



# Dual BRAF-EGFR Targeting by Lantadene and Peronemin Derivatives from *Peronema canescens*: A Molecular Docking and ADMET-Based Computational Study Against Drug-Resistant Non-Small Cell Lung Cancer (NSCLC)

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## ABSTRACT

Non-Small Cell Lung Cancer (NSCLC) accounts for roughly 85% of all diagnosed lung cancers, making it the dominant clinical subtype of the disease and a leading contributor to cancer mortality worldwide. Two receptor-linked signalling nodes, driven respectively by the epidermal growth factor receptor (EGFR) and the serine/threonine kinase BRAF, sit at the centre of NSCLC pathogenesis; their reciprocal crosstalk sustains downstream MAPK signalling, drives aggressive tumour progression, and underlies clinical resistance to single-target therapy. These observations justify a search for agents capable of engaging both nodes simultaneously. *Peronema canescens* (locally known as sungkai), a Kalimantan medicinal plant long used in Dayak traditional practice, has attracted growing pharmacological interest for its anticancer properties. This study evaluated the in silico anticancer potential of ten natural compounds isolated from *P. canescens* leaves alongside five reference/standard compounds against three structurally characterised NSCLC-relevant targets, namely wild-type EGFR (PDB 1M17), the resistance-associated mutated EGFR (PDB 5UG8), and BRAF (PDB 6B8U), using AutoDock Vina. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles were subsequently predicted using the SwissADME platform. The docking results identified Lantadene A, Lantadene B, and Peronemin A3 as the most consistently favourable ligands across all three receptors. Against mutated EGFR specifically, Lantadene B, Lantadene A, and Peronemin A3 achieved binding energies of  $-9.1$ ,  $-8.8$ , and  $-8.6$  kcal mol<sup>-1</sup>, respectively, while Peronemin A3 additionally displayed the highest interaction similarity to the native ligand (82.35%) of all compounds tested. All three lead compounds also engaged BRAF favourably and exhibited acceptable ADMET and drug-likeness profiles. Collectively, these computational findings position Lantadene A, Lantadene B, and Peronemin A3 as promising dual BRAF-EGFR-directed lead candidates for NSCLC that merit further in vitro and in vivo validation.

**Keyword:** *Peronema canescens*, Lantadene, Peronemin, Molecular Docking, BRAF, EGFR, NSCLC, ADMET

## ABSTRAK

Kanker Paru-Paru Sel Non-Kecil (NSCLC) mencakup sekitar 85% dari seluruh kasus kanker paru-paru yang terdiagnosis, menjadikannya sub tipe klinis dominan dari penyakit ini dan salah satu penyebab utama kematian akibat kanker di seluruh dunia. Dua simpul pensinyalan yang terkait reseptor, yang masing-masing didorong oleh reseptor faktor pertumbuhan epidermal (EGFR) dan serin/treonin kinase BRAF, berada di pusat patogenesis NSCLC; interaksi timbal balik di antara keduanya mempertahankan pensinyalan MAPK hilir, mendorong perkembangan tumor yang agresif, dan mendasari resistensi klinis terhadap terapi target tunggal. Pengamatan ini membenarkan pencarian agen yang mampu melibatkan kedua simpul tersebut secara bersamaan. *Peronema canescens* (yang secara lokal dikenal sebagai sungkai), tanaman obat Kalimantan yang telah lama digunakan dalam



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praktik tradisional Dayak, telah menarik minat farmakologis yang semakin besar karena sifat antikankernya. Penelitian ini mengevaluasi potensi antikanker secara *in silico* dari sepuluh senyawa alami yang diisolasi dari daun *P. canescens* bersama dengan lima senyawa referensi/standar terhadap tiga target yang relevan dengan NSCLC dan telah dikarakterisasi secara struktural, yaitu EGFR tipe liar (PDB 1M17), EGFR mutan yang terkait dengan resistensi (PDB 5UG8), dan BRAF (PDB 6B8U), menggunakan AutoDock Vina. Profil penyerapan, distribusi, metabolisme, ekskresi, dan toksisitas (ADMET) kemudian diprediksi menggunakan platform SwissADME. Hasil docking mengidentifikasi Lantadene A, Lantadene B, dan Peronemin A3 sebagai ligan yang paling konsisten menunjukkan hasil yang menguntungkan pada ketiga reseptor tersebut. Secara khusus terhadap EGFR yang bermutasi, Lantadene B, Lantadene A, dan Peronemin A3 mencapai energi ikatan masing-masing sebesar  $-9,1$ ,  $-8,8$ , dan  $-8,6$  kcal mol $^{-1}$ , sedangkan Peronemin A3 juga menunjukkan kesamaan interaksi tertinggi dengan ligan asli (82,35%) di antara semua senyawa yang diuji. Ketiga senyawa utama tersebut juga berinteraksi secara menguntungkan dengan BRAF dan menunjukkan profil ADMET serta kesesuaian sebagai obat yang dapat diterima. Secara keseluruhan, temuan komputasi ini menempatkan Lantadene A, Lantadene B, dan Peronemin A3 sebagai kandidat senyawa utama yang menjanjikan untuk NSCLC yang menargetkan BRAF dan EGFR secara ganda, yang layak untuk validasi lebih lanjut secara *in vitro* dan *in vivo*.

**Kata kunci:** *Peronema canescens*, Lantadene, Peronemin, Docking Molekuler, BRAF, EGFR, NSCLC, ADMET

## 1. Introduction

Lung cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related death worldwide, with an estimated 2.48 million new cases and 1.82 million deaths recorded in 2022 alone [1]. Among all malignancies, lung cancer alone is responsible for close to one-fifth of global cancer mortality, a burden exceeded by no other tumour type [2]. Non-Small Cell Lung Cancer (NSCLC), which encompasses adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, constitutes approximately 85% of these cases, leaving small-cell lung cancer as a comparatively minor share of the overall disease burden. Because NSCLC is frequently diagnosed at an advanced, unresectable stage, systemic and targeted pharmacotherapy occupies a central place in patient management, and the molecular drivers of the disease have therefore become the primary focus of contemporary drug discovery efforts [3].

