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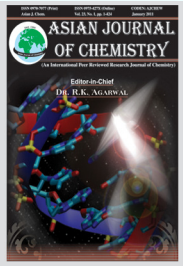

QSAR Studies on 3-Iodo-4-phenoxypyridinone Series Against HIV-1 Activity

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The QSAR studies have been carried out on a set of 27 molecules of 3-iodo-4-phenoxypyridinone series which were reported as inhibitor of HIV-1. The present study was undertaken to identify the important physico chemical parameters that affect the antiviral (anti HIV-1 activity) of the given series of drug molecules. The best QSAR model thus obtained, have high statistical significance (> 99.9 %) and moderate correlation coefficient (r = 0.795) led us to know that molar refractivity and resonance are showing negative effect on the pyridinone moiety, whereas the field effect is positively influencing the moiety. As there is only one substituent one can see the steric effect is negative for the result.

Key Words: QSAR, 3-Iodo-4-phenoxypyridinone series, Multiparameter regression, Descriptors.

INTRODUCTION

The initial discovery that acquired immunodeficiency syndrome (AIDSa) is caused by the human immunodeficiency virus (HIV), the disease has grown into a global pandemic. At the end of 2005, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported more than 4 million new cases of HIV infection for the year, bringing the worldwide number of HIV-infected individuals up to more than 40 million[1]. Given the rate at which HIV infection is spreading, despite the current number of AIDS therapeutics and vast resources being poured into AIDS research, it is quite clear that curbing the spread of AIDS is becoming one of the most challenging medical problems of the century.

The regimen has been successful in reducing the morbidity and mortality associated with AIDS progression to a level at which the disease can be treated as a chronic ailment with associated drug toxicities[2-4]. Non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs), *albeit* not the mainstays of HIV/AIDS treatment, have become increasingly important in highly active antiretroviral therapy (HAART) due to their unique mechanism of action. The 3-iodo-4-phenoxypyridinone (IOPY) is representative of a new family of pyridinone based non-nucleoside reverse transcriptase inhibitors (NNRTI's) which are highly active *in vitro* against a broad panel of HIV-1 mutant strains encountered in AIDS patients[5].

In order to identify the essential physico-chemical and structural parameters for anti-HIV activity, the QSAR studies have been carried out and are reported here.

EXPERIMENTAL

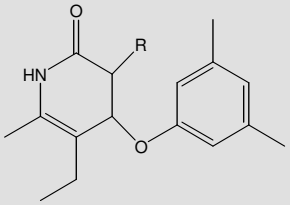
All the 27 molecules were considered for the QSAR analysis (Table-1)[6]. The inhibitory activity of the compounds was expressed as IC_{50} value in the nanomolar range (nM). The IC_{50} values were converted into -log IC_{50} for the use in the QSAR studies.

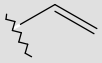
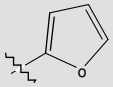
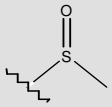
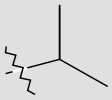
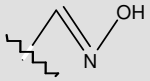
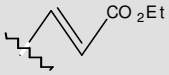
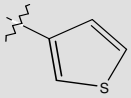
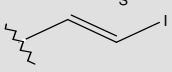
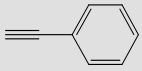
The molecules (Table-1) were rationally divided into the training set (21 molecules) and test set (6 molecules) according to their biological activity (-log IC_{50}) and structural features so that both the sets represents almost entire range of biological activity.

The QSAR analysis was carried out on these compounds for their anti HIV activity IC_{50} (nm) as dependent and different physico-chemical parameters[7] such as hydrophobicity (π), molar refractivity (MR), field effect (F) and resonance effect (R) as independent variable. These independent variables were evaluated by Hansch constant. The parameters used in the study are hydrophobicity π: $R_1\pi$ (hydrophobicity for position R_1); field effect F: R_1F (field effect for R_1); molar refractivity MR: R_1MR (molar refractivity for R_1); resonance effect R: R_1R (resonance effect for R_1). In Table-1, we gave only those values which were involved to predict the best model than other models.

The values for physico-chemical parameters were taken from the literature[8]. The multiparameter regression analysis was executed on personal computer using Systat version 7.2[9]. Pearson correlation matrix (Table-2) was constructed to determine the intercorrelation between physico-chemical parameters used in QSAR analysis.

