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Original Article

# QSAR, molecular docking, and pharmacokinetic analysis of thiosemicarbazone-indole compounds targeting prostate cancer cells

Abdulrahman Ibrahim Kubo, M.Sc [a,c,*], Adamu Uzairu, PhD [b], Ibrahim Tijjani Babalola, PhD [a], Muhammad Tukur Ibrahim, PhD [b] and Abdullahi Bello Umar, PhD [b]

[a] *Department of Chemistry, Faculty of Science, Yobe State University, Damaturu, Nigeria*
[b] *Department of Chemistry, Faculty of Physical Science, Ahmadu Bello University, Zaria, Nigeria*
[c] *Department of Pure and Applied Chemistry, Faculty of Science, Adamawa State University, Mubi, Nigeria*

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**الملخص**

**أهداف البحث:** بحلول عام 2030، من المتوقع أن يتسبب سرطان البروستاتا في 1.7 مليون حالة جديدة و499 ألف حالة وفاة. أهداف هذا البحث هي إنشاء نموذج يربط بين تصرفات ثيوسيميكاربازون-إندول كعامل مضاد للسرطان ضد خط خلايا بي سي 3، وإجراء تحليل الالتحام بين المركبات والإنزيم المستهدف، والتنبؤ بالحركية الدوائية والتشابه الدوائي للمركبات قيد التحقيق.

**طريقة البحث:** استخدمت الطريقة العلاقة الكمية بين البنية والنشاط لبناء النموذج، وأجرت الالتحام الجزيئي بين المركبات والإنزيم المستهدف، وفحصت تشابهها مع الأدوية وتحليل الحرائك الدوائية للمركبات المثبطة.

**النتائج:** تم استخدام منهج الانحدار متعدد الخطوط لخوارزمية الوظيفة الجينية في بناء نموذج العلاقة بين الهيكل الكمي والنشاط. المعلمات التالية من نموذج البناء الأول، كأفضل، آر2 (معامل التحديد) = 0.972517، "رادج" (المعدل آر- التربيعي) = 0.964665، "سي آر بي 2" = 0,780922، و "إل أو إف" (التحقق من صحة التقاطع لمرة واحدة) = 0.076524، ظهر بقوة على الواصفات الجزيئية. كانت "إس إتش بي دي" و "إس إس سي إتش 3" و "جاي جي آي 2" و "أر دي إف 60 بي" تعتمد بشكل كبير على النشاط التكاثري. تتمتع المركبات ذات المعرفين 7 و22 بالقدرة على العمل كمثبطات لمستقبلات الأندروجين، كما اقترحت دراسات الالتحام الجزيئي بين الأدوية والإنزيمات المستهدفة. تظهر المركبات ذات المعرفين 7 و22 قيد التحقيق درجات ربط تبلغ -8.5 سعرة حرارية/مول و-8.8 سعرة حرارية/مول، على التوالي. كانت الجزيئات ذات المعرفين 7 و22 ضمن الحد الأقصى المقبول لجزيئات الدواء لتكون متاحة بيولوجيا عن طريق الفم.

**الاستنتاجات:** يقدم هذا البحث رؤى قيمة حول العلاقة بين الواصفات الجزيئية والمثبطات المحتملة والخصائص الدوائية في علاج بي سي 3. تساهم هذه النتائج في فهم الخيارات العلاجية الجديدة لمرضى سرطان البروستاتا وتطويرها المحتمل.

**الكلمات المفتاحية:** الحرائك؛ الجزيئي الالتحام؛ الخلايا خط؛ لسيليكو في؛ البروستاتا سرطان؛ الدوائي التشابه؛ الدوائية سي ي

**Abstract**

**Objectives:** By 2030, prostate cancer is estimated to account for 1.7 million new cases and 499,000 deaths. The objectives of this research were to create a model revealing the activity of thiosemicarbazone-indole compounds as anticancer agents against the PC3 cell line; perform docking analysis between the compounds and the target enzyme; and predict the pharmacokinetics and drug-likeness of the compounds under investigation.

**Methods:** The quantitative structureactivity relationship (QSAR) method was used to build the model; molecular docking between the compounds and the target enzyme was performed; and the drug-likeness and pharmacokinetics of the inhibiting compounds was examined.

**Results:** The genetic function algorithm-multilinear regression approach was used for building the QSAR model. Build model 1 had the best performance, with $R^2$ (coefficient of determination) = 0.972517, $R_{adj}$ (adjusted R-squared) = 0.964665, ($CRp^2$) = 0.780922, and LOF

* Corresponding address: Department of Chemistry, Faculty of Science, Yobe State University, Damaturu, Nigeria.
E-mail: abdulrahmankuboibrahim@gmail.com (A.I. Kubo)
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(leave-one-out cross-validation) = 0.076524, demonstrated strongly indicated by the molecular descriptors. SHBd, SsCH3, JGI2, and RDF60P were highly dependent on proliferative activity. Compounds ID 7 and 22 had the potential to act as androgen receptor inhibitors, as suggested by molecular docking studies between the drugs and their target enzymes. Compounds ID 7 and 22 exhibited binding scores of −8.5 kcal/mol and −8.8 kcal/mol, respectively. The approved maximum medication molecules for oral bioavailability included the molecules with IDs 7 and 22.

