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2D-Qsar Assisted Design, and Molecular Docking of Novel Indole Derivates as Anti-cancer Agents

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ABSTRACT

Computer Aided Drug Designing (CADD) is an important aspect of the any currently employed drug discovery process for a medicinal chemist. In the current study, research was initiated with a two dimensional Quantitative Structural Activity Relationship (QSAR) model generation through previously synthesized compounds. The 2-D QSAR model generated is then engaged for the predicting of the activity of our proposed compounds to be synthesized. This ligand-based approach of computer aided drug designing (CADD) is complimented further with the molecular docking simulations. Molecular docking of our proposed compounds was done to study the interaction of these compounds with the target protein i.e. tyrosine kinase receptor. Almost all the compounds showed significant results. Among them the most potent compound is SSIV which has-11.8 K/Cal/Mole.

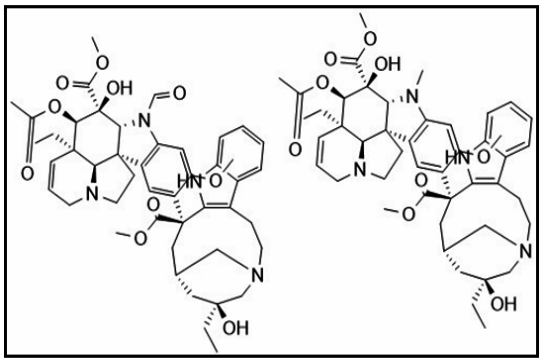
Keywords: Cancer, CADD, *In silico*, 2D QSAR, Indole.

INTRODUCTION

Cell cycle and apoptosis are two utmost important processes of human cell growth and programmed cell death[1]. Cancer is considered a complex disease which occurs when human body fails to regulate these two processes[2]. These uncontrolled dividing cancer cells hijacks the process of normal cell division[3]. As per the WHO, cancer has accounted for around 10 million deaths worldwide in 2020. Most common types of cancers are rectum, lung, breast, prostate and colon tumors. It has also been projected by the WHO that by 2040, there will be around 16.3 million deaths per year worldwide due to this deadly disease[4].

This has posed an eminent threat and challenge to the medicinal chemists to develop novel molecules which can more effectively treat the occurrence of cancer. To serve this purpose, heterocyclic moieties have played an indispensible role in the development of many lifesaving drugs against several ailments[5]. Indole scaffold is one is one of the promising heterocycles present in many drugs

employed in the cancer treatment such as naturally occurring alkaloids vincristine and vinblastine[6].



Structure of Vincristine and Vinblastine

Traditional drug discovery process is associated with high cost and consumes lots of time for the development of any novel potential drug[7].To overcome this, computer aided drug designing (CADD) approaches are employed by the medicinal chemists for reducing this cost and to reduce the overall time in the entire drug discovery process8. QSAR technique is a ligand-based drug designing (LBDD) approach of CADD in which a mathematical relationship is developed for the chemical properties of already reported compounds and their biological activities. In the similar manner, molecular docking simulation is structure-based drug designing (SBDD) method of CADD which works on lock & key mechanism in which proposed ligand is placed inside the active cavity of the receptor and Gibbs free energy (Dock Score) of the system is calculated[9].

In the current study, first a 2D-QSAR model is generated against anticancer activity and this QSAR equation generated is employed for the designing of our novel indole-based drug moieties. The newly synthesised indole-based molecules were subjected to *in-vitro* anticancer activity. The results obtained from the anticancer activity are further validated via molecular docking simulations.

MATERIALS & METHODS

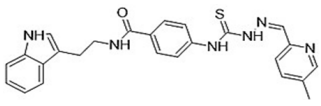
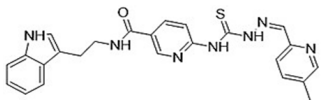
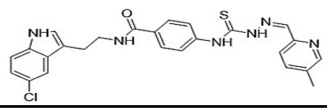
All the computational work has been performed by using Lenovo thinkpad system having intel core i5@2.40GHz, having RAM capacity of 8GB and a 512GB hard disk. Marvin sketch of Chemaxon has been employed for all the molecular modelling work including drawing of structures, energy minimization etc. QSARINS software of the University of Insurbia is employed to develop and externally validate the generated QSAR model[10]. AutoDock tools and AutoDock vina of the scripps research institute is employedin the molecular docking simulations[11].

