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2D-QSAR ANALYSIS AND MOLECULAR DESCRIPTOR INSIGHTS FOR DESIGNING POTENT ANTICANCER PYRAZOLOPYRIMIDINE DERIVATIVES

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ABSTRACT

This study presents a 2D-QSAR analysis of 33 substituted pyrazole-pyrimidine derivatives to identify key physicochemical and structural features influencing their biological activity. Molecular descriptors were generated using VLifeMDS (v4.6), with compounds optimised via the MMFF force field. The dataset was divided into training, test, and validation sets employing manual, random, and spherical exclusion techniques to ensure robust model development. The optimal QSAR model, with a constant of 4.2686, incorporated four significant descriptors: HydrogensCount (positive correlation), T_O_O_2, SAMostHydrophobicHydrophilicDistance, and DipoleMoment (negative correlation). This model demonstrated strong statistical validity, with an r^2 of 0.7562, q^2 of 0.6095, and a predicted r^2 of 0.5584, indicating excellent internal and external predictivity. By highlighting the influential physicochemical properties, the model can guide the rational design of more potent derivatives. Notably, among the evaluated compounds, XIIE showed the highest predicted activity, underscoring its potential as a lead candidate for anticancer drug development. Overall, the model provides valuable insights into the structure-activity relationship, facilitating the development of novel anticancer agents with improved efficacy.

Keywords: QSAR, Molecular Descriptors, Pyrimidine, Cancer, Multiple Linear Regression.

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INTRODUCTION

Cancer is a disease that causes unregulated cell proliferation and aberrant cell division that eventually ends in death. Since targeted anti-neoplastic medications have become a viable cancer treatment option in recent years, pharmaceutical companies are now focusing on targeted medications against various and separate cancer categories.[1] Million people die from malignancies each year; in 2020, there were around 10 million fatalities and 19.3 million fresh instances worldwide. Approximately 400,000 youngsters are diagnosed with cancer each year. Different nations have different most frequent malignancies. In 23 nations, the most frequent cancer is cervical cancer.[2] In 2022, it is projected to be 1.46 million new cases of cancer in India, translating to a gross incident figure of 200.8 cases per 200,000. There is a forecast that cases of cancer will increase by 12.8% by the end of the year 2025.[3] The development of cancer is caused by mutations or overexpression of specific signalling protein classes that disrupt normal cellular regulation. One of the most significant extracellular communication messengers, receptor tyrosine kinases (RTKs), is often altered in cancer. The 56 RTKs present in the zoological genome can be divided into 20 unequal clans based on their structural properties.[4-6] In the battle against cancer, pyrazole and pyrimidine scaffolds have played a vital role for decades. Substituted pyrazole with pyrimidine a naturally occurring bioisostere, purine nucleoside heterocyclic base has been suggested to be a necessary a structural component of a few therapeutically relevant molecules.[7] Therapeutically, differently substituted pyrazole nucleus with pyrimidine have a variety of actions and act against inflammation, bacteria, fungi, virus, microbes, CNS stimulant, CVS agent and act against cancer.[8-16]

The QSAR is one of the very crucial features of chemical analysis, serving as a useful software often used in drug development and pharmaceutical chemical research. Molecular, physical, and biochemical characteristics, which may be predicted or calculated using a range of methods depending on the molecular structure, are closely related to biochemical and pharmacological consequences. Chemical and

biological effects are tightly linked to molecular physicochemical qualities, which may be anticipated or computed using a variety of techniques based on their structure. Heuristic procedures (HM), PLS (partial least squares), MLR (multiple linear regression) method and other types of artificial neural network's method (ANN) are just a few of the methods that may be utilized to create QSAR.[17] Using QSAR modelling to inform the rational development of different pharmacological substances such as antioxidant, neuroprotective, and anticancer medicines, was successfully demonstrated by the researchers in our lab.[18] PLS approach has been adopted in the present work to create a novel QSAR model for the anticancer activity of 33 substituted pyrazoles with pyrimidine derivatives. The purpose of QSAR analysis was to quantify the correlation between the physicochemical and structural characteristics of 1-phenyl-1H-pyrazolo[3,4-d] pyrimidine-derived products and their biological activity.

