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Original Research Article

Molecular Docking and ADMET Properties of Six Selected Cytotoxic Compounds From *Citrus Aurantium* And *Commiphora africana* Against Human Protein Tyrosine Kinase (PTK6) And Human Androgen Receptor (HAR)

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ABSTRACT

Cancer is a life-threatening disease affecting both the young and the aged populations globally. A computational approach is a fast and robust method used in the virtual screening of compounds against target protein diseases such as cancer. This technique gives insight into selecting a candidate drug for design and development. The present study investigated six selected previously reported cytotoxic compounds using *in silico* studies for their potential use as anticancer inhibitors. Four acridone alkaloids (5-hydroxynoracronycine, citracridone-I, citracridone-III, and citrusinine-I) from *Citrus aurantium* and two resveratrol compounds (3-hydroxy-5-methoxybenzoic acid and pinostilbene) from *Commiphora africana* were selected as ligands. Target proteins: human protein tyrosine kinase (PTK6) and human androgen receptor (HAR) were retrieved from the RCSB Protein Data Bank (PDB) web server with ID 1E3G and 6CZ4, respectively. Ligand-protein interactions were modeled using molecular docking. The pharmacokinetic properties of compounds were established via SwissADME and ADMET web servers. Pinostilbene and 5-hydroxynoracronycine revealed the highest binding affinity scores of -8.8 and -9.6 kcal/mol against target proteins-1E3G and 6CZ4, respectively. The docking scores of reference drugs-cyclophosphamide and 5-fluorouracil were -5.4 and -5.2 Kcal/mol, respectively, for 1E3G, while 6CZ4 showed -5.7 and -5.1 Kcal/mol scores, respectively. All the studied compounds, including the reference drugs, revealed high gastrointestinal absorption with water solubility ranging from moderately soluble to very soluble and complied with Lipinski's Rule of 5 without any violation. The present investigation suggests pinostilbene and 5-hydroxynoracronycine as potential inhibitors against cancer proliferation.

Keywords: Cancer, Computational approach, Cytotoxic compounds, Molecular docking, Pharmacokinetic properties

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Introduction

Cancer is a global disease with a vast burden effect on the young and old populations in both the developed and developing nations. It is a foremost cause of untimely death globally, with a prediction of high prevalence over the next five decades due to population aging in different regions of the world.[1] As a global disease, it accounts for the second mortality in the United States.[2] Africa is not left out, as there has been a surge of reported cancer cases over the last two decades. Specifically, Nigeria, with an estimated population of well above 200 million, contributed new cases of 128,815 cancer patients, 78,899 mortalities in 2020, and 233,911 prevalent cases were predicted in the next five years.[3] Topmost among the ranked cases of cancer types in Nigeria include prostate and breast.

Cancer treatment is mainly through surgery, chemotherapy, and radiotherapy. These modes of therapy are expensive and not readily available to low-income earners in developing countries. This has, in no small measure, contributed immensely to patronizing herbal medical practitioners as a means of alternative complementary medicine for cancer patients, especially in the continent of Africa. The discovery and development of drugs from natural sources, especially medicinal plants, have been an age-long practice. In particular, developing countries, especially rural dwellers, take an exceptional interest in using herbal medicines due to their accessibility, affordability, and availability. Since 1981, natural products derived drugs have contributed to most approved drugs.[4] To this end, many researchers from Africa have explored the diverse flora to validate field-based observations in rationalizing traditional claims of medicinal plants in managing inflammation and cancer through a laboratory-based approach. In recent times, many scientific reports on the isolation of cytotoxic bioactive compounds from Nigerian flora have been well-documented based on the ethnobotanical use of these plants in managing cancer and inflammation, thereby justifying their usage as folk medicine. However, most of these isolated compounds and indigenous sources of medicinal plants have not been developed to the pre-clinical stage or even formulated as herbal drugs.