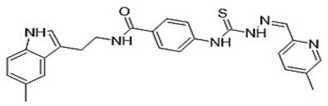
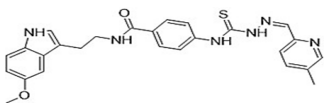
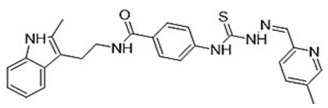
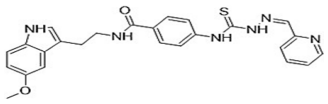
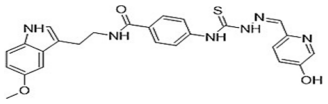
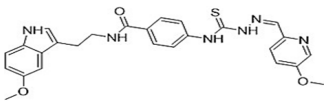
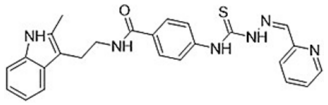
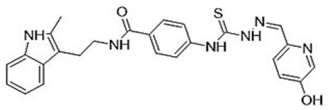
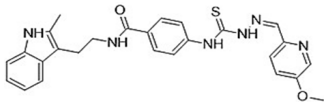
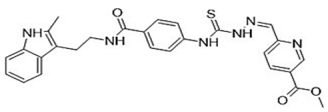
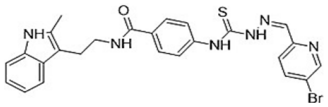
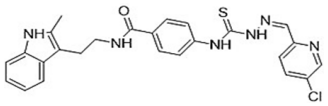
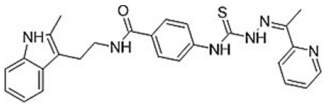
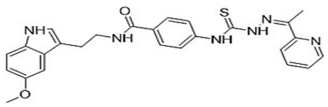
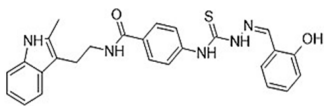
QSAR studies

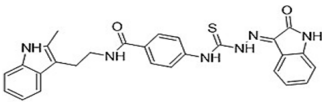
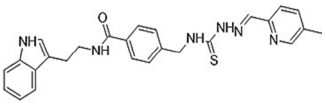
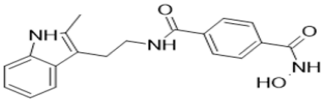
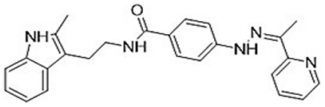
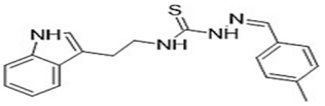
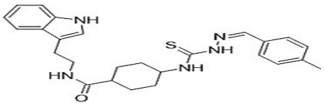
Collection of the Dataset and data Optimization

24 already reported and synthesized thiosemicarbazone-indole derivatives were utilized for the creation of the 2D-QSAR model[12]. Inhibitory potential of the reported compounds was in micromolar range and exhibits the minimum required concentration of the compounds to restrain 50% of the growth of PC3 cell lines (IC_{50}). To remove the skewness in the data, IC_{50} values of these 24 compounds has been changed to negative logarithm values (PIC_{50})[13]. The chemical structures of thiosemicarbazone-indole derivatives along with their inhibitory concentrations are given in the Table 1.

Table 1: Structure of the 24 compounds used for the generation along with their IC_{50} & calculated PIC_{50} values

Sr. No.	Compound structure	IC_{50} value	PIC_{50} value
1		0.241±0.050	6.61
2		0.512±0.120	6.29
3		0.121±0.032	6.91

4		0.081±0.012	7.09
5		0.061±0.020	7.21
6		0.054±0.012	7.26
7		0.133±0.014	6.87
8		2.485±0.395	5.6
9		0.093±0.053	7.03
10		0.091±0.024	7.04
11		1.501±0.176	5.82
12		0.084±0.030	7.07
13		1.601±0.742	5.79
14		0.322±0.020	6.49
15		0.454±0.051	6.34
16		0.707±0.032	6.15
17		0.947±0.086	6.02
18		5.321±0.263	5.27

19		16.987±0.178	4.77
20		1.424±0.153	5.84
21		20	4.69
22		0.406±0.091	6.39
23		0.601±0.042	6.21
24		2.223±0.345	5.65

Molecular descriptor calculations

Molecular descriptors of the 24 derivatives were calculated using PADEL descriptor software[14]. All the structures of the 24 derivatives were drawn in the mol format and then subjected to PADEL which computes a total of 1875 descriptors which includes autocorrelation, geometrical, electrostatic, topological, spatial, constitutional and thermodynamic descriptors.

