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PREDICTION OF ANTI-HIV ACTIVITY OF PHENYL ETHYL THIOUREA (PET) DERIVATIVES: QSAR APPROACH

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In the present work, quantitative structure activity relationship studies were performed on a series of phenyl ethyl thiourea (PET) derivatives as anti-HIV agents. Stepwise multiple linear regressions analysis was applied to identify the structural and physicochemical requirements for anti-HIV activity, which was further evaluated for statistical significance and predictive power by internal and external validation. The developed QSAR indicates that the coefficient of density and van der Waal's energy shows that the activity increases with increase in density and van der Waal's energy of molecules. The coefficient of molar refractivity shows that the activity decreases with increase in volume and critical pressure of the molecules is detrimental to activity. The information generated from the present study may be useful in the design of more potent PET derivatives as anti HIV agents.

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Keywords: QSAR; anti-HIV; phenyl ethyl thiourea derivatives

1. Introduction

V- 1 (Human Immunodeficiency Virus Type-1) is the pathogenic retrovirus and causative agent of AIDS or AIDS- related complex (ARC) [1]. When viral RNA is translated into a polypeptide sequence, it is assembled in a long polypeptide chain, which includes several individual proteins namely, reverse transcriptase, protease, integrase, etc. Before these enzymes become functional, they must be cut from the longer polypeptide chain.

Acquired immune deficiency syndrome (AIDS) is a formidable pandemic that is still wreaking havoc world wide. The catastrophic potential of this virally caused disease may not have been fully realized. The causative moiety of the disease is human immunodeficiency virus (HIV), which is a retrovirus of the lentivirus family [2]. The three viral enzymes; reverse transcriptase, protease and integrase encoded by the gag and gag-pol genes of HIV play an important role in the virus replication cycle. Among them, viral reverse transcriptase (RT) catalyzes the formation of proviral DNA from viral RNA, the key stage in viral replication. Its central role in viral replication makes RT a prime target for anti-HIV-therapy [3].

Two main categories of HIV RT inhibitors have been discovered to date. The first category of inhibitors is nucleoside analogues (e.g., AZT, 3TC, ddI, ddC) and the second category of inhibitors is nonnucleoside analogues. Nevirapine, delaviridine and efavirenz are the only nonnucleoside reverse transcriptase inhibitors (NNRTI) that have received regulatory approval with several NNRTIs (MKC442, Troviridine, S-1153/ AG1549. PNU142721, ACT and

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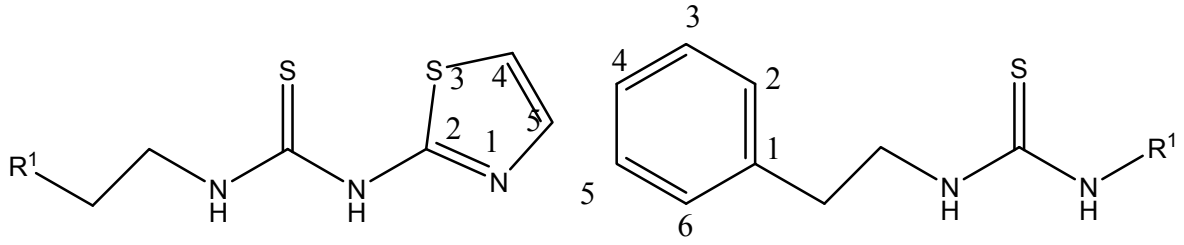
HBY1293/GW420867X) are currently undergoing clinical trials. Efavirenz was the first potent anti-HIV drug to be approved by FDA and studies have shown that efavirenz penetrates into the cerebrospinal fluid, a common viral sanctuary. The therapeutic efficacy of the drug is mainly restricted due to the development of viral resistance associated with mutations that includes K103N, L1001 and Y188L [4].