Among the oncogenic drivers implicated in NSCLC, the epidermal growth factor receptor (EGFR) and the RAF-family kinase BRAF stand out for their frequency and their druggability. EGFR-activating mutations, most commonly exon 19 deletions and the L858R substitution in exon 21, constitute the single most common targetable alteration in non-squamous NSCLC, occurring in 10–15% of Caucasian and up to 50% of East Asian patients [4]. BRAF alterations are comparatively rarer, present in only 1.5–4% of NSCLC cases, yet they carry particular clinical significance because the V600E substitution renders the kinase constitutively active and confers sensitivity to dabrafenib-trametinib combination therapy, an approach with demonstrated efficacy in both clinical trials and real-world cohorts [4], [5]. Importantly, EGFR and BRAF do not operate as isolated, parallel circuits. Both converge on the RAS-RAF-MEK-ERK (MAPK) cascade, and emerging evidence indicates that inhibition of one node can trigger compensatory activation of the other, a form of pathway crosstalk that is now recognised as a principal mechanism of acquired resistance to single-agent tyrosine kinase inhibitor (TKI) therapy [5]. Clinically, this manifests as the secondary T790M gatekeeper mutation and, subsequently, the C797S substitution that undermines even third-generation inhibitors such as osimertinib, alongside BRAF-mediated reactivation of downstream ERK signalling that restores tumour proliferative capacity despite ongoing EGFR blockade [5]. These resistance phenomena explain why monotherapy directed at a single node of the EGFR-BRAF axis eventually fails in the majority of patients and why combination or dual-targeting strategies have become an active area of investigation [6].

This therapeutic landscape creates a clear rationale for identifying chemical entities capable of engaging both EGFR and BRAF concurrently, ideally while retaining activity against clinically relevant resistance mutations such as T790M [7]. Natural products offer a longstanding and still-productive route toward such multi-target leads, owing to the structural complexity and stereochemical diversity that plant-derived secondary metabolites bring to medicinal chemistry pipelines, diversity that is difficult to replicate through purely synthetic combinatorial approaches [8]. *Peronema canescens* Jack (Verbenaceae/Lamiaceae), known locally as sungkai and traditionally used by the Dayak community of Kalimantan for its antipyretic and general

medicinal properties, has increasingly been investigated for pharmacological activities that extend well beyond its traditional indications, including antioxidant, antibacterial, anti-hyperuricemic, immunomodulatory, and, most relevantly here, anticancer effects [9, 10]. Leaf extracts and isolated fractions of *P. canescens* have demonstrated selective cytotoxicity against several human cancer cell lines, including colorectal (HT-29), cervical (HeLa), and lung adenocarcinoma (A549) cells, with the ethanolic extract in particular showing an IC<sub>50</sub> in the range of 105 µg/mL against A549 cells while sparing normal fibroblasts [11, 12]. Among the constituents responsible for this bioactivity are the pentacyclic triterpenoids Lantadene A and Lantadene B, together with a family of furano-terpenoids unique to the genus *Peronema* known as peronemins (A1, A2, A3, B1, B2, B3, C1, and D1). Lantadenes in particular already possess a substantial pharmacological pedigree outside of *P. canescens*: derived originally from *Lantana camara*, they are established inhibitors of IKK-β-mediated NF-κB signalling and have shown selective cytotoxicity against multiple NCI-60 tumour cell panels, including lung adenocarcinoma lines, through structure-activity relationship (SAR) studies that have been corroborated by molecular docking [13, 14].

Despite this accumulating evidence for the anticancer relevance of *P. canescens* metabolites, a specific and significant research gap remains. Prior investigations of *Peronema*-derived compounds have largely examined cytotoxicity in a target-agnostic manner, using whole-cell viability assays without resolving which molecular target is engaged, or have profiled binding against a single receptor in isolation [14]. None of the available literature, to the best of the authors' knowledge, has systematically evaluated *Peronema canescens* metabolites against the specific combination of wild-type EGFR, the clinically important drug-resistant mutated EGFR, and BRAF within a single, internally consistent computational framework, nor has it benchmarked these natural compounds directly against clinically approved inhibitors such as erlotinib, osimertinib, and dabrafenib under matched docking conditions [15]. This is a meaningful omission, because the resistance mutation captured in the 5UG8 crystal structure is precisely the alteration that limits the durability of first- and second-generation EGFR-TKIs in clinical practice, and any natural lead intended for translational development must demonstrate activity against this resistant genotype, not merely against the wild-type receptor [16]. Addressing this gap is the central motivation of the present study.

Accordingly, this study aimed to (i) computationally screen ten secondary metabolites isolated from *P. canescens* leaves, together with five clinically relevant reference compounds, for binding affinity toward EGFR (1M17), mutated EGFR (5UG8), and BRAF (6B8U) using molecular docking; (ii) characterise the nature of the ligand-receptor interactions, including hydrogen bonding, hydrophobic contacts, and overall binding-mode similarity to native/reference ligands, for the most promising candidates; and (iii) evaluate the pharmacokinetic and drug-likeness profile of the leading compounds through in silico ADMET prediction, in order to assess their translational feasibility as dual BRAF-EGFR-directed anticancer leads for NSCLC.

## 2. Methods

### 2.1. Ligand and Protein Preparation

Ten secondary metabolites previously reported from the leaves of *Peronema canescens* were selected for evaluation: Lantadene A, Lantadene B, Lantanolic Acid, and the furano-terpenoids Peronemin A2, Peronemin A3, Peronemin B1, Peronemin B2, Peronemin B3, Peronemin C1, and Peronemin D1 [17-22]. Five reference compounds were included as pharmacological benchmarks, comprising the native co-crystallised ligand of each target protein together with the clinically approved inhibitors erlotinib (a first-generation EGFR-TKI), osimertinib (a third-generation, T790M-directed EGFR-TKI), and dabrafenib (a BRAF V600E inhibitor). Three-dimensional structures of all ligands were retrieved or constructed in SDF/MOL format, energy-minimised, and converted to the PDBQT format required by AutoDock Vina, with rotatable bonds assigned to allow conformational flexibility during docking. The three-dimensional crystal structures of the target proteins were retrieved from the RCSB Protein Data Bank: wild-type EGFR tyrosine kinase domain in complex with erlotinib (PDB ID 1M17), the T790M-mutated EGFR kinase domain (PDB ID 5UG8), and the BRAF kinase domain (PDB ID 6B8U). Each protein structure was prepared by removing co-crystallised water molecules and non-essential heteroatoms, adding polar hydrogens, and assigning Kollman charges, followed by conversion to PDBQT format.

