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Quantitative Structure Activity Relationshipstudy of pyrimidine derivatives as AXL kinase inhibitors for their anticancer activity

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ABSTRACT- Quantitative structure-activity relationship studies were carried out to forecast the anticancer potential of pyrimidine derivatives. According to two-dimensional (2D) QSAR investigations, bulky groups and different topological descriptors have a favorable impact on activity, which suggests the N-substituted piperazine ring may boost biological activity.

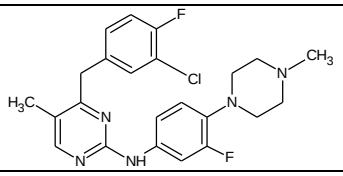
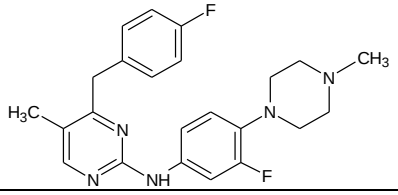
Key words: QSAR, Pyrimidine derivatives, Anticancer activity

I. INTRODUCTION

Multi-domain transmembrane proteins fall under the category of receptor tyrosine kinases (RTKs). These proteins serve as the ligands' extracellular sensors. Multiple downstream signaling cascades are recruited, phosphorylated, and activated as a result of this metabolic activity. Numerous cancers, including non-small cell lung cancer (NSCLC), osteosarcoma, breast cancer, acute myeloid leukemia, prostate cancer, and colorectal cancer, have been found to overexpress AXL. Additionally, the development of drug resistance to chemotherapy and targeted treatments is brought on by the epithelial-mesenchymal transition (EMT) caused by the AXL signaling pathway in tumor cells. Because the kinase domain of the AXL receptor and the majority of AXL kinase inhibitors are identical,

The structures of AXL kinase receptor inhibitors are depicted in Figure 1. The novel pyrimidine derivatives have been shown to have selective and potent inhibitory activity against AXL kinase.The correlation of the structural parameter (independent variable) with the biological activity (dependent variable) of the derivatives was performed using the 2D-QSAR technique. Here, multiple regression methods were accomplished for QSAR model development. We have generated the quantitative structure-activity relationship (QSAR) model of pyrimidine derivatives for the prediction of biological activity. These details could be applied to modify the structure and improve the biological activity of pyrimidine derivatives against the AXL kinase receptor.

Table 1. Structure of pyrimidine and observed activity

S.No.	Compounds	IC_{50}
1		2.8
2		6.1

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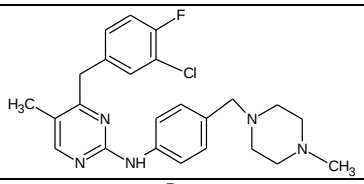
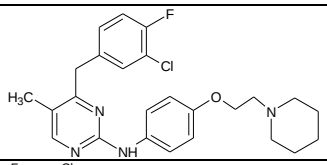
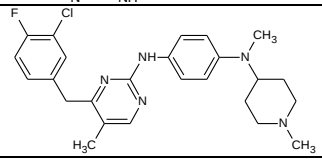
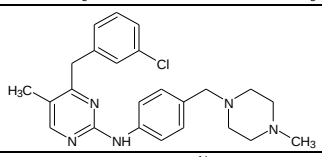
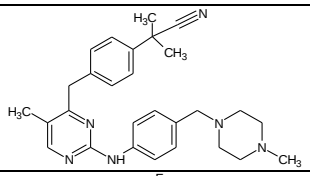
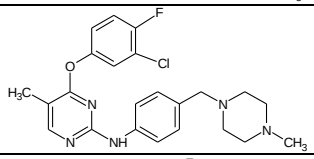
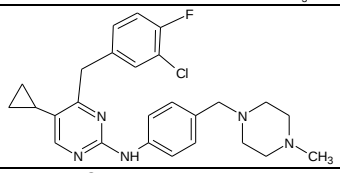
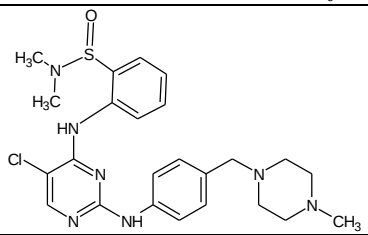
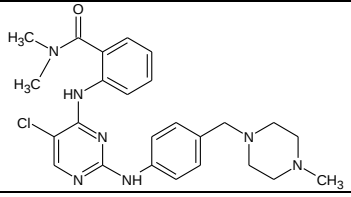
3		0.73
4		1.63
5		0.42
6		0.44
7		0.29
8		1.4
9		3.4
10		0.027
11		0.088