QSAR analyses of HIV-1 reverse transcriptase inhibitors [5], HIV-1 protease inhibitors [6,7] and HIV-1 integrase inhibitors [8] and gp 120 envelope glycoprotein [9] were reported. The present group of authors has developed a few quantitative structure-activity relationship models to predict anti-HIV activity of different group of compounds [10-22]. As a part of ongoing efforts to design novel molecules with potent anti-HIV activity, a QSAR analysis was performed to relate anti-HIV activity of PET [23,24] derivatives to its physicochemical properties using modeling software WIN CAChe 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan) and statistical software STATISTICA version 6 (StatSoft, Inc., Tulsa, USA).

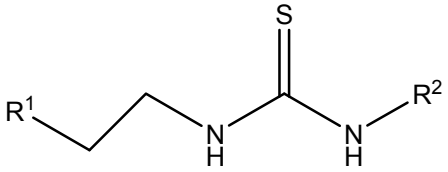
2. Modeling

In the present work we have taken 71 PET compounds and their anti-HIV activity from the reported work [23,24]. Many of these compounds inhibited wild type HIV-1 with ED_{50} values between 0.001 μM and 0.005 μM in MT-4 cells. One of these thiourea derivatives troviridine showed good anti-HIV activity (0.02 μM, in clinical trial) with low cytotoxicity for MT4 cells [24]. There is

Table 1. Structures of PET analogs.



Compound 1- 25 Compound 26-38

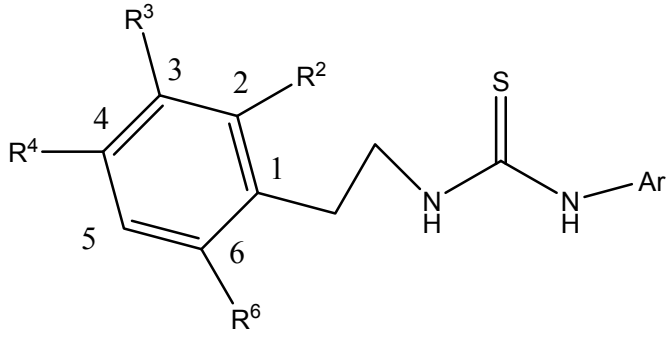


Compound 39-46

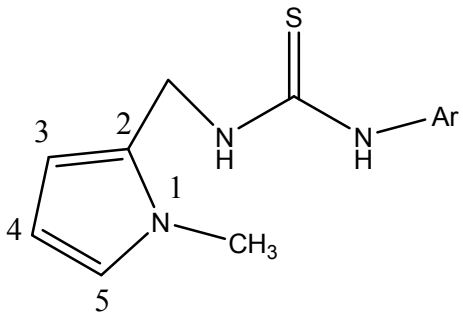
Comp. No	R^1	R^2	pED_{50} (μM)
			Experimental[b]
1	Phenyl	-	-0.1139
2	2-fluorophenyl	-	1
3[a]	3-fluorophenyl	-	0.6021
4	4-fluorophenyl	-	-0.5185
5[a]	2-methoxyphenyl	-	0.3979
6	3-methoxyphenyl	-	0.2218
7	4-methoxyphenyl	-	-0.7404
8	2-methylphenyl	-	0.0227