### 2.2. Molecular Docking Protocol

Molecular docking was performed using AutoDock Vina, with the grid box for each receptor centred on its respective native ligand binding pocket to ensure a targeted, biologically relevant search space [23]. For EGFR (1M17), a grid box of 60 × 60 × 60 Å with 0.375 Å spacing was centred at coordinates (23.568, 1.787, 54.227). For mutated EGFR (5UG8), a grid box of 40 × 40 × 40 Å with 0.375 Å spacing was centred at (−13.156,

15.093, -25.719). For BRAF (6B8U), a grid box of  $24 \times 26 \times 24$  Å with 1 Å spacing was centred at (-23.905, 5.081, -6.037). The docking protocol for each receptor was validated by re-docking the native co-crystallised ligand into its original binding site and calculating the RMSD between the docked and experimental poses. RMSD values of 1.608 Å, 1.535 Å, and 0.758 Å were obtained for EGFR, mutated EGFR, and BRAF, respectively, all within the generally accepted 2.0 Å threshold, confirming that the docking parameters reliably reproduced the experimentally observed binding geometry for each target. Following validation, each of the ten test compounds and applicable reference compounds was docked into all three prepared receptors. Binding energies ( $\text{kcal mol}^{-1}$ ) were recorded for the lowest-energy, most energetically favourable pose of each ligand-receptor pair, and compounds were ranked accordingly within each receptor system [24].

### 2.3. Interaction and Binding-Site Analysis

For the subset of compounds showing the most favourable binding energies, in-depth interaction analysis was performed to characterise hydrogen-bonding partners and hydrophobic contact residues within the binding pocket, given its particular relevance to clinical drug resistance. Two-dimensional ligand-interaction diagrams were generated to visualise these contacts. Binding-mode similarity of each ligand to the native co-crystallised ligand was additionally quantified as a percentage overlap of shared interacting residues, providing a complementary measure of pharmacophoric relevance beyond binding energy alone.

### 2.4. ADMET and Drug-Likeness Prediction

Absorption, distribution, metabolism, excretion, and toxicity properties of the three lead compounds identified from the docking stage were predicted using the SwissADME web server [25]. Parameters evaluated included molecular weight, fraction of  $\text{sp}^3$ -hybridised carbons, rotatable bond count, hydrogen bond donor/acceptor count, topological polar surface area (TPSA), molar refractivity, consensus lipophilicity (Log P), aqueous solubility class, cytochrome P450 isoform inhibition (CYP1A2, 2C19, 2C9, 2D6, 3A4), predicted skin permeability (log Kp), and compliance with Lipinski's rule of five and leadlikeness criteria. Acute oral toxicity was classified separately using Toxtree v3.1.0 [51], an open-source, rule-based expert system that assigns chemical structures to one of three Cramer classes (I, II, or III) on the basis of a decision-tree analysis of structural alerts, providing an estimate of the threshold of toxicological concern; a Cramer Class III designation indicates the presence of structural features associated with a comparatively higher level of toxicological concern, warranting further investigation rather than indicating a specific, confirmed toxic effect. ADMET evaluation was restricted to Lantadene A, Lantadene B, and Peronemin A3 because these were the only three compounds that ranked consistently among the top three to four binders across all three receptor systems examined (Table 1), providing the strongest computational evidence of genuine multi-target engagement. Other compounds, including Peronemin A2, which showed the single most favourable score against wild-type EGFR ( $-9.2 \text{ kcal mol}^{-1}$ ), ranked markedly lower against the more clinically consequential mutated EGFR (7th/8th of 12 compounds) and BRAF (5th of 12 compounds) targets (Table 1) and were therefore not prioritised for downstream ADMET profiling at this stage; ADMET characterisation of the remaining compounds is recommended as an extension of this work.

## 3. Results and Discussion

### 3.1. Docking Validation and Binding Energy Landscape

Re-docking of the native ligands into their respective binding pockets yielded RMSD values of 1.608 Å (EGFR, 1M17), 1.535 Å (mutated EGFR, 5UG8), and 0.758 Å (BRAF, 6B8U), all comfortably below the 2.0 Å threshold conventionally used to certify a docking protocol as reliable. This validation step is a necessary prerequisite for interpreting the subsequent binding-energy comparisons with confidence, since it confirms that the scoring function and search algorithm employed here reproduce the experimentally observed ligand pose rather than converging on a spurious, energetically favourable but biologically implausible conformation [24]. The complete ranked binding-energy results for all three receptors are summarised in Table 1.

Table 1. Ranked binding energy ( $\text{kcal mol}^{-1}$ ) of *Peronema canescens* natural compounds and native/reference ligands toward EGFR (1M17), mutated EGFR (5UG8), and BRAF (6B8U).

| Compound              | EGFR (1M17) | Mutated EGFR (5UG8) | BRAF (6B8U) |
|-----------------------|-------------|---------------------|-------------|
| Native Ligand         | —           | -9.0                | -13.3       |
| Erlotinib (native/CD) | -7.5        | —                   | —           |
| Osimertinib (CD)      | —           | -8.6                | —           |

| Compound        | EGFR (1M17) | Mutated EGFR (5UG8) | BRAF (6B8U) |
|-----------------|-------------|---------------------|-------------|
| Dabrafenib (CD) | —           | —                   | −9.6        |
| Lantadene A     | −8.4        | −8.8                | −9.1        |
| Lantadene B     | −8.8        | −9.1                | −9.4        |
| Lantanolic Acid | −8.8        | −8.3                | −7.1        |
| Peronemin A2    | −9.2        | −8.3                | −8.2        |
| Peronemin A3    | −8.8        | −8.6                | −8.0        |
| Peronemin B1    | −7.6        | −7.2                | −7.7        |
| Peronemin B2    | −7.6        | −7.3                | −7.8        |
| Peronemin B3    | −8.3        | −8.2                | −7.7        |
| Peronemin C1    | −8.3        | −8.0                | −8.0        |
| Peronemin D1    | −8.3        | −8.5                | −8.0        |

Note: “CD” denotes clinically approved comparator drug; “Native Ligand” denotes the co-crystallised reference ligand of each PDB structure. Values are the lowest-energy binding pose (kcal mol<sup>−1</sup>) obtained per ligand-receptor pair.

