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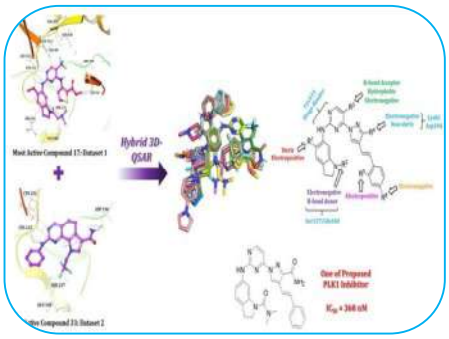
COMBINING MOLECULAR DOCKING STUDY WITH QSAR ANALYSIS OF INHIBITORS OF POLO LIKE KINASE 1 (PLK1)

Dr. Garima

ABSTRACT :



In 21st century protein kinase has become a most important drug target due to application of these kinases in overexpression of cells, inflammatory disease, nervous tissues, cardiovascular disease as well as in number of cancers. PLKs (Polo Like Kinases) (PLK1-5) belongs to ser/thr protein kinase family that plays an important role in multiple stages of mitosis. Among them PLK1 is most widely studied member of this family. Due to overexpression of different cancer types PLK1 is capable target in oncology. PLK1 is the ser/thr kinase plays main role in cell cycle proliferation. Polo like kinase 1(PLK1) is the key target for cancer study. As per the OECD guidelines, a QSAR model has been developed for these 35 compounds dataset. BI 2536 and BI 6727 are two PLK1 inhibitors which are under clinical trials for cancer study. Three descriptors (naaAromAtom, SaasC, P2v) are considered for the development of the QSAR model. The statistical parameters (R^2=0.9233) obtained proves the predictivity and reliability of the QSAR model. QSAR are the statistical model which relates quantitatively the structure and activity of the compounds in the form of molecular descriptors also known as variables. Different validation parameters and various methods like subjective feature selection, dataset division etc., are adopted for QSAR study. The inhibitors reported in this study have more potent inhibition against PLK1 and good isoform selectivity. With the help of structure- based drug design study the most active inhibitor from the dataset is selected. This compound is further studied by molecular docking studies. The interaction between protein and ligand are find out with the help of molecular docking. The combination of polo like kinase inhibitors with the other anticancer drugs creates more opportunities for cancer therapy. The current study helps in development of these drugs. The result obtained from this study is expected to be significant.

KEYWORDS : *statistical model , molecular docking studies , various methods.*

INTRODUCTION:

In 21st century protein kinase has become an important drug target for cancer-based drug discovery. PLKs consists of five members in its family naming as PLK1-5. PLKs (Polo like kinases), belongs to ser/thr protein kinase family is the main selector of mitotic progression. Their structure consisting of *C*-terminal and *N*-terminal conserved catalytic domain with single or double polo boxes.[1-3] Among these, in proliferating cells PLK1 is highly expressed and it is the most dominating member of the family due to its overexpression in many tumors like gastric, prostatic, breast, ovarian, , head, neck, pancreatic, and endometrial cancer etc.[1, 4-8] PLK1 involves in various biological functions like kinetochore, cytokinesis, centrosome maturation and spindle formation.[9-11] In mitosis there is high level of PLK1, although in proliferating cells PLK2 and PLK3 are not particularly expressed. Due to lack of

kinase domain, PLK5 may not involve in the cell cycle progression.[12-13] So, PLK1 inhibitor development with homologue specificity is very important. PLK1 become a significant feature in cancer therapy due to inhibition of PLK1 enzymatic activity of small molecules. This can be done by catalytic domain hindering and on the basis of enzyme's oncogenic transformation potential.[4]

The Polo Box Domain (PBD) negatively controls the catalytic domain's kinase activity and is critical to PLK1 localization. PLK1 is an idealistic target for developing antitumor drugs due to its different biological actions in different directions.[14] Therefore, medicinal chemists are involved in the growth of PLK1 inhibitors. At present, some inhibitors such as GSK461364, PHA-680626, Volasertib, HMN-214 and NMS-P937 of PLK1 are under clinical trials which are effectively allowed in human being.[1, 13, 15]Figure.1 represents the structure of all these inhibitors.