The drug discovery and development process is tedious, time-consuming, and involves a lot of resources. One way to develop bioactive small molecules into drugs as a starting raw material is to subject them to *in silico* studies. This procedure saves time and resources in drug discovery and development by selecting and predicting the properties of the screened bioactive molecules. It is, therefore, paramount to screen bioactive compounds using the molecular docking approach to gain insight into selecting a candidate drug as a potential inhibitor and to understand its pharmacokinetic properties, which can be utilized as a starting raw material for drug development and large-scale industrial pharmaceutical use. The molecular docking technique is commonly used to screen bioactive

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compounds and predict the structure-relationship activity of receptor (protein) with the drug molecule (ligand) through non-covalent interactions, mainly by hydrogen bonding.[5] The protein-ligand complexes binding is vital in research applications relating to structural bioinformatics and drug discovery.[6]

Traditionally, *Commiphora africana* is used to treat malaria, cancer, and microbial infections[7,8], while *Citrus aurantifolia* has been used as an anticancer, antianxiety, antiobesity, antibacterial, antioxidant, pesticidal, and antidiabetic.[9,10] In the present study, six selected compounds based on their previously reported cytotoxicity against breast and prostate human carcinoma cells[11,12] from *C. aurantium* and *C. africana* were investigated for their ADMET properties (absorption, distribution, metabolism, excretion, and toxicity) and their potential inhibitors through binding interactions against human protein tyrosine kinase (PTK6) and human androgen receptor (HAR). Insight into the mechanism of action of these compounds through computer-aided drug design, which may be a potential inhibitor against the target proteins, is lacking in the literature. Of the six cytotoxic test compounds, 4 are acridone alkaloids from *C. aurantium*, while 2 are resveratrol derivatives from *C. africana*. The cytotoxic compounds and reference drugs (cyclophosphamide and 5-fluorouracil) were docked against PTK6, which has been reported as a significant and diverse crystalline protein structure in many diseases, including breast and prostate cancer and against HAR, whose mutations in the androgen receptor gene has been attributed to several disease states like prostate cancer.[13] Therefore, the current study aims to use a computational approach to identify the potential inhibitors of these compounds through ligand-protein modelling interactions and to document their ADMET properties.

Materials and Methods

Ligand preparation

Four test acridone alkaloids, namely 5-hydroxynoracronycine, citracridone-I, citracridone-III, and citrusinine-I isolated from *Citrus aurantium* and two test resveratrol compounds, namely 3-hydroxy-5-methoxybenzoic acid and pinostilbene previously isolated from *Commiphora africana* as reported in the literature were used as ligands in the present investigation. The 3D structure data file (SDF) format of the selected compounds and reference drugs (cyclophosphamide and 5-fluorouracil) was obtained from the PubChem database. The Open Babel software (version 3.1.1, 2020) converted the SDF format to Protein Data Bank (PDB) format.[14]

Protein Preparation

The target protein crystalline structure PTK6 (PDB ID: 6CZ4) and HAR (PDB ID: 1E3G) were retrieved from the RCSB Protein Data Bank (PDB). The downloaded protein in PDB format was visualized in BIOVIA Discovery Studio Visualizer 2021, version 21.1.0.20298. The protein coordinates (XYZ) from the bound ligand of 6CZ4 and 1E3G were used to define the active sites. The binding sphere was defined based on the current selection of ligand/inhibitor attached to the residue proteins 1E3G and 6CZ4. Prepared protein was obtained by removing water molecules and adding polar hydrogen to the selected macromolecules, which were saved in PDB format.[15]

Docking Preparation

Virtual screening docking analysis of the target protein-ligand was conducted using AutoDock Vina (version 1.5.6, 2010).[16,17] AutoDock Vina is a molecular docking program designed to carry out rigid-flexible docking procedures.[16,17] It utilizes multiple CPUs at a time with exceptional accuracy and speed. Vina is based on a Slope optimization algorithm with instant clustering of results and optimization.[17] The 2D and 3D protein-ligand interactions with the best pose were visualized in Discovery Studio Visualizer 2021.

ADMET Screening

The SwissADME server (http://www.swiss.adme.ch) was used in predicting the pharmacokinetic (absorption, distribution, metabolism, excretion, and toxicity), physicochemical parameters, and medicinal drug-likeness of the six selected test compounds and reference drugs.[18,19] The conical smiles of test compounds and reference drugs were copied from PubChem and pasted on the SwissADME web server for analysis.

Results and Discussion

The 2D structures of the six test compounds namely 5-hydroxynoracronycine, citracridone-I citracridone-III, citrusinine-I, 3-hydroxy-5-methoxybenzoic acid, and pinostilbene as depicted in figure 1 were modeled and used as a target for the current docking studies against two target proteins (PTK6 and HAR) which have been reported to be responsible for breast and prostate cancer. The 3D crystal structures of the target proteins, 1E3G from PTK6 and 6CZ4 from HAR, are presented in Figure 2 as visualized in Discovery Studio Visualizer.

