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Investigation of Pharmacokinetics, Molecular Docking, and Dynamics of Xanthomicrol-Derived Compounds Against Various Mutated Proteins in Lung Cancer Cells

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Abstract

Lung cancer remains one of the leading causes of global mortality, primarily due to drug resistance and the adverse effects of conventional therapies. Therefore, the discovery of novel compounds that are both effective and safe is crucial for the development of alternative treatments. This study employed a computational approach to evaluate the therapeutic potential of Xanthomicrol-derived compounds targeting mutated proteins commonly associated with lung cancer. Four derivatives (u1a, u2a, u3a, and u4a) were assessed using pharmacokinetic (ADMET) predictions, molecular docking, and molecular dynamics simulations against ten mutated lung cancer-related proteins (1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k). ADMET predictions revealed that all compounds had good gastrointestinal absorption, did not cross the blood–brain barrier, and exhibited favourable safety profiles. Among them, compound u3a showed the highest binding affinity toward seven mutated proteins, with docking scores ranging from -5.9 to -9.4 kcal/mol. Molecular dynamics simulations further supported the stability of u3a protein interactions, indicated by low RMSF values and an optimal radius of gyration. These results suggest that u3a is a promising candidate for targeted lung cancer therapy and warrants further experimental validation.

Keywords: Lung cancer protein mutations, Molecular docking, Molecular dynamics, Pharmacokinetics, Xanthomicrol derivatives

INTRODUCTION

Lung cancer represents a highly significant global health challenge. Among Asian countries, Indonesia ranks 23rd, with reported rates of 19.4 incidents and 10.9 mortalities per 100,000 individuals, predominantly affecting males (KEMENKES, 2024). Traditional lung cancer treatments, such as surgery, chemotherapy, radiation, and hormone therapy, often result in severe side effects on healthy tissues and continue to face persistent issues with drug resistance (Dipiro, et al., 2008; Frimayanti, Djohari, & Khusnah, 2021). Consequently, there is growing interest in identifying alternative compounds that offer low toxicity while maintaining high therapeutic efficacy in the development of new anticancer agents. Recent evidence underscores the importance of natural compounds in cancer prevention and treatment, with methoxyflavone standing out due to its natural occurrence in various plants, low toxicity, and minimal allergenic potential (Hui, et al., 2013; Attari, Keighobadi, Abdollahi, Arefian, & Reza, 2021). However, research on methoxyflavone derivatives remains limited, especially regarding their interactions with target proteins involved in cancer cell signaling pathways (Turkmenoglu, et al., 2015).

Xanthomicrol, a methoxyflavone distinguished by its methoxy group (-OCH_3), is a notable active compound in the extracts of *Dracocephalum kotschyi Boiss*, *Siparuna guianensis*, and *Clinopodium douglasii*. These plants, widely used in traditional Iranian herbal medicine, are known for their bioactive properties with potential anticancer effects (Poormolaie et al., 2023). Studies on Xanthomicrol derivatives have revealed anti-apoptotic and anti-proliferative effects across various cancer types, including lung and liver cancers (Nguyen et al.,

2020), breast cancer (Attari et al., 2020), and cervical cancer (Nieddu et al., 2023). Therefore, Xanthomicrol is a promising anticancer therapy candidate (Poormolaie et al., 2023).

In computational chemistry, molecular docking serves as a powerful technique to enhance the efficiency and precision of drug design. It has become an essential component of modern drug discovery in pharmaceutical, chemical, and biomedical fields. By reducing the time and cost associated with synthesis and biological testing, molecular docking offers a cost-effective strategy for early-stage drug screening (Siswandono, 2000; Dinata et al., 2014). It enables the prediction of drug target interactions by assessing binding affinities and estimating biological activities. Additionally, it provides valuable insight into the spatial orientation of ligands within the active site of target proteins (Pratama, Rifai, & Marzuki, 2017). Stronger interactions, indicated by lower binding affinity values, suggest higher biological activity and therapeutic potential (Ningrat, 2022). In this context, the present study offers a new perspective by focusing on Xanthomicrol derivatives as potential inhibitors specifically targeting a set of mutated proteins associated with lung cancer an approach that has not been extensively explored in previous computational studies.

Several proteins harboring clinically relevant mutations in lung cancer were analyzed in this study, represented by the following PDB codes: 1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k. These mutations are associated with key molecular pathways involved in lung cancer progression. For instance, 1nq1 is linked to impaired thyroid hormone binding (Huber et al., 2003), while 1x2j reflects oxidative stress regulation through Keap1-Nrf2 dysfunction (Padmanabhan et al., 2006). Mutation in 4b3z results in the loss of the metastasis-inhibitory function of CRMP-1 (Liu et al., 2015), and 4j97 is associated with enhanced FGFR2 signaling activity (Chen et al., 2013). Additionally, STK40 (5l2q) is implicated in the dysregulation of tumor protein degradation (Durzynska et al., 2017), whereas 6pwa, a HEK293-derived system, is widely used for gene therapy due to its high transfection efficiency (Rumachik et al., 2020). The structure 6usx represents the KRAS G12C inhibitor, a novel class of targeted therapies (Fell et al., 2020). Meanwhile, 7pgk and 7pgl are associated with Hedgehog pathway regulation via HHIP (Griffiths et al., 2021), and 7r7k corresponds to lorlatinib, a third-generation ALK inhibitor used in the treatment of ALK-mutated non-small cell lung cancer (NSCLC). These structures reflect diverse therapeutic targets and pathways, highlighting their relevance in the development of precision medicine strategies for NSCLC (Shiba et al., 2022).