**Conclusion:** This research provides valuable insights into the relationships among molecular descriptors, potential inhibitors, and pharmacokinetic properties in the treatment of PC3. These findings may contribute to the understanding and potential development of new therapeutic options for prostate cancer patients.

**Keywords:** In silico; Molecular docking; (PC3) cell line; Pharmacokinetics; Prostate cancer; QSAR



## Introduction

The continuing emergence of novel diseases, coupled with the diminishing effectiveness of existing treatments, underscores the urgent need for innovative solutions. This need for new treatments has led to increased exploration of diverse resources, particularly plants and microorganisms.[1,2] The conventional trial-and-error approach to drug design is costly, environmentally disruptive, and time-consuming.[3] Consequently, computational and theoretical chemistry methods, such as quantitative structure−activity relationship (QSAR) and structure−activity relationship, have substantially advanced the understanding of metabolism of new drugs in early development stages.[4]

One groundbreaking advancement in drug design has been the development of computational chemistry and molecular modeling approaches. These tools have become indispensable for the discovery, optimization, and design of novel drug candidates.[4,5] According to GLOBOCAN (2018), 1,276,106 new cases of prostate cancer were recorded worldwide. This cancer is more common in developed countries, which have shown a death rate of 358,989. With increases in the global population, prostate cancer is expected to reach 1.7 million new cases and 499,000 deaths by the year 2030.[6−8] Current therapies such as chemotherapy, radiation therapy, and surgery have become ineffective because of severe adverse effects and multidrug resistance.[9] Despite the abundance of medications on the market, their clinical effectiveness remains insufficient.[10] Therefore, this chronic illness is considered a major issue requiring prompt pharmaceutical treatment.[11]

Nature is the primary source of several cures for various illness.[12] In this context, the present study focused on the exploration of thiosemicarbazone derivatives, which exhibit promising biological activity.[13] These compounds are rich in sulfur and nitrogen, and have diverse biological and therapeutic properties.[14] Notably, thiosemicarbazones have gained attention for their anticancer potential, thus prompting computational investigations into their pharmacological activity.[15]

Thiosemicarbazones have demonstrated remarkable potential in medicinal chemistry, in applications including pharmaceutical, bacterial, and material synthesis.[15] Their ability to bind transition metals has prompted interest in catalysis and medicinal applications.[16,17] The compounds are recognized for their antiproliferative effects and are considered potential candidates for anticancer drugs.[18−20] Given their demonstrated biological activity, including antituberculosis, antiviral, antifungal, antimalarial, and, notably, antineoplastic actions, thiosemicarbazones have become pharmacophores of interest to chemists and biologists.[18,21−25] Several derivatives, including thiosemicarbazone and its derivatives, are currently undergoing investigation in phase I and phase II clinical trials against various cancers.[26−28] The search for potent and safer anticancer compounds remains a critical focus of contemporary cancer research.[29]

Indole scaffolds are known to avert the multiplication and invasion of many cancer cells.[30] Moreover, indole derivatives, because of their pharmacological attributes, have emerged as a promising research field and have piqued the interest of researchers.[31−33] These derivatives are widely used as synthons for the preparation of a wide variety of biologically important heterocycles.[34] Additionally, indole is present in important synthetic therapeutic compounds such as anti-HIV[35] and anti-cancer[36] drugs.

In prostate cancer research, the PC3 cell line is particularly prominent among the three commonly used prostate cancer cell lines, PC3, DU145, and LNCaP. Therefore, investigating the activity of thiosemicarbazone derivatives against PC3 prostate cancer cell lines is of substantial relevance.

To facilitate drug candidate discovery, a systematic and robust approach is essential. This study used QSAR and molecular docking techniques to predict the activity of thiosemicarbazone derivatives against PC3 prostate cancer cell lines. Our aim was to unravel the intricate relationship between these compounds and their receptor, to gain a deeper understanding of their mechanism of action.

## Materials and Methods

### *Sourcing of data*

A series of thiosemicarbazone-indole derivatives with antiproliferative activity ($IC_{50}$) against the PC3 cancer cell line were identified from the literature.[37] Antiproliferative activity ($IC_{50}$), measured in micromolar concentrations (m), was transformed to a logarithmic scale ($pIC_{50}$), and

the negative base 10 logarithm of all compounds was determined with equation (1).

$$pIC_{50} = -\log_{10}(IC_{50} \times 10^{-6}) \quad (1)$$

*Drawing of 2D-molecular structures and geometric optimization*

ChemDraw v12.0 software was used to draw the 2D structures of all molecules in the data set. The 2D structures of all molecules were converted to 3D in Spartan 14.1.1.0v software. Energy minimization was performed to decrease structural constraints before the stable conformation of the molecules in terms of possible energy was determined.[38] The Bee-3-Lee Yang per method of optimization, with density functional theory calculations in the 6-31G* Basic set in Spartan 14.1.1.0v software, were employed to ascertain the connections' geometrical structure. Spartan 14.1.1.0v software was used to perform optimization aimed at positioning the stable structures of all molecules at the universal minimum on the potential energy surface.[38]

*Model development and validation*

The generated model was evaluated with Friedman's formula,[39] as follows:

$$LOF = \frac{SEE}{\frac{(1-c+dP)^2}{M}} \quad (2)$$

where Friedman lack of fit (LOF) is the estimated robustness of a model, SEE is the standard error of estimation, P is the total number of descriptions in the model, d is the user-defined smoothing parameter, C is the number of terms in the model, and M is the number of compounds in the training set.

