

IN SILICO INVESTIGATION OF PHYTOCONSTITUENTS OF MEDICINAL HERB
PLUMBAGO ZEYLANICA AGAINST CANCER BY MOLECULAR DOCKING

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ABSTRACT

Background: Plumbago zeylanica Linn. (*Chitrak*) is a traditional medicinal herb in the Ayurvedic pharmacopoeia, valued for its anticancer, anti-inflammatory, and antimicrobial properties. While plumbagin, the principal bioactive naphthoquinone from this plant, has been extensively investigated, other phytoconstituents including chitranone and droserone remain largely unexplored as potential anticancer candidates. **Objective:** This study aimed to evaluate the anticancer potential of chitranone and droserone, two naphthoquinone derivatives from *P. zeylanica*, against the epidermal growth factor receptor (EGFR) kinase domain (PDB ID: 8A2B) using molecular docking and ADMET prediction, with doxorubicin as a reference standard. **Methods:** Phytoconstituents were identified from the IMPPAT database. The EGFR kinase domain crystal structure (resolution: 1.69 Å) was validated via Ramachandran plot analysis using PROCHECK. Molecular docking was performed using Auto Dock Vina 1.5.6. Binding interactions were visualized using Discovery Studio and PyRx. ADMET profiling was conducted using Swiss ADME and ProTox-II. **Results:** Chitranone demonstrated the highest binding affinity (-10.5 kcal/mol) with three hydrogen bonds and 16 total interactions, surpassing doxorubicin (-8.8 kcal/mol, four hydrogen bonds, 11 interactions). Droserone showed a binding energy of -7.1 kcal/mol with one hydrogen bond and seven interactions. Both naphthoquinones exhibited zero Lipinski violations, high gastrointestinal absorption, and favorable drug-likeness. Chitranone had a predicted LD₅₀ of 1000 mg/kg (toxicity class 4) vs. 205 mg/kg (toxicity class 3) for doxorubicin. **Conclusion:** Chitranone exhibited superior binding affinity to the EGFR kinase domain compared to doxorubicin, suggesting its potential as a lead compound for anticancer drug development. Both naphthoquinones warrant further in vitro and in vivo validation.

KEYWORDS: *Plumbago zeylanica*, *Chitranone*, *Droserone*, *EGFR*, *Molecular docking*, *ADMET*, *Naphthoquinone*, *Anticancer*, *In silico*.

1. INTRODUCTION

Cancer remains one of the foremost public health challenges worldwide, accounting for approximately 10 million deaths annually, thereby necessitating an ongoing search for novel therapeutic agents with improved efficacy and reduced adverse effects.^[1] The epidermal growth factor receptor (EGFR), a transmembrane receptor tyrosine kinase belonging to the ErbB family, plays a pivotal role in cellular proliferation, differentiation, migration, and survival signaling.^[2] Aberrant EGFR activation through mutation or

overexpression is implicated in numerous malignancies, particularly non-small-cell lung cancer (NSCLC), colorectal cancer, and head and neck cancers, making it a critical therapeutic target in oncology.^[3]

Medicinal plants have historically served as invaluable reservoirs of bioactive compounds for drug discovery, with an estimated 49% of currently used anticancer small molecules being either natural products or their direct derivatives.^[4] In this context, *Plumbago zeylanica* Linn. (commonly known as *Chitrak* in Ayurveda), a perennial

herbaceous plant belonging to the family Plumbaginaceae distributed across tropical and subtropical regions, has garnered considerable attention for its diverse pharmacological properties.^[5,6] This plant has been employed in the Indian Ayurvedic system of medicine for over 2,500 years for treating skin diseases, digestive disorders, rheumatic pain, hemorrhoids, and inflammatory conditions.^[7]