9	2-nitrophenyl	-	-0.0414
10	2-hydroxyphenyl	-	-0.602
11	2-chlorophenyl	-	0.3979
12	3-ethoxyphenyl	-	0.8239
13	3-propoxyphenyl	-	-0.3424
14[a]	3-isopropoxyphenyl	-	0.3979
15	3-phenoxyphenyl	-	-0.4471
16	2,6-dimethoxyphenyl	-	1.0457
17	2,5-dimethoxyphenyl	-	0.3979
18	3-bromo-6-methoxyphenyl	-	1.301
19	2-fluoro-6-methoxyphenyl	-	0.5229
20[a]	2-ethoxy-6-fluorophenyl	-	0.6989
21	2,6-difluorophenyl	-	1.6989
22	2-chloro-6-fluorophenyl	-	1.301
23	2-pyridyl	-	-0.1139
24	3-pyridyl	-	-0.8062
25	2-furyl	-	-0.716
26	4-methylthiazol-2-yl	-	0.3979
27	4-ethylthiazol-2-yl	-	0.1549
28	4-propylthiazol-2-yl	-	-0.2041
29	4-isopropylthiazol-2-yl	-	-0.1139
30[a]	4-butylthiazol-2-yl	-	-0.1139
31	4-cyanothiazol-2-yl	-	0.6989
32	4-(trifluoro methyl)thiazol-2-yl	-	0.301
33	4-(ethoxy carbonyl)thiazol-2-yl	-	0.301
34	5-chlorothiazol-2-yl	-	-0.4314
35	1,3,4-thiazol-2-yl	-	-0.7243
36	2-pyridyl	-	0.6989
37	5-bromo-2-pyridyl	-	1.301
38	5-methyl-2-pyridyl	-	0.8239
39[a]	2,6-difluorophenyl	4-cyano thiazoly-2-yl	1.5229
40	2,6-difluorophenyl	5-bromo-2-pyridyl	2
41	2,6-difluorophenyl	5-methyl-2-pyridyl	2
42[a]	2-ethoxy-6-fluorophenyl	5-methyl-2-pyridyl	0.6989
43	2-ethoxy-6-fluorophenyl	5-bromo-2-pyridyl	1.6989
44	2-pyridyl	5-methyl-2-pyridyl	0.5228
45	2-pyridyl	5-bromo-2-pyridyl	1.6989
46	2,6-difluorophenyl	4-ethylthiazol-2-yl	1.0969

Table 2. Structures of PET analogs



Compound 47-69



Compound 70 & 71

Comp.	R^2	R^3	R^4	R^6	Ar	pED_{50} (μM)

No.						Experimental[b]
47	F	$(CO)N(Me)_2$	H	F	5-bromo-2-pyridyl	1.0969
48	F	CH_2NAc	H	F	5-bromo-2-pyridyl	0.0457
49	F	CN	H	F	5-chloro-2-pyridyl	2.2218
50	F	$N(Me)_2$	H	F	5-chloro-2-pyridyl	1.3979
51[a]	F	$N(Me)_2$	H	F	5-bromo-2-pyridyl	1.3979
52	F	OCH_3	H	F	5-bromo-2-pyridyl	1.8239
53[a]	F	OC_2H_5	H	F	5-bromo-2-pyridyl	2.2218
54	F	CH_2OCH_3	H	F	5-bromo-2-pyridyl	2.2218
55	Cl	OC_2H_5	H	F	5-bromo-2-pyridyl	2.1549
56	Cl	OC_2H_5	H	F	5-chloro-2-pyridyl	2.0969
57	Cl	OC_2H_5	H	F	5-iodo-2-pyridyl	1.8239
58	Cl	OC_2H_5	H	F	5-cyano-2-pyridyl	2.5229
59	H	OCH_3	H	OCH_3	5-chloro-2-pyridyl	1.3979
60	H	OC_2H_5	H	OC_2H_5	5-bromo-2-pyridyl	1.7447
61	F	H	H	OC_2H_5	5-bromo-2-pyridyl	1.886
62	F	F	H	OC_2H_5	5-bromo-2-pyridyl	2.1549
63[a]	F	F	H	OCH_3	5-bromo-2-pyridyl	2.1589
64	F	OCH_3	H	OCH_3	5-chloro-2-pyridyl	2.6989
65	F	OC_2H_5	H	OCH_3	5-chloro-2-pyridyl	2.301
66	OCH_3	OCH_3	H	F	5-bromo-2-pyridyl	1.9208
67	F	$N(Me)_2$	H	F	5-bromo-2-pyridyl	1.7447
68	F	CN	H	F	5-bromo-2-pyridyl	1.886
69	Cl	OC_2H_5	Cl	F	5-bromo-2-pyridyl	1.886
70	-	-	-	-	5-cyano-2-pyridyl	0.959
71[a]	-	-	-	-	5-chloro-2-pyridyl	0.602

a - test set compounds, b - the experimental ED_{50} values (in micro molar) were converted into $-\log ED_{50}$ (pED50, in micro molar). Taken from Ref. 23 & 24.