Several previous studies have highlighted the anticancer potential of natural compounds, including Xanthomicrol and its derivatives. Nguyen et al. (2020) investigated bioactive compounds from *Adenosma bracteosum* (Bonati), demonstrating that Xanthomicrol-based derivatives, particularly 5,4′-dihydroxy-6,7,8,3′-tetramethoxyflavone (AB_2), exhibited strong antiproliferative effects against lung (NCI-H460) and liver (HepG2) cancer cells, with IC_{50} values of 4.57 ± 0.32 μg/mL and 5.67 ± 0.09 μg/mL, respectively. AB2 also increased intracellular ROS levels and disrupted mitochondrial membrane potential, triggering caspase-3 activation. In a study by Lin et al. (2022), the effects of Xanthomicrol on in vivo liver cancer models were investigated using Huh7 cells. Results demonstrated that Xanthomicrol effectively suppresses metastasis by reducing the Mu-opioid receptor (MOR) activity, thereby limiting the migratory and invasive capabilities of Huh7 cells. Similarly, research by Nieddu et al. (2023) examined Xanthomicrol's impact on HeLa cancer cells, finding that after 24 hours of incubation, there was a marked decrease in cell viability and significant changes in lipid profile, suggesting that Xanthomicrol modulates lipid metabolism in HeLa cells, affecting their growth and function. In another study, Muttaqin, Ismail, and Muhammad (2019) performed molecular docking on nafridine derivatives targeting protein kinase 2-α in leukemia, identifying the top ten ligands with low values for Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF), indicating stable ligand-to-protein interactions. ADMET toxicity assessments revealed that these ligands presented lower toxicity risks, underscoring their promise as drug candidates. Furthermore, a study by Rochlani et al. (2024) reported that three limonoid compounds derived from citrus Obacunone, Limonin, and Nomilin exhibited favorable molecular interaction profiles. Among them, Obacunone demonstrated the most promising results across all analyses conducted, indicating its strong potential as an anticancer agent. These findings are supported by previous studies emphasizing the therapeutic potential of citrus-derived bioactive compounds (Nguyen et al., 2020; Lin et al., 2022; Nieddu et al., 2023; Muttaqin, Ismail, & Muhammad, 2019; Rochlani et al., 2024).

This study aims to identify Xanthomicrol-derived compounds (u1a, u2a, u3a, and u4a) with the potential to inhibit mutated proteins involved in lung cancer

progression, represented by PDB codes 1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k. To achieve this, a computational chemistry approach was employed, integrating pharmacokinetic (ADMET) profiling, molecular docking, and molecular dynamics simulations. The goal of this investigation is to discover promising lead compounds with favorable pharmacological characteristics and strong binding affinities, which could serve as potential candidates for the development of more effective and safer therapeutic strategies against lung cancer.

METHODOLOGY

Materials

This research utilized computational techniques. The materials involved Xanthomicrol and its derivatives (Figure 1), obtained from the literature (Nguyen et al., 2020), as well as protein structures relevant to lung cancer cells (1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k) sourced out of the Protein Data Bank (PDB). This investigation used these protein structures as the dependent variables.

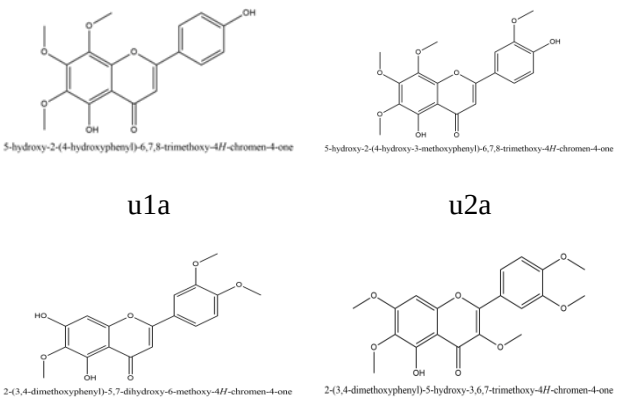


Figure 1. The structure of synthesized Xanthomicrol derivative compounds.

Instrumentals

This research was conducted using a computer system featuring an Intel i5 processor from the 8th generation, a 500GB hard drive, and 4GB of RAM. Tools applied in the study included HyperChem® (v8.0.7) using AM1 semi-empirical calculations, complemented by BIOVIA Discovery Studio Visualizer (v4.5), Open Babel, PyRx (v0.8), SwissADME, and ProTox (v3.0) (Budiarto, Wijianto, & IH, 2023).

Methods

Pharmacokinetic Evaluation

Pharmacokinetic analysis addressed both drug-likeness predictions and ADMET factors, encompassing absorption, distribution, metabolism, excretion, and toxicity. These were analyzed using the SwissADME platform at http://swissadme.ch/index.php. This analysis utilized filters according to the guidelines of Lipinski, Ghose, Veber, Egan, and Muegge to predict important molecular parameters including molecular weight, log P values, partitioning coefficients, and hydrogen bond donor and acceptor counts. These properties are vital in understanding how a compound behaves pharmacokinetically within the human body. Furthermore, synthetic accessibility was rated on a scale of 1 to 10, and bioavailability scores were computed. Additional ADMET predictions were conducted using both the SwissADME and ProTox version 3.0 platforms (http://swissadme.ch/index.php and https://tox.charite.de/protox3/index.php?site=home), providing further insights into the drug candidacy of Xanthomicrol derivatives (Hadni & Elhallaoui, 2020; Kurniawan et al., 2023; Kothandan et al., 2017).

Molecular Docking Simulation

The 3D crystal structures of several proteins associated with lung cancer cells (1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k) were sourced retrieved via the Protein Data Bank (PDB) by RCSB platform (https://www.rcsb.org/) for conducting molecular docking analyses (Rochlani et al., 2024). Before initiating docking, these protein structures underwent preparation by eliminating all heteroatoms and previously bound water molecules, ensuring accurate tautomeric forms by incorporating polar hydrogen atoms into the residues (Rathod et al., 2022; Rochlani et al., 2024). BIOVIA Discovery Studio Visualizer (v4.5) was used for this preparation (Dassault Systèmes, 2023). The purified protein structures, derived from X-ray crystallography and representing lung cancer cell states, were transformed into macromolecules suitable for docking with AutoDock. Docking simulations were executed using the AutoDock Vina functionality included in PyRx (v0.8) (Stanzione et al., 2021; Eberhardt et al., 2021; Gaikwad et al., 2022; Rochlani et al., 2024). For the docking process, the selected protein structures and Xanthomicrol derivatives were uploaded into the Vina Wizard, with the grid box calibrated to include the entire protein structure. An exhaustiveness setting above 128 was established to enhance ligand conformation refinement (Kurniawan et al., 2023).