### 3.2. Binding Affinity Toward Wild-Type EGFR (1M17)

Against wild-type EGFR, Peronemin A2 obtained the most favourable computed binding energy of the compounds tested, at −9.2 kcal mol<sup>−1</sup>, compared with −7.5 kcal mol<sup>−1</sup> for the native ligand erlotinib. Lantadene B, Lantanolic Acid, and Peronemin A3 formed a closely clustered second tier at −8.8 kcal mol<sup>−1</sup>, followed by Lantadene A at −8.4 kcal mol<sup>−1</sup>. Notably, all ten natural compounds screened returned a more favourable docking score than the reference inhibitor erlotinib under the conditions used here. This finding should be interpreted with appropriate caution: a computed difference of one to two kcal mol<sup>−1</sup> lies within the range of uncertainty typically associated with empirical scoring functions such as AutoDock Vina, and a more favourable docking score does not, by itself, establish that a compound would inhibit EGFR more potently than a clinically optimised drug in a biological system [26]. The finding is nonetheless useful as a screening signal, suggesting that the fused polycyclic terpenoid scaffold shared by the lantadenes and peronemins is reasonably well accommodated within the EGFR ATP-binding cleft, plausibly through extensive hydrophobic contact with the lipophilic residues lining this pocket rather than the more specific hinge-region hydrogen bonding that defines erlotinib's binding mode [27]. Because first-line EGFR-TKI therapy already achieves durable early responses in EGFR-mutant NSCLC, the comparison of greatest clinical relevance is against the resistance-associated mutated receptor, discussed next [28].

### 3.3. Binding Affinity Toward Mutated EGFR (5UG8): The Resistance-Relevant Target

The docking results against mutated EGFR are of particular translational interest because this structure captures the gatekeeper-mutated conformation responsible for clinical resistance to first- and second-generation EGFR-TKIs. Here, Lantadene B returned the most favourable computed binding energy of all compounds tested, −9.1 kcal mol<sup>−1</sup>, compared with −9.0 kcal mol<sup>−1</sup> for the native ligand. Lantadene A followed at −8.8 kcal mol<sup>−1</sup> and Peronemin A3 at −8.6 kcal mol<sup>−1</sup>, both within approximately 0.5 kcal mol<sup>−1</sup> of the value obtained for osimertinib (−8.6 kcal mol<sup>−1</sup>). Differences of this magnitude are small relative to the typical error margin of AutoDock Vina's scoring function, on the order of 1–2 kcal mol<sup>−1</sup>, and should therefore be read as indicating a broadly comparable, rather than superior, predicted affinity for the mutant receptor conformation; they do not constitute evidence that these natural compounds would inhibit mutated EGFR more effectively than osimertinib in a biochemical or cellular assay. It is also important to note that osimertinib acts primarily through covalent engagement of the Cys797 residue, a mechanism that contributes substantially to its clinical potency and duration of action and that is not captured by the non-covalent docking scores compared here [5, 29]. With this caveat in mind, the finding remains pharmacologically relevant: it indicates that Lantadene A, Lantadene B, and Peronemin A3 retain a comparable predicted affinity for the resistance-conferring mutant conformation of EGFR, rather than showing the marked loss of affinity that is characteristic of many first- and second-generation inhibitors against this target, a property that would be a prerequisite, though not sufficient proof, of a viable next-generation or combination lead compound [30, 31].

### 3.4. Binding Affinity Toward BRAF (6B8U)

At the BRAF kinase domain, the native ligand returned an exceptionally favourable computed binding energy of  $-13.3 \text{ kcal mol}^{-1}$ , considerably more favourable than any other compound evaluated, including the clinical comparator dabrafenib ( $-9.6 \text{ kcal mol}^{-1}$ ); such a gap is commonly observed in docking studies of this kind, since the native co-crystallised ligand is typically a compound optimised for maximal, often non-drug-like, occupancy of the ATP pocket rather than a balanced pharmacological agent. Among the *P. canescens* metabolites, Lantadene B ( $-9.4 \text{ kcal mol}^{-1}$ ) and Lantadene A ( $-9.1 \text{ kcal mol}^{-1}$ ) again produced the most favourable scores, approaching but not reaching the value obtained for dabrafenib, while Peronemin A2 ( $-8.2 \text{ kcal mol}^{-1}$ ) and Peronemin A3 ( $-8.0 \text{ kcal mol}^{-1}$ ) occupied an intermediate tier. The consistency with which Lantadene A and Lantadene B rank among the top-performing compounds across all three independent receptor systems, wild-type EGFR, mutated EGFR, and BRAF, is arguably the most informative pattern to emerge from the docking screen as a whole. Rather than exhibiting narrow, single-target selectivity, these two triterpenoids display a broad, cross-receptor binding profile that is consistent with, though not by itself proof of, the dual BRAF-EGFR targeting rationale established in the introduction. This pattern is broadly in line with recent computational work showing that natural-product scaffolds can engage sub-pockets within EGFR mutants relevant to overcoming resistance [33]. The structural basis of this cross-receptor binding profile, particularly how the rigid terpenoid framework is accommodated within both wild-type and mutated kinase domains, warrants further structural and, ultimately, experimental investigation [34].