The phytochemical profile of *P. zeylanica* is characterized by naphthoquinones, flavonoids, alkaloids, coumarins, triterpenoids, and glycosides.^[8] Among these, plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is the most extensively studied constituent, with well-documented anticancer and antiproliferative activities against breast, lung, prostate, pancreatic, esophageal, and squamous cell carcinomas.^[9-11] Plumbagin exerts its anticancer effects through the modulation of multiple signaling cascades, including inhibition of NF- κ B, STAT3, PI3K/AKT, and Bcl-2 pathways.^[9-12]

However, beyond plumbagin, *P. zeylanica* harbors several other naphthoquinone derivatives whose anticancer potential remains relatively underexplored. Chitranone, a binaphthoquinone (Molecular weight- 374.34 g/mol; C₂₂H₁₄O₆), was first isolated from the roots of *P. zeylanica* alongside zeylanone, maritnone, and 2-methylnaphthazarin.^[13] Droserone (3,5-dihydroxy-2-methyl-1,4-naphthoquinone; Molecular weight- 204.18 g/mol; C₁₁H₈O₄) is a naturally occurring naphthoquinone found in the *Plumbaginaceae* and *Droseraceae* families.^[14] Recent investigations have demonstrated droserone's antiviral activity against measles virus and its antiausterity activity against

pancreatic cancer cells, suggesting broader pharmacological significance.^[15,16]

Molecular docking has emerged as an indispensable computational tool in structure-based drug discovery, enabling rapid prediction of ligand-receptor binding affinities and interaction profiles. The present study employs in silico molecular docking to evaluate the binding interactions of chitranone and droserone with the EGFR kinase domain (PDB ID: 8A2B), complemented by ADMET profiling. Doxorubicin, a widely used anthracycline chemotherapeutic agent, was used as a reference standard.

2. MATERIALS AND METHODS

2.1 Identification of Phytoconstituents

The phytoconstituents of *P. zeylanica* were traced from the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database.^[17] Chitranone and droserone were selected for molecular docking based on their structural characteristics and reported biological activities.

2.2 Protein Target Selection and Preparation

The three-dimensional crystal structure of the EGFR kinase domain (PDB ID: 8A2B), classified as a transferase, was retrieved from the RCSB Protein Data Bank. This structure represents the EGFR kinase domain with L858R/V948R mutations, from *Homo sapiens* expressed in *Spodoptera frugiperda*, resolved at 1.69 Å by X-ray crystallography (R-Value Free: 0.258; R-Value Work: 0.210; R-Value Observed: 0.212).^[4] Protein preparation involved removing co-crystallized ligands, water molecules, and heteroatoms, adding hydrogen atoms, and performing energy minimization using UCSF Chimera.

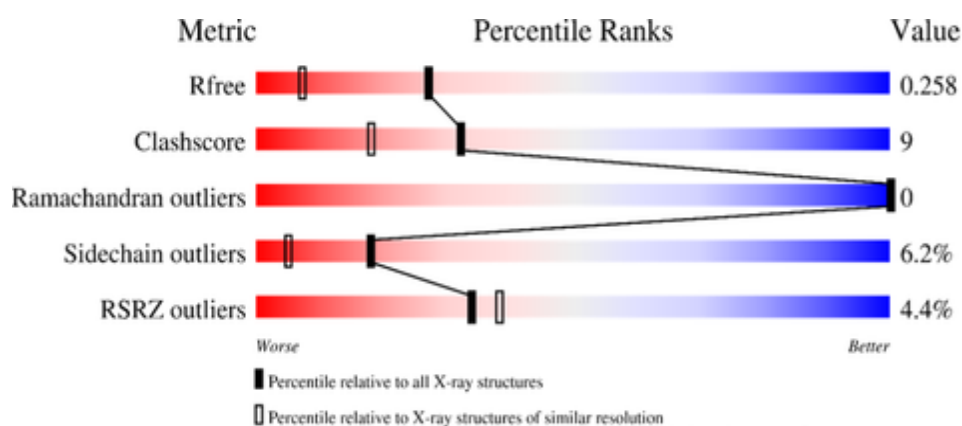


Fig1- PDB- Structure validation of 8A2B

Stereochemical quality was validated via Ramachandran plot analysis using PROCHECK.^[18] Of 239 non-glycine, non-proline residues, 223 (93.3%) occupied the most favored regions [A,B,L], 15 (6.3%) were in additionally allowed regions [a,b,l,p], 1 (0.4%) in generously allowed regions, and 0 (0.0%) in disallowed regions. The total

number of residues was 272, with 3 end-residues, 15 glycine and 15 proline residues.

