International Research Journal of Innovations in Engineering and Technology (IRJIET)

ISSN (online): 2581-3048

Volume 8, Issue 8, pp 156-166, August-2024

https://doi.org/10.47001/IRJIET/2024.808017

QSAR, Molecular Docking Studies and Pharmacokinetics Properties Prediction of some Thiosemicarbazone Derivatives containing Indole Fragments Targeting Prostate Cancer Cell

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Abstract

Purpose: **Prostate cancer afflicts thousands of men around the world. This condition is the most common in men among all cancer diagnoses, and it ranks second in terms of fatality after lung cancer. Six out of ten males in the 65-year-old age group have been diagnosed with prostate cancer, making it a common malignancy among this age group and accounting for about 80% of all reported instances of prostate cancer.**

Method: **Quantitative structure-activity relationship (QSAR) techniques was utilized to construct five models on (24) prostate cancer PC3 cell line therapeutic agents.**

Result: **Among the five models built, model one was the best because of its statistical fitness of (R^2) = 0.9882, (R^2_{adj}) = 0.9828, (SEE) = 0.0488, (MEA) = 0.0258 and (CCC) = 0.9235 and based on docking results, the top ranking compounds with high docking scores at the range of (-7.7 to -8.2kcal/mol) respectively. Furthermore, none of the top ranking compounds was found to violate any of the five filters in the study, therefore, displaying good pharmacokinetics and drug- likeness properties.**

Conclusion: **Three top ranking compounds were identified using molecular docking virtual screening and compound 12 was recognized to have the most excellent docking score of (-8.2 kcal/mol). Also, the most common type of interaction among the chosen ligands is hydrogen bond interaction, electrostatic and hydrophobic interaction.**

Keywords: QSAR, Prostate cancer, PC3 cell line, Molecular docking, Pharmacokinetics.

I. BACKGROUND

One of the most serious and troublesome diseases in the world today is cancer. Unquestionably, there is growing concern about cancer and its mortality rate [1]. Cancer continues to represent a severe threat to human health despite ongoing research efforts due to its exceptionally high death rate and limited cure rate [2]. Drug targets, including proteins, enzymes, and receptors, are crucial to the discovery of new anticancer drugs, and mechanism-based drug discovery would greatly speed up the process. [3-5].

Prostate cancer afflicts thousands of men around the world. This condition is the most common in men among all cancer diagnoses, and it ranks second in terms of fatality after lung cancer [6]. Six out of ten males in the 65-year-old age group have been diagnosed with prostate cancer, making it a common malignancy among this age group and accounting for about 80% of all reported instances of prostate cancer [7–9].The drug development procedures are facing considerable challenges due to low clinical trial success rates and the inability to identify novel medications that are appropriate. Many drugs assessed in clinical trials were not successful in going to market because of inadequate pharmacokinetic parameters or intolerable side effects, despite substantial cost and effort. A drugs pharmacokinetic characteristics, in addition to its potency, determine whether it will be successful and effective in clinical trials [10].

Chemists and biologists have focused a great deal of attention on thiosemicarbazone as promisingpharmacophore due to its potential biological activity, which includes the ability to overcome multidrug resistance, antituberculosis, antiviral, antifungal, and, most interestingly, antineoplastic activity [11–16]. Furthermore, because of their pharmacological characteristics, indole derivatives have emerged as a promising research field and have continually piqued the interest of researchers on a regular basis [17–19]. Derivatives of indole are frequently employed as synthons for the synthesis of numerous physiologically significant heterocyclic compounds [20].

The quantitative structure-activity relationship (QSAR) is a reasoning and effective approach in drug development. It is an essential phase in the development and optimization of lead compounds, which improves their biological activity. Natural products are the metabolites of living things, they bind with biomolecular drug targets more easily. They are thus a perfect resource for the development of novel drugs. The energy of the chemical structure of the compound was minimized in the

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ISSN (online): 2581-3048
Volume 8, Issue 8, pp 156-166, August-2024
https://doi.org/10.47001/IRJIET/2024.808017

current study using quantum chemistry techniques. The compound was first computed at the DFT level of theory B3LYP and then refined using 6- 31+G basis set [21].

1.1 Source of data

The anticancer activity of 24 series of thiosemicarbazones containing indole fragments was reported by Zhangxu He et al. [22]. In the present study, this series was employed to conduct QSAR analyses. The anticancer activity was reported in IC_{50} by Zhangxu He et al., and it was converted to pIC_{50} for carrying out QSAR studies and included in Table 1 using equation 1 below.

$$pIC_{50} = - \log IC_{50} \text{ X } 10^{-6} \quad (1)$$

1.2 Geometry optimization

The 24 derivatives in the data set were drawn using ChemDraw version 12.1 software in 2D format. They were then converted into 3D form for geometric optimization by employing Density Functional Theory (DFT) Quantum Mechanical Calculations in the Spartan version 14.1.0 software, utilizing the parameters B-3/Lee Yang Per (B3LYP) standard principle and 6-31G* basis set in order to find the most stable structures of all studied molecules on the potential energy surface at the global minimum. The optimized structures were saved in a separate folder in PDB format.

