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Exploring QSARs for inhibitory effect of a set of EGFR tyrosine kinase inhibitors by GA-MLR and molecular Docking simulations

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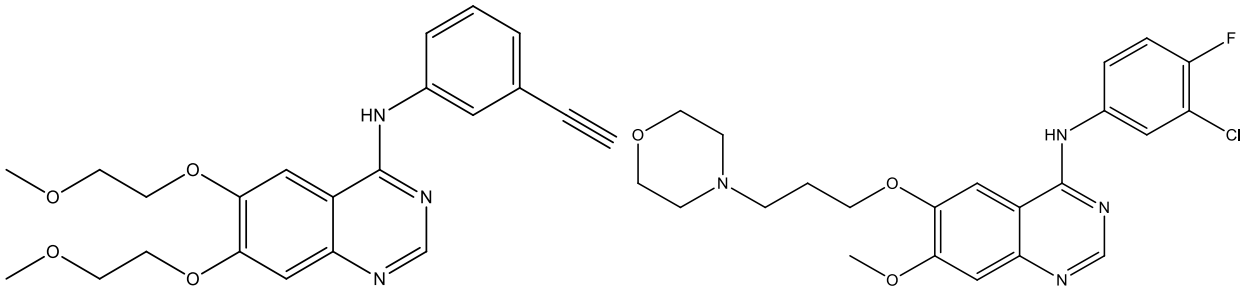
ABSTRACT: *In this study, EGFR as a target for the anticancer activity of a series of 113 inhibitors were taken from the literature. Current work aims to derive statistically robust and appropriately validated multiple QSAR models using easily interpretable molecular descriptors and molecular docking analysis. It will be simpler to identify important structural trends and how they relate to anticancer activity as a result. The MLR model has been used to suggest some novel compounds with improved activity. It has been demonstrated how the predicted compounds interact with the enzyme using the docking study. All predicted compounds were discovered to have several hydrogen bonds with the receptor and involve their bulky groups in strong steric interactions with specific places of the enzyme. The proposed compounds exhibit good pharmacokinetic properties, according to the analysis of their pharmacokinetic profiles.*

KEYWORDS: EGFR, QSAR, Docking, Tyrosine Kinase inhibitors

INTRODUCTION

Many human malignancies have to overexpress the epidermal growth factor receptor (EGFR), which is linked to a poor prognosis. Since EGFR tyrosine autophosphorylation is a growth signal pathway that can be inhibited, inhibitors of this mechanism have attracted a lot of attention as potential anticancer medications. Associated 4-Anilinoquinazolines through competitive binding to the ATP site, 4-anilinopyrido[d]- pyrimidines are practical and selective, reversible inhibitors of both isolated EGFR and EGF stimulated EGFR autophosphorylation in cells, and two of these

drugs, CP-358,774 and ZD 1839 (Iressa), are currently undergoing clinical trials. It is anticipated that achieving sufficiently high intracellular levels of such inhibitors may be challenging to permanently inhibit EGF-stimulated autophosphorylation in some cell lines due to high intracellular ATP levels [1-8].



CP-358,774 ZD 1839

In a sizeable majority of human malignancies, overexpression of the tyrosine kinase for the epidermal growth factor receptor (EGFR) is linked to a poor prognosis [9-10]. Potentially a new class of anticancer treatments is substances that block EGFR autophosphorylation and concurrently EGF-stimulated signal transmission [11-13]. The 4-anilinoquinazolines and associated 4-anilinopyrido- [d]pyrimidines are the most effective and selective EGFR inhibitors [14-18]. The EGFR's ATP binding domain is reversibly bound by these substances.

A crucial enzyme target for cancer treatment is the epidermal growth factor receptor (EGFR) [19-21]. It is overexpressed in a sizeable part of human malignancies and is essential for growth signaling [22-25]. Identifying the 4-anilinoquinazoline class of chemicals represented a significant advancement in the development of EGFR-targeted medicines [26-30].

Through competitive binding at the enzyme's ATP site, these compounds are practical and specific inhibitors of the tyrosine kinase activity of the EGFR. Potent inhibition of the enzyme is linked to tiny, lipophilic electron-donating groups at the 6- and 7-positions of the quinazoline and electron-withdrawing groups at the 3-position of the aniline ring.

A well-liked subset of CADD is the field of QSAR, which focuses on estimating activity/property and mechanistic interpretation. Structure and activity are found to have a mathematical relationship in QSAR. Complex descriptors are frequently the only ones found in a statistically sound QSAR model. Complex descriptors are challenging to interpret mechanistically with structural aspects. Since then, synthetic chemists have had limited success using the known QSAR models. Deriving multiple fully validated QSAR models with one or more readily understandable descriptors in each derived model is one way to get around this significant constraint [31-36].

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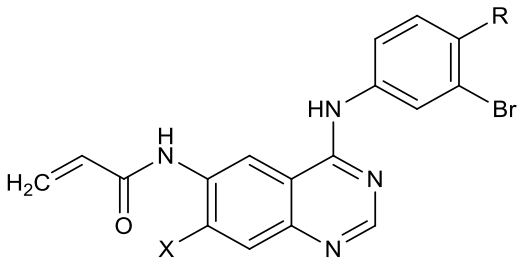
In this study, EGFR as a target for the anticancer activity of a series of 113 inhibitors were taken from the literature [37-40]. Current work aims to derive statistically robust and appropriately validated multiple QSAR models using easily interpretable molecular descriptors and molecular docking analysis. It will be simpler to identify important structural trends and how they relate to anticancer activity as a result.

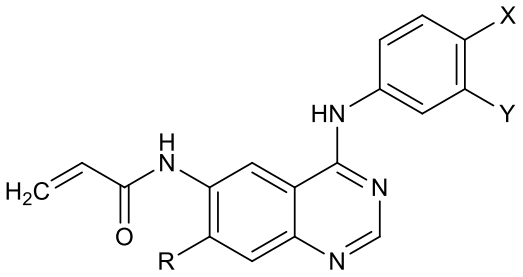
EXPERIMENTAL METHODOLOGY

Dataset:

The dataset consists of one hundred and thirteen derivatives of 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides, Methyl amino-Substituted Derivatives of 4-[(3-Bromophenyl)amino]-6-(methylamino)- pyrido[3,4-d]pyrimidine based compounds, Pyrrolo- and Pyrazoloquinazoline and 6-Substituted 4-Anilinoquinazolines and 4-Anilinopyrido[3,4-d]pyrimidines with a variety of substituents at different positions are listed in Table-1. The general molecular structures of the compounds used in the presented study are given in Figure-1. These substances were evaluated for their ability to inhibit the EGFR enzyme. All the molecular structures of 113 compounds were drawn using the hyper chem software Version 7.5: Hypercube, Inc, USA, http://www.hyper.com) With default settings [41]. Followed by energy minimization using AM1 forcefield. These minimized molecules were further used for the descriptor calculation.



