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QSAR Study on Isatin Analogues Acting as HIV-Reverse Transcriptase Inhibitors

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ABSTRACT: The broad spectrum chemotherapeutic properties of isatin analogues prove its importance for Human Immunodeficiency Virus (HIV) treatment. Some isatin analogues act as anti-HIV drugs and also show efficacy against opportunistic infections associated with it like tuberculosis, hepatitis and other bacterial diseases. Molecular modeling is helpful in the discovery of potentially effective inhibitors. Here we report a Quantitative Structure-Activity Relationship (QSAR) study on a series of potential reverse transcriptase inhibitors containing isatin nucleus. The data set of 22 compounds was divided into a training set (17) and test set (5). The QSAR analysis reveals the inhibitory potencies of these series of compound is governed by a topological parameter ($^1\chi^v$), lipophilicity of R_1 substituent (π) and indicator parameter (I) with r^2_{cv} = 0.87 and r^2_{pred} = 0.89. Based on these results the mechanism of drug-receptor interaction is discussed and it can be of great help to design and develop new potent reverse transcriptase inhibitors.

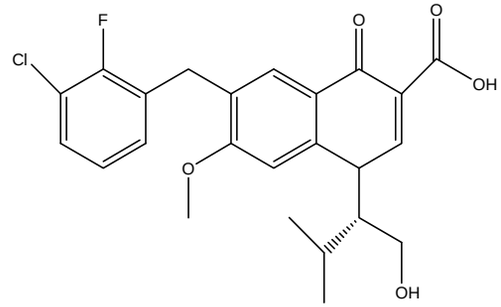
KEYWORDS: QSAR, Isatin analogs, Anti-HIV agents, Reverse transcriptase inhibitors.

Introduction

From the early 1980s the Acquired Immunodeficiency Syndrome (AIDS) and its causative organism Human Immunodeficiency Virus (HIV) has puzzled scientist all over the world-wide. Today AIDS has become a major world-wide epidemic[1,2]. The currently available anti-HIV therapy includes nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NTRIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIS), protease or entry inhibitors and HIV integrase inhibitors. NNRTIS are structurally diverse group of compounds which binds to the viral enzyme reverse transcriptase (RT) where it interacts with a specific allosteric non-substrate binding pocket site (Non-nucleoside binding pocket-NNBP). NNRTIS non-competitively inhibit RT enzyme, block its mechanism and make it unable to produce a viral DNA[3]. Currently drugs used to treat AIDS under NNRTIs for anti-AIDS therapy are Nevirapine, Delaviridine, Efavirenz, Etravirine and Rilpivirine.

Isatin (1H-indole-2,3-dione) analogues, due to the importance of indole back bone have shown a variety of biological activities such as antibacterial[4,5], antifungal[5,6], anti-HIV[7,8] and anticonvulsant activity[9]. Owing to the broad spectrum chemotherapeutic properties, it appears as an ideal drug for AIDS treatment which suppresses HIV replication by acting as non-nucleoside reverse transcriptase inhibitor[7,8,10-12]. Therefore isatin analogues act as anti-HIV drugs as well as possess efficacy against opportunistic infections associated with AIDS like tuberculosis, hepatitis and other bacterial disease.

Replication of Human Immunodeficiency Virus (HIV) involves integration of viral DNA into host genome and is catalyzed by virally encoded enzyme integrase (IN). Integration creates a difficult hurdle in viral eradication and thus impacts the chemotherapy of infected hosts[13, 14]. Thus process offers and appealing venue for the design and development of anti-HIV drugs. The integrase inhibitors target a viral enzyme involved in the replication cycle of HIV *i.e.,* the inversion of HIV-1 proviral DNA into the host's cellular genome. Thus it represents one of the most promising targets into HIV life cycle for therapeutic intervenation[15,16]. Some of the reported integrase inhibitors include Raltegravir[17,18], Elvitegravir[19,20].