EXPERIMENTAL

Choosing the Dataset

33 molecules have been selected from the literature as part of the dataset.[19,20] The biotic actions of the selected data set are displayed in Tables-1, 2, 3, 4, 5, 6, and 7. pIC50 was created from biological data reported as IC50 (μM) for computer analysis using Sanjeev's labs, also giving the following equation:[21]

$$pIC_{50} = -\log_{10}(IC_{50} \text{ in } \mu M \text{ units})$$

2D QSAR Investigation

The compounds' structures from a few chosen series were illustrated using VLifeMDS software (version 4.3), 2D draw application option, and the results were then exported to the software.[22] The compounds' energy was reduced using the MMFF (Merck molecular force field) approach until the root mean square (rms) gradient was 0.01 kcal/moleA°. Choosing from the following, they underwent batch optimisation and 2D QSAR investigations as the molecules in the data set increased in quantity; the number of descriptors (physical, chemical, orientation unrelated, and atom type independent of orientation) was established. Dataset Descriptors that were computed and biological activity were regarded as independent and dependent variables, respectively. Numerous physicochemical descriptors were computed, including: Individual (H-Acceptor count, H-Donor count, X logP, SMR, polarizability, etc.); retention index (Chi); atomic valence connectivity index (ChiV); Path count, Chi chain, Chiv chain, Chain Path Count, Cluster, Path cluster, Kapa; Element count (H, N, C, S, O, Cl, Br, F); Estate numbers (SsCH3 Count, SdCH2 Count, StCH count, etc.); Estate contribution (SsCH3-index, SdCH2-index, St CH index), and Polar surface area. Using the above characteristics, over 250 orientation-independent descriptions have been generated. Several scenarios are (T_2_2_0), (T_2_T_0), (T_2_C_3), (T_2_N_1), (T_O_Cl_5), etc.

Structured features	A Few Selected Features
* Topographic Range Minimum – 0 Maximum - 7	2 3 T (any) H (Count for Hydrogens) C (Count for Carbons) S (Count for sulphurs) O (Count for Oxygens) N (Count for Nitrogens) C (Count for Chlorines) F (Count for Fluorines) B (Count for Bromines)

Development of the Compound Sets (Training - Test)

To assess the QSAR algorithm, the data set has been split into test, validation, and training sets using the random selection and manual selection approaches.

Random Selection Method

To construct and validate the QSAR models both internally and externally, the data sets were randomly divided into training sets (80%-60% (80%,85%,70%,65%, and 60%) of the total data set), test sets (10%-

30% (10%,15%,20%, and 30%) of the total data set), and validation sets (0-20% (0%,10%,15%,20%) of the total data set). Ten trials were carried out in each case.

Selection of Data by Manual

The overall collection of activity had been arranged in both upward and downward sequence, and the test set was divided into the 4th, 5th, 6th,7th, 8th, 9th and 10th compounds.

Sphere Exclusion Method

The data sets were first divided into training, test, and validation sets using the sphere exclusion algorithm. A concept for managing the size of the training, test sets and validation test set is provided by the dissimilarity value in this technique. Trial and error must be used to modify it until the training, test sets and validation test set are divided as desired. As the dissimilarity value increases, so does the number of molecules in the test set.

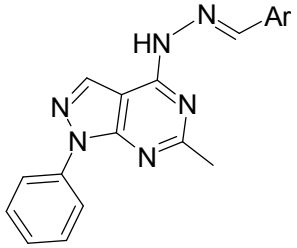
Statistical Computations

Stepwise multiple linear regression (MLR), partial least squares regression (PLSR), and partial component regression (PCR) are the statistical techniques that were employed to create QSAR models. The predicted correlation coefficient, coefficient of cross-validated squared correlation (q2), coefficient of squared correlation (r2), and F-test (F-test for statistical significance of the model) were considered when determining the statistical significance of QSAR models.

