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QSAR, Design, Molecular Docking Study, Drug- Likeness Evaluation and ADMET Properties of Potential Inhibitors Against Prostate Cancer (PC3) Cell Line Through Computational Approach

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Abstract: Quantitative Structure- Activity Relationship (QSAR) analyses were conducted on a series of 1, 9-diheteroarylnona-1, 3, 6, 8 -tetraen-5 -one derivatives to assess their antiproliferative activity against the prostate cancer PC3 cell line. The developed QSAR model demonstrated excellent internal validation metrics: R^2 = 0.9998, adjusted R^2 = 0.9997, SEE = 0.0071, Q^2 (LOO) = 0.9917 and MAE = 0.0159. External validation also supported the models reliability, with Concordance Correlation Coefficient (CCC) = 0.8299. The antiproliferative activity was found to be strongly influenced by the molecular descriptors SIC2, SpMin3_Bhe, GATS7c, MATS3c, and ZMIC1. Molecular docking studies was conducted with the androgen receptor (1z8l) showed binding affinities ranging from (-6.6 to -10.6 kcal/mol) with compound 15 displaying the strongest interaction. This compound was used as a structural template to design two novel compounds. The two compounds (D1 and D2) exhibited higher binding affinities (-10.7 to -10.9 kcal/mol) than the template (-10.6 kcal/mol) and reference compound (-10.1 kcal/mol) respectively. Drug- likeness and ADMET assessments indicated that the new compounds have favorable ADME profiles and conforms to Lipinski's rule of five.

Keywords: *QSAR, PC3, Pharmacokinetic, ADMET, Docking Study.*

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I. INTRODUCTION

The emergence of new diseases, along with the growing resistance of existing ones to current treatments, has created a constant demand for new medications and therapies. This ongoing demand has negatively impacted the environment, especially affecting plants and microorganisms [1, 2]. Traditional drug discovery methods, which often rely on trial and error, have contributed to the depletion of valuable natural resources, ecological imbalance, and in some instances, environmental pollution. Moreover, developing a potential drug candidate through these conventional approaches is typically time-consuming [3]. In contrast, computational techniques offer more efficient, cost-effective, and environmentally friendly alternatives. Computer-aided drug design (CADD) utilizes software tools to simulate the behavior of certain compounds, enabling the prediction of biological activity in other compounds with similar pharmacophore features [4, 5]. Cancer is a broad term encompassing nearly 120 different diseases that can affect various body systems. It is characterized by the uncontrolled growth of cells and the invasion of healthy tissues [6].

Prostate cancer ranks as the second most common malignancy among men [7]. It is marked by abnormal enlargement of the prostate gland, which often results in reduced urinary flow and is a leading cause of illness and mortality globally [8]. Among male cancers, prostate cancer is one of the most frequently diagnosed, second only to skin cancer and more prevalent than lung cancer. It primarily affects older men, with aged 65 and above accounting for roughly 60% of cases. In fact, around 80% of all prostate

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cancer diagnoses occur within this age group. Although the mortality rate is relatively low with a five year survival rate of approximately 98%, prostate cancer remains a major contributor to cancer related deaths in men [9, 10].

Despite advances in technology and healthcare, cancer continues to present a severe threat to human health due to its high fatality rate and limited treatment success [11, 12]. One of the main hurdles in drug discovery and development is the difficulty in identifying effective new drugs, along with low clinical trial success rates. Many potential drugs fail to reach the market after clinical trials, largely due to poor pharmacokinetics or harmful side effects, despite significant investment in their development. In drug discovery, not only a compound potency but also its pharmacokinetic and toxicity profiles are crucial in determining its success in clinical applications [13]. The emergence of quantitative structure-activity relationship (QSAR) analysis has introduced a cost effective and efficient approach to drug discovery. QSAR operates on the principle that compounds with similar chemical structures are likely to exhibit comparable biological activities [14].

II. MATERIALS AND METHODS

➢ *Data Collection*

In this study, a series of 1, 9-diheteroarylnona-1, 3, 6, 8-tetraen-5- one derivative, previously synthesized and evaluated for anticancer activity against PC3 prostate cancer cell line [15], were selected for quantitative structure- activity relationship (QSAR) analysis. The biological activity of these compounds was originally reported in IC_{50} values in micromolar concentrations (M), which were converted to pIC_{50} values for use in this study using equation 1.

$$pIC_{50} = -log_{10}\,(IC_{50} \times 10^{-6}) \qquad \text{Equ 1}$$

➢ *Geometry Optimization*

The 2D chemical structures of the compounds were first drawn using ChemDraw version 12.1. These structures were then converted into 3D models for geometry optimization, which was achieved using Density Functional Theory (DFT) in the Spartan 14 software. The B3LYP functional and 6-31G* basis set were employed to identify the lowest energy conformations of each molecule. The optimized molecular structures were saved in PDB file format for further analysis [16- 18].

➢ *Generation of Models*

For the QSAR modeling, five different models were developed using a combination of Genetic Function Algorithm (GFA) and Multiple Linear Regression (MLR) techniques in the DTC Lab software (https://teqip.jdvu.ac.in/QSAR_Tools/). Among these, Model 1 was identified as the most reliable, based on statistical parameters used to evaluate the performance and predictive accuracy of each model.