Pretreatment of the data, divisionof dataset and generation of QSAR equation

Before the development of the QSAR model, descriptors having almost same values and descriptors which are inter correlated were removed for the development of a robust and reliable equation. For this purpose, both constant and inter correlated descriptors showing variance more than 80% were removed. A random approach is used for dividing the dataset into training and test dataset in which 70% of the compounds divided into training and remaining 30% were divided into test data set. For generating the QSAR model, a search heuristic approach called as Genetic Algorithm (GA) is used which mimics the techniques of natural selection like inheritance, crossover, mutation, and selection.

Internal validation

The cross-validation method was used for the assessing the predictability ofcreated QSAR equation through internal validation. The following equation is used for calculating the cross validated $Q2_{cv}$:

$$Q^2_{cv} = 1-[\Sigma(Y-Y_{pred})^2/\Sigma(Y-Y_{mean})^2]$$

Here, Y represents the experimental biological activity value (PIC_{50}), Y_{pred} stands for predicted biological activity by QSAR model & Y_{mean} stands for the average of Y of the training set compounds.

Another parameter for assessing the quality and reliability through internal validation is squared correlation coefficient R^2 value of the training set. But this value can be biased as its value is not as reliable if we increase the quantity of descriptors. To prevail over this hindrance, a freshfactor R^2_{adj} is used which is calculated as follows:

$$R^2_{adj} = R^2-p(n-1)/n-p+1$$

Where p is the number of the descriptors employed and n is the number of compoundsemployed in the training set for the generation of QSAR model. There is an acceptable fact that if difference between R^2 and R^2_{adj} is less than 0.3 then we can infer that numbers of descriptors selected are acceptable[9].

External validation

For assessing a QSAR model for its robustness, Golbraikh and Tropsha has given some statistical parameters[15] which are given in Table 2. Where R^2_0 is coefficient of squared correlation among experimental and predicted values and R'^2_0 is same among predicted and experimentalvalues of test set.

Table 2: Golbraikh and Tropsha parameters for the validation of the 2D QSAR model

S. No	Parameter	Threshold value
1	Q^2	Threshold value $Q^2>0.5$
2	R^2_{train}	Threshold value $R^2_{train}>0.6$
3	$\|R^2_0-R^2_0\|$	Threshold value $\|r^2_0-r^2_0\|<0.3$
4	K or k'	0.85<k<1.15 & 0.85<k'<1.15
5	$R^2_{test}-R^2_0/R^2_{test}$	Threshold value $R^2-R^2_0/R^2<0.1$

Y randomization test

Y randomization test is done to evaluate that QSAR equation generated is not resulted through by a fluke instead is a robust model. This test is performed by shuffling the value of biological activity while keeping the values of descriptors constant. This shuffling is done n number of times and robustness of the developed model is assessed through comparing R^2 and Q^2 of Y randomized equations with original QSAR equation and it should be as low as possible[16].

Applicability Domain

Applicability Domain (AD) is a chemical space of developed QSAR model where all the predictions done by the model is of the utmost accuracy. As per the 3rd principle of Organization for economic Co-operation and development (OECD), it is highly suggested to describeAD of a QSAR equation. AD is used intended for identifying response outliers as well as influencers in QSAR equation[17].

In the current study, Williams plot and insurbia graph is employed for defining AD of the formed QSAR model[10]. This is a simple approach in which every new chemical is defined whether it will be within the AD or will be an outlier. The leverage hi of each chemical of training as well prediction dataset is calculated as follows:

$$h_t = x_t^t(X^tX)x_t$$

Where x_t is the descriptor vector of the under consideration data point, X as the descriptor matrix and X^t as the transpose of the descriptor matrix. The threshold leverage h^* is calculated as:

$$h^* = 3(p+1)/n$$

Where, p = number of variables

n = the number of compounds in the training set

For every chemical the value of h_t calculated should be less than the threshold value, otherwise it is considered as outside the AD but if it has small standardized residual than it may not be considered as outlier. For standardized residuals a cut-off value of ±3 is considered to be inside the AD.

Predicting the biological activity of the designed molecules

Biological activity of all our proposed 11 compounds was predicted from the mathematical equation obtained from our QSAR model developed. Initially, molecular descriptor calculation was performed of these derivatives using PADEL software and then substituting the values of these descriptors in the QSAR equation we obtained our predicted biological activity.