### 3.5. Binding-Site and Interaction Analysis Against Mutated EGFR

To move beyond binding energy alone and assess whether the docked poses of the leading candidates were chemically plausible and pharmacophorically meaningful, detailed interaction analysis was performed for the top-ranked compounds against mutated EGFR, the receptor of greatest translational interest. Table 2A summarises the hydrogen-bonding partners, hydrophobic contact residues, and overall binding-mode similarity relative to the native ligand for Lantadene A, Lantadene B, osimertinib, and Peronemin A3.

**Table 2.** Binding-site interaction profile of leading compounds against mutated EGFR (5UG8).

| Compound         | Binding Energy (kcal/mol) | Hydrogen Bonding               | Hydrophobic Interaction (key residues)                                                                                         | Similarity to Native (%) |
|------------------|---------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Native Ligand    | -9.0                      | Asn842                         | Phe723, Arg841, Leu718, Gly796, Pro794, Leu844, Met793, Val726, Leu792, Ala743, Met790, Lys745, Thr854, Gly719, Phe856, Cys797 | 100.00                   |
| Lantadene B      | -9.1                      | Arg841, Phe723                 | Arg748, Ala722, Gly721, Asn842, Phe856, Asp837, Arg858, Lys875, Gly857, Leu747                                                 | 23.53                    |
| Lantadene A      | -8.8                      | Arg841, Asn842, Phe723, Ala722 | Gly857, Lys875, Gly874, Arg858, Asp837, Pro877, Gly721, Arg748                                                                 | 23.53                    |
| Osimertinib (CD) | -8.6                      | —                              | Arg858, Ala722, Phe723, Gly721, Ser720, Leu718, Gly796, Met793, Thr854, Leu844, Val726, Arg841, Asn842, Phe856, Asp837, Pro877 | 64.71                    |
| Peronemin A3     | -8.6                      | —                              | Gly719, Gly796, Asn842, Cys797, Phe723, Phe856, Arg841, Thr854, Leu844, Ala743, Met793, Leu718, Leu792, Val726                 | 82.35                    |

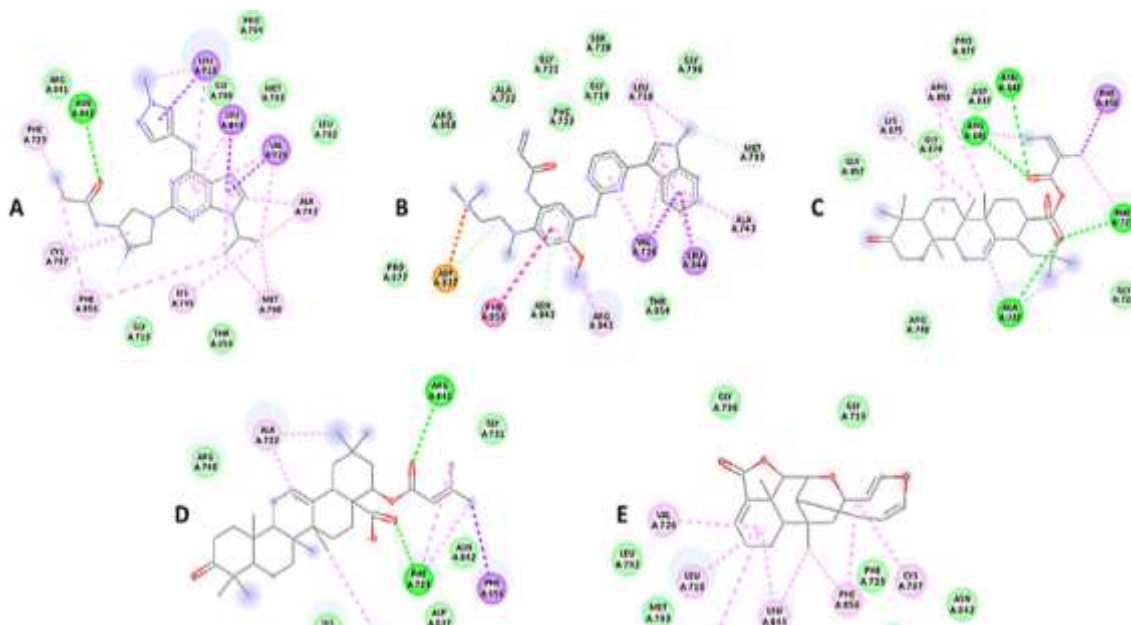


Figure 1. 2D illustration of interactions between mutated EGFR (5UG8) and ligand. (A) Native ligand, (B) Osimertinib, (C) Lantadene A, (D) Lantadene B, and (E) Peronemin A3.

The two-dimensional ligand-interaction diagrams shown in Figure 1 corroborate and visually contextualise the residue-level data summarised in Table 2. Panel A (native ligand) and panel B (osimertinib) both display an extended hydrophobic contact footprint that wraps around the hinge and back-pocket residues of the mutated EGFR active site, including Leu718, Leu844, Val726, and Phe856, consistent with their high binding-mode similarity scores. Panel C (Lantadene A) and panel D (Lantadene B) instead show a more compact, peripherally oriented set of contacts anchored by Arg841 and Phe723, with Lantadene B forming a distinct hydrogen bond to Arg841 (panel D) that is absent from the native ligand and osimertinib interaction maps, a structural difference consistent with the comparatively low binding-mode similarity (23.53%) recorded for both lantadenes despite their strong binding energies [35]. Panel E (Peronemin A3) reveals a dense cluster of hydrophobic contacts spanning Leu792, Leu718, Leu844, Phe723, Phe856, Cys797, and Asn842, a footprint that visibly overlaps with both the native ligand and osimertinib maps, reinforcing the quantitative 82.35% similarity value obtained for this compound and lending further visual support to the conclusion that Peronemin A3 occupies the mutated EGFR pocket in a pharmacophorically native-like manner [32].