Conformations that exhibited the most promising binding affinities for the various Xanthomicrol derivatives were captured, and the binding interactions with the target proteins were visualized utilizing BIOVIA Discovery Studio Visualizer (v4.5). (Rochlani et al., 2024).

Molecular dynamics Simulation

Simulations of molecular dynamics were conducted using in silico techniques to evaluate protein flexibility (Edache et al., 2023). The protein-ligand complexes were simulated through the CABS-flex 2.0 platform (http://biocomp.chem.uw.edu.pl/CABSflex2), which utilizes coarse-grained (CG) models and requires an input file in the *.pdb format. This server is built upon the established CABS model, specifically designed for coarse-grained protein modeling. It generates models that depict the structural flexibility of proteins, yielding ensembles of ten full-atom conformations, fluctuation plots (RMSF), and contact maps (Yang, 2023). In this research, *.pdb files of seven mutated proteins complexed with the compound u3a, derived from molecular docking studies, were employed for molecular dynamics analysis on the CABS-flex 2.0 platform. The parameters used included stiffness set to 1.0, a temperature range of 1.40, C-alpha restraints of 1.0, RNG seed as 8204, inter-pathway cycle of 150, and a global weight of 1.0 (Edache et al., 2023; Yang, 2023).

Data Analysis

The three-dimensional representations of several proteins were sourced and retrieved using the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/) and analyzed by calculating the docking scores between Xanthomicrol derivative ligands and the target proteins. These docking scores were compared with those of the natural ligands of the proteins to evaluate their binding efficiency. The docking outcomes were illustrated to determine the active sites where the proteins interacted with the test compounds, along with the types and distances of the interactions. Both 2D and 3D models were created with BIOVIA Discovery Studio Visualizer (v4.5) (Mulyati & Panjaitan, 2021). The concluding stage of the analysis involved conducting simulations of molecular dynamics focused on the most effective test compounds in combination with multiple protein mutations, producing RMSF graphical representations along with radius of gyration information, providing valuable information on the complexes' stability and structural resilience (Maahury & Allo, 2021).

RESULTS AND DISCUSSION

Pharmacokinetic evaluation results

A comprehensive pharmacokinetic evaluation was conducted to calculate the drug-likeness variables and ADMET properties of Xanthomicrol derivatives, offering valuable insights for drug design. This evaluation is crucial for predicting how these compounds interact with the human body, particularly in terms of gastrointestinal absorption, which is vital for orally administered drugs. Inadequate absorption can adversely affect the distribution and metabolism of drugs, potentially resulting in harmful outcomes such as neurotoxicity and nephrotoxicity. Furthermore, key therapeutic parameters were analyzed, which includes gastrointestinal (GI) absorption along with permeability across the blood-brain barrier (BBB), status as a substrate for P-glycoprotein (P-gp), and inhibition of metabolic enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4). The evaluation also encompassed drug-likeness based on the criteria established by Lipinski, Ghose, Veber, Egan, and Muegge, along with assessments of bioavailability metrics, synthetic accessibility, potential carcinogenicity, acute oral toxicity, and overall toxicity classification. Collectively, these factors indicated favorable pharmacokinetic profiles for the Xanthomicrol derivatives (Mohapatra et al., 2023). The predicted pharmacokinetic properties of the tested Xanthomicrol derivatives are summarized in Table 1.

Table 1. Drug-Likeness, Pharmacokinetics, and ADMET Predictions in Xanthomicrol Derivative Studies.

Molecules	GI *absorption*	BBB *permeant*	P-gp	Inhibitors					Drug-likeness		
			Subs	CYP 1A2	CYP 2C19	CYP 2C9	CYP 2D6	CYP 3A4	Lipinski	Ghose	Veber
u1a	High	Negative	Negative	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
u2a	High	Negative	Negative	Yes	No	Yes	No	Yes	Yes	Yes	Yes
u3a	High	Negative	Negative	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
u4a	High	Negative	Negative	No	No	Yes	No	Yes	Yes	Yes	Yes

Table 2. Drug-Likeness, Pharmacokinetics, and ADMET Predictions in Xanthomicrol Derivative Studies (contd).

Drug-likeness		Bioavailability	Synthetic	Carcinogens	Acute Oral Toxicity	Class
Egan	Muegge	Score	accessibility		LD_{50} (mg/kg)	Toxicity
Yes	Yes	0.55	3.50	Safe agents	4000	V
Yes	Yes	0.55	3.65	Safe agents	5000	V
Yes	Yes	0.55	3.39	Safe agents	5000	V
Yes	Yes	0.55	3.81	Safe agents	5000	V

In Table 1 and Table 2, all Xanthomicrol derivatives demonstrated high gastrointestinal (GI) absorption, indicating efficient uptake by the human intestinal Caco-2 model, commonly employed in vitro to predict oral drug absorption. GI absorption is an essential factor in determining how much of a drug is absorbed through the gastrointestinal system, which serves as the primary route for oral drug administration. Absorption rates below 30% are typically considered insufficient (Mohapatra et al., 2023). Additionally, the blood-brain barrier (BBB), a specialized and adaptable boundary composed of distinct vascular cells, tight junction complexes, pericytes, along astrocytes, controls the movement of substances from the bloodstream into the brain, maintaining the stable environment vital for neuronal function. The analysis showed that none of the compounds were able to cross the BBB, suggesting limited or no exposure to the central nervous system for these derivatives (Murugan et al., 2024).