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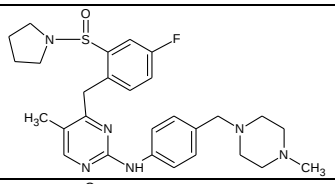
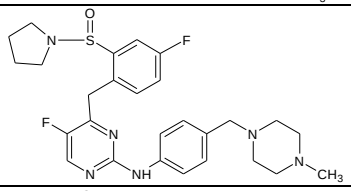
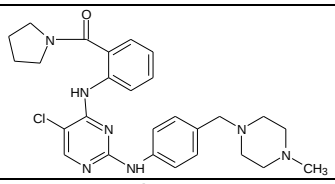
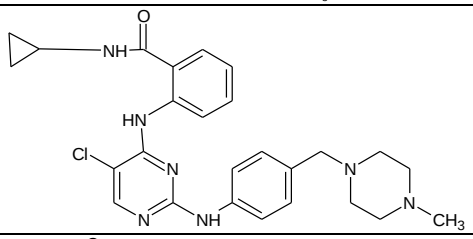
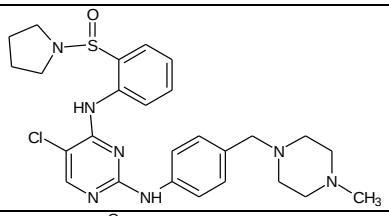
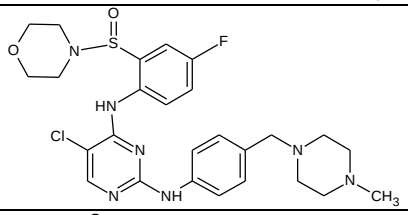
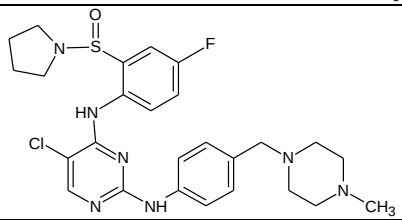
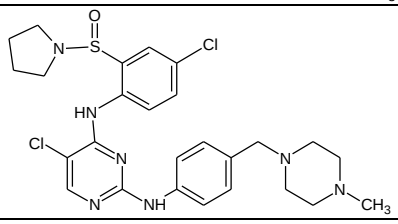
12		2.93
13		1.15
14		0.061
15		0.032
16		0.019
17		0.24
18		0.037
19		1.08

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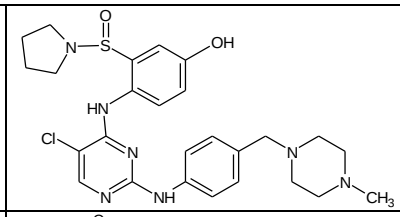
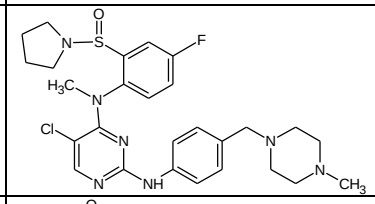
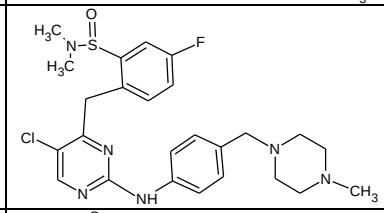
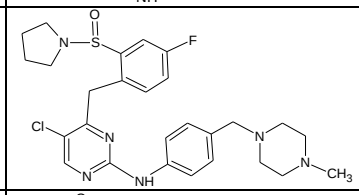
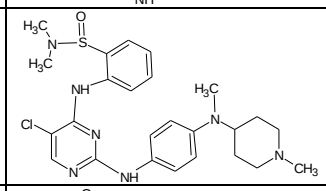
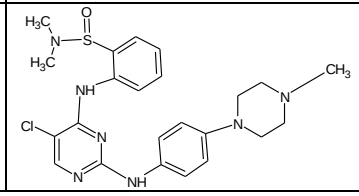
20		1.32
21		3.91
22		0.082
23		0.091
24		0.056
25		1.73

The chemical structures were created in Chemsketch 19 and saved as.mol files. The 25 descriptor values shown in Table 2 were computed using the Dragon software. Indices are 2D descriptors that consider the internal atomic structure of compounds and store in numerical form details about the size, shape, branching, presence of heteroatoms, and number of bonds in a given molecular structure. Given their ease of use and speed of calculation, indices are a particularly helpful tool for QSAR. This is especially useful nowadays since it allows for the analysis of QSAR study structures before high throughput production and testing.