1.3 Validation of the selected model

1.3.1 Internal validation

The generated model underwent internal validation through the use of statistical tools such as the coefficient of determination (R^2), adjusted coefficient of determination (R^2adj), standard error of estimation (SEE), and mean absolute error (MEA). These values are essential but insufficient. Tovalidate the dependability of a model apart from the coefficient of determination R^2 and the adjusted coefficient of determination R^2_{adj}, the VIF considers the degree of co-linearity between the descriptors in an equation in order to assess the reliability of a model. It is elucidated as:

$$VIF = \frac{1}{(1-R2)} \quad (2)$$

The R^2 is the correlation coefficient, and the greater the number, the stronger the relationship between the model parameters. When the VIF value is less than 10, the equation is stable, when it is greater than 10, the equation is inefficient and should not be used [23].

The value of each descriptors mean effect is used to determine how much each descriptor contributes to the chosen model. The symbol on the model parameters indicates the various contributions of each parameter in the overall equation, either an increase or decrease of the model parameter. The mean effect displays the key parameters that determined the generated equation [24]. It is elucidated as:

$$\text{Mean effect} = \frac{\beta j \sum_i^n Dj}{\Sigma^m(\beta i \sum_i^n Dj)} \quad (3)$$

The model parameters are denoted by m, the prediction set molecules are represented by n, the descriptor coefficient j is represented by βj, and the matrix value of the model parameter in the prediction set is represented by Dj. To verify the robustness of the model, a random multiple linear regression model is built using a training set of Y-scramble tests. Therefore, for the QSAR model to be robust in this case, the R^2 and Q^2 values need to be low as displayed in table 3 [25].

1.3.2 External validation

A test set was used to externally validate the generated model by evaluating the value of Concordance Correlation Coefficient (CCC) which must be greater than 0.8 [26], is elucidated as:

$$CCC = \frac{2\sum_{i=1}^{nEXT}(Yi - \bar{Y})\left(Y\hat{i} - \bar{Y\hat{i}}\right)}{\sum_{i=1}^{nEXT}(Yi - \bar{Y})^2 + \sum_{i=1}^{nEXT}\left(Y\hat{i} - \bar{Y\hat{i}}\right)^2 + \text{nEXT}\left(Y\hat{i} - \bar{Y\hat{i}}\right)^2} \quad (4)$$

Where Yi is the experimental value, $\bar{Y}$ is the average of experimental value, $\bar{Y\hat{i}}$ is the predicted value of activity and $\bar{Yi}$ is average of the predicted value of the activity. EXT is the external prediction set or test set.

1.4 Molecular docking

Predicting the affinity of a protein/ligand binding is one of the most challenging problems in computational chemistry. In the present study, effective binding interactions between the target drugs and their proposed (4r0i) target were identified by molecular docking. AutoDock Pyrex was used for docking, and Discovery Studio was used to visualize the results.

1.5 Pharmacokinetics properties and drug- likeness prediction

SwissADME web tools (http://www.swiss adme.ch/index.php) can be accessed and used to examine the properties of small compounds that resemble drugs [27]. They are used to identify new therapeutic candidates, reduce the amount of experimental studies conducted, and increase success rates.

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II. RESULTS AND DISCUSSION

Drug development has been expedited by the use of computational approaches. Considering this, we employed QSAR (Quantitative Structure-Activity Relationship) analysis in the current study to analyze a set of 24 thiosemicarbazone-containing indole fragments that have been reported to have potential anticancer activity against the prostate cancer (PC3) cell line. Additionally, we carried out a comprehensive QSAR study using Spartan 14 software, Pyrex software for molecular docking, Swissadme for pharmacokinetics prediction, and drug-likeness to speed up the drug process in order to identify the top-ranking compounds with anti-prostate cancer activity. Five QSAR equations were constructed using the Genetic Function Approximation (GFA) approach to forecast the anti-proliferative activities of thiosemicarbazone containing indole-fragments, and model 1 was the best based on its statistical validity.

Model 1:

pIC50 = 2.8638 (*__MATS6m*__) -0.3002 (*__SHBint2__) +1.5284 (*__RDF20u__) -0.0301 (*__ETA_Etap_B_RC__) -61.7424 (*__SpMin8_Bhv__) -0.3774.

