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QSAR STUDIES OF SUBSTITUTED 1, 3, 4-OXADIZOLE NAPHTHYRIDINES A HIV-1 INTEGRASE INHIBITORS USING TOPOLOGICAL PARAMETERS

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ABSTRACT: -

Since long time there is lot of progress in anti-HIV-1 therapy, still antiviral chemotherapy suffers from various side effects and drug resistance. The oxadiazole compound has proved to inhibit integration activity to block viral replication at non-toxic concentrations. To understand the properties, a linear quantitative structure activity relationship (QSAR) model is presented for modeling and predicting the inhibition of HIV-1 integrase. The model was produced by using the stepwise multiple linear regression technique on a database that consist of 67 recently discovered 1, 3, 4-oxadiazole substituted naphthyridine derivatives. The developed QSAR model was evaluated for statistical significance and predictive power; Physicochemical Parameters of all compounds have been calculated using chemsketch 12 program of ACD labs. Further topological indices were calculated using commercial version of dragon software and connectivity indices along with correlation matrix was used to find out the relationship among compound. The compounds are divided into training set of 55 compounds which includes 82% of whole data set and test set of 12 compounds which include 18% of whole data set. Then the models are made by using observed and estimated values and by plotting graph between them. Thus, the key conclusion of this study is its connectivity index order 1, lowest unoccupied molecular orbitals and further it has significant affect on the inhibition of HIV-1 integrase activity by 1, 3, 4-oxadiazole substituted naphthyridine derivatives. The study will be helpful in designing potent antagonists of HIV-1 integrase.We have observed that in our case R^2 for models with biparameteric, tetraparametric molecular descriptors are 0.7368 and 0.7560 respectively while as Veerasamy Ravichandran et al reported 0.643 and 0.748. That's why our results are much more superior then the result reported by Veerasamy Ravichandran et al.

Keywords:

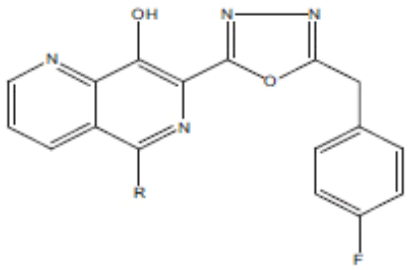
Human Immunodeficiency Virus type-1 (HIV-1), QSAR, 1, 3, 4-oxadiazole substituted naphthyridine derivatives.

1. INTRODUCTION:-

Contributor to rational drug design. Quantitative structure activity relationship (QSAR) results in a quantitative correlation between chemical structure and biological activity. In this research paper a QSAR study on 1,3,4-oxadiazole substituted naphthyridine derivatives as HIV-1 IN inhibitors[36] is performed using computational softwares.The developed QSAR model was evaluated for statistical significance and predictive power. The selected parameters serve as a first guideline for the design of novel and potent antagonists of HIV-1 integrase.

The general structure of 1,3,4-oxadiazole substituted naphthyridine Human Immunodefeciency Virus(HIV-1) integrase (IN) is an enzyme required for viral replication[1]. HIV-1 IN displays a conserved catalytic triad of metal-coordinating carboxylates , which catalyzes two reactions: the 3'-processing (3'P)that occurs in the cellular cytoplasm and processes the retrotranscribed viral cDNA, and the strand transfer reaction (ST), which catalyzes the initial joining of the processed 30-ends to the 50-ends of the host-cell DNA[2,3].The raltegravir and the 4,5-dihydroxyprimidine carboxamide derivatives inhibit the ST reaction and are classified as integrase strand transfer inhibitors(INSTIs).

Computational chemistry has developed into an important derivatives is as shown below:



2. MATERIALS AND METHODS :-

2.1. Data Set:-

All data of the present investigation were obtained from the reference (Veerasamy Ravichandran et al., 2010). The data set for this investigation consisted of 67 compounds of 1,3,4-oxadiazole naphthyridines derivatives as HIV-1 integrase inhibitors).

2.2. Molecular Descriptor Generation:-

To obtain a QSAR model, compounds are often represented by the molecular descriptors. The calculation process of the molecular descriptors was described as below: The two-dimensional molecular structures of 67 compounds of 1,3,4-oxadiazole naphthyridines derivatives). were drawn by Chem Sketch 12.0 then calculated some parameters. Then this optimize structure files were exported into software Dragon 6.0 to calculate all kinds of descriptors. The software Dragon 6.0 can calculate Physicochemical parameters, constitutional, topological, geometrical, descriptors and has been successfully used in various QSAR researches.Then value of all parameters put into NCSS statistical and data analysis software or SPSS (We can also use MSTAT instead of SPSS & NCSS) statistical and data analysis software to get data regression and correlation. Constitutional descriptors are related to the number of atoms and bonds in each molecule. Topological descriptors include valence and non-valence molecular connectivity indices calculated from the hydrogen-suppressed formula of the molecule, encoding information about the size, composition, and the degree of branching of a molecule. The topological descriptors describe the atomic connectivity in the molecule. The geometrical descriptors describe the size of the molecule and require 3D-coordinates of the atoms in the given molecule. The electrostatic descriptors reflect characteristics of the charge distribution of the molecule. The quantum chemical descriptors offer information about binding and formation energies, partial atom charge, dipole moment, and molecular orbital energy levels.

