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Molecular Docking and in Silico Pharmacokinetic Analysis of Peronemin As A Potential 17β-Hsd1 Inhibitor For Estrogen-Dependent Cancer Therapy

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Abstract
High levels of estradiol (E2) are important in the development of endometrial cancer. This hormone is mostly produced when the enzyme 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) changes estrone (E1) into estradiol (E2). Inhibiting this enzyme can reduce estrogen production in cancers that rely on estrogen. This study examined three Peronemin derivatives (A2, A3, C1) as potential 17β-HSD1 inhibitors through detailed computer analysis. PASS predictions showed these compounds likely have antineoplastic activity (Pa > 0.85). Their physicochemical properties, based on Lipinski's rule, suggest they have good ADME profiles, with high gastrointestinal absorption and a predicted ability to cross the blood-brain barrier.Molecular docking results showed that all three compounds interacted stably with the 17β-HSD1 active site. Peronemin C1 had the strongest binding (ΔG = -6.56 kcal-mol-¹; Ki = 15.56 μM). Mapping the interactions revealed that A2 formed hydrogen bonds with Tyr155, A3 formed hydrogen bonds with Lys159, and C1 exhibited strong hydrophobic interactions. The results suggest that Peronemin A2, A3, and especially C1 could be promising for further development as 17β-HSD1 inhibitors. However, further laboratory studies are needed to confirm the effectiveness of these compounds and determine their practical application.

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INTRODUCTION

Endometrial cancer is among the most common gynecological cancers worldwide, and both its incidence and mortality are rising, especially in postmenopausal women (Sung et al., 2021). The disease is closely linked to estrogen, as long-term or unopposed exposure can cause excessive endometrial cell growth and increase cancer risk (Morice et al., 2016). The balance between estrone (E1) and estradiol (E2) is important for controlling estrogen activity in endometrial tissue. Estradiol is the most potent estrogen and stimulates cell growth more than estrone. The 17β-hydroxysteroid dehydrogenase (17β-HSD) family of enzymes mainly handles this conversion. Of these, 17β-HSD1 is especially important, as it uses NADPH to turn E1 into E2 (Miller & Auchus, 2019). Higher levels of 17β-HSD1 are found in several estrogen-dependent cancers, such as endometrial and breast cancer, making it a promising target for lowering local estrogen production (Ruan et al., 2023).

Recent advances in structural biology have helped explain how 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) works and how it can be inhibited. High-resolution crystal structures show different enzyme complexes with estrone and $NADP^+$, pointing to a unique substrate inhibition or “dead-end” mechanism involving important active-site residues like His221 (Li et al., 2019). These discoveries are important for designing drugs, especially non-

steroidal inhibitors that block the enzyme and lower estrogen production in hormone-dependent cancers. In addition to lab experiments, computational methods like molecular docking are now essential in the early stages of drug discovery. Molecular docking predicts how molecules bind to proteins, their interactions, and how strong these bonds are, which speeds up screening and lowers costs (Meng et al., 2011). Computer tools also check drug-likeness, absorption, distribution, metabolism, and toxicity (ADMET), helping researchers find promising compounds before testing them in the lab.

Natural products remain important sources of new anticancer drugs because of their diverse structures and biological activity. Diterpenoids, for example, show strong anticancer effects by blocking enzymes and affecting cancer-related signaling pathways. Peronemin, a diterpenoid from Peronema canescens Jack, has shown anticancer properties. Its derivatives, Peronemin A2, A3, and C1, have different structures but share a common core, making them good candidates for early structure-activity relationship studies. Many 17β-HSD1 inhibitors have been developed, but most, especially steroidal ones, have low selectivity, cause hormonal side effects, and have poor pharmacokinetics (Li et al., 2019; Ruan et al., 2023). These problems highlight the need for new non-steroidal inhibitors with better drug-like properties and new chemical structures.