Table 1 reveals the biological, anticipated, and residual values of thiosemicarbazone containing-indole fragments compounds. Model 1 as the best has a correlation coefficient (R^2) of 0.9882, adjusted correlation coefficient (R^2adj) of 0.9828, standard error of estimation (SEE) of 0.0488, and a mean absolute error (MEA) of 0.0258, as shown in Table 2. Y-scrambled test results, as indicated in Table 3, also demonstrate the models suitability with low R^2 and Q^2 values. External validation using the Concordance Correlation Coefficient (CCC) test of 0.9235 demonstrated that model number 1 passed external validation parameters which displayed the validity of the model based on the method. The descriptors derived from mathematical model 1 were specified and categorized as displayed in Table 4.

To determine the impact of each descriptor in the model as well as the correlation between the individual descriptors, additional statistical analysis was performed on the model parameters, and the outcomes are displayed in Table 5. To illustrate the link between derivatives, a graph was created by plotting the computed activities against the biological activities, as shown in Figure 1. The calibration and validation compound values on both sides of the graph are displayed in Figure 2, indicating that there are no systematic inaccuracies between the standardized residual and biological activities. The average result derived from the model parameters indicates that SHBint2 has a positive effect, indicating that raising this descriptor will raise the derivative bioactivities. MATS6m, RDF20u, ETA_Etap_B_RC, and Spmin8_Bhv having a negative coefficient suggest that a drop in the descriptor would likewise lead to an increase in the compounds experimental activities in thiosemicarbazone containing indole fragment.

Table 1: Biological, Anticipated and Residual values of thiosemicarbazoneindole compounds

S/No	IC_{50}	pIC_{50}	Residues	Docking score
1.	5.7569	5.6976	-0.059	-6.6
2.	6.0132	5.9913	-0.020	-6.7
3.	6.0087	6.0495	0.040	-6.5
4.	4.7092	4.7074	-0.001	-6.1
5.	6.2218	6.1617	-0.060	-7.2
6.	6.0315	6.2184	0.186	-7.2
7.	6.2518	6.2142	-0.039	-6.9
8.	6.5528	6.6104	0.057	-6.5
9.	6.4559	6.3619	-0.093	-7.0
10.	5.9706	5.9567	-0.013	-7.2
*11.	6.4685	6.1925	-0.276	-7.5
12.	6.1739	6.1498	-0.024	-8.2
*13.	6.2839	6.4532	0.169	-7.6
14.	6.2924	6.3505	0.058	-7.3
15.	6.8538	6.8174	-0.036	-7.5
16.	6.7958	6.7858	-0.009	-7.6
17.	6.7212	6.6807	-0.040	-5.9
18.	5.9625	6.0190	0.056	-6.2
*19.	6.3979	5.9254	-0.472	-7.4
20.	6.1426	6.1423	-0.003	-7.7
*21.	6.1487	6.1045	-0.042	-7.8
*22.	5.8153	6.1060	0.290	-7.6
*23.	4.7137	6.3304	1.616	-6.6
*24.	4.7242	6.2255	1.501	-7.6

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*Denote test set

Table 2: Validation parameters in the build model 1

S/No.	Parameters	Value
1.	R^2	0.9882
2.	R^2adj	0.9828
3.	SEE	0.0488
4.	MEA	0.0258
5.	CCC	0.9235

Table 3: Y- Scrambled Test

Model type	R^2	Q^2
Original	0.951872	0.918508
Random 1	0.151453	-2.18328
Random 2	0.509148	-0.20426
Random 3	0.21644	-1.29648
Random 4	0.052579	-1.6261
Random 5	0.670783	0.333496
Random 6	0.426469	-0.43535
Random 7	0.34314	-0.74916
Random 8	0.411624	-0.06304
Random 9	0.368401	-0.46062
Random 10	0.188778	-1.70371
Summary:		
R^2		0.951871924
Q^2		0.918508033
Average R^2		0.331298462
Average Q^2		-0.756193552

Table 4: Definition of descriptors and their class for model 1

Name	Definition	Class
MATS6m	Moran autocorrelation- lag 6/weighted by mass	2D
SHBint2	Sum of E- state descriptors of strength for potential hydrogen bonds of path length 2	2D
RDF20u	Radial distribution function- 020/un weighted	3D
ETA_Etap_B_RC	Branching index Etab (with ring correction) relative to molecular size	2D
SpMin8_Bhv	Smallest absolute eigen value of burden modified matrix - n8/weighted by relative Van der waals volumes	2D