A



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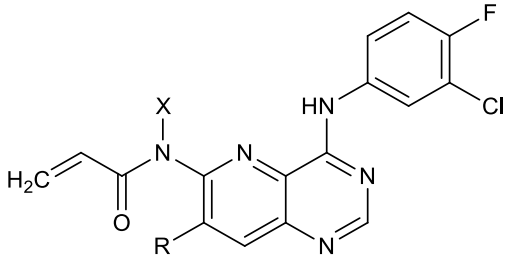

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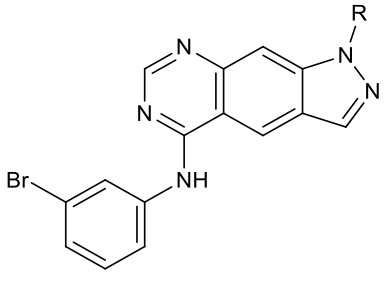

2a-2b, 2f, 2h

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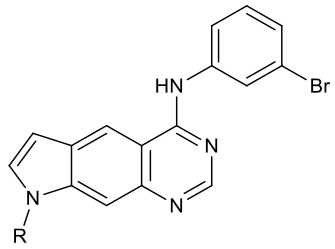
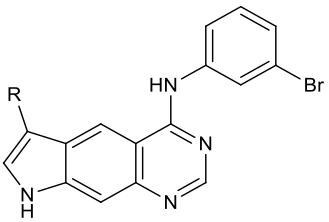


3a-3h



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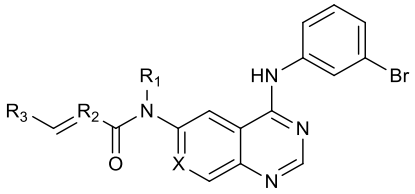
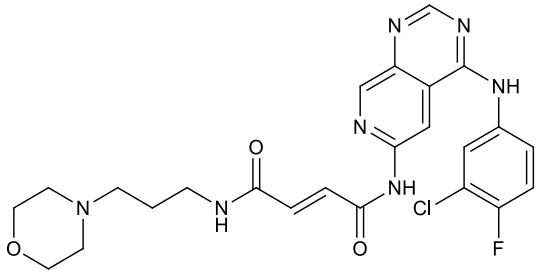
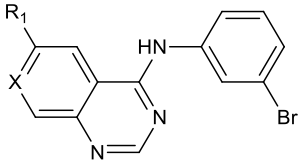


I



II



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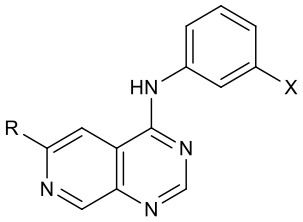
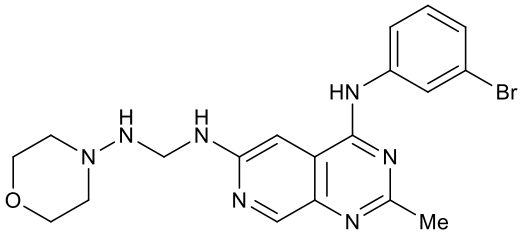


5-9



10n

Figure-1: General Molecular structures of the compounds (Table-1)

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Descriptor Calculation:
A huge number of molecular descriptors were calucalted using Dragon software [42] version 6. Approximately 4885 descriptors comprising 0D,1D,2D and 3D were calculated using the Dragon Software followed by feature selection method in QSARINS software [43]. This considerable reduced set of 1024 descriptors were further used in QSAR model development.

RESULTS AND DISCUSSION

The exploratory search was limited to seven variables per model in order to create simple and information rich QSAR models. The sixty-nine-molecule dataset was divided periodically into training (56 molecules, 80%) and prediction sets (28 molecules, 25%), using a random splitting mechanism, to create the GA-MLR QSAR models.

Table 1 includes a list of all the compounds and their topological and EGFR inhibition activity. For QSAR studies, out of 113 compounds, 85 Compounds (75%) were selected for the training set by random selection, using QSARINS software, for the generation of the QSAR model, and the remaining 28 compounds (25%) were used for the test set to evaluate the predictability of the developed model. Among all the calculated physicochemical and topological descriptors, only seven descriptors, which were found to be correlated with the activity, are listed in **Table 1**. In this Table-1, test set compounds are marked with a superscript 'b', and the compounds marked with the superscript 'c' are those that acted as outliers and thus were removed in the model development. The following were the key structural characteristics that were discovered to control how the compounds behaved:

MATS6m = Moran autocorrelation of lag 6 weighted by mass
MATS1e = Moran autocorrelation of lag 1 weighted by Sanderson electronegativity
RDF155u= Radial Distribution Function - 155 / unweighted
G2e = 2nd component symmetry directional WHIM index / weighted by Sanderson electronegativity.
HATS0e = leverage-weighted autocorrelation of lag 0 / weighted by Sanderson electronegativity
R4p = R autocorrelation of lag 4 / weighted by polarizability
R4s+ = R maximal autocorrelation of lag 4 / weighted by I-state
The variables describe either the electrical properties or the bulk of the molecules. [44-47].
A GA-MLR (Genetic Algorithm Multiple linear regression) analysis was performed using QSARINS Software [43] on the compounds of the training set to determine a link between observed activity and various calculated descriptors of the compounds. The most significant correlation achieved was as shown by Eq. (1).

$$pIC_{50} = 4.1964\ (\pm 1.3072)\ MATS6m - 5.1627\ (\pm 1.1754)\ MATS1e + 0.0523(\pm 0.0186)\ RDF155u - 10.0407\ (\pm 5.2439)\ G2e + 1.5473\ (\pm 0.5098)\ HATS0e - 0.9664(\pm 0.2574)\ R4s^{+} - 3.6180(\pm 0.8589)\ R4p + 11.3277 \quad (1)$$

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n =76, r^2 = 0.819, r^2_{cv} = 0.767, r^2_{pred} = 0.379, s = 0.230, $F_{3,28}$ = 44.07(2.53)

In Eq. (1), n denotes the number of data points used in the correlation, r^2 is the square of the correlation coefficient, r^2_{cv} is the square of cross-validated correlation coefficient obtained by the leave-one-out (LOO) jackknife procedure, and the square of the correlation coefficient for the test set compounds, or r^2_{pred}, is used to assess the correlation's external validity. Eqs. (2) and (3), where $y_{i,obsd}$ in Eq. (2) refers to the observed activity of compound i in the training set and that in Eq. (3) refers to compound i in the test set, are used to determine the values of r^2_{cv} and r^2_{pred}, respectively. Similar to this, $y_{i,pred}$ in Eq.(2) refers to the expected activity of compound i in the training set obtained using the leave-one-out jackknife approach, and $y_{i,pred}$ in Eq.(3) refers to the predicted activity for the compounds in the test set by the model obtained in the training set. However, $y_{av,obsd}$ in the equations refers to the average activity of the training set compound.

$$r^2_{cv} = 1 - [\Sigma_i (y_{i,obsd} - y_{i,pred})^2 / \Sigma_i (y_{i,obsd} - y_{av,obsd})^2] \quad (2)$$

$$r^2_{pred} = 1 - [\Sigma_i (y_{i,obsd} - y_{i,pred})^2 / \Sigma_i (y_{i,obsd} - y_{av,obsd})^2] \quad (3)$$

S is the standard deviation and F is the Fischer-ratio between the variances of the calculated and observed activities. These two statistical parameters make up the final two. The percentage confidence intervals are indicated by the numbers in parenthesis with a sign. The standard F-value at the 99 percent level is shown by the F-value in parentheses. A strong association is indicated by a F value greater than this. As a result, all of the descriptors utilised in this correlation are found to be extremely significant, and if we eliminate them one at a time, the correlation's significance is prominently reduced.

According to the findings, Eq. (1) significantly correlates the inhibitory activity values with the compound structural descriptors. The association has strong predictive power despite lacking any mechanistic elements.

A graph (Fig. 2) that compares the calculated and actual activities for the training and test sets demonstrates that the model is having a strong predictive power. As seen in Figure 2, nearly all the points lie close to the straight line except few. Using GA-MLR model (eq.1) we predicted some new compounds reported in Table 2, each of the predicted molecules has a greater activity value than any compound in the existing series (Table 1).