➢ *Validation of Model*

To evaluate the predictive strength of the developed model, internal validation was conducted using several statistical parameters: the coefficient of determination (R^2), adjusted R^2 (R^2adj), standard error of estimation (SEE), and mean absolute error (MAE). While these metrics provide insight into model quality, they alone are not sufficient to confirm the model robustness. Therefore, further assessment was performed using the Variance Inflation Factor (VIF), which measures the degree of multicollinearity among the descriptors used in the regression analysis. VIF is computed as follows:

$$VIF = \frac{1}{(1-R^2)} \qquad \text{Equ 2}$$

A high R^2 value indicates a strong correlation between the model parameters [19], VIF values below 10 suggest the regression equation is stable, whereas values exceeding 10 indicate inefficiency and unreliability of the model. The individual contribution of each descriptor to the model was assessed through the mean effect (M/E) values. The mean effect highlights how each descriptor influences the resulting QSAR equation, with the sign positive or negative denoting whether the parameter increases or decreases the predicted activity [20]. The mean effect is defined as:

$$Mean\ Effect = \frac{\beta j \Sigma_i^n Dj}{\Sigma^m (\beta j \Sigma_i^n Dj)} \qquad \text{Equ 3}$$

Where m represents the number of descriptors in the model, βj is the coefficient of descriptor j, n refers to the number of molecules in the prediction set, and Dj is the matrix value of descriptor j in the prediction set.

For external validation, a test set was used, and the model performance was assessed using the Concordance Correlation Coefficient (CCC). A CCC value greater than 0.8 is considered indicative of a reliable model, the CCC is calculated as follows:

$$CCC = \frac{2\ \sum_{i=1}^{nEXT}(Yi-\bar{Y})\,(Yi-\hat{Y}i)}{\Sigma_{i=1}^{nEXT}(Yi-\bar{Y})^2 + \Sigma_{i=1}^{nEXT}(Yi-\hat{Y}i)^2 + nEXT\,(Yi-\hat{Y}i)^2} \qquad \text{Equ 4}$$

Yi is the observed activity value, $\bar{Y}$ is the mean of observed activity values, $\hat{Y}i$ is the predicted activity value, and $\hat{\bar{Y}}$ is the mean of the predicted activity values. EXT refers to the external validation set or test set [21].

➢ *Y- Randomization*

An important method for evaluating the reliability of a QSAR model is the Y-randomization test. In this approach, the dependent variables are randomly shuffled while the independent variables remain unchanged. This test is conducted on the training set, and for a model to be considered valid, it should yield significantly lower R^2 and Q^2- Loo values compared to the original model. Such results confirm that the model is not based on random correlations and is both robust and dependable. This supports a strong correlation between the molecular descriptors of the compounds and their inhibitory activity against the PC3 prostate cancer cell line.

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➢ *Docking Study*

In this study, molecular docking was conducted to investigate the binding interactions between the synthesized compounds as ligands and the protein receptor (PDB: 1z8l). Docking simulations were carried out within the active site of the protein receptor to evaluate the binding affinities and potential interactions.

➢ *SwissADME and ADMET Profiles*

In this present study, SwissAdme and ProTox 3.0 online free software tool were utilized to predict the drug- likeness and pharmacokinetics toxicity of ligands of interest under investigation.

III. RESULTS AND DISCUSSION

MLR equation: pIC_{50} = 8.4456 (*SIC2) +0.9536 (*SpMin3_Bhe) -2.9246 (*GATS7c) +0.4083 (*MATS3c) +0.098 (*ZMIC1) +0.0038 Equ 5

➢ *Internal Validation Metrics:*

Number of Training set data points: 19

R^2 = 0.9998, R^2 (Adjusted) = 0.9997, (SEE) = 0.0071, Q^2 (LOO) = 0.9917, (MAE) = 0.0159.

External Validation metrics using a Test set:

Number of Test set data points: 6

CCC (Test) = 0.8299

In the current study, a series of compounds synthesized by Zhang et al. Ref [15], along with their reported biological activity against PC3 prostate cancer cell line, were utilized for quantitative structure- activity relationship (QSAR) analysis. Five QSAR models were constructed using a combination of the Genetic Function Algorithm (GFA) and Multiple Linear Regression (MLR) in DTC Lab (https://teqip.jdvu.ac.in/QSAR_Tools/). Among these, Model 1 exhibited the highest statistical robustness and was identified as the most reliable. This model showed strong validation metrics for both internal and external evaluations, with R^2 and adjusted R^2 values exceeding 0.9 for the training set, and a concordance correlation coefficient above 0.8 for the test set. The external validation of 0.8299 indicates that it provides a good fit for emulating anti-prostate cancer inhibitory functions. These findings confirm that the model accuracy was not due to random chance and that a significant relationship exists between the molecular structures and their inhibitory activity on the PC3 cell line. The parameters of Model 1 further support its strong predictive capability, as the predicted activities closely matched the experimentally observed values. Therefore, the predicted compounds are considered active against PC3 cell line and may serve as promising lead candidates for prostate cancer therapy.

The compounds, their molecular descriptors, observed pIC_{50} values, predicted pIC_{50} values, residuals, and docking scores derived from the developed model 1 are presented in Table 1. The most active compounds in the dataset are compound 15, 16, and 17 had observed pIC_{50} values of 4.823, 4.795, and 4.769, with corresponding predicted pIC_{50} values of 4.831, 4.783, and 4.769, respectively. Table 2 outlines the definitions and classifications of the descriptors used in the final model. Table 3 is the Y-randomization test results, which yielded low R^2 and Q^2- Loo values, indicating that the model performance is not due to chance and affirming its statistical validity. Table 4 provides further statistical analysis, including the correlations among descriptors and their individual contributions to the model.