Table 5: Statistical analysis of model 1 parameters

	MATS6m	SHBint2	RDF20u	ETA_Etap_B_RC	SpMin8_Bhv	VIF	M/E
MATS6m	1	0.014569	0.394492	-0.5166	0.075127	2.546374	-0.02152
SHBint2	0.014569	1	0.010492	-0.70987	-0.87697	4.977014	0.271833
RDF20u	0.394492	0.010492	1	-0.30035	0.099759	1.353192	0.674028
ETA_Etap_B_RC	-0.5166	-0.70987	-0.30035	1	0.676177	5.642234	0.001215
SpMin8_Bhv	0.075127	-0.87697	0.099759	0.676177	1	5.975327	0.074447

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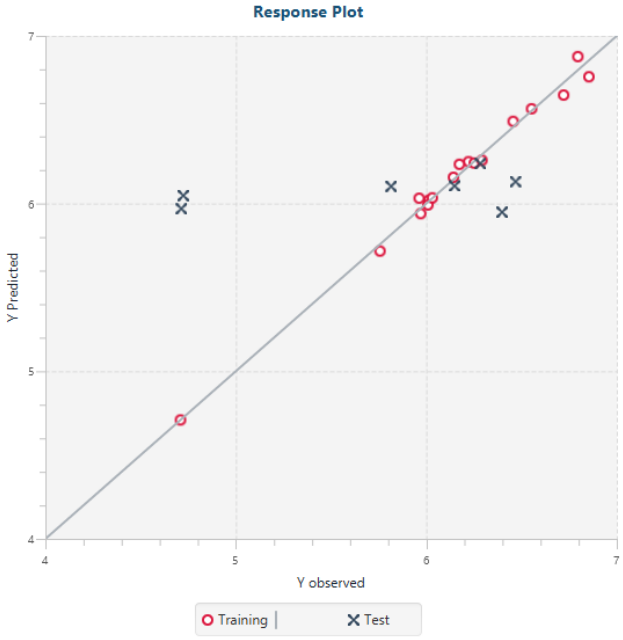

Figure 1: Computed activities against the biological activities

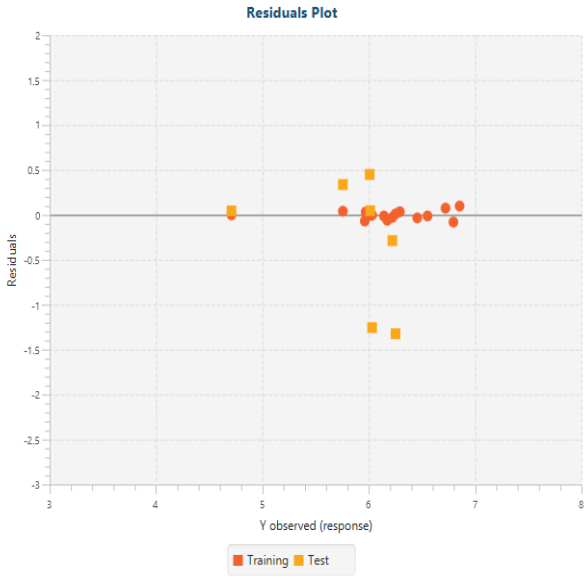

Figure 2: Standardized residual against the biological activities

2.1 Docking Results

In this present study, we examine how a few specific thiosemicarbazones that include an indole fragment interact with the (4r0i) receptor as ligands. To investigate potential interactions between the ligand and the protein target, a molecular docking study was conducted in the binding pockets of (4r0i) to investigate the binding efficacy of all the compounds under investigation. (Table 6) displayed the best binding scores of all the inhibitory compounds, ranging from -7.7 to 8.2 kcal/mol, respectively.

Compound 12, which has the highest binding score of -8.2 kcal/mol, formed a conventional hydrogen bond with SER-214 at a distance of 4.93 Å and a carbon hydrogen bond with GLY-219 at a distance of 5.32 Å. Pi-cation with HIS-57 at a distance of 5.26 Å, Pi-sulfur with CYS-42 at a distance of 4.49 Å, Pi-pi T-shaped with TYR- 60G at a distance of 5.60 Å, and Pi-donor hydrogen bonding with HIS-57 at a distance of 5.15 Å. Additionally, it formed alkyl and pi-alkyl at a distance of 5.94 and 4.62 Å with ILE-60, respectively. Both 2D and 3D pictorial representations of ligand 12 in the active site of the 4r0i receptor under study are displayed in Figure 3.

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Compound 21 with a binding score of -7.8 kcal/mol formed three conventional hydrogen bonds with ASP-60B at a distance of 4.49 Å, HIS-40 at a distance of 4.18 and 4.62 Å.Pi-Pi T shaped with TRY-60 at a distance of 4.84 and 5.40 Å, respectively. A 2D and 3D pictorial representation of ligand 21in the active site of the 4r0i protein receptor is displayed in Figure 4.