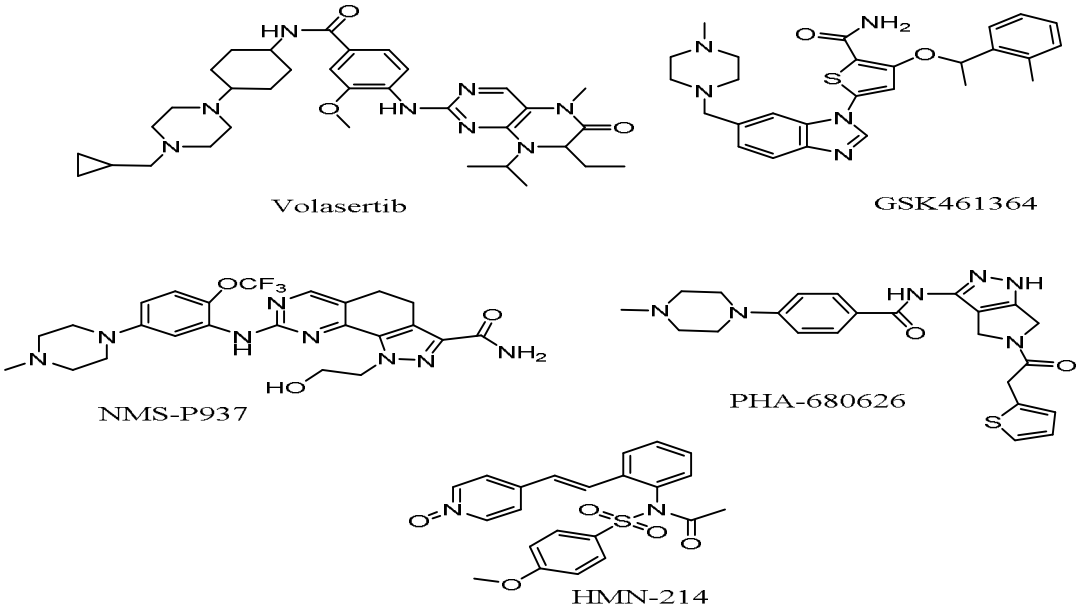


Figure.1: Structure of some known PLK1 inhibitors

CADD has become an important tool for designing and improving the lead compounds with the help of calculations, computer simulation and computing the correlation between the drugs and receptor. The combined form of molecular docking and QSAR approach is used to estimate the protein inhibitor interactions along with the factors affecting their biological activity.[16] The combined form of these methods are also used to guess the inhibition potential of unidentified compound or a new drug compound.

QSAR approach is very useful tool for discovering the biological activities of the compound using their chemical structures.[17-20] Molecular descriptors are of different types and are used to quantify the structure as they contain information related with electronic, topological and geometrical characteristic of the compounds. From the different available descriptors, we have to select the variables which best explains the experimental activity under consideration. In the past various SAR has been described for PLK1 inhibitors. Here, in the present research QSAR model of dataset using 35 PLK1 inhibitors has been developed. For this, conformational independent QSAR approach and calculation of descriptors for constitutional and topological representation of the inhibitor is considered.[1] Approximately, 20-30 compounds are under preclinical and clinical stage development which includes natural and synthetic drugs.[12]

In order to have a detailed insight of the structural features and molecular mechanisms of PLK1 inhibitors, QSAR model have been developed and the most potent compound was selected for molecular docking to decipher the structural necessities and molecular mechanisms.[21] In this model,

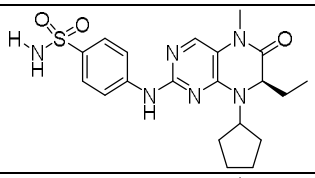
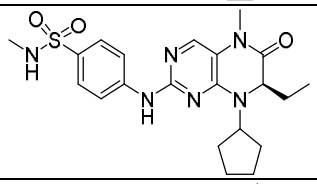
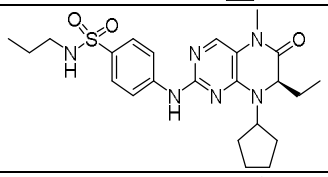
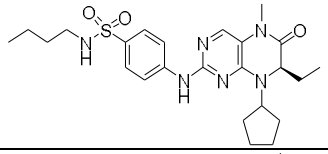
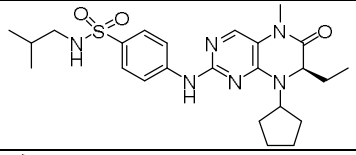
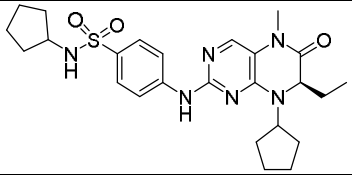
specific structural features like hydrophilicity, hydrophobicity and functional groups targeted for a particular enzyme are discussed.[22]