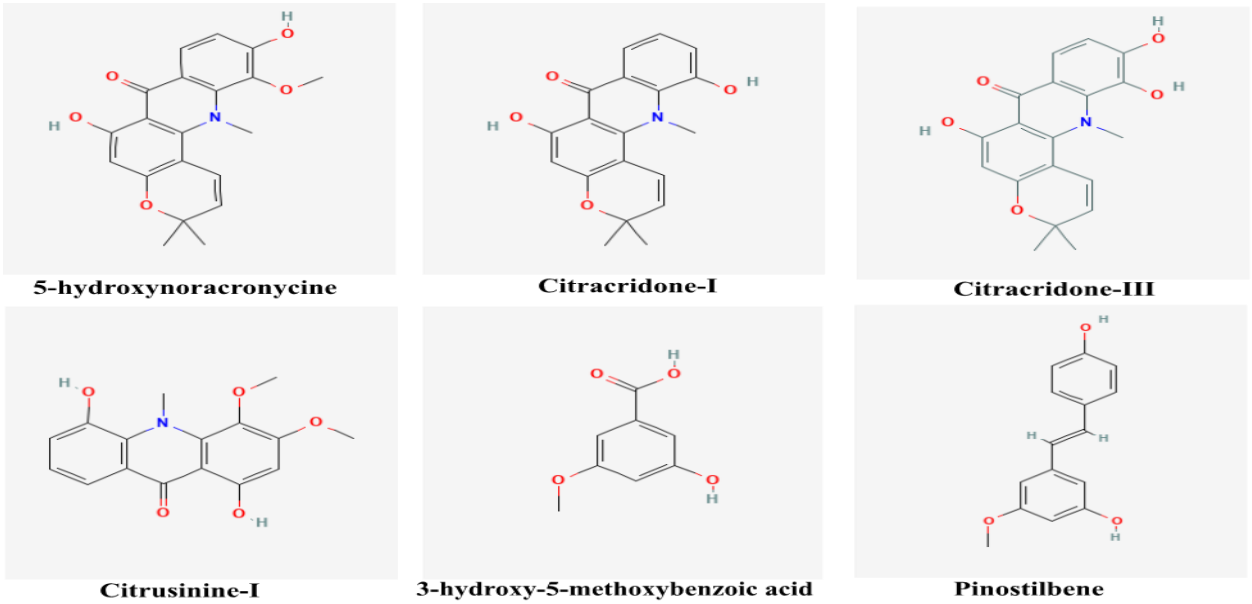

Figure1: 2D structures of studied compounds

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Figure 2: 3D structure of target proteins1E3G and 6CZ4 in Discovery Studio Visualizer

In the current study, the use of AutoDock Vina and flexible docking were utilized in precisely predicting the binding affinity and docking scores of the selected cytotoxic compounds from *Citrus aurantium* and *Commiphora africana* against PTK6 (1E3G) and HAR (6CZ4). All six compounds chosen in the current study were successfully docked with crystalline protein structures 1E3G and 6CZ4, a target against cancer disease. The docking scores of the compounds and reference drugs were between -5.1 and -9.6 Kcal/mol, as presented in Table 1. Pinostilbene had the highest binding affinity score of -8.80 Kcal/mol, closely followed by 5-hydroxynoracronycine and citracridone-III, with both having docking scores of -7.50 Kcal/mol for 1E3G. In contrast, for 6CZ4, 5-hydroxynoracronycine had the highest binding affinity score of -9.6 Kcal/mol, closely followed by citracridone-III and citracridone-I with docking scores of -9.5 and -9.4 Kcal/mol, respectively (Table 1). The docking scores of cyclophosphamide and 5-fluorouracil were -5.4 and -5.2 Kcal/mol, respectively, for 1E3G, while for 6CZ4, the docking scores were -5.7 and -5.1 Kcal/mol scores, respectively (Table 1). The least activity was observed in 3-hydroxy-5-methoxybenzoic acid with -6.3 Kcal/mol for 1E3G and -6.0 Kcal/mol for 6CZ4 (Table 1).