Table 2.Values of topological descriptors and Anticancer Activity used in regression analysis

S.No.	IC50	MSD	ON1V	piPC08	piPC09	IDE	Eta_A	X5A	X0sol	ChiA_D
1	2.8	7.809	1.895	6.586	6.905	3.886	0.477	0.077	20.717	0.005
2	6.1	7.664	1.859	6.547	6.864	3.862	0.469	0.078	19.347	0.006
3	0.73	8.275	1.921	6.506	6.812	3.976	0.484	0.081	21.424	0.005
4	1.63	8.846	1.98	6.45	6.767	4.074	0.482	0.083	21.968	0.005

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5	0.42	8.291	1.984	6.532	6.838	3.976	0.484	0.078	22.294	0.005
6	0.44	8.063	1.886	6.46	6.758	3.933	0.49	0.082	21.424	0.005
7	0.29	9.062	2.15	6.619	6.921	4.117	0.482	0.08	24.131	0.004
8	1.4	8.275	1.88	6.506	6.812	3.976	0.478	0.081	21.424	0.005
9	3.4	8.342	2.109	6.661	6.974	3.981	0.485	0.077	22.416	0.005
10	0.027	8.577	2.001	6.567	6.86	4.021	0.491	0.08	24.867	0.004
11	0.088	8.577	2.052	6.567	6.86	4.021	0.481	0.08	24.579	0.004
12	2.93	8.974	2.276	6.683	6.987	4.089	0.482	0.077	25.196	0.004
13	1.15	8.974	2.249	6.683	6.987	4.089	0.477	0.077	24.326	0.004
14	0.061	8.895	2.24	6.629	6.93	4.08	0.482	0.078	25.407	0.004
15	0.032	8.81	2.19	6.593	6.901	4.068	0.481	0.079	24.7	0.004
16	0.019	8.895	2.188	6.629	6.93	4.08	0.491	0.078	25.696	0.004
17	0.24	9.138	2.245	6.691	6.997	4.12	0.482	0.079	26.403	0.004
18	0.037	8.974	2.224	6.683	6.987	4.089	0.486	0.077	25.696	0.004
19	1.08	8.974	2.224	6.683	6.987	4.089	0.497	0.077	27.066	0.004
20	1.32	8.974	2.23	6.683	6.987	4.089	0.487	0.077	26.566	0.004
21	3.91	8.903	2.274	6.72	7.033	4.078	0.486	0.075	26.566	0.004
22	0.082	8.693	2.062	6.619	6.909	4.038	0.488	0.079	24.867	0.004
23	0.091	8.974	2.249	6.683	6.987	4.089	0.488	0.077	25.696	0.004
24	0.056	8.611	2.063	6.592	6.884	4.023	0.491	0.077	25.738	0.004
25	1.73	8.143	1.938	6.589	6.893	3.941	0.49	0.078	24.16	0.005

II. MATERIALS AND METHODS

On the collection of 35 compounds shown in Table 1, a QSAR analysis was performed using the adenosine A3 agonist pC3 as a dependent parameter and several topological factors as independent parameters. Using NCSS version 2019, the multiparameter regression analysis was carried out on a personal computer. To ascertain the inter-correlation between the physiochemical parameters employed in QSAR analysis, the Pearson correlation matrix was created [11–14]. Table 3 displays the correlation matrix that was created. The mean information content based on vertex degree equality and edge equality were the descriptors that the models employed.

The correlation matrix for the aforementioned indicators is presented in Table 3 and shows that there is significant correlation among the descriptors. From the correlation matrix, we can also conclude that each of the aforementioned indices is highly correlated with activity. This means that it is possible to obtain a statistically significant mono-parametric model. Based on the correlation matrix, we conclude that only multi-parametric regressions involving combinations of the indices mentioned before may result in a statistically significant regression expression [15–18].

III. RESULTS AND DISCUSSIONS

QSAR models were obtained by stepwise multiple linear regression (MLR) analysis. The stepwise selection of variables, a combination of forward selection and backward elimination, was used to select the most relevant subset of descriptors. Regression analysis was performed by NCSS 2019 software. The descriptors and their correlation with anticancer activity are shown in Table 3. In the case of each regression problem, NCSS produces many models and ranks them based on standard error of calibration and coefficient of multiple determinations (R^2), where some models have a large number of input variables and are thus over-fitted [13–16].