P-glycoprotein (P-gp) functions as a biological barrier by expelling toxins and xenobiotics from cells, playing important roles in the gastrointestinal tract and central nervous system. It is often overexpressed in various cancers, contributing to drug resistance. The compounds analyzed in Table 1 and Table 2 are predicted neither to inhibit nor act as substrates for P-gp, allowing them to bypass this resistance mechanism. Additionally, the interaction of these compounds with cytochrome P450 (CYP450) enzymes was evaluated, focusing on the absorption and inhibition of five key CYP450 isoforms, as detailed in Table 1 and Table 2. Cytochrome P450 is the principal superfamily of enzymes responsible for drug elimination via biotransformation into water-soluble compounds. Inhibition of one or more CYP450 isoenzymes can disrupt drug metabolism and lead to toxic effects. According to Salazar et al. (2024), 50% to 90% of drugs interact with the five primary CYP450 isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), where inhibiting any of these enzymes might produce negative repercussions. Therefore, it is critical to assess whether the tested compounds inhibit these CYP450 isoforms. Unlike some compounds that inhibit all isoforms, the compounds in Table 1 and Table 2 displayed varying levels of CYP450 inhibition, but none inhibited all five isoforms, indicating a reduced risk of widespread metabolic interference (Salazar et al., 2024).

Each of the compounds fulfilled the drug-likeness standards outlined by Lipinski (Pfizer), Ghose (Amgen), Veber (GlaxoSmithKline), Egan (Pharmacia), and Muegge (Bayer). These guidelines are extensively utilized by leading pharmaceutical companies to evaluate drug-likeness, allowing them to filter compounds from high-quality chemical libraries (Salazar et al., 2024). Specifically, the Lipinski rule includes criteria such as molecular weight (MW) $\leq$ 500, MLOGP $\leq$ 4.15, 10 or fewer nitrogen or oxygen atoms, and 5 hydrogen bond donors' maximum. The Ghose rule sets parameters of $160 \leq MW \leq 480$, $-0.4 \leq WLOGP \leq 5.6$, a molar refractivity (MR) range between 40 to 130, and 20 to 70 atoms. The Veber rule limits rotatable bonds to ≤ 10 in number and the total surface polar area (TPSA) to ≤ 140 Å^2. The Egan rule specifies a WLOGP ≤ 5.88 and TPSA ≤ 131.6 Å^2. The Muegge rules outline criteria such as MW between 200 and 600, $-2 \leq XLOGP \leq 5$, TPSA ≤ 150 Å^2, maximum 7 rings, over 4 carbons, at least 1 heteroatom, no more than 15 rotatable bonds, containing no more than 10 hydrogen bond acceptors and 5 hydrogen bond donors (Kurniawan & Baari, 2024). The bioavailability score quantifies the amount of drug that reaches systemic circulation as a percentage of the dose administered, was also evaluated. This is especially important for orally administered drugs, as absorption may be reduced due to incomplete gastrointestinal uptake or first-pass metabolism. While intravenous drugs exhibit 100% bioavailability, the tested compounds showed a bioavailability score of 55%, indicating favorable absorption when administered orally (Islamoglu & Hacifazlioglu, 2022; Muhammad & Baari, 2024). The compounds were further evaluated for acute toxicity using LD_{50} values, a standard measure of a drug's potential harmful effects. All compounds were classified as non-carcinogenic, with LD_{50} values ranging between 4000 and 5000 mg/kg, placing them in toxicity class V. This classification suggests minimal toxicity risks, making the compounds

generally safe as potential lung cancer treatments. However, some side effects may still occur.

The findings of this study can be considered complementary to those of Nguyen's research, despite the differing approaches. Nguyen et al. (2020) reported that the u2a compound exhibited higher IC_{50} values, indicating lower toxicity based on cytotoxicity assays. In contrast, our study focused on evaluating the drug-likeness and safety profiles of Xanthomicrol-derived compounds through a computational approach. All tested compounds satisfied the major drug-likeness criteria based on key pharmaceutical guidelines (Lipinski, Ghose, Veber, Egan, and Muegge), demonstrated favorable bioavailability scores (55%), and were categorized under toxicity class V with LD_{50} values ranging from 4000 to 5000 mg/kg, indicating a low level of acute toxicity. However, since Nguyen's study did not report specific drug-likeness or ADMET parameters, a direct comparison remains limited. Nevertheless, both studies collectively highlight the promising potential of natural compounds as safe and effective candidates for anticancer drug development.

The BOILED-Egg model, which stands for Brain Or Intestinal Estimated, is an effective visual tool for the analysis of pharmacokinetic properties pertaining to passive absorption in the gastrointestinal tract (HIA) and blood-brain barrier permeability (BBB permeant), as shown in Figure 2. There is a model, based on WLOGP versus TPSA, categorizing compounds into two main regions: in the white space, denoting the possibility of passive absorption via the gastrointestinal tract (HIA), and in the yellow area indicating potential passive absorption at the blood-brain barrier (BBB permeant). Additionally, within our model, the blue dots represent P-glycoprotein substrates (PGP+), while the red dots indicate non-substrates (PGP-). In Figure 2, all compounds are located in the white region, suggesting efficient gastrointestinal absorption (HIA) and non-substrate status for P-glycoprotein (PGP-) (Ranjith & Ravikumar, 2019; Sardar, 2023; Sardar et al., 2024; Mahanthesh et al., 2024).

Molecular docking simulation results

Molecular docking simulations are used to establish and demonstrate the relationship between biological data in vitro as well as the inhibitor's affinity for the target proteins. These simulations evaluate the binding strength and efficacy of Xanthomicrol derivatives by comparing data on docking scores to analyze interaction numbers with specific target proteins. This study focused on ten mutated lung cancer target proteins: 1nq1, 1x2j, 4b3z, 4j97, 5l2q, 6pwa, 6usx, 7pgk, 7pgl, and 7r7k. The interactions between compounds and proteins were visualized using both 2D and 3D representations, as shown in Figure 3, while the binding affinity values for each compound-protein interaction are presented in Table 3 (Khalaf et al., 2024).