***In-silico* molecular docking analysis**

The drawing of the molecular structure & their initial 3D optimization is performed on the marvinsketch of Chemaxon. Molecular docking of all our proposed molecules is performed against the tyrosine kinase receptor (PDB ID 6Z4B) and taking Osimertinib as the reference for comparative study. All the ligand & Protein preparation steps were performed using AutoDock tools 1.5.6 whereas Molecular docking was done by employing AutoDock vina of The Scripps Research Institute.

RESULTS

QSAR studies

The QSAR model was generated through employing Genetic Algorithm to get the multiple linear regression (MLR) model. 3 descriptors were used for generating the QSAR equation. The equation of developed QSAR model is given as follows:

$$PIC_{50} = 16.61 - 0.8581ATSC3e - 8.8485GATS8v - 0.5174nHBDon\_Lipinski \quad (1)$$

Where, N_{train}:17, R^2: 0.8622 ,R^2_{adj}: 0.8304, Q^2_{loo}: 0.7730, N_{test}: 07, R^2_{test}: 0.7770 & MAE (external): 0.2784. From looking above the QSAR equation, it is evident that the all of the descriptors employed for the generation of the model have contributed negatively in the biological activity. The details of the descriptors employed have been given in the Table 3. The graph between the predicted and observed PIC_{50} values of the molecules employed for generation of the equation is given in the Figure 1.

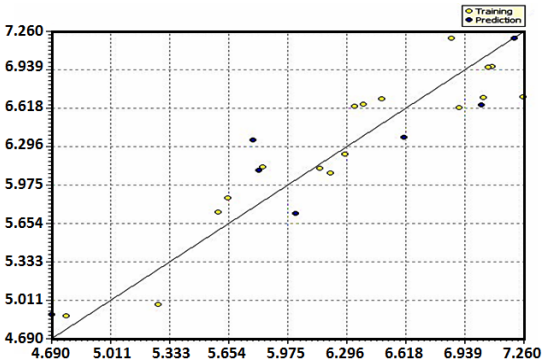


Fig. 1. The predicted and observed PIC_{50} values of the compounds employed for the generation of the 2D QSAR model obtained from the QSARINS software

The quality of any QSAR equationdeveloped is assessed both internally and externally. For the validation of the equation internally, our QSAR equation possesses R^2: 0.8622 & R^2_{adj}: 0.8304 values respectively which signifies that predicted biological activity of the developed is well correlated with the experimental values. Further the robustness of the model and validation that the current model is not developed by fluke is done through Y randomization test. In this, we developed 50 random QSAR models and their values of R^2 & Q^2 clearly suggests that they are far behind the values obtained from our original 2D-QSAR equation Figure 2.

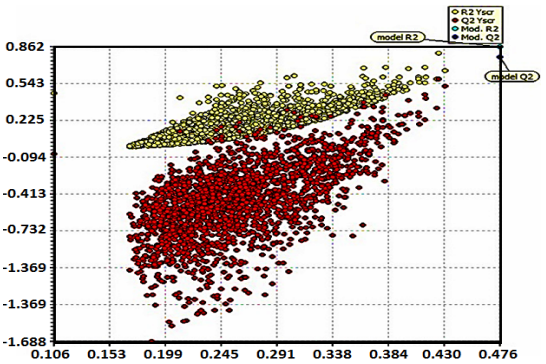


Fig. 2. Y scrambling plot of generated 2D QSAR modelobtained from the QSARINS software

In defining the Applicability Domain, none of the moleculesused for the development of QSAR model falls outside the AD. This clearly suggests that our QSAR model has a great predictability evident through the Williams plot Figure 3.

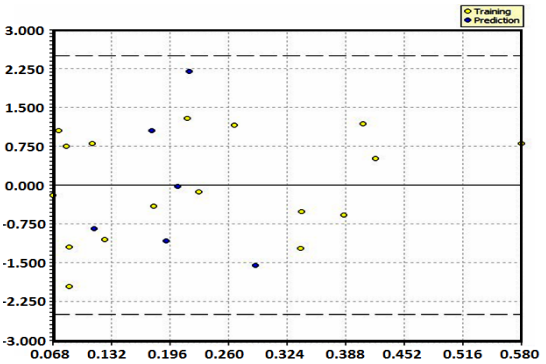


Fig. 3. Williams plot for AD of the generated 2D QSAR modelobtained from the QSARINS software

The criteria given by the Golbraikh and Tropsha for validating any QSAR model externally are the most acceptable parameters till date. Our model has clearly passes all the criteria set by theGolbraikh and Tropsha for a successful QSAR model Table 4.