3. RESULTS AND DISCUSSION:-

By using the multiple linear regression analysis (MLRA) method of 2D-QSAR, regression models were developed for 67 compounds of 1,3,4-oxadiazole naphthyridines derivatives . To select the sets of descriptors that are most relevant to pIC_{50} values and effectively show the relation between descriptors and pIC_{50} values of these compounds, four subsets with the descriptors from one to four were determined to establish the QSAR models. Multi-linear regression method for descriptor selection proceeds with a reselections of descriptors by sequentially eliminating descriptors which do not match any of the following criteria: (i) the F-test greater than one unit; (ii) R^2 value less than a value defined at the start (default 0.01); (iii) the student's t-test less than that defined (default 0.1); and (iv) duplicate descriptors having a higher squared inter-correlation coefficient than a predetermined level (usually 0.8). The next step involves correlation of the given property with (i) the top descriptor in the above list with each of the remaining descriptors, and (ii) the next one with each of the remaining descriptors, etc. The goodness of the correlation is tested by the correlation coefficient (R^2) and The stability of the correlations was tested against the cross-validated coefficient (R^2CV). Besides, it will demonstrate which descriptors have bad or missing values, which descriptors are insignificant, and which descriptors are highly intercorelated .This information will be helpful in reducing the number of descriptors involved in the search for the best QSAR/QSPR model. We have observed that in our case R^2 for models with biparameteric, tetraparametric molecular descriptors are 0.7368 and 0.7560 respectively while as Veerasamy Ravichandran et al reported 0.643 and 0.748. That's why our results are much more superior then the result reported by Veerasamy Ravichandran et al.

***Table-1:- Values of calculated topological parameters* :**

Comp.no.	W	J	Jhet-Z	Jhetm	Jhetv	Jhete	Jhetp	BAC
1	2924.0000	1.2690	1.8410	1.8420	1.1930	1.7480	1.1410	17.0000
2	2495.0000	1.2400	1.7120	1.7120	1.1660	1.7070	1.0840	10.0000
3	2721.0000	1.2460	1.7070	1.7080	1.1690	1.7030	1.0870	10.0000
4	2950.0000	1.2560	1.7080	1.7080	1.1740	1.7030	1.0920	10.0000
5	2130.0000	1.3580	1.8890	1.8900	1.2930	1.8840	1.2040	19.0000
6	2301.0000	1.3900	1.9300	1.9310	1.3150	1.9250	1.2230	28.0000
7	3103.0000	1.3670	1.8700	1.8700	1.2440	1.8650	1.1540	31.0000
8	3263.0000	1.4190	1.9320	1.9330	1.3070	1.9270	1.2120	54.0000
9	2721.0000	1.2460	1.7100	1.7110	1.1630	1.7060	1.0810	10.0000
10	4190.0000	1.2390	1.6540	1.6540	1.1080	1.6480	1.0250	39.0000
11	2719.0000	1.2490	1.7200	1.7210	1.1580	1.7150	1.0740	17.0000
12	2495.0000	1.2400	1.7150	1.7160	1.1610	1.7100	1.0780	10.0000
13	3261.0000	1.2460	1.6950	1.6950	1.1320	1.6900	1.0480	19.0000
14	2495.0000	1.2400	1.7180	1.7180	1.1550	1.7130	1.0720	10.0000
15	2721.0000	1.2460	1.7160	1.7160	1.1630	1.7110	1.0810	10.0000
16	2694.0000	1.2600	1.8220	1.8220	1.1870	1.7470	1.1290	17.0000
17	2323.0000	1.3760	2.0070	2.0070	1.3110	1.9240	1.2500	28.0000