SEE was determined as follows:

$$SEE = \frac{\sqrt{(Y_{exp} - Y_{prd})}}{N - P - 1} \quad (3)$$

where $Y_{exp}$, $Y_{pred}$ are the verified and calculated $pIC_{50}$ values of the modeling set samples, N is the number of samples in the modeling data set, and P is the number of independent variables present in the generated model.[40]

The correlation coefficient $R^2$ of the build model was another parameter considered; values closer to 1.0 indicated a better built model. $R^2$ is represented as:

$$R^2 = 1 - \frac{\sqrt{\Sigma(Y_{exp} - Y_{prd})^2}}{\Sigma(Y_{exp} - Y_{trn})^2} \quad (4)$$

where $Y_{prd}$, $Y_{exp}$, and $Y_{trn}$ are the predicted, experimental, and average experimental activity in the training set, respectively.

The strength of the model did not depend on the value of $R^2$, because the value of $R^2$ was directly proportional to the number of descriptors in the model. Therefore, for an authentic and robust model, $R^2$ was modified accordingly.

$$R^2_{adj} = \frac{(n-1)(R^2-P)}{n-P-1} \quad (5)$$

where P is the number of descriptors in the model, and n is the number of compounds used in the training set. The cross-validation coefficient, $Q^2_{cv}$ was as follows:

$$Q^2_{cv} = 1 - \frac{\sum(Y_{prd} - Y_{exp})^2}{\sum(Y_{exp} - Y_{mtrn})^2} \quad (6)$$

where $Y_{prd}$, $Y_{exp}$, and $Y_{mtrn}$ are the anticipated, investigational, and standard experimental activity in the training set, respectively.

A test set was used to externally validate the generated model by assessing the value of $R_{pred}{}^2$, as follows:

$$R^2_{prd} = 1 - \frac{\sum(Y_{prd} - Y_{exp})^2}{\sum(Y_{exp} - Y_{mtrn})^2} \quad (7)$$

where $Y_{prd}$ and $Y_{exp}$ are the predicted experimental and average experimental activity of the test set, respectively, and $Y_{mtrn}$ is the average experimental activity of the training set.[41]

*Y-randomization test*

Random multiple linear regression models were generated with a training set of Y-randomized tests. In this case, the $R^2$ and $Q^2$ values were required to be low for the QSAR model to be constructed.[41] Additionally, the coefficient of determination $cR^2p$ was required to exceed 0.5 to pass this test and was also calculated in the Y-randomization test, as follows:

$$cR^2p = Rx(R^2 - R^2r)^2 \quad (8)$$

*SwissADME*

SwissADME, an online tool available to predict pharmacokinetics, drug-likeness, physiochemical properties, and medicinal chemistry,[42] was used to estimate the potency was estimated based on their in silico characteristics, and we were asked to modify these compound, CPY1A2, CPY2C19, CPY2C9, CPY2D6, CPY34A, and Lipinski's rule of five.[43]

*Molecular docking studies of the investigated compound against the PC3 receptor*

The optimized compounds underwent molecular docking with the androgen receptor 5T8E (Figure 1) downloaded from the Protein Data Bank and were prepared in Discovery Studio software. The ligands were also transformed to PDB format. Pyrex docking software was used to calculate the binding affinities of the ligands and receptors.[44] The target receptor may play a role in remodeling the effectiveness and strength of the recommended compounds as potential cancer drugs.

## Results and discussion

In silico methods are computational approaches used to obtain and optimize potential drug candidates. QSAR models the activity of various compounds as a linear combination of specific molecular descriptors. A molecular descriptor is a numerical value representing a particular molecular property of a compound.[45,46] A robust QSAR model uses molecular descriptors that significantly influence the activity of the compounds and can be used to predict the activity of other similar compounds.[47]

In this study, a QSAR model was constructed to predict the antiproliferative activity of thiosemicarbazone-indole derivatives. The Kennard-Stones algorithm was used in Dataset Division GUI v1.2 software to split the data into test and training sets. The training set was used to construct the model, whereas the test set was used to validate the model. Using the genetic function algorithm, we constructed five distinct QSAR models. Model 1 had the best performance, according to its statistical fitness. The selected QSAR model was powerful and predictable, with $R^2$ (coefficient of determination) = 0.972517, $R_{adj}$ (adjusted r-squared) = 0.964665, $cRp^2$ = 0.780922, and LOF (leave-one-out cross-validation) = 0.076524, respectively.

Model 1:

$$Y = -1.0308891697*SHBd + 0.407863672* SsCH3 - 115.07794375*JGI2 - 0.150532229*RDF60p \quad (9)$$

The biological, computed, and residual values of thiosemicarbazone-indole compounds are presented in Table 1. The low residual values, derived from the difference between biological and computed activity, displayed high predictive power in equation (1) (residual = biological activity − computed activity). Descriptors from model 1 are interpreted and displayed in Table 2, and each molecular descriptor significantly contributed to predicting compound activity.

The average effect of the model 1 parameters revealed that SsCH3 had a positive coefficient; therefore, an increase in this factor would elevate the bioactivity of these derivatives. In contrast, SHBd, JGI2, and RDF60p had negative coefficients; therefore, a decrease in these descriptors would increase the experimental activity of thiosemicarbazone-indole compounds. These findings highlight the contribution of each descriptor to predicting the response activity.