Multiple Linear Regressions Method

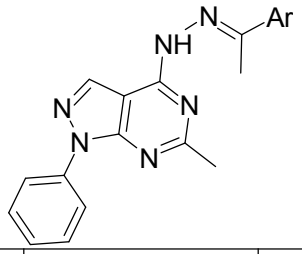
Every single particle was subjected to relapse analysis using a stepwise forward in backward variables identification approach in conjunction with multiple immediate rebounds. The correlation breakage criterion was set at 0.5, the term assessment frameworks were set at r2, the F test had been set at 4, and there were 5 elements examined in the conclusive precondition and 5 variables were examined in the confirmatory precondition, the F-test in was set at 4, the correlation breakage threshold was set at 0.5, the term assessment frameworks were set at r2, and the F-test out was set at 3.99. The total number of erratic cycles was set to 10, and the different boundary was set to 0, and automatic scaling was selected as the scaling option. Following the identification of a suitable model, an information fitness graph as well as a dedication overview are used to reproduce its rundown.

Table-1: Molecular Structural for Substituted Pyrazole with Pyrimidine Analogues as well as their Therapeutic Value (data set of 8 chemical compounds)



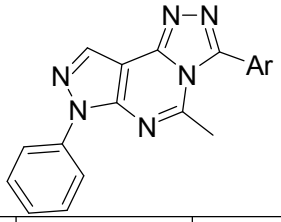
S. No.	Compound Code	Ar	MCF-7 IC50	p IC 50
1.	5A	C_6H_5	21.13	4.675
2.	5B	4-OH-C_6H_5	10.48	4.979
3.	5C	2,6-Cl-C6H_5	66.61	4.176
4.	5D	4-OMe-C_6H_5	19.36	4.713
5.	5E	4-CH=CH-C_6H_5	16.07	4.793
6.	5F	4-NO_2-C_6H_5	100.2	3.999
7.	5G	2,6-Cl-C_6H_5	100	3.998
8.	5H	4-CH=CH-C_6H_5	100.3	3.997

Table-2: Molecular Structure for Substituted Pyrazole with pyrimidine analogues as well as their Therapeutic Value (data set of 4 chemical compounds)



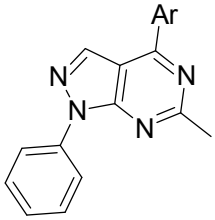
S.No.	Compound Code	Substituted. Ar	MCF-7 IC50	p IC 50
1.	5I	C_6H_5	3.81	5.419
2.	5J	4-NH_2-C_6H_5	36.04	4.443
3.	5K	4-OMe-C_6H_5	88.29	4.054
4.	5L	2-Br-4-Cl-C_6H_5	29.15	4.535

Table-3: Molecular Structural for Substituted Pyrazole with Pyrimidine Analogues as well as their therapeutic value (data set of 3 chemical compounds)



S.No.	Compound Code	Ar	MCF-7 IC50	p IC 50
1.	6A	H	49.65	4.304
2.	6B	CF_3	39.10	4.407
3.	6C	CCl_3	54.19	4.266

Table-4: Molecular Structure for Substituted Pyrazole with Pyrimidine Analogues as well as their Therapeutic Value (data set of 3 chemical compounds)



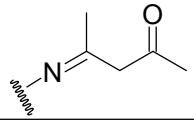
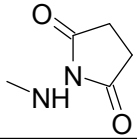
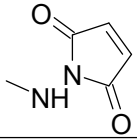
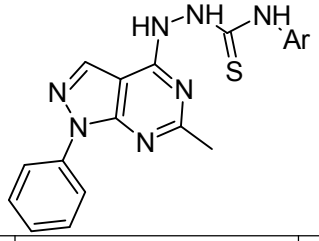
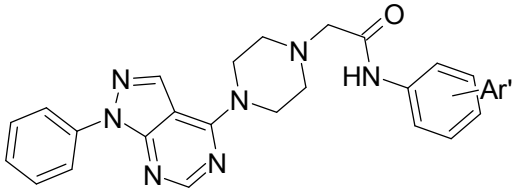
S.No.	Compound Code	Substituted. Ar	MCF-7 IC50	p IC 50
1.	6D		84.58	4.072
2.	7		81.02	4.091
3.	8		79.46	4.099

