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Qsar Study Of Piperidine Substituted Thiophene[3,2-D] Pyrimidine Derivatives As Anti- Hiv-1 Activity

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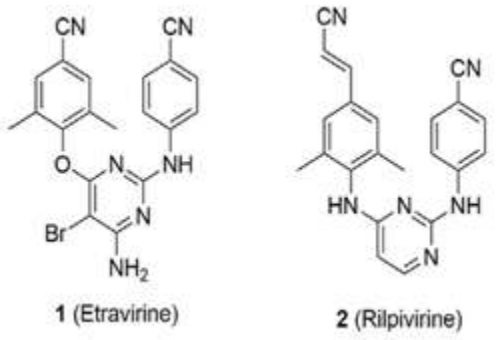
ABSTRACT: Using a quantitative structure-activity relationship (QSAR) analysis, a group of new piperidine-substituted thiophene [3,2-d] pyrimidine derivatives' antiHIV-1 efficacy was examined. the load of eta descriptors, information, connectedness, and eigenvalues. We established a quantifiable link between structural characteristics and anti-HBV activity using, among other types of descriptors. The Eq. tetra parametric model is the most accurate at forecasting the IC50 activity of the current set of chemicals, according to a multivariate linear regression research. The best QSAR model, with R2 = 0.8781, Q-ratio = 4.867, F-ratio = 23.415, and N = 22, and a high correlation coefficient. Later, this model was validated using the leave-one-out (LOO) cross validation procedure using Ridge regression analysis.

KEYWORDS: QSAR analysis, anti-HIV-1 activity, LOO.

I. INTRODUCTION:

Human immunodeficiency virus (HIV), which can enter the host cell and ultimately lead to a marked decline in the host immune system, is the cause of acquired immune deficiency syndrome (AIDS). Due to the fact that it changes the HIV-1 genome from single-stranded RNA to double-stranded DNA, reverse transcriptase (RT) is crucial for the development of novel anti-AIDS drugs.[1]Non-nucleoside reverse transcriptase inhibitors (NNRTIs), among HIV-1 RT inhibitors, have occupied a special position in (HAART) highly active anti-retroviral therapy regimens due to their particular antiviral potency, high specificity, and low toxicity.[2,4]

Nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV) were FDA-approved as the first-generation NNRTIs for treating AIDS.[5] Drug-resistant mutants, however, soon surface due to their low genetic barrier. This frequently led to resistance to NVP and EFV.[6]



1 (Etravirine) **2** (Rilpivirine)

Despite the fact that they could successfully prevent the majority of the RT-resistant mutations brought on by the first-generation NNRTIs.[7,8]Additionally, side effects such as hypersensitivity reactions and other negative outcomes were commonly recorded in individuals taking second-generation NNRTIs.[9,10]Therefore, there is an urgent need for novel NNRTIs that combine enhanced effectiveness against these mutations with a good profile of safety and tolerability.[11,13] Compared to ETR.Exhibit excellent activity against drug-resistant mutations.[14,15]

We can infer that the hydrophobic channel still has adequate room to accommodate structurally varied groups from the fact that both compounds share a flexible extended right wing with piperidine-linked benzenesulfonamide structure and a thiophene [3,2-d] pyrimidine central scaffold. In the current study, we focused on investigating the structure-activity relationships (SARs) of this understudied region in the NNIBP by adding various aromatic structures to the left wing of, including thiophene, furfuran, and substituted benzene rings, with the goal of developing novel, potent NNRTIs with improved drug resistance profiles. These novel thiophene [3,2-d] pyrimidine derivatives anti-HIV activities, preliminary SARs, and modelling analyses will be covered.[16-18]

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PRESENTATION OF DATA: In present study table 2 represents the structure of piperidine-substituted thiophene[3,2-d] pyrimidine derivatives' antiHIV-1, while table 2 shows the Calculated Information, Connectivity indices, Burdeneigen values, & Eta descriptors piperidine-substituted thio phene[3,2-d] pyrimidine derivatives antiHIV-1, table 3 represents the correlation matrix between different Information, Connectivity indices, Burdeneigenvalues, and Eta descriptors.