The model contain 2D topological descriptors: SIC2 defined as Structural information content index (neighborhood symmetry of 2- order), SpMin3_Bhe defined as Smallest absolute eigen value of Burden modified matrix- n3/ weighted by relative sanderson electro-negativities, GATS7c defined as Geary autocorrelation- lag 7/ weighted by charges, MATS3c defined as Moran autocorrelation- lag 3/ weighted by charges and ZMIC1 defined as Z- modified information content index (neighborhood symmetry of 1- order). The mean effect analysis of the model parameters indicates that SIC2 (+0.9536), GATS7c (+0.4083), MATS3c (+0.098), and ZMIC1 (+0.0038) have positive coefficients, suggesting that increasing these descriptors enhances the biological activity of the compounds. While SpMin3_Bhe (-2.9246) has a negative coefficient, implying that a reduction in this descriptor would also boost the inhibitory activity of the 1, 9-diheteroarylnona-1, 3, 6, 8-tetraen-5-one derivatives against the PC3 prostate cancer cell line. Figure 1 presents a residual plot, where residuals for both data sets are distributed evenly above and below the zero line, indicating the absence of systematic errors in the model. Figure 2 illustrates a scatter plot of predicted pIC_{50} versus actual pIC_{50} values for both training and test sets. The close alignment of data points along the diagonal line confirms the strong predictive accuracy of the model.

Table 1 The Compounds, Descriptors, Observed IC_{50}, Predicted IC_{50}, Residual and Docking scores of 1, 9- Diheteroarylnona- 1, 3, 6, 8- Tetraen- 5 Ones

S/N	SIC2	SpMin3 _Bhe	GATS7c	MATS3c	ZMIC1	Observed pIC_{50}	Predicted pIC_{50}	Residue	Docking Scores
1.	0.658	0.973	0.965	-0.010	1.887	6.000	5.999	-0.001	-6.9
2.	0.729	1.467	1.638	-0.120	49.482	5.698	5.694	-0.004	-7.7
3.	0.751	1.490	1.311	-0.002	48.438	5.522	5.524	0.001	-7.4
4.	0.702	1.537	1.472	-0.146	51.160	5.397	5.400	0.003	-7.9
*5.	0.736	1.515	1.385	-0.015	58.487	5.301	5.503	0.202	-8.3

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*6.	0.692	1.633	1.437	-0.120	51.813	5.221	5.102	-0.119	-9.2
*7.	0.712	1.617	1.289	-0.067	53.422	5.154	5.119	-0.035	-7.8
*8.	0.681	1.650	1.195	-0.021	57.176	5.096	4.973	-0.123	-7.9
*9.	0.700	1.644	1.402	-0.075	57.176	5.045	5.087	0.041	-8.0
10.	0.662	1.685	1.509	-0.034	60.861	5	4.994	-0.005	-8.3
11.	0.657	1.694	1.510	-0.118	62.767	4.958	4.961	0.002	-8.4
12.	0.711	1.681	1.208	-3.58E	55.633	4.920	4.911	-0.009	-8.2
13.	0.711	1.680	1.182	-0.070	55.633	4.886	4.897	0.0115	-8.2
14.	0.741	1.680	0.998	0.091	52.899	4.853	4.855	0.002	-8.8
15.	0.604	1.726	1.322	0.041	82.697	4.823	4.831	0.008	-10.6
*16.	0.659	1.718	1.101	0.021	74.381	4.795	4.783	-0.012	-10.2
17.	0.651	1.742	1.266	0.062	72.317	4.769	4.769	0.024	-10.1
18.	0.665	1.738	1.137	0.017	73.817	4.744	4.744	-0.000	-8.5
19.	0.677	1.740	1.035	0.045	75.262	4.721	4.717	-0.003	-8.2
20.	0.636	1.740	1.066	-0.047	77.408	4.698	4.690	-0.008	-9.9
21.	0.650	1.740	0.975	0.052	78.710	4.677	4.680	0.003	-8.4
22.	0.752	1.491	1.310	-0.003	48.439	5.523	5.524	-0.001	-6.8
23.	0.681	1.623	1.432	-0.121	52.713	5.201	5.403	-0.202	-7.1
24.	0.666	1.638	1.127	0.0117	73.717	4.733	4.743	-0.01	-7.0
25.	0.701	1.643	1.403	-0.074	56.177	5.044	5.086	-0.042	-6.6

*represent test set

Table 2 Descriptors of the Build Model One and Their Class

Descriptors	**Definition**	**Class**
SIC2	Structural information content index (neighborhood symmetry of 2- order)	2D
SpMin3_Bhe	Smallest absolute eigen value of Burden modified matrix- n3/ weighted by relative sanderson electronegativities	2D
GATS7c	Geary autocorrelation- lag 7/ weighted by charges	2D
MATS3c	Moran autocorrelation- lag 3/ weighted by charges	2D
ZMIC1	Z- modified information content index (neighborhood symmetry of 1- order)	2D

Table 3 Y- Randomization

MODEL TYPE	**R^2**	**Q^2-LOO**
Original	0.9998	0.9917
Random 1	0.4042	-37.7421
Random 2	0.2887	-1.2011
Random 3	0.2347	-2.7472
Random 4	0.1291	-11.4834
Random 5	0.4314	-4.9652
Random 6	0.1034	-1.6445
Random 7	0.3930	-51.5507
Random 8	0.5710	-33.8378
Random 9	0.2143	-142.248
Random 10	0.3000	-129.748
Summary		
R^2	Original Model	0.9998
Q^2-LOO	Original Model	0.9917
Average R^2	10 Random Models	0.3070
Average Q^2-LOO	10 Random Models	-41.7168

