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Proceeding Paper

Computational Investigations of Arylnaphthalene Lignan Lactones as Anticancer Agents †

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Abstract: Cancer is a significant global health challenge, comprising over 200 distinct types that severely impact life expectancy and account for high mortality rates in the 21st century. This complexity underscores the urgent need for ongoing research, preventive strategies, and improved treatment options. In the quest for new anticancer drug candidates, Arylnaphthalene lignan lactones—natural compounds found in plants like *Phyllanthus* and *Cleistanthus* have gained attention due to their antioxidant, anti-inflammatory, and anticancer properties. An in-silico study was conducted to evaluate their potential against colon cancer by targeting the Epidermal Growth Factor Receptor (EGFR), a key tyrosine kinase. Docking simulations revealed that these compounds exhibit excellent stability within the active site of the EGFR, with docking scores of −8.02 and −7.96 kcal/mol. Further, the derivatives demonstrated significant interactions, including hydrogen bonds with Met 769 and hydrophobic contacts within the EGFR cavity, akin to those formed by the known inhibitor 4-Anilinoquinazoline. ADMET analysis was also performed to evaluate their pharmacokinetic properties and toxicity; further supporting their potential as promising anticancer agents.

Keywords: Arylnaphthalene Lignan Lactones; colon cancer; molecular docking; tyrosine kinase

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1. Introduction

Cancer includes a wide range of diseases characterized by the abnormal growth of cells that divide without control and have the ability to invade and destroy healthy tissues in the body, and can spread throughout the body. It remains the second leading cause of death globally, claiming approximately 9.6 million lives in 2018 [1]. However, survival rates are improving for many cancer types due to advancements in detection, treatment, and prevention strategies. Currently, there are over 200 types of cancer, including prominent forms such as breast, skin, lung, and colon cancer.

The goals of cancer treatment are to cure patients whenever possible and to significantly extend their lifespan with the best possible quality of life. Cancer treatments come in various types, which can be used alone or in combination. The selection of treatments is based on the type of cancer, its stage, and its location. Traditional treatments classified as "local" include surgery and radiotherapy, whereas "systemic" treatments encompass chemotherapy and hormone therapy. In recent years, there has been a resurgence of interest in traditional plant-based medicines, which have demonstrated enduring therapeutic value. These plants contain compounds that may aid in the treatment of cancer. Among these compounds, Arylnaphthalene Lignan Lactones have emerged as notable candidates due to their potential anticancer properties [2]. These natural products, derived from various plant sources, exhibit a range of biological activities, including the ability to inhibit

cancer cell growth and induce apoptosis in malignant cells. Among the various targets for drug development in cancer chemotherapy, the EGFR has garnered attention due to its critical role in cancer progression [3,4].

In the other hand, molecular modeling is a modern approach that enhances our understanding of chemical and biological phenomena, including molecular docking and property prediction [5]. These techniques are particularly useful for predicting interactions between ligands and their target proteins. Molecular docking, in particular, offers insights into how ligands engage with protein receptors, influencing relevant biological mechanisms [6].

In this study, we investigated two natural arylnaphthalene lignan lactones using molecular docking to assess their potential to inhibit the EGFR enzyme. ADMET analysis was also conducted to evaluate their pharmacokinetic properties. This research aims to contribute to the development of novel cancer therapies derived from natural sources.

2. Materials and Methods

2.1. Molecular Docking

The human EGFR complexed with 4-Anilinoquinazoline (PDB ID: 1M17) was obtained from the Protein Data Bank [7], and was prepared with Protein Preparation Wizard tool implemented in Schrodinger suite, assigning bond orders, adding hydrogens and optimizing H bonding networks. The three-dimensional structures of the derivatives were constructed using Maestro software, and prepared with Ligprep using Optimized Potentials for Liquid Simulation OPLS3e force field with a convergence of heavy atoms of 0.30 Å [8].

2.2. ADMET Prediction

To predict the pharmacokinetic properties of compounds through ADMET analysis, we utilized several reliable online servers, including SwissADME and Molsoft [9], which offer free access to predictive models. These tools streamline the drug discovery process by reducing time and costs while enhancing the identification of viable drug candidates for clinical applications."

3. Results and Discussion

3.1. Molecular Docking

To understand the interactions between the EGFR active site and the arylnaphthalene lignan lactone compounds (**1**, **2**), we performed molecular docking simulation. The accuracy of the docking protocol was evaluated by re-docking the reference ligand (**4-Anilinoquinazoline**) into the active site of EGFR enzyme. The docked reference ligand and the co-crystallized one occupied nearly the same position in the receptor (RMSD = 0.40 Å), confirming the validity of our docking protocol, which employed the extra precision (XP) scoring function. The results of this study, including the estimated scores of the docked positions, are presented in Table 1. The compounds **1** and **2** demonstrated excellent stability (−8.02 and −7.96 kcal/mol) within the binding cavity, with slip scores higher than that of the reference ligand (−7.85 kcal/mol).