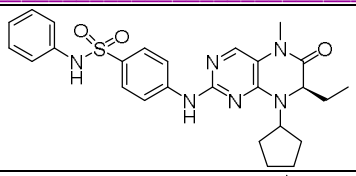
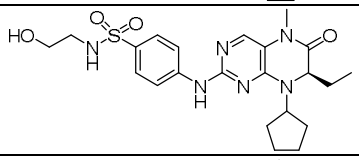
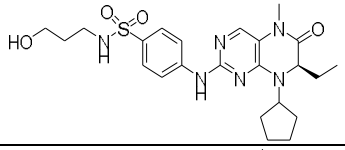
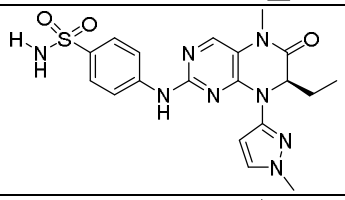
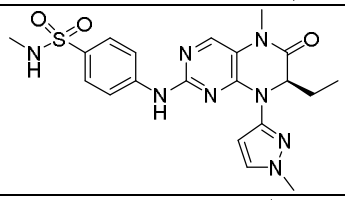
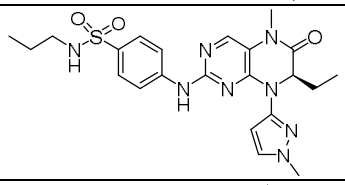
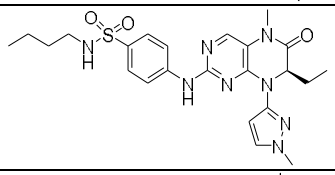
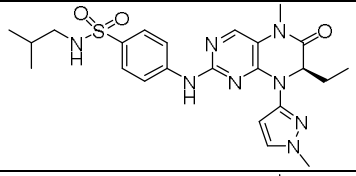
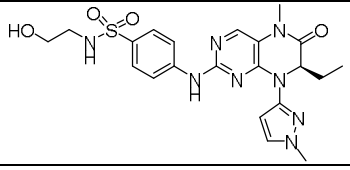
MATERIALS AND METHODS

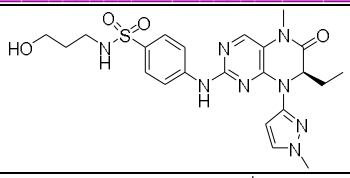
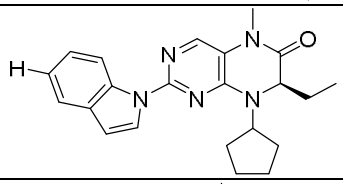
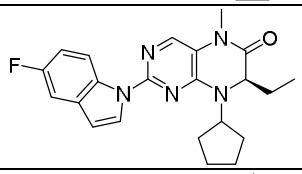
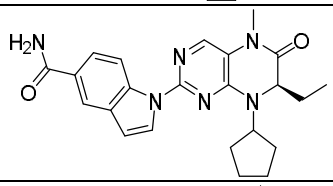
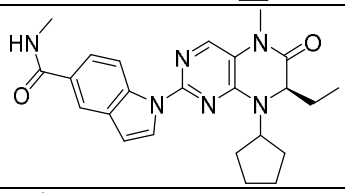
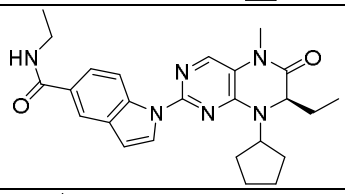
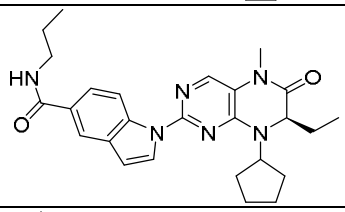
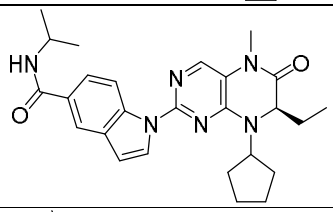
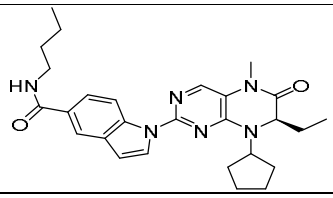
Datasets

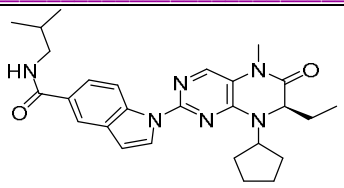
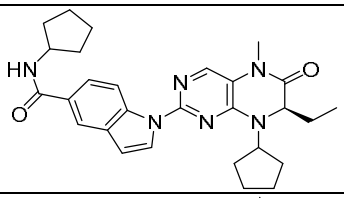
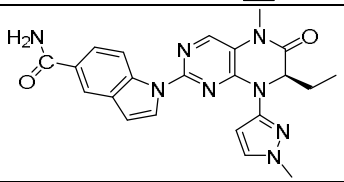
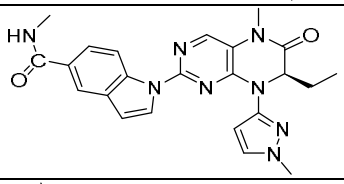
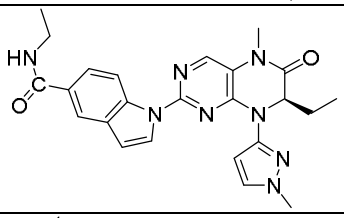
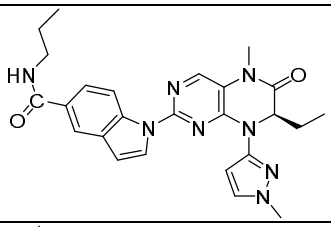
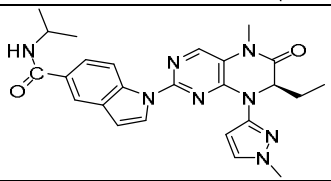
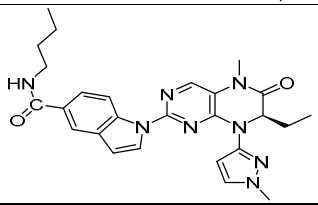
In the present study tetrahydropteridin dataset of 35 compounds was collected from the literature[23-24]. The reported IC_{50}(nM) value was changes into pIC_{50} (expressed in molar) by taking negative logarithmic of IC_{50} *i.e.,* ($-\log_{10} IC_{50}$).[25] Chem Draw and MarvinSketch software was used for drawing the structures of the datasets and these structures were saved as MDL.mol format. Details are shown in Table.1