Two findings from this interaction analysis merit detailed discussion. First, Peronemin A3 achieved the highest binding-mode similarity to the native ligand of any compound examined, at 82.35%, compared with 23.53% for each lantadene and 64.71% for the clinical comparator osimertinib. It is important to note that this metric reflects the degree of overlap in the residues contacted rather than a measure of relative inhibitory potency: a higher similarity value indicates a more native-like binding pose but does not, on its own, imply stronger or more effective target inhibition than osimertinib. With that caveat, the high degree of residue overlap suggests that Peronemin A3 occupies the mutated EGFR ATP pocket in a manner that broadly mirrors the native ligand's own binding geometry, engaging a substantially overlapping hydrophobic residue network that includes Gly719, Gly796, Asn842, Cys797, Phe723, Phe856, Arg841, Thr854, Leu844, Ala743, Met793, Leu718, Leu792, and Val726, several of which are shared with the osimertinib interaction footprint as well. Notably, this residue set includes Cys797, the residue to which osimertinib forms its covalent bond, suggesting that Peronemin A3 approaches this pharmacologically important region of the binding site even though its own predicted interaction is non-covalent [36, 37]. Second, in contrast to Peronemin A3, Lantadene A and Lantadene B display a comparatively lower binding-mode similarity (23.53%) despite achieving comparable or marginally more favourable computed binding energies relative to the native ligand and to osimertinib. This apparent discrepancy is informative rather than contradictory: it suggests that the lantadenes achieve their predicted binding through an alternative, only partially overlapping subset of hydrophobic contacts, most notably engaging Arg858, Lys875, Gly857/Gly874, and Asp837, residues located toward the periphery of the pocket that are not prominently engaged by either the native ligand or osimertinib. Structurally, this is consistent with the bulkier, more rigid pentacyclic triterpenoid scaffold of the lantadenes occupying a somewhat different sub-volume of the binding cleft compared with the more compact peronemin furanoterpenoid or the elongated osimertinib pyrimidine scaffold [38, 39]. From a medicinal chemistry standpoint,

this divergence is potentially useful rather than disadvantageous: a computed binding mode that is energetically comparable to, but topologically distinct from, that of osimertinib could in principle retain activity against tumours that acquire resistance mutations specifically directed at the osimertinib binding geometry, such as C797S, although this remains a hypothesis that can only be confirmed through dedicated resistance-mutant docking and, ultimately, biochemical assay [40]. Given that the C797S mutation typically prevents formation of the covalent acrylamide-cysteine linkage required for osimertinib's activity, the non-covalent, structurally distinct binding orientation of the lantadenes may, in principle, avoid direct reliance on residue 797 for anchoring, although this too would require dedicated experimental confirmation [41, 42].

### 3.6. Binding-Site and Interaction Analysis Against BRAF

To evaluate the dual-targeting hypothesis more directly, the same residue-level interaction analysis performed for mutated EGFR was extended to the BRAF binding site for the three lead compounds, Lantadene A, Lantadene B, and Peronemin A3. Two-dimensional interaction diagrams were generated to identify van der Waals contact residues and residues engaged through  $\pi$ -mediated or alkyl-type interactions (Pi-Sigma, Alkyl, Pi-Alkyl) within the BRAF ATP-binding pocket. No hydrogen-bonding contact was observed for any of the three compounds against this target under the conditions used here, in contrast to the mutated EGFR complexes described above. The results are summarised in Table 3 and illustrated in Figure 2.

Table 3. Binding-site interaction profile of the lead compounds against BRAF (6B8U).

| Compound     | Binding Energy (kcal/mol) | Pi-Sigma / Alkyl / Pi-Alkyl Interactions (key residues)                         | van der Waals Contact Residues                                 |
|--------------|---------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------|
| Lantadene A  | −9.1                      | His574 (Pi-Sigma); Val504 (Alkyl); Arg575, Tyr633 (Pi-Alkyl)                    | Glu501, Leu505, Asp594, Asp576, Gly593, Ile572, Ile573, Leu567 |
| Lantadene B  | −9.4                      | Phe595, Val471, Ala481, Leu514, His539, Trp531, Phe583, Ile463 (Alkyl/Pi-Alkyl) | Gln530, Thr529, Ser535, Cys532, Gly596, Asn580, Ser536         |
| Peronemin A3 | −8.0                      | Trp531, Phe583, Phe595 (Pi-Alkyl)                                               | Gly534, Glu533, Ile463, Ser535, Cys532, Ser536                 |

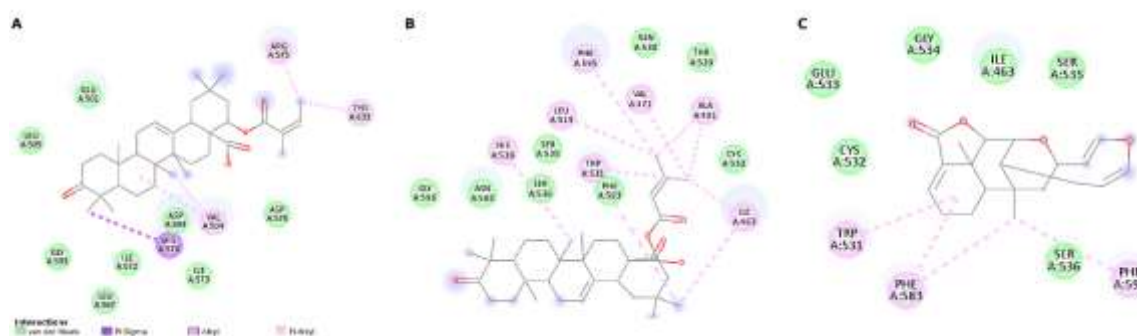


Figure 2. 2D illustration of interactions between BRAF (6B8U) and the lead compounds. (A) Lantadene A, (B) Lantadene B, and (C) Peronemin A3.