Table 1. Docking score (kcal/mol) of arylnaphthalene lignan lactone compounds (**1**, **2**), and the reference ligand (4-Anilinoquinazoline) against EGFR enzyme.

Compound	Docking Score (kcal/mol)
1: Podophyllotoxin	−8.02
2: 2′,3′,4′,5′-tetramethylcleistanthin	−7.96
4-Anilinoquinazoline	−7.58

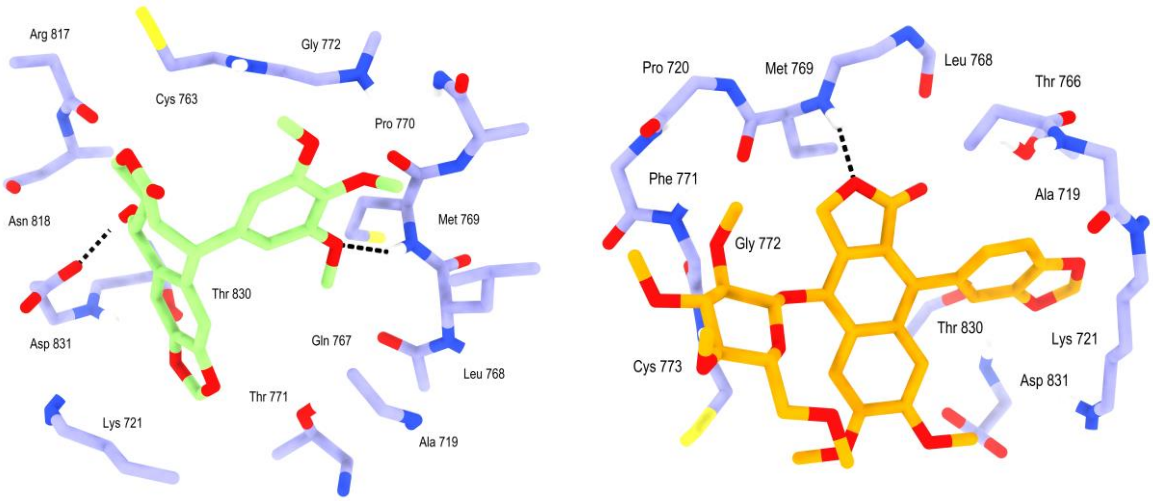
Molecular docking results revealed that interactions within the active site of the EGFR enzyme were primarily driven by hydrogen bonds and hydrophobic forces. These findings are crucial in determining the binding affinity and specificity of arylnaphthalene lignan lactone compounds within the EGFR binding pocket.

The reference ligand formed a key hydrogen bond between the nitrogen atom of the quinazoline fragment and the Met 769 residue, which plays a significant role in EGFR inhibition. Additionally, the reference ligand engaged in hydrophobic interactions with several residues, including Phe 999, Phe 771, Thr 830, Lys 721, Lys 704, Asp 831, Glu 738, and Pro 770, creating strong attractions with the aromatic rings of the ligand.

Podophyllotoxin formed two hydrogen bonds in the inhibition of tyrosine kinase. The first bond occurs between the hydroxyl (OH) group and Asp 831, while the second is between the methoxy oxygen and Met769.

Additionally, Podophyllotoxin engages in significant hydrophobic interactions through its two aromatic rings and the heterocycle, interacting with Pro 770, Cys 773, Met 769, Leu 820, and Met 742, all residues are located within the active pocket of the EGFR enzyme. Furthermore, the Podophyllotoxin is stabilized by two π-cation interactions with Lys 721.

Compound **2** formed a hydrogen bond with Met 769 and exhibited hydrophobic interactions between its aromatic ring and several residues, including Pro 720, Phe 771, Cys 773, Thr 766, Thr 830, Lys 721, and Asp 831. Additionally, it established through a π-cation interaction with Lys 721 (Figure 1). Both compounds **1** and **2** demonstrated superior inhibition of the EGFR enzyme compared to the reference ligand. The hydroxyl groups, along with the heterocycles and aromatic rings, played a crucial role in achieving this result.



1: Podophyllotoxin **2: 2′,3′,4′,5′-tetramethylcleistanthin**

Figure 1. 3D binding interactions of compounds **1** and **2** after docking calculations in the active site of EGFR enzyme. The amino acid residues were shown as purple stick model and H-bonds were shown as black lines.