Compound 20 with a binding score of -7.7 kcal/mol formed three conventional hydrogen bonds with TRP-141 at a distance of 610 Å, HIS-57 at a distance of 410 Å, and ILE-41 groups of enzymes at a distance of 3.34 and 3.57 Å, respectively. A carbon-hydrogen bond is formed between compound 20 and GLN-192 at a distance of 4.70 Å, Pi-sigma with HIS- 40 at a distance of 4.42 Å, Pi-alkyl with TRY- 60G at a distance of 4.72 Å, and Pi-Pi Tshaped with HIS- 40 at a distance of 5.00 Å, respectively. 2D and 3D pictorial representations of ligand 20 under investigation in complex with the 4r0i protein receptor are shown in Figure 5.

Table 6: Molecular docking interaction of the top ranking compounds under investigation

Compounds	Binding Affinities (Kcal/mol)	Hydrogen bond interactions	Electrostatic and Hydrophobic interactions	Bond length Å
12	-8.2	Conventional hydrogen bond SER-214 Carbon hydrogen bond GLY- 219	Pi- cation HIS- 57 Pi- Sulfur CYS- 42 Pi- Pi Tshaped TYR-60G Pi- donor HB HIS-57 Alkyl ILE-60 Pi- alkyl ILE- 60	4.93 5.32 5.26 4.49 5.60 5.15 5.94 4.62
21	-7.8	Conventional hydrogen bond ASP-60B and HIS- 40	Pi-Pi stacked TRY- 60G	4.49 4.18 4.62 4.84 5.40
20	-7.7	Conventional hydrogen bond TRP-141, HIS- 57 and ILE- 41 Carbon hydrogen bond GLN- 192	Pi- sigma HIS- 40 PI- alkyl TRY- 60G Pi- Pi Tshaped HIS- 40	6.10 4.01 3.34 3.57

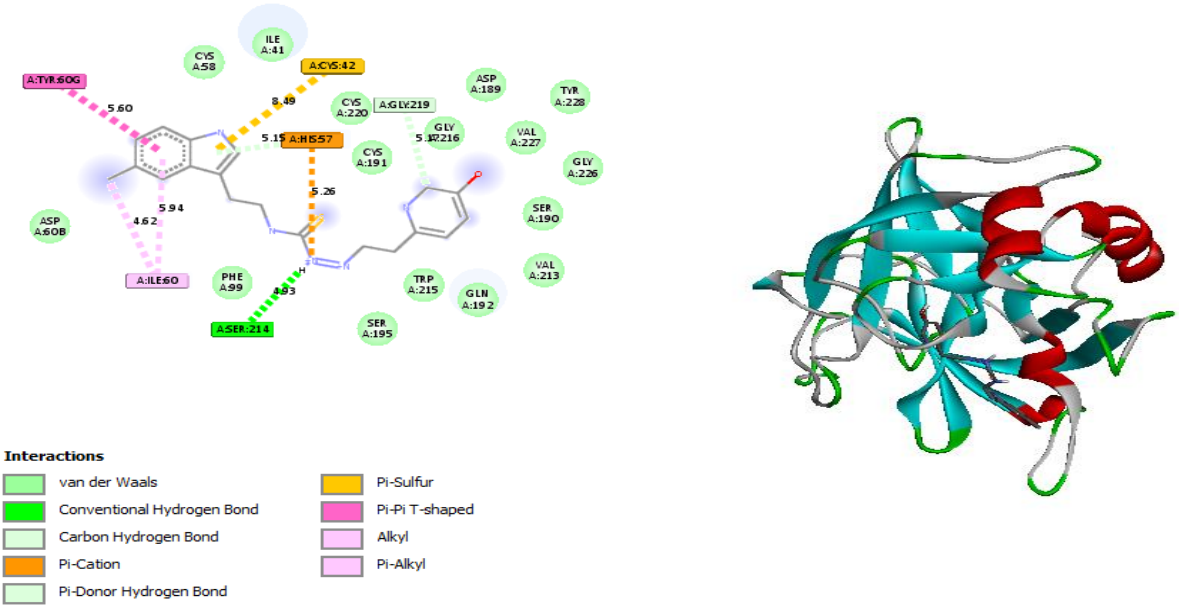

Figure 3: 2D and 3D representation of ligand 12 in the active site of the 4r0i receptor