Docking Analysis

To determine these compounds' binding modes, LeadIT FlexX software was used to perform a molecular docking analysis on the predicted compounds (Table 2). A molecule's potency is determined by its capacity to interact with an enzyme. The linked enzyme's crystal structure, which can now be accessed from the RCSB protein data library, is essential for the research of molecular docking. The enzyme with the PDB entry code 2bgf (http://www.pdb.org) was chosen. The

enzyme was docked with each of the anticipated chemicals listed in Table 2, and Table 3 reports the docking conclusions.

All projected molecules in the enzyme underwent a molecular docking analysis. To demonstrate the greatest possible interactions between the inhibitors and the enzyme 2bgf , we only quoted compounds 10 and 1 here (Figs. 3 and 4), with compound 10 having the highest projected activity and compound 1 having the highest docking score (Table 3). It is evident from these Figs. 3 and 4 that the predicted compounds interact well with the enzyme. All of them go through hydrogen bonding, and steric interactions, wherein other active clefts of the enzyme encircle other chemical moieties. Any inhibitor's flexibility will determine whether or not a given moiety can enter an enzyme cavity. These steric interactions may entail dispersion interactions, a type of electronic contact.

Pharmacokinetic Studies:
Data Warrior software [49] was used to determine the predicted compounds' pharmacokinetic profiles, and the findings are shown in Table 4. Molecular weight (M.W.), ClogP, the number of hydrogen bond acceptors (H.A.s), the number of hydrogen bond donors (H.D.s), and the number of rotatable bonds (NRBs) are all included in these pharmacokinetic profiles [50-51]. Lipinski's rule of five asserts that any drug must satisfy at least three of the following four characteristics to be considered active:

(i) The value of its logP shouldn't be more than 5.
(ii) There shouldn't be more than ten hydrogen bond acceptors in it.
(iii) There shouldn't be more than five hydrogen bond donors (the sum of the N-H and O-H bonds).
(iv) Its molecular weight shouldn't exceed 500

Remember that all numbers are multiples of five, which is why it is called the rule of five. The ability to absorb and permeate is considered suitable for compounds with M.W. < 500 and ClogP < 5. Similarly, Viber's rule states that molecules with NRB < 10 have good oral bioavailability. As a result, the pharmacokinetic characteristics of all projected substances are excellent [52-54].

CONCLUSION

It has been discovered that a number of Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides, Methyl amino-Substituted Derivatives of 4-[(3-Bromophenyl)amino]-6-(methylamino)-pyrido[3,4-d]pyrimidinebased compounds, Pyrrolo- and Pyrazoloquinazoline and 6-Substituted 4-Anilinoquinazolines and 4-Anilinopyrido[3,4-d]pyrimidines derivatives inhibitory action is closely related to a number of different physicochemical characteristics. The MLR model [Eq. 1] has been used to suggest some novel compounds with improved activity. It has been demonstrated how the predicted compounds interact with the enzyme using the docking study. All predicted

compounds were discovered to have several hydrogen bonds with the receptor and involve their bulky groups in strong steric interactions with specific places of the enzyme. The proposed compounds exhibit good pharmacokinetic properties, according to the analysis of their pharmacokinetic profiles.

Table-1: Dataset compounds and their activity.

Compound Number	Index	R	X	Y	IC_{50}	PIC_{50}
001	A	H	H		0.70	9.155
002	A	CH_2NMe_2	H		45.00	7.346
003	A	$OCH_2CH_2NMe_2$	H		27.00	7.568
004	B	$O(CH_2)_3$4-Mepip	H	Br	1.70	8.769
005	B	$O(CH_2)_3$morpholide	H	Br	3.60	8.444
006	B	$O(CH_2)_4NMe_2$	H	Br	3.90	8.409
007	B	$O(CH_2)_3$imidazoy1	H	Br	3.00	8.523
008	B	$S(CH_2)_3NEt_2$	H	Br	0.78	9.108
009	B	H	H	CH	0.42	9.376
010	B	$O(CH_2)_3$4-Mepip	H	CH	2.00	8.698
011	B	$O(CH_2)_3$morpholide	H	CH	1.50	8.823
012	B	H	H	Br	0.69	9.161
013	B	$O(CH_2)_3$morpholide	H	Br	1.80	8.745
014	B	H	H	C1	0.75	9.125
015	B	$O(CH_2)_3$morph	F	C1	1.50	8.823
016	B	$[O(CH_2)_2]_2(CH_2)_2OH$	F	C1	1.70	8.769
017	C	H	F		0.75	9.125
018	C	$CH=CH(CH_2)_2$morpholide	F		0.16	9.795
019	C	$(CH_2)_4$morpholide	F		2.70	8.568
020	C	OMe	H		0.95	9.022
021	C	$O(CH_2)_2OMe$	H		0.97	9.013
022	C	$O(CH_2)_3$morpholide	H		1.50	8.823
023	C	$O(CH_2)_3$morpholide	Me		20.00	7.698
024	C	$O(CH_2)_3$4-Mepip	H		6.60	8.180

Compound number	Index	R	IC_{50}	PIC_{50}
025	2a	H	0.44	9.356
026	2b	Me	0.37	9.432
027	2c	CH $_2$CH(O.H.)CH2OH	12.00	7.920
028	2d	$(CH_2)_2$NMe 2b	40.00	7.398
029	2f	$(ch_2)_2$Nmorpholidec	3.70	8.432
030	2h	CH_2COOH	53.00	7.275
031	3a	H	0.44	9.356
032	3b	Me	0.80	9.097

033	3c	$CH_2CH(O.H.)CH_2OH$	1.60	8.795
034	3d	$(CH_2)_2NMe_2$	41.00	7.387
035	3e	$(CH_2)_3NMe_2$	21.00	7.677
036	3f	$(ch_2)_2$Nmorpholide	3.70	8.432
037	3g	$(ch_2)_3$Nmorpholide	8.80	8.055
038	3h	CH_2COOH	5.10	8.292
039	4	$CH_2N(CH2CH_2OH)_2$	3.50	8.455
040	5	CH_2 NMe_2	2.60	8.585
041	6	Ch_2Nmorpholide	4.80	8.318
042	7	$CH_2N(Me)(CH_2)$ $_2$Nme	7.50	8.124
043	8	$CH_2N(Me)CH_2COOMe$	3.40	8.468
044	9	$CH_2N(Me)CH$ $_2COOH$	0.72	9.143

Compound Number	Index	X	R_1	R_2	R_3	IC_{50}	PIC_{50}
045	I	N	H	H	H	0.91	9.040
046	I	C	H	H	H	0.70	9.154
047	II					1.50	8.823
048	I	N	Me	H	H	0.17	9.769
049	I	N	H	Me	H	1.60	8.795
050	I	C	H	Me	H	1.20	8.920
051	I	N	H	H	Me	0.50	9.301
052	I	C	H	H	Me	0.55	9.259
053	I	N	H	H	Cis-CI	0.69	9.161
054	I	C	H	H	CF_3	1.75	8.756
055	I	N	H	H	$CH=CH_2$	1.10	8.958
056	I	C	H	H	$=CH_2$	1.60	8.795
057	I	N	H	H	Ph	9.10	8.040
058	I	C	H	H	COMe	1.20	8.920
059	I	C	H	H	COOH	0.37	9.431
060	I	C	H	H	COOEt	2.70	8.568
061	I	N	H	H	COOEt	1.50	8.823
062	I	N	$(CH_2)_2NMe_2$	H	H	4.20	8.376
063	I	N	$(CH_2)_3$-N-morpholiny1	H	H	2.70	8.568
064	I	C	$(CH_2)_3$-N-morpholiny1	H	H	3.30	8.481
065	I	C	H	H	$COO(CH_2)_3NMe_2$	2.40	8.619
066	I	C	H	H	$CONH(CH_2)_3NMe_2$	0.44	9.356
067	I	N	H	H	$CONH(CH_2)_3NMe_2$	1.10	8.958
068	I	N	H	H	$CONH(CH_2)_3NEt_2$	0.73	9.136
069	I	N	H	H	$CONH(CH_2)_3$-N-morpho	0.81	9.091
070	I	N	H	H	$CONH(CH_2)_3$-N-imidazo	0.56	9.251