3.2. ADMET Study

The study of ADMET parameters (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is vital in drug development, directly impacting a compound's efficacy and safety. These parameters encompass the drug's ability to be absorbed into the bloodstream, its distribution within tissues, the metabolic processes it undergoes, its elimination from the body, and assessments of potential toxicity.

A key advancement in this area is Lipinski's "Rule of Five," which provides criteria for determining a compound's drug-likeness and oral bioavailability, including molecular weight, LogP, and hydrogen bond counts.

The pharmacokinetic parameters of the studied compounds are summarized in Table 2. Compound **1** has a molecular weight of 414.41 g/mol (<500), indicating that it is a low molecular weight drug.

The number of hydrogen bond acceptors and donors in compound **1** falls within Lipinski's limits, with 8 hydrogen bond acceptors (<10) and 1 hydrogen bond donor (<5). Additionally, compounds **1** and **2** exhibit good lipophilicity, as indicated by their iLogp values of 2.83 and 4.65, respectively, both of which are less than 5.

The Topological Polar Surface Area (TPSA) is essential for predicting the bioavailability of drug molecules and indicates their capacity to form hydrogen bonds. The TPSA of compounds **1** and **2** was found to be in the range of 92.68–118.60 Å^2, both below the threshold of 140 Å^2. Furthermore, the ADME study revealed that compound **1** does not violate Lipinski's Rule of Five.

The drug-likeness score (DLS) helps determine whether a chemical compound is a suitable candidate for medication. Compound **1**, which exhibited the highest stability in the active site of the EGFR enzyme (docking score: −8.02), demonstrated a favorable drug-likeness score (DLS: 0.11), making it suitable for oral administration. In contrast, compound **2** showed a DLS score of −0.42. (Figure 2)

Table 2. Pharmacokinetic parameters and DLS of arylnaphthalene lignan lactone compounds (**1**, **2**) and 4-Anilinoquinazoline.

Property	Entry 1	Entry 2	4-Anilinoquinazoline
Molecular (g/mole)	414.41	598.59	393.44
Rotatable Bonds	4	10	10
H-bond acceptor	8	12	6
H-bond donor	1	0	1
Log Po/WiLogP	2.83	4.65	3.67
Log S ESOL	−3.71	−5.31	−4.11
GI	High	High	High
Bioavailability Score	0.55	0.17	0.55
TPSA (Å^2)	92.68	118.60	74.73
BBB	No	No	Yes
Log Kp (cm/s)	−7.40	−7.53	−6.35
Violations	0	2	0
DLS	0.11	−0.42	0.90

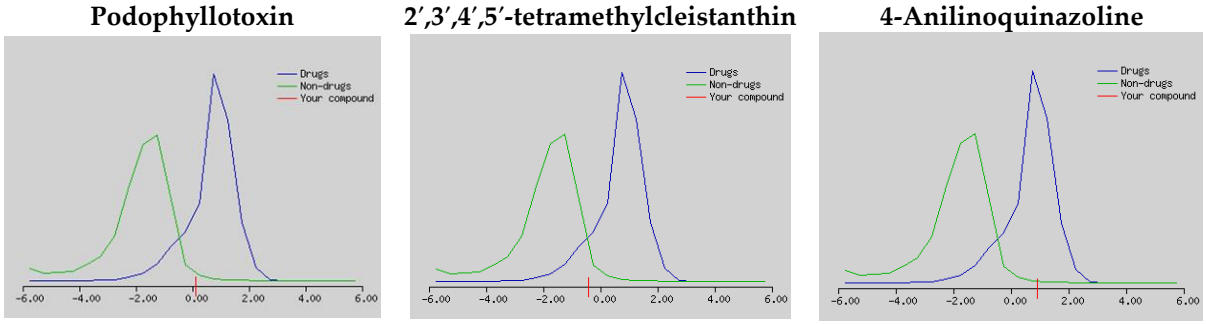


Figure 2. Estimation curve of the DLS of studied compounds and 4-Anilinoquinazoline.

4. Conclusions

The results of the molecular docking study demonstrated that the two natural arylnaphthalene lignan lactones interact with EGFR effectively. Compounds **1** and **2** exhibited better docking scores compared to the reference ligand, with scores of −8.02 and −7.96 kcal/mol, respectively. We also investigate the ADMET profiles of compounds **1** and **2**, evaluating them against the Lipinski rule of five to assess their bioactivity, molecular

descriptors, and drug-likeness. The results indicate that compounds exhibit favorable oral bioavailability, highlighting their potential as viable candidates for further pharmaceutical development.

This study identified that compounds are a promising new template for the development of EGFR inhibitors.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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