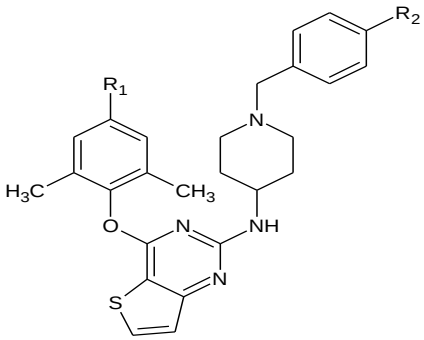
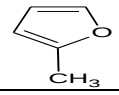
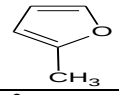
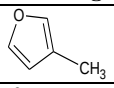
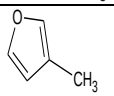
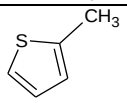
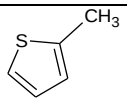
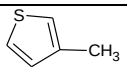
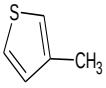
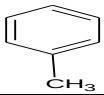
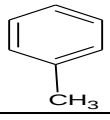


TABLE1. THE STRUCTURE OF COMPOUNDS STUDIED d their ec_{50}(nmol/l)[a] activity AND THEIR EC_{50}(NMOL/L)[A] ACTIVITY

SO.NO.	R1	R2	EC_{50}(nmol/L)[a]
1		SO_2NH_2	17.7
2		$CONH_2$	93.3
3		SO_2NH_2	63.6
4		$CONH_2$	57.5
5		SO_2NH_2	49.5
6		$CONH_2$	203
7		SO_2NH_2	31.6
8		$CONH_2$	240
9		SO_2NH_2	43.8
10		$CONH_2$	47.7

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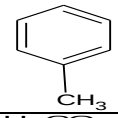
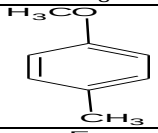
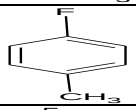
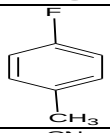
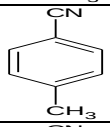
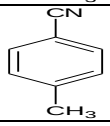
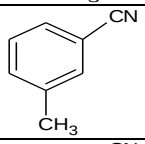
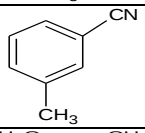
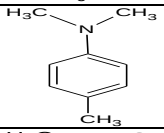
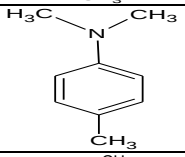
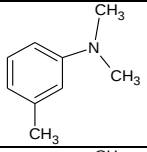
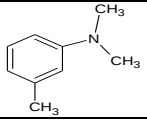
11		SO_2NH_2	61.1
12		$CONH_2$	52.6
13		SO_2NH_2	11.3
14		$CONH_2$	12.8
15		SO_2NH_2	17
16		$CONH_2$	9.93
17		SO_2NH_2	13.3
18		$CONH_2$	23.4
19		SO_2NH_2	79.2
20		$CONH_2$	176
21		SO_2NH_2	882
22		$CONH_2$	163

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TABLE2. CALCULATED INFORMATION,CONNECTIVITY INDICES,BURDENEIGEN VALUES, & ETA DESCRIPTORS AND EC_{50} ACTIVITY OF COMPOUND

EC_{50}	CIC4	X4A	SpMax5_Bh(s)	Eta_sh_p
17.7	0.146	0.115	5.38	0.103
93.3	0.1	0.115	5.051	0.09
63.6	0.146	0.115	5.38	0.103
57.5	0.1	0.115	5.052	0.09
49.5	0.146	0.115	5.38	0.101
203	0.1	0.115	5.05	0.087
31.6	0.146	0.115	5.38	0.101
240	0.1	0.115	5.05	0.087
43.8	0.143	0.115	5.38	0.1
47.7	0.098	0.116	5.051	0.087
61.1	0.136	0.115	5.532	0.119
52.6	0.093	0.116	5.38	0.107
11.3	0.14	0.115	5.532	0.112
12.8	0.095	0.115	5.38	0.1
17	0.136	0.115	5.534	0.114
9.93	0.093	0.116	5.38	0.102
13.3	0.136	0.115	5.534	0.114
23.4	0.093	0.115	5.38	0.102
79.2	0.178	0.115	5.533	0.139
176	0.14	0.116	5.057	0.107
882	0.178	0.114	5.533	0.139
163	0.136	0.115	5.38	0.128