high structural diversity and a sufficient range of the biological activity in the selected series of PET derivatives. It insists as to select these series of compounds for our QSAR studies. All the anti-HIV activities used in the present study were expressed as $pED_{50} = -\log_{10} ED_{50}$. Where ED_{50} is the micro molar concentration of the compounds producing 50% reduction in the cytopathic effect caused by the virus is stated as the means of at least two experiments. ED_{50} values were assessed by XTT assays [25]. The compounds which did not show confirmed anti-HIV activity in the above cited literature have not been taken for our study.

From the structures of 71 PET analogues, sixty compounds constituted as a training set and eleven compounds were used in the test set. All 71 PET compounds were built on workspace of Win CAChe 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan) and energy minimization of the molecules was done using Allinger's MM2 force field followed by semi empirical PM3 method available in MOPAC module until the root mean square gradient value becomes smaller than 0.001 kcal/mol Å. Most stable structure for each compound was generated and used for calculating various physico-chemical descriptors like thermodynamic, steric and electronic values of descriptors. Some of the descriptors were calculated using the above optimized structure of the compounds by modeling software Molecular modeling pro 6.1.0, trial version (ChemSW, Inc., www.chemsw.com).

All the calculated descriptors and indicator variables (30 descriptors, the complete descriptors data set of all compounds will be provided on request) were considered as independent variable and biological activity as dependent variable. STATISTICA software was used to generate QSAR models. Statistical measures used were n-number of compounds in regression, r-correlation coefficient, r^2-squared correlation coefficient, F- test (Fischer's value) for statistical

significance, SEE- standard error of estimation, q^2- cross validated correlation coefficient and correlation matrix to show correlation among the parameters. The predictive ability of the generated correlations was evaluated by cross validation method employing a 'leave-one-out' scheme. Validation parameters considered were cross validated r^2 or q^2, standard deviation based on predicted residual sum of squares (S_{PRESS}) and standard error of prediction (SDEP). The robustness of a QSAR model was checked by Y – randomization test. In this technique, new QSAR models were developed by shuffling the dependent variable vector randomly and keeping the original independent variable as such. The new QSAR models are expected to have low r^2 and q^2 values. If the opposite happens then an acceptable QSAR model can not be obtained for the specific modeling method and data.

3. Results and discussion

A data set of 71 PET compounds (Table 1 and 2) for anti-HIV activity was used for the present QSAR study. The QSAR studies of the PET series resulted in several QSAR equations. The descriptors involved in the selected models are given in Table 3. The following best models were derived:

pED_{50} = - 1.349 (± 0.266) + 0.227 (± 0.025) VDW (PT1)

n = 60, r = 0.760, r^2 = 0.578, r^2_{adj} = 0.571, SEE = 0.659, $F_{(1, 58)}$ = 79.51, P <0.001, q^2 = 0.541, S_{PRESS} = 0.682.

pED_{50} = -4.074 (± 0.939) + 0.195 (± 0.026) VDW + 2.270 (± 0.075) D (PT2)

n = 60, r = 0.798, r^2 = 0.636, r^2_{adj} = 0.623, SEE = 0.617, $F_{(2, 57)}$ = 49.81, P <0.001, q^2 = 0.584, S_{PRESS} = 0.648.

pED_{50} = -2.660 (± 1.224) + 2.528 (± 0.755) D – 0.040 (± 0.023) CP + 0.133 (± 0.044) VDW (PT3)

n = 60, r = 0.809, r^2 = 0.655, r^2_{adj} = 0.637, SEE = 0.606, $F_{(3, 56)}$ = 35.45, P <0.001, q^2 = 0.588, S_{PRESS} = 0.646.

pED_{50} = 3.896 (± 1.528) + 4.115 (± 0.670) D – 0.086 (± 0.015) MR - 0.103 (± 0.021) CP + 0.218 ((± 0.038) VDW (PT4)

n = 60, r = 0.884, r^2 = 0.781, r^2_{adj} = 0.765, SEE = 0.488, $F_{(4, 55)}$ = 48.96, P <0.001, q^2 = 0.710, S_{PRESS} = 0.585, SDEP = 0.536.

