

Molecular Docking and ADME-T Analysis of Cytotoxic Quinoline Derivatives: Potential Applications for the Treatment of Skin Cancer [†]

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Abstract

Recent advances in computational drug discovery have significantly improved the search for effective treatments for skin cancer, where molecular docking and pharmacokinetics play an important role in identifying new drug-like compounds. This study explores the inhibitory potential of pyrrolopyrazole (4BKY), an enzyme linked to skin cancer progression, using 62 cytotoxic quinoline derivatives. Among these, Ligand 1 and Ligand 4 demonstrated the strongest binding affinities, with docking scores of -8.9519 kcal/mol and -8.7030 kcal/mol, respectively. Their enhanced stability and interaction with key residues GLU 87 and CYS 89 suggest promising inhibitory properties. In addition to docking analysis, these compounds underwent ADMET (Absorption, Distribution, Metabolism, and Excretion) analysis profiling using SWISSADME, pkCSM, to assess their pharmacokinetic. Additionally, toxicity assessment was performed using the ProTox-II web server (https://tox-new.charite.de/protox_II/), predicting mutagenicity, carcinogenicity, immunotoxicity, and hepatic toxicity. Findings indicate favorable drug-likeness, efficient synthesis, and compliance with Lipinski's rule of five, supporting their viability as targeted skin cancer therapeutics. Based on these results, Ligand 1 and Ligand 4 emerge as strong candidates for further research and development in oncology. Future studies will focus on experimental validation and clinical trials to confirm their effectiveness and safety, potentially paving the way for innovative skin cancer treatment strategies involving quinoline-based compounds.

Keywords: docking; pyrrolopyrazole; cytotoxic quinolines; MOE

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1. Introduction

Skin cancer is a type of cancer that originates in the skin cells and is the most common form of cancer globally. It develops when abnormal skin cells grow uncontrollably, often due to damage caused by ultraviolet (UV) radiation from the sun or tanning beds. There are several types of skin cancer, the most common being basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma and squamous cell carcinoma are often referred to as non-melanoma skin cancers and are usually less aggressive. Melanoma, however, is more dangerous as it tends to spread to other parts of the body if not detected

and treated early. Risk factors for skin cancer include prolonged exposure to UV radiation, fair skin, a history of sunburns, and a family history of skin cancer. Preventive measures such as using sunscreen, wearing protective clothing, and avoiding excessive sun exposure can significantly reduce the risk of developing skin cancer. Early detection through regular skin examinations is crucial for successful treatment outcomes [1].

The drug discovery process is a complex and multifaceted endeavor that requires a deep understanding of molecular interactions, pharmacokinetic properties, and toxicity profiles to identify potential therapeutic candidates. Quinoline-4-carboxylic acids represent a class of compounds with significant biological activity, including antineoplastic properties. Their versatility and ability to be chemically modified make them attractive for drug discovery endeavors. Advancements in computational chemistry have provided researchers with powerful tools for drug design. MOE (Molecular Operating Environment) [2] is widely used for molecular docking studies, allowing researchers to predict how small molecules, like quinoline-4-carboxylic acids, interact with target proteins. SwissADME [3] offers comprehensive insights into ADME (Absorption, Distribution, Metabolism, Excretion) properties, crucial for understanding the pharmacokinetic profile of potential drug candidates. ProTox-II [4] aids in predicting the toxicity of compounds, helping to identify candidates with the lowest risk of adverse effects. In this study, we designed 65 quinoline-4-carboxylic acid derivatives and evaluated their potential as drug candidates through a series of computational analyses. Our aim was to identify molecules with strong binding affinity, favorable ADME profiles, and low toxicity, thereby streamlining the drug discovery process.

Quinoline-4-carboxylic acids represent a significant class of compounds with a broad range of biological activities. The quinoline ring system, a bicyclic structure comprising a benzene ring fused to a pyridine ring, is known for its versatility in medicinal chemistry. The carboxylic acid group at the 4-position enhances the compound's ability to form hydrogen bonds, crucial for its interaction with biological targets. These compounds have been extensively studied for their antimicrobial, antiviral, anti-inflammatory, and anticancer properties. Modifications at various positions on the quinoline ring can lead to derivatives with improved potency, selectivity, and pharmacokinetic properties [5,6]. The structure-activity relationship (SAR) of quinoline-4-carboxylic acids indicates that the position and nature of substituents on the quinoline ring significantly influence biological activity. For instance, halogenated derivatives often show enhanced anticancer activity due to increased lipophilicity and improved membrane permeability. Additionally, electron-donating groups can enhance the interaction with nucleophilic sites on target proteins, further increasing the compound's efficacy.

