug. The halogen compounds are electro withdrawing in nature. Rotatable Bond Friction (RBF) is also very important phenomenon in order to get drug receptor binding affinity in particular sets of compound. The resulted QSAR model is best fit in particular set of compound and show the greater relationship with the inhibitory concentration (pIC50) and we can say that the presence of indicator parameter alongwith the RBF and Yindex is important non conventional topological parameter and shows higher relationship. Figure 2.

Conclusion

We have used a small set of compound in order to know the role of some non conventional topological parameter and statistical analyses based non conventional descriptors led us to propose the explanation of the structure-activity relationships and enzyme-inhibitor complex. In addition, this study shows that the use of non conventional topological parameter is also very important to know the mechanism of drug receptor interaction.

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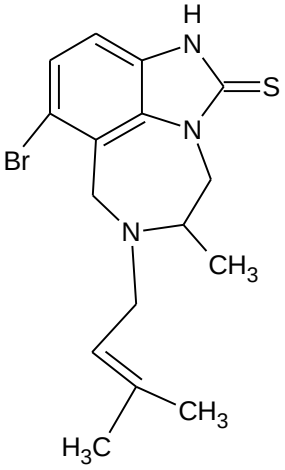
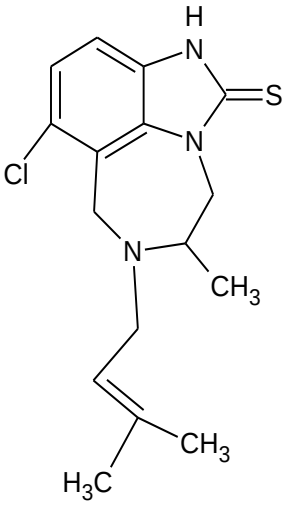
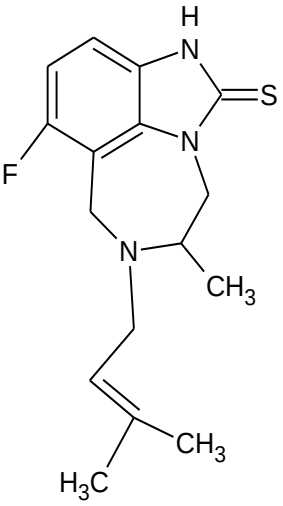
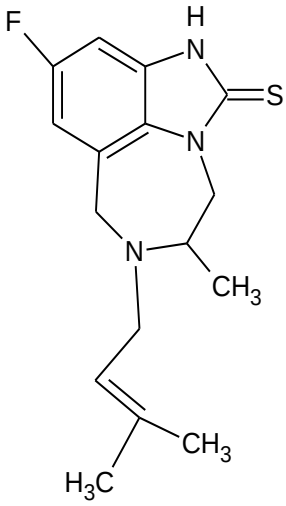
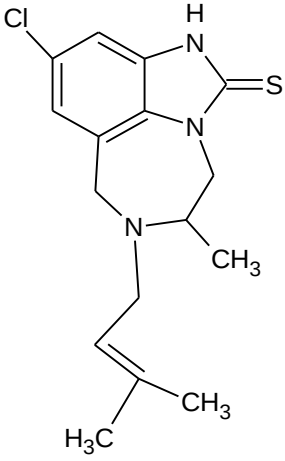
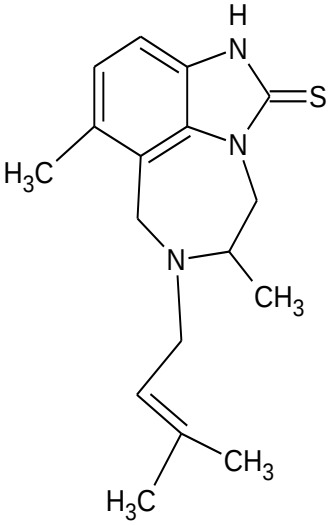
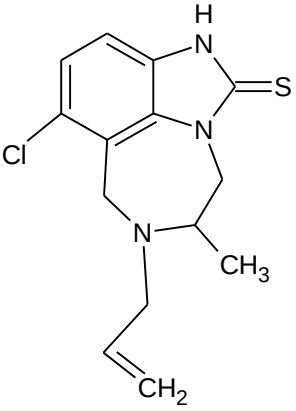
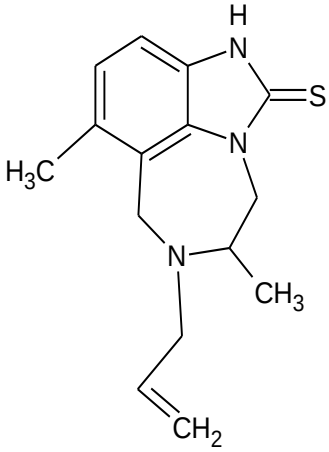
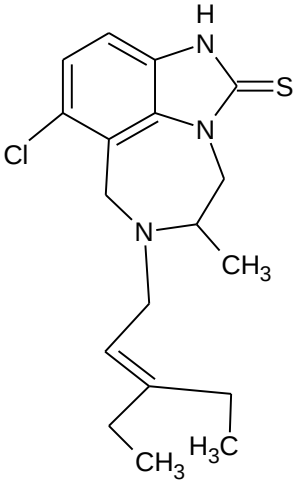
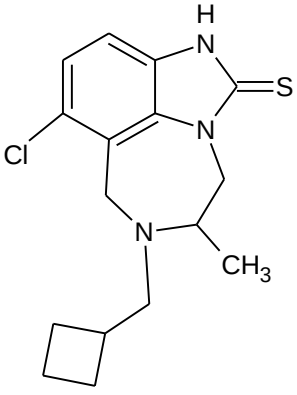
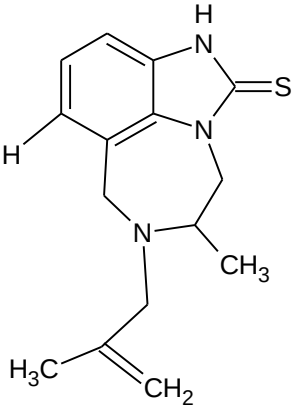
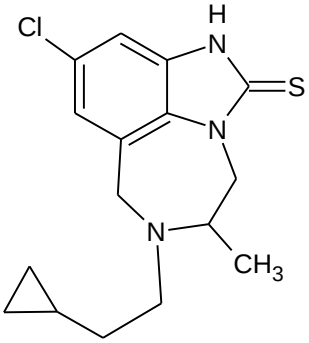
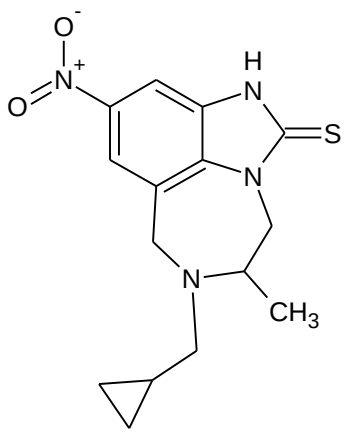
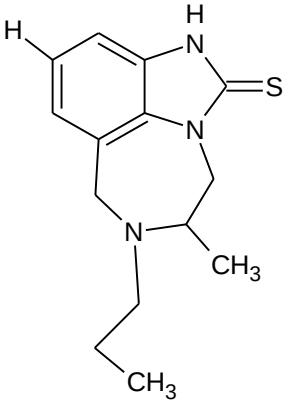
Table 1: Structures of the compound used in present study

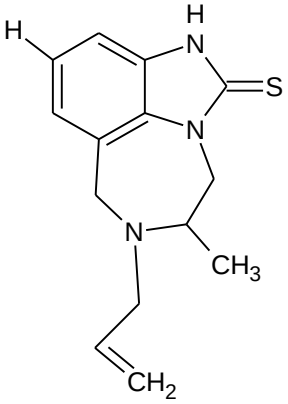
 Comp1	 Comp2	 Comp3	 Comp4
 Comp5	 Comp6	 Comp7	 Comp8
 Comp9	 Comp10	 Comp11	 Comp12