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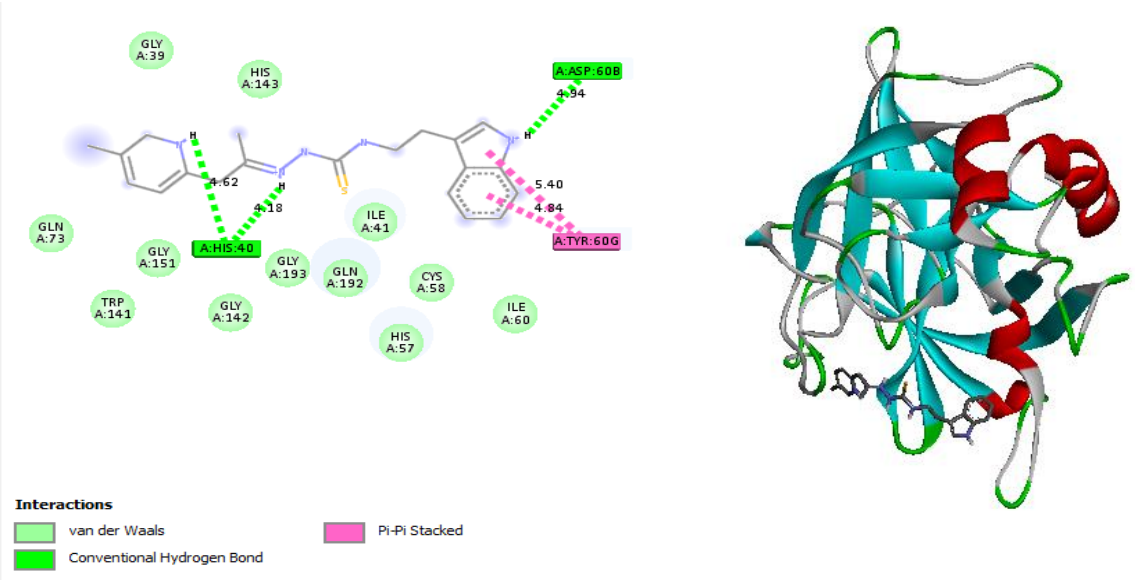

Figure 4: 2D and 3D representation of ligand 21 in the active site of 4r0i receptor

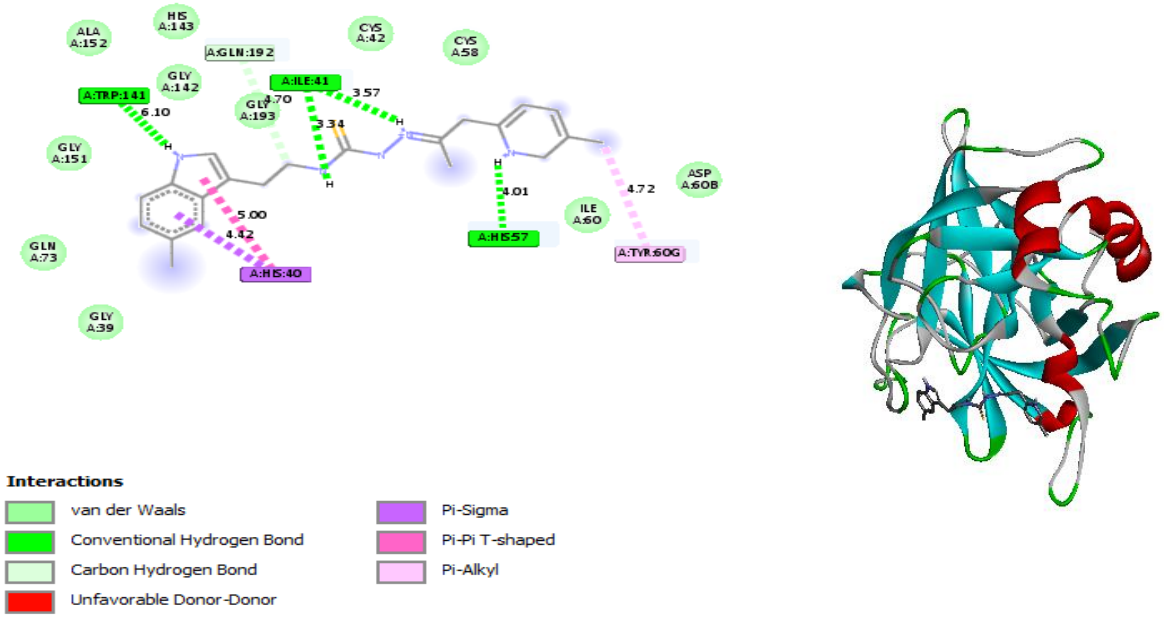

Figure 5: 2D and 3D pictorial representation of ligand 20 in the active site of 4r0i receptor

2.2 Pharmacokinetics and drug- likeness prediction

The physicochemical characteristics of the compounds under study, such as their topological surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, and molar refractivity, are displayed in Table 7. One of the physicochemical characteristics of a molecule that significantly influences the precise prediction of its bioavailability as a therapeutic candidate is the number of hydrogen bond donors and acceptors present. According to the SwissADME profile (Table 8), every test compound under study is considered soluble. Also, the Log S (ESOL) model of water solubility showed a solubility level in the range of −3.64 to -4.52, with compound 20 being the least soluble. Water solubility is important for drug candidates, and low water solubility might lead to ineffective absorption [28].