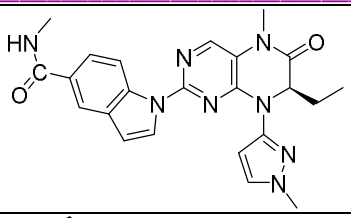
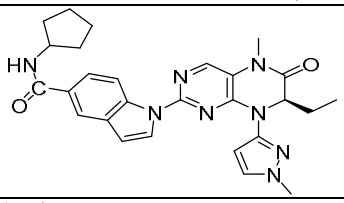
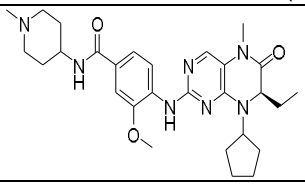
Table 1: The structure of Compounds with the Numerical Values of *pIC50* along with descriptor values

S.No.	Name as per literature	Structure of the compound	pIC_{50} (Molar)	Descriptor		
				naAromAtom	SaasC	P2v
1	C01		7.1886	12	2.7238	0.1845
2	C02		7.7945	12	2.9461	0.1807
3	C03		7.4594	12	2.9946	0.1814
4	C04		7.3904	12	3.0087	0.1471
5	C05		7.3318	12	2.9879	0.1883
6	C06		7.2809	12	3.0657	0.1868

7	C07		6.9626	18	3.4438	0.1344
8	C08		7.6062	12	2.7570	0.1935
9	C09		7.4802	12	2.8211	0.2073
10	C10		5.9796	17	2.8153	0.1965
11	C11		6.1296	17	3.0461	0.1769
12	C12		6.3371	17	3.0970	0.1747
13	C13		6.3357	17	3.1119	0.1472
14	C14		6.0542	17	3.0896	0.1823
15	C15		5.6178	17	2.8415	0.1845

16	C16		6.1717	17	2.9087	0.2023
17	C17		5.9101	15	2.3528	0.2558
18	C18		5.2509	15	1.8366	0.2599
19	C19		6.5464	15	2.5791	0.2090
20	C20		7.0278	15	2.7666	0.1779
21	C21		7.2059	15	2.7906	0.1527
22	C22		7.0978	15	2.8064	0.1269
23	C23		7.0099	15	2.7847	0.1415
24	C24		6.7916	15	2.8176	0.1175

25	C25		6.9154	15	2.8012	0.1285
26	C26		7.3624	15	2.8632	0.1142
27	C28		5.3018	20	2.7574	0.2096
28	C29		5.4983	20	2.9533	0.1756
29	C30		5.375	20	2.9786	0.1650
30	C31		5.607	20	2.9954	0.1356
31	C32		5.819	20	2.9720	0.1429
32	C33		5.9404	20	3.0076	0.1391

33	C34		5.5924	20	2.9533	0.1756
34	C35		5.9161	20	3.0571	0.1155
35	B12536		8.2749	12	3.6948	1.1365

Calculation of Descriptors

In the present work, standard method as proposed by different researchers and OECD guidelines were applied. Before QSAR model development it is important to convert the structural details into numerical details and these numerical values, named as descriptors. For calculation of descriptors PaDEL-Descriptor software was used.[26-27] All these, molecular descriptor includes 1D, 2D, 3D and fingerprints, remove salt, detect aromaticity, standardize nitro groups, retain 3D coordinates and retain molecular order of the molecules. To decrease the amount of unnecessary and corrupted data the pre-treatment of descriptors was done. Since all the descriptors calculated by the software don't contains relevant information so pre-treatment of these descriptors is done. The DTC software http://dtclab.webs.com/software tools are used to minimize the fix values (variance <0.001) and associated (|r|>0.99) variables in prior to development of model.[28-29]Values of calculated descriptors are shown in Table.1