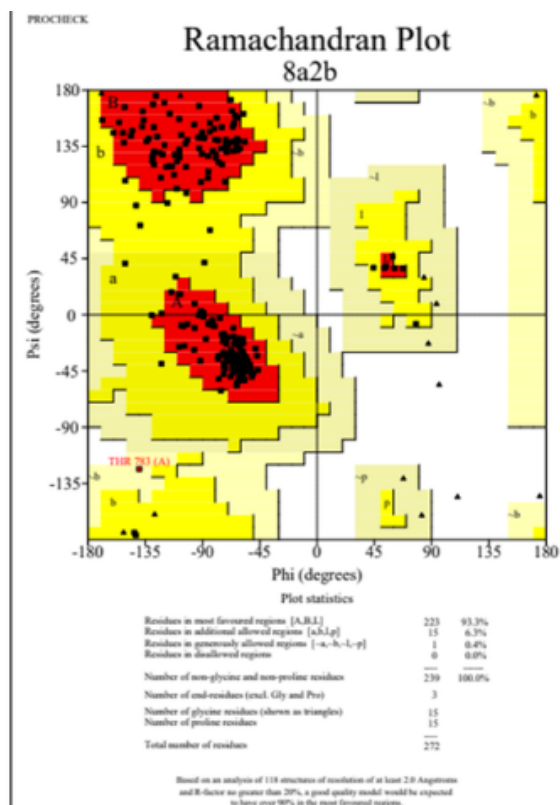


Fig 2 (A)- Ramchandran Plot

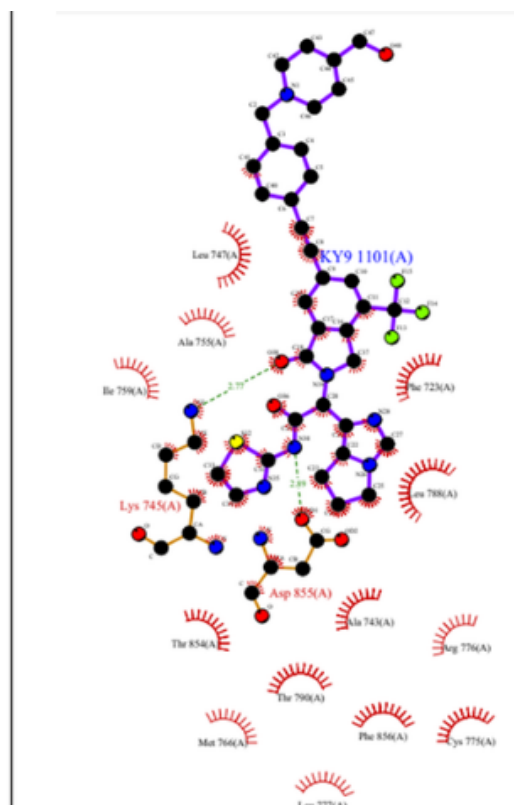


Fig 2(B)- LIGPLOT of interactions involving ligand KY9

2.3 Ligand Preparation

Three-dimensional structures of chitranone (28 atoms, 31 bonds, 1 rotatable bond, TPSA: 108.74 Å², logP: 3.28, molecular refractivity: 100.98), droserone (15 atoms, 16 bonds, 0 rotatable bonds, TPSA: 74.60 Å², logP: 1.45, molecular refractivity: 53.22), and doxorubicin (39 atoms, 43 bonds, 5 rotatable bonds, TPSA: 206.07 Å², logP: 0.7, molecular refractivity: 132.66) were obtained from PubChem. The ligands were prepared by optimizing their geometry, assigning Gasteiger charges, and converting them to PDBQT format for docking using AutoDock Tools.