pED_{50} = 4.564 (± 1.417) + 5.646 (± 0.767) D – 0.107 (± 0.015) MR - 0.149 (± 0.024) CP + 0.240((± 0.036) VDW + 0.007 (± 0.002) HF (PT5)

n = 60, r = 0.905, r^2 = 0.818, r^2_{adj} = 0.802, SEE = 0.448, $F_{(5, 54)}$ = 48.68, P <0.001, q^2 = 0.759, S_{PRESS} = 0.557, SDEP = 0.490.

Out of the five QSAR models, equations PT1, PT2 and PT3 had low r value and their predictive ability was also less. Models PT4 and PT5 were considered to be statistically significant according to statistical criteria and predictive ability. The predicted activities of the compounds by the above models are shown in Fig.1 and 2.

Table 3. Descriptors in Significant QSAR Models of PETT Derivatives as Anti-HIV Agents.

Comp. No.	D	MR	CP	VDW	HF
1	1.246	77.438	37.135	5.537	96.679
2	1.298	77.288	34.561	5.374	54.259
3[a]	1.298	77.288	34.561	5.286	53.414
4	1.299	77.288	34.561	5.307	53.229
5[a]	1.269	83.699	31.955	8.034	60.224
6	1.270	83.699	31.955	7.707	58.659
7	1.269	83.699	31.955	7.690	58.470
8	1.215	82.056	32.579	6.483	88.286
9	1.588	87.828	35.600	3.545	55.993

10	1.360	79.430	42.831	5.483	33.317
11	1.326	82.305	34.889	6.119	91.067
12	1.217	88.317	28.750	8.642	53.478
13	1.195	92.935	26.004	9.197	53.679
14[a]	1.199	92.935	26.218	9.401	48.184
15	1.234	103.188	27.183	10.610	88.754
16	1.294	89.960	27.789	10.603	23.929
17	1.294	89.960	27.789	10.560	22.680
18	1.516	91.464	33.999	10.091	63.758
19	1.322	83.549	29.893	9.237	14.440
20[a]	1.266	88.167	26.986	10.378	6.200
21	1.354	77.138	32.246	6.419	10.924
22	1.379	82.155	32.541	7.367	43.649
23	1.275	76.760	41.947	5.257	104.849
24	1.275	76.760	41.947	5.430	108.816
25	1.386	70.312	43.340	2.840	65.023
26	1.216	82.056	32.579	7.208	90.442
27	1.193	86.674	29.282	8.603	80.299
28	1.172	91.292	26.461	9.052	79.150
29	1.139	91.292	26.680	8.762	80.189
30[a]	1.153	95.910	24.029	10.171	75.502
31	1.285	84.272	31.668	5.499	136.215
32	1.457	86.674	25.925	7.666	-71.273
33	1.269	94.679	26.598	9.981	9.333
34	1.327	82.305	34.889	5.314	91.173
35	1.277	76.760	41.947	6.774	123.037
36	1.162	78.237	32.064	10.138	80.596
37	1.425	86.002	34.119	10.486	89.683
38	1.144	82.855	28.384	10.824	68.850
39[a]	1.390	83.972	27.789	8.664	42.589
40	1.521	85.702	29.795	10.270	6.496
41	1.249	82.555	25.075	10.401	-11.724
42[a]	1.226	88.966	23.451	13.341	-6.711
43	1.482	92.113	27.701	12.811	12.883
44	1.171	82.177	31.562	10.392	78.308
45	1.458	85.324	38.340	10.086	112.218
46	1.294	86.374	25.820	8.281	-7.064
47	1.509	105.240	23.248	13.388	-31.940
48	1.502	104.902	24.338	9.325	-43.268
49	1.385	89.638	23.248	10.340	29.929
50	1.325	95.980	21.694	13.667	-9.718
51[a]	1.472	98.878	24.006	13.753	4.271
52	1.526	91.963	26.031	12.211	-29.275
53[a]	1.460	96.581	23.657	12.925	-35.143
54	1.493	96.581	23.657	13.415	-35.537
55	1.476	101.598	23.842	14.057	1.722
56	1.335	98.700	21.553	13.992	-14.901
57	1.595	106.633	21.856	14.284	8.549
58	1.303	100.667	19.965	12.775	31.028
59	1.296	95.626	23.248	14.939	0.496
60	1.339	107.760	21.433	16.495	4.347
61	1.418	96.731	25.100	13.357	5.744
62	1.459	96.581	23.657	12.522	-35.069
63[a]	1.483	92.113	27.701	12.898	8.078
64	1.489	98.374	24.314	14.885	-25.827

