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DFT, molecular docking, and ADMET prediction of compounds from *Cinnamomum zeylanicum* for dengue inhibitor DEN2 NS2B/NS3 serine protease

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ABSTRACT

Dengue, an infectious disease transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, is caused by a virus. This study aimed to assess whether compounds isolated from cinnamon (*Cinnamomum zeylanicum*) possess antidengue properties and whether the bonds formed after docking these compounds are stable. Three compounds from the NADI database were chosen as samples, with panduratin A serving as the positive control. Molecular docking simulations were conducted alongside density functional theory (DFT) studies using Gauss View 5. The docking results indicated that delta-Cadinene (compound **3**) exhibited the lowest binding free energy of -4.93 kcal/mol, with a binding factor of 9. According to density functional theory (DFT) calculations, panduratin A, and compound **3** displayed gap values of -0.26 and -0.24, respectively. Thus, compound **3** demonstrates potential as a highly stable inhibitor of dengue DEN2 NS2B/NS3 serine protease.

Keywords: *Cinnamomum zeylanicum,* dengue, DFT, docking, ADMET

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INTRODUCTION

Dengue virus is a positive single-stranded RNA virus transmitted through mosquito bites from the Flaviviridae family of the genus Flavivirus[1]. Dengue virus is transmitted through the saliva of infected mosquitoes[2]. Viruses use host cell ribosomes for the translation of genomic RNA into polyproteins. The translation of genomic RNA into polyproteins forms structural and non-structural proteins[3]. NS2B and NS3 proteins are attractive targets for new antiviral therapies. The N-terminal NS3 with its cofactor NS2B is a protease that can cleave the polyprotein in the virus. NS2B/NS3 functions as a link to the flavivirus replication complex and modulates viral pathogenesis and the host immune response[4]. NS3 activity depends on its cofactor NS2B (47 amino acids) in forming the NS2B/NS3 complex[5]. Disturbances in NS2B and NS3 inhibit viral replication[6].

Drug discovery is a time-consuming and expensive process. Molecular docking is a computational procedure used to predict the chemical bonding between a protein (receptor) and small molecule (ligand) in order to form a stable complex. it aims to predict the complex intermolecular structures formed between two or more molecular constituents, which can ultimately be used to predict the binding affinities of two molecules[7,8]. Another computational method that can be employed is the density functional theory (DFT) method. DFT is a useful approach for solving the Schrödinger equation in systems with multiple particles. The underlying principle of this method is that the energy of a molecule can be determined based on its electron density. Unlike traditional methods, DFT does not treat electrons as discrete entities. But rather calculates results based on the electron density. This method is convenient because it can produce results that are comparable to experimental data without requiring a significant amount of time.

Cinnamon (*Cinnamomum zeylanicum*), a tropical plant, is renowned for its culinary use and associated health benefits[9]. Its leaves and bark are commonly used as flavourings and cooking seasonings. Notably, cinnamon essential oil, derived from this plant, contains key compounds such as cinnamaldehyde (60.72%), eugenol (17.62%), and coumarin (13.39%)[10]. Research suggests that cinnamon essential oil can serve as an effective repellent against *Aedes aegypti* mosquitoes, which transmit diseases such as dengue fever. The strong aroma of essential oils is unappealing to mosquitoes, prompting them to avoid areas where such scents are present, thereby reducing the risk of mosquito-borne illnesses.

This study involved acquiring compounds from the NADI database which is a repository of natural products. Three similar compounds (cadalene, cadina-1(2), 4-diene, and delta cadinene) sourced from *Cinnamomum zeylanicum* were selected for computational analysis. Similar compounds in this context are chemical compounds with comparable structural or functional characteristics that potentially influence their biological activities or chemical behaviors[10]. These compounds were chosen for their similarity in terms of chemical composition or properties, facilitating comparative analysis in this study. These compounds were subjected to docking simulations to assess their potential bioactivity. In addition, their drug-likeness was evaluated to predict their pharmacokinetic properties as potential drugs. Furthermore, density functional theory (DFT) calculations were performed on these compounds to ascertain their efficacy as inhibitors against dengue DEN2 NS2B/NS3 viruses. To date, although there has been research on the discovery of new dengue inhibitors using *in silico* tools, it has not been extensively studied. Thus, the primary aim of this research was to identify novel inhibitors derived from *Cinnamomum zeylanicum* that target the NS2B/NS3 serine protease against the dengue virus.

METHODOLOGY

Molecular docking

The structure of the isolated compound from *Cinnamomum zeylanicum* is accessible through http://www.nadi-discovery.com. Three similar compounds were selected as the ligands. Chemdraw Professional 15.0, was used to sketch the molecular structures of the ligands, and Panduratin A was used as a positive control. The 3D structure was then prepared using the Molecular Operating Environment (MOE) 2022.0901 software package with an MMFF94x force field and 0.0001 gradient. Figure 1 shows the molecular structure of the ligands.