In molecular docking, the lowest binding energy in Kcal/mol indicates a better ligand-receptor binding affinity.[20] Therefore, the compound with the most reduced binding energy was interpreted as the most effective compound in suppressing the protein target, as the reduced binding energy implies greater affinity. The observed differences in the binding affinities could be attributed to the interaction between the residual amino acids and the compounds. This assertion agrees with previous report on molecular docking and ADMET prediction of natural compounds towards SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 Main protease.[20]

The 3D and 2D molecular interactions of the amino acid residues of 1E3G with pinostilbene, 5-hydroxynoracronycine, citracridone-III, and citrusinine-I are presented in figure 3 while the 3D and 2D molecular interactions of the amino acid residues of 6CZ4 with 5-hydroxynoracronycine, citracridone-III, citracridone-I and pinostilbene are presented in figure 4. The molecular docking results of the compounds depict the interaction of compounds with several interesting amino acids (Figures 3 and 4). The compounds interacted with the amino acid residues through several forces such as conventional hydrogen bonding, carbon-hydrogen bonds, and π-interactions including π-Sulphur, alkyl, π-alkyl, π- π T shaped, π-Sigma and π- π stacked.

The two major interacting forces involved in docking these selected compounds and reference drugs are hydrogen bonds (conventional and carbon-hydrogen bonds) and π-interactions. Interactions involving hydrogen bonds have been reported to be stronger than other bonds.[21,22] The main drivers of cell-to-cell communication and dysregulation result from molecular interactions between small molecules and proteins, which have been implicated in many diseases such as cancer, neurodegeneration, and autoimmunity.[23] Consequently, the bonding interactions between the test compounds and receptors could have played a significant role in the suppression of the attractive charge as well as the enzymes.

Pinostilbene and resveratrol had earlier been reported to exhibit moderate in vitro cytotoxicity against breast and prostate cancer with IC_{50} values of 29.36 and 38.44 µg/mL, respectively.[12] This moderate experimental activity of pinostlbene as a potential cytotoxic property agrees with the binding affinity scores observed in its docking against 1E3G and the ability to target amino acid residues from the crystalline protein structure of the macromolecule. In the same report, 3-methoxy-5-methoxybenzoic acid isolate from the same plant had IC_{50} values > 200 µg/mL for both breast and prostate cancer cell lines. This may also explain the low binding affinity scores observed when docked against 1E3G and 6CZ4 protein crystalline structure in the present investigation.

However, the acridone alkaloids, namely 5-hydroxynoracronycine, citracridone-III, and citracridone-I, which are classified as tetracyclic alkaloids based on their nucleus, had -9.6, -9.5, and -9.4 Kcal/mol as binding affinity scores, respectively against 6CZ4 target protein. These acridone alkaloids target HAR (6CZ4) more than the PTK6 (1E3G) based on the binding affinity scores. However, experimental in vitro cytotoxicity values previously reported suggested activity as citracridone-I > citracridone-III > 5-hydroxynoracronycine[11]. Interestingly, their binding affinity scores are comparable with slight differences, while amino acid residue ARG 316 is also a unique target in 5-hydroxynoracronycine and citracridone-I.

Small molecules like alkaloids have been previously reported as inhibitors targeting epidermal growth factor receptors (EGFR). In an *in silico* study using Autodock Vina for thirty-two alkaloids against EGFR, sanguinarine, an alkaloid, was found to be most potent with -10.7 Kcal/mol binding affinity compared to erlotinib (-7.5 Kcal/mol)[24]. Their study also identified alkaloids as small inhibitors against cancers. The present molecular docking of acridone alkaloids also attests to their potential cytotoxic compounds based on their binding affinity scores and could be selected as an essential starting point in drug discovery against diseases like cancer. Molecular docking has always been an effective tool in drug simulation using computer-aided drug design (CADD). Molecular docking is applied in the computation of the binding affinity of ligand molecules, which is salient in elucidating their metabolic activities.[25] The sole aim of docking studies is to establish interactions between macromolecules such as receptors and small molecules such as inhibitors or potential drugs/substrates.[26] It also helps to identify potential inhibitors for various targets and aids in precise prediction.[27] Recently, *in silico* studies on medicinal plants, drug design, and vaccines have taken a central stage in drug development.[28,29] This has been further benefitted by combining pharmacological applications of natural products in managing myriad diseases.[30] Hence, the need for molecular docking of pharmacologically active small molecules will give an insight into interactions of receptors with drug molecules, which can improve the selection and development of more effective candidate drugs in drug discovery.