18	2769.0000	1.3970	2.0680	2.0680	1.3040	1.9430	1.2550	40.0000
19	3155.0000	1.2830	1.8800	1.8800	1.1900	1.7700	1.1370	26.0000
20	2921.0000	1.2720	1.8530	1.8540	1.1830	1.7610	1.1310	26.0000
21	3853.0000	1.2400	1.9020	1.9030	1.2210	1.7110	1.2050	26.0000
22	2745.0000	1.2360	1.6910	1.6910	1.1550	1.6860	1.0730	10.0000
23	1750.0000	1.3360	1.8610	1.8620	1.2870	1.8570	1.2010	11.0000
24	3615.0000	1.2210	1.6900	1.6910	1.1160	1.6410	1.0530	27.0000
25	4373.0000	1.1890	1.5620	1.5620	1.0640	1.5570	0.9860	29.0000
26	2520.0000	1.2270	1.7540	1.7540	1.2670	1.7500	1.1910	5.0000
27	2520.0000	1.2270	1.7650	1.7660	1.2550	1.7610	1.1770	5.0000
28	2520.0000	1.2270	1.7610	1.7610	1.2620	1.7570	1.1860	5.0000
29	2520.0000	1.2270	1.7570	1.7570	1.2630	1.7530	1.1860	5.0000
30	2520.0000	1.2270	1.7680	1.7680	1.2440	1.7640	1.1640	5.0000
31	3259.0000	1.2430	1.7770	1.7770	1.3010	1.7740	1.2260	18.0000
32	4202.0000	1.2350	1.7350	1.7350	1.2890	1.7310	1.2160	29.0000
33	2745.0000	1.2360	1.7690	1.7690	1.2820	1.7650	1.2050	10.0000
34	3579.0000	1.2340	1.7590	1.7590	1.2760	1.7550	1.1980	19.0000
35	3813.0000	1.2540	1.8750	1.8760	1.3300	1.7930	1.2840	28.0000
36	3331.0000	1.2190	1.7440	1.7440	1.2830	1.7400	1.2100	18.0000
37	3331.0000	1.2190	1.7420	1.7420	1.2880	1.7390	1.2150	18.0000
38	3646.0000	1.2120	1.7260	1.7270	1.2810	1.7230	1.2080	19.0000
39	3963.0000	1.2100	1.7170	1.7170	1.2780	1.7140	1.2060	28.0000
40	4346.0000	1.1960	1.6840	1.6840	1.2610	1.6810	1.1900	29.0000
41	3965.0000	1.3060	1.9680	1.9680	1.3680	1.8580	1.3270	39.0000
42	4253.0000	1.2190	1.8300	1.8300	1.3030	1.7400	1.2640	39.0000
43	3693.0000	1.2950	1.9390	1.9390	1.3600	1.8480	1.3130	28.0000
44	4305.0000	1.3010	1.9570	1.9570	1.3590	1.8370	1.3230	40.0000
45	4641.0000	1.2080	1.8110	1.8110	1.2890	1.7120	1.2550	40.0000
46	3675.0000	1.2040	1.7190	1.7190	1.2550	1.7160	1.1800	19.0000
47	3933.0000	1.2180	1.8190	1.8190	1.3020	1.7440	1.2570	28.0000

48	3423.0000	1.2870	1.9130	1.9130	1.3590	1.8400	1.3040	27.0000
49	3519.0000	1.2520	1.8590	1.8590	1.3320	1.7930	1.2790	27.0000
50	3615.0000	1.2210	1.8110	1.8110	1.3080	1.7500	1.2560	27.0000
51	3049.0000	1.2200	1.7500	1.7500	1.2890	1.7470	1.2150	11.0000
52	2298.0000	1.2230	1.7400	1.7400	1.2300	1.7360	1.1520	5.0000
53	2298.0000	1.2230	1.7280	1.7280	1.2180	1.7240	1.1400	5.0000
54	2298.0000	1.2230	1.7080	1.7080	1.1470	1.7030	1.0610	5.0000
55	2519.0000	1.2290	1.7140	1.7140	1.1430	1.7090	1.0560	10.0000
56	1750.0000	1.3360	1.8680	1.8680	1.3120	1.8640	1.2280	11.0000
57	1915.0000	1.3600	1.8930	1.8930	1.3250	1.8890	1.2400	18.0000
58	1915.0000	1.3600	1.8960	1.8960	1.3190	1.8910	1.2330	18.0000
59	2107.0000	1.3730	1.9010	1.9010	1.3290	1.8960	1.2430	19.0000
60	2549.0000	1.3840	1.8890	1.8890	1.3250	1.8840	1.2390	29.0000
61	2576.0000	1.3710	1.8710	1.8720	1.3050	1.8670	1.2190	21.0000
62	2855.0000	1.3610	1.8360	1.8360	1.2920	1.8320	1.2080	22.0000
63	3165.0000	1.3460	1.8020	1.8020	1.2590	1.7980	1.1760	23.0000
64	3001.0000	1.2350	1.6660	1.6670	1.1620	1.6620	1.0850	10.0000
65	3285.0000	1.2320	1.6480	1.6480	1.1540	1.6440	1.0770	17.0000
66	3285.0000	1.2320	1.6450	1.6450	1.1580	1.6410	1.0820	17.0000
67	3259.0000	1.2410	1.6680	1.6690	1.1680	1.6640	1.0900	17.0000