Table-5: Molecular Structural for Substituted Pyrazole with Pyrimidine Analogues as well as their Therapeutic Value (data set of 5 chemical compounds)



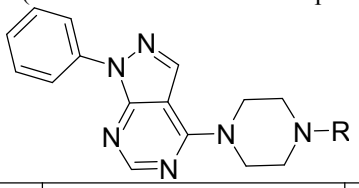
S.No.	Compound Code	Ar	MCF-7 IC50	p IC 50
1.	9A	$-CH_2CH_3$	7.61	5.118
2.	9B	$-CH_2CH_2CH_3$	34.18	4.466
3.	9C	$-CH_2-CH_2CH_2CH_3$	31.42	4.502
4.	9D	$-=CH_2$	35.19	4.453
5.	9E	-Phenyl	8.99	5.046

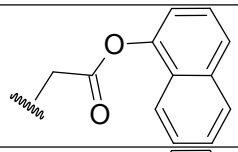
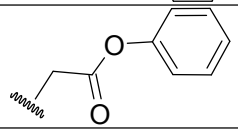
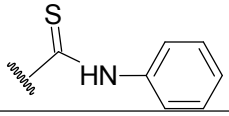
Table-6: Molecular Structural for Substituted Pyrazole with Pyrimidine Analogues as well as their Therapeutic Value (data set of 6 chemical compounds)

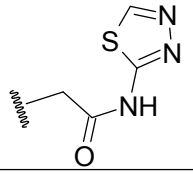


S.No.	Compound Code	Ar’	MCF-7 IC50	p IC 50
1.	XIIa	4-H	60.38	5.181
2.	XIIb	4-Br	63.24	5.238
3.	XIIc	4-Cl	72.43	5.416
4.	XIId	4-OMe	52.81	5.072
5.	XIIe	4-Me	25.80	4.525
6.	XIIf	3-Me	25.18	4.498

Table-7: Molecular Structural for Substituted Pyrazole with Pyrimidine Analogues as well as their Therapeutic Value (data set of 4 chemical compounds)



S.No.	Compound Code	R	MCF-7 IC50	p IC 50
1.	XIII		45.57	4.922
2.	XIV		27.53	4.579
3.	XV		16.49	4.295

4.	XVI		83.90	5.718

RESULTS AND DISCUSSION

2D-QSAR analysis on a series of pyrazoles with pyrimidine derivatives was performed by using V-Life software. The physiochemical descriptors and inhibitory activity were taken as independent and dependent variables respectively. Correlations were established between the biological activity and calculated molecular physiochemical descriptors through Multiple linear regression (Stepwise forward-backward). The summary of the model is given below.

Table-8: Best QSAR Model Produced using MLR Data Selection Techniques

S.No.	Model No.	Metrhod	Trail	Significant Models		
				r^2	q^2	pred_r^2
1.	01	MLR	9	0.7562	0.6095	0.5584

Table-9: List of Test Set Used in Random Selection (Training set = 60%; Test set = 25%; Validation Test set code= 15% of total data set)

Trail	Test Set	Validation Test Set
1	5H,9E,5G, XIIa,5K, XVI,5L,5E	XIID,5H,9B,9E, XIIC, 6A
2	XIID, XIIa,9A, XIII,9D,9B,6A, XIV	XIIF, XVI, XIII,6A,5I,5E
3	XIIF,5K, XIIa,5D, XIIC,5I,7, XIV	5A,5E,8, XIIE,5D,6B
4	XV,9C,XIII,XIIF,9B,5L,XIIB,5E	6A,5C, XIIE, XIIB,9D, XIV
5	5B,6B,9B, XIIF,9A,6A,5K, XIIC	5I,5B,6B,9C,6C, XV
6	5I,5A,6B,5K, XIIB,9D, XIIE,6A	XIV,5I,6D,5K,5B,5C
7	XVI,6C,5F, XIII,5H,5J,5C,5L	XIIE,5L,9D,9E,5H,XIID
8	5K,6C,5C, XIV, XIID, XIIC,9A,5L	7, XIID,5H, 9B,9E,XIIC
9	8, XIIC,6B, XIII,5H,9E, XV,9C	XIIF, XIIa,6A, XIIE,5K,5I
10	5A,5E,8, XIIE, 5D, 6B ,6D,XIIa	XIIB, XIID,5B,5I,6D,5D