Table 3: The types of descriptorsthat were employed for the generation of the 2D QSAR model

Sr. No	Name of Descriptor	Type	Description	Contribution
1	ATSC3e	2D	Autocorrelation	Negative
2	GATS8v	2D	Geary autocorrelation of lag 8 weighted by van der Waals volume	Negative
3	nHBDon_Lipinski	2D	Number of Hydrogen Bond Donors	Negative

Table 4: Golbraikh and Tropsha parameters obtained of the developed QSAR model

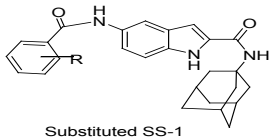
S. No	Parameter	Threshold value	Model Score
1	Q^2	Threshold value $Q^2>0.5$	0.7730
2	R^2_{test}	Threshold value $R^2_{test}>0.6$	0.8622
3	$\|R^2_0-R'^2_0\|$	Threshold value $\|r^2_0-r'^2_0\|<0.3$	0.0318
4	K or k'	0.85<k<1.15 & 0.85<k'<1.15	0.9967 or 1.0007
5	$R^2_{test}-R^2_0/R^2_{test}$	Threshold value $R^2-R^2_0/R^2<0.1$	0.04138

Virtual Screening & *In-silico* docking analysis

The 2D-QSAR model developed in ourresearch is further used for virtual screening through by predicting the PIC_{50} value of our proposed molecules. The predicted PIC_{50} of the proposed compounds is given in the Table 5. In the virtual screening, all our compounds have shown remarkable predicted biological activity except the compounds 1R & 1U.

The proposed compounds were further evaluated via molecular docking analysis to study their interactivity with the receptor. The results of our docking analysis are given in the Table 6.

Table 5: Predicted PIC_{50} values of synthesized molecules along with values of their descriptors



Substituted SS-1

Sr. No	Name	R	ATSC3e	GATS8v	nHBDon_Lipinski	Predicted activity (PIC_{50})
1	SS-1D	H	0.01801	1.18328	3	4.575756
2	SS-1E	4-OH	-0.3156	1.16946	4	4.466878
3	SS-1H	2,6-di-hydroxy	-0.14666	1.128865	5	4.163588
4	SS-1N	2-ethyl	0.232791	1.161088	3	4.587754
5	SS-1O	4-amino	-0.01767	1.124904	5	4.087935
6	SS-1R	3,5-diamino	-0.1903	1.212957	7	2.422408
7	SS-1S	3,5-dichloro	-0.35424	1.152108	3	5.170913
8	SS-1U	4-amino-2-hydroxy	-0.16527	1.116822	6	3.768681
9	SS-1V	3-methoxy-2-nitroxy	0.440941	1.111587	3	4.846998
10	SS-1X	3-formyl	0.131693	1.166851	3	4.62353
11	SS-1Y	4-formyl-3-hydroxy	-0.00632	1.132459	4	4.528773

Table 6: The dock score of the synthesized compounds along with their interactions with the different amino acids

Sr. No	Compound name	Dock score\ (KCal/Mole)	H-Bond number Bonding	Amino acid Residues involved in Hydrogen	Amino Acids involved in the interaction with ligand
1	Osimertinib	-9.4	01	LYS745	ILE759, LEU777, MET766, LEU788, LYS745, MET790, LEU718, LEU844, VAL726, ALA743,
2	SS-1D	-10.7	01	LYS745	LEU777, LEU788, MET766, LEU858, LYS745, ASP855, MET790, LEU844, VAL726, ALA743, CYS797
3	SS-1E	-10.9	00	NIL	LEU777, LEU788, MET766, PHE856, VAL726, LEU718, LEU797, ALA743, MET790, LYS745
4	SS-1H	-11.2	01	LYS745	MET790, LEU777, LEU788, MET766, ALA743, VAL726, LEU797, CYS797, LEU858
5	SS-1N	-10.6	00	NIL	MET790, LEU777, LEU788, LYS745, ALA743, VAL726, LEU844, LEU718, GLY719, CYS797
6	SS-1O	-10.9	00	NIL	LEU777, LEU788, MET766, MET790, LYS745, ALA743, VAL726, CYS797, LEU718, LEU844
7	SS-1R	-11.1	01	PHE856	LEU777, LEU788, MET766, MET790, LYS745, ALA743, VAL726, LEU718, LEU844
8	SS-1S	-11.0	00	NIL	MET790, LYS745, ALA743, VAL726, LEU743, MET793, LEU792, LEU718, LEU844, CYS797, ASP855, LEU788, LEU861, LEU862, MET766, LEU861
9	SS-1U	-11.3	01	LYS745	LEU777, LEU788, MET766, MET790, ASP855, VAL726, LEU743, CYS797, LEU844
10	SS-1V	-11.8	00	NIL	LEU777, LEU788, MET766, LEU861, LEU862, LEU858, LEU743, VAL726, MET790, LYS745, CYS797, LEU844, LEU718
11	SS-1X	-10.8	00	NIL	LYS745, VAL726, MET790, LEU844, LEU718, LEU788, LEU743, LEU747, LEU861, LEU862, LEU858, MET766
12	SS-1Y	-10.8	00	NIL	LEU788, MET766, ASP855, LYS745, LEU777, LEU743, MET790, VAL726, CYS797, LEU718