2.4 Molecular Docking Protocol

Molecular docking studies were performed using Auto Dock Vina version 1.5.6.^[19] The grid box was centered on the active site of the EGFR kinase domain with appropriate dimensions to encompass the binding pocket. The exhaustiveness parameter was set to ensure thorough conformational sampling. The docking results were ranked based on binding energy (kcal/mol), and the best poses were selected for interaction analysis. Binding interactions, including hydrogen bonds, hydrophobic contacts, electrostatic interactions, and pi-stacking interactions, were analyzed and visualized using PyRx, Discovery Studio Visualizer molecular graphics software.

2.5 ADMET and Drug-likeness Prediction

Pharmacokinetic and drug-likeness properties of chitranone, droserone, and doxorubicin were predicted

using Swiss ADME.^[20] Parameters evaluated included physicochemical properties, lipophilicity, water solubility, pharmacokinetics (gastrointestinal absorption, blood-brain barrier permeability, P-glycoprotein substrate status, and cytochrome P450 enzyme inhibition), and drug-likeness criteria (Lipinski, Ghose, Veber, Egan, and Muegge filters). Toxicity was predicted using ProTox-II^[21], which provided LD₅₀ values, toxicity class, organ toxicity, Tox21 nuclear receptor and stress response pathways, molecular initiating events, and metabolic enzyme interactions.

3. RESULTS

3.1 Protein Structure Validation

The Ramachandran plot analysis confirmed excellent stereochemical quality with 93.3% of residues in most favored regions and none in disallowed regions.^[18] The co-crystallized ligand KY9 1101(A) showed interactions with Leu747, Ala755, Ile759, Phe723, Lys745, Leu788, Asp855, Ala743, Arg776, Thr854, Thr790, Met766, Phe856, Lys775, and Leu777, confirming the binding site architecture.

3.2 Molecular Docking Analysis

The docking results revealed differential binding affinities summarized in Table 1.

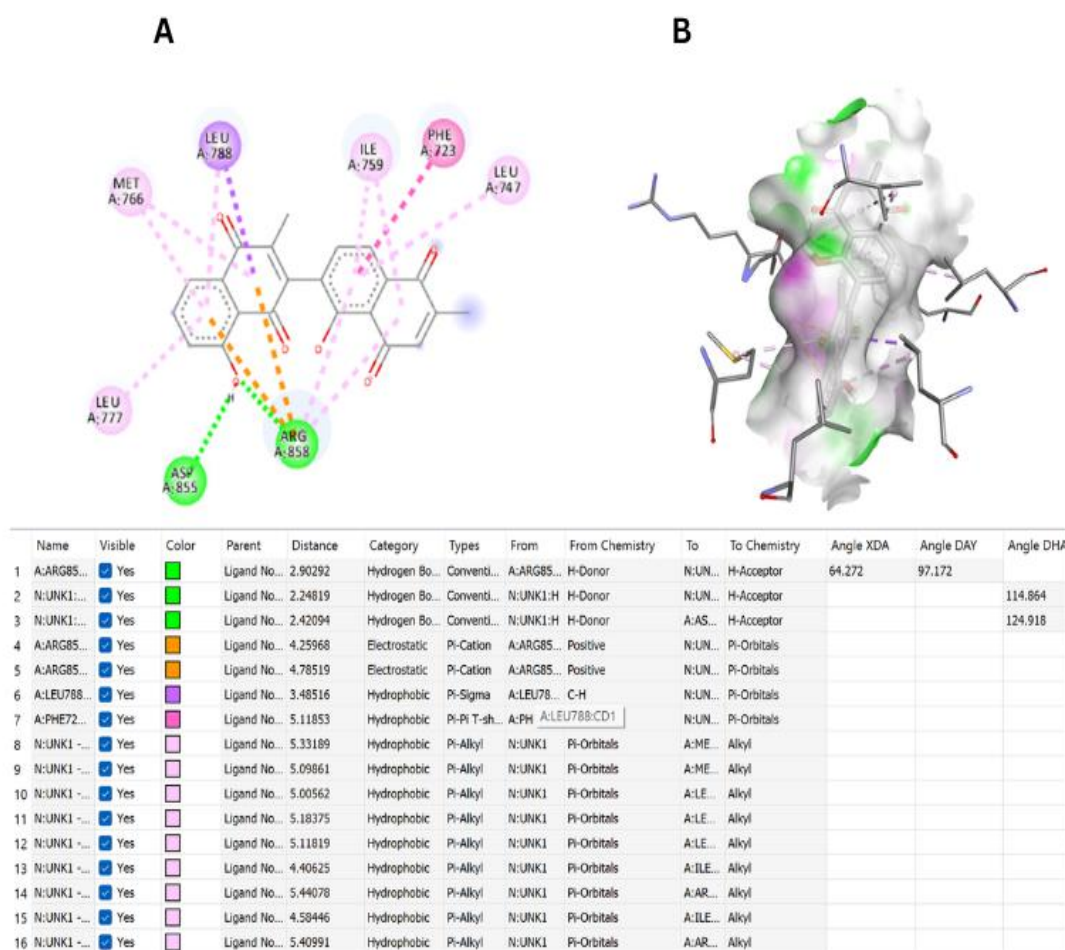
Table 1: Molecular docking results of ligands with EGFR kinase domain (PDB ID: 8A2B).