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071	I	N	Me	H	$CONH(CH_2)_3NMe_2$	1.45	8.838
072	II					0.61	9.214
073	III	N	$NHSO_2CH=CH_2$			0.76	9.119
074	III	C	$NHSO_2CH=CH_2$			1.40	8.853
075	III	N	$SO_2CH_2CH_2OH$			93.5	7.029
076	III	N	$SO_2CH=CH_2$			0.43	9.366
077	III	N	$SOCH=CH_2$			4.60	8.337

Compound number	Index	R	X	IC_{50}	PIC_{50}
078	5a	NH_2	Br	0.130	9.886
079	5b	NHMe	Br	0.008	11.096
080	5c	NMe_2	Br	0.006	11.221
081	5d	$NHCH_2CH_2OH$	Br	0.190	9.721
082	5e	$N(Me)CH_2CH_2OH$	Br	0.220	9.657
083	5f	$NHCH_2CH(OH)CH_2OH$	Br	0.180	9.744
084	5g	$N(Me)CH_2CH(OH)CH_2OH$	Br	0.560	9.252
085	5h	$NH(CH_2)_2NMe_2$	Br	1.100	8.958
086	5i	$NH(CH_2)_3NMe_2$	Br	1.200	8.920
087	5j	$NH(CH_2)_4$ NMe_2	Br	1.800	8.744
088	5k	$NHCH_2CH(OH)CH_2NEt_2$	Br	4.600	8.337
089	5I	$NH(CH_2)_2N(Me)CH_2CH_2OH$	Br	1.700	8.769
090	5m	$N(Me)(CH_2)_2NMe_2$	Br	8.100	8.091
091	5n	$NH(CH_2)_3$morpholinyI	Br	0.650	9.187
092	5o	$NH(CH_2)_2$morpholinyI	Br	1.000	9.000
093	5p	$NH(CH_2)_3$NmepiperazinyI	Br	3.900	8.408
094	5q	$NH(CH_2)_2N(CH_2CH_2OH)_2$	Br	0.930	9.032

095	5r	$NH(CH_2)_3N(CH_2CH_2OH)_2$	Br	0.350	9.455
096	5s	$NHCH_2$(3-pyridyI)	Br	1.500	8.824
097	5t	$NHCH_2CH_2$(2-pyridyI)	Br	1.200	8.920
098	5u	$NH(CH_2)_2$(4-imidazolyI)	Br	0.780	9.107
099	5v	$NH(CH_2)_3$(1-imidazolyI)	Br	1.700	8.769
100	5w	4-MepiperazinyI	Br	6.400	8.193
101	5x	$NHCH_2COOH$	Br	0.280	9.553
102	5y	$N(Me)CH_2COOH$	Br	0.440	9.356
103	5z	$NH(CH_2)_2COOH$	Br	0.270	9.568
104	6b	NHMe	H	9.000	8.045
105	7b	NHMe	CI	0.190	9.721
106	8b	NHMe	CF_3	1.100	8.958
107	9a	NH_2	Me	3.100	8.508
108	9b	NHMe	Me	0.450	9.346
109	9c	NMe_2	Me	2.800	8.553
110	9n	$NH(CH_2)_2$morpholinyI	Me	1.500	8.824
111	9o	$NH(CH_2)_3$morpholinyI	Me	1.800	8.744
112	9u	$NH(CH_2)_2$(4-imidazolyI)	Me	1.300	8.886
113	10n			117.000	6.931

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Table- 2: Structural parameters used in the present study

ID	MATS 6m	MATS 1e	RDF155u	G2e	HATS 0e	R4p	R4s+	Obs.pI C_{50}	Pred. pIC_{50} using eq. 1	$\Delta pI C_{50}$	Pred. LOO
1	0.03	-0.10	0.00	0.18	0.16	0.30	0.20	9.16	9.13	-0.03	9.12
2	-0.23	-0.06	1.48	0.15	0.27	0.59	0.20	7.35	7.33	-0.02	7.31
3	-0.03	-0.06	2.22	0.17	0.26	0.52	0.19	7.57			
4[b]	0.04	-0.04	3.77	0.15	0.19	0.62	0.10	8.77	8.35	-0.42	-
5	0.05	-0.06	3.95	0.15	0.21	0.56	0.17	8.44	8.69	0.25	8.70
6	0.05	-0.05	2.58	0.16	0.23	0.50	0.17	8.41	8.71	0.30	8.72
7	0.03	-0.08	2.90	0.17	0.24	0.48	0.24	8.52	8.72	0.20	8.72
8[c]	0.06	-0.03	5.93	0.15	0.20	0.61	0.13	9.11			
9	0.02	-0.07	0.00	0.16	0.70	0.36	0.21	9.38	9.74	0.36	9.83
10	0.05	-0.02	5.22	0.16	0.17	0.60	0.10	8.70	8.31	-0.39	8.29
11	0.07	-0.04	4.75	0.16	0.20	0.54	0.18	8.82	8.66	-0.16	8.65
12[b]	0.02	-0.08	0.00	0.16	0.18	0.30	0.20	9.16	9.22	0.06	-
13	0.05	-0.06	3.13	0.15	0.22	0.56	0.18	8.75	8.65	-0.10	8.64
14	-0.03	-0.08	0.00	0.16	0.18	0.29	0.20	9.13	9.04	-0.09	9.02
15	0.05	-0.06	3.36	0.15	0.22	0.55	0.18	8.82	8.70	-0.12	8.69
16[b]	0.04	-0.09	3.88	0.16	0.25	0.45	0.15	8.77	9.17	0.40	-
17	-0.03	-0.08	0.00	0.16	0.18	0.29	0.20	9.13	9.04	-0.09	9.02
18[c]	0.01	-0.05	6.86	0.16	0.24	0.50	0.18	9.80			
19	0.00	-0.05	3.65	0.14	0.23	0.53	0.18	8.57	8.64	0.07	8.65