Elvitegravir

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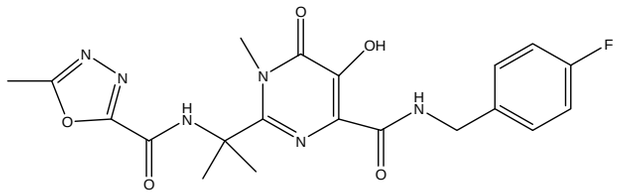


Raltegravir

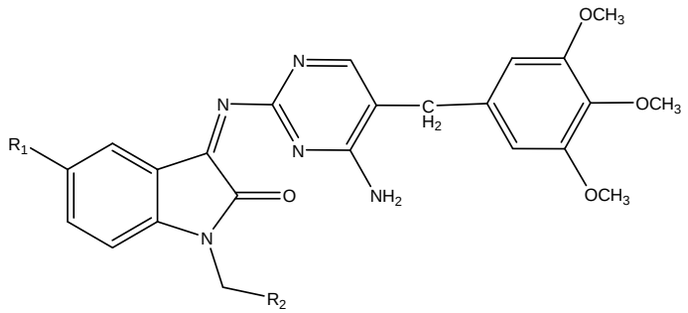
Materials and Methods

A series of substituted isatin analogues and their HIV reverse transcriptase inhibitory activity was reported by Pawar *et al*., (Table 1)[21]. Various physicochemical and topological descriptors were calculated and those were used to derive the best QSAR model. Only Kier's first-order valence molecular connectivity index ($^1\chi^v$) and calculated lipophilicity (π) were found to be the most important parameter and some indicator parameters were also found to govern the activity. These indicator parameters have been defined later. The molecular connectivity index ($^1\chi^v$) was calculated according to Kier and Hall[22,23].

Results and Discussion

The whole data set contains 22 compounds. This set is divided into two subsets, the training and test sets. The test set compounds were selected keeping in mind while the structural diversity and span activity data. The compounds are shown in Table 1.

Table 1 Structures of isatin analogues (1-22)



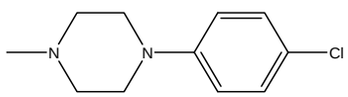
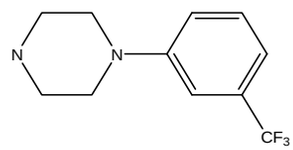
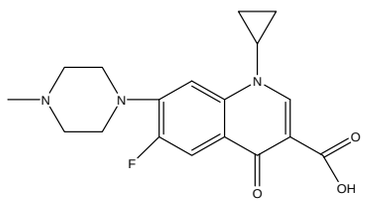
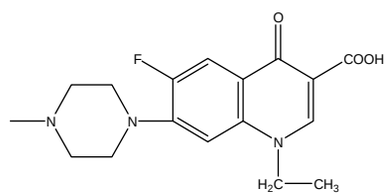
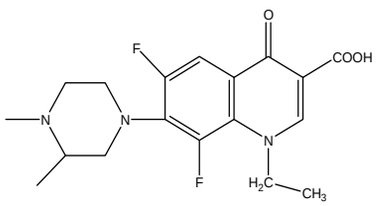
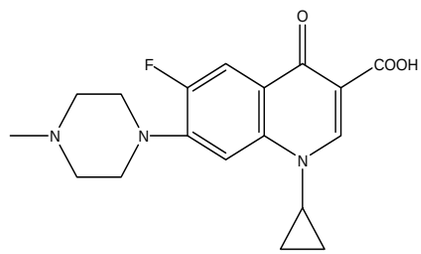
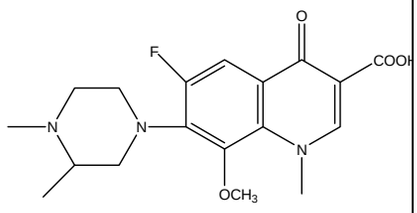
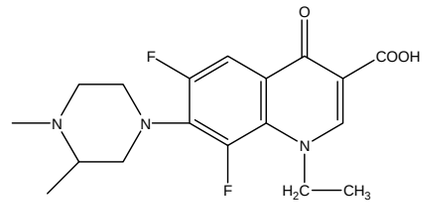
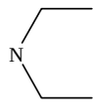
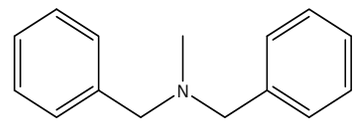
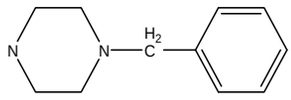
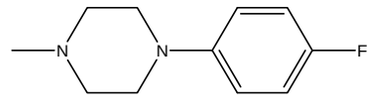
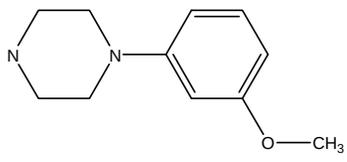
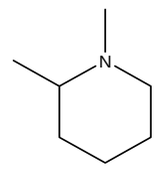
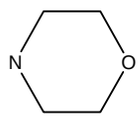
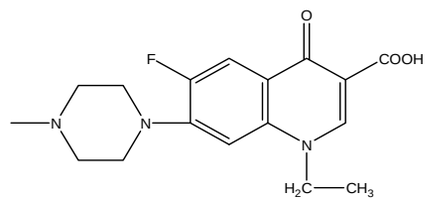
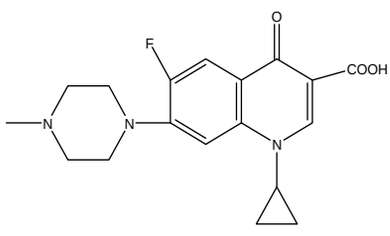
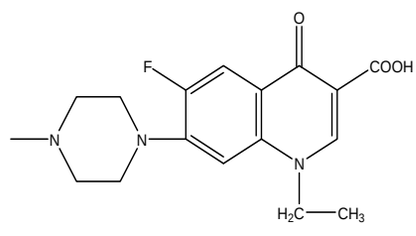
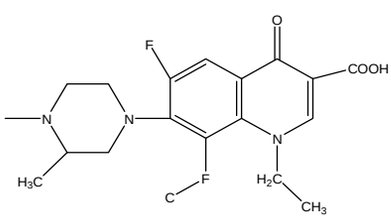
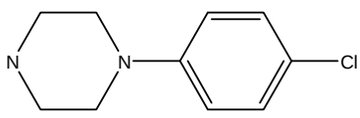
Compd no.	R_1	R_2	Compd no.	R_1	R_2
1	CH_3		12	F	
2	CH_3		13	F	
3	CH_3		14	F	