Table 2 displays the 2D and 3D descriptors of these models, including SHBd, SsCH3, JGI2, and RDF60p. For instance, SHBd is a 2D sum of estate for the (strong) hydrogen bond donor, SsCH3 is a 2D sum of atom-type E states: CH3 and JGI2 represent the 2D average topological charge exponents of order 2, and RDF0p is the 3D radial distribution function, weighted by 060/relative polarizability.

Table 3 provide the accepted QSAR validation tool and the minimum required values for evaluating the model.[48] The accuracy of the equation was assessed according to the $pIC_{50}$ values of the calibration compounds and the validity of compounds.

To confirm the stability, reliability, and robustness of the built QSAR model, we conducted Y-randomization tests. The results of multiple trials for $R^2$ and $Q^2$ values are presented in Table 4. A $cR^2p$ value above 0.5 signifies that the model has a good fit and is capable of making accurate predictions, reflecting the model's robustness and reliability in predictive tasks. Table 5 shows the statistical parameters of the built models. Additionally, a graph of calculated $pIC_{50}$ values versus biological $pIC_{50}$ values was plotted to illustrate the relationships among the derivatives in Figure 2. Figure 3 depicts a plot of experimental activity versus standardized residuals for the derivatives.

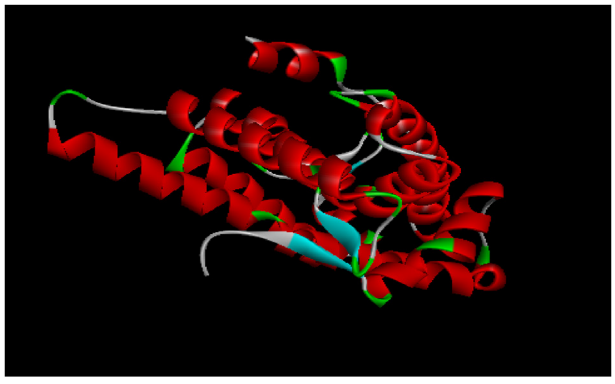


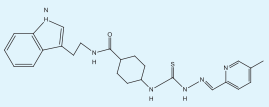
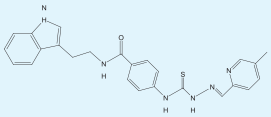
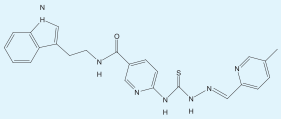
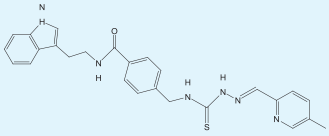
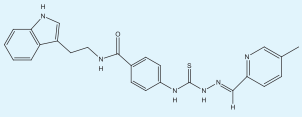
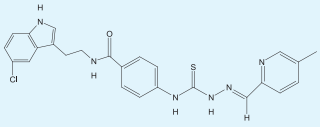
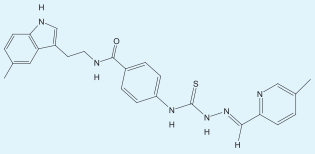
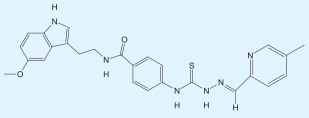
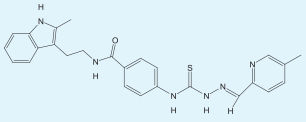
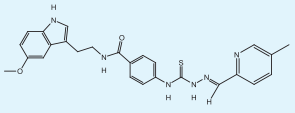
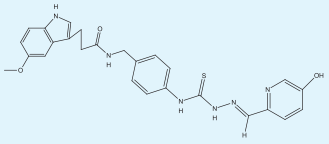
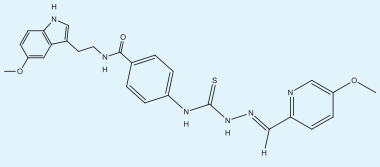
**Figure 1:** Crystal structure of the prepared androgen receptor (PDB ID: 5T8E).

### *Docking results*

In silico molecular docking methods can be used to examine the binding relationship between a ligand and receptor. Macromolecules known as receptors are typically found in tissues, biological receptors, and enzymes. The primary focus of molecular docking is on the type of interaction between the receptor and the ligands, as well as the binding affinity or energy.[49,50] In silico compounds are created with structure-based techniques, and the results of molecular investigations are used. The investigated compounds (thiosemicarbazone-indole) targeting PC3 cell lines underwent docking studies with the protein target (PDB ID: 5T8E). The binding scores, representing the affinity of a compound to its receptor, and indicating the robustness of the interaction, are displayed in Table 1.

The relationship between compounds 22 and 7 and the androgen receptor, including binding affinity, is described in Table 6, which shows the nature of their interactions and the amino acid residues involved in interacting with the receptor. Because of their docking scores of −8.8 and −8.5 kcal/mol, respectively, compounds 22 and 7 were chosen for these experiments, and demonstrated robust contact between the docking ligand and the receptor. The most common interactions among the chosen ligands were alkyl and pi-alkyl, although the range of bonding interactions also included Van der Waals, conventional hydrogen bonds, and carbon hydrogen bonds. According to the molecular docking results, the most frequent amino acid residues for all studied compounds were VAL, ALA, LYS, GLY, PRO, TRY, ARG, GLU, and GLN (Table 6).

