QSAR Study on Pyridinone Derivatives as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor: A Mixed Approach

P. Vasanthanathan[1,*], M. Lakshmi[1] and A. Raghuram Rao[2]

[1]*Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Chinhut, Lucknow, India,*
[2]*Medicinal Chemistry Division, University Institute of Pharmaceutical Science, Punjab University, Chandigarh, India*

Abstract: HIV-1 reverse transcriptase inhibitory activity of a series of substituted pyridinone derivatives (non-nucleoside) was subjected to classical QSAR study by using mixed approach (Hansch and Free-Wilson). The study was carried out with indicator parameter encoding different group contributions and some physico chemical parameters namely hydrophobic (π), electronic (σ), steric (MR) and STERIMOL values of aromatic substitutents. The best generated models were validated by leave-one- out technique (LOO-internal validation) and predicting the activity of the test (external validation). Further bootstrapping method was adopted to assess the robustness of the models. The analysis explores the substitutional requirements of the pyridinone moiety of the compounds for effective inhibition of HIV-1 RT enzyme.

Key Words: AIDS, QSAR, pyridinone derivatives, non-nucleoside, hansch analysis, hydrophobic constant.

INTRODUCTION

In the present era, Acquired Immuno Deficiency Syndrome (AIDS) is the most fatal disorder for which no completely successful chemotherapy has been developed so far. The pandemic spread of this disease has prompted an unprecedented scientific and clinical efforts to understand and combat it. The causative agent of AIDS has been identified as a retrovirus of the *Lentiviridae* family [1,2]. Two genetically distinct subtypes, HIV-1 and HIV-2, have been characterized [3, 4] of which the former has been found to be prevalent in causing the disease. The HIV-1 infection, which targets monocytes expressing surface CD-4 reports, eventually produces profound defects in cell mediated immunity. In course of time infection leads to severe depletion of $CD\text{-}4^+$ T-lymphocytes, resulting in opportunistic, neurologic and neoplastic diseases, and ultimately death [5].

The HIV cycle begins with high-affinity binding of viral gp-120 envelope protein to its receptor CD-4 on the host cell surface. The CD-4 receptor is a protein molecules found predominately on a subset of T-lymphocytes responsible for helper or inducer function in the immune response. Following binding, the fusion of virus with host cell membrane occurs *via* the gp-41 molecules and the HIV genome RNA is uncoated and internalized. The enzyme reverses transcription of genomic RNA in to double-stranded DNA. The DNA migrates in to nucleus to be integrated in to host cell chromosome through the action of virally encoded enzyme, *integrase.* The incorporation of this provirus in to the cell genome is permanent. The provirus may remain transcriptionally inactive or manifest a high level of gene expression with active production of virus. The activation of provirus from the latent state by selective and constitutive host transcription factors, notably the NF-K β family of DNA enhancer binding proteins, leads to the sequential production of various viral m-RNAs. Thus, the replicative cycle of HIV-1 present several viable targets that could be exploited for the development of anti-HIV chemotherapy. Ideally anti-HIV agents should arrest the virulence and further infection of healthy cells without displaying toxicity toward normal cellular physiology.

The process of reverse transcription of genomic RNA in to double stranded DNA by the RT is central to the replication of HIV. Therefore, the inhibition of this key biochemical event in the viral life cycle provides the most attractive targets for anti-HIV drug developments. In this, there are two classes of drugs developed namely nucleoside derivatives and non-nucleoside derivatives. Zidovudine (AZT), zalcitabine (DDC), didanosine (DDI), stavudine (D4T), lamivudine (3TC) and abacavir succinate and non-nucleoside RT inhibitors were developed (Nevirapine, delavirdine and efavirenz). Some of the potent inhibitors proceeded in to clinical developments (tivirapine and MKC-442) [6-8] also. Mechanism of inhibition of non nucleoside RT analogues has been found to be through non competitive interaction with an allosteric site, leading to inactivation of enzyme [9-10].