Table 1 *Contd…*

Compd no.	R_1	R_2	Compd no.	R_1	R_2
4	CH_3		15	F	
5	Br		16	Cl	
6	Br		17	Cl	
7	Br		18	Cl	
8	Br		19	Br	
9	Br		20	Cl	
10	Br		21	Cl	$N(C_4H_9)_2$
11	F		22	Cl	$N(C_2H_5)_2$

A multiple regression analysis is performed on the training set and the best correlation that we could find is equation (1).

$$\log (1/EC_{50}) = 0.331(\pm 0.275)^{1}\chi^{v} - 0.026(\pm 0.023)(^{1}\chi^{v})^{2} - 1.157(\pm 0.429)\pi + 0.437(\pm 0.279)I + 0.917(\pm 0.826)$$

$$n = 15,\ r = 0.907,\ s = 0.141,\ F_{4,11} = 11.545(6.64) \quad \text{.....(1)}$$

Where $^{1}\chi^{v}$ refers to molecular connectivity index of R_2-substituents and π refers to lipophilicity of R_1-substituents. The indicator variable *I* is used with the value of 1 for R_1 = Br while *I* = 0 for other than Br substituents. We tried many other physicochemical parameters, but the best correlation that we could find in equation (1).

In this equation, EC_{50} refers to the molar concentration of the drug leading to 50% inhibition of HIV. Among the statistical parameters, n is the number of data points, *r* is the correlation coefficient obtained from the leave-one-out (LOO) jackknife procedure, *s* is the standard deviation, *F* is the ratio between the variances of calculated and observed activities and the data within the parenthesis with ± sign are 95% confidence intervals. The figure with in the parenthesis following the *F*-value is the standard *F*-value at 99% level. The values of these statistical parameters in equation (1) show that the correlation obtained is quite significant. This correlation suggest that the HIV inhibition activity of the series of compound is basically controlled by the lipophilicity of R_1-substituent and the molecular connectivity takes into account the nature (valence and unsaturation) of the atoms, their connectivity and size of the molecule. The presence of large number of atoms with low valence and high saturation leads to high value of $^{1}\chi^{v}$. Thus, R-substituent containing such atoms may have high inhibition activity. Such group may be more hydrophobic and this may be involved in hydrophobic interaction with the receptor. The validity of the correlation is judged by the values of its r_{cv}^{2} which is calculated as

$$r_{cv}^{2} = 1 - [\Sigma(y_{i,\,obsd} - y_{i,\,cald})^{2}/\Sigma(y_{i,obsd} - \hat{y}_{,obsd})^{2}] \quad \text{.....(2)}$$

Table 2 Physicochemical properties and observed, calculated and predicted activities of compounds of Table 1