From the docking analysis, it was interesting to see that all our proposed compounds showed higher dock score when compared to the Osimertinib the reference standard used in the molecular docking analysis. The highest docking store was shown by the compound 1V having the dock score of -11.8 Kcal/mole but this compound didn't show any hydrogen bond interaction Figure 4.

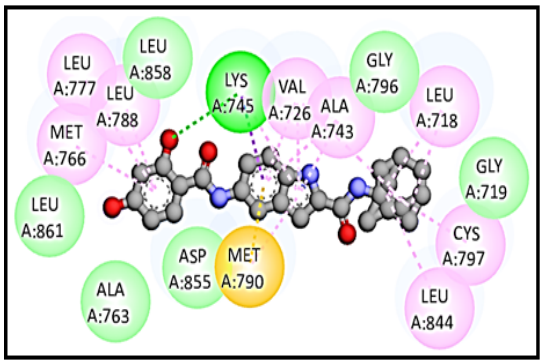


Fig. 4. Interaction of the compound SS-1H with the target proteinobtained from the Biovia Discovery studio academic visualizer

The standard used Osimertinib has shown one hydrogen bond interaction with the receptor amino acid Lysine745 Figure 5. The same type of hydrogen bond interactions are also possessed by the compounds 1D, 1H & 1U with the same amino acids. The compound 1R has also possessed one hydrogen bond interaction with the amino acid Phenyl Alanine 856.

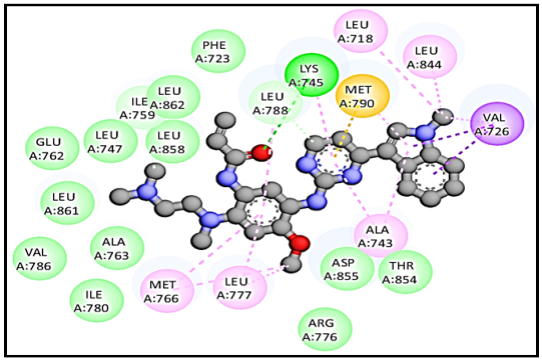


Fig. 5. Interaction of the Osimertinib with the target protein obtained from the Biovia Discovery studio academic visualizer

DISCUSSION

A robust 2-D QSAR model is developed in the current study with high predictability as evident through the validation parameters both internal and external. The Y-randomization test has also further verified that our model was not developed merely coincidentally. The graph between the predicted and experimental biological activities clearly indicates that both these values have close relationship near to the straight line.

The developed 2-D QSAR model was then employed for the screening of our proposed compounds by predicting their biological activities. This is further evaluated through the molecular docking simulations to see the interactions of our compounds with the target receptor. The molecular docking studies have shown an interesting fact that all of our proposed compounds have higher dock score when compared to the standard used Osimertinib.

CONCLUSION

CADD approach has become the backbone of any drug discovery process for a medicinal chemist. In the current study, we incorporated both the 2D-QSAR & Molecular docking analysis of the Ligand & Structure based drug designing approaches respectively for designing the novel indole- based compounds for the anti-cancer activity. The current *In-silico* studies conducted has opened new horizons for us to transfer the current research further for the synthesis and *In-vitro* screening. Therefore from the current study it is inferred that this study should further be shifted for *In-vivo* and in-vitro research against cancer.

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Conflict of interests

There is no conflict of interest.

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