**Table 1: Verified and calculated $pIC_{50}$ values of thiosemicarbazone-indole series against the PC3 cancer cell line.**

| S/No | Compounds | $pIC_{50}$ | Predicted $IC_{50}$ | Residual | Docking score (kcal/mol) |
|---|---|---|---|---|---|
| 1. |  | 6.4244 | 6.6179 | −0.1935 | −6.2 |
| 2.[a] |  | 5.6531 | 5.7726 | 0.1195 | −7.7 |
| 3. |  | 6.2907 | 6.3862 | 0.955 | −8.3 |
| 4. |  | 5.8465 | 5.9383 | 0.0918 | −7.9 |
| 5. |  | 6.6179 | 6.7237 | 0.1058 | −8.1 |
| 6. |  | 7.0915 | 7.1495 | 0.058 | −8.1 |
| 7.[a] |  | 6.9172 | 6.4973 | −0.4199 | −8.5 |
| 8. |  | 7.2146 | 7.1707 | −0.0439 | −8.4 |
| 9. |  | 7.2676 | 7.2529 | −0.0147 | −7.4 |
| 10. |  | 5.6047 | 5.5104 | −0.0942 | −7.7 |
| 11.[a] |  | 6.8762 | 6.7675 | −0.1087 | −8.1 |
| 12. |  | 7.0315 | 7.2046 | 01731 | −8.3 |

(*continued on next page*)

**Table 1** (*continued*)

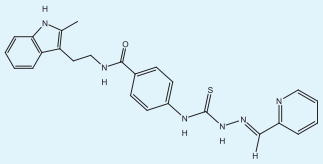
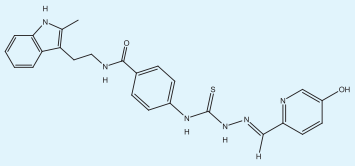
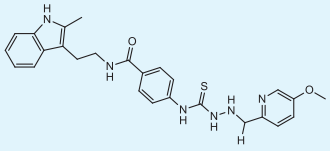
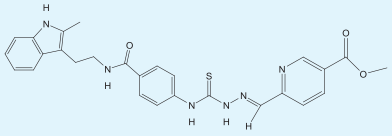
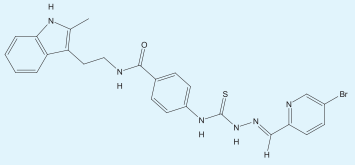
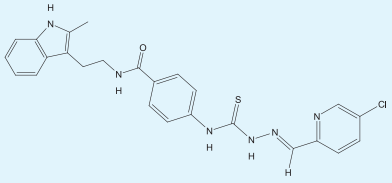
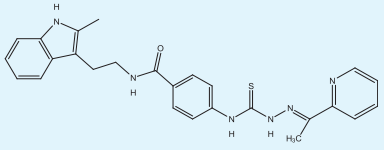
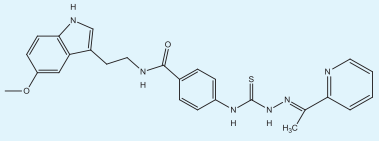
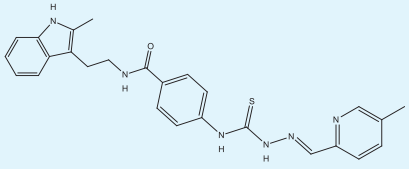
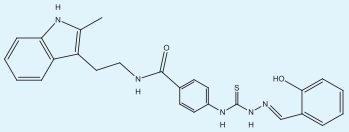
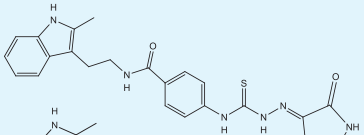
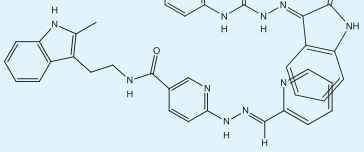
| S/No | Compounds | $pIC_{50}$ | Predicted $IC_{50}$ | Residual | Docking score (kcal/mol) |
|---|---|---|---|---|---|
| 13. |  | 7.0409 | 6.8889 | −0.152 | −7.7 |
| 14. |  | 5.8236 | 5.9321 | 0.1085 | −7.5 |
| 15. |  | 7.0757 | 7.0517 | −0.024 | −8.1 |
| 16. |  | 5.7956 | 5.9655 | 0.1699 | −7.9 |
| 17. |  | 6.3429 | 6.3676 | 0.0247 | −7.4 |
| 18.[a] |  | 6.4922 | 6.1244 | −0.3678 | −8.2 |
| 19. |  | 6.1506 | 6.1608 | 0.0102 | −8.2 |
| 20. |  | 6.0236 | 6.0866 | 0.063 | −8.4 |
| 21. |  | 7.2676 | 7.0765 | −0.1911 | −7.9 |

**Table 1** (*continued*)

| S/No | Compounds | $pIC_{50}$ | Predicted $IC_{50}$ | Residual | Docking score (kcal/mol) |
|---|---|---|---|---|---|
| 22. |  | 4.7698 | 4.6825 | −0.0873 | −8.8 |
| 23.[a] |  | 5.2740 | 4.9504 | −0.3236 | −8.0 |
| 24. |  | 6.3915 | 6.2922 | −0.0993 | −8.4 |

[a] Denotes test set.