Table-10: Realistic and Expected Activities for Training Set of Model 01

S.No.	Compound	Expected	Realistic
1.	5A	4.675	4.664
2.	5B	4.979	4.725
3.	5C	4.176	4.268
4.	5D	4.713	4.822
5.	5E	4.793	4.88
6.	5F	4.999	3.934
7.	5G	4.998	4.243
8.	5J	4.443	5.227
9.	5L	4.535	4.328
10.	6C	4.266	5.825
11.	7	4.091	4.242
12.	9A	5.118	4.712
13.	9B	4.466	4.883
14.	9D	4.453	4.479
15.	XIIa	5.181	5.249
16.	XIIB	5.238	4.968
17.	XIID	5.072	5.096
18.	XIV	4.579	4.684
19.	XVI	4.295	4.260

Table-11: Observed and Estimated Activity for Model 01 Test Set

S.No.	Compound	Expected	Realistic
1.	5H	3.997	4.63
2.	6B	4.407	4.242
3.	8	4.099	4.251
4.	9C	4.502	4.873
5.	9E	5.046	4.794
6.	XIIC	5.416	4.968
7.	XIII	4.922	4.341
8.	XV	5.718	5.158

Table-12: Shows the Actual and Anticipated Activities for the Model 01 Validation Test Set

S.No.	Compound	Actual	Predicted
1.	5I	5.419	5.049
2.	5K	4.054	5.254
3.	6A	4.304	5.116
4.	XIIa	5.181	5.249
5.	XIIE	4.525	5.381
6.	XIIF	4.498	5.371

Table-13: The Model 01 Max-Min Table for Their Test Set, Training Set Activities, and Validation Test Set

Column	Average	Maximum	Minimum	Standard Deviation	Sum
Training set	4.709947	5.825	3.934	0.45506	89.48
Test set	4.657125	5.158	4.242	0.348629	37.25

Fitness Plots of Models

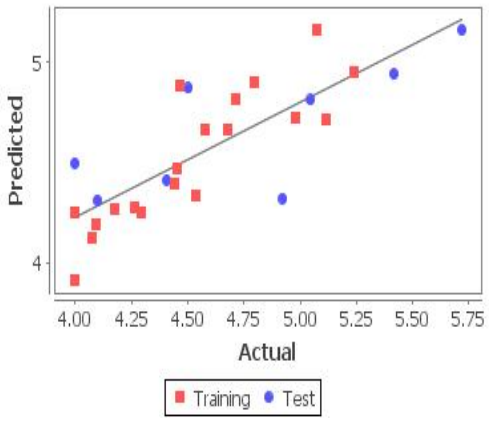


Fig.-1: Training and Test Set Data Fitness Plot for Model -01

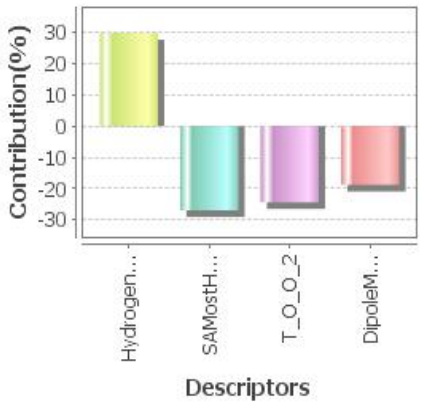


Fig.-2: Contribution Graphic for Model 01 of Several Biological Activity Descriptors