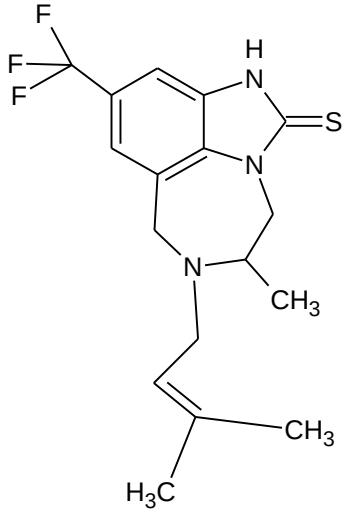
Comp13



Comp14



Comp15



Comp16

Table 2: Details of descriptor used in present study

Symbol	Meaning	Type of descriptor	References
ARR	Aromatic Ratio	Constitutional descriptors	Handbook of Molecular descriptor. Wiley-VCH , Weinheim (Germany) Author Todeschini, R. & Consonni, V. (2000)
RBF	Rotatable Bond Friction		
RBN	Number of Rotatable Bond		
Dz	Pogliani index	Topological descriptors	J. Phy. Chem., Pogliani, L. (1996) 100, 18065-18077
Xu	Xu index		J. Chem. Inf. Comput. Sci., Ren, B. (1999) 39,139-143
SPI	Superpendentic index		J. Chem. Inf. Comput. Sci., Gupta,S., Singh, M.& Madan, A.K. (1999) 39,272-277
w	Detour index		Croat.Chem. Acta, Amic, D. & Trinajistic, N. (1995) 68,53-62
Uindex	Balaban U index	Information indices	J.Math.Chem., Balaban, A.T. & Balaban, T.S.(1991) 8, 383-397
Vindex	Balaban V index		
Xindex	Balaban X index		
Yindex	Balaban Y index		
EPS0	Edge connectivity index of order 0	Edge adjacency indices	J. Chem. Inf. Comput. Sci.,Estrada,E. (1995) 35,31-33
EPS1	Edge connectivity index of order 0		J. Chem. Inf. Comput. Sci., Estrada,E. (1995) 35,701-707
Ui	Unsaturation index	Molecular properties	Handbook of Molecular descriptor. Wiley-VCH , Weinheim (Germany) Author Todeschini, R. & Consonni, V. (2000)
AMR	Ghose-Crippen molar refrctivity		J. Chem. Inf. Comput. Sci.,Vishwanadhan, V.N., Ghose, A.K.Revenkar, G.R. (1995) 29,163-172

Table3: Value of observed and calculated pIC50 for given sets of compound

Compound no	Observed pIC50	Calculated pIC50	Residual
1	8.520	8.349	0.1707
2	8.340	8.349	-0.0093
3	8.240	8.349	-0.1093
4	7.838	8.274	-0.4357
5	8.480	8.274	0.2063
6	7.850	6.916	0.9341
7	8.330	7.953	0.3796
8	7.850	6.746	1.1036
9	7.920	8.443	-0.5235
10	7.880	6.823	1.0574
11	7.850	6.508	1.3419
12	6.380	7.113	-0.7334
13	5.610	5.574	0.0357
14	5.780	6.697	-0.9172
15	4.170	6.244	-2.0738
16	6.310	6.734	-0.4244

Table 4: Non conventional topological and indicator parameter used in present study

Compound no.	RBF	Yindex	IX
1	0.12	0.879	1
2	0.12	0.879	1
3	0.12	0.879	1
4	0.12	0.859	1
5	0.12	0.859	1
6	0.13	0.879	0
7	0.08	1.014	1
8	0.1	1.014	0
9	0.14	0.784	1
10	0.07	0.775	1
11	0.1	0.951	0
12	0.09	0.732	1
13	0.09	0.764	0
14	0.1	1.001	0
15	0.08	1.001	0
16	0.13	0.831	0

RBF= Rotatable Bond Friction
Yindex= Balaben Yindex
IX= Indicator parameter, if halogen is present at X position then 1 otherwise 0