**Table 2: Definition and class of molecular description in the build model.**

| Name | Definition | Class |
|---|---|---|
| SHBd | Sum of estate for (strong) hydrogen bond donors | 2D |
| SsCH3 | Sum of atom-type E state: CH3 | 2D |
| JGI2 | Mean topological charge index of order 2 | 2D |
| RDF60p | Radial distribution function 060/weighted by relative polarizability | 3D |

**Table 3: QSAR validation tool.**

| Validation tool | Interpretation | Accepted value |
|---|---|---|
| $R^2$ | Coefficient of determination | ≥0.6 |
| $R_{cv}^2$ | Cross validation coefficient | >0.5 |
| $R_{adj}^2$ | Adjusted coefficient of determination | >0.5 |
| $R^2 - Q_{cv}^2$ | Difference between $R^2$ and $Q_{cv}^2$ | ≤0.03 |
| $N_{ext/test\ set}$ | Minimum number of external test set | ≥5 |
| $R^2_{\ test\ set}$ | Coefficient of determination of external and test set | ≥0.5 |

**Table 4: Y-randomization test.**

| Model | R | $R^2$ | $Q^2$ |
|---|---|---|---|
| Original | 0.914764 | 0.836794 | 0.754947 |
| Random 1 | 0.282576 | 0.079849 | −0.37938 |
| Random 2 | 0.274074 | 0.075117 | −0.5798 |
| Random 3 | 0.224871 | 0.050567 | −1.49993 |
| Random 4 | 0.248583 | 0.061793 | −0.79437 |
| Random 5 | 0.415275 | 0.172453 | −0.21632 |
| Random 6 | 0.336942 | 0.11353 | −0.85686 |
| Random 7 | 0.444572 | 0.197644 | −0.1481 |
| Random 8 | 0.32334 | 0.104549 | −0.42676 |
| Random 9 | 0.176534 | 0.031164 | −0.42356 |
| Random 10 | 0.559751 | 0.313321 | −0.14548 |
| Random model parameters | | | |
| Average r: | 0.328652 | | |
| Average $r^2$: | 0.119999 | | |
| Average $Q^2$: | −0.54706 | | |
| $CRp^2$: | 0.780922 | | |

**Table 5: Statistical parameters for the developed models.**

| Parameter | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| Friedman LOF | 0.076524 | 0.085553 | 0.104593 | 0.104676 | 0.105337 |
| R-squared | 0.972517 | 0.969275 | 0.962437 | 0.962407 | 0.962169 |
| Adjusted R-squared | 0.964665 | 0.960496 | 0.951705 | 0.951666 | 0.951361 |
| Significant regression | YES | YES | YES | YES | YES |
| Significance-of-regression F-value | 123.8526 | 110.4132 | 89.67639 | 89.60198 | 89.01778 |
| Critical SOR F-value (95%) | 3.160163 | 3.160163 | 3.160163 | 3.160163 | 3.160163 |
| Replicate points | 0 | 0 | 0 | 0 | 0 |
| Computed experimental error | 0 | 0 | 0 | 0 | 0 |
| Lack-of-fit points | 14 | 14 | 14 | 14 | 14 |
| Minimum experimental error for non-significant LOF (95%) | 0.099165 | 0.104852 | 0.115934 | 0.11598 | 0.116346 |

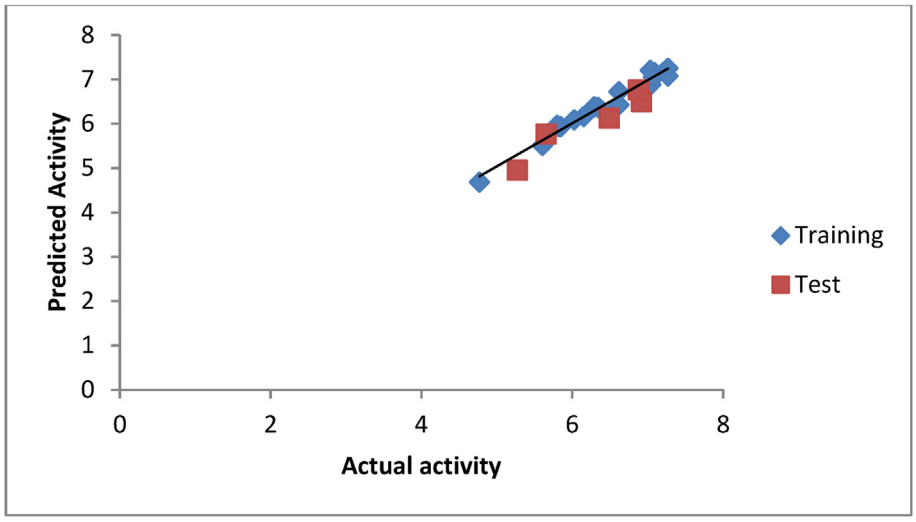



**Figure 2:** Scatter plot of biological activity against calculated activity.

Figure 4 illustrates the interaction of compound 22 with the receptor, whereas Figure 5 shows the interaction of compound 7 with its receptor. The unique compound-receptor binding outcomes were attributed to the existence of salt bridges, pi-sulfur, and pi-sigma interactions.