Many researchers have reported using molecular docking to determine, evaluate, and select active compounds from ineffective ones. For example, a computational study of isolates from *Graviola* plants is well documented as a potential lead source of anticancer compounds.[31] Similarly, other researchers[32] have reported the interactions of four cytotoxic compounds isolated from *Diospyros quercina* and *Salacia leptoclada* against angiogenesis target protein H1F-1α and human androgen receptor. The cytotoxic compounds were concluded to serve as a potential alternative therapy against breast and prostate cancer. In addition, cytotoxic and antiproliferative evaluation of compounds from African medicinal plants against fourteen selected targets to verify their potential binding to anticancer drug targets have also been reported.[33] Their results suggest that African medicinal plants represent a veritable source for discovering anticancer drugs.

In the present investigation of the six selected potential cytotoxic compounds against protein crystalline structure of 1E3G and 6CZ4, an

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insight into the binding of these small molecules to amino acids residue of the target protein, their binding affinity scores and their interacting forces with hydrogen bonding which is responsible for the stability of the test compounds are essential in the selection process and developing lead drugs for potential future anticancer inhibitors. Our findings in predicting selected cytotoxic molecules as a lead compound in drug design and development of anticancer drugs using *in silico* analysis agrees with a previous report in which some chosen abundant bioactive molecules from antiviral plants were screened for their therapeutic effect on different HIV drug targets, with the help of molecular docking.[22]

All the test compounds predicted druglike on SwissADME except 3-hydroxy-5-methoxybenzoic acid, which violated Muegge, having a violation in MW < 200 (Table 2). Similarly, cyclophosphamide had no druglikeness violation, but 5-fluorouracil violated Ghose (MW < 160, MR < 40, atoms < 20) and Muegge (MW < 200, C < 5) as shown in Table 2. The bioavailability score and synthetic accessibility (SA) of drugs are also presented in Table 2. A comparable bioavailability score of 0.55 was observed in all the test compounds and reference drugs except in 3-hydroxy-5-methoxybenzoic acid, with a 0.85 bioavailability score. The Lipinski rule of 5 was satisfactorily complied with by all tested compounds having molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5, lipophilicity (Log P) ≤ 5 and molar refractivity ranging from 40 to 130 as presented in Table 3.

Gastrointestinal absorption was high for studied drug compounds, while water solubility ranged from moderately to very soluble (Table 4). Pinostilbene exhibited the highest rotatable bonds (3) compared with the reference drug cyclophosphamide (5). The lowest lipophilicity of studied compounds was found in 3-hydroxy-5-methoxybenzoic acid (1.13), closely followed by citrusinine-I (2.04), citracridone-III (2.51) and 5-hydroxynoracronhcine (2.84) in comparison with reference drugs cyclophosphamide (1.23) and 5-fluorouracil (0.13) Table 4. Pinostilbene (49.69 Å^2) was observed with the lowest topological polar surface area (TPSA) of the tested compounds in comparison with cyclophosphamide (51.38 Å^2) and 5-fluorouracil (65.72 Å^2) Table 4. All the investigated compounds had negative values for Log Kp (Table 4).

Most biologically active compounds end up being toxic after tedious isolation procedures that consume time and resources. To avoid wasting resources and time during the voyage of drug discovery, design, and development, potential drug candidates must be subjected to toxicological and drug-likeness using a simple, rapid, and economic computational approach.[34] Small molecules derived from medicinal plants are considered a potential drug for further development if they exhibit high biological activity and low toxicity. Computational models could be an alternative to experimental work by rapidly predicting critical parameters for collecting molecules to support the drug discovery voyage.

SwissADME website is a free web tool that allows computational physicochemical descriptors as well as prediction of ADMET characters (absorption, distribution, metabolism, excretion, and toxicity), pharmacokinetic properties, druglike nature, and medicinal chemistry friendliness of small molecules to support drug discovery and development. ADMET predictions of these compounds were assessed within a biological system based on their pharmacological and pharmacodynamic properties. The physicochemical properties and drug-likeness of the investigated compounds were evaluated for Lipinski's rule of 5 (RO5).[35] Lipophilicity (Log P) of a drug compound is the octanol/water partition coefficient, which is known to affect the digestion of a drug compound in the body. Generally, an increase in Log P denotes decreased digestion within the body and is acceptable as ≤ 5. Also, penetration of a drug molecule through the cell layer is determined by the number of donors and acceptors hydrogen bonds it possesses within the acceptable range. All the studied compounds, including the reference drugs, were found to observe all Lipinski's RO5 without any violation. Test compounds also complied with Ghose, Veber, Egan, and Muegge rules except for 3-hydroxy-5-methoxybenoic acid, which violated one of Muegge's rules, and 5-fluorouracil violated three of Ghose's rule and two of Muegge's rule.