Quantitative Structure–Activity Relationship (QSAR) study is a useful tool for rational search of bioactive compounds. QSAR study describes a definite role in a quantitative term of a structural feature in a molecule with a definite contribution to the activity of a particular physiochemical property of the structural feature. Thus, QSAR studies have predictive ability and simultaneously provide deeper insight into the mechanism of drug receptor interactions. In continuation of our efforts to obtain potent model of QSAR of compounds for various biological interests [11-14], we present here a QSAR study in the pyridinone series [15] to discuss in quantitative term their relative biological merit and to provide guidelines for designing better analogues with superior pharmacokinetic and efficacy profiles.

EXPERIMENTAL WORK

All the compounds of Table **1** and Table **2** used in the QSAR analysis were those synthesized and screened by

*Address correspondence to this author at the Faculty of Pharmacy, Babu Banarasi Das National Institute of Technology and Management, Chinhut, Lucknow, India; Fax no: +915222815294;
E-mail: nobelvasanth@gmail.com

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Table 1. QSAR Parameters and HIV-RT Inhibition Activity of Pyridinone Derivatives-Figure 1

Comp. no	Substitutents			* pIC_{50}	*πR*	*σpR*	IVo/*s*	*BiR*	*MRR*	*LR*	*BiiR*	*FL*
	X	L	R_{Ar}									
1	O	$-CH_2CH_2-$	H	1.6382	0	0	1	1	-0.05	2.06	1	-0.1
2	O	$-CH_2CH_2-$	4-Me	0.4814	0.56	-0.07	1	1.52	-0.05	3	2.04	-0.1
3	O	$-CH_2CH_2-$	4-Cl	1.2076	0.71	0.23	1	1.8	-0.05	3.52	1.8	-0.1
4	O	$-CH_2CH_2-$	4-F	1.8239	0.14	0.06	1	1.35	-0.05	2.65	1.35	-0.1
5	O	$-CH_2CH_2-$	7-Me	1.3979	0.56	-0.07	1	1.52	-0.05	3	2.04	-0.1
6	O	$-CH_2CH_2-$	7-Cl	1.4089	0.71	0.23	1	1.3	-0.05	3.52	1.8	-0.1
7	O	$-CH_2CH_2-$	7-F	1.4317	0.14	0.06	1	1.35	-0.05	2.65	1.35	-0.1
8	O	$-CH_2CH_2-$	4,7-$(Me)_2$	1.5528	1.12	-0.14	1	3.04	-0.05	6	4.05	-0.1
9	O	$-CH_2CH_2-$	4,7-Cl_2	1.8538	1.42	0.46	1	3.6	-0.05	7.04	3.6	-0.1
10	O	$-CH_2CH_2-$	4,7-F_2	1.8538	0.25	0.12	1	2.7	-0.05	5.3	2.7	-0.1
11	O	$-CH_2CH_2-$	6-Me	0.7495	0.56	0	1	1.52	-0.05	3	2.04	-0.1
12	O	$-CH_2CH_2-$	6-F	0.3545	0.14	0	1	1.35	-0.05	2.65	1.35	-0.1
13	O	$-CH_2CH_2-$	5-F	-0.2304	0.14	0	1	1.35	-0.05	2.65	1.35	-0.1
14	S	$-CH_2CH_2-$	H	1.6197	0	0	0	1	-0.05	2.06	1	-0.1
15	S	$-CH_2CH_2-$	4,7-$(Me)_2$	1.2839	1.12	-0.14	0	3.04	-0.05	6	4.08	-0.1
16	S	$-CH_2CH_2-$	4,7-Cl_2	1.5228	1.41	0.46	0	3.6	-0.05	7.04	3.6	-0.1
17	S	$-CH_2CH_2-$	4,7-F_2	1.823	0.25	0.12	0	2.7	-0.05	5.3	2.7	-0.1
18	S	$-CH_2CH_2-$	4-F	1.886	0.14	0.06	0	1.35	-0.05	2.65	1.35	-0.1
19	S	$-CH_2CH_2-$	7-F	1.3665	0.14	0.06	0	1.35	-0.05	2.65	1.35	-0.1
20	S	$-CH_2CH_2-$	4-Cl	1.5228	0.71	0.23	0	1.8	-0.05	3.52	1.8	-0.1
21	S	$-CH_2CH_2-$	7-Cl	1.5376	0.71	0.23	0	1.8	-0.05	3.52	1.8	-0.1
22	NH_2	$-CH_2CH_2-$	H	-2.000	0	0	0	1	0.26	2.06	1	-0.51
23	O	$-OCH_2$	H	0.7189	0	0	1	1	0.26	2.06	1	-0.51
24	O	$-OCH_2$	4,7-Cl_2	1.0555	1.42	0.46	1	3.6	0.2	7.04	3.6	-0.18
25	O	SCH_2	4,7-Cl_2	1.0555	1.42	0.46	1	3.6	0.52	7.04	3.6	0.01
26	O	$SOCH_2$	4,7-Cl_2	1.9586	1.42	0.46	1	3.6	0.54	7.04	3.6	0.22
27	O	SO_2CH_2	4,7-Cl_2	-0.1461	1.42	0.46	1	3.6	-0.11	7.04	3.6	-0.74
28	O	$NHCH_2$	H	0.6882	0	0.46	1	1	-0.11	2.06	1	-0.74
29	O	$NHCH_2$	4,7-Cl_2	1.6989	1.42	0.46	1	3.6	0.07	7.04	3.6	-0.08
30	O	CH_2NH	H	-0.0969	0	0.46	1	1	0.07	2.06	1	-0.08
31	O	-CH=CH-[a]	H	-0.7708	0	0.46	1	1	-0.04	2.06	1	-0.13
32	O	-CH=CH-[b]	H	-0.4771	0	0.46	1	1	0.38	2.06	1	-0.28
33	O	$-CH_2-$	H	-1.65321	0	0.46	1	1	-0.05	2.06	1	-0.1
34	O	$-(CH2)_3-$	H	-1.20411	0	0.46	1	1	-0.05	2.06	1	-0.1