65	1.429	102.992	22.166	15.664	-31.341
66	1.489	98.374	24.314	15.071	-22.869
67	1.473	98.878	24.006	13.391	1.196
68	1.456	105.862	22.313	13.108	87.007
69	1.530	106.465	22.676	14.918	-1.725
70	1.217	84.860	25.820	6.482	119.369
71[a]	1.258	82.893	28.173	6.826	72.539

D = Density, MR = Molar Refractivity, CP = Critical Pressure, VDW = van der Wall's Energy, HF = Heat of Formation.

Model-PT4 showed good correlation coefficient (r) of 0.884 between steric, thermodynamic descriptors (Density, molar refractivity, critical pressure and van der Waal's energy) and anti-HIV activity. Square of correlation coefficient (r^2) of 0.781 explained 78.10% variance in biological activity. This model also indicated statistical significance > 99.9% with $F_{(4,55)} = 48.96$. Cross-validated square of correlation coefficient of this model was 0.710, which showed good internal prediction power of this model. The maximum VIF value of the selected descriptors was 2.024.

Model-PT5 explained 81.8% and predicted 75.9% of the variance of the anti-HIV activity data. The calculated and predicted anti-HIV activity values by model-PT5 are graphically represented in Fig. 1-2. There was no inter-correlation between selected descriptors except MR (Table 4). We included MR in this model even it was highly inter-correlated with other descriptors, because it was not showing multi-colinearity problem (variance inflation factor (VIF) was less than two). This model showed good correlation coefficient (r) of 0.905 between descriptors [steric (Density) and thermodynamic (molar refractivity, critical pressure, heat of formation and van der Waal's energy) descriptors] and anti-HIV activity. This model also indicated statistical significance > 99.9% with $F_{(5, 54)} = 48.68$. The maximum VIF value of the selected descriptors was 2.065. Model-PT5 was selected as best model on the basis of statistical significance and predictivity.

The predictive ability of the selected model was also confirmed by external r^2_{CVext} method. According to Tropsha *et al*., the proposed QSAR model was predictive as it satisfied the conditions $r^2_{CVext} = 0.799 > 0.5$ and $r^2_{Pred} = 0.816 > 0.6$. The robustness of this model was checked by Y–randomization test. The low r^2 and q^2 values (Table 5) indicated that good results in our original model were not due to a chance correlation or structural dependency of the training set. In this QSAR equation, the positive contribution of D on the biological activity shows that the increase in density of molecules leads to better anti-HIV activity. The negative coefficient of MR shows that increase of volume is detrimental for the activity. The negative coefficient of CP indicates that increase of critical pressure of the molecules does not favor for activity. The positive contribution of VDW and HF on the biological activity indicates that van der Waal's energy and heat of formation is responsible for the anti-HIV activity of the PET derivatives. So the substitution of higher alkane's and aromatic rings to the phenyl ethyl ring or N-phenyl ring of PET derivatives may not be favorable for anti-HIV activity.