This study aims to investigate the binding interaction of Peronemin A2, A3, and C1 to 17β-HSD1, examining their interaction patterns and pharmacokinetic properties through molecular docking and computational analysis. The goal is to find promising lead compounds for new treatments for estrogen-dependent cancers, especially endometrial cancer. To date, the inhibitory potential of Peronemin derivatives against 17β-HSD1 has not been reported.

METHOD

Materials and Tools

The software used in this study included ChemDraw Professional 15.0, Chem3D 15.0, AutoDock Tools 1.5.6 and AutoDock 4.2, BIOVIA Discovery Studio Visualizer 2021, SwissADME, ProTox-II, and the WAY2DRUG PASS online server. The studied compounds were Peronemin A2, A3, and C1, while 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) served as the molecular target.

Bioactivity Prediction, Physicochemical and Pharmacokinetics Analysis

Compounds from Peronema canescens Jack. were evaluated for anticancer potential using the WAY2DRUG PASS webserver and the CLC Pred 2.0 platform. For physicochemical and pharmacokinetic analysis, the selected compounds were subsequently evaluated for their ADMET properties using SwissADME and Protox II. The SMILES structures of each compound were obtained from the PubChem database or generated using ChemDraw.

Ligand and 3D Protein Structure Preparation

The ligand was first drawn as a 2D structure using ChemDraw Professional 15.0. The geometry was then optimized with Chem3D 15.0. Next, polar hydrogens were added, the ligand was assigned Gasteiger charges, and torsional bonds were defined using AutoDock software. The protein used is 17β-Hydroxysteroid Dehydrogenase 1 (17β-HSD1), as taken from Protein Data Bank (ID: 6MNC). The 3D structure validation was carried out using PROCHECK on the website https://www.ebi.ac.uk/thornton-srv/software/PROCHECK.

Molecular Docking

Molecular docking simulations were performed using AutoDock 1.5.6 with the Lamarckian Genetic Algorithm (LGA), employing a maximum energy evaluation of 2,500,000, and a

population size of 100. The maximum energy evaluation of 2,500,000, a population size of 150, a mutation rate of 0.02, a crossover rate of 0.80, and 100 runs. Docking analysis focused on the lowest inhibition constant (Ki), binding energy (ΔG), and ligand–amino acid interactions. Results were visualized and analyzed with BIOVIA Discovery Studio and BIOVIA Discovery Studio Visualizer 2021, including two-dimensional views of hydrogen bonds and hydrophobic interactions.

RESULTS AND DISCUSSION

Prediction of Bioactive Compounds in Soursop Leaf Extract

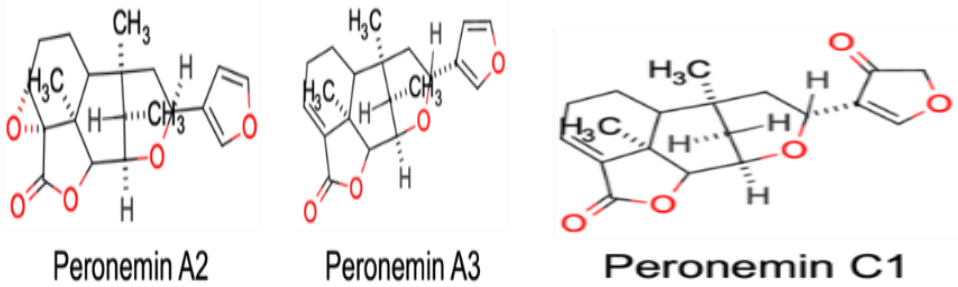

Figure 1. Peronemin A2, A3 and C1

Table 1. PASS online Prediction

Compounds	Pa	Pi	Activity
Peronemin C1	0.916	0.005	Antineoplastic
Peronemin A2	0.890	0.005	Antineoplastic
Peronemin A3	0.870	0.005	Antineoplastic

***Pa : Probability of activity**
Pi : probability of inactivity

Lipinski's Rule of Five

Table 2. Physicochemical Properties

Compounds	MW (g/mol)	HBA	HBD	TPSA (Å²)
Peronemin A2	344.40	5	1	61.20
Peronemin A3	328.40	4	1	48.67
Peronemin C1	344.40	5	1	61.83