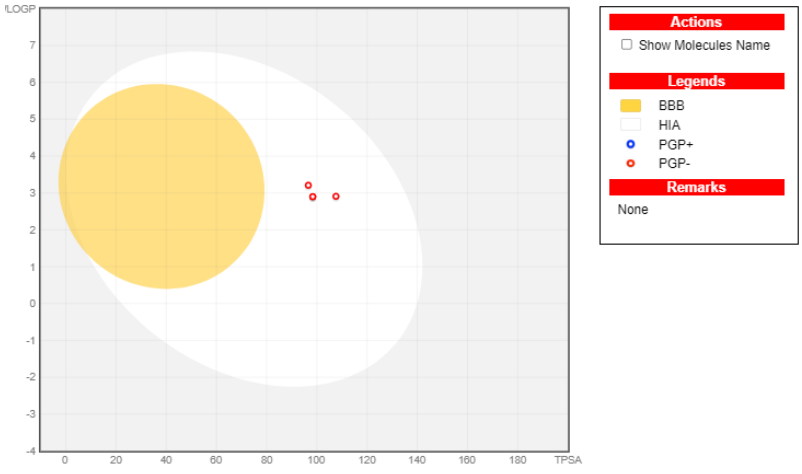


Figure 2. The BOILED-Egg model intuitively evaluates human Absorption in the gastrointestinal tract (HIA) and permeation of the blood-brain barrier (BBB). Compounds positioned in the white space demonstrate a high potential for passive absorption through the gastrointestinal tract (HIA), and the compounds in the yellow area show potential for blood-brain barrier permeability (BBB). The blue dots indicate P-glycoprotein (P-gp) positive substrates, on which the red dots indicate P-gp negative compounds. The position of each molecule on the WLOGP-versus-TPSA graph offers a visual assessment of its pharmacokinetic properties (Choudhury et al., 2022).

Table 3. Binding Affinity Results for Xanthomicrol Derivatives Against Lung Cancer Protein Mutants

Compounds	Molecular Docking of lung cancer protein (kcal/mol)									
	Mutations I	Mutations II	Mutations III	Mutations IV	Mutations V	Mutations VI	Mutations VII	Mutations VIII	Mutations IX	Mutations X
u1a	-8.1	-8.5	-7.6	-8.6	-7.1	-7.6	-8.6	-6.3	-5.7	-7.7
u2a	-8.2	-8.7	-8	-8.6	-7.1	-7.3	-8.9	-6.4	-5.8	-7.9
u3a	-8.2	-9.4	-8.3	-7.5	-7.4	-7.7	-8.7	-6.5	-5.9	-7.9
u4a	-8	-8.3	-7.2	-6.8	-7.1	-7	-8	-6.7	-5.9	-7

Table 3 presents the docking values between Xanthomicrol derivatives and mutated lung cancer proteins, highlighting high and varied binding affinities. These results underscore the potential of Xanthomicrol derivatives as inhibitors of lung cancer, particularly across the 10 mutated proteins. Among the derivatives, compound u3a demonstrated the strongest binding affinity against seven of the mutated proteins, with binding energies of -8.2, -9.4, -8.3, -7.4, -7.7, -5.9, and -7.9 kcal/mol, followed by compounds u2a, u1a, and u4a (Maslov et al., 2024). In contrast to the results reported by Nguyen et al. (2020), where compound u2a exhibited high IC50 values and was considered to have a strong correlation with binding to target proteins, this study found that compound u3a demonstrated the strongest binding affinity toward the seven mutated proteins analyzed. This difference can be explained by several important factors. First, the type of target protein used plays a critical role. Nguyen et al. (2020) most likely utilized proteins in their wild-type (non-mutated) form, whereas the present study focused on mutated proteins, which are commonly associated with lung cancer. These mutations can induce structural changes in the active site, allowing compounds with specific structural features such as u3a to exhibit higher affinity for the mutant variants. Second, IC_{50} values and binding affinity represent distinct biological concepts. IC_{50} reflects the concentration required to inhibit a biological function by 50%, often measured in cellular or biochemical assays, and encompasses factors like compound solubility, membrane permeability, and metabolic stability. In contrast, binding affinity often derived from molecular docking indicates the strength of interaction between a compound and its target protein under idealized *in silico* conditions. Therefore, a compound may exhibit strong binding affinity but still have limited biological efficacy or toxicity due to pharmacokinetic constraints (Nguyen et al., 2020).

The molecular docking simulations revealed a range of interactions between the Xanthomicrol derivatives and amino acid residues, featuring various interactions such as conventional hydrogen bonds, van der Waals forces, π-π stacking, alkyl and π-alkyl interactions, carbon-hydrogen bonds, π-donor hydrogen bonds, T-shaped π-π interactions, and π-σ interactions, as well as unfavorable donor-donor and acceptor-acceptor interactions (Figure 3). For the first mutation, compound u3a formed carbon-hydrogen bonds with ALA318, GLY357, and GLN243, π-π stacking interactions with TRP239, and alkyl/π-alkyl interactions with LEU365, VAL319, and ARG320. In the second mutation, conventional hydrogen bonds were observed with VAL465, ILE416, and VAL604, along with carbon-hydrogen bonds involving GLY417 and LEU365, and alkyl interactions with ALA607 and VAL561. For the third mutation, conventional hydrogen bonds were formed with ARG245 and ASN486, π-π stacking with PHE486, and alkyl interactions with LYS374 and ARG485. In the fifth mutation, u3a displayed hydrogen bonds with HIS161 and ASN158, π-π T-shaped interactions with HIS161, and alkyl interactions with CYS145 and LEU141. For the sixth mutation, hydrogen bonds were observed with ASN611 and HIS632, while π-σ interactions occurred with ILE524 and alkyl interactions with LEU636 and PHE631. For the ninth mutation, u3a formed hydrogen bonds with ARG185 and GLU147, with alkyl interactions involving LEU178 and CYS179. Finally, in the tenth mutation, hydrogen bonds were established with MET1199 and LEU1122, along with π-σ interactions with LEU1122 and alkyl interactions with LYS1150 and VAL1130. These detailed molecular interactions provide valuable insights into optimizing Xanthomicrol derivatives for improved efficacy in lung cancer inhibition. Such information could facilitate the development of more effective therapies targeting specific mutations in lung cancer proteins (Gul et al., 2024; Mulyati & Panjaitan, 2021).