TABLE-1
BIOLOGICAL ACTIVITIES AND PHYSICO-CHEMICAL DATA FOR 3-IODO-4-PHENOXYPYRIDINONE SERIES



Compd. No.	Substituents	Values of the Hansch parameters used			-log IC_{50}	
	R	RMR	RF	RR	Obser.	Calcd.**
1*	CH_2OH	7.19	0.00	0.00	-1.2988	-1.7643
2	Br	8.88	0.44	-0.17	-0.2988	-0.0331
3*	Cl	6.03	0.41	-0.15	-0.7993	-1.1134
4		10.99	0.07	-0.08	-0.4913	-1.3161
5		19.97	0.42	-0.62	-1.1986	-1.3179
6		27.22	0.40	-0.19	-1.0969	-1.6587
7	Et	10.30	-0.05	-0.10	-0.4913	-1.3403
8		13.53	-0.03	-0.19	-0.7993	-1.1134
9	SMe	13.82	0.20	-0.18	-0.2988	-0.8193
10#		13.70	0.52	0.01	-1.1986	1.36641
11#	SPh	33.55	0.36	-0.19	-1.0000	-2.2999
12*	OMe	7.87	0.26	-0.51	-0.3979	1.6101
13	CF_3	5.02	0.38	0.19	-0.4913	-1.7326
14		14.96	-0.05	-0.10	-1.2988	-1.7643
15	I	13.94	0.40	-0.19	-0.0969	-0.4502
16	CO_2Et	17.47	0.33	0.15	-2.8000	-2.7300
17		10.28	0.25	-0.13	-1.4996	-0.6870
18		27.43	0.40	0.07	-3.8000	-3.0883
19		17.15	0.07	-0.08	-1.8000	-1.8766
20	H	1.03	0.00	0.00	-2.5998	-0.9577
21*	$CONMe_2$	19.22	0.34	0.05	-3.7007	-2.3304
22		15.52	0.03	-0.21	-1.5998	-1.0882
23*		28.11	0.42	-0.27	-1.6998	-1.2731
24*		23.90	0.47	-0.27	-2.0000	-0.8085
25		18.42	0.23	-0.18	-2.0969	-1.1891
26	Set	6.33	0.51	0.19	-1.8998	-1.6400
27	CN	33.21	0.12	0.05	-4.1999	-3.9619

*Compounds included in the test set; **It is the activity calculated from equation 5; # Compound as outlier. RMR = Molar refractivity for R; RF = Field effect for R; RR = Resonance effect for R.

TABLE-2
PEARSON CORRELATION MATRIX

	$-\log IC_{50}$	RMR	RF	RR
$-\log IC_{50}$	1.000			
RMR	-0.541	1.000		
RF	0.015	0.059	1.000	
RR	-0.464	-0.095	0.357	1.000

RMR = Molar refractivity for R; RF = Field effect for R;
RR = Resonance effect for R.

RESULTS AND DISCUSSION

Different combination of physico-chemical parameters (independent) showing some acceptable correlation with the biological activity (dependent) were carried out using stepwise multiple regression analysis in order to develop QSAR equations.

$$-\log IC_{50} = -0.067(\pm0.024)\ RMR - 3.128(\pm1.163)\ RR - 0.701(\pm0.423) \quad (1)$$

N = 21, r = 0.640, r^2 = 0.409, s = 0.908, F = 6.233

$$-\log IC_{50} = -0.071(\pm0.025)\ RMR + 0.938(\pm1.067)\ RF - 3.245(\pm1.178)\ RR - 0.877(\pm0.471) \quad (2)$$

N = 21, r = 0.659, r^2 = 0.435, s = 0.914, F = 4.360

On careful analysis of these equations as these were not giving efficient result compound number **10** and **11** were identified as outliers. Thus removal of them led to the following equations which are significantly improved and giving more efficient result as well.

$$-\log IC_{50} = -0.097(\pm0.027)\ RMR - 5.488(\pm1.517)\ RR - 1.875(\pm0.1.191)\ RF + 0.103(\pm0.251)\ Rp - 0.909(\pm 0.472) \quad (3)$$

N = 19, r = 0.797, r^2 = 0.636, s = 0.803, F = 6.106

$$-\log IC_{50} = -0.088(\pm0.024)\ RMR - 4.551(\pm1.435)\ RR - 0.506(\pm0.408) \quad (4)$$

N = 19, r = 0.752, r^2 = 0.566, s = 0.820, F = 10.432

$$-\log IC_{50} = -0.091(\pm0.023)\ RMR + 5.425(\pm1.467)\ RR - 1.629(\pm0.599)\ RF - 0.864(\pm0.446) \quad (5)$$

N = 19, r = 0.795, r^2 = 0.631, s = 0.780, F = 8.561

where, N is the number of compounds from which the equation was calculated, r is the correlation coefficient, s is the standard deviation of the regression and F is the value of Fischer's test for overall significance of the equation.

Among these equations, the eqn. 5 with highest correlation coefficient (r = 0.795) with r^2 = 0.631 was considered to be the best model. The low standard error of estimate (s) and a high F value suggests that the model is statistically highly significant. The data showed overall statistical significance > 99.9 % with F = 8.561 against tabulated value for Fischer's test at 99.9 % significance [$F_{3,15\ \alpha0.001(obs.)}$ = 3.06].