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Table 3. Correlation Matrix between Calculated Descriptors

	IC_{50}	MSD	ON1V	piPC08	piPC09	IDE	Eta α A	X5A	X0sol	ChiA_D
IC_{50}	1.0000	-0.4683	-0.2175	0.0503	0.1198	-0.4751	-0.4941	-0.3068	-0.4427	0.5946
MSD		1.0000	0.8851	0.618	0.589	0.9985	0.3296	-0.1948	0.8363	-0.8606
ON1V			1.0000	0.8603	0.8461	0.8725	0.2406	-0.5638	0.8432	-0.8126
piPC08				1.0000	0.995	0.5915	0.1857	-0.8203	0.7472	-0.6454
piPC09					1.0000	0.5638	0.1331	-0.8322	0.7	-0.588
IDE						1.0000	0.3119	-0.1623	0.8137	-0.8473
Eta α A							1.0000	-0.0982	0.5861	-0.4467
X5A								1.0000	-0.4694	0.3122
X0sol									1.0000	-0.9054
ChiA_D										1.0000

Definitive validity of model is examined by mean of external validation also, which evaluates how well equation generalizes. The set is used to derive an adjustment model that is used to predict activities of set members. Nearness of experimental to predicted activity reported in table 3 also adds to this fact. Contribution charts for all the significant models are presented in figure 1, which gives percentage contribution of descriptors used in deriving the QSAR models[16-21].

With reference to table 3 the selected descriptors are used for mono-parameteric QSAR Model No.1 development which shows the importance of IP1 descriptors which is directly proportional with the inhibitory activity.

Model No.1

IC50 =-5.7961(±1.9895) + 1590.6(±448.49) ChiA_D

N= 25, R^2 = 0.3535,Se = 1.2685, Adj R2=0.3254,F-Ratio = 12.578,$R^2_{CV=}$-0.8285

A statistical result indicates needs for the development of biparametric and more QSAR models follow rule of thumb. The QSAR Model No.2 hassignificant;

Model No.2

IC50 = -111.2557(±21.601) + 2719.3794(±392.36) ChiA_D + 14.5414(±2.9722)piPC09

N = 25, R^2 = 0.6904, Se = 0.8976,AdjR2=0.6470, F-Ratio = 24.528,R^2_{CV} =0.5217

Model No.3

IC50 = -82.9815 (±30.167) + 245.785(±434.4904)ChiA_D + 13.8393(±2.9713)piPC09-45.9548(±34.8085)EtaαA

N = 25, R^2 = 0.7141, Se = 0.8828, AdjR2=0.6733, F-Ratio = 17.485,R^2_{CV} =0.5837

The QSAR model No.2 and model No.3 show their significant statistical importance which ChiaA_D and piPC09 show directly proportional with anti cancer activity whileEtaα_Ashow inversely relation with the anticancer activity. The variance of QSAR model No.3 is 71% with the major role play by ChiaA_D and piPC09. The deletion of outlier compounds no. **03, 05,12** and **21**.

Model No.3

IC50= -583419(±18.8133) + 2598.998(±267.6879)ChiA_D + 9.2038(±1.94763)piPC09 -32.1700(±21.3052) EtaαA

N = 21, R^2 = 0.8949, Se = 0.5310, AdjR2=0.8768, F-Ratio = 48.245,R^2_{CV} =0.883

These models were generated in stepwise manner by stepwise forward selection method starting with best single variable and adding further significant variable according to their significant variable according to their contribution to the model. Various models of the data set were obtained which showed individual correlation of all calculated parameters with anticancer activity.

Among the generated QSAR models; three models were selected on the basis of various statistical parameters such as squared correlation co-efficient which is relative measure of quality of fit. Fischer's value which represent F-Ratio between the variance of calculated and observed activity.

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Table-5 Cross-validation

MODEL NO	N	PRESS	SSY	PRESS/SSY	R^2	Adj R^2	R^2_{CV}	PSE	SPRESS
1	25	37.0103	20.2400	1.8285	0.3535	0.3254	-0.8285	6.0836	1.2685
2	25	18.5237	38.7267	0.4783	0.6764	0.6470	0.5217	4.3039	0.9175
3	25	16.8285	40.4219	0.4163	0.7061	0.6641	0.5837	4.1022	0.8951
4	21	4.7784	40.8402	0.1170	0.8953	0.8768	0.883	2.1859	0.5301

We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

Table 5. Experimental and predictedanticancer activitiesof the molecules under study