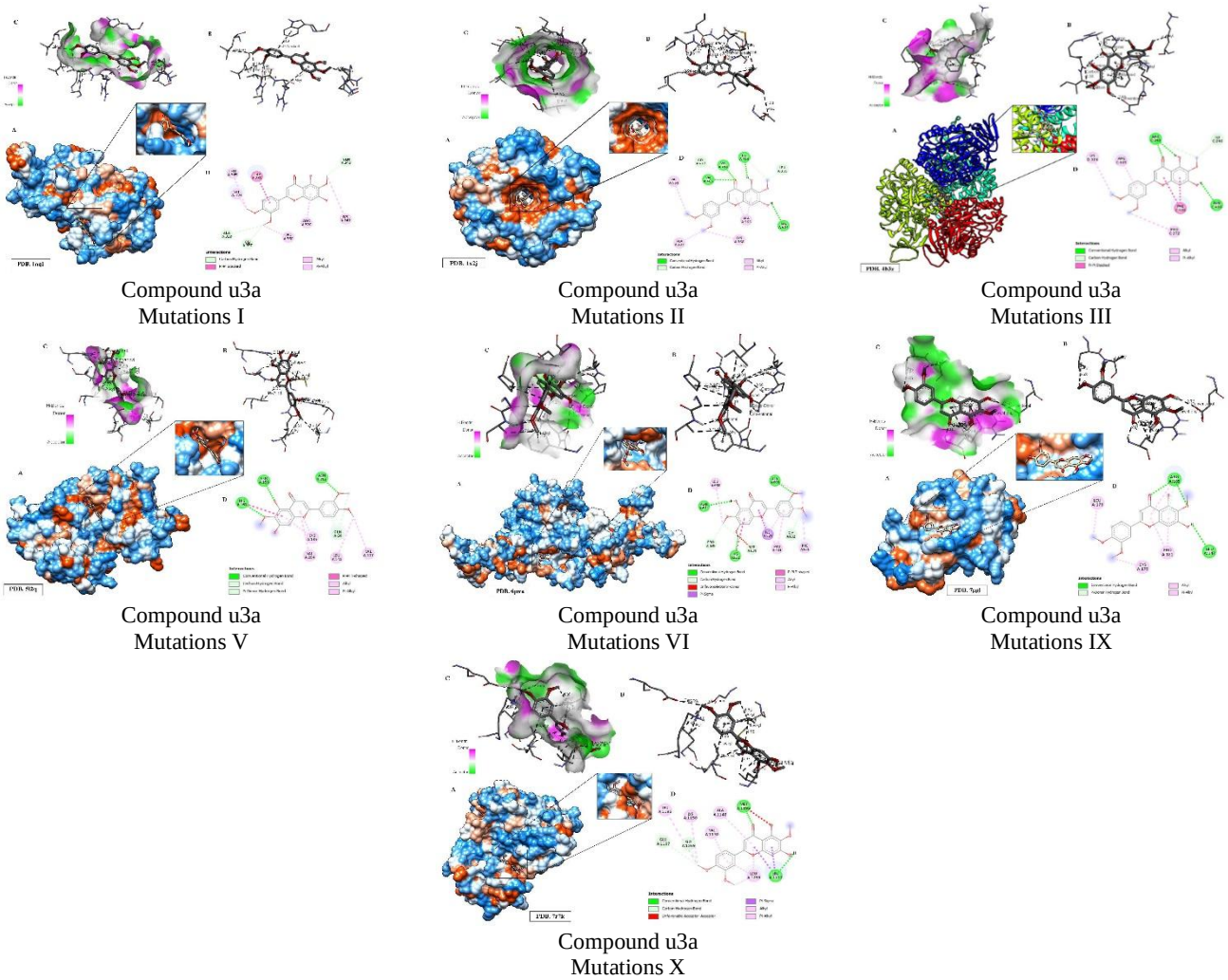


Figure 3. Docking results visualizations for compound u3a in mode 1, presented in 2D and 3D formats, were generated with Discovery Studio Visualizer version 4.5. The visualization illustrates the mechanism of interaction between compound u3a and the mutated lung cancer protein active site. Key interactions, including hydrogen bonding, van der Waals forces, and π-π stacking, are prominently displayed in the 2D representation., while the 3D model provides a spatial overview of the ligand-protein binding configuration (Kurniawan et al., 2023).

Molecular dynamics results

Molecular dynamics simulations of the seven mutated lung cancer protein complexes were performed using CABS-flex 2.0, revealing significant flexibility in certain regions, as indicated by the Root Mean Square Fluctuation (RMSF) value peaks. High flexibility of the protein structure is characterized by elevated RMSF values, while more rigid or constrained areas are represented by lower RMSF values, as shown in Figure 4. Additionally, the interaction patterns between protein residues can be further explored via "radius of gyration," which offers insight into the overall compactness of the protein complex, and/or by examining the contact map, as depicted in Figure 5. The results offer valuable perspectives on the dynamic nature of protein-ligand complexes, which is fundamental to improving drug formulation.

Figure 4's analysis of RMSF highlights the dynamic nature of protein residue flexibility, showing the average positional deviations from their starting points throughout molecular dynamics simulations. Higher RMSF values correspond to greater fluctuations, indicating increased mobility in specific protein regions, while lower RMSF values suggest more rigid, stable areas. Figure 4 shows that the simulated protein complexes exhibit notable fluctuations throughout their structures, with CABS-flex 2.0 simulations revealing higher overall residue fluctuations, capturing larger protein movements. In flexible systems, regions with elevated RMSF values often correlate with higher radius of gyration (Rg)

values, as depicted in Figure 5. This relationship occurs because greater mobility allows regions to explore broader conformational spaces, contributing to an expanded Rg. However, increased flexibility does not always result in a larger Rg if the movement of flexible regions is constrained (Yang, 2023). The Rg values, color-coded in the model, reflect the overall compactness of the protein during the simulation trajectory, typically consisting of 1000 Å models that capture structural changes over the entire simulation process. The RMSF values from the docking complexes reveal varied yet stable fluctuations, providing in silico evidence of the potential effectiveness of Xanthomicrol derivatives as drug candidates for lung cancer treatment (Edache et al., 2023).