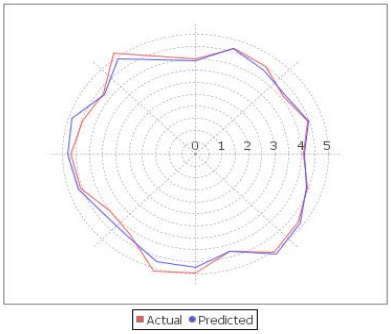


Fig-3: Activity training set

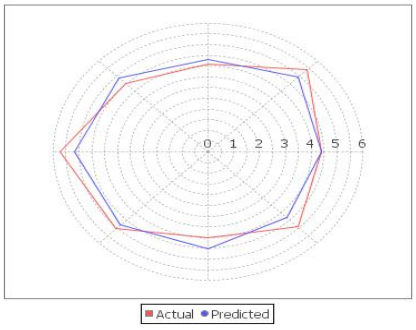


Fig-4: Activity test set

(Random 60% Trial-09) Using MLR regression analysis is as follows:

pIC50= 0.0741 Hydrogens Count -0.6721 T_O_O_2 -0.0674 SAMostHydrophobicHydrophilicDistance -0.1946 Dipole Moment 4.2686 Constant. This indicates that a rise in HydrogenCount has a positive impact on pIC50, indicating increased activity with more hydrogen atoms. T_O_O_2, SAM, most Hydrophobic Hydrophilic Distance, and Dipole Moment, on the other hand, have a negative effect on pIC_{50}, suggesting that larger values in these descriptors decrease biological activity. The baseline pIC_{50} value in the model is adjusted by the positive constant term (4.2686).

n = 19, Degree of freedom = 14, F test = 10.8570, r^2 = 0.7562, q^2 = 0.6095, pred_r^2 = 00.5584 r^2_se = 0.2170, q^2_se = 00.5875, Pre_r^2se = 0.2746, ExternalValidation_r^2se = 00.8019. The Model-01 explains 75.62% (r^2= 00.7562) of the aggregate variability in the data used for the training set, and the model has internal (q^2=0.6095) and external (pred_r^2=0.5584) predictive capability of 60.95% also 55.84% successively. F-test = 10.8570 indicates that 99.99% of the model is statistically significant within 10,000. As an outcome, the QSAR approach could be applied. The observed vs. hypothesised activity figure indicates how effectively the model was trained to predict the external test set activity. The model's predictive performance is demonstrated by the Figure, which shows that it can accurately forecast the activity of both the external test set and the training set. The training and test set fitness plots and the descriptor contribution chart for model 1 are displayed in Fig.-1and 2. Figure-3 and 4 show the activity graph of training and test sets for model 1.

Table-14: Statistical and Predictive Evaluation of 2D-QSAR Model

Compound Code	Hydrogens Count	SA Most Hydrophobic Hydrophilic Distance	T_O_O_2	Dipole Moment	Prediction
5A_1_3D.mol2	16	8.332	0	1.173	4.664
5B_2_3D.mol2	16	4.421	0	2.211	4.725
5C_3_3D.mol2	15	12.659	0	1.329	4.268
5D_4_3D.mol2	18	4.329	0	2.511	4.822
5E_5_3D.mol2	18	4.187	0	2.261	4.88
5F_6_3D.mol2	15	4.336	1	2.471	3.934
5G_7_3D.mol2	14	10.44	0	1.845	4.243
5H_8_3D.mol2	18	10.296	0	1.426	4.63
5I_9_3D.mol2	18	4.195	0	1.391	5.049
5J_10_3D.mol2	19	3.829	0	0.979	5.227
5K_11_3D.mol2	20	4.275	0	1.069	5.254
5L_12_3D.mol2	16	10.676	0	2.087	4.328
6A_13_3D.mol2	10	4.365	0	1.956	4.307
6B_14_3D.mol2	9	9.566	0	2.036	4.394
6C_15_3D.mol2	9	8.636	0	1.023	4.256
6D_16_3D.mol2	17	11.309	0	3.28	4.127
7_17_3D.mol2	15	8.225	0	2.994	4.242
8_18_3D.mol2	13	8.785	0	1.996	4.251
9A_19_3D.mol2	17	9.483	0	0.908	4.712
9B_20_3D.mol2	19	9.066	0	0.932	4.883
9C_21_3D.mol2	21	10.381	0	1.294	4.873
9D_22_3D.mol2	15	9.996	0	1.165	4.479
9E_23_3D.mol2	17	6.493	0	1.524	4.794
XIIa_24_3D.mol2	23	4.578	0	2.131	5.249
XIIB_25_3D.mol2	22	7.227	0	2.275	4.968
XIIC_26_3D.mol2	22	6.826	0	2.416	4.968
XIID_27_3D.mol2	25	5.431	0	3.384	5.096
XIIE_28_3D.mol2	25	5.085	0	2.039	5.381
XIIF_29_3D.mol2	25	4.805	0	2.189	5.371
XIII_30_3D.mol2	24	5.393	1	3.44	4.341
XIV_31_3D.mol2	22	4.489	1	1.229	4.684
XVI_33_3D.mol2	19	11.934	0	3.141	4.26