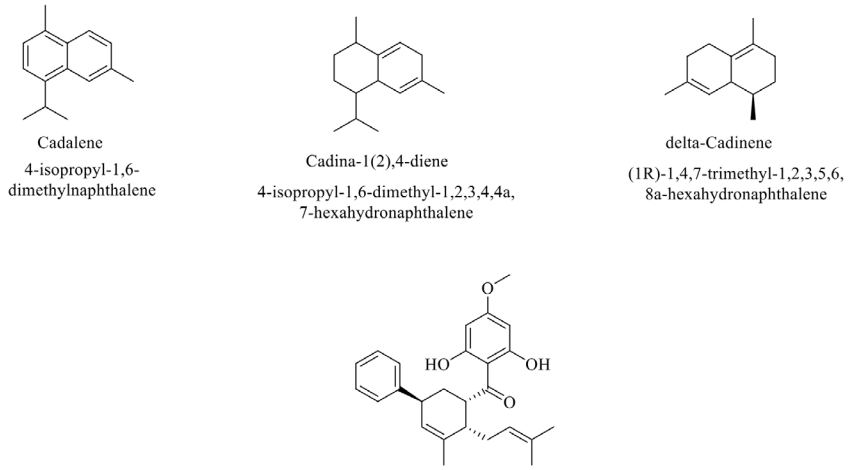


Figure 1. Molecular structure of ligands

The protein structure was obtained from the https://www.rcsb.org/ website, identified by the PDB code 2FOM. The crystallographic representation of this protein was generated using MOE 2022.0901 and DSV 2020 (Biovia). Chains A and B constitute two chains that form the 2FOM protein. Water molecules, natural ligands, and Cl^- ions associated with the protein were excluded. The molecular arrangement of the protein was established using the MOE 2022.0901 software package. The construction of the protein involved setting the parameter, specifically the root mean square (RMS) gradient, to 0.01 kcal/mol/A, employing CHARMM27 as the force field. Energy minimization was applied to alpha the carbon, H, and backbone atoms[11]. Following this, the constructed structure was saved in the PDB format to facilitate its later use as a docking receptor.

A site finder was used to identify the protein's active site prior to docking. Leu128, Asp129, Phe130, Ser131, Pro132, Ser135, Tyr150, Gly151, and Gly153 composed site whereas His51, Lys74, Asp75, Gly151, Asn152, Gly153, and Val154 composed site 13. Site 13 was established as a dummy atom to serve as the docking target site. Subsequently, the ligand structure, contained within an MDB file, was selected as the ligand, and the site was configured in the docking menu to function as a dummy atom. Following this, the refinement parameters were adjusted to rigid, the posture to 50 and 10, and the placement set to triangle visualization. Optimal docking sites, demonstrating similar binding interactions to the positive control, were identified based on several criteria, including binding free energy, root mean square deviation (RMSD), and binding factor.

Density functional theory

The Gaussian software was employed for molecular simulations. Density functional theory (DFT) was utilized to optimize the molecular geometry of each molecule in the gas phase. All quantum chemical calculations were conducted at the B3LYP level using the 6-31G basis set.

Drug-likeness and ADMET properties

SwissADME, an online tool developed by the Swiss Institute of Bioinformatics and accessible at http://www.swissadme.ch, was used for *in silico* ADME screening and drug-likeness assessment[12]. This screening process targeted compounds with high binding free energy scores. Various physical and chemical parameters such as atom counts, polar surface area (PSA), molecular weight (MW) and molecular refractivity (MR), were calculated. The drug-likeness of candidates was evaluated using the Rules of 5 (RO5) criteria established by many scientists. Abbot Bioavailability scores, based on the total charge, TPSA, and compliance with Lipinski's filter, were computed to predict the likelihood of at least 10% oral bioavailability for a given chemical. Lipophilicity was assessed using the iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT models, and a consensus log Po/w[12] was derived. The solubility (log S) of the selected ligands was determined using three alternative models: ESOL[13], Ali[14], and SILICOS-IT[12].

RESULTS and DISCUSSION

Molecular docking

Molecular docking is a computational method employed to predict the interaction between a macromolecule (receptor) and small molecule (ligand) by simulating their chemical bonding based on their structures[15]. This technique is crucial in drug design as it enables the prediction of how small drug molecules bind to target proteins and facilitates the estimation of free binding energy and molecular activity[16].