Table 4 Statistical Analysis of the Build Model One

	SIC2	***SpMin3_Bhe***	***GATS7c***	***MATS3c***	***ZMIC1***	***VIF***	***M/E***
SIC2	1	0.7913	0.3600	-0.0577	0.6652	4.2939	0
SpMin3_Bhe	0.7913	1	0.0468	0.2348	0.9335	6.7899	0.3300
GATS7c	0.3600	0.0468	1	-0.6798	0.0273	2.4471	0.2439
MATS3c	-0.0577	0.2348	-0.6798	1	0.2607	2.1771	-0.0017
ZMIC1	0.6652	0.9335	0.0273	0.2607	1	8.1330	0.4277

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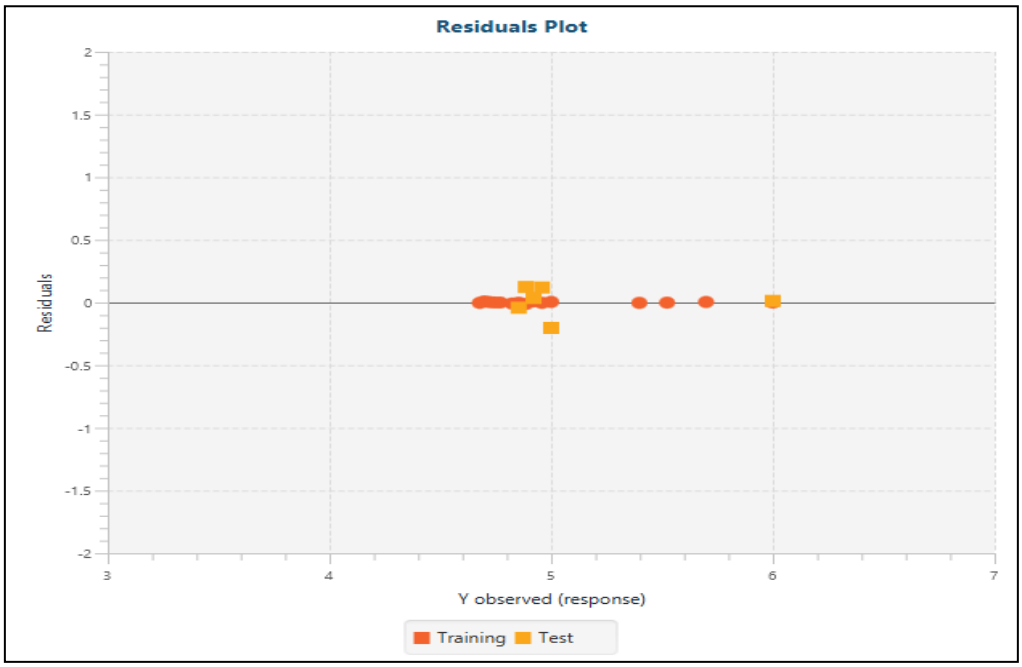

Fig 1 Scatter Plot of Standardized Residual Versus the Investigational Activities

Fig 2 Scatter Plot of Biological Activities Against Calculated Activities.

➢ *Docking Result*

A molecular docking study was conducted using PyRx AutoDock Vina software, targeting the binding site of the androgen receptor (PDB ID: 1z8l). Docking poses were selected based on their docking scores, with the highest scoring conformations chosen, ranging from (-10.1 to -10.6 kcal/mol) respectively, as shown in Table 1. These scores indicate strong binding affinities between the selected compounds and the androgen receptor. Structural modification of compound 15 with highest binding affinity (-10.6 kcal/mol) to generate two novel analogues resulted in notable improvements in both binding affinities and toxicity profiles.

- *Design of A Novel Compounds*

Two (2) novel compounds were designed, (D1 and D2) as shown in Table 5 against prostate cancer PC3 cell line. The newly designed compounds were carried out by manipulation of compounds 15 with the aim of enhancing and increasing their pharmacokinetics towards the protein receptor. The main interaction types identified include hydrogen bonding and hydrophobic interactions. Visualization of the ligand-receptor interactions within the receptor binding pocket were carried out using Discovery Studio software.

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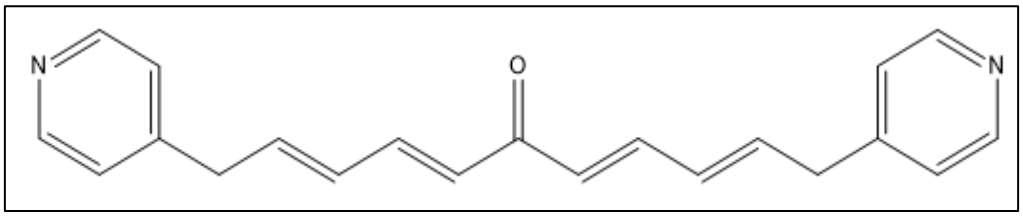


Fig 3 2D Structure of Compound 15 Used as a Template to Designed Novel Compounds

Table 5 Newly Designed Compounds with Their Docking Score

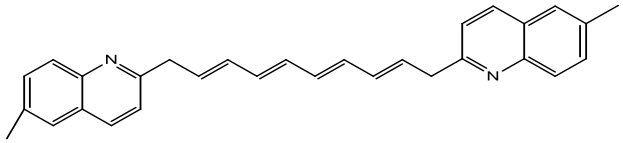
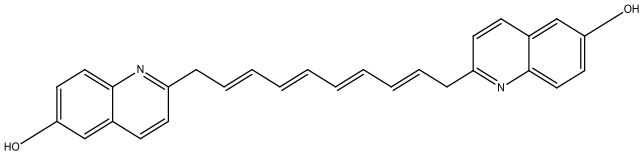
S/No	Compounds	Docking Score (Kcal/Mol)
D1.		-10.9
D2.		-10.7