[a] Cis form , [b] Trans from, * activity values are given as pIC_{50}, which is the negative logarithm of 50 % inhibition concentration. π, Hydrophobic constant; *σp,* electronic constant; *IVo/s*, indicator variable; *Bi,Bii*, STERIMOL parameter; *MR*, Molar refractivity; *F*, Field effect.

Table 2. QSAR Parameters and HIV-RT Inhibition Activity of Pyridinone Derivatives-Figure-2

Comp. no	Substitutents			pIC_{50}	*Substituent constant*							
	R_5	R_6	R_{Ar}		*πR*	*σpR*	IVo/*s*	*BiR*	*MRL*	*LR*	*BiiR*	*FL*
35	Me	Me	H	0.7695	0	0.46	1	1	10.3	2.06	1	0.01
36	n-Pr	Me	H	1.08092	0	0.46	1	1	10.3	2.06	1	0.01
37	i-Pr	Me	H	1.31875	0	0.46	1	1	10.3	2.06	1	0.01
38	Ph	Me	H	-0.0413	0	0.46	1	1	10.3	2.06	1	0.01
39	CN	Me	H	0.50863	0	0.46	1	1	10.3	2.06	1	0.01
40	NH_2CO	Me	H	-1.6180	0	0.46	1	1	10.3	2.06	1	0.01
41	$OHCH_2$	Me	H	-0.5314	0	0.46	1	1	10.3	2.06	1	0.01
42	CH_3OCH_2	Me	H	-0.3222	0	0.46	1	1	10.3	2.06	1	0.01
43	Me_2N	Me	H	-0.2671	0	0.46	1	1	10.3	2.06	1	0.01
44	Et	H	H	0.75202	0	0.46	1	1	10.3	2.06	1	0.01
45	Me	Me	4,7-Cl_2	1.01322	1.42	0.46	1	3.6	10.3	7.04	3.6	-0.74
46	n-Pr	Me	4,7-Cl_2	1.46852	1.42	0.46	1	3.6	10.3	7.04	3.6	-0.74

***** Activity values are given as pIC_{50}, which is the negative logarithm of 50 % inhibition concentration. π, Hydrophobic constant; *σp,* electronic constant; *IVo/s*, indicator variable; *Bi, Bii*, STERIMOL parameter; *MR*, Molar refractivity; *F*, Field effect.