Consistent with the binding-energy ranking in Table 1, Lantadene B and Lantadene A engaged the BRAF pocket through the most extensive residue networks. Lantadene A formed a Pi-Sigma contact with His574 together with Alkyl/Pi-Alkyl contacts at Val504, Arg575, and Tyr633, alongside eight van der Waals contact residues spanning the hydrophobic back pocket (Glu501, Leu505, Asp594, Asp576, Gly593, Ile572, Ile573, and Leu567). Lantadene B engaged a broader Alkyl/Pi-Alkyl network comprising Phe595, Val471, Ala481, Leu514, His539, Trp531, Phe583, and Ile463, consistent with its marginally more favourable computed binding energy ( $-9.4$  kcal mol $^{-1}$ ) relative to Lantadene A ( $-9.1$  kcal mol $^{-1}$ ). Peronemin A3 showed a comparatively smaller interaction footprint, limited to three Pi-Alkyl contacts (Trp531, Phe583, Phe595) and six van der Waals residues, in line with its lower computed binding energy at this target ( $-8.0$  kcal mol $^{-1}$ ). Notably, Ile463, Phe595, Trp531, Phe583, and Ser535/Ser536 recur across two or more of the three compounds, suggesting a shared sub-pocket that may anchor this class of terpenoid scaffold within the BRAF active site regardless of the specific substitution pattern. None of the three compounds formed a conventional hydrogen bond with BRAF under the conditions used here, in contrast to their interaction with

mutated EGFR (Table 2); their predicted engagement with BRAF therefore appears to be governed predominantly by hydrophobic and  $\pi$ -mediated contacts rather than directional polar interactions. Taken together with the mutated EGFR interaction data in Section 3.5, this cross-target residue mapping provides additional, though still purely computational, support for the dual EGFR-BRAF engagement hypothesised for Lantadene A, Lantadene B, and Peronemin A3; as with all docking-derived observations in this study, confirmation would require biochemical kinase assays.

### 3.7. ADMET and Drug-Likeness Profile of the Lead Compounds

Binding affinity alone is an insufficient criterion for prioritising a natural product as a translatable drug lead; pharmacokinetic plausibility and an acceptable predicted toxicity profile are equally essential. Table 4 summarises the SwissADME- and Toxtree-predicted physicochemical, pharmacokinetic, and medicinal chemistry properties of Lantadene A, Lantadene B, and Peronemin A3.

Table 4. Predicted physicochemical, pharmacokinetic, and drug-likeness (ADMET) properties of Lantadene A, Lantadene B, and Peronemin A3 (SwissADME; Toxtree).

| Parameter                                 | Lantadene A            | Lantadene B            | Peronemin A3           |
|-------------------------------------------|------------------------|------------------------|------------------------|
| Molecular weight (g/mol)                  | 552.78                 | 552.78                 | 332.43                 |
| Fraction Csp <sup>3</sup>                 | 0.80                   | 0.80                   | 0.85                   |
| Rotatable bonds                           | 4                      | 4                      | 1                      |
| H-bond acceptors                          | 5                      | 5                      | 4                      |
| H-bond donors                             | 1                      | 1                      | 0                      |
| Molar refractivity                        | 160.54                 | 160.54                 | 90.15                  |
| TPSA (Å <sup>2</sup> )                    | 80.67                  | 80.67                  | 44.76                  |
| Consensus Log P                           | 6.42                   | 6.52                   | 3.18                   |
| Solubility class                          | Poorly soluble         | Poorly soluble         | Moderately soluble     |
| CYP1A2 / 2C19 / 2C9 / 2D6 / 3A4 inhibitor | No / No / No / No / No | No / No / No / No / No | No / No / No / No / No |
| log Kp – skin permeation (cm/s)           | −4.15                  | −3.97                  | −5.84                  |
| Lipinski violations                       | 2                      | 2                      | 0                      |
| Bioavailability score                     | 0.56                   | 0.56                   | 0.55                   |
| Leadlikeness violations                   | 2                      | 2                      | 0                      |
| Synthetic accessibility                   | 6.73                   | 6.71                   | 5.30                   |
| Predicted toxicity class                  | III                    | III                    | III                    |

The ADMET profile reveals a clear distinction between the two lantadenes and Peronemin A3. Both Lantadene A and Lantadene B carry a molecular weight of 552.78 g/mol and a consensus Log P above 6.4, values that breach two of Lipinski's rule-of-five thresholds (molecular weight >500 and Log P >5) and place both compounds in the “poorly soluble” aqueous solubility class. Two Lipinski violations do not automatically disqualify a compound from further development, particularly for oncology indications where somewhat larger, more lipophilic molecules are tolerated more readily than in other therapeutic areas, but the combination of high lipophilicity and poor aqueous solubility does signal a formulation challenge that would need to be addressed, for example through nanoparticle encapsulation, prodrug strategies, or co-solvent systems, before either compound could progress to in vivo testing [43]. Peronemin A3, by contrast, presents a comparatively favourable predicted drug-likeness profile: zero Lipinski violations, zero leadlikeness violations, a substantially lower molecular weight (332.43 g/mol), moderate aqueous solubility, and a favourable synthetic accessibility score of 5.30 compared with approximately 6.7 for the two lantadenes. It should be emphasised that these are rule-based in silico predictions rather than direct measurements; compliance with such criteria increases the plausibility of, but does not guarantee, favourable oral bioavailability, safety, or clinical efficacy.

None of the three lead compounds was predicted to inhibit any of the five major cytochrome P450 isoforms evaluated, a favourable indication for low drug-drug interaction liability, and all three compounds were assigned to Cramer Class III by Toxtree, indicating the presence of structural features associated with a comparatively higher level of toxicological concern under this rule-based scheme, a classification broadly shared with several marketed small-molecule oncology agents; this remains a structure-based computational estimate rather than a measured toxicological endpoint and does not substitute for experimental toxicity testing [44, 51].

Considered jointly with the docking results, this ADMET profile suggests a differentiated development pathway for the two chemotypes rather than a single, uniform verdict of “promising” or “unpromising.” Peronemin A3 combines a comparatively favourable predicted drug-likeness profile with the highest binding-mode similarity to both the native EGFR ligand and osimertinib, which together make it a reasonable priority candidate for further validation, notwithstanding its comparatively modest absolute binding energies relative to the lantadenes [32]. Lantadene A and Lantadene B, conversely, deliver the strongest and most consistent computed binding energies across all three receptors, an encouraging pharmacodynamic signal, but will likely require formulation optimisation to address their poor predicted intrinsic aqueous solubility before this pharmacodynamic promise could plausibly translate into adequate pharmacokinetic performance in vivo [45]. It should be stressed that the present ADMET evaluation was limited to the physicochemical, pharmacokinetic, and acute toxicity-class parameters available through the prediction platform used here; mutagenicity (e.g., AMES), cardiac ion-channel liability (e.g., hERG), and other specialised toxicity endpoints were not assessed in this study and would need to be evaluated, computationally and experimentally, before any conclusion regarding the safety of these compounds could be drawn.