Table 6 Various Interaction Between the Potential Hit Compounds and the Active Site of 1z8l Androgen Receptor

S/No	Binding affinities	H-Bond Interactions	Distance (Å)	Hydrophobic interactions	Distance (Å)
D 1.	-10.9			LYS A:213 TYR A:700 ARG A:20 PHE A:209 LEU A:428 LEU A:261 ALA A:264	7.28 6.44 2.88, 4.48 3.72, 3.92 3.98, 4.72 3.52, 4.05, 4.53 3.97
D 2.	-10.7	ARG A:536 GLU A:457 TYR A:687 LEU A:261 ASN A:262 GLY A:263	2.61 2.24 2.83 2.07 2.20 2.33	LEU A:4.91 TYR A:552 PHE A:209 ARG A:210	4.91 4.66 4.23, 5.18 4.31, 4.36
Reference	-10.1	GLY A:206 VAL A:208 SER A:454	1.83 2.32 2.72	TYR A:552 PHE A:209 TYR A:205 ARG A:536 GLU A:457	3.64, 4.97, 5.04 4.75 5.37 3.23 4.20

The two newly designed compounds exhibited the strongest binding affinities, with docking scores of (-10.9 and -10.7 kcal/mol), outperforming both the parent scaffold (-10.6 kcal/mol) and the standard drug Abiraterone acetate (-10.1 kcal/mol). This improvement is largely attributed to the rational substitutions incorporated, which enhanced the stability of the ligand- receptor complex by fostering multiple hydrogen bonds and hydrophobic contacts with crucial amino acid residues.

Compound D1, with the best docking score (-10.9 kcal/mol), demonstrated a diverse interaction profile within the receptor pocket. It engaged in a Pi- cation interaction with LYS213 at a distance of (7.28Å) and a Pi- Pi T-shaped contact with TYR700 at a distance of (6.44Å). Several Pi- alkyl interactions were observed with ARG20 at a distance of (2.88Å and 4.48Å), PHE209 at a distance of (3.72Å and 3.92Å), and LEU428 at a distance of (3.93Å and 4.72Å) respectively. Additionally, amide- Pi stacking interactions were established with LEU261 at a distance of (3.52Å, 4.05Å and 4.53Å), while ALA264 contributed an alkyl interaction at a distance of (3.97Å). Collectively, these interactions reinforced the binding stability of D1, explaining its superior affinity compared to the parent and reference drug. 3D and 2D visualization of D1 interaction is displayed in figure 4 using Discovery studio software.

Compound D2**,** achieved a docking score of (-9.7 kcal/mol), exhibited a rich network of stabilizing interactions within the receptor binding pocket. It formed multiple conventional hydrogen bonds interactions with ARG536 at a distance of (2.61Å), GLU457 at a distance of (2.24Å), TYR687 at a distance of (2.83Å), LEU261 at a distance of (2.07Å), ASN262 at a distance of (2.20Å), and GLY263 at a distance of (2.33Å), underscoring the importance of polar contacts in its binding. In addition, hydrophobic alkyl

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interactions were detected with LEU261 at a distance of (4.91Å), while Pi- Pi T-shaped stacking interaction was observed with TYR552 at a distance of (4.66Å). Further stabilization arose from Pi- alkyl contacts with PHE209 at a distance of (4.23Å and 5.18Å) and ARG210 at a distance of (4.31Å and 4.36Å) respectively. Both 3D and 2D visualization of D2 interaction is displayed in figure 5 using Discovery studio software.

For comparison, the reference drug Abiraterone acetate with docking score (-10.1 kcal/mol) established fewer but notable interactions, it engaged in hydrogen bonding with GLY206 at a distance of (1.83Å), VAL208 at a distance of (2.32Å), and SER454 at a distance of (2.72Å). Its hydrophobic profile involved Pi- alkyl interactions with TYR552 at a distance of (3.64Å, 4.97Å and 5.04Å), PHE209 at a distance of (4.75Å), and TYR205 at a distance of (5.37Å). Additionally, it displayed Pi- anion interaction with ARG536 at a distance of (3.23Å) and a Pi- cation contact with GLU457 at a distance of (4.20Å). 3D and 2D visualization of Abiraterone acetate interaction is displayed in figure 6 using Discovery studio software. Overall, D2 distinguished itself through its extensive hydrogen-bonding network and complementary hydrophobic contacts, which likely contribute to its promising receptor stabilization potential.