20	0.01	-0.09	0.00	0.17	0.41	0.42	0.25	9.02	9.00	-0.02	9.00
21	-0.02	-0.08	1.97	0.15	0.33	0.39	0.19	9.01	9.17	0.16	9.19
22[b]	0.05	-0.06	3.95	0.15	0.22	0.55	0.17	8.82	8.74	-0.08	-
23[c]	0.08	-0.05	3.80	0.14	0.21	0.58	0.16	7.70			
24	0.03	-0.05	0.37	0.15	0.20	0.60	0.16	8.18	8.21	0.03	8.21
25	0.03	-0.03	0.00	0.19	0.95	0.40	0.19	9.36	9.54	0.18	9.65
26	0.04	0.04	0.00	0.18	0.75	0.41	0.11	9.43	9.05	-0.38	8.92
27	0.02	-0.11	0.10	0.18	0.32	0.56	0.47	7.92	8.19	0.27	8.23
28	0.02	0.06	2.82	0.17	0.28	0.61	0.12	7.40	7.66	0.26	7.70
29	0.08	0.05	8.74	0.19	0.26	0.59	0.11	8.43	8.12	-0.31	8.04
30[b]	0.02	-0.09	0.00	0.19	0.41	0.52	0.62	7.28	8.12	0.84	-
31[b]	0.02	-0.13	0.00	0.17	0.48	0.49	0.20	9.36	9.15	-0.21	-
32	0.03	-0.06	0.00	0.16	0.42	0.53	0.19	9.10	8.71	-0.39	8.69
33	0.02	-0.15	1.36	0.16	0.31	0.56	0.30	8.80	8.82	0.02	8.82
34[b]	0.02	-0.02	1.85	0.19	0.28	0.61	0.12	7.39	7.82	0.43	-
35[b]	0.07	-0.01	1.27	0.17	0.25	0.60	0.11	7.68	8.14	0.46	-
36[b]	0.07	0.01	5.13	0.17	0.25	0.59	0.11	8.43	8.28	-0.15	-
37	0.06	0.02	8.28	0.18	0.22	0.60	0.12	8.06	8.16	0.10	8.18
38	0.02	-0.13	0.00	0.17	0.40	0.54	0.34	8.29	8.71	0.42	8.74
39[b]	0.04	-0.15	0.00	0.16	0.24	0.65	0.15	8.46	8.54	0.08	-
40	0.02	-0.07	0.00	0.16	0.29	0.58	0.11	8.59	8.41	-0.18	8.40
41	0.05	-0.03	0.00	0.15	0.23	0.63	0.10	8.32	8.17	-0.15	8.15
42	0.02	-0.08	0.00	0.17	0.24	0.56	0.09	8.12	8.38	0.26	8.39
43	0.01	-0.07	0.87	0.17	0.27	0.53	0.26	8.47	8.32	-0.15	8.31

44	0.05	-0.13	0.44	0.15	0.30	0.54	0.31	9.14	8.94	-0.20	8.92
45[b]	0.02	-0.12	0.00	0.18	0.43	0.45	0.22	9.04	9.05	0.01	-
46	0.03	-0.10	0.00	0.16	0.44	0.46	0.19	9.15	9.20	0.05	9.20
47	0.05	-0.06	2.69	0.15	0.22	0.53	0.25	8.82	8.67	-0.15	8.66
48[c]	0.08	-0.07	0.00	0.16	0.36	0.50	0.26	9.77			
49[b]	0.00	-0.10	0.00	0.17	0.39	0.46	0.18	8.80	8.90	0.10	-
50	0.01	-0.08	0.00	0.16	0.38	0.47	0.17	8.92	8.90	-0.02	8.90
51	0.04	-0.10	0.00	0.16	0.41	0.44	0.17	9.30	9.28	-0.02	9.28
52	0.05	-0.08	0.00	0.17	0.41	0.45	0.18	9.26	9.08	-0.18	9.07
53	0.04	-0.13	0.00	0.16	0.47	0.46	0.51	9.16	9.13	-0.03	9.13
54	0.02	-0.07	0.00	0.17	0.49	0.44	0.31	8.76	8.93	0.17	8.94
55[b]	0.01	-0.10	0.00	0.16	0.42	0.46	0.19	8.96	9.08	0.12	-
56	0.05	-0.10	0.00	0.18	0.43	0.45	0.27	8.80	9.02	0.22	9.03
57	0.02	-0.08	2.08	0.17	0.38	0.50	0.17	8.04			
58	0.00	-0.08	0.38	0.18	0.40	0.46	0.17	8.92	8.74	-0.18	8.73
59[b]	0.02	-0.14	0.03	0.17	0.44	0.46	0.20	9.43	9.25	-0.18	-
60	0.05	-0.08	0.47	0.16	0.33	0.45	0.34	8.57	8.92	0.35	8.94
61	0.04	-0.10	1.84	0.18	0.33	0.44	0.33	8.82	8.90	0.08	8.91
62	0.04	-0.04	0.52	0.15	0.26	0.51	0.16	8.38	8.63	0.25	8.64
63	0.07	-0.04	2.61	0.15	0.22	0.57	0.23	8.57	8.52	-0.05	8.51
64	0.07	-0.03	1.23	0.15	0.22	0.59	0.17	8.48	8.38	-0.10	8.37
65	0.06	-0.06	9.07	0.17	0.23	0.55	0.27	8.62	8.77	0.15	8.78
66[b]	0.06	-0.08	13.16	0.15	0.22	0.57	0.31	9.36	9.17	-0.19	-
67	0.06	-0.09	10.13	0.16	0.22	0.56	0.25	8.96	9.05	0.09	9.06

68	0.10	-0.07	13.49	0.15	0.20	0.60	0.24	9.14	9.23	0.09	9.25
69	0.06	-0.07	14.56	0.15	0.21	0.58	0.23	9.09	9.21	0.12	9.25
70	0.03	-0.11	8.33	0.15	0.25	0.53	0.26	9.25	9.18	-0.07	9.17
71	0.08	-0.06	7.15	0.15	0.22	0.56	0.28	8.84	8.89	0.05	8.90
72	0.05	-0.08	11.63	0.17	0.25	0.58	0.25	9.21	8.91	-0.30	8.86
73[b]	0.03	0.02	0.00	0.16	0.42	0.45	0.52	9.12	8.26	-0.86	-
74[b]	0.05	0.05	0.00	0.16	0.37	0.50	0.39	8.85	8.06	-0.79	-
75	0.05	-0.04	0.00	0.17	0.42	0.50	1.83	7.03	7.11	0.08	7.50
76[c]	0.05	0.04	0.00	0.16	0.47	0.49	0.43	9.37			
77	0.05	0.00	0.00	0.18	0.41	0.51	0.43	8.34	8.10	-0.24	8.08
78[b]	0.02	-0.21	0.00	0.17	0.51	0.45	0.19	9.89	9.77	-0.12	-
79[b]	0.05	-0.14	0.00	0.18	0.45	0.44	0.18	11.10	9.38	-1.72	-
80[b]	0.06	-0.07	0.00	0.17	0.40	0.48	0.17	11.22	8.95	-2.27	-
81	0.04	-0.18	0.00	0.16	0.42	0.42	0.18	9.72	9.77	0.05	9.78
82	0.07	-0.13	0.00	0.16	0.35	0.50	0.18	9.66	9.24	-0.42	9.23
83	0.03	-0.20	0.00	0.16	0.35	0.44	0.22	9.74	9.62	-0.12	9.60
84	0.07	-0.16	0.00	0.17	0.30	0.51	0.30	9.25	9.07	-0.18	9.06
85[b]	0.06	-0.08	1.31	0.16	0.28	0.54	0.11	8.96	8.83	-0.13	-
86	0.06	-0.06	2.54	0.16	0.26	0.54	0.09	8.92	8.78	-0.14	8.78
87	0.07	-0.05	4.39	0.17	0.29	0.51	0.14	8.74	8.87	0.13	8.88
88	0.06	-0.10	0.65	0.16	0.24	0.56	0.13	8.34	8.74	0.40	8.76
89	0.08	-0.12	0.00	0.16	0.27	0.54	0.17	8.77	8.98	0.21	8.99
90[b]	0.02	-0.02	0.00	0.15	0.26	0.57	0.09	8.09	8.26	0.17	-
91[b]	0.07	-0.06	0.00	0.17	0.23	0.66	0.13	9.19	8.07	-1.12	-