Among several equations, we can see eqn. 5 is the best from the rest, as eqn. 4 is having four parameters whereas based on the criteria that there should be a minimum of five molecules for each parameter and eqn. 3 is having low efficient value of r and having high standard deviation. The correlation between observed and predicted activities of all compounds using eqn. 3 (best equation) has been represented graphically as shown in Fig. 1.

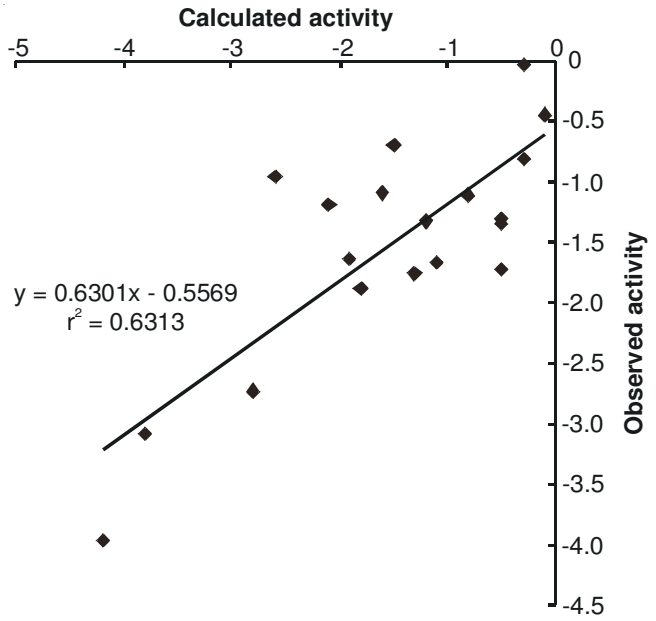


Fig. 1. Observed *vs.* predicted activity (IC_{50}) for training set of 19 compounds

It is clear from eqn. 5, that molar refractivity and resonance are showing negative effect on the pyridinone moiety whereas the field effect is positively influencing the moiety. As there is only one substituent one can see the steric effect is negative for the result.

External validation: The validation of the best model (eqn. 5) has been done on a test set of 6 compounds where good correlation (r^2 = 0.6872) was observed between the predicted and the observed activity. The eqn. 6, Fig. 2 describes the correlation between observed (y) and predicted (x) activities of test set.

$$y = 0.9888x + 0.9223 \qquad r^2 = 0.6872 \quad (6)$$

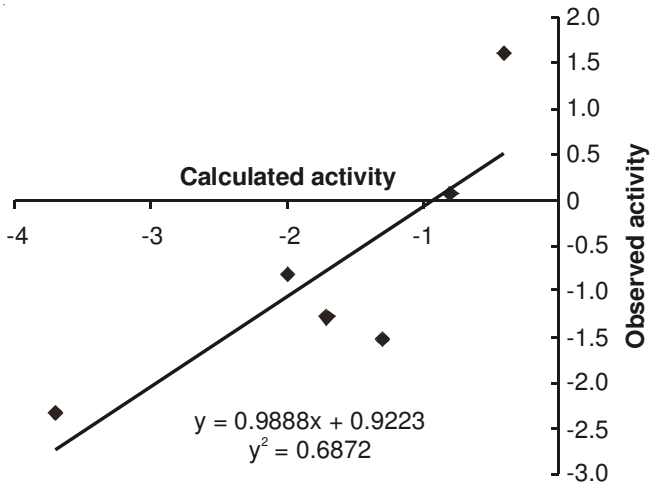


Fig. 2. Observed *vs.* calculated activity for test series

Conclusion

Thus, above 2D QSAR analysis led to the identification of important physico-chemical parameters in explaining the variation in activity in 27 molecules. The above discussion shows that the activity is highly influenced by the field effect of pyridinone moiety whereas molar refractivity and resonance effects are showing negative effect on the moiety. Hence, the

model can be useful in the optimization of the activity in this class of molecules leading to the improved inhibitors for assessment as anti HIV therapeutics.

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REFERENCES

1. AIDS Epidemic Update, Joint United Nations Programme on HIVAIDS (UNAIDS), Geneva, pp. 1-98 (2005).
2. P. Bean, *Am. Clin. Lab.*, **21**, 12 (2002).
3. W.G. Powderly, *J. AIDS*, **31**, 3 (2002).
4. U.A. Walker, *J. HIV Ther.*, **6**, 17 (2001).
5. A. Benjahad and J. Guillemont, *Bioorg. Med. Chem. Lett.*, **13**, 4309 (2003).
6. A. Benjahad and S. Oumouch, *Bioorg. Med. Chem. Lett.*, **17**, 712 (2007).
7. C. Hansch, A. Leo and D. Hoekmon, In Exploring QSAR: Hydrophobic, Electronic and Steric Constants, American Chemical Society, Washington DC, Vol. 2, p. 1 (1995).
8. C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley-Interscience, New York, p. 48 (1979).
9. Systat, SPSS Inc., 444 North Michigan Avenue, Chicago, IL 60611, USA.