Vero cells are a line of cells derived from the kidney of an African green monkey and are commonly used in cell culture. These cells are extensively utilized in virology, toxicology, and vaccine production due to their consistent growth and susceptibility to various viruses. In this study, Vero cells were used as a model system to investigate the cytotoxic effects of quinoline-4-carboxylic acid derivatives, providing insights into their potential toxicity and therapeutic efficacy. The application of Vero cells in toxicity testing is crucial for ensuring the safety of new compounds intended for therapeutic use. These cells provide a robust model for studying the mechanisms of drug action and toxicity at the cellular level. In addition to their use in cytotoxicity assays, Vero cells can be employed to study viral replication, vaccine efficacy, and other applications in biomedical research [7].

2. Materials and Methods

2.1. Computational Tools

Throughout this investigation, we used a Dell system equipped with a dual CPU @2.60 GHz, Intel® Core i5-1145G7, and 16 GB RAM. Windows 10 Professional was used as the Computer Operating System. Computational studies, including docking molecular, simulation and free energy calculations, were conducted using Moe version 17.5 (Moe 2017), while ChemDraw Ultra 16.0 was used for drawing the molecular structures. AD-MET predictions were analyzed using Swiss ADME [3] and ProTox II [4] online software.

- MOE (Molecular Operating Environment)

MOE is a comprehensive suite for molecular modeling and simulations, offering tools for docking, structure-based design. It facilitates the prediction and analysis of molecular interactions, providing a detailed view of how ligands interact with their protein targets. MOE's advanced features include flexible receptor docking, which allows for the consideration of protein flexibility during the docking process, enhancing the accuracy of the predictions [8].

- ChemDraw Ultra 16.0

ChemDraw Ultra 16.0 is a powerful and user-friendly software used for creating professional representations of organic, organometallic, polymeric, and bio-polymer materials [9]. <https://perkinelmer-chemdraw-professional.software.informer.com/16.0/>.

2.1.1. Data Set and Ligand Preparation

A set of 62 cytotoxic quinolines derivative inhibitors against the Vero cell line. The 2D structures of the cytotoxic quinolines derivatives were drawn using ChemDraw Ultra 16.0. was then used to convert the ligands into three-dimensional structures and minimize them. Atomic charges were determined, We used MOE software [2] for ligand optimization by the AM1 semi-empirical method [10].

2.1.2. Protein Preparation

The crystal structure of unphosphorylated Maternal Embryonic Leucine zipper Kinase (MELK) in complex with a pyrrolopyrazole inhibitor was retrieved from the Protein Data Bank (PDB ID: 4BKY, resolution 1.83 Å) [11]. Prior to docking, the protein was prepared using MOE software: all water molecules, cofactors, and ions were removed; protonation states were adjusted to physiological pH; ligands were treated as flexible, while the enzyme was modeled as a rigid body. This simplification of the enzyme structure is a critical step in molecular modeling, allowing for faster and more efficient calculations. The resulting model provides a reliable framework for evaluating ligand interactions within the active site.

2.2. Molecular Docking

Protein–ligand interactions play a key role in the organization of biological systems. This opens the way for the prediction of their 3D structure, which is a major challenge for the pharmaceutical industry [12]. Molecular docking is one of the most widely used in silico methods. Its purpose is to understand the interactions between a ligand and a receptor to form a protein–ligand complex by studying all the mechanisms and interactions involved in the formation of molecular complexes [13].

Docking essentially comprises two complementary sections:

Docking (selection step): placing the ligand in the active site of the protein and sampling the possible conformations, positions, and orientations, retaining only those that represent the most favorable interaction modes [14].

Scoring (ranking step): estimating the interaction strength and binding affinity between two molecules after docking and assigning a score to the poses obtained [15].

In this context, we conducted a study of the interactions between the enzyme 4BKY and derivatives of cytotoxic quinolines using MOE software [2].

In this context, we conducted a study of the interactions between the enzyme 4BKY and derivatives of cytotoxic quinolines using the MOE software. In our study, we downloaded the protein structure (Figure 2) available in the PDB (ID: 4BKY) [11], co-crystallized with the pyrrolopyrazole inhibitor of the formula (3'-{[(4-bromo-1-methyl-1H-pyrrol-2-yl)carbonyl]amino}-N-[(1S)-1-phenyl-2-(pyrrolidin-1-yl)ethyl]-1',4'-dihydro-5'H-spiro[cyclopropane-1,6'-pyrrolo[3,4-c]pyrazole]-5'-carboxamide: C26 H30 Br N7 O2) using the MOE software [2]. During molecular docking, the inhibitors are oriented towards the active site containing pyrrolopyrazole. The scoring of poses is obtained after 10 search cycles. This result allows for ranking the best poses based on their interaction energies obtained by the "E score". RMSD is another factor that can be generated from a conformational search to explore the possible conformational space efficiently and exhaustively.