TABLE 3. CORRELATION MATRIX

	EC50	CIC4	X4A	SpMax5_Bh_s_	Eta_sh_p
EC50	1.0000				
CIC4	0.4054	1.0000			
X4A	-0.4908	-0.4936	1.0000		
SpMax5_Bh_s_	0.0801	0.5739	-0.3599	1.0000	
Eta_sh_p	0.4659	0.7361	-0.3651	0.7501	1.0000

22 molecules made up of an external test set were also employed. Since the molecules in this set were not involved in the modelling step, their predicted values can be used to determine the models final predictive ability as determined by the regression coefficient, standard error, fisher criterion, adjusted regression coefficient, and cross validated regression coefficient.

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TABLE 4. RESULT OF CROSS VALIDATION

Model No	N	Press	SSY	Press/SSY	R^2	R^2cv	MSE	Spress
1	22	5387	1828	2.946	0.253	-1.946	26938.43	164.129
2	22	4592	2623	1.751	0.363	-0.751	24170.14	155.467
3	22	3142	4073	0.771	0.564	0.228	17456.73	132.123
4	22	3124	4091	0.763	0.567	0.236	18376.85	135.561
5	18	8661	6241	1.387	0.878	-0.387	6662.572	81.624

II. RESULTS AND DISCUSSION:

In order to understand the experimental EC_{50} activity data of 22substituted thiophene [3,2-d] pyrimidine derivatives as Anti-HIV-1 Activity. Preliminary analysis was carried out in terms of correlation analysis (Table-3). A correlation matrix constructed for EC_{50} activity is presented in Table3 Information(CIC4), Connectivityindices (X4A),Burdeneigenvalues (SpMax5_Bh(s), and Eta (Eta_sh_p) descriptors of the molecules under consideration using Hansch andFujita.[35-36]

Developing a QSAR model requires a diverse set of a data and there by a large number of descriptors have to be considered descriptors are numerical values that encode different structural features of the molecules selection of a set of appropriate descriptors from a large number ofthem requires a method, which is able todiscriminate between the parameters. Pearson'scorrelation matrix has been performed on alldescriptors by using NCSS statistical Software.[31] The analysis of the matrix revealed 4descriptors for the development of MLR model.The value of descriptors selected for MLR modelare presented in Table 4 these parameters arecalculated using the software dragon supplied byVcc lab.[30]

In QSAR study on the studied molecules, this compound has also detected as no outlier. (Table 5) describe the QSAR models resulted for 22 compounds using different sets of descriptors. Again, among the groups of descriptors obtained from the whole molecular structure, resulted in a significant QSAR model for predicting EC_{50} inhibitory activity of the studied molecules. It has a good statistical quality for predicting the activity of the inhibitors. The analysis of the matrix revealed 4 descriptors for the development of MLR models. The values of descriptors used in MLR analysis are presented in Table1.

Model No.1 $\mathbf{EC_{50}}$ **=** 23082.68221-199553.7623 **X4A** **[1]**
N = 22, R^2 = 0.253, MSE = 26938.43, AR^2 = 0.216, F-Ratio = 6.787, Q-VALUE = 0.000018 From QSAR model No.1 the low statistical results indicates needs for the development of Bi parametric or more multiparametric QSAR models follow by rule of thumb. The effect of descriptors on the inhibitory activity pyrimidine derivatives of the compounds are described by QSAR model No.1.