***Table-2:- Values of calculated connectivity indices*:**

Comp.no.	***0χ***	***1χ***	***2χ***	***3χ***	***0χ*v**	***1χ*v**	***2χ*v**	***3χ*v**
1	22.2940	15.4210	14.6760	12.4160	17.5880	11.5840	9.4440	7.0700
2	20.6650	14.5970	13.4080	11.7870	15.7480	9.4520	6.9850	4.9820
3	21.3720	15.0970	13.7610	12.0370	16.4550	9.9520	7.3390	5.2320
4	22.0790	15.5970	14.1150	12.2870	17.1620	10.4520	7.6920	5.4820
5	19.6730	13.5080	12.5610	10.1700	14.6790	8.3350	6.0430	3.9680
6	20.5430	13.9360	12.9390	11.0360	15.6260	8.7290	6.4140	4.4430
7	22.6650	15.4570	13.9110	11.7850	16.7030	9.4890	6.5360	4.3660
8	23.6980	15.7570	14.6570	12.6950	17.9820	9.8020	7.4000	4.8640

9	21.3720	15.0970	13.7610	12.0370	16.2480	9.6590	7.0590	4.9980
10	25.3970	17.3130	16.1530	13.9310	19.5500	11.1300	8.4800	5.7820
11	21.5350	15.0080	13.9130	12.3870	16.4880	9.5860	7.1920	5.1250
12	20.6650	14.5970	13.4080	11.7870	15.5410	9.2020	6.7200	4.7650
13	22.9490	16.0460	14.4850	12.8080	17.3490	10.2710	7.4810	5.3730
14	20.6650	14.5970	13.4080	11.7870	15.4490	9.0910	6.6020	4.6690
15	21.3720	15.0970	13.7610	12.0370	16.2480	9.7020	7.0740	4.9890
16	21.5870	14.9210	14.3230	12.1660	16.8810	11.0840	9.0910	6.8200
17	20.5960	13.7990	13.6960	10.2700	15.8120	10.2180	7.9840	4.5190
18	22.1730	14.7420	14.2790	11.7470	17.2590	10.4350	8.6350	5.7920
19	23.1650	15.8410	15.0950	13.2040	18.3280	11.5300	9.5510	7.2790
20	22.4570	15.3410	14.7420	12.9620	17.6210	11.0300	9.1980	7.0620
21	24.5790	16.7980	16.0970	13.2120	19.1210	11.9270	9.3870	6.5210
22	21.3720	15.0810	13.8670	11.8920	16.2480	9.6480	7.1080	4.9910
23	18.0960	12.6520	11.3400	9.9200	13.7710	7.8810	5.6110	3.9100
24	23.8720	16.2920	15.8130	12.9110	19.0350	12.3920	9.9680	6.9630
25	25.2330	17.3850	16.0730	13.6490	20.0560	11.6110	8.8880	6.1820
26	20.5010	14.6870	13.2340	11.5650	15.6580	9.2920	6.7270	4.7200
27	20.5010	14.6870	13.2340	11.5650	15.5270	9.1510	6.5760	4.5810
28	20.5010	14.6870	13.2340	11.5650	15.5270	9.1410	6.6030	4.6080
29	20.5010	14.6870	13.2340	11.5650	15.5270	9.1410	6.5970	4.6270
30	20.5010	14.6870	13.2340	11.5650	15.3970	9.0010	6.4520	4.4790
31	22.9490	15.9910	14.7660	12.6130	16.9360	9.8800	7.2470	5.0560
32	25.2330	17.3850	16.1290	13.3180	19.5660	11.3500	8.5700	5.4910
33	21.3720	15.0810	13.8670	11.8920	16.1580	9.4910	6.9870	4.8330
34	23.6560	16.4740	15.2580	12.5430	17.9880	10.4060	7.6230	5.1290
35	24.5790	16.8530	15.8010	13.6460	19.1210	11.9270	9.4830	6.7720
36	22.9490	15.9910	14.7540	12.6740	16.9360	9.8800	7.2440	5.0780
37	22.9490	15.9910	14.7540	12.6740	17.0660	9.9450	7.3030	5.1160
38	23.6560	16.5290	14.8960	13.1800	17.9880	10.4060	7.5180	5.3210
39	24.5260	16.9020	15.6130	13.5260	18.9360	10.7740	8.1380	5.4850
40	25.2330	17.3850	16.1170	13.3790	19.5660	11.3500	8.5670	5.5130