2.3. ADME-T Property Evaluation and Toxicity Assessment

To assess the pharmacokinetic behavior of the selected compounds, their 3D structures were submitted to the SwissADME web tool. The evaluation encompassed key ADME parameters, including gastrointestinal absorption, blood–brain barrier permeability, and potential interactions with cytochrome P450 isoenzymes. These data enabled the prediction of each molecule's pharmacokinetic profile, facilitating the identification of candidates with favorable drug-like properties for further development.

For toxicity prediction, the molecular structures were analyzed using the ProTox-II platform. This tool provided estimates of acute toxicity levels and highlighted possible adverse effects on major organs and biological systems. Compounds exhibiting the lowest predicted toxicity and acceptable safety margins were prioritized for subsequent investigation.

3. Results and Discussion

3.1. Molecular Docking

Molecular docking analysis was performed to assess the binding affinity of selected quinoline derivatives with the 4BKY protein, a target associated with skin cancer. As presented in Table 1, ligand L_1 exhibited the most favorable binding energy (−8.95 kcal/mol), indicating a strong and stable interaction with the active site residues. Ligands L_3 and L_4 also showed comparable binding energies, suggesting promising inhibitory potential. Notably, L_4 achieved the lowest RMSD_refine value (0.7583 Å), reflecting high spatial accuracy and reliable docking conformation (Figure 1).

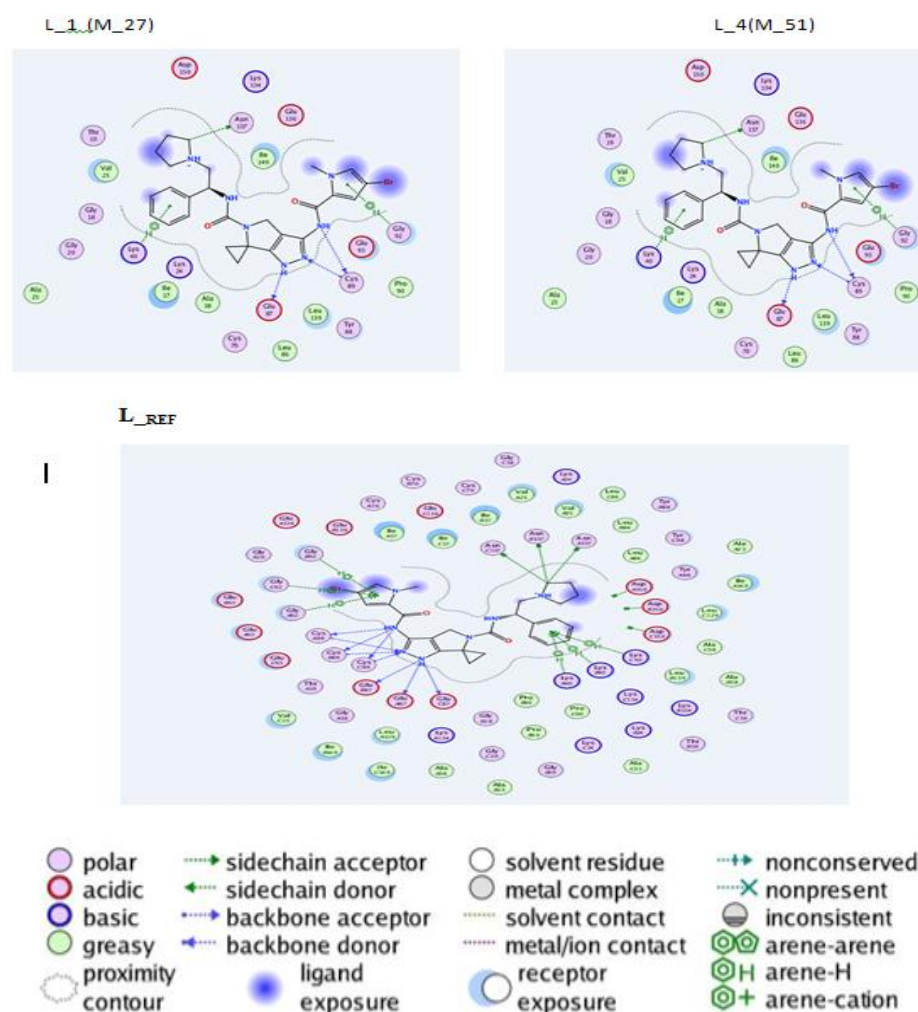


Figure 1. 2D interactions and 3D illustration of 4BKY-active site and L₁, L₄.