Based on three top ranking compounds, the consensus log P-value was used to estimate the lipophilicity of the test compounds. The partition coefficient of n-octanol in water is an experimental measure of a compounds lipophilicity. With a Log P value of.72, Compound 21 was predicted to be the most lipophilic and has a better chance of being absorbed than the other

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compounds. To precisely ascertain the efficiency of a compounds absorption into the systemic circulation, it is imperative to take into account the absorption rate in the gastrointestinal tract. High water solubility is a necessary component of drug-likeness and is correlated with low lipid solubility levels. However, if a drugs lipophilicity is too low, it might not be able to reach its intended therapeutic target.

Compounds with high water solubility, on the other hand, significantly lessen the absorption mechanism and return low lipophilicity and poorly permeated membranes. Compound 20, with a log P value of.59, was the least lipophilic. Enzymes belonging to the cytochrome p450 play a major role in drug metabolism. The compounds 12, 21, and 20 under investigation were predicted as non-substrates of P-gp and as inhibitors of CYP1A2, CPY2C19, CPY2C9, CPY2D6, and CPY3A4, respectively, as displayed in Table 9. The fact that none of the three lead compounds can pass through the blood-brain barrier (BBB) is also a plus for a therapeutic candidate whose target site is external to the brain, as penetration could lead to unfavorable drug effects.

The top-ranking compounds bioavailability and drug-likeness profiles, as displayed in Table 10, produced a positive bioavailability score of 0.55. Positive findings were found in the drug-likeness predictions using five rule-based filters, namely: the Lipinski, Ghose, Verber, Egan, and Muegge filters. No rule-based filter was violated by any of the top-ranking compounds. Predicting drug-likeness is a cost-effective method that is crucial in the early phases of drug development. It forecasts the degree of drug-likeness of a small molecular-weight molecule. The bioavailability radars of molecules 12, 21, and 20 under investigation are displayed in (Figure 6). Figure 7 shows the WLOGP against the TPSA-boiled molecule of the top-ranking molecules under investigation.

Table 7: Physiochemical properties of the topranking compounds under investigation

Compound	Num. H-bond Donors	Num. H-bond Acceptors	Molar refractivity	TPSA
12	4	3	99.27	117.42Å
21	3	2	97.05	97.19Å
20	3	2	107.2	97.19Å

Table 8: Predicted lipophilicity and water solubility of the top ranking compound under investigation

Compound	Molecular Weight g/mol	LOG *S* (ESOL)	ESOL Solubility	Consensus Log P
12	359.83	-3.88	Soluble	.59
21	323.42	-3.64	Soluble	.72
20	371.81	-4.52	Moderately soluble	.59

Table 9: Pharmacokinetics parameters of the top ranking compounds under investigation

Compound	GI Absorption	BBB Permeant	P-gb Substrate	CYP Inhibitors 1A2	2C19	2C9	2D6	3A4
12	High	No	No	Yes	Yes	Yes	Yes	Yes
21	High	No	No	Yes	Yes	Yes	Yes	Yes
20	High	No	No	Yes	Yes	Yes	Yes	Yes

Table 10: Drug- likeness and Bioavailability score of the top ranking compounds under investigation

Compound	Lipinski Violation	Ghose violation	Viber violation	Egan violation	Muegge violation	Bioavailability score
12	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
21	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55
20	Yes, 0 violation	Yes	Yes	Yes	Yes	0.55

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Compound 12 **compound 21** **compound 20**

Figure 6: The bioavailability radar of molecule 12, 21 and 20 under investigation