Ligand	Binding Energy (kcal/mol)	H-bonds	Total Interactions	Key Interacting Residues
Chitranone	-10.5	3	16	ARG858, ASP855, LEU788, MET766, PHE723, ILE759, LEU747, LEU777
Droserone	-7.1	1	7	ASP855, ARG858, LEU788, MET766, LEU777
Doxorubicin	-8.8	4	11	MET793, THR854, ASP855, VAL726, LEU718, ARG841, LEU844, ALA743

3.2.1 Chitranone-EGFR Interactions

Chitranone demonstrated the highest binding affinity (-10.5 kcal/mol) with 16 total interactions. Three conventional hydrogen bonds were identified: ARG858 as H-donor to ligand H-acceptor (2.90 Å; angle XDA: 64.27°, DAY: 97.17°), ligand H-donor to ligand H-acceptor (2.25 Å; angle DHA: 114.86°), and ligand H-donor to ASP H-acceptor (2.42 Å; angle DHA: 124.92°).

Two pi-cation electrostatic interactions were observed with ARG858 (4.26 and 4.79 Å). A pi-sigma hydrophobic interaction was formed with LEU788 (3.49 Å), and a pi-pi T-shaped interaction with PHE723 (5.12 Å). Nine pi-alkyl contacts engaged MET766 (two contacts), LEU777, LEU747 (two contacts), ILE759, and ARG858 (two contacts), with distances ranging from 4.41 to 5.41 Å.

**Fig-3- Chitranone- EGFR interactions -(A)- 2D representation and (B) binding mode representation**

3.2.2 Droserone-EGFR Interactions

Droserone showed a binding energy of -7.1 kcal/mol with seven interactions. One conventional hydrogen bond was formed between a ligand H-donor and ASP H-acceptor (2.56 Å; angle DHA: 101.62°, HAY: 99.82°).

Two pi-cation electrostatic interactions involved ARG858 (4.06 and 4.76 Å). A pi-sigma interaction with LEU788 (3.54 Å) and three pi-alkyl contacts with MET766 (5.22 Å) and LEU777 (4.99 and 4.84 Å) completed the profile.