Table 5: Topological and indicator parameter used in present study

---------- CORRELATION MATRIX ----------

HEADER DATA FOR: D:TIBO16 LABEL:
NUMBER OF CASES: 16 NUMBER OF VARIABLES: 20

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	pIC50	ARR	RBF	RBN	Dz	Xu	SPI	w
pIC50	1.00000							
ARR	-.43317	1.00000						
RBF	.39107	-.56102	1.00000					
RBN	.32106	-.62368	.96380	1.00000				
Dz	.08509	-.60432	.52000	.63707	1.00000			
Xu	.20489	-.70073	.57655	.71024	.96445	1.00000		
SPI	-.05489	-.54040	.51423	.54059	.76815	.64553	1.00000	
w	.16447	-.68331	.54897	.68757	.97788	.99617	.68658	1.00000
Uindex	.31344	-.72386	.82723	.87814	.86948	.87849	.78390	.87868
Vindex	.00551	.45014	-.06569	-.25071	-.68173	-.76426	-.16304	-.74679
Xindex	.01750	.34376	.11801	-.07925	-.60917	-.67434	-.08975	-.66474
Yindex	-.05171	.53394	-.19592	-.37076	-.73275	-.82459	-.22566	-.80246
EPS0	.39160	-.97305	.58882	.68644	.64818	.74833	.54916	.73715
EPS1	.11724	-.61521	.39293	.54807	.95046	.97289	.58179	.97374
AROM	.35738	-.53306	.21104	.12592	-.28049	-.20735	.07523	-.22177
Ui	.04513	.30075	.29984	.26061	.30143	.22741	.19345	.23083
AMR	.47219	-.76452	.66997	.77717	.73680	.87822	.40490	.85034
IX	.60154	-.51979	.11292	.10581	.14949	.29035	-.17554	.24522
ICl	.34616	-.37284	-.13565	-.04337	.06555	.20186	-.18237	.18365
IR	.43067	-.51979	.69696	.57137	.42881	.43284	.47541	.40494

	Uindex	Vindex	Xindex	Yindex	EPS0	EPS1	AROM	Ui
Uindex	1.00000							
Vindex	-.37485	1.00000						
Xindex	-.25186	.96412	1.00000					
Yindex	-.48005	.98976	.92888	1.00000				
EPS0	.77571	-.46452	-.36709	-.54948	1.00000			
EPS1	.75452	-.86350	-.80187	-.89453	.65042	1.00000		
AROM	.05448	.39728	.44738	.33491	.46890	-.33197	1.00000	
Ui	.34015	.07668	.09024	.04594	-.23745	.17847	-.56654	1.00000
AMR	.82317	-.63533	-.53076	-.71569	.81371	.79882	.02425	.14716
IX	.21116	-.34577	-.36910	-.38124	.48995	.25907	.30397	-.21901
ICl	.05014	-.35697	-.44621	-.35194	.40439	.21890	.20941	-.33302
IR	.61953	-.04940	.09539	-.14613	.40066	.32540	.21694	.24729

	AMR	IX	ICl	IR
AMR	1.00000			
IX	.48529	1.00000		
ICl	.37832	.68313	1.00000	
IR	.46743	.26984	-.16265	1.00000

CRITICAL VALUE (1-TAIL, .05) = + Or - .42706
CRITICAL VALUE (2-tail, .05) = +/- .49580

N = 16

Table 6: Step by step outlier from best mathematical model

Eq No	Equation	N	r	Se	F
4	pIC50= 1.4145(± .3976) IX + 13.1246(± 9.4688) RBF + 5.4864 (± 2.2448) Yindex + 0.4788	15	0.7708	.7166	5.367
5	pIC50= 1.1781(± .2908) IX + 10.8689(± 6.7612) RBF + 7.3058 (± 1.6811) Yindex -0.5877	14	0.8688	.5092	10.262
6	pIC50= 1.0676(± .2128) IX + 22.0414(± 6.0055) RBF + 8.7668 (± 1.2969) Yindex -3.1137	13	0.9405	.3676	22.977

Figure 2: Graph plotted between observed and calculated pIC50