*Drug-likeness and pharmacokinetics studies*

SwissADME is an online tool designed for studying the pharmacokinetic, physicochemical, and medicinal chemistry

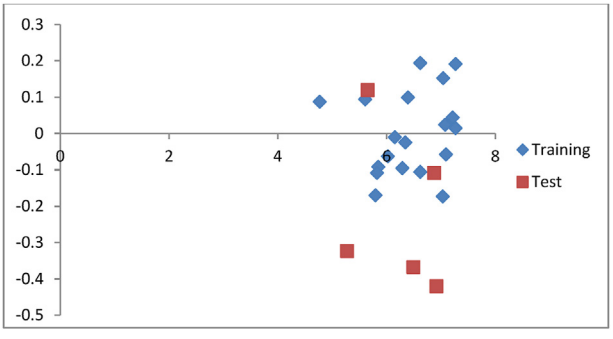



**Figure 3:** Scatter plot of standardized residual versus investigational activity.

sensitivity of small molecules.[51] After the molecules are imported into SwissADME, the results are displayed in a web browser for ease of visualization, and a PDF version of the report is saved.[52] The compounds under investigation were examined to determine drug-likeness. The molecular weight of these compounds was $\leq$500 MW, the number of hydrogen bond donors (HBD) was five or fewer, and the number of hydrogen bond acceptors (HBA) was 10.6 (Table 7). Their bioavailability score of 0.55 indicated the compounds' ability to be absorbed, and their synthetic accessibility of 3.42−3.52 predicted their ability to be conveniently synthesized in laboratory settings. Hence, our findings suggested that compounds 22 and 7 inhibitors were candidates for synthesis.

Drug metabolism depends on the class of enzymes (cytochrome p450), including CPY1A2, CPY2C19, CPY2C9, CPY2D6, and CPY3A4. The investigated compounds had favorable predicted pharmacokinetic properties (Table 8). These compounds are inhibitors of CPY1A2, 2C19, 2C9, and 34A. Additionally, they are not substrates of P-gp and cannot penetrate the blood−brain barrier. Therefore, these compounds have positive pharmacokinetic properties and may serve as potential drugs for inhibiting the PC3 cancer cell line, because they passed the analysis for drug friendliness, had additional favorable physicochemical qualities, and

**Table 6: Molecular docking interactions in select compounds.**

| Compound | Binding affinity (kcal/mol) | Amino acid | Interaction |
|---|---|---|---|
| 22 | −8.8 kcal/mol | VAL A:715, ALA A:748, LYS A:808 GLY A:683, PRO A: 682, TRY A:763 PRO A:766, VAL A:684, ARG A:752 PHE A:804, GLU A:681, TRP A:751 GLN A:711 | Van der Waals, salt bridge, attractive charge, conventional hydrogen bond, carbon hydrogen bond, unfavorable positive-positive, pi-sulfur, alkyl, pi-alkyl |
| 7 | −8.5 kcal/mol | PRO A: 766, TYR A:763, ASN A:756 GLU A:681, ARG A:718, LYS A:808 LEU A:744, TRP A:718, VAL A:715 ALA A:748, GLN A:711, GLY A:683 PRO A:682, VAL A:684 | Van der Waals, pi-sigma, conventional hydrogen bond, carbon hydrogen bond, unfavorable positive-positive alkyl, pi-alkyl |