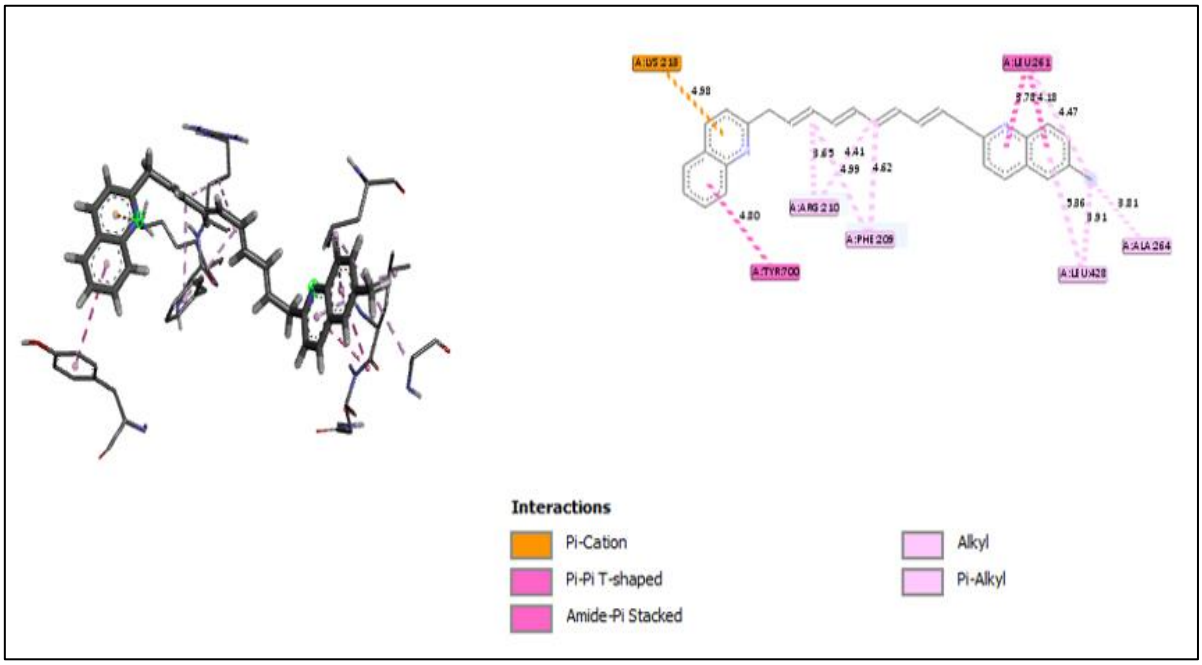

Fig 4 3D and 2D view of D1 Interaction Using Discovery Studio

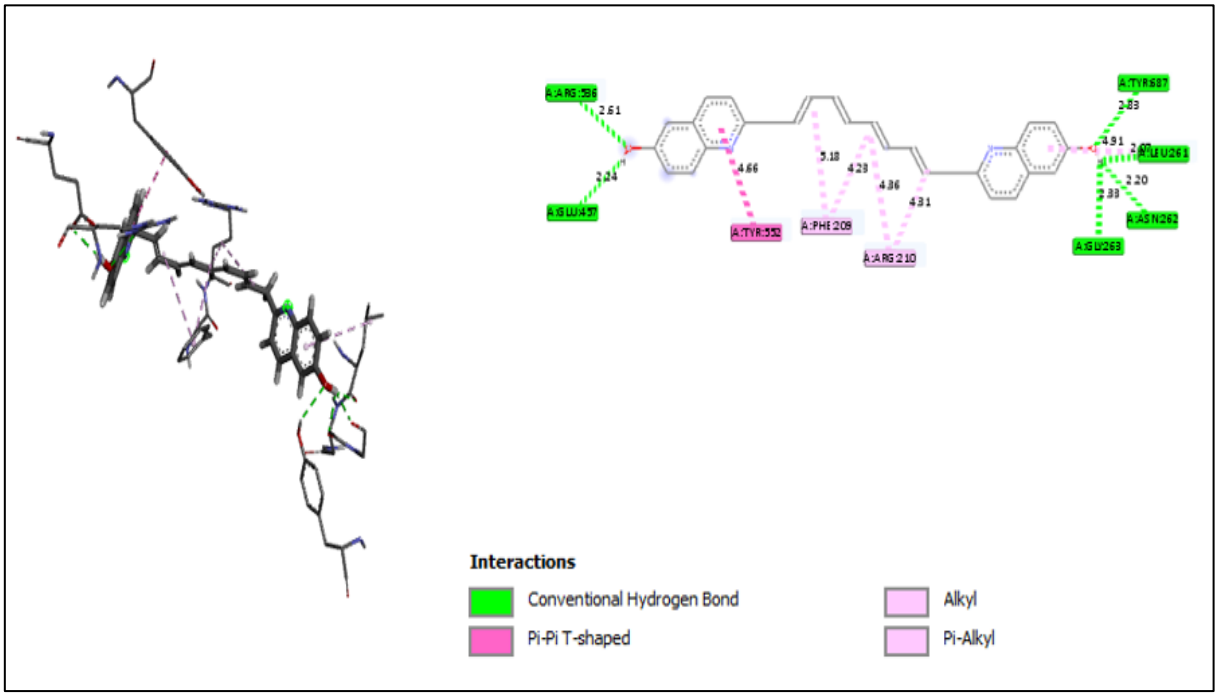

Fig 5 3D and 2D view of D2 Interaction Using Discovery Studio

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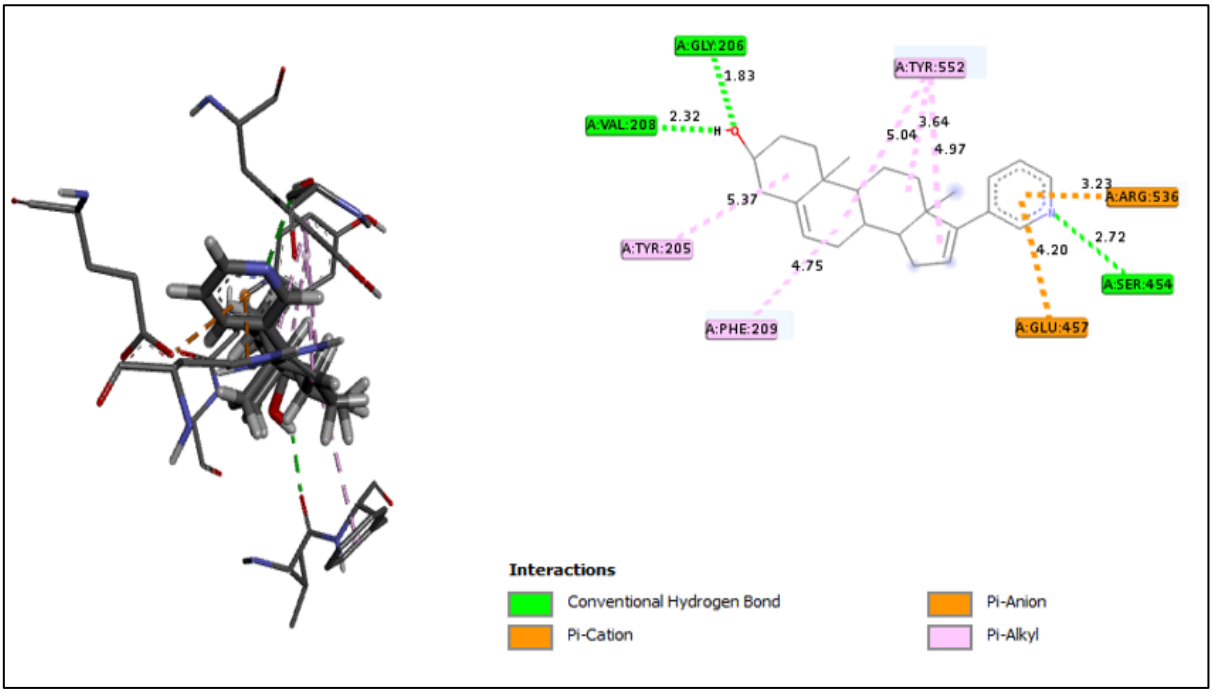

Fig 6 3D and 2D View of Abiraterone Acetate Interaction Using Discovery Studio

➢ *Drug- Likeness and Toxicity of the Newly Designed Compounds*

The drug- likeness and toxicity properties of the newly designed compounds were evaluated using SwissADME and ProTox 3.0, a tool that predicts key physicochemical, pharmacokinetic, and toxicity parameters for single or multiple molecules. A major challenge in drug discovery has been the high attrition rate of candidates due to poor ADMET properties, which often prevent promising molecules from advancing to clinical trials. However, with the growing emphasis on ADMET profiling during the early stages of drug development, the number of failures attributed to these limitations has substantially declined [22]. In the present study, all designed compounds demonstrated a favorable safety profile, showing no predicted activity toward toxicity endpoints such as carcinogenicity, mutagenicity, or blood-brain barrier penetration. This absence of genotoxic underscores their potential pharmacological safety. Furthermore, cytochrome P450 (CYP) enzymes particularly the major isoforms 1A2, 2C19, 2C9, 2D6, 3A4, and 2E1 were considered as key metabolic determinants in the ADMET evaluation (Table 8). The computational predictions indicated variable interactions of the compounds as substrates or non-substrates across these isoenzymes. Importantly, none of the designed molecules exhibited concerning toxicity risks, highlighting their suitability for further optimization and potential preclinical exploration.