Splitting of dataset and development of QSAR model

QSAR model development can be Qualitative or Quantitative. [28]Before the development of QSAR model the above dataset was separated into two parts i.e., training set (70%) and data set (30%). GA-MLR (Genetic Algorithm Multiple Linear Regression) method was used for generation of model. In this model Random (Faster) method of division is used. On the basis of different criteria explained in the literature the best model will be selected. GA-MLR method is applied on these datasets. From this method we get the best possible combination of descriptors for the given datasets. The compounds were splitting into test and training sets by using Random(*Faster) method in the DTC-QSAR software tool which was taken from http://dtclab.webs .com/software-tools.

Validation of the model

The developed QSAR model need to be validated properly by using external and internal validation parameters otherwise it was unreliable. We have determined various external validation parameters such as scaled and delta R_m^2, Q^2_{F1} and Q^2_{F2}, mean absolute error (MAE), and CCC (Concordance correlation coefficient). The internal validation parameters such as R^2 and R^2_{adj} *i.e.,* (determination and adjusted determination coefficient), SEE (Standard error of estimation), Q^2_{LOO} etc were evaluated. The developed model was in the range of the validation parameters as mentioned by OECD [30]. The various statistical parameters as given below were satisfied by the developed model.

$R^2_{tr} \geq 0.6, Q^2_{loo} \geq 0.5, Q^2_{LMO} \geq 0.6, R^2 > Q^2, R^2_{ext} \geq 0.6, RMSE_{tr} < RMSE_{cv}, \Delta K \geq 0.05, CCC \geq 0.80, Q^2 - F^n \geq 0.60, r^2_m \geq 0.6, \frac{(1-r^2)}{r^2_0} < 0.1, 0.9 \leq k \leq 1.1 \; or \; \frac{(1-r^2)}{r'^2_0} < 0.1, 0.9 \leq k' \leq 1.1, \left|r^2_0 - r'^2_0\right| <$ 0.3 *with RMSE and MAE close to zero*.

Y-Randomization

Here, to perform the Y-randomization of the developed QSAR model DTC software was used. This is done in order to check that the model was established by accidental or not. From different variables selection numerous models can be developed by permutation of both X and Y variables according to their fit in the noted models. But here in the present study only Y-variables were permuted upon 50 combinations. The number of arrangements may differ.[31]

Molecular Docking

Autodock tools software system was utilized to perform the docking. The co-crystalized protein structure was recovered from the RCSB protein data base having **PDB ID: 2RKU**. This software had various graphics tools to display different docking poses of the molecule[32-33]. Before docking all the water molecules and hetero atoms were separated from the protein molecule with the help of Autodock tools. Both the protein and ligand file were converted into pdbqt format by using OpenBabel software. This is very important step before docking[34]. Discovery Studio Visualizer was used to visualize the docking results. Grid box was prepared by taking grid parameters X=52, Y=48, Z=54 having grid spacing of 0.375 was generated[35].The population size of 150 was set having mutation rate 0.02 developed for 10 existences. Lamarckian Genetic Algorithm was considered[31]. The validity of the docking protocol is checked by calculating RMSD value. If this value is less than 2Å than docking protocol is good. This result validates the docking[36-37]. The best pose from all the docked poses was further taken for Molecular Dynamics study. Different visualization software like Pymol[38], UCSF ChimeraX[39], Discovery Studio Files was used for visualization of docking results[40-41].

Applicability Domain

In QSAR applicability domain is the biological space and structural, information or knowledge, physicochemical on which we developed the training set of data and it is able to make predictions for new compounds on the basis of that data. The Applicability domain of a QSAR model describes a hypothetical region in chemical space which can be defined using response and descriptors of the respective model, in which we can obtained the predictive reliability. The applicability domain is checked for both training set and data set so that we came to know that any of the compound is present outside this applicability domain or not.

RESULTS AND DISCUSSIONS

QSAR models

Generally, for the development of QSAR model SFS (subjective feature selection) method is used. To get maximum information about the connection between structure and activity is the main motive and very first principle of QSAR model development. So, in order to achieve this goal simply explainable descriptors were taken into account during generation of the model and numerous QSAR model were developed by means of divided and undivided datasets. Before selection of descriptors the datasets were separated into training (70%) and test or prediction (30%) set into a random manner. It is not necessary that the datasets present in one model may or may not be same for another model. Thus, different QSAR model confirms that almost all the information is obtained from the selected molecular descriptors about the biological activity of the compounds. For the selection of particular descriptors Genetic Algorithm (GA) tool of QSARINS-Chem2.2.1 was utilized. Here, statistically reliable and acceptable local models were proposed which includes simple 2D descriptors.[42] In Figure 2. a graph between predicted and experimental end point was plotted which gives very reliable result. Here, both

training and prediction sets was shown with different points. And the value of regression parameter i.e., R^2 is 0.9233.