***MW: molecular weigth**
HBA: Hydrogen bond acceptor
HBD : Hydrogen bond donor
TPSA: topology polar surface area

Table 3 Pharmacokinetics and druglikeness

Compounds	Lipinski	GI Absorption	BBB	Bioavailability
Peronemin A2	Yes	High	Yes	0.55
Peronemin A3	Yes	High	Yes	0.55
Peronemin C1	Yes	High	Yes	0.55

***GI : gastrointestinal absorption**
BBB: Blood brain barier

PASS online analysis revealed that all three Peronemin derivatives Peronemin C1, A2, and A3 exhibited high Pa values for antineoplastic activity. The term *antineoplastic* is often used synonymously with *anticancer*, as both refer to the ability of a compound to inhibit the proliferation, growth, or spread of neoplastic or cancer cells. Thus, the significant predicted antineoplastic activity of these compounds indicates their strong potential as anticancer agents. Peronemin C1 has a Pa value of 0.916, peronemin A2 has 0.890, and peronemin A3 has 0.870, showing that all three have high antineoplastic activity. Their low Pi values suggest there is little chance of antagonistic effects.

Analysis of pharmacokinetic profiles and predicted physicochemical properties indicates that peronemin A2, A3, and C1 comply with Lipinski's rule, suggesting they could be promising anticancer drug candidates. PASS Online results show that peronemin C1 has the highest Pa value as an antineoplastic agent, while A2 and A3 also have favorable Pa values. Although these results suggest anticancer potential, further studies are necessary to confirm these findings. This includes cytotoxic activity assays, ADME profiling, and toxicity tests in both in vitro and in vivo models to determine if peronemins are suitable as anticancer drug candidates. According to Table 2, each compound has a molecular weight under 500 g/mol, fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, and TPSA values in the optimal range for oral drugs. Meeting Lipinski's rule suggests these compounds are likely to have good membrane permeability and absorption.

Pharmacokinetic predictions in Table 3 show that all compounds have high gastrointestinal absorption and can cross the blood–brain barrier. This means they could be useful for treating cancers in the central nervous system, such as glioma and brain metastases. The compounds have a bioavailability score of 0.55, which is considered optimal for oral drugs. This score indicates that approximately 55% of the dose is expected to reach the bloodstream unchanged, allowing it to act at the target site.

Analysis of the pharmacokinetic profiles and predicted physicochemical properties indicates that peronemin A2, A3, and C1 comply with Lipinski's rule, suggesting their potential as anticancer drug candidates. PASS Online results demonstrate that peronemin C1 exhibits the highest Pa value as an antineoplastic agent compared to peronemin A2 and A3. Both A2 and A3 also exhibit favorable antineoplastic activity, as indicated by their Pa values. While these findings suggest potential anticancer activity, further studies, including cytotoxic activity assays, ADME profiling, and toxicity evaluations in both in vitro and in vivo models, are necessary to confirm the suitability of peronemins as anticancer drug candidates.

Receptor preparation

The receptor preparation was conducted by obtaining the 3D structure of 17β-Hydroxysteroid Dehydrogenase 1 from the Protein Data Bank (https://www.rcsb.org). The receptor was subsequently refined by removing solvent molecules, the native ligand, and any non-standard residues using BIOVIA Discovery Studio to ensure a structurally clean and docking-ready model.

A Ramachandran plot was used to check the structural integrity and stereochemical quality of the 6mnc chain A receptor complex. This plot maps where amino acid residues are found in the protein structure, using the Φ (phi) angle on the x-axis and the ψ (psi) angle on the y-axis. The plot is divided into four sections.

Based on the results of structural validation, 93.2% of the protein is located in the favoured region. Most of the residues are located in the favored region, which indicates that this protein model has good structural quality (Ramadhani et al., 2020). Residues in highly favoured regions indicate that stable secondary structures, such as α-helices and β-sheets, are present. These match the low-energy shapes seen in high-resolution protein structures. Previous studies

found that models with over 90% of residues in favoured regions are usually good quality and suitable for further analysis (Williams et al., 2018; Prisant et al., 2020). This supports using the model for further studies, such as ligand–protein interactions and drug design.