Their favorable bioavailability score (0.55) combined with relatively low synthetic accessibility values (3.44 and 3.61) indicates an optimal balance between drug-likeness and practical feasibility of synthesis an essential criterion in the drug discovery and development pipeline. These findings suggest that the designed compounds have suitable characteristics for drug development. Also, the study demonstrated that the newly designed molecules showed their potential for further drug discovery efforts.

Figures 7 and Figure 8 indicate the molecular weight distribution for D1 and D2. In these diagrams, the red line represents the mean molecular weight and the black line indicates the actual molecular weight, while the LD50 distribution is similarly depicted with the mean in red and the predicted median lethal dose in black. Overall, these results suggest that, with careful consideration of potential carcinogenicity, these compounds could serve as viable candidates for further clinical trials.

Table 7 Drug- Likeness of Newly Designed Compounds

S/No	MW	HBA	HBD	TPSA Å	Lipinski	Drug-Likeness	Bioavailabilty score	Synthetic accessibility
D1.	402.53	2	0	25.78	0	Yes	0.55	3.61
D2.	420.50	4	2	66.2	0	Yes	0.55	3.44

Table 8 Toxicity Prediction of the Newly Designed Compounds

Property	D1	Probability	D2	Probability
Carcinogenicity	Inactive	0.80	Inactive	0.56
Mutagenicity	Inactive	0.88	Inactive	0.89
BBB	Inactive	0.86	Inactive	0.84

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CYP 1A2	Active	0.55	Inactive	0.52
CYP 2C19	Active	0.51	Active	0.61
CYP C29	Active	0.52	Active	0.83
CYP 2D6	Active	0.55	Inactive	0.76
CYP 3A4	Active	0.50	Inactive	0.65
CYP 2E1	Inactive	0.97	Inactive	0.99