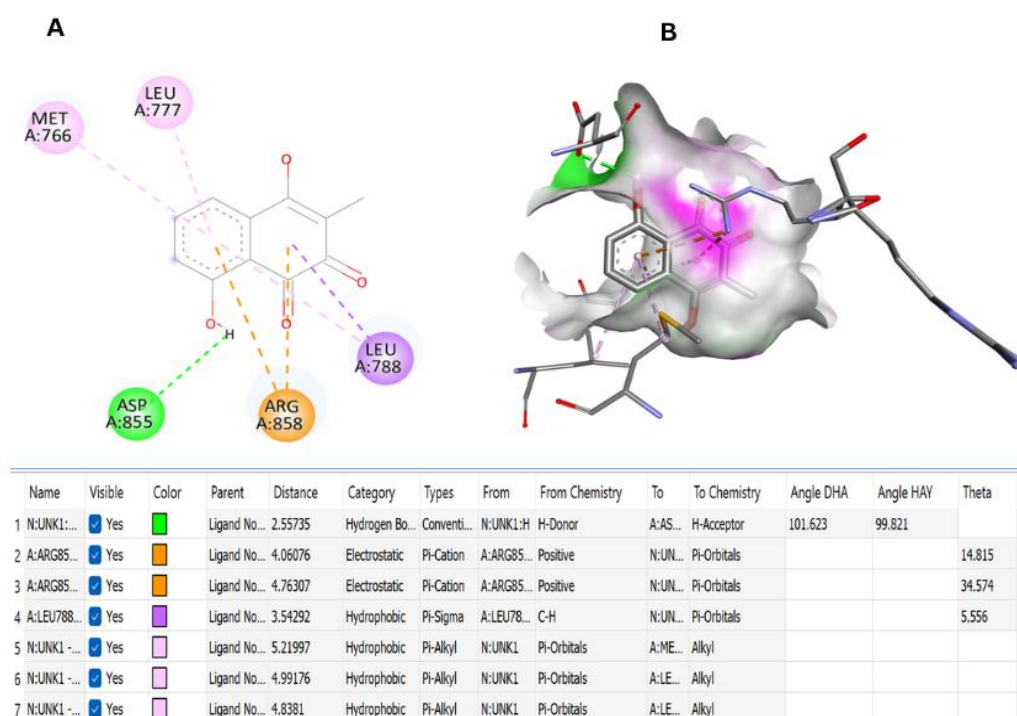


Fig 4- Droserone-EGFR Interactions- (A)- 2D representation and (B) -binding mode representation

3.2.3 Doxorubicin-EGFR Interactions

Doxorubicin showed a binding energy of -8.8 kcal/mol with 11 interactions. Four hydrogen bonds involved MET793 (3.39 Å), THR854 (2.79 Å), and two ligand-ASP/ligand contacts (2.25 and 2.20 Å). Two pi-sigma

interactions with LEU718 (3.64 Å) and VAL726 (3.89 Å), two alkyl contacts with ARG841 and LEU844, and three pi-alkyl contacts with ALA743, LEU844, and LEU completed the interaction profile.