All tested ligands interacted consistently with key amino acids—GLU87, CYS89, ASN137, LYS40, and GLY92—through hydrogen bonding and π -H interactions, with bond distances ranging from 2.79 to 4.73 Å. The reference compound (L_REF) recorded a binding energy of −8.55 kcal/mol and formed an additional ionic interaction with ASP150, serving as a benchmark for comparison. In contrast, ligand L₂₆ displayed the weakest binding affinity (−6.74 kcal/mol), which may limit its therapeutic relevance in the context of skin cancer, as detailed in Table 1.

Table 1. Molecular Docking Interactions with 4BKY Protein.

Ligands	Binding Energy (kcal/mol)	RMSD_refine (Å)	Interacting Amino Acid	Bond Type	Bond Distance (Å)
L ₁	−8.9519	1.2586	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₃	−8.7152	1.3524	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₄	−8.7030	0.7583	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₆	−8.3433	1.1752	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₈	−8.1755	1.2124	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₁₅	−7.5312	1.0356	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₂₀	−7.2856	0.8678	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73
L ₂₆	−6.7414	0.9157	GLU87, CYS89, ASN137, LYS40, GLY92	H-donor, H-acceptor, π -H	2.79–4.73

L_REF	-8.5579	1.5611	GLU87, CYS89, ASN137, LYS40, GLY92, ASP150	H-donor, H-acceptor, π -H, ionic	2.79–4.73 (ionic: 3.79)
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3.2. ADME-Tox Evaluation of Selected Compounds

The ADME–Tox profile of compounds L1, L4, and L_REF reveals that L1 and L4 possess favorable pharmacokinetic properties, despite minor deviations from ideal drug-likeness criteria. Both compounds comply with Lipinski’s Rule of Five and exhibit high gastrointestinal absorption, indicating good oral bioavailability. L4 stands out with the lowest molecular weight (416.47 g/mol) and the best synthetic accessibility score (3.37), suggesting it is easier to synthesize and optimize. However, both L1 and L4 show elevated Log P values, which may affect solubility and distribution. Toxicity alerts such as carcinogenicity, hepatotoxicity, immunotoxicity, and mutagenicity were observed in L1 and L4, requiring further structural refinement. In contrast, L_REF demonstrates a safer toxicity profile but shows blood–brain barrier permeability, which may lead to off-target CNS effects. Overall, L1 and L4 remain promising candidates due to their strong docking performance and acceptable ADME properties, provided that toxicity risks are addressed in future optimization steps.

Table 2. ADME-T Evaluation of Candidate Ligands Targeting 4BKY Protein.

Properties	Selected Marine Compounds			General Acceptable Criteria
	L1	L4	LREF	
Molecular weight	472.53	416.47	552.47	≤500 g/mol *
Hydrogen bond acceptors	6	5	4	≤10 *
Hydrogen bond donors	1	1	3	≤5 *
Log P value	5.04	4.73	1.98	≤4.15 *
Rotatable Bond	9	7	9	≤10 **
TPSA (Å ²)	71.07	61.84	98.29	≤140 Å ² **
Lipinski Rule of five	Yes	Yes	Yes	Yes
Veber Rule Violations	Yes	Yes	Yes	Yes
Ghose	No	No	No	MW: 160–480, Log P: −0.4 to +5.6, atoms: 20–70
PAINS Alert	0	0	0	0
Leadlikeness	No	No	No	MW ≤ 350, Log P ≤ 3, ≤3 H-bond d/a
Bioavailability Score	0.55	0.55	0.55	The higher, the better
GI absorption	High	High	High	High preferred
Blood Brain Barrier Permeability	No	No	Yes	No
Synthetic accessibility	3.70	3.37	4.89	The lesser, the better
Cytochrome CYP1A2	No	Yes	No	No
CYP3A4 inhibitor	No	Yes	No	No
CYP2D6 inhibitor	Yes	Yes	No	No
Log K_p (cm/s)	−5.00	−4.89	−8.05	less permeable (acceptable: −6 to −2)
hERG I inhibitor	No	No	No	Non-inhibitor
hERG II inhibitor	Yes	Yes	Yes	Preferably No
Ames Toxicity	No	No	No	Non-AMES Toxic
Skin Sensitisation	No	No	No	No
Oral Rat Acute Toxicity (LD50)	2.871	2.988	2.832	>2.0 mol/kg
Carcinogenicity	Yes	Yes	Yes	Non-Carcinogen
Hepatotoxicity	Yes	Yes	No	Non-Hepatotoxicity
Immunotoxicity	Yes	Yes	No	No
Mutagenicity	Yes	Yes	Yes	No
Cytotoxicity	No	No	No	No

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