Table 4. Correlation Matrix of Selected Physico-Chemical Parameters and Anti-HIV Activity of PET Derivatives.

	pED50	D	MR	CP	VDW	HF
pED50	1					
D	0.529	1				
MR	0.533	0.447	1			
CP	-0.639	-0.191	-0.719	1		
VDW	0.737	0.381	0.732	-0.698	1	
HF	-0.582	-0.542	-0.543	0.635	-0.623	1

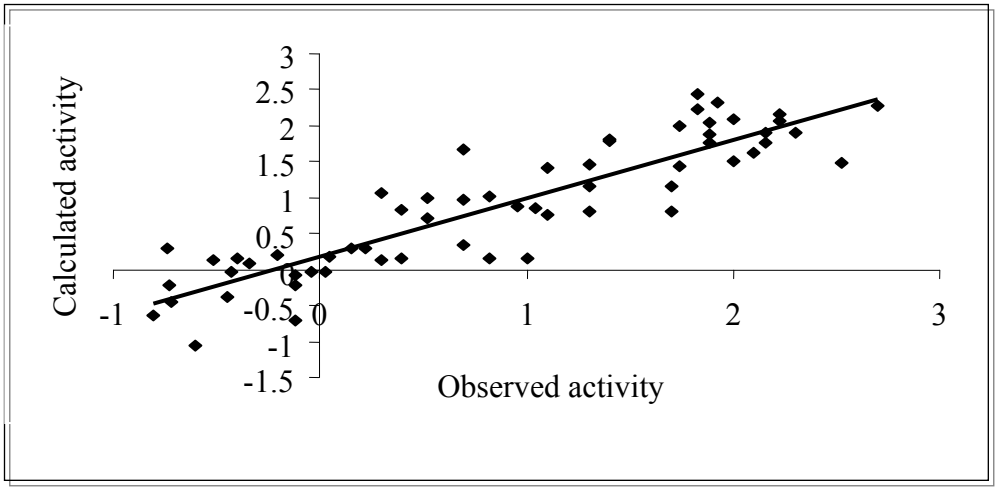


Fig. 1. Observed vs. Calculated Anti-HIV Activity of Training Set of PET Derivatives for Model-PT5.

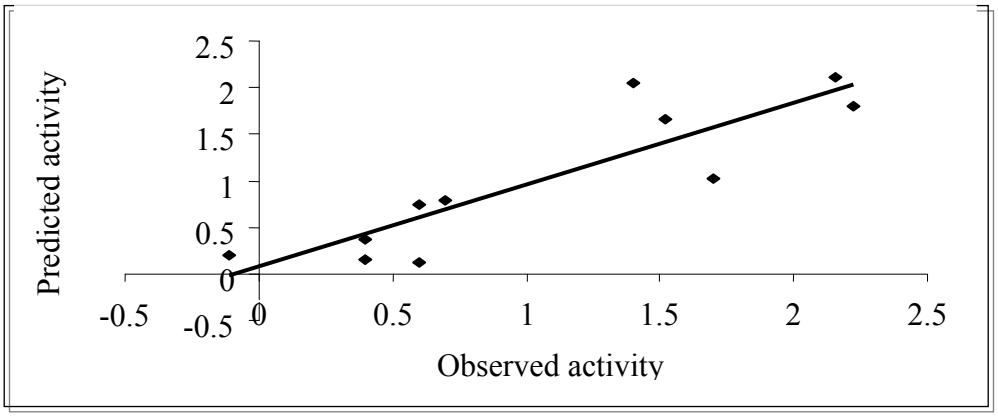


Fig.2. Observed vs. Predicted Anti-HIV Activity of Test Set of PET Derivatives for Model-PT5

Table 5. Y–Randomization Test for Anti-HIV Activity of PET Derivatives

Iteration	r^2	q^2
1		
2	0.005	0.000
3	0.025	0.001
4	0.108	0.003
5	0.124	0.008
6	0.192	0.006
7	0.053	0.002
	0.075	0.008

4. Conclusions

Therefore, obtained data by adequate designed QSAR studies allow observing aspects and essential structural characteristics to have an increased biological activity, suggesting certain structural requirements for an increased anti-HIV potential. Our results open very interesting perspectives regarding PET derivatives with anti-HIV activity.

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