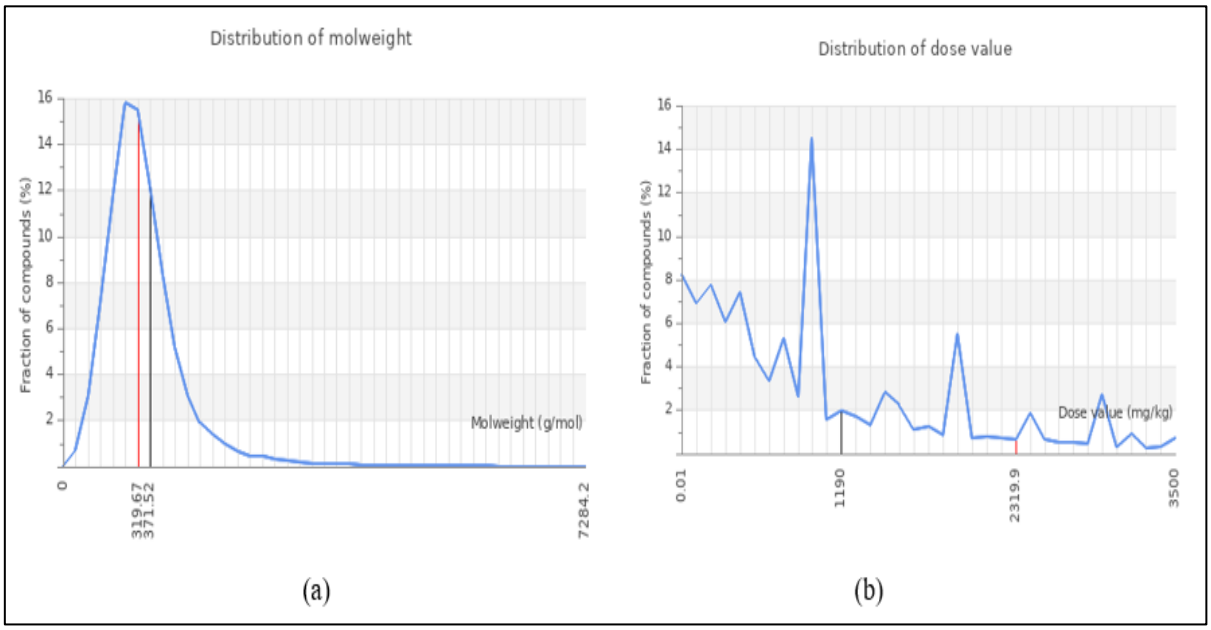

Fig 7 (a) The Molecular Weight (MW) Distribution and (b) LD50 Values of D1

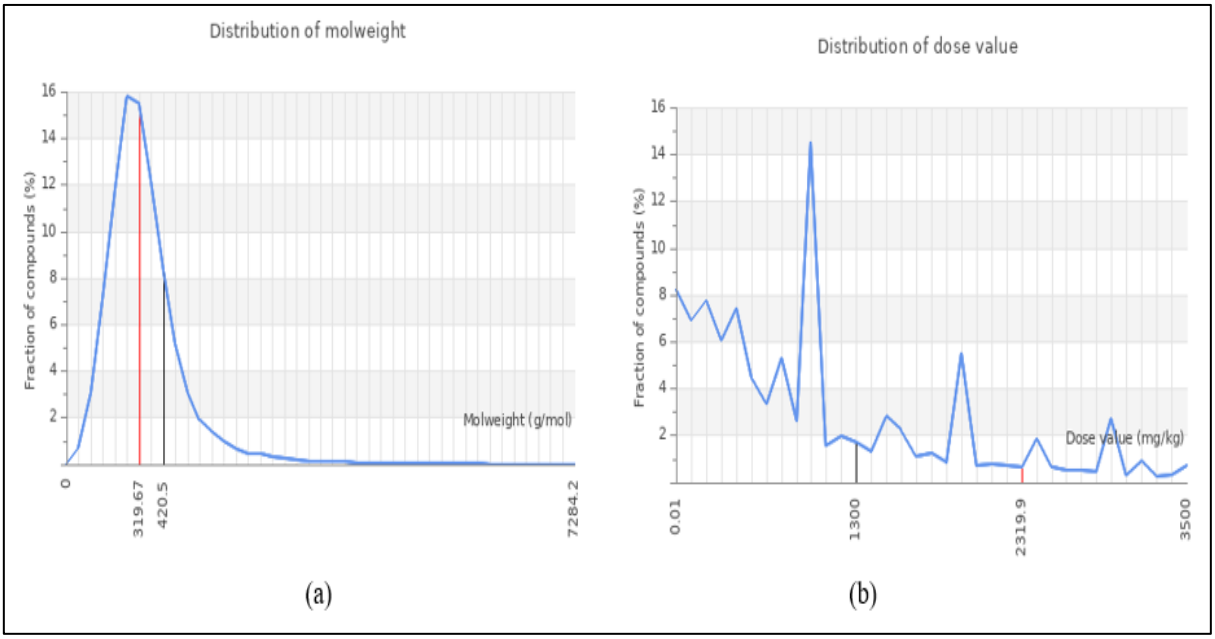

Fig 8 (a) The Molecular Weight (MW) Distribution and (b) LD50 Values of D2

IV. CONCLUSION

The QSAR model developed was shown to be robust, stable, and predictive, validated through both internal and external methods. Molecular docking studies involving 25 compounds were conducted to gain structural insights and support the QSAR model findings. The newly designed compounds, D1 and D2 exhibited higher binding affinities than the original template and the reference drug, indicating enhanced activity. SwissADME and Protox 3.0 proved to be a valuable tool for assessing these novels compounds, and can aid in identifying candidates with strong potential for future in vitro and in vivo therapeutic evaluation.

➢ *Declaration of Interest Statement*

Authors declare no conflict of interest.

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