### 3.8. Integrated Discussion: Toward a Dual BRAF-EGFR-Directed Natural Lead

Synthesising the docking and ADMET findings, three convergent lines of evidence support the therapeutic rationale outlined at the outset of this article, while still falling short of demonstrating actual biological activity. First, Lantadene A, Lantadene B, and Peronemin A3 were the only compounds among the ten *Peronema* metabolites screened that ranked consistently among the top three or four performers across all three independent receptor systems, wild-type EGFR, mutated EGFR, and BRAF, a pattern not shared by any of the remaining seven peronemins or by lantanolic acid, which performed competitively at some but not all targets [46]. This consistency is the computational signature one would expect of a genuinely dual/multi-target chemotype, as opposed to a compound that happens to bind one receptor well by chance, although it remains a hypothesis generated from docking scores alone. Second, at the clinically most consequential target, mutated EGFR, all three lead compounds achieved computed binding energies broadly comparable to that of osimertinib, the current standard-of-care third-generation inhibitor, with differences of well under 1 kcal mol<sup>-1</sup> that fall within the typical uncertainty of the scoring function used; Peronemin A3 additionally achieved a binding-mode similarity to the native ligand that was numerically higher than osimertinib's own similarity score, engaging the Cys797 region implicated in covalent third-generation inhibitor design, though again this indicates pocket overlap rather than demonstrated inhibitory superiority [47]. Third, the ADMET evaluation indicates that at least one of the three candidates, Peronemin A3, possesses a favourable predicted small-molecule drug-likeness profile with zero rule-of-five violations, while the other two, though computationally the strongest binders overall, present a well-characterised and potentially addressable solubility limitation rather than an outright disqualifying liability [48].

These findings should be interpreted strictly within the boundaries of a computational screening study, and none of the comparative language used above should be read as evidence of actual EGFR or BRAF inhibition, still less of anticancer efficacy. Molecular docking, irrespective of the sophistication of the underlying scoring function, provides only a static, rigid-receptor approximation of what is in reality a dynamic, solvent-mediated, and often entropically driven binding event; docking scores correlate with, but do not equal, true binding free energy, and they cannot capture time-dependent phenomena such as induced-fit conformational adjustment or covalent bond formation, nor do they establish whether a compound would actually inhibit the catalytic activity of EGFR or BRAF in a biochemical kinase assay [49]. Similarly, in silico ADMET and Toxtree-based toxicity prediction cannot substitute for empirically measured pharmacokinetic and toxicological parameters obtained from actual biological systems [50, 51]. Molecular dynamics simulation, which could further validate the stability of the docked poses and provide a more rigorous estimate of binding free energy (for example via MM-PBSA/MM-GBSA), was not undertaken in the present study; this is consistent with the intended scope of the present work, a docking- and ADMET-based computational screen, and is identified as a valuable direction for subsequent, more resource-intensive studies rather than as a deficiency of the current screening

exercise. Consequently, the present results should be understood as a hypothesis-generating computational screen that identifies Lantadene A, Lantadene B, and Peronemin A3 as candidates warranting downstream experimental validation, specifically kinase inhibition assays against EGFR and BRAF and cell-based cytotoxicity assays in NSCLC lines, rather than as evidence of confirmed anticancer efficacy. This framing is consistent with how comparable *in silico* studies of both lantadene derivatives and *Peronema*-derived compounds against lung cancer targets have themselves been presented, namely as a rational triage step preceding, not replacing, *in vitro* and *in vivo* pharmacology [13, 14].

#### 4. Conclusion

This study computationally evaluated ten secondary metabolites from *Peronema canescens* leaves against wild-type EGFR, resistance-associated mutated EGFR, and BRAF, and identified Lantadene A, Lantadene B, and Peronemin A3 as the most consistent candidates for further evaluation as dual EGFR-BRAF-directed leads for NSCLC. Molecular docking showed favourable predicted binding at all three targets, with computed binding energies against mutated EGFR of  $-8.8 \text{ kcal mol}^{-1}$  (Lantadene A),  $-9.1 \text{ kcal mol}^{-1}$  (Lantadene B), and  $-8.6 \text{ kcal mol}^{-1}$  (Peronemin A3), each within a narrow margin of the value obtained for osimertinib; given the inherent uncertainty of docking scoring functions, these values should be read as broadly comparable rather than superior to those of the reference inhibitors. Residue-level interaction analysis extended to the BRAF binding site showed that all three lead compounds engage this target predominantly through hydrophobic and  $\pi$ -mediated (Alkyl/Pi-Alkyl/Pi-Sigma) contacts, with several residues, including Ile463, Phe595, Trp531, and Phe583, recurring across two or more compounds, lending further computational support to the dual-targeting hypothesis. Peronemin A3 additionally showed the highest binding-mode similarity to the native ligand at mutated EGFR (82.35%) and a comparatively favourable predicted ADMET profile, while the lantadenes showed the strongest and most consistent binding across all three receptors but would likely require solubility-oriented formulation strategies; all three compounds were classified as Cramer Class III by Toxtree, indicating a level of structural toxicological concern typical of many small-molecule oncology agents rather than a specific confirmed hazard. These results should be regarded as a hypothesis-generating *in silico* screen rather than proof of anticancer efficacy or of EGFR/BRAF inhibition. Future work should prioritise: (i) *in vitro* kinase inhibition and NSCLC cell-based cytotoxicity assays, including cell lines with acquired osimertinib resistance, to test whether the predicted computational advantage translates into measurable biological activity; (ii) solubility-oriented formulation strategies for the lantadenes; and (iii) molecular dynamics simulation and free-energy calculations for the lead complexes, which fall outside the intended scope of the present docking- and ADMET-based screening study but would provide a valuable, more resource-intensive extension in future work.

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#### 6. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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