Haffman *et al*. [15]. The reported biological activity (IC_{50}) data was converted to pIC_{50} to get the linear relationship in the equation ΔG=-RT ln K,[16] (Table **1** and Table **2**). The physico-chemical parameters namely hydrophobic constant (π), molar refractivity (*MR*), Field effect *(F*), Resonance effect (*R*), electronic constant (σ *meta* and σ *para /ortho*) and STERIMOL parameters (*Bi, Bii, Biii, Biv, Bv* and *L*) have been calculated for concerned substituents as suggested by Hansch and Leo [17] (Table **4**). Apart from this we used some substituent parameter (indicator variables). The values of physico-chemical and indicator parameter are listed in Table **1** and Table **2**. The term and definition of descriptors contributed in the present analysis is given in Table **3**. The compound set (46 compounds) was first divided in to two major sets; the first set consisting of 25 and the second set consisting all 46 compounds. In these 25 compounds were further divided in to two set based on the structural diversity, one is the training set composed of 15 compounds (compound number 38, 36, 40, 41, 46, 23, 15, 17, 43, 45, 39, 29, 37, 30, 4) , another is test set composed of 10 (compound number 10, 3, 1,2, 6,5,12,21,14,16) compounds and we derived the equation 1-4. In another major set consisting of 46 compounds. 30 training compounds 26, 28, 12, 38, 32, 20, 2, 39, 45, 36, 44, 42, 35, 25, 33, 11, 19, 43, 46, 23, 29, 1, 7, 41, 16, 37, 31, 40, 34, 8 and 16 test com pounds (27, 5,21, 14,24,17,9,6,10,30,15,4,22,,13,3,18) were selected based on structural diversity and we have derived the equation 5-7. Then it has been validated by leave-one-out technique (internal validation) and predicted the activity of test set (external validation). Some compounds were excluded during derivation of QSAR equation because of presence of uncommon structural feature, non availability of parametric values or outlier behavior. The auto-correlated parameters were eliminated depending on their individual correlation with the biological activity in order to avoid simple collinearity problem. All possible combinations of parameters were considered for the QSAR study.

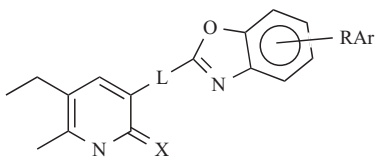

Fig. (1).

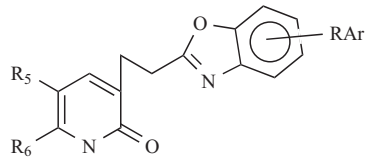

Fig. (2).

The predictive powers of the equations were validated by Leave-One- Out (LOO) cross-validation method [18]. Predicted residual sum of square (Spress), total sum of squares (SSY), cross-validated R^2 (Q^2), and standard deviation error of prediction (SDEP) were considered for the validation of these models.

The results from cross-validated analysis were expressed as the cross-validated squared correlation coefficient (Q^2). The Q^2 is defined as,

$$Q^2 = 1 - \sum (Y_{pred} - Y_{act})^2 / \sum (Y_{act} - Y_{mean})^2$$

Table 3. Terms and Definition of Indicator Variables

πR	Hydrophobic constant for substituent at R position
σpR	Electronic parameter sigma at para position of substituent R
IVo/s	Indicator parameter having 1 if oxygen is present at X position of pyridinone ring, value 0 otherwise.
BiR	STERIMOL constant for substituent at R position (width parameter)
MRL	Molar refractivity (steric parameter) for substituent at L position
LR	STERIMOL constant for substituent at R position (Length parameter)
BiiR	STERIMOL constant for substituent at R position (width parameter)
FL	Field effect for substituent at L position

Where Y_{pred}, Y_{act}, and Y_{mean} are predicted, actual and mean values of the target property ($-\log IC_{50}$) respectively. $\sum (Y_{pred} - Y_{actual})^2$ is the Predictive Residual Error Sum of Squares (Spress).

Spress is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. To further access the robustness and statistical confidence of the derived models, bootstrapping analysis was performed (25 runs). The r^2_{bs} is average squared correlation coefficient calculated during the validation procedure which is computed from a subset of variables used one at a time for the validation procedure. The statistical parameters which were considered to compare the generated QSAR models includes correlation coefficient (r), standard deviation (std), F-test, Cross-validated R^2 (Q^2). A data point is considered as an outlier if it has a large magnitude (when the residual value exceeds twice the standard error of estimate of the model). All the statistical work was calculated by *VALSTAT* software [19], which was developed in our laboratory.