Model No.2 $\mathbf{EC_{50}}$ **=** 2478.52851- 667.8385**X4A** **+** 11220.0555**CIC0** **[2]**
N= 22, R^2 = 0.363, MSE= 24170.14, AR^2 = 0.296, F-Ratio = 5.427, Q-VALUE = 0.000024

Model No.3 $\mathbf{EC_{50}}$ **=** 25319.071 - 192796.651(±66892.889**)** **X4A** - 762.457 (±235.111) **SpMax5_Bh(s)** +9917.1341(±2929.651)**Eta_sh_p[3]**
N= 22, R^2 = 0.564, MSE=17456.73, AR^2 = 0.492, F-Ratio = 7.779, Q-VALUE = 0.000043

Model No.4 $\mathbf{EC_{50}}$ =26260.582 - 535.941(±1705.457**)** **CIC4** - 200958.142(±73382.674) **X4A**-762.568(±241.228) **SpMax5_Bh** + 10544.191(±3607.89**)** **Eta_sh_p** **[4]**
N= 22, R^2 = 0.567, MSE=18376.85, AR^2 = 0.465, F-Ratio = 5.567, Q-VALUE = 0.000040

The above described all models are not statistically excellent indicates the deletion of outliers compounds whose activity are not uniform and **after deletion of the compound no. 11,19,20 and 22** resulting the development of high statistically QSAR model no.4 indicates the importance of Information, Connectivity indices, Burdeneigenvalues, and Eta descriptors in EC_{50} inhibitory activity.

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Model No.5 $\mathbf{EC_{50}}$=14072.212+496.896 (±1212.278**) CIC4-**75723.681(±59552.837)**X4A-**1470.61(±222.241) **SpMax5_Bh**(+24619.7673(±3382.972)**Eta_sh_p [5]**

N= 18, R^2 = 0.878, MSE= 6662.572, AR^2 = 0.841, F-Ratio = 23.415, Q-VALUE = 0.000014

TABLE 5. RESIDUAL REPORT OF 18 COMPOUNDS

	Observed	Predicted	
Comp.No	EC_{50}	EC_{50}	Residual
1	17.7	60.543	-42.843
2	93.3	201.457	-108.157
3	63.6	60.543	3.057
4	57.5	199.986	-142.486
5	49.5	11.304	38.196
6	203.0	129.068	73.932
7	31.6	11.304	20.296
8	240	129.068	110.932
9	43.8	-14.807	58.607
10	47.7	50.880	-3.180
11	52.6	56.963	-4.363
12	11.3	55.609	-44.309
13	12.8	-38.658	51.458
14	17	99.919	-82.919
15	9.93	-66.136	76.066
16	13.3	99.919	-86.619
17	23.4	9.588	13.812
18	882	813.478	68.522

III. CONCLUSIONS

We have evaluated the piperidine-substituted thiophene[3,2-d] pyrimidine derivatives with antiHIV-1 activity.

1. Information, Connectivityindices, Burdeneigenvalues, and Etaparameters may be used for modeling of these compounds.
2. CIC4, X4A, SpMax5_Bh_s_, Eta_sh_p, parameters is more effective and useful for this QSAR study.

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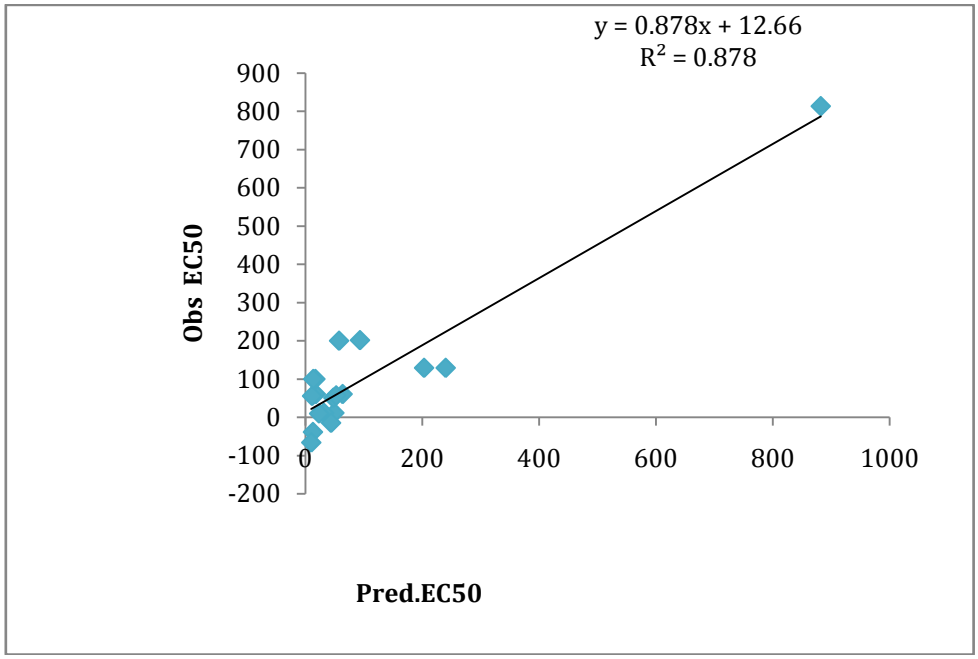