Table 2: Descriptor along with their type and correlation with the model

Descriptor	Description	Type	Correlation with Model
naAromAtom	Number of aromatic atoms	2D Aromatic Atoms Count Descriptor	Negative
SaasC	Sum of atom-type E-State: :C:-	2D Electrotopological State Atom Type Descriptor	Positive
P2v	2nd component shape directional WHIM index / weighted by relative van der Waals volumes	3D WHIM Descriptor	Negative

In this section to explain the effective concentration (pIC_{50}) 3D- QSAR models are discussed. The developed 3D-QSAR model were found to have reliable and satisfactory values for all validation matrices which includes R^2, Q^2, Q^2_{LMO}, $r^2_{m(LOO)}$, $\Delta r^2_{m(LOO)}$, MAE and RMSE.

Also, results of predicted end point and predicted model equation residues were plotted which shows the activity of all the compounds were lie within the required range as shown by Figure 3.

Table 3 explains all the results obtained from the 2D QSAR model development. The values of all the statistical parameters were obtained within the required range which represents a successful and consistent model. The value of R^2 obtained from the model was 0.9233 which shows a very decent result. The values of all the required statistical parameters like R^2, Q^2, MAE, including fitting criteria, internal and external validation criteria, predictions by LOO and model equation were shown by Table 3.

$$\boldsymbol{pIC50 = 10.3975(\pm 1.9091) - 0.2596(\pm 0.0381) \times naAromAtom + 0.5843(\pm 0.4229) \times SaasC - 8.0871(\pm 3.8681) \times P2v}$$

Table 3: Values of statistical parameters obtained from QSAR model

Statistical parameters	Result	Statistical parameters	Result
N_{tr}	25	No.of descriptors	3
N_{ex}	10	θ*	-0.0781°
Fitting Criteria			
R^2_{tr}	0.9233	$RMSE_{tr}$	0.2284
R^2_{adj}	0.9124	MAE_{tr}	0.1957
R^2_{tr}- R^2_{adj}	0.011	RSS_{tr}	1.3047
LOF	0.0904	CCC_{tr}	0.9601
Kxx	0.3579	s	0.2493
ΔK	0.1884	F	84.2848
Internal Validation Criteria		**External Validation Criteria**	
$R^2_{cv}(Q^2_{loo})$	0.897	$RMSE_{ext}$	0.2414
R^2- Q^2_{loo}	0.0264	MAE_{ext}	0.1949
$RMSE_{cv}$	0.2648	$PRESS_{ext}$	0.5825
MAE_{cv}	0.2306	R^2_{ext}	0.9395
$PRESS_{cv}$	1.7532	Q^2-F^1	0.9013
CCC_{cv}	0.9464	Q^2-F^2	0.8997
Q^2_{LMO}	0.8916	Q^2-F^3	0.9144

R^2_{Yscr}	0.1239	CCC_{ext}	0.9521
Q^2_{Yscr}	-0.2592	R^2_m aver.	0.9109
$RMSE^{AV}_{Yscr}$	0.7710	R^2_m delta	0.0118
Predictions by LOO			
Exp(x) vs. Pred(y) R^2	0.8972	Pred(x) vs. Exp(y) R^2	0.8972
R'^2_o	0.8884	R^2_o	0.897
k'	0.9993	k	0.9991
Clos'	0.0098	Clos	0.0002
R'^2_m	0.8131	R^2_m	0.8858
External predictions by model equation			
Exp(x) vs. Pred(y) R^2	0.9395	Pred(x) vs. Exp(y) R^2	0.9395
R'^2_o	0.939	R^2_o	0.9382
k'	1.022	k	0.9776
Clos'	0.0006	Clos	0.0014
R'^2_m	0.9168	R^2_m	0.905

R^2: coefficient of determination; R^2adj.: adjusted R^2, LOF: lack of fit; CCC_{tr}: concordance correlation coefficient for training set; CCC_{cv}: concordance correlation coefficient of cross-validation; F: Fischer's statistics; R^2_{Yscr}: response scrambling coefficient; Q^2_{Yscr}: cross-validation response scrambling coefficient; Q^2_{LOO}: leave one out cross validation coefficient; Q^2_{LMO}: leave many out cross validation coefficient; Q^2F_1, Q^2F_2, Q^2F_3: External validation criteria; Delta K: difference in the correlation; RMSE: root mean square error; MAE: mean absolute error; S: standard error