RESULT AND DISCUSSION

Eqn.1 explains the importance of hydrophobicity and steric effect at position R and field effect at position L. These three parameter explains 80% of variance in activities. All regression coefficients of eqn.1 are significant at 95% levels. The 95% confidences of intervals of the regression coefficient are shown within parenthesis.

pIC_{50}= [1.68606(± 0.831985)] +*πR* [1.16113(± 0.385725)] +*MRR* [-0.156878(± 0.0788598)] +*FL* [-2.82229(± 3.63907)] n=15, r=0.896721, r^2=0.804108, variance=0.251497, std= 0.501495, F=15.0511, r^2_{bs} =0.842882, Q^2 =0.643468, Spress =0.676562, SDEP=0.579373, TEST r^2pred=0.431562 (Eqn-1)

here n is number of compounds, r is correlation coefficient, std, F, r^2_{bs}, Q^2, Spress, SDEP are standard deviation, probability factor related to F-ratio, bootstrapping squared correlation coefficient, Cross validated squared correlation coefficient, predictive residual error sum of square and standard deviation error of prediction respectively. Test predicted squared correlation coefficient is 0.431. But after removal of compound **30**,

pIC_{50}= [1.8662(± 0.596524)] + *πR* [1.20788(± 0.2731)] + *MRR* [-0.166236(± 0.0558207)] + *FL* [-1.90143(± 2.6264)] n=14, r=0.954098, r^2=0.910303, variance=0.120888, std= 0.347689, F=33.82, r^2_{bs} =0.671036 Q^2=0.700404, Spress= 0.635435, SDEP=0.537041,TEST r^2pred =0.628856 (Eqn-2)

Table 4. Tables of Physico-Chemical Parameters Used in this Study (Substituent Constant)

S.No	Substituents	Substituent constant						
		π	***MR***	***σp***	***σm***	***L***	***Bi***	***Bii***
1	H	0.00	0.10	0.00	0.00	2.06	1.00	1.00
2	CH_3	0.56	0.56	0.96	0.83	2.87	1.52	4.08
3	Cl	0.71	0.60	0.53	0.38	3.52	1.80	1.35
4	F	0.14	0.09	0.06	0.34	2.65	1.35	1.35
5	*n-Propyl*	1.55	1.50	0.32	0.31	4.92	1.52	3.49
6	*i-Propyl*	1.53	1.49	-0.05	-0.07	4.11	2.04	2.76
7	Ph	1.96	2.53	-0.01	0.66	6.28	1.70	1.70
8	CN	-0.57	0.63	0.66	0.56	4.23	1.66	1.60
9	NH_2CO	-0.97	1.49	0.00	0.21	5.15	1.50	3.61
10	CH_2OH	-1.03	0.71	0.00	0.00	3.37	1.52	2.70
11	CH_3OCH_2	-0.78	1.20	0.03	0.02	4.91	1.52	2.88
12	NMe_2	0.44	2.11	0.03	0.03	3.88	2.00	2.97

there is a tremendous improvement of equation-1to equation-2 statistically, i.e. it explain 91% variance in the biological activity and test predicted squared correlation coefficient is 0.6288. The presence of Field effect reveals that there is strong interaction between the electron rich substituents at L position with receptor. Negative contribution of this parameter demands for electron withdrawing group on the aromatic nucleus to enhance the inhibitory activity. The positive contribution between hydrophobic constant π and biological activity explain the possible hydrophobic interaction of the substituent at R position with the binding site.

pIC_{50}= [1.06046(± 1.29273)] + πR [0.953597(± 0.450673)] + *MRR* [-0.115622(± 0.0915389)] +*BiR* [0.179027(± 0.329464)] n=15, r=0.883302, r^2=0.780222, variance=0.282164, std= 0.531191, F=13.0168, r^2_{bs} =0.826314, Q^2=0.609694, Spress= 0.707882, SDEP= 0.606194, TEST r^2pred=0.814872

(Eqn-3)

Eqn-3 can explain 78% variance *vis-a-vis* predict 60.9% variance in reverse transcriptase inhibitory activity. All regression coefficient are significant at 95% level. The robustness and statistical confidence of the derived model is also quite good. The large, positive coefficient for the substituent parameter π in equation 3 indicates that hydrophobic substituents are favored, whereas the large, negative coefficient of *MR* indicates that sterically bulky substituents lower the binding affinity. *BiR* is the STERIMOL parameter for the substituent at R position. *Bi* is a measure of the width of the first atom of a substituent. Its positive contribution suggests that minimum width of a substituent is favorable for the inhibitory activity. These parameter and applications have been discussed [17].