92[b]	0.08	-0.07	0.00	0.15	0.25	0.66	0.12	9.00	8.40	-0.60	-
93	0.07	-0.10	2.85	0.16	0.23	0.64	0.13	8.41	8.60	0.19	8.61
94	0.08	-0.15	1.74	0.18	0.25	0.56	0.15	9.03	8.94	-0.09	8.93
95[b]	0.07	-0.14	1.17	0.17	0.25	0.55	0.16	9.46	8.94	-0.52	-
96	0.04	-0.11	0.00	0.17	0.30	0.52	0.13	8.82	8.81	-0.01	8.81
97	0.07	-0.09	0.02	0.16	0.27	0.54	0.12	8.92	8.83	-0.09	8.83
98	0.06	-0.15	0.00	0.16	0.31	0.51	0.14	9.11	9.25	0.14	9.25
99	0.05	-0.10	1.67	0.18	0.29	0.52	0.13	8.77	8.78	0.01	8.78
100	0.04	-0.11	0.00	0.17	0.25	0.59	0.09	8.19	8.52	0.33	8.55
101[b]	0.03	-0.18	0.00	0.16	0.40	0.43	0.23	9.55	9.62	0.07	-
102	0.07	-0.14	0.00	0.16	0.36	0.49	0.44	9.36	9.10	-0.26	9.08
103	0.06	-0.16	0.00	0.16	0.35	0.49	0.50	9.57	9.08	-0.49	9.04
104[b]	-0.11	-0.11	0.00	0.18	0.40	0.37	0.11	8.05	8.80	0.75	-
105	0.04	-0.13	0.00	0.18	0.47	0.41	0.28	9.72	9.33	-0.39	9.30
106[b]	-0.20	-0.08	0.00	0.18	0.50	0.40	0.56	8.96	7.88	-1.08	-
107	-0.03	-0.16	0.00	0.18	0.39	0.43	0.14	8.51			
108	0.06	-0.09	0.00	0.18	0.36	0.42	0.09	9.35	9.19	-0.16	9.18
109	0.12	-0.02	0.00	0.16	0.32	0.47	0.09	8.55	9.04	0.49	9.11
110	0.11	-0.04	1.02	0.15	0.23	0.58	0.08	8.82	8.72	-0.10	8.71
111	0.07	-0.03	1.56	0.15	0.21	0.58	0.07	8.74	8.51	-0.23	8.49
112	0.11	-0.11	1.04	0.18	0.27	0.48	0.13	8.89	9.16	0.27	9.19
113[c]	0.07	-0.06	0.43	0.16	0.23	0.56	0.08	6.93			

b= test set, c = Outlier

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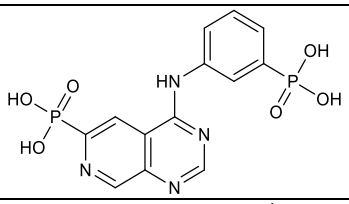
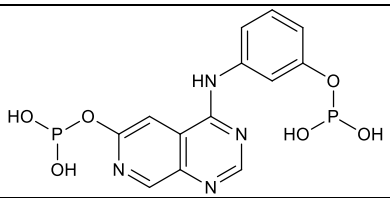
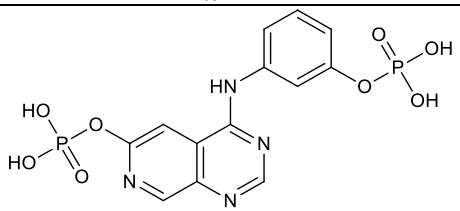
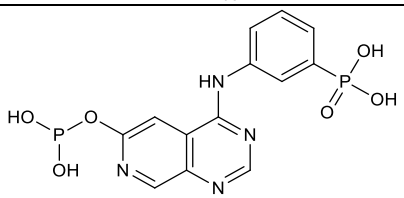
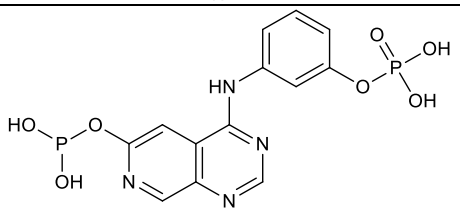
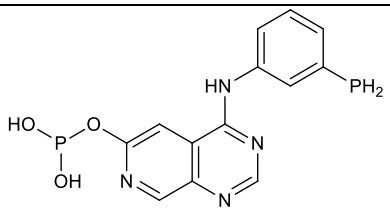
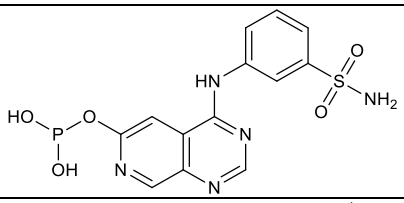
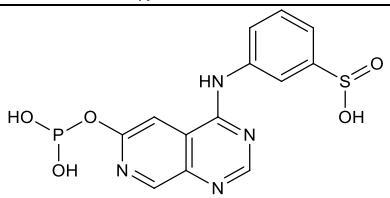
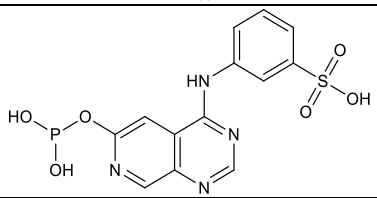
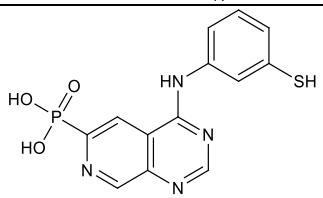
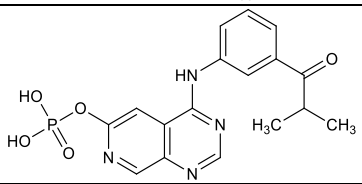
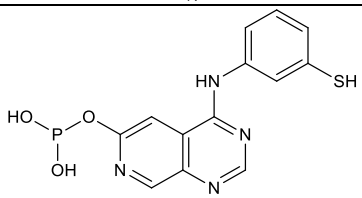
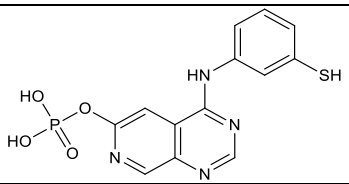
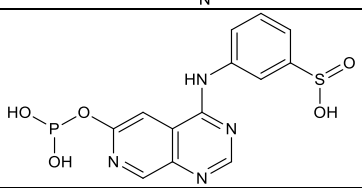
Table-3: Some predicted compounds belonging to the series of Table-1 and their predicted activity using eq. 1

Compd No.	Molecular Structure	MATS6m	MATS1e	RDF155u	G2e	HATS0e	R4p	R4s+	Pred. pIC_{50}
1.		0.03	-0.42	0.00	0.16	0.43	0.46	0.30	10.72
2.		0.05	-0.48	0.00	0.18	0.45	0.50	0.42	10.69
3.		0.04	-0.48	0.00	0.20	0.40	0.45	0.58	10.40
4.		0.04	-0.45	0.00	0.16	0.49	0.46	0.44	10.88
5.		0.04	-0.48	0.00	0.16	0.45	0.46	0.41	10.99
6.		0.18	-0.31	0.00	0.18	0.50	0.44	0.41	10.66

7.		0.05	-0.27	0.00	0.16	0.48	0.44	0.41	10.09
8.		0.06	-0.30	0.00	0.18	0.53	0.45	0.42	10.08
9.		0.04	-0.26	0.00	0.16	0.55	0.43	0.43	10.06
10.		0.13	-0.36	0.00	0.17	0.64	0.42	0.48	11.10
11.		0.13	-0.28	0.00	0.16	0.36	0.47	0.53	10.11
12.		0.15	-0.39	0.00	0.17	0.51	0.47	0.40	10.91
13.		0.14	-0.39	0.00	0.18	0.54	0.42	0.80	10.67
14.		0.06	-0.30	0.00	0.18	0.53	0.45	0.42	10.08

