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QSAR Studies on the N-Aryl-oxazolidinone-5-carboxamides Against HIV-1 Protease

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N-Aryl-oxazolidinone-5-carboxamides are new effective target against the HIV-1 protease. Quantitative structure activity relationship (QSAR) has been carried out in this series. The data set was divided into two subsets *i.e.* training set and test set. The 2D QSAR studies activity is negatively influenced by the resonance effect at position R_3. The best QSAR model with good correlation coefficient ($r^2 = 0.859$), of high statistical significance (> 99.9 %) well explained the variance in activity.

Key Words: QSAR, N-Aryl-oxazolidinone-5-carboxamides.

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) protease plays a critical role in the virus life cycle by processing the viral Gag and Gag-Pol polyproteins into structural and functional proteins essential for viral maturation. Inhibition of HIV-1 protease leads to the production of non infectious virus particles and hence is a promising therapeutic target for antiviral therapy in AIDS patients[1]. One possible strategy to reduce the probability of drug resistance is to design inhibitors that interact with the same residues of HIV-1 protease that are necessary to recognize the substrate[1].

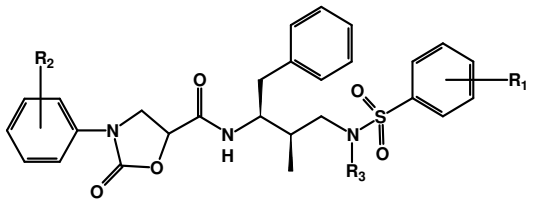
The different functional groups of N-aryl-oxazolidinone-5-carboxamides are utilized as P2 ligands in HIV-1 protease inhibitors.

QSAR studies have been demonstrated to be an effective computational tool in understanding the correlation between the structure of molecules and their activities[2]. HIV infection remains incurable although there are several drugs against it. Therefore it's an upcoming job to design a better potent drug against HIV.

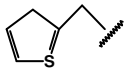
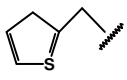
EXPERIMENTAL

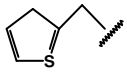
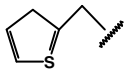
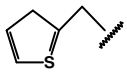
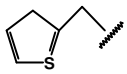
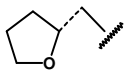
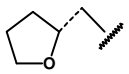
In present study, a set of 38 molecules was investigated (Table-1). The QSAR analysis was carried out on these compounds for their anti HIV activity Ki (nm) as dependent and different physicochemical parameters[3] such as hydrophobicity (Pi), molar refractivity (MR), field effect (F) and

TABLE-1
BIOLOGICAL ACTIVITIES AND PHYSICO-CHEMICAL DATA FOR N-ARYL-OXAZOLIDINONE-5-CARBOXAMIDES



Compd. no.	Substitution			Values of the Hansch parameters used	-log IC_{50}	
	R_1	R_2	R_3	R_3F	Obsvd.	Calcd.
1	4-OCH_3	H		-0.09	1.0000	1.00563
2	4-OCH_3	3-F		-0.09	1.0809	1.00563
3*	4-OCH_3	3,4-diF		-0.09	1.1804	1.00563
4	4-OCH_3	3-CF_3		-0.09	2.2218	1.00563
5	4-OCH_3	3-Ac		-0.09	3.0969	1.00563
6*	4-OCH_3	4-Ac		-0.09	2.3979	1.00563
7	4-OCH_3	3-OCH_3		-0.09	1.3467	1.00563
8	4-NH_2	H		-0.09	0.2757	1.00563
9	4-NH_2	3-F		-0.09	0.7695	1.00563
10*	4-NH_2	3,4-diF		-0.09	0.6382	1.00563
11	4-NH_2	3-CF_3		-0.09	1.3767	1.00563
12	4-NH_2	3-Ac		-0.09	1.4948	1.00563
13	4-NH_2	4-Ac		-0.09	0.7351	1.00563

14*	3,4-OCH_2O)-	3-F		-0.09	0.9706	1.00563
15	3,4-OCH_2O)-	3,4-diF		-0.09	1.0705	1.00563
16	3,4-OCH_2O)-	3-CF_3		-0.09	1.7958	1.00563
17	3,4-OCH_2O)-	3-Ac		-0.09	2.2218	1.00563
18*	3,4-OCH_2O)-	4-Ac		-0.09	1.7958	1.00563
19	3-F,4-OCH_3	3-F		-0.09	1.1549	1.00563
20	3-F,4-OCH_3	3,4-diF		-0.09	0.4647	1.00563
21	3-F,4-OCH_3	3-CF_3		-0.09	1.1426	1.00563
22*	3-F,4-OCH_3	3-Ac		-0.09	0.8761	1.1057
23	3-F,4-OCH_3	4-Ac		-0.09	1.0969	1.00563
24	4-OCF_3	3CF_3		-0.09	-1.0000	1.00563
25	4-OCF_3	3-Ac		-0.09	-0.3010	1.1057
26*	3-OCH_3	H		-0.09	-0.5797	1.1057
27	3-OCH_3	4-Ac		-0.09	0.0757	1.00563
28	4-OCH_3	3-F		-0.10	0.5900	1.00563
29	4-OCH_3	3,4-diF		-0.10	0.2365	1.00563
30*	4-OCH_3	4-Ac		-0.10	0.0969	1.00563
31	3-OCH_3	H		0.22	-2.3778	-2.09654
32	3-OCH_3	3-F		0.22	-2.2760	-2.19661