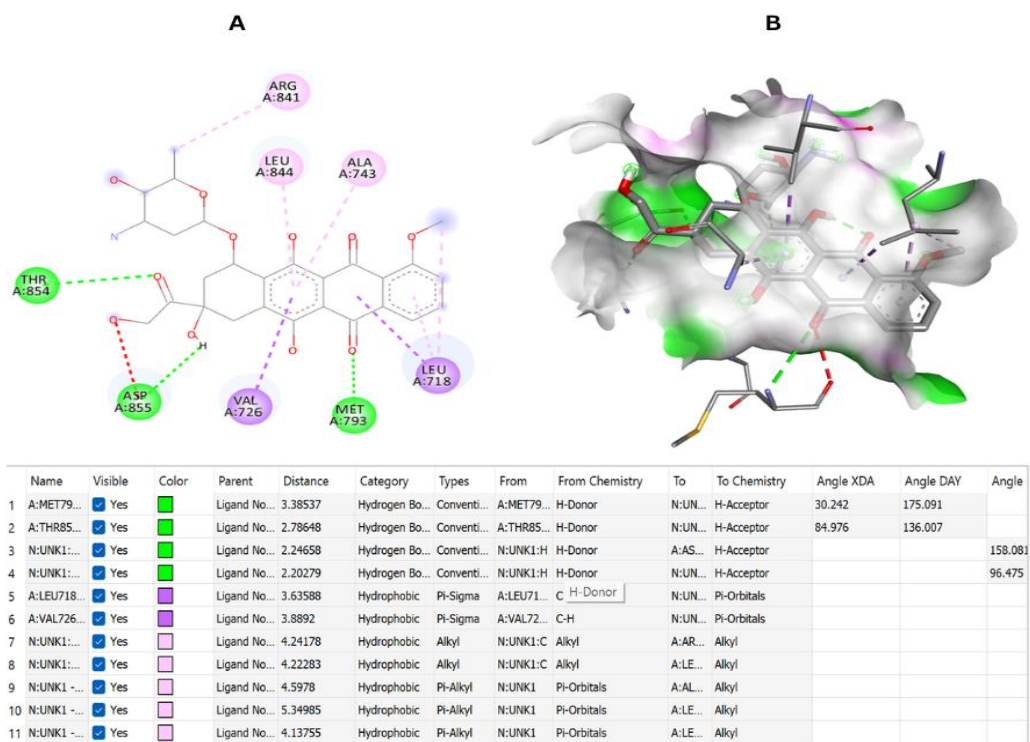


Fig 5- Doxorubicin-EGFR Interactions- (A)- 2D representation and (B) -binding mode representation

3.3 ADMET and Drug-likeness Profiling

The Swiss ADME profiles are summarized in Table 2.

Table 2: Comparative physicochemical, pharmacokinetic, and drug-likeness profiles (Swiss ADME).

Parameter	Chitranone	Droserone	Doxorubicin
Formula	C ₂₂ H ₁₄ O ₆	C ₁₁ H ₈ O ₄	C ₂₇ H ₂₉ NO ₁₁
Molecular Weight (g/mol)	374.34	204.18	543.52
Rotatable Bonds	1	0	5
H-bond Acceptors / Donors	6 / 2	4 / 2	12 / 6
TPSA (Å ²)	108.74	74.60	206.07
Consensus Log P	2.88	1.13	0.52
GI Absorption	High	High	Low
BBB Permeant	No	No	No
P-gp Substrate	No	No	Yes
CYP1A2 / CYP2C9 / CYP3A4 Inh.	Yes / Yes / Yes	Yes / No / Yes	No / No / No
CYP2C19 / CYP2D6 Inh.	No / No	No / No	No / No
Lipinski	Yes; 0 violation	Yes; 0 violation	No; 3 violations
Bioavailability Score	0.55	0.85	0.17
PAINS	2: ene_one_D, quinone_A	2: imine_one_A, quinone_D	1: quinone_A
Brenk	0 alert	1: diketo_group	1: hydroquinone
Leadlikeness	No; MW>350, XLOGP3>3.5	No; MW<250	No; MW>350
Synthetic Accessibility	3.52	2.62	5.81

3.4 Toxicity Prediction (ProTox-II)

Comparative toxicity predictions are shown in Table 3.

Table 3: ProTox-II toxicity predictions.

Parameter	Chitranone	Droserone	Doxorubicin
Predicted LD ₅₀ (mg/kg)	1000	707	205
Toxicity Class	4	4	3
Hepatotoxicity	Inactive (0.63)	Inactive (0.6)	Inactive (0.86)
Neurotoxicity	Inactive (0.78)	Inactive (0.84)	Active (0.74)
Nephrotoxicity	Active (0.56)	Active (0.50)	Active (0.80)
Respiratory Toxicity	Active (0.66)	Active (0.66)	Active (0.91)
Cardiotoxicity	Inactive (0.84)	Inactive (0.78)	Active (0.64)
Immunotoxicity	Active (0.95)	Active (0.52)	Active (0.99)
Mutagenicity	Inactive (0.74)	Active (0.73)	Active (0.98)
Cytotoxicity	Inactive (0.68)	Inactive (0.71)	Active (0.94)
BBB Barrier	Active (0.51)	Active (0.50)	Inactive (1.0)
Clinical Toxicity	Active (0.58)	Active (0.63)	Active (0.84)