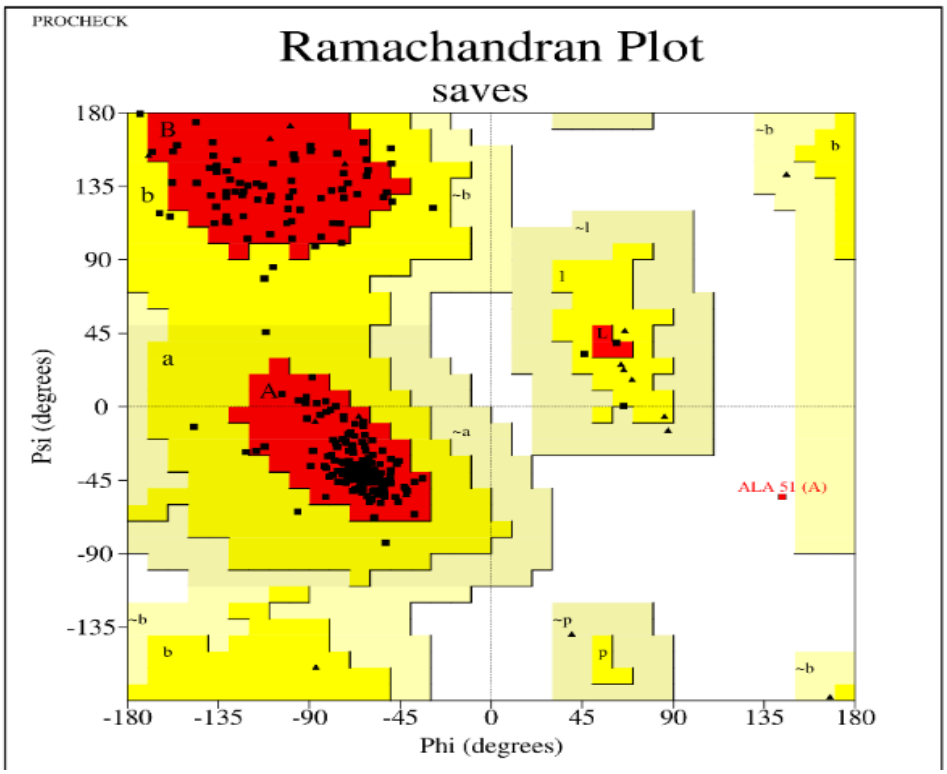

Figure 2. Ramachandran plot 6mnc

After verifying the quality using a Ramachandran plot, the macromolecule (receptor) was prepared for docking by removing water molecules and the native ligand. Next, it was re-optimized in AutoDock Tools 1.5.6 by adding hydrogen ions and Kollman partial charges for scoring calculations during docking and help assess the quality and stability of interactions between the ligand and the receptor. Adding hydrogen ions made the docking environment closer to the body's physiological pH.