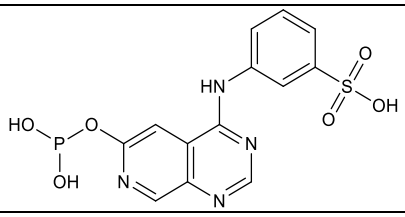
15.		0.04	-0.26	0.00	0.16	0.55	0.43	0.43	10.06

Table 4: Docking results of predicated molecules

Compd. No.	No. of Hydrogen Bonds	H-bonds	H-bonds Length (Å)	Score
1	5	O(19)-Thr9 O(20)-Leu71 O(21)-Leu8 O(23)-Leu73 O(25)-Arg72	-1.28 -3.97 -3.15 -3.15 -8.30	-22.5530
2	6	N(8)-Thr66 O(19)-Ala46 H(30)- Thr66 H(34)-Ile44 H(36)-Asn60 H(37)-Tyr59	-2.88 -2.80 -4.03 -4.21 -4.19 -4.66	-14.1107
3	6	N(8)-Thr66 O(19)-Ala46 O(20)-His68 O(20)-Ala46 O(21)-Gly47 H(32)-Thr66	-2.88 -2.64 -7.75 -0.07 -1.01 -2.88	-18.1582
4	4	O(23)-Ala46 O(24)-His68 H(34)-Asn60 H(35)-Asn60	-2.63 -7.18 -3.16 -4.07	-21.8494
5	5	O(24)-His68 O(25)-Gly47 H(31)-Thr66 H(35)-Asn60 H(36)-Tyr59	-5.59 -4.70 -4.70 -3.55 -4.37	-19.9797
6	4	N(17)-Glu16 O(19)-Lys33 H(27)-Lys29 H(32)-Thr14	-3.55 -2.23 -4.70 -2.87	-13.8025
7	5	O(23)-Ala46 O(24)-Ala46 N(25)-His68	-1.62 -1.34 -8.15	-21.3615

		H(30)-Thr66 H(35)-Glu64	-1.93 -2.42	
8	4	O(23)-Ala46 O(24)-His68 H(33)-Asn60 H(34)-Asn60	-3.07 -8.26 -3.36 -4.37	-22.2968
9	4	O(24)-His68 O(25)-His68 H(34)-Asn60 H(35)-Ser65	-7.27 -0.01 -3.67 -3.50	-22.4985
10	5	O(19)-Leu71 O(19)-Thr7 O(20)-Leu8 O(21)-Thr9 H(33)-Thr9 H(27)-Leu71	-3.44 -0.64 -2.33 -0.88 -3.20 -0.52	-20.8022
11	4	N(8)-Thr66 H(32)-Thr66 O(25)-Ala46 O(25)-His68	-2.74 -4.70 -2.01 -3.74	-20.6122
12	4	H(32)-Asn60 H(33)-Asn60 H(27)-Tyr59 H(31)-Asp58	-3.74 -2.68 -4.52 -0.86	-16.6336
13	3	H(32)-Asp58 H(28)-Tyr59 O(21)-Gln62	-1.15 -4.66 -4.13	-15.6645
14	4	O(23)-Ala46 O(24)-His68 H(33)-Asn60 H(34)-Asn60	-3.07 -8.26 -3.36 -4.37	-22.2958
15	4	O(24)-His68 O(25)-His68 H(34)-Asn60 H(35)-Ser65	-7.27 -0.01 -3.50 -3.67	-22.5024

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Table-4: Pharmacokinetic properties of the proposed compounds

Compd. No.	M.W.	cLogP	cLogS	H-Acceptors	H-Donors	Total Surface Area	Mutagenic	Tumorigenic	Reproductive Effective	Irritant
1.	382.23	-5.10	0.02	10	5	248.3	none	none	none	none
2.	382.23	-2.20	-3.77	10	5	234.26	none	none	none	none
3.	414.23	-4.54	-1.13	12	5	268.3	none	none	none	none
4.	382.23	-3.53	-2.26	10	5	241.28	none	none	none	none
5.	398.23	-3.37	-2.45	11	5	251.28	none	none	none	none
6.	334.23	0.22	-4.28	7	3	198.06	none	none	none	none
7.	381.34	-1.01	-3.76	10	4	241.91	none	none	none	high
8.	366.32	-1.82	-3.69	9	4	233.88	none	none	none	none
9.	382.32	-2.01	-2.46	10	4	239.74	none	none	none	high
10.	334.32	-1.42	-2.69	7	3	227.69	none	none	none	none
11.	388.35	-0.40	-3.65	9	3	276.6	none	none	none	none
12.	334.32	0.16	-4.96	7	3	220.67	none	none	none	none
13.	350.32	-1.00	-3.65	8	3	237.69	none	none	none	none

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14.	366.32	-1.82	-3.69	9	4	233.88	none	none	none	None
15.	382.320	-2.01	-2.46	10	4	239.74	none	none	none	high