4. DISCUSSION

The present in silico investigation reveals that chitranone demonstrates remarkable binding affinity (−10.5 kcal/mol) to the EGFR kinase domain, surpassing doxorubicin by 1.7 kcal/mol. This difference is pharmacologically significant, as each kcal/mol corresponds to approximately a 5-fold change in binding constant at physiological temperature.^[22] Both chitranone (−10.5 kcal/mol) and droserone (−7.1 kcal/mol) exceeded the −7.0 kcal/mol threshold indicating strong binding.^[23]

Chitranone's superior affinity derives from its expanded bi-naphthoquinone scaffold enabling 16 interactions including nine pi-alkyl contacts, complemented by hydrogen bonds with catalytically important ARG858 and ASP855 residues. The L858R mutation in 8A2B is one of the most common activating mutations in EGFR-

driven NSCLC. Chitranone's favorable interaction with this mutant suggests relevance for targeting clinically important EGFR variants.

The interaction profiles overlap substantially between chitranone and droserone at key residues LEU788, MET766, LEU777, ASP855, and ARG858, which span the hinge region and activation loop critical for kinase catalytic activity.^[24,25] PHE723 engagement via pi-pi T-shaped interaction mirrors patterns observed for established EGFR inhibitors gefitinib and erlotinib.^[24] Droserone's recently reported anti-austerity activity against PANC-1 cells via Akt pathway suppression, combined with its EGFR binding demonstrated here, suggests multi-target therapeutic potential along the EGFR–Akt axis.^[26]

The ADMET analysis reveals markedly superior drug-likeness for both naphthoquinones compared to doxorubicin. Zero Lipinski violations, high gastrointestinal absorption, and absence of P-gp substrate activity contrast sharply with doxorubicin's three Lipinski violations and P-gp substrate status that contributes to multidrug resistance.^[27,28] Droserone's bioavailability score (0.85) was highest among all compounds. The absence of cardiotoxicity predictions for both naphthoquinones contrasts favorably with doxorubicin's well-documented dose-limiting cardiotoxicity.^[29] Higher LD₅₀ values (chitranone: 1000 mg/kg; droserone: 707 mg/kg) compared to doxorubicin (205 mg/kg) further support improved safety profiles.

PAINS alerts for quinone-containing structural motifs^[30] necessitate careful experimental validation to distinguish genuine target-specific activity from assay artifacts. The predicted mutagenicity of droserone requires investigation via appropriate genotoxicity assays. Synthetic accessibility scores indicate droserone (2.62) is more readily synthesizable than chitranone (3.52), potentially influencing development feasibility. These findings align with recent network pharmacology studies identifying EGFR as a key *P. zeylanica* target in breast and prostate cancers^[26,31], extending knowledge to specific chitranone and droserone interactions.

It should be noted that molecular docking represents a preliminary computational assessment. Predicted affinities require validation through enzyme inhibition kinetics, cell-based proliferation assays, and ultimately in vivo efficacy studies. The anti-cell proliferation effects of other *P. zeylanica* naphthoquinone dimers, such as maritnone, have been experimentally confirmed^[32], providing precedent for the potential bioactivity of structurally related chitranone.

5. CONCLUSION

This study demonstrates that chitranone from *P. zeylanica* exhibits superior binding affinity (−10.5 kcal/mol, 16 interactions) to the EGFR kinase domain compared to doxorubicin (−8.8 kcal/mol, 11 interactions), with extensive hydrogen bond, electrostatic, and hydrophobic interactions at key active site residues. Droserone also showed favorable binding (−7.1 kcal/mol) with excellent drug-likeness (bioavailability score: 0.85). Both naphthoquinones demonstrated superior ADMET profiles with zero Lipinski violations, high GI absorption, no P-gp substrate activity, and lower predicted toxicity than doxorubicin. These findings provide a strong rationale for experimental validation of chitranone and droserone as potential anti-EGFR anticancer agents.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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