Fig.1 Graph Plotted Between pred. and obs. EC_{50} values

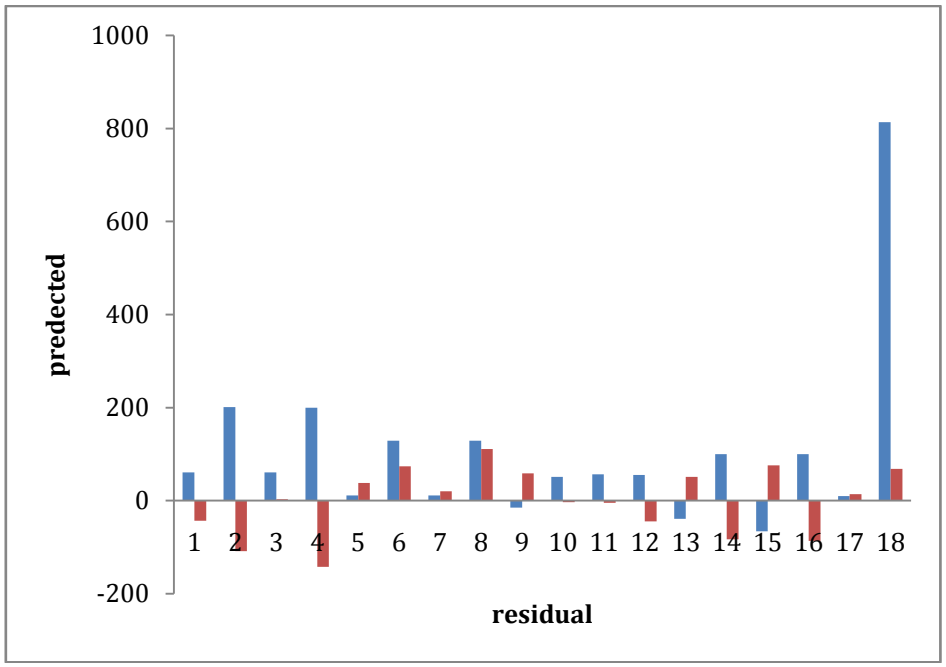

Fig.2 Plot of the Residual values again the pred. EC_{50} values

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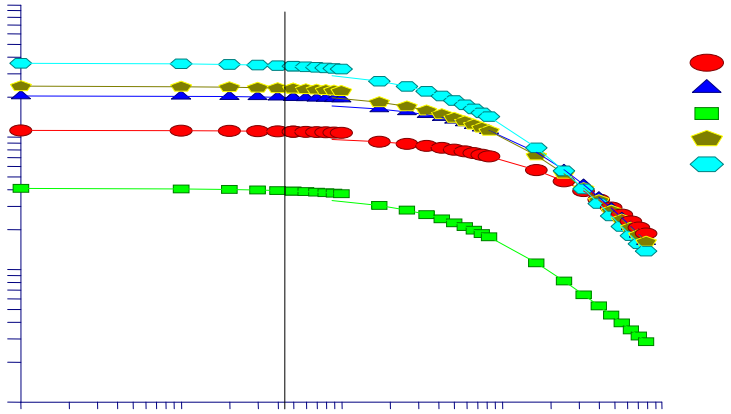

Fig. 3 Graph of Ridge Regression

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