33	3-OCH_3	4-Ac		0.22	-1.4698 -2.19661
34*	2,4,5-triF	H		0.22	-2.2309 -2.09654
35	2,4,5-triF	3-F		0.22	-2.2046 -2.09654
36	2,4,5-triF	4-Ac		0.22	-2.2245 -2.09654
37*	3-OCH_3	H		0.23	-1.6232 -2.09654
38	3-OCH_3	3-F		0.23	-2.1760 -2.09654

*Compounds included in the test set.

resonance effect (R) as independent variable. These independent variables were evaluated by Hansch constant. The total of 38 compounds was divided into training and test set of 32 and 6 compounds, respectively. The training set of 32 compounds was analyzed for correlation between the variation in inhibitory activity. The values for physico-chemical parameters were taken from the literature[4]. The multiparameter regression analysis was executed on personal computer using Systat version 7.2[5]. Pearson correlation matrix (Table-2) was constructed to determine the intercorrelation between physico-chemical parameters used in QSAR analysis.

TABLE-2
PEARSON CORRELATION MATRIX

	-log BA	R_3F
-log BA	1.000	
R_3F	-0.858	1.000

RESULTS AND DISCUSSION

Different combination of physio-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. The equations are of statistical significance with correlation value > 0.859 and with regression coefficient values significant more than 99.9 %.

$$-\log BA = -11.196(\pm1.981)\ R_3F + 0.208(\pm0.288)\ R_3MR - 4.051(\pm5.761)$$
$$N = 32,\ r = 0.861,\ r^2 = 0.742,\ s = 0.760,\ F = 41.672 \quad (1)$$

$$-\log BA = -11.196(\pm1.981)\ R_3F + 0.208(\pm0.28)\ R_3MR - 4.051(\pm5.761)$$
$$N=32,\ r = 0.861,\ r^2 = 0.742,\ s = 0.760,\ F = 41.672 \quad (2)$$

$$-\log BA = -10.222(\pm1.137)\ R_3F - 0.740(\pm0.310)\ R_2Pi +$$
$$0.048(\pm0.077)\ R_1MR_1 - 0.210(\pm0.566) \quad (3)$$

$$-\log BA = -10.007(\pm1.091)\ R_3F + 0.105(\pm0.138) \quad (4)$$
$$N = 32,\ r = 0.859,\ r^2 = 0.737,\ s = 0.754,\ F = 84.167$$

where the N is the number of compounds from which the equation was calculated, r^2 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.

From above equation, it is clear that substituent at position R_3 effects biological activity of the parent compound significantly. In the various descriptors, taken for study, field effect the biological activity negatively.

Conclusion

Among these equations, the eqn. 4 was considered to be the best model with correlation coefficient (r = 0.859) explaining 73.7 % variance in activity. The low standard error of estimate(s), a high F value and one-third value of coefficients suggests that the model is statistically highly significant. The data showed overall statistical significance > 99.9 % with F = 84.167 against tabulated value for Fischer's test at 99.9 % significance [$F_{1,30a0.001} = 13.29$]. The above model (eqn. 4) also predicted well the inhibitory activity of the molecules of the test set as shown in Fig. 1, where the comparable correlation coefficient value (r = 0.859) was observed.

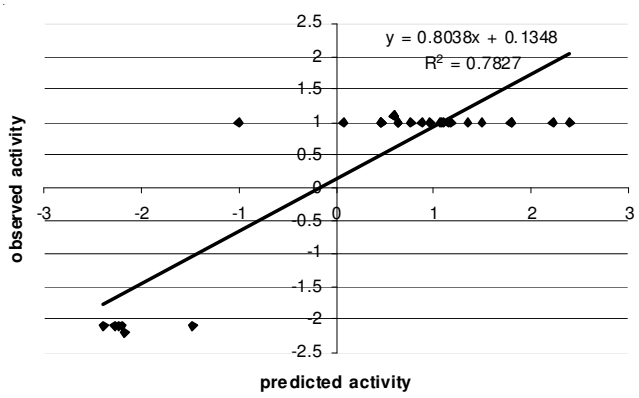


Fig. 1. Observed *vs.* predicted activity (Ki) for 32 compounds

The above studies indicate that due to the negative contribution by R_3F, the molecules having the resonance effect at R_3 position should not be preferred.

External validation: The validation of the best model (eqn. 4) has been done on a test set of 6 compounds where good correlation ($r^2 = 0.752$) was observed between the predicted and the observed activity. The eqn. 5 describes the correlation between observed (y) and predicted (x) activities of test set (Fig. 2).

$$y = 0.8343x - 0.0644 \quad r^2 = 0.752 \tag{5}$$

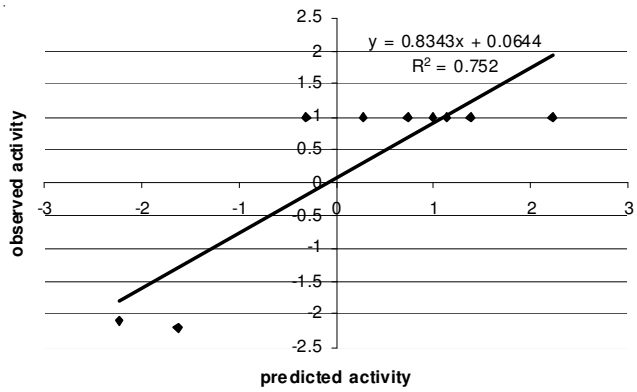


Fig. 2. Observed *vs.* predicted activity (Ki) for 6 compounds

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