41	25.4490	17.2520	16.3660	14.1220	20.0690	12.2630	10.2650	7.4470
42	25.4490	17.2350	16.4230	14.2270	20.0690	12.2570	10.3250	7.4090
43	24.5790	16.8690	15.7320	13.5940	19.1210	11.9330	9.4200	6.8460
44	26.1560	17.7250	16.9770	13.6170	20.6990	12.8760	10.3160	7.2120
45	26.1560	17.7080	17.0340	13.7260	20.6990	12.8700	10.3760	7.1760
46	23.6560	16.4740	15.2460	12.6110	17.9880	10.4060	7.6200	5.1520
47	24.5790	16.8530	15.7890	13.7030	19.1210	11.9270	9.4800	6.8100
48	23.8720	16.3090	15.7560	12.7910	18.6210	12.0450	9.6140	6.3700
49	23.8720	16.2920	15.8250	12.8540	18.6210	12.0390	9.6770	6.3190
50	23.8720	16.2920	15.8130	12.9110	18.6210	12.0390	9.6740	6.3570
51	22.0790	15.6190	14.0250	12.3830	16.5270	9.6760	7.0510	4.9610
52	19.7940	14.1870	12.8800	11.3150	14.9110	8.7630	6.3730	4.4680
53	19.7940	14.1870	12.8800	11.3150	15.0030	8.8750	6.4450	4.5260
54	19.7940	14.1870	12.8800	11.3150	14.8970	8.7380	6.2870	4.3740
55	20.6650	14.5810	13.5140	11.6500	15.8200	9.1580	6.7380	4.5920
56	18.0960	12.6520	11.3400	9.9200	13.2180	7.6040	5.4730	3.7790
57	18.9660	13.0250	12.0790	10.1660	13.7560	7.8740	5.7260	3.9060
58	18.9660	13.0250	12.0790	10.1660	13.6260	7.8090	5.6670	3.8760
59	19.6730	13.5630	12.2210	10.6840	14.6790	8.3350	5.9410	4.1150
60	21.2500	14.4190	13.4420	10.8830	16.2560	9.2780	6.9900	4.3080
61	21.0870	14.5630	12.9550	11.0530	15.5410	9.0050	6.3410	4.2860
62	21.7940	15.0630	13.3090	11.3030	16.2480	9.5050	6.6940	4.5090
63	22.5010	15.5630	13.6620	11.5530	17.2090	9.8850	6.9640	4.6990
64	22.0790	15.5970	14.0930	12.3780	16.8630	10.0180	7.2660	5.1740
65	22.9490	15.9910	14.7150	12.7890	17.9020	10.5210	7.9570	5.6660
66	22.9490	15.9910	14.7150	12.7890	17.4790	10.5160	7.8850	5.6270
67	22.9490	15.9910	14.7260	12.7050	17.1560	10.1020	7.4380	5.2010

***Table –3:- correlation matrix of parameters*:**

	pIC50	***W***	***J***	***JhetZ***	***Jhetm***	***Jhetv***	***Jhete***	***Jhetp***	***BAC***	***0χ***	***1χ***	***2χ***	***3χ***
pIC_{50}	1.0000												
W	0.4591	1.0000											
J	-0.5424	-0.4251	1.0000										
JhetZ	-0.1213	-0.1520	0.7587	1.0000									
Jhetm	-0.1221	-0.1525	0.7592	1.0000	1.0000								
Jhetv	-0.0693	0.0360	0.4595	0.7458	0.7450	1.0000							
Jhete	-0.3283	-0.3904	0.8771	0.9067	0.9066	0.7707	1.0000						
Jhetp	0.0361	0.1542	0.3812	0.7674	0.7666	0.9799	0.7068	1.0000					
BAC	0.0950	0.6374	0.3556	0.4828	0.4826	0.3590	0.3132	0.4264	1.0000				
0χ	0.4571	0.9864	-0.3304	-0.0514	-0.0518	0.0697	-0.3063	0.1924	0.7034	1.0000			
1χ	0.5044	0.9846	-0.4817	-0.2020	-0.2025	-0.0174	-0.4433	0.1028	0.5581	0.9808	1.0000		
2χ	0.5393	0.9635	-0.4132	-0.0571	-0.0575	0.0327	-0.3526	0.1751	0.6466	0.9791	0.9653	1.0000	
3χ	0.5787	0.9267	-0.5344	-0.2190	-0.2192	-0.1038	-0.4884	0.0298	0.5140	0.9347	0.9582	0.9400	1.0000
*0χ*v	0.4840	0.9694	-0.3379	-0.0324	-0.0327	0.0338	-0.3190	0.1706	0.6967	0.9864	0.9639	0.9831	0.9331
*1χ*v	0.545	0.875	-0.340	0.058	0.058	0.037	-0.289	0.202	0.615	0.907	0.880	0.950	0.874