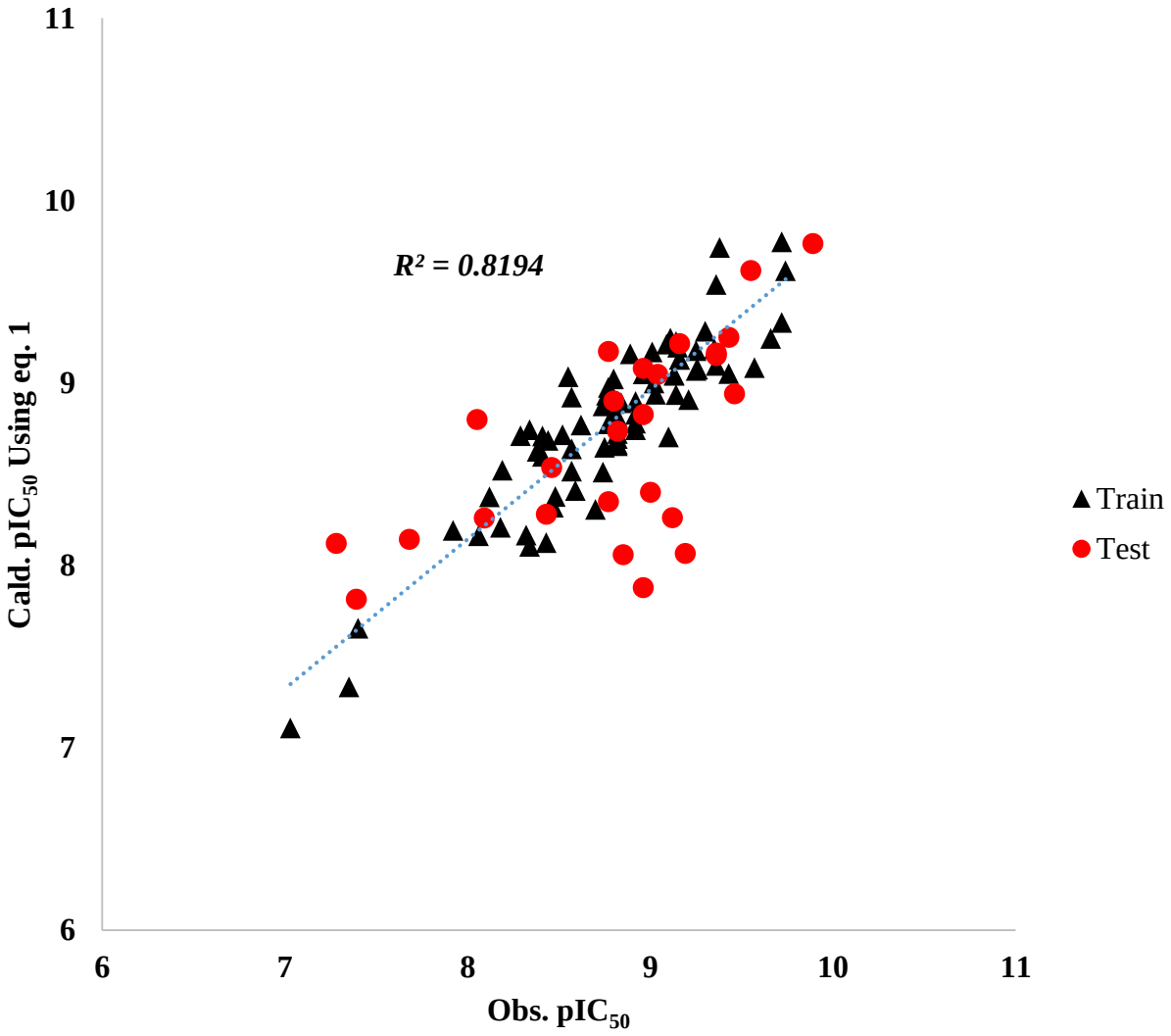

Figure 2: A graph between predicted and observed activities of compounds of Table 1

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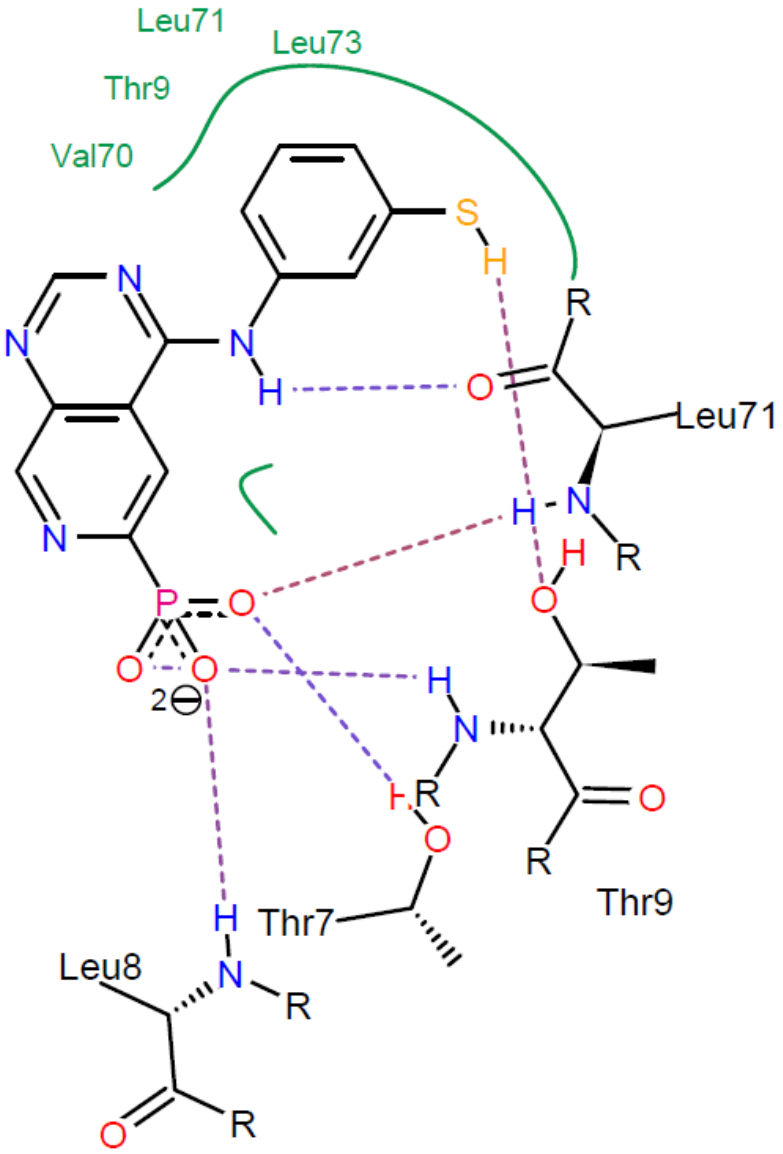

Figure-3 :A representation of binding of predicted compound 10 in 2bgf

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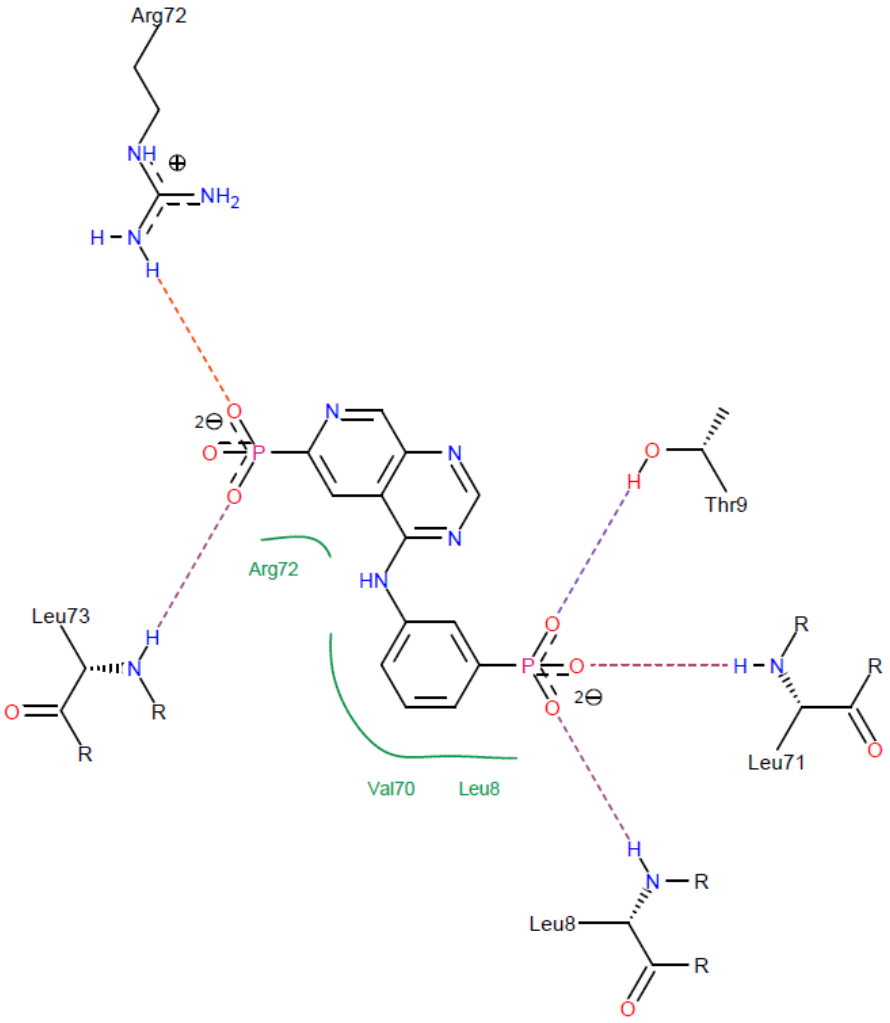

Figure-3:A representation of binding of predicted compound 1 in 2bgf

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