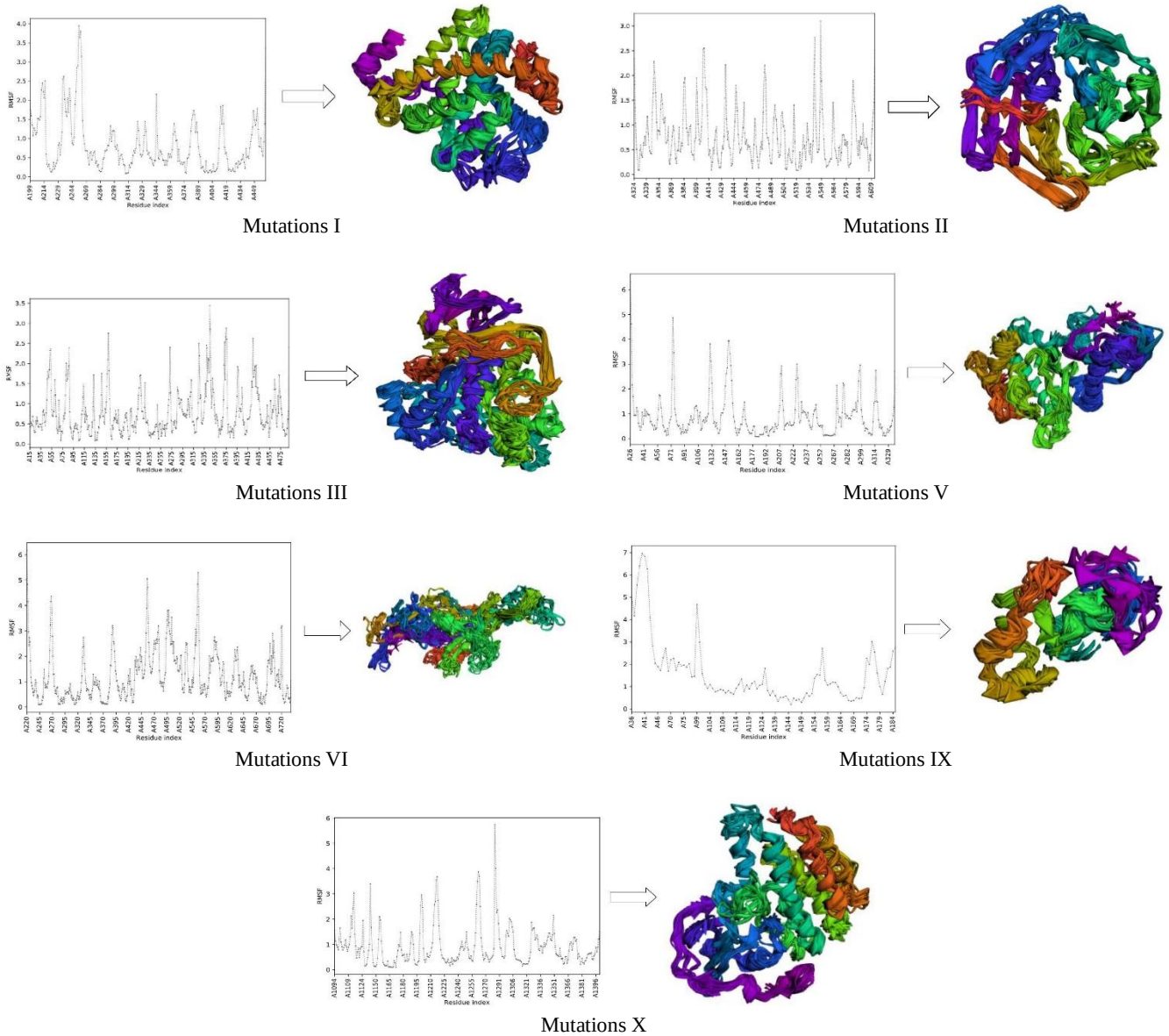
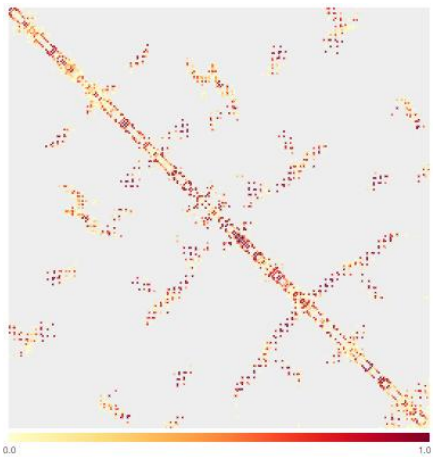
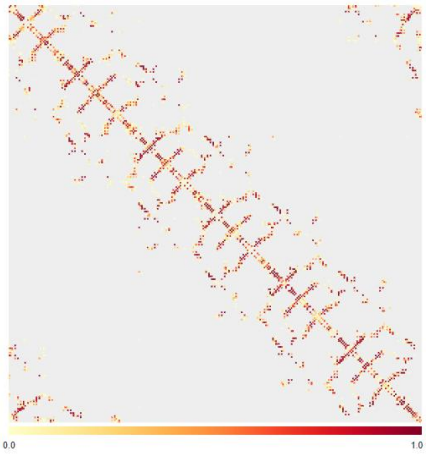


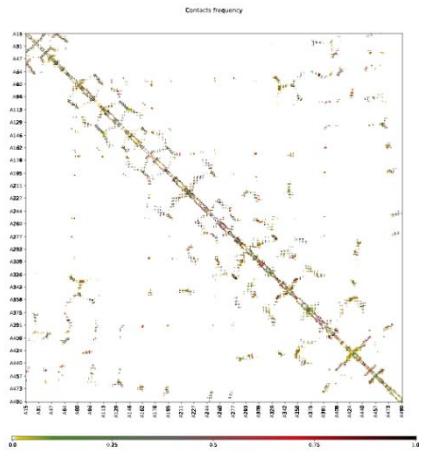
Figure 4. A diagram showing the Root Mean Square Fluctuation (RMSF) for the derived molecular dynamics of complexed Xanthomicrol derivatives bound to various mutated lung cancer protein receptors. The RMSF plot shows the average deviation of protein residues over time, highlighting regions of flexibility and rigidity. Peaks on the RMSF plot show regions of higher fluctuation, indicating more flexible regions of the protein, while lower values indicate more stable and confined regions. Insights into the structural dynamics and stability of protein-ligand interactions are gained from this analysis. (Herdiansyah et al., 2024).