	5	0	0	6	3	5	0	1	4	2	2	8	6
*2χ*v	0.5416	0.8001	-0.2683	0.1656	0.1654	0.0755	-0.2019	0.2472	0.6390	0.8447	0.7978	0.9051	0.8236
*3χ*v	0.5720	0.7398	-0.3210	0.1089	0.1089	-0.0177	-0.2665	0.1588	0.5352	0.7857	0.7575	0.8475	0.8331

	0χv	***1χv***	***2χv***	***3χv***
*0χ*v	1.0000			
*1χ*v	0.9491	1.0000		
*2χ*v	0.9021	0.9818	1.0000	
*3χ*v	0.8486	0.9398	0.9678	1.0000

Best parametric model reported :-

Using correlation matrix When training set was used the best tetrametric model obtained contain J, Jhete, Jhetv and 1χv having R^2 =0.7560, much better statistical model was obtained .The model is as shown below

pIC_{50} = 0.2630(±0.0310)1χv -13.1714(±1.6816)J -5.4898(±1.1186)Jhetv

+11.7054(±1.7564)Jhete+1.9108

n=55 R^2 =0.7560 R^2A=0.7364 Se=0.2604557 F-Ratio=38.720 Q=3.33831

When test set was used the best biparametric model was obtained having W and J as parameters having R^2 =0.7367. The model is as shown below

pIC_{50} = -0.0002(±0.00018) W -16.7248(±3.5044)J+23.1092

n=12 R^2 =0.7367 R^2A=0.6782 Se=0.4068452 F-Ratio=12.592 Q=2.10968

Table- 4Observed and estimated values using tetraparametric model of training set

Comp. No.	**Observed pIC_{50}**	**Estimated pIC_{50}**	**Residual**
1	2.6990	2.1540	0.5450
2	1.7210	1.6440	0.0770
3	1.0560	1.6330	-0.5770
4	1.6020	1.6050	-0.0030
5	1.1430	1.1710	-0.0280

6	1.5530	1.2120	0.3410
7	1.4810	1.4020	0.0790
8	1.0710	1.1790	-0.1080
9	1.4200	1.6240	-0.2040
10	1.6380	1.7260	-0.0880
11	1.8240	1.6980	0.1260
12	1.8860	1.7680	0.1180
13	1.8860	1.6800	0.2060
14	1.9590	1.6940	0.2650
15	2.0970	2.1630	-0.0660
16	1.7210	1.7980	-0.0770
17	1.8240	1.8390	-0.0150
18	2.2220	2.2300	-0.0080
19	2.3980	2.1760	0.2220
20	1.1310	1.0580	0.0730
21	1.7210	2.1690	-0.4480
22	1.9210	1.6880	0.2330
23	1.5380	1.7220	-0.1840
24	1.5230	1.8790	-0.3560
25	1.6990	1.9350	-0.2360
26	1.9210	1.7600	0.1610
27	2.0000	1.8150	0.1850
28	1.8240	1.7490	0.0750
29	1.7450	1.8540	-0.1090
30	2.3980	1.8970	0.5010
31	2.3980	2.1720	0.2260
32	1.7450	2.2920	-0.5470
33	2.3980	2.1570	0.2410
34	1.9210	2.2030	-0.2820
35	2.3980	2.3470	0.0510

36	2.3980	1.9860	0.4120
37	2.5230	2.2710	0.2520
38	1.9590	2.2040	-0.2450
39	2.2220	2.2610	-0.0390
40	2.0460	2.2980	-0.2520
41	1.8240	1.7590	0.0650
42	1.6380	1.6750	-0.0370
43	1.9210	1.6300	0.2910
44	1.6780	1.8610	-0.1830
45	0.6200	0.9300	-0.3100
46	1.0000	0.9060	0.0940
47	0.9210	0.9160	0.0050
48	0.7210	0.9000	-0.1790
49	0.8860	0.9110	-0.0250
50	1.1490	0.8360	0.3130
51	0.7210	0.9160	-0.1950
52	0.8860	1.3540	-0.4680
53	1.3570	1.3590	-0.0020
54	1.5690	1.3000	0.2690
55	1.1310	1.2870	-0.1560