Molecular Docking

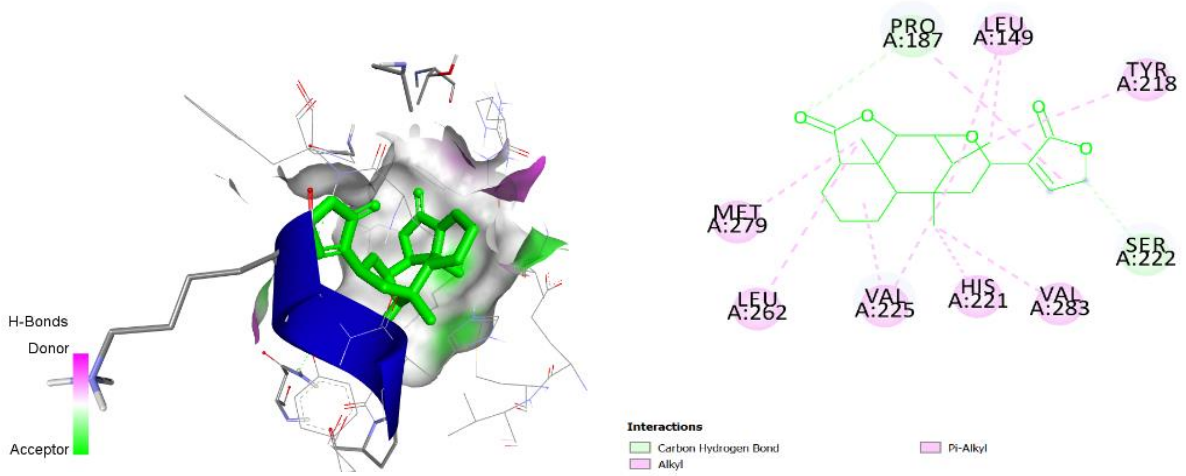

Figure 3. Interacton of Peronemin C1 with 6mnc

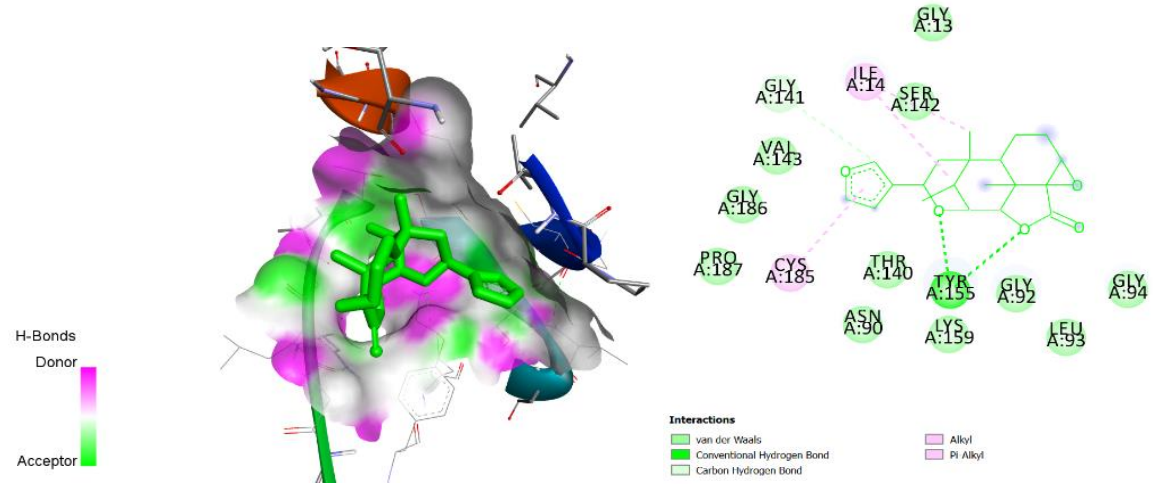

Figure 4. Interacton of Peronemin A2 with 6mnc

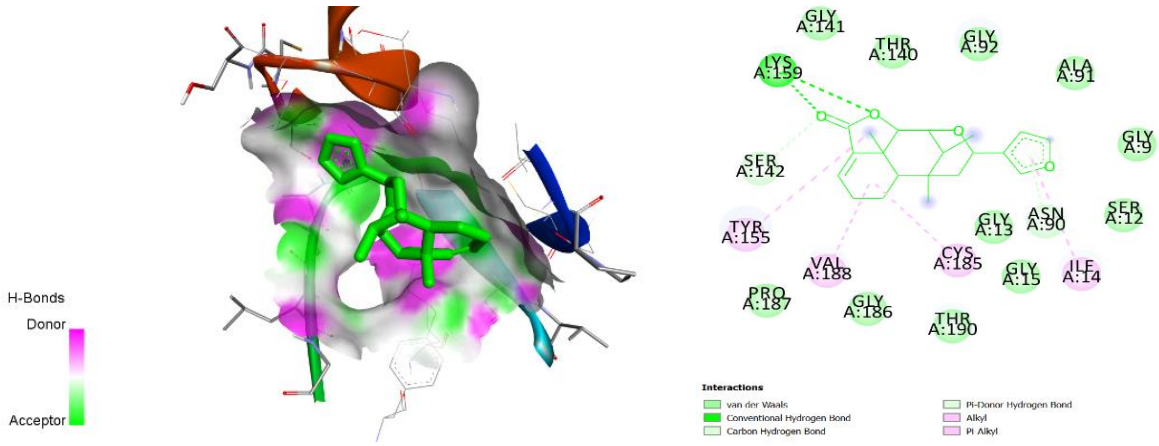

Figure 5. Interacton of Peronemin A3 with 6mnc

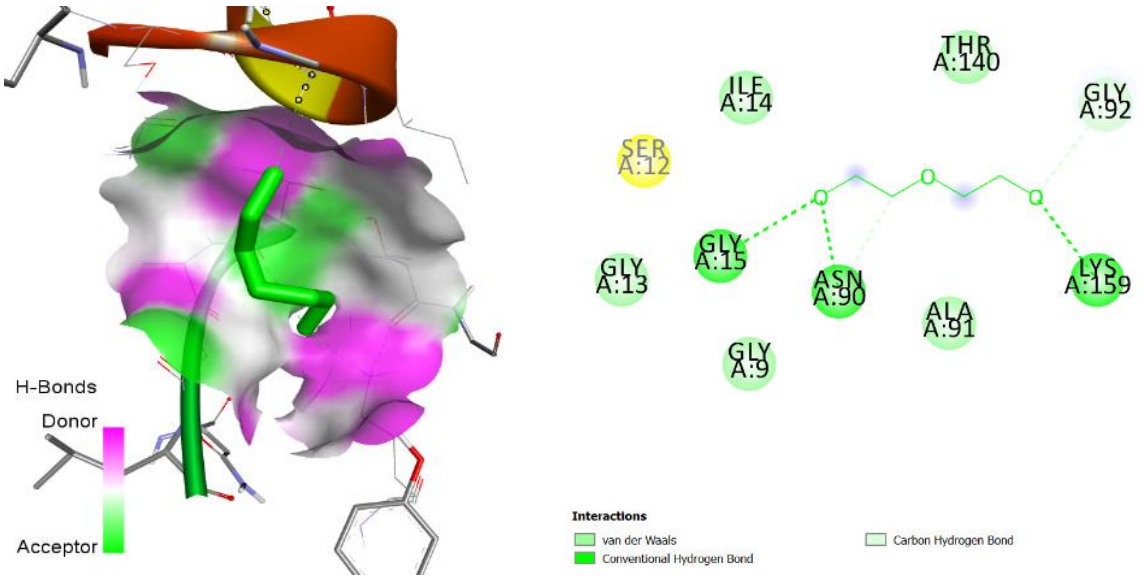

Figure 6. Interacton of Native ligan with 6mnc

The molecular docking results were used to study the interaction between the receptor and ligands. The docking data, saved in PDB format, were analyzed with Discovery Studio Visualizer 2021. Using the Receptor-Ligand Interactions module, we created two-dimensional interaction diagrams. All images were exported and saved for later analysis.

Table 4. Results of molecular docking

Ligand	Binding Free Energy (kcal·mol⁻¹)	Inhibition Constant (μM)	Hydrogen Bonds
C1 : Peronemin C1	-6,56	15,56	-
A2 : Peronemin A2	-5,84	52,58	TYR155
A3 : Peronemin A3	-6,09	34,47	LYS159
N : Native Ligand	-2,35	-	GLY15, ASN90, LYS159

The binding free energies (ΔG) indicated that Peronemin C1 exhibited the strongest binding at −6.56 kcal·mol⁻¹, followed by A3 at −6.09 kcal·mol⁻¹ and A2 at −5.84 kcal·mol⁻¹. The native ligand demonstrated a substantially weaker binding affinity of −2.35 kcal·mol⁻¹. The inhibition constants (Ki) for C1 (15.56 μM), A3 (34.47 μM), and A2 (52.58 μM) corroborate these findings, indicating that all three compounds interact effectively with the enzyme.