Analysis of equation 4 reveals that STERIMOL length (L) parameter for the substituent R is found to dominate the activity. It explains 77.9 percent variance in the activity. It has good correlation (r=0.882) and high statistical significance >95% and standard deviation (0.532). Eqn.3 with good Q^2 (0.608) is proposed as the acceptable equation describing inhibition of HIV-1 RT activity.

pIC_{50}= [1.05834 (± 1.31004)] +πR [0.956304 (± 0.450923)] +*MRR* [-0.116159(± 0.0915962)] + *LR* [0.091635 (± 0.171746)]
n =15, r=0.882774, r^2=0.779291, variance = 0.28336, std =0.532315, F=12.9464, r^2_{bs},= 0.814349, Q^2= 0.608752, Spress= 0.708736, SDEP=0.606926, TEST r^2pred =0.818346

(Eqn-4)

HIV-1 Reverse transcriptase inhibitory activity of 46 compounds were subjected to multiple regression with 30 training compounds and 16 test set and the best model selected from this analysis is given as equation 5

pIC_{50}= [0.5653(± 2.03912)] + πR [-0.117623(± 3.79305)] +σpR [-2.38755(± 2.22205)] +*IVo/s* [-0.365691(± 1.03479)] +*BiR* [1.45512(± 2.27845)] +*BiiR* [-0.87684 (± 1.9205)] n=30, r=0.763969, r^2 = 0.583649 , std=0.732199, F=5.37364, Q^2=0.376359, Spress= 0.896122 , SDEP=0.78464

(Eqn-5)

Eqn-5 shows explained variance of 58.3% and predicted variance of 37.6% from this eqn-5 we have removed comp. no 33, because it behaved as an outlier, and we got eqn-6.

pIC_{50}= [0.528215(± 1.79612)] + πR [-0.250969(± 3.34209)] +σpR [-2.69733(± 1.97052)] +*IVo/s* [-0.365023(± 0.911366)] +*BiR* [1.31597(± 2.00935)] +*BiiR* [-0.721829(± 1.69535)] n=29, r=0.793441, r^2 = 0.629548, variance=0.413455, std= 0.643005, F=6.23115 (Eqn-6)

Eqn-6 is statistically better than eqn-5 as there is a tangible increase in the predicted variance and explained variance. And again eqn-6 show one outlier (compound number 34), when this compound was excluded, there is tremendous improvement in the predicted and explained variance of equation 7, standard deviation and F values also are better than eqn-5 and 6. The predicted squared correlation coefficient of test compound is 0.673.

pIC_{50}= [0.4947(± 1.60288)] + πR [-0.37148 (± 2.98367)] +σpR [-2.97729 (± 1.77249)] + *IVo/s* [-0.36442(± 0.8132)] +*BiR* [1.19021(± 1.79574)] +*BiiR* [-0.581739(± 1.51689)]
n = 28 , r= 0.820661 , r^2 = 0.673485 std = 0.572094, F= 7.21925, Q^2 = 0.427777, Spress= 0.757353, SDEP=0.655887 , TEST r^2 = 0.673485

(Eqn-7)

The parameters contributed in this equation are Hydrophobic constant for substituent R (πR) and STERIMOL width parameter for substituent R *(BiR)* which is already discussed in eqn-1-4. The coefficient of STERIMOL parameter for substituent R *(BiiR)* indicate that moderate width of substituent enhance the inhibitory activity. Negative contribution of electronic constant for *para* substituted substituent in aromatic ring show that it is detrimental for the activity. Here it reflects the importance of *ortho* or *meta* substitution in aromatic ring which favors the biological activity. Indicator parameter (*IV o/s*) suggest that presence of sulphur or amino group at position x of the pyridinone nucleus which is favorable for inhibitory activity while a oxygen atom at the same position decrease the affinity, this may be due to electron density difference in atom that may favor interaction with binding site.