Comp. No	ActualIC_{50}	PredictedIC_{50}	Residual
1	2.8	2.860404	-0.0604
2	6.1	5.339405	0.760595
3	1.63	1.429425	0.200575
4	0.44	1.08923	-0.64923
5	0.29	0.247817	0.042183
6	1.4	1.972277	-0.57228
7	3.4	3.238107	0.161893
8	0.027	-0.60315	0.630147
9	0.088	-0.28145	0.369447
10	1.15	1.01612	0.13388
11	0.061	0.330651	-0.26965
12	0.032	0.09591	-0.06391
13	0.019	0.041121	-0.02212
14	0.24	0.947308	-0.70731
15	0.037	0.726589	-0.68959
16	1.08	0.372719	0.707281
17	1.32	0.694419	0.625581
18	0.082	-0.05565	0.137649
19	0.091	0.662249	-0.57125
20	0.056	-0.38226	0.438255
21	1.73	2.331747	-0.60175

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The plot of observed vs predicted activity is shown in Fig. From the plot it can be sheen that MLR model is able to predict the activity of training set quit well (all Points are close to regression line) as well as external.

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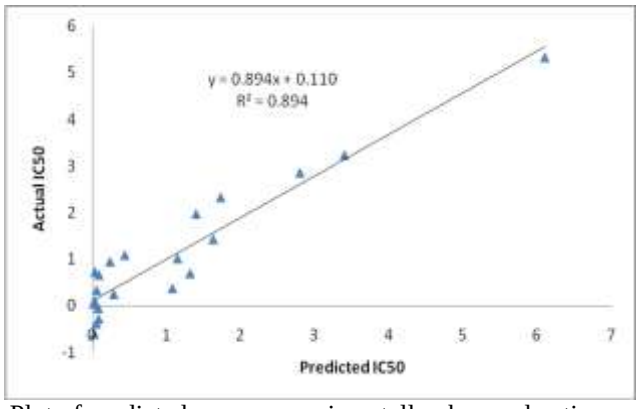

Figure1.- Plot of predicted versus experimentally observed anticancer activity

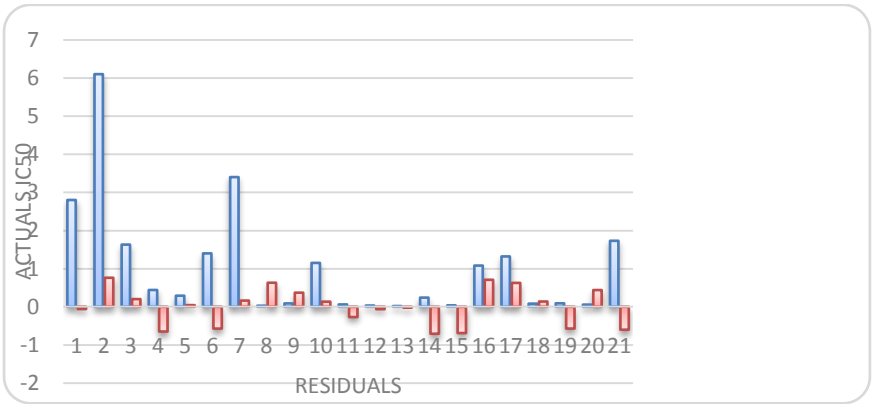

Figure2.- Plots of residual against experimental values of Anticancer Activity.

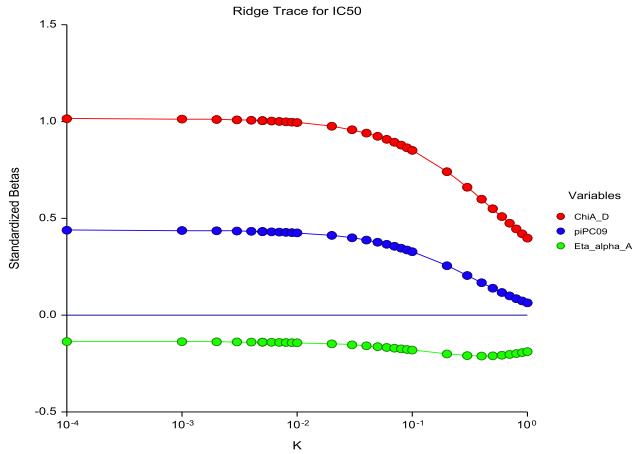

Figure 3. Graph Ridge Regression between the Descriptors and Biological Activity

IV. CONCLUSION

QSAR models are seen to express highly significant correlations between the inhibitory potencies and the descriptor suggests that the bulky groups are favourable for the anticancer activity of the molecules.N-substituted piperazine ring may increase the anticancer activity. An introduction of F, Cl or CF_3 groups may lead to significant change in the inhibitory activity of compounds while hydrophobic substitution leads an increase in anticancer activity.

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