In computational drug discovery, binding energies of −6.0 kcal·mol⁻¹ or lower and Ki values in the micromolar range usually suggest early-stage or hit-level inhibitors. Based on these standards, Peronemin C1 and A3 are promising for further study, and A2 also shows good inhibitory potential. The Peronemin derivatives are comparable to those of previously reported 17β-HSD1 inhibitors, including both steroidal and non-steroidal compounds. Prior studies have reported binding free energies for reference inhibitors ranging from approximately −5.5 to −9.0 kcal·mol⁻¹, depending on the compound and methodology employed (Li et al., 2019; Ruan et al., 2023). Within this context, Peronemin C1 (ΔG = −6.56 kcal·mol⁻¹; Ki = 15.56 μM) falls within the range for non-steroidal inhibitors at the early discovery stage, indicating its potential as a lead compound rather than a final therapeutic agent.

The analysis showed that Peronemin A2 formed a hydrogen bond with Tyr155, and Peronemin A3 interacted with Lys159. Both are important residues in the 17β-HSD1 active site. Peronemin C1 did not form hydrogen bonds but had the highest binding affinity, suggesting that hydrophobic and van der Waals interactions mainly stabilized the complex. These interactions are typical for non-steroidal inhibitors, which often bind to specific sub-pockets in steroid-binding enzymes (Salmaso & Moro, 2018; Silva et al., 2019). The native ligand formed hydrogen bonds with Gly15, Asn90, and Lys159, showing a different binding pattern.

The docking results match the PASS predictions, which identified Peronemin C1, A2, and A3 as having strong antineoplastic potential. Their ability to form stable interactions with 17β-HSD1 supports the idea that blocking estrogen biosynthesis may help explain their predicted anticancer effects. Antineoplastic mechanisms often involve changes in key enzyme pathways associated with hormone-dependent cancers, underscoring the significance of these findings (You et al., 2021).

Although these results are promising, it is essential to acknowledge the limitations of in silico methods. Molecular docking provides a static view of ligand-protein interactions and does not fully account for protein flexibility, solvent effects, or entropic factors. Likewise, PASS and ADME predictions originate from computational models, rather than experiments. These findings are preliminary and require further validation through molecular dynamics simulations and laboratory studies. Peronemin derivatives were predicted to cross the blood–brain barrier (BBB). While BBB permeability is not considered a therapeutic advantage for endometrial cancer, which is a peripheral tumor, it may exhibit good membrane permeability and

lipophilicity, facilitating distribution in the body. However, the potential effects on the central nervous system should be investigated in future studies to prevent neurological side effects. Therefore, BBB permeability should be viewed as a property that warrants further experimental study, rather than as a clear therapeutic benefit.

CONCLUSION

This study shows that Peronemin C1, A2, and A3 have strong potential as early-stage inhibitors of 17β-HSD1. PASS predictions indicate strong antineoplastic activity, and physicochemical and ADME tests confirm that they meet drug-likeness standards. The molecular docking results indicate that the compounds bind well to the active site of 17β-HSD1, with Peronemin C1 exhibiting the highest affinity ($\Delta G = -6.56$ kcal/mol^{-}). These results suggest that Peronemin derivatives, especially C1, could be promising lead compounds for developing treatments for estrogen-dependent cancers. More experimental work is needed to confirm their biological activity.

RECOMMENDATIONS

Molecular docking can give useful early insights, but it has limits because it does not account for full protein movements, detailed solvent effects, or changes in entropy during binding. To make predictions more reliable and accurate, it is best to follow up with molecular dynamics (MD) simulations. These methods help provide a more comprehensive understanding of the complex's stability and the ligand's binding to the protein.

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