From all the above observations, it can be concluded that the substituent that increases the electron density on the phenyl ring appear to increase binding affinity and positive correlation with hydrophobicity which frequently correlates between ligand and receptor interaction. This is thought to be a reflection of hydrophobic facilitation of membrane penetration. Steric bulk on the ring is not detrimental to the activity as is evident from positive *BiR* and *BiiR* coefficient, which is also an indication that these compounds may be protected from the degradation inside the biological system. Negative contribution of indicator variable *IVo/s* suggests sulphur or amino group on x position of pyridinone ring favor the inhibitory activity. Now, it is clear from the above discussion that the binding of non-nucleoside reverse transcriptase inhibitors in their binding with receptor involve mainly the hydrophobic interaction and only a few polar interaction or hydrogen bonding. The above QSAR studies may throw

some light on the substitutional requirements for the further development of these compounds for more potent activity.

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REFERENCES

[1] Barre–sinoossi, F.; Chermann, J.C.; Rey, F.; Nugergre, M.T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun,F.; Rouziouz, C.; Rozenbaum, W.; Montagnier, L. *Science*, **1983**, *220*, 868.

[2] Popovic, M.; Sarngadharan, M.G.; Read, E.; Gallo, R.C. *Science*, **1984**, *224*, 497.

[3] Clavel, F.; Guyader, M.; Guetard, D.; Salle, M.; Montagnier, L.; Alizon, M. *Nature*, **1986**, *324*, 891

[4] Guyader, M.; Emerman, M.; Sonigo, P.; Clavel, F.; Montagnier, L.; Alizon, M. *Nature*, **1987**, *326*, 662.

[5] Embretson, J.; Zupancic, M.; Ribas, J.L.; Burke, L.; Racz, P.; Tenner-Racz, K.; Haase, A. T. *Nature*, **1993**, *362*, 359.

[6] De Clercq, E. *II Farmaco,* **1999**, *54*, 26.

[7] http:/www.niaid.nih.gov/daids/dtpdb/fdadrug.htm

[8] Garg, R.; Gupta, S.P.; Gao, H.; Babu, M.S.; Debnath, A.K.; Hansch. C. *Chem. Rev.* **1999**, *99*, 3525.

[9] De Clercq, E. *Med. Res. Rev*. **1993**, *13*, 229.

[10] De Clercq, E. *Exp. Opin. Invest. Drugs*, **1994**, *3*, 253.

[11] Vasanthanathan P.; Lakshmi M.; Arockia babu. M; Gupta. A.K.; Kaskhedikar. S.G. *Chem. Pharm. Bull*., **2006**, *54*(4), 583.

[12] Lakshmi, M; Dixit, A; Saxena, A.K. *Indian J. Chem,* **2006**, *45A*, 34.

[13] Vasanthanathan P.; Lakshmi M.; Arockia babu. M; Kaskhedikar. S. G. *Bio. Pharm. Bull*., **2006** *29*(6), 1262.

[14] Vasanthanathan P.; Lakshmi M.; Arockia babu. M; Kaskhedikar. S. G. *Med. Chem*., **2006**, 2(4), 363.

[15] Hoffman, J.M.; Smith, A.M.; Rooney, C.S.; Fisher, T.E.; Wai, J.S.; Thomas, C.M.; Bamberger, D.L.; Barnes, J.L.; Williams, T. M.; Jones, J.H.; Olson, S.D.; O'Brien, J.A.; Goldman, M.E.; Nunberg, J.H.; Quintero, J.C.; Shileif, W.A.; Emini, E.A.; Anderson, P.S. *J. Med. Chem*., **1993**, *36*, 953.

[16] Kubinyi, H. QSAR Hansch and related approaches in methods and principles in medicinal chemistry, vol.1, VCH, Wienheim. **, 1993.**

[17] Hansch C., Leo A., Exploring QSAR — Fundamentals and Applications in Chemistry and Biology; Heller, S.R., Ed.; *American Chemical Society*: Washington, DC, **1995**.

[18] Wold, S.; Eriksson, L. *Chemometric Methods in Molecular Design*, Edited by Waterbeemd H van de (VCH, Weinheim), **1995**, 321.

[19] Gupta, A.K.; Arockia babu, M.; Kaskhedikar, S.G. *Indian J. Pharm. Sci.*, **2004**, *66*, 396.

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