S.No.	$^{1}\chi^{v}$	$(^{1}\chi^{v})^{2}$	π	I	*p*EC_{50}		
					Obsd	Calcd	Pred (LOO)
1	4.493	20.187	0.560	0	1.236	1.233	2.527
2[a]	6.915	47.817	0.560	0	2.060	2.611	-
3	6.812	46.403	0.560	0	1.453	1.321	1.282
4	8.993	79.798	0.560	0	1.326	1.157	0.975
5	2.730	7.453	0.860	1	1.283	1.070	0.993
6[a]	4.424	19.571	0.860	1	0.892	1.315	-
7	4.478	20.052	0.860	1	1.354	1.322	1.312
8	1.893	3.583	0.860	1	0.748	0.893	1.223
9	8.993	79.798	0.860	1	1.090	1.247	1.514
10[a]	8.040	64.641	0.860	0	0.881	1.340	-
11	4.493	20.187	0.140	0	1.559	1.719	1.804
12	4.598	21.142	0.140	0	1.793	1.729	1.689
13[b]	6.848	46.895	0.140	0	1.083	1.802	-
14[a]	7.140	50.980	0.140	0	1.258	1.793	-
15	7.848	61.591	0.140	0	1.757	1.756	1.752
16	5.432	29.506	0.710	0	1.017	1.129	1.155
17[b]	4.053	16.427	0.710	0	1.749	1.010	-
18	3.802	14.155	0.710	1	1.513	1.424	1.389
19	6.848	46.895	0.710	0	1.143	1.147	1.143
20	6.848	46.895	0.710	0	1.053	1.147	1.169
21[a]	4.971	24.711	0.860	1	1.207	1.362	-
22	3.723	13.861	0.710	1	1.373	1.406	1.408

[a]Compounds from test set, [b]Compounds not included in the derivation of equation (1)

Where $y_{i,\ obsd}$ and $y_{i,\ cald}$ are the observed and calculated activity value of compound i, respectively and $\hat{y}_{,\ obsd}$ is the average of the observed activities of all compounds is supposed to be valid if $r^2_{cv} > 0.60$. From this point of view, the correlation expressed by equation (1) seems to be quite valid. However, the predictive ability of any correlation equation is measured by using it to predict the activity of the compounds in the test set and calculating the value of r^2_{pred}, which is defined as:

$$r^2_{pred} = 1 - [\Sigma_i (y_{i,\ obsd} - y_{i,\ pred})^2 / \Sigma_i (y_{i,\ obsd} - \hat{y}_{,\ obsd})^2] \quad .....(3)$$

Where $y_{i,\ pred}$ is the predicted activity of compound i. A value of $r^2_{pred} > 0.5$ signifies a good predictive ability of the correlation. For equation (1), r^2_{pred} value is as high as 0.892. The activity values predictive from this equation for test set compounds are given in Table 2. A comparison shows that these predicted values are in very good agreement with the corresponding observed ones. In the training set also, the calculated values are found to be in excellent agreement with the observed ones. All these observations can be better visualized in the graphs drawn between the calculated predicted and observed activities (Fig. 1 and 2).

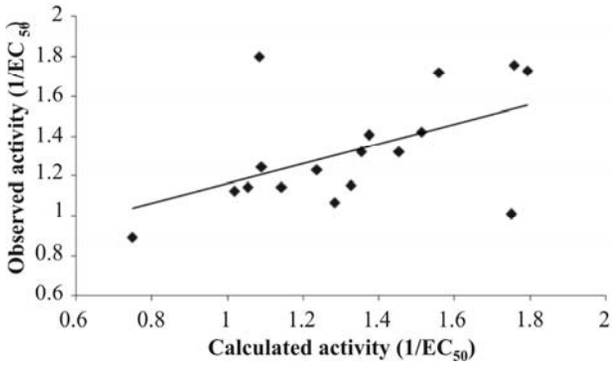


Fig. 1 Graph of observed *vs* predicted activity of training set compounds.

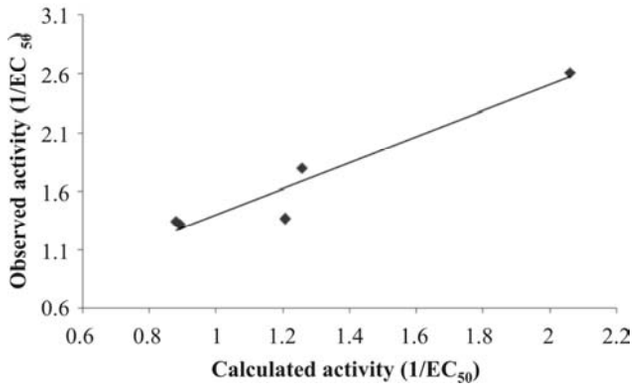


Fig. 2 Graph of observed *vs* predicted activity of test set compounds.

The indicator parameter *I* have positive coefficient in correlation suggesting that some R-substituents of particular nature will be contributing towards activity.

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