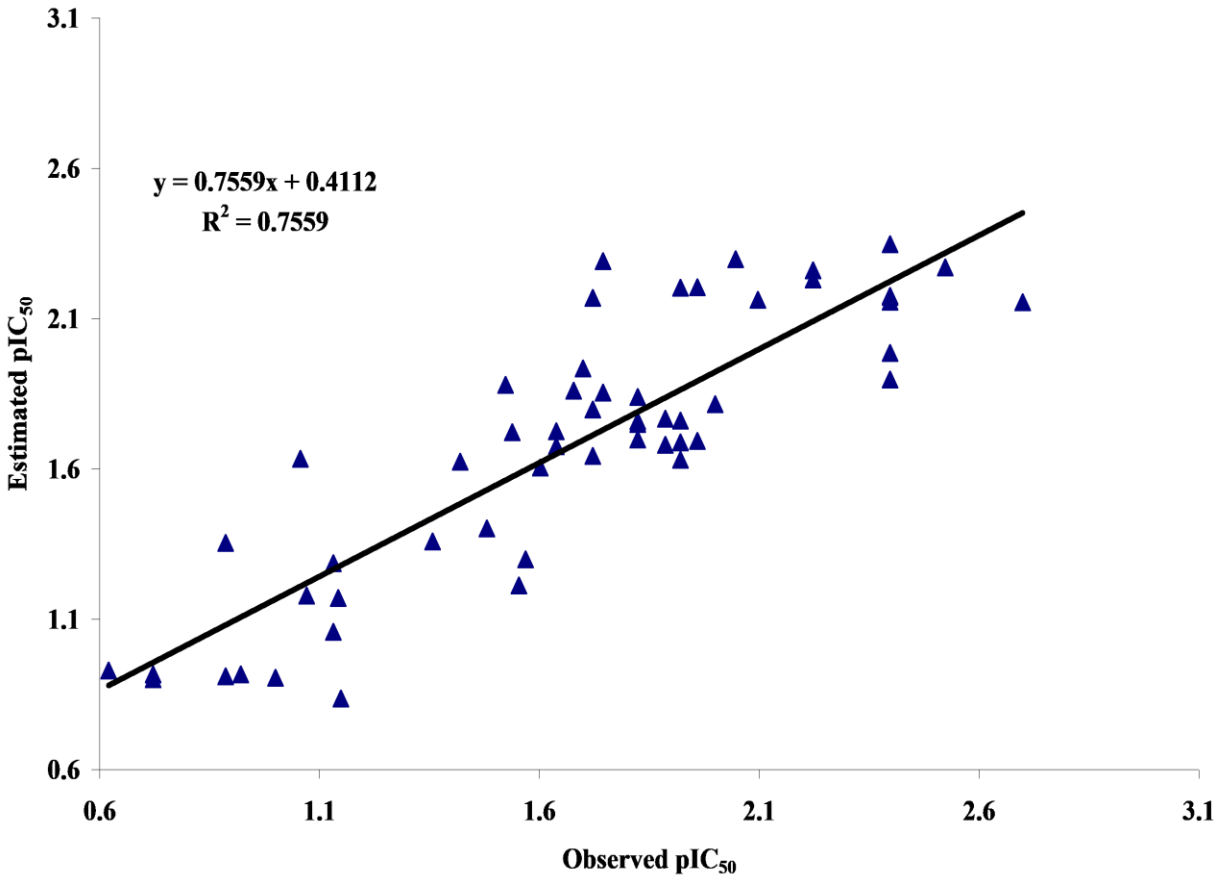


Fig-1:- Correlation between Observed and Estimated values of pIC_{50} Using tetraparametric model of training set.

Table –5:- Cross-validated parameters for training set

Model. No.	Parameters Used	PRESS	SSY	PRESS/SSY	R^2cv	PSE	S_{PRESS}
1	3χv	7.0419	6.8566	1.0270	-0.027	0.3578	0.3645
2	J,Jhetz	5.4780	8.4204	0.6505	0.3495	0.3155	0.3245
3	J,Jhetz,3χv	4.5150	9.3834	0.4811	0.5189	0.2865	0.2975
4	J,Jhetv,Jhete,1χv	3.3918	10.5067	0.3228	.6772	0.2483	0.2604

Table -6:- Observed and estimated values using biparametric model of Test set.