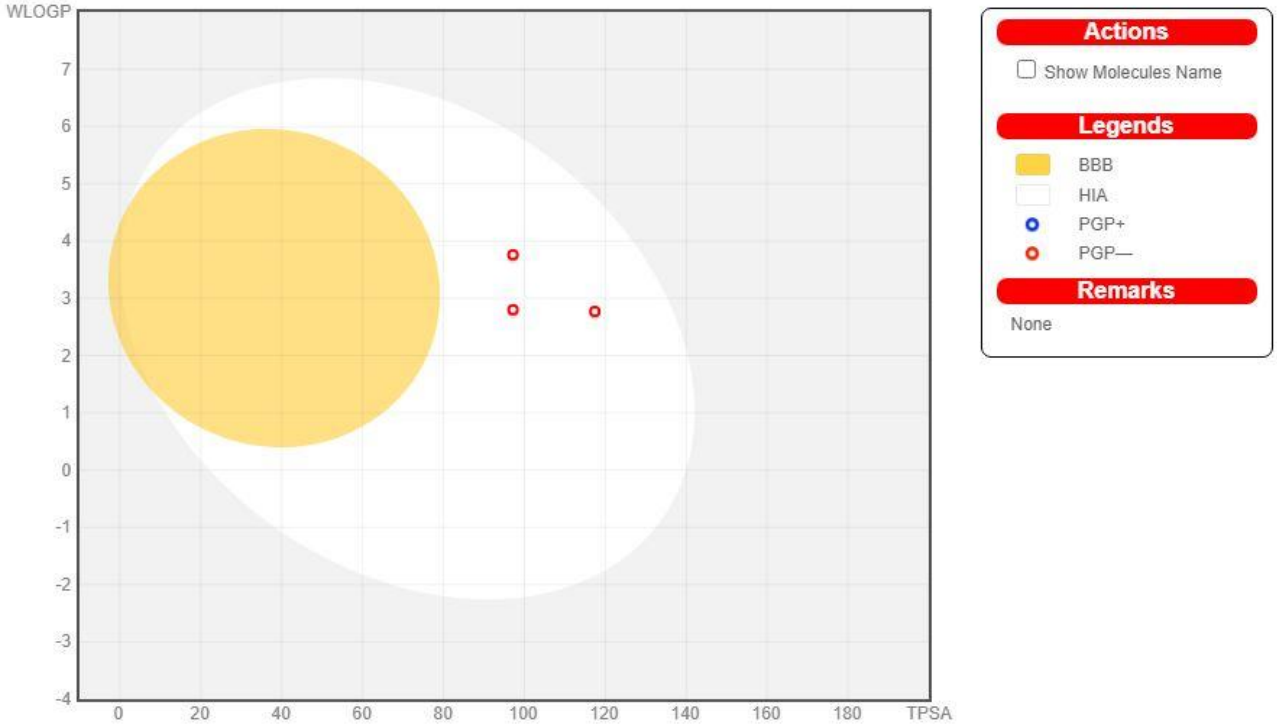

Figure 7: Boiled molecule of WLOGP against TPSA of the top ranking compounds under investigation

III. CONCLUSION

In conclusion, based on docking results, the top ranking compounds with high docking scores at the range of (-7.7 to -8.2kcal/mol) were compound 12, 21 and 20 respectively. Among the five models built, model one was the best because of its statistical fitness of R^2 = 0.9882, R^2_{adj} = 0.9828, SEE = 0.0488, MEA = 0.0258 and CCC = 0.9235. Also, the most common type of interaction among the chosen ligands were hydrogen bonding interaction, electrostatic and hydrophobic interactions.

The QSAR model indicate that SHBint2 has a positive effect, indicating that raising this descriptor will raise the derivatives bioactivities. MATS6m, RDF20u, ETA_Etap_B_RCand Spmin8_Bhv having a negative coefficient suggests that a drop in the descriptor would likewise lead to an increase in the compounds experimental activities in thiosemicarbazone containing indole fragment.

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Authors' contribution:

AIK device and designed the experiment, performed the experiment, analyze and interpret the data, wrote the paper. IBB performed the experiment and wrote the paper.

Statement in authors' contribution:

The authors have critically reviewed and approved the final draft.

Ethical approval:

There is no ethical issue.

Conflict of interest:

Authors declare no conflict of interest.

Acknowledgement:

The authors sincerely acknowledged Tertiary Education Trust Fund (Tetfund) for sponsoring this research under the Tetfund IBR research project grant (Reference number: TEFT/ DR& D/ UNI/ MUBI/ RG/ 2023/ Vol.1) as well as Adamawa State University, Mubi for its technical support in the course of this research.

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ISSN (online): 2581-3048
Volume 8, Issue 8, pp 156-166, August-2024
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Citation of this Article:

Abdulrahman Ibrahim Kubo, & Ibrahim Birma Bwatanglang. (2024). QSAR, Molecular Docking Studies and Pharmacokinetics Properties Prediction of some Thiosemicarbazone Derivatives containing Indole Fragments Targeting Prostate Cancer Cell. *International Research Journal of Innovations in Engineering and Technology - IRJIET*, 8(8), 156-166. Article DOI https://doi.org/10.47001/IRJIET/2024.808017

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