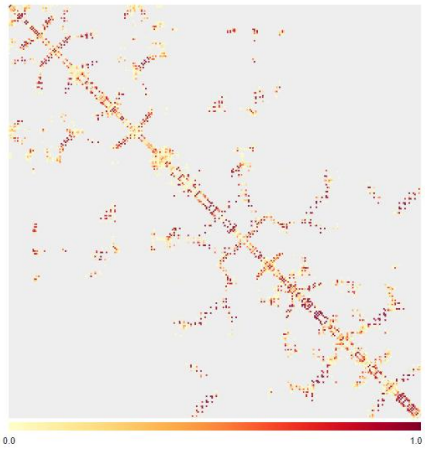
Mutations I



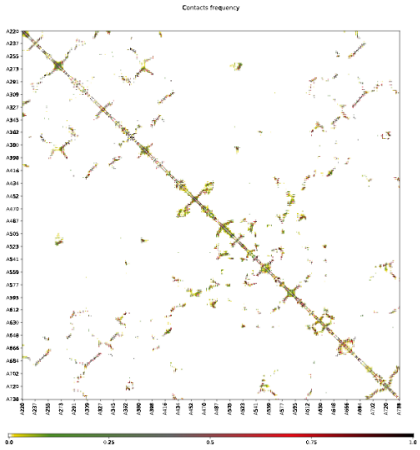
Mutations II



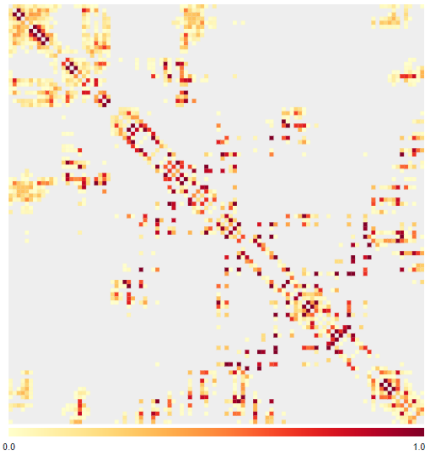
Mutations III



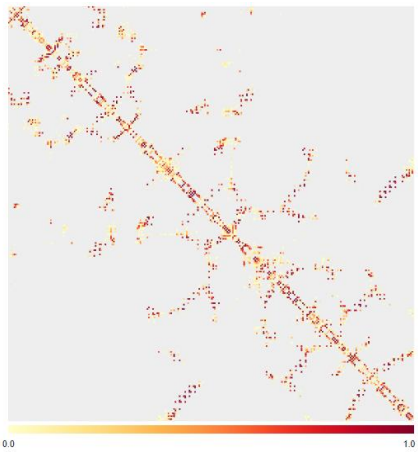
Mutations V



Mutations VI



Mutations IX



Mutations X

Figure 5. The radius of gyration (Rg) values of complexed Xanthomicrol derivatives bound to several mutated lung cancer protein receptors. The compactness of the protein-ligand complex is measured by Rg during molecular dynamics simulations. A stable Rg value, such as the observed Σ Rg of 1,000 Å, indicates consistent structural integrity in the protein-ligand complex over the simulation, suggesting they maintain a stable conformation when interacting with the target protein (Herdiansyah et al., 2024).

CONCLUSION

This study aimed to identify the most promising Xanthomicrol derivative as a therapeutic candidate targeting mutated proteins involved in lung cancer using a computational chemistry approach. To achieve this, a comprehensive evaluation was conducted on four derivatives (u1a, u2a, u3a, and u4a), assessing their pharmacokinetic properties, molecular docking affinities, and dynamic interaction stability. Pharmacokinetic testing indicated that all compounds displayed favorable profiles, characterized by high gastrointestinal (GI) absorption, inability to penetrate the blood-brain barrier (BBB), and non-substrate status for P-glycoprotein, facilitating safe drug distribution within the body. In contrast to the findings of Nguyen et al. (2020), where compound u2a demonstrated strong anticancer potential based on its low IC_{50} values in wild-type lung and liver cancer cells, this study identified compound u3a as having the highest binding affinity to mutated lung cancer proteins, with docking scores ranging from -5.9 to -9.4 kcal/mol. The key difference lies in the biological context and methodological approach: Nguyen's study evaluated cytotoxicity through in vitro assays, while this study applied in silico methods (docking and molecular dynamics simulations) targeting proteins with mutations commonly observed in lung cancer. Furthermore, interaction analysis of u3a revealed a diverse range of stabilizing forces at the binding sites hydrogen bonds, van der Waals interactions, π-π stacking, and others underscoring its strong and specific affinity for mutated targets. These structural differences may explain the discrepancy in compound performance, highlighting how mutation-induced changes in protein conformation can influence ligand-binding behavior and therapeutic potential. Molecular dynamics simulations further supported the potential of u3a, revealing good structural stability, characterized by moderate Root Mean Square Fluctuation (RMSF) values and a favorable radius of gyration, indicating sufficient flexibility for adapting to conformational changes of the target protein while maintaining overall structural integrity. As a result of these findings, u3a emerges as the most promising drug candidate for further development as a therapeutic agent for lung cancer. Experimental validation through laboratory and clinical studies to confirm its efficacy and safety under biological conditions is recommended.

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