Comp. No.	Observed pIC_{50}	Estimated pIC_{50}	Residual
1	1.921	1.971	-0.050
2	1.377	1.753	-0.376
3	2.155	1.998	0.157
4	1.959	2.184	-0.225
5	2.097	2.184	-0.087
6	1.097	1.897	-0.800
7	2.097	1.525	0.572
8	2.699	2.188	0.511
9	2.222	2.188	0.034
10	2.398	2.255	0.143
11	2.398	2.287	0.111
12	0.066	0.057	0.009

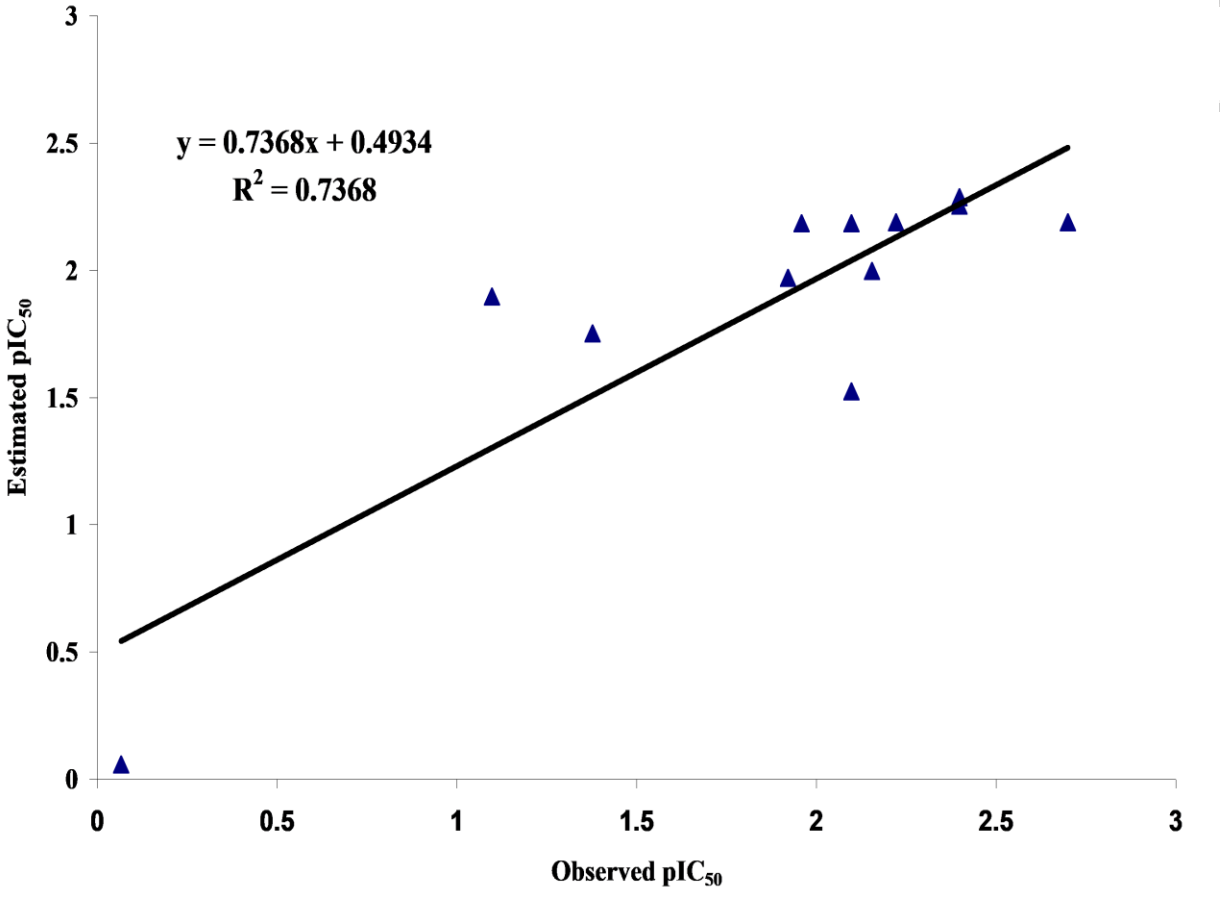


Fig-2:- Correlation between Observed and Estimated values of pIC_{50} using biparametric model of test set.

Table-7:- Cross-validated parameters for test set

Model. No.	Parameters Used	PRESS	SSY	PRESS/SSY	R^2cv	PSE	SPRESS
1	J	1.5880	4.0703	0.3901	0.6099	0.3637	0.3984
2	W,J	1.4897	4.1686	0.3573	0.6427	0.3523	0.4068

CONCLUSION:----------

In this study ,it was possible to obtain a QSAR model for a set of sixty seven 1,3,4-oxadiazole substituted naphthyridine derivatives that have the capability of inhibiting the in vitro HIV-1 IN activity.The external validation indicated that model is significant with good internal and external predictability. The results can be used in developing of new HIV-1 IN inhibitors.

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