Furthermore, the synthetic accessibility (SA) scores range from 1 to 10, where 1 denotes simplicity in synthesizing the compounds and 10 represents difficulty in synthesizing.[36] All the six selected potential cytotoxic compounds displayed synthetic accessibility ranging from 1.40 to 3.51. The bioavailability score ascertains the penetrability of a candidate drug molecule as well as the bioavailability characteristics.[37] A bioavailability score of 0.55 was observed in all studied compounds except 3-hydroxy-5-methoxybenzoic acid, with 0.85.

The penetration of a drug molecule through a biological barrier depends on the molecular weight (MW) and topological polar surface area (TPSA). Generally, the drug molecule can penetrate with lower MW and TPSA values. Rotatable bonds should be less than 7 as they influence drug-likeness properties. Pinostilbene with the lowest TPSA (49.69 Å^2), a moderate molecular weight of 242.27 g/mol, and three rotatable bonds could be considered to have a penetration through the biological blood-brain barrier (BBB) coupled with the highest binding affinity score recorded from docking with 1E3G. All studied compounds have high gastrointestinal (GIT) absorption, suggesting that these compounds have the potential to be absorbed in the GIT upon oral administration.[38] Permeability of small molecules through selective barriers such as the skin occurs at diverse rates and depends on the drug's physicochemical properties.[39] Thus, the skin permeability denoted by Log K_p is a crucial determinant in evaluating molecules for their penetrability through transdermal administration. In the current study, all the investigated compounds had negative values for Log K_p, implying that they could not be successfully administered through the transdermal tissues.[40]

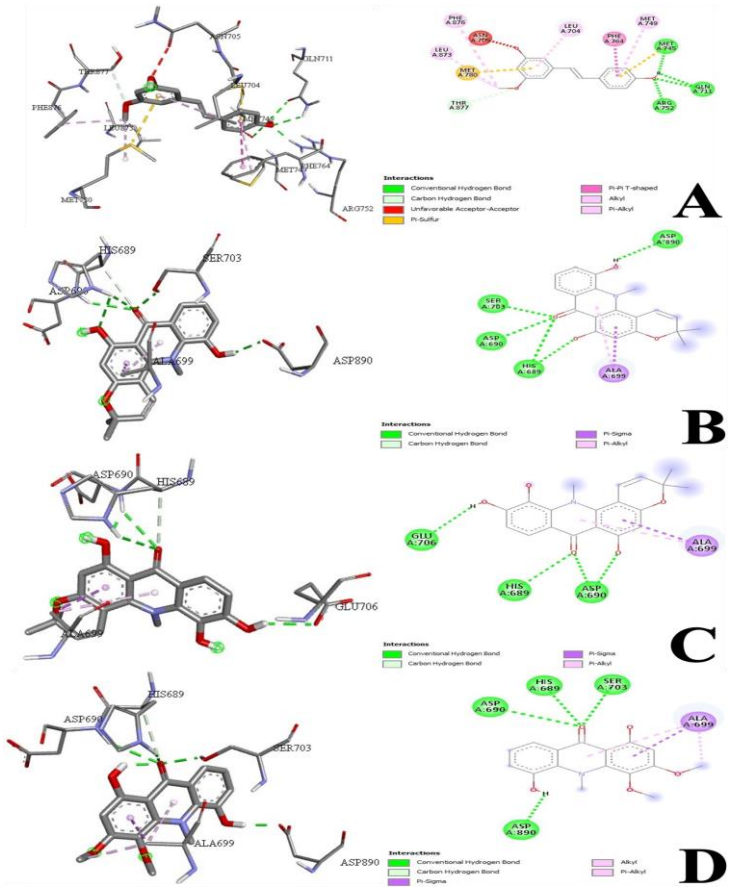

Figure 3: 3D (left) and 2D (right) interaction of compounds with the target protein (1E3G) docked using AutoDock Vina, visualized in Discovery Studio
(A) Pinostilbene, (B) 5-hydroxynoracronycine, (C) Citracridone-III, (D) Citrusinine-I