Through molecular docking, various parameters were derived, including root mean square deviation (RMSD) and binding free energy (ΔG) measured in kcal/mol. The binding free energy signifies the energy required for a ligand to bind to a protein, where smaller values indicate a more stable association between the ligand and the protein[17]. RMSD values, on the other hand, indicate discrepancies or errors in docking. Lower RMSD values suggest smaller deviations or errors during the docking process. The selection of the best ligand-protein complex poses was based on the combination of the lowest binding free energy and RMSD values. Additionally, Van der Waals interactions and

hydrogen bonding were considered as supportive parameters to evaluate the stability of the ligand in relation to the receptor[16].

Based on the docking results presented in Table 1, panduratin A was used as a positive control, it showed a binding free energy of -6.8354 kcal/mol and an RMSD of 0.8704. Panduratin A forms Van der Waals interactions with the amino acid residue Asp75, which facilitates its binding to other amino acids. Moreover, panduratin A interacts with amino acid residues including Tyr161, Gly 53, His51, Pro132, Asn152, Ser131, Leu128, Tyr150, Phe130, Ser135, and Gly151. The spatial arrangement of panduratin A the protein can be seen in Figure 2.

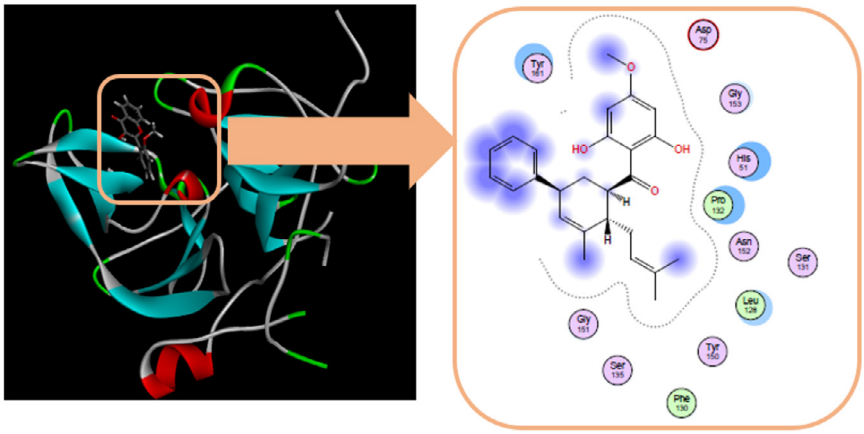


Figure 2. Spatial arrangement of the binding site for panduratin A as positive control

Table 1. Docking results

Compounds	Binding free energy (kcal/mol)	RMSD	Hydrogen bond	Hydrophobic interaction	Van der Waals interaction	Another interaction	Binding factor
Panduratin A	-6.83	0.87	-	-	Asp75	Tyr161, Gly153, His51, Pro132, Asn152, Ser131, Leu128, Tyr150, Phe130, Ser135, Gly151	12
1	-4.62	0.79	-	Arg54	**Asp75**	Trp50, Val72, **His51, Gly151, Asn152, Gly153, Tyr161**	6
2	-4.34	0.58	Tyr161	Arg54	**Asp75**	Val72, Trp50, **His51, Gly153**	3
3	-4.93	1.29	Tyr161, His51	-	-	**Ser135, Ser131, Gly153, Gly151, Pro132, Asn152, Tyr150, Phe130, Leu128**	9

Based on the docking data for compound **1**, an RMSD value of 0.79 and a binding free energy of -4.62 kcal/mol bind through Arg54, Asp75, Trp50, Val72, His51, Gly151, As152, Gly153, and Tyr161. Upon visualization, interactions were observed between compound **1** and the amino acid residues Arg54 and Asp75 through hydrophobic and Van der Waals bonds, respectively. Additionally, other interactions were observed between compound 1 and the amino acid residues Trp50, Val72, His51, Gly151, Asn152, Gly153, and Tyr161.

Superimposition analysis of compound 1 with a positive control (panduratin A) showed that compound **1** did not bind to the active site. The size of compound **1** is not able to penetrate deeply into the cavity of the NS2B/NS3 serine protease active site. Therefore, compound **1** cannot be classified as a potential inhibitor of NS2B or NS3. The spatial arrangement of compound **1** and its superimposition with panduratin A is shown in Figure 3.