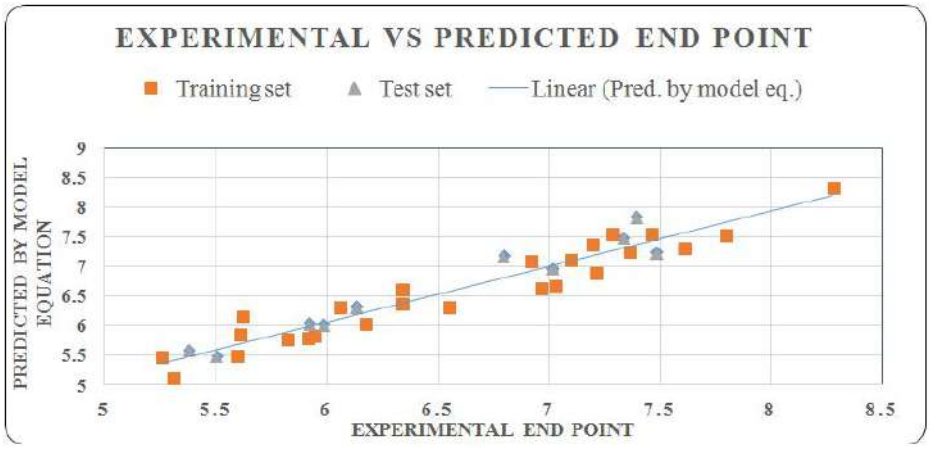


Figure.2: Description of plot of predicted versus experimental end point

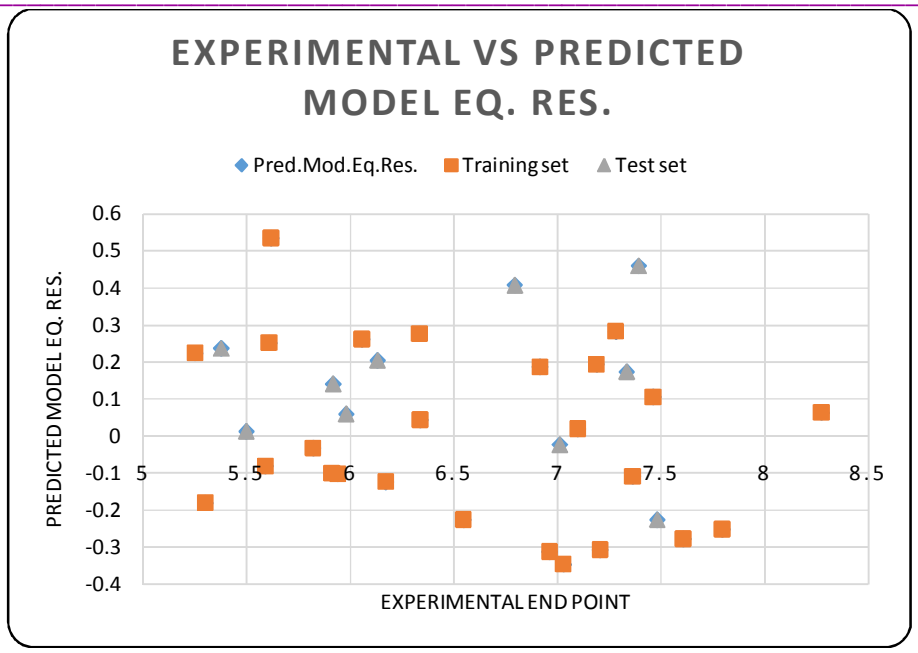


Figure.3: Description of predicted model equation residuals versus experimental end point

Molecular Docking

To study the necessary interactions among ligand and protein after QSAR analysis Molecular Docking is a comprehensive tool. Molecular docking provides a detail insight of the structure and quantitative relationship as modeled by QSAR models. The probable binding conformation was explored from the Autodock software. Generally, the reliability of docking protocol was determined by RMSD (<2 Å) value of the redocked conformation. For internal ligand RMSD value was found to be less than 2 Å which confirms the reliability and reproducibility of the docking protocol. Furthermore, Figure.4 represents the possible interactions of internal ligand with the active site of the receptor. After successful validation of the docking protocol molecular docking was executed to elucidate the binding mechanism of the most active compound **C02** within the active site of PLK1. With the help of induced fit docking we used an advanced sampling procedure to generate 10 binding poses for the compound C02. All the poses were extracted to see their bonding, non-bonding interactions including docking score. Out of these 10 docking poses the best pose which has similar binding position and docking score as that of observed for protein and co-crystallised ligand. The most potent compound C02, forms hydrogen bond with the key residue GLU101 with hydrogen of OH group. HIS105, CYS67, LEU130, LYS82, PHE183, GLY180, ASN181, LYS178 and LEU139 shows hydrophobic interactions with the ligand as shown in Figure 5. The most potent ligand fit tightly within the binding pocket of the protein(2RKU). Overall similar interactions were observed for the most potent ligand as those of internal ligand with protein. Hence, the docked pose validated the strong binding conformation of the potent compound[19, 21, 43].