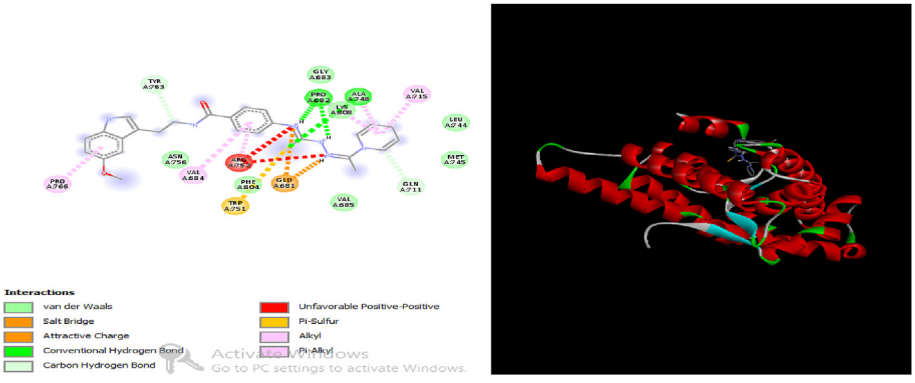



**Figure 4:** 2D and 3D representations of compound 22 in the active site of the 5T8E receptor.

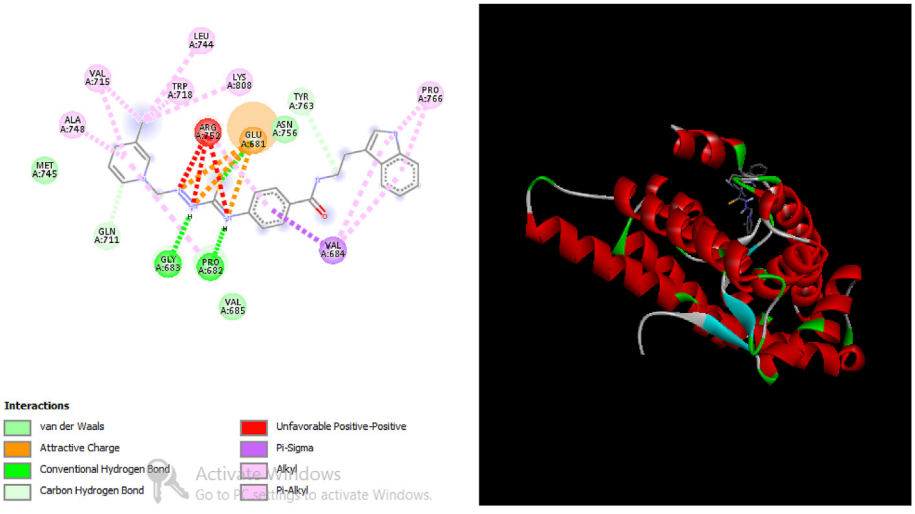



**Figure 5:** 2D and 3D representations of compound 7 in the active site of the 5T8E receptor.

**Table 7: Predicted drug-likeness properties of the selected compounds.**

| Molecule | Molecular weight | HBA | HBD | MLogP | Synthetic accessibility | Bioavailability score | Lipinski violation | Drug-likeness |
|---|---|---|---|---|---|---|---|---|
| 22 | 470.59 | 3 | 4 | 2.41 | 3.52 | 0.55 | 0 | Yes |
| 7 | 491.01 | 3 | 4 | 2.68 | 3.42 | 0.55 | 0 | Yes |

**Table 8: Predicted pharmacokinetic properties of the selected compounds.**

| S/no | GI absorption | BBB permeant | P-gp substrate | CPY inhibitors | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | CPY1A2 | CPY2C19 | CPY2C9 | CPY2D6 | CPY34A |
| 22 | Low | No | No | Yes | Yes | Yes | No | Yes |
| 7 | Low | No | No | Yes | Yes | No | No | Yes |

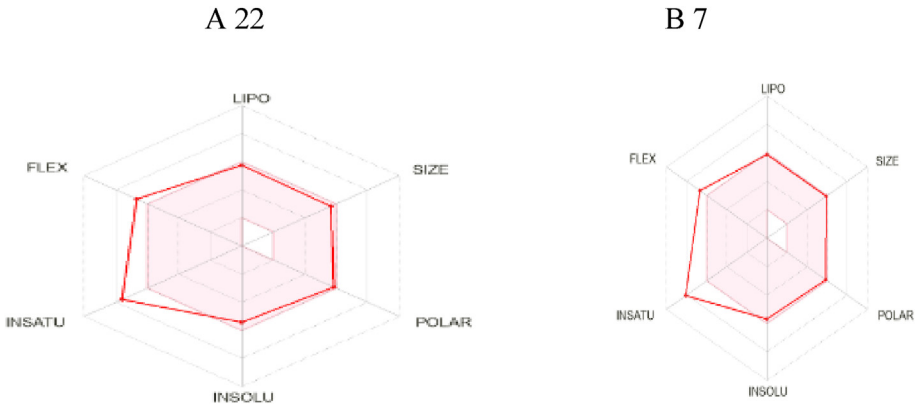



**Figure 6:** Bioavailability tracking system for molecules 22 and 7.

followed Lipinski's rule of five. Consequently, the selected compounds may be candidates for preclinical trials. In addition, the bioavailability radars of molecules 22 and 7 are displayed in Figure 6.

This study provides insight into the activity of thiosemicarbazone compounds, and offers information to support future studies on molecular modification and the in silico design of other thiosemicarbazone compounds, with the aim of improving the receptor binding affinity of ligands 22 and 7. However, further validation through in vivo and in vitro analysis is recommended, because thiosemicarbazone might be a promising plant source for a drug molecule that can treat prostate cancer.

## Conclusion

This study used QSAR, molecular docking, and pharmacokinetic techniques on thiosemicarbazone-indole derivatives to generate a model. Of the five models constructed, model 1 was selected and found to be statistically fit, as evidenced by the following validation parameters: $R^2 = 0.972517$, $R_{adj} = 0.964665$, $cRp^2 = 0.780922$, and LOF = 0.076524. The QSAR model indicated that an increase in SsCH3, and decreases in SHBd, JGI2, and RDF60p, would enhance the biological activity of the thiosemicarbazone-indole derivatives, thereby suggesting the potential of these compounds as effective remedies for treating the PC3 cancer cell line.

The best compounds, 22 and 7, were subjected to molecular docking, and demonstrated positive stability and interactions with amino acid residues at the crucial target site. The most common residues across all reported compounds were VAL, ALA, LYS, GLY, PRO, TRY, ARG, GLU, and GLN.

Pharmacokinetic and drug-likeness predictions indicated that both compounds 22 and 7 were within the maximum accepted oral bioavailability ranges for drug molecules. Moreover, the two chosen compounds adhered to Lipinski's rule of five. Overall, our findings suggest that compounds 22 and 7 may be promising potential candidates for further development as orally bioavailable drugs targeting the PC3 cancer cell line.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Ethical approval

There are no ethical issues.

## Authors contributions

AIK devised and designed the experiment, performed the experiment, analyzed and interpreted the data, and wrote the paper. AU provided directives and technical advice. MTI performed the experiment and wrote the paper. ITB and ABU provided technical assistance. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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