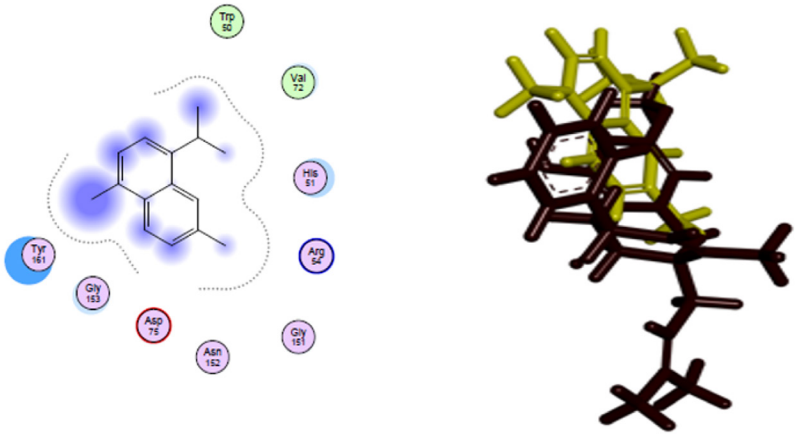


Figure 3. Visualization of (a) spatial arrangement of compound **1** (b) superimposition of compound **1** (yellow) and panduratin A (brown)

Based on the docking analysis, compound **2** exhibited a binding free energy value of -4.34 kcal/mol, with an RMSD value of 0.5809. Comparatively, panduratin A (used as the positive control) had a lower negative binding free energy than compound **2**. It is important to note that no hydrogen bonding was observed between compound **2** and the amino acid residues surrounding its binding site. However, the compound did engage in hydrophobic interactions with the amino acid residue Arg54 and interacted with the catalytic triad Asp75 through Van der Waals interactions. Despite these interactions, compound **2** only demonstrated three binding factors with the positive control, suggesting that it may not penetrate deeply into the active site cavity of NS2B/NS3 serine protease. Consequently, compound **2** may not be a potential inhibitor of dengue virus DEN2 NS2B/NS3 serine protease. The spatial arrangement of compound **2** with the protein and superimposition is depicted in Figure 4.

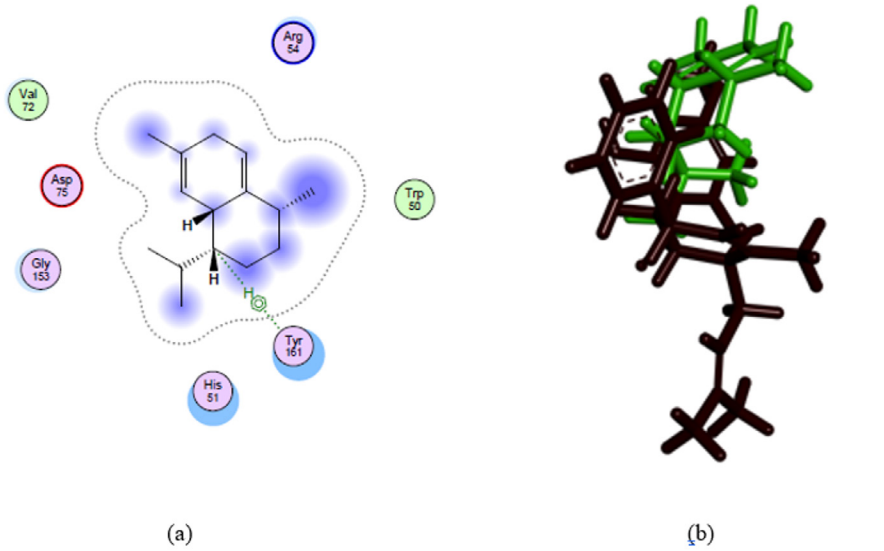


Figure 4. Spatial arrangement of compound **2** (a) and (b) superimposition of compound **2** (green) and positive control (brown)

The docking method was verified by superimposing the ligand and the positive control. This demonstrated how several significant residues could effectively bind to the ligands during the binding process. Superimposition was also utilized[18-20] to determine the properties of the active components that can stabilize the interaction between the ligand and the protein target. Additionally, superimposition was used to simultaneously evaluate the orientation of the ligands and the receptor simultaneously[20].

Based on the docking results in Table 1, compound **3** was found to have a binding free energy value of -4.93 kcal/mol and an RMSD of 1.62. Panduratin A had a more negative value than compound **3**, indicating that it was more challenging for compound 3 to bind to the active site of the NS2B/NS3 serine protease. Based on visualization of the docking results, it was observed that compound **3** interacted through hydrogen bonding with the amino acid residues Tyr161 and His51. In addition, compound **3** was able to interact with other amino acids (Ser135, Ser131, Gly153, Gly151, Pro132, Asn152, Tyr150, Phe130, and Leu128 through different interactions). The presence of hydrogen bonding with one of the catalytic triads (His51) may potentially explain why compound **3** had a better binding free energy compared to compounds **1** and **2**. The spatial arrangement of compound **3** and its superimposition with panduratin A are shown in Figure 5.