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Table 1: Binding Affinity Values for Compounds and Reference Drugs Docked with Crystalline Protein Structure 1E3G and 6CZ4, a Target Against Cancer Disease

Compounds/References	**1E3G**			**Compounds/References**	**6CZ4**		
	Binding Affinity (kcal/mol)	**Hydrogen Bonding**	**Interacting Amino Acids Residues**		**Binding Affinity (kcal/mol)**	**Hydrogen Bonding**	**Interacting Amino Acids Residues**
5-hydroxynoracronycine	-7.5	6	SER 703, ASP 690, HIS 689, ASP 890, ALA 699	5-hydroxynoracronycine	-9.6	5	ASN 317, TYR 342, GLY 332, TYR 201, ARG 316
Citracridone-I	-7.3	3	GLN 783, LYS 883, ARG 779	Citracridone-I	-9.4	6	ARG 316, TRP 353, ASP 312, ALA 314
Citracridone-III	-7.5	5	GLU 706, HIS 689, ASP 690, ALA 699	Citracridone-III	-9.5	5	LYS 240, ARG 243, TRP 260, TYR 251
Citrusinine-I	-7.4	6	ASP 690, HIS 689, SER 703, ALA 699, ASP 890	Citrusinine-I	-7.6	4	MET 267, THR 264, LYS 219, LEU 197, ALA 217, VAL 205, LEU 333, ILE 262
3-hydroxy-5-methoxy benzoic acid	-6.3	4	GLU 681, LYS 808, GLN 711, PRO 682, ALA 748, ARG 752, GLY 683, VAL 685	3-hydroxy-5-methoxy benzoic acid	-6.0	3	ARG 186, TYR 251, TRP 210, ALA 252, VAL 214
Pinostilbene	-8.8	5	ARG 752, GLN 711, MET 745, THR 877, PHE 876, LEU 873, MET 780, ASN 705, LEU 704, PHE 764, MET 749	Pinostilbene	-8.3	2	THR 264, SER 199, VAL 205, ALA 217, LEU 319
Cyclophosphamide	-5.4	3	LYS 808, PRO 682, GLU 681, ARG 752	Cyclophosphamide	-5.7	4	ASP 312, ASN 317, GLY 332, ASP 330
5-Fluorouracil	-5.2	4	LYS 808, GLN 711, ALA 748, PRO 682	5-Fluorouracil	-5.1	3	THR 264, GLU 265, MET 267, LEU 319, VAL 205, ALA 217

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Table 2: Druglikeness Prediction for Compounds and Reference Drugs

Compounds/Reference	Druglikeness Prediction Output						
	Lipinski Violation	**Ghose Violation**	**Veber Violation**	**Egan Violation**	**Muegge Violation**	**Bioavailability Score**	**Synthetic Accessibility**
5-hydroxynoracronycine	0	0	0	0	0	0.55	3.31
Citracridone-I	0	0	0	0	0	0.55	3.51
Citracridone-III	0	0	0	0	0	0.55	3.35
Citrusinine-I	0	0	0	0	0	0.55	2.60
3-hydroxy-5-methoxy benzoic acid	0	0	0	0	1	0.85	1.40
Pinostilbene	0	0	0	0	0	0.55	2.17
Cyclophosphamide	0	0	0	0	0	0.55	4.15
5-Fluorouracil	0	3	0	0	2	0.55	1.52

Table 3: Lipinski's Rule of 5 Results for Compounds and Reference Drugs
Where MW ≤ 500; H-bond Acceptors ≤ 10; H-bond Donors ≤ 5; Lipophilicity (Log P) ≤ 5; Molar Refractivity – (40-130)

Compounds/Reference	Parameter				
	MW (g/mol)	**H-bond Acceptors**	**H-bond Donors**	**Log P**	**Molar Refractivity**
5-hydroxynoracronycine	323.34	4	2	2.82	95.14
Citracridone-I	353.37	5	2	3.29	101.63
Citracridone-III	339.34	5	3	2.85	97.17
Citrusinine-I	301.29	5	2	2.52	84.01
3-hydroxy-5-methoxy benzoic acid	168.15	4	2	1.20	41.92
Pinostilbene	242.27	3	2	2.32	72.35
Cyclophosphamide	261.09	4	1	1.92	62.60
5-Fluorouracil	130.08	3	2	0.44	27.64

Table 4. SwissADME Results for Compounds and Reference Drugs
Where TPSA (Å^2) < 140; Consensus Log P < 5; Rotatable bond < 7.