Elucidation of the Result

The current study's statistically significant model was produced by combining MLR with the selection of variables in a stepwise forward-backwards manner. Attested by the pIC_{50} regression clone, Hydrogens Count has a positive impact on activity (+0.0741), meaning that a larger hydrogen concentration increases potency. T_O_O_2 (−0.6721) and SA Most Hydrophobic Hydrophilic Distance (−0.0674) Dipole Moment (-0.1946), on the other hand, have a negative effect on activity, indicating that some oxygen-based topologies and a higher separation of hydrophobic/hydrophilic areas lower bioactivity. The baseline activity is represented by the intercept (4.2686). Predicted and actual pIC_{50} values are well aligned in the fitness plot (Fig.-1), with training data closely following the straight line and test data displaying appropriate dispersion. This suggests that the model is both accurate and generalizable, since it has a good fitting ability and a fair predictive performance on unknown data. The proportional impact of chemical descriptors on the model's prediction of pIC_{50} values is displayed in the contribution plot (Fig.-2). Hydrogen Count has the most beneficial impact among the descriptors. The training set's actual and projected pIC_{50} values are contrasted in the radar plot (Fig.-3). The model matches the training data well, as seen by the close overlap between the blue (predicted) and red (actual) lines, which shows a low variance and a good correlation. The actual and expected pIC_{50} values for the test set are contrasted in the radar map (Fig.-4). A blue (expected) and red (realistic) lines closely overlap, indicating strong predictive accuracy with little variation across most data points. Based on their chemical characteristics, the developed compounds' anticipated actions are compiled in Table-14. The compounds with the highest anticipated activity levels (about 5.2–5.4), such as 5J, 5K, XIIa, XIIE, and XIIF, may have significant biological potential.

CONCLUSION

A number of thirty-three substituted pyrazoles with pyrimidine derivatives were subjected to traditional quantitative structure-activity relationship studies using the MLR with a stepwise forward-backwards variable selection approach. The best model, consisting of significant values of $r^2 = 0.7562$, $q^2 = 0.6095$ and pred_r^2=0.5584, with the greatest statistical importance. Using SWFB-MLR and four important descriptors—Hydrogens Count (positive), SA Most Hydrophobic Hydrophilic Distance, T_O_O_2, and Dipole Moment, a dependable QSAR model was created with a constant of 4.2686. Based on important structural and physicochemical characteristics, the model may be used to find powerful molecules and is statistically significant and externally predictive. Among all tested derivatives, XIIE exhibited the highest predicted activity, indicating its strong potential as a lead compound for anticancer drug development. These studies can be statistically treated to uncover the molecular properties that are crucial for potency. The SWFB-MLR (Stepwise Forward-Backwards conjugated with Multiple Linear Regression) technique was used to effectively construct one optimised model in this QSAR experiment, and all these models showed excellent performance. The dependability of the models was confirmed by external prediction and statistical significance validation. The crucial connection between molecular structure, physicochemical characteristics, and biological activity is highlighted by this work. By predicting the activity of freshly developed compounds and efficiently guiding the selection of appropriate substituents to increase potency, the most robust model can provide important insights for the creation of more active molecules for designing novel anticancer agents.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation, and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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