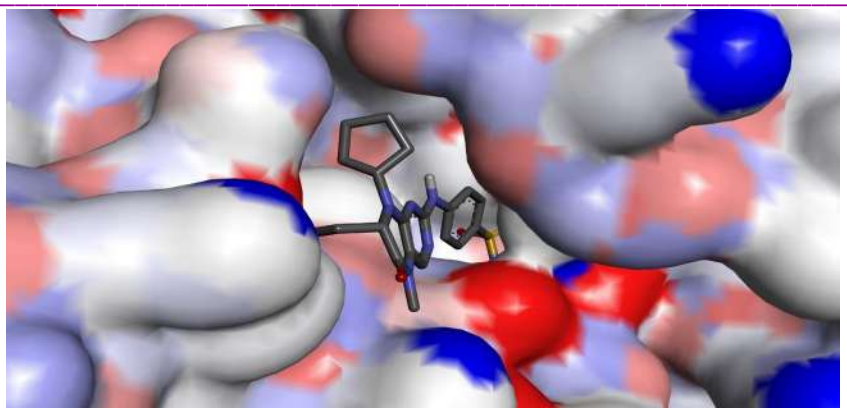


Figure 4 : 3D sturcture and cartoon structure of ligand C02 and receptor 2RKU

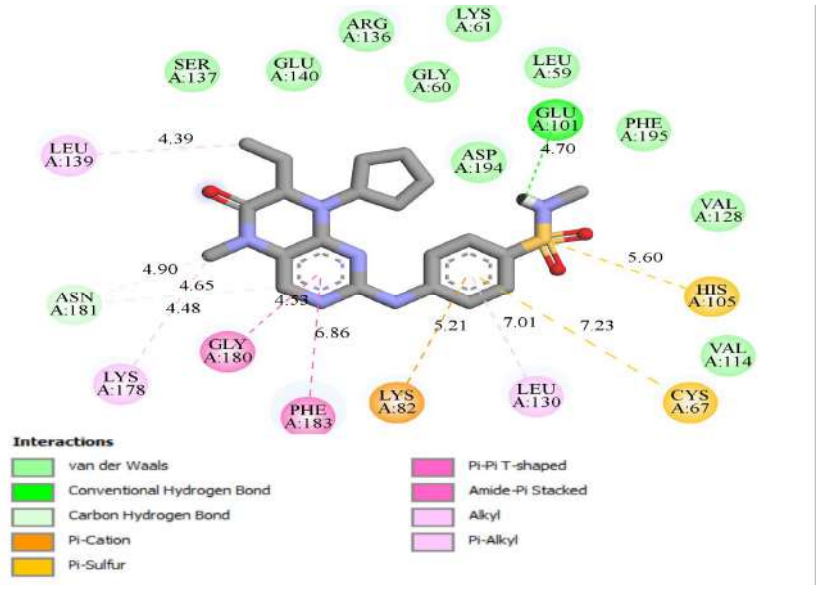


Figure 5: 2D structure of C02 with receptor 2RKU

CONCLUSION

In this present work, a reliable QSAR model has been developed by taking a dataset of 35 tetrahydropteridin derivatives. The developed QSAR model is robust statistically and has good predictive quality. The numerical values of different statistical parameters are 0.9233, 0.9124, 0.8970, 0.9395 and 0.9521 for R^2, R^2_{adj}, Q^2_{loo}, R^2_{ext} and CCC_{ext} respectively. A molecular docking study of the most active compound (C02) is done to find the best interaction between protein and ligand. From the docking results, it is found that the most potent compound C02, forms hydrogen bond with the key residue GLU101 with hydrogen of OH group. Hence, the results of the present investigation may be employed to identify and develop effective inhibitors for the treatment of PLK1-related pathophysiological disorders.

Abbreviations Used

PLK1- Polo Like Kinase 1; **QSAR-**Quantitative structure activity relationship; **QSARINS-** QSAR Insubria; **MLR-**Multiple Linear Regression; **GA-**Genetic Algorithm; **CCC-**Concordance Correlation Coefficient; **OECD-**Organization for Economic Co-operation and development; **AD-** Applicability Domain; **LOO-**Leave-one-out; **LOO-CV-**Leave-one-out-cross-validation; **MAE-**Mean Absolute Error; **PLS-**

Partial Least Squares; **$RMSE_{ext}$** -Root Mean Square Error -external dataset; **$RMSE_{cv}$**-Root Mean Square Error- cross- validation; **RMSE**-Root Mean Square Error; **R^2_{cv}**-Coefficient of determination-cross-validation; **R^2_{ext}**-Coefficient of determination-external dataset; **R^2**-Coefficient of determination.

Conflicts of Interest

The author(s) pronounces that there is no known source of competing financial interests or personal relationship that could have seemed to impact the work stated in this paper.

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Data availability statement

The data will be made available on request.

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