Compounds/Reference	Filters							
	Physicochemical properties		**Lipophilicity**	**Pharmacokinetics**			**Water solubility**	**Lead likeness**
	TPSA (Å^2)	**No. of rotatable bonds**	**Consensus Log P**	**GI Absorption**	**BBB**	**Log Kp (cm/s)**		
5-hydroxynoracronycine	71.69	O	2.84	High	Yes	-6.01	Moderately soluble	No
Citracridone-I	80.92	1	2.88	High	No	-5.96	Moderately soluble	No
Citracridone-III	91.92	0	2.51	High	No	-6.11	Moderately soluble	Yes
Citrusinine-I	80.92	2	2.04	High	No	--6.08	Soluble	Yes
3-hydroxy-5-methoxy benzoic acid	66.76	2	1.13	High	No	-6.01	Soluble	No
Pinostilbene	49.69	3	2.88	High	Yes	-5.33	Soluble	No
Cyclophosphamide	51.38	5	1.23	High	Yes	-7.45	Very soluble	Yes

5-Fluorouracil	65.72	0	0.13	High	No	-7.73	Very soluble	No

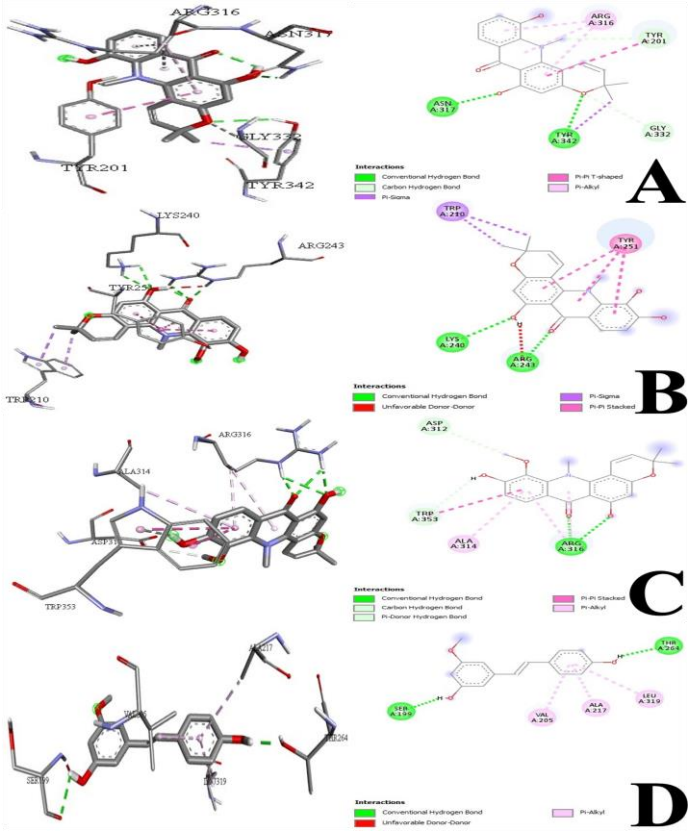

Figure 4: 3D (left) and 2D (right) interaction of compounds with the target protein (6CZ4) docked using AutoDock Vina, visualized in Discovery Studio
(A) 5-hydroxynoracronycine, (B) Citracridone-III, (C) Citracridone-I, (D) Pinostilbene

Conclusion

The present investigation of six selected cytotoxic compounds revealed pinostilbene from *Commiphora africana* and 5-hydroxynoracronycine from *Citrus aurantium* with a binding affinity of -8.8 kcal/mol against 1E3G and -9.6 Kcal/mol against 6CZ4 target protein, respectively are most effective potential inhibitors against cancer. These compounds demonstrate potential anticancer properties against breast and prostate cancer by binding to the protein targets. These compounds also showed better penetration through the blood-brain barrier and gastrointestinal absorption. To this end, virtual screening of these biologically active compounds through molecular docking and SwissADME properties could lead to a rapid strategy in developing these drugs in the pharmaceutical industry as potential inhibitors against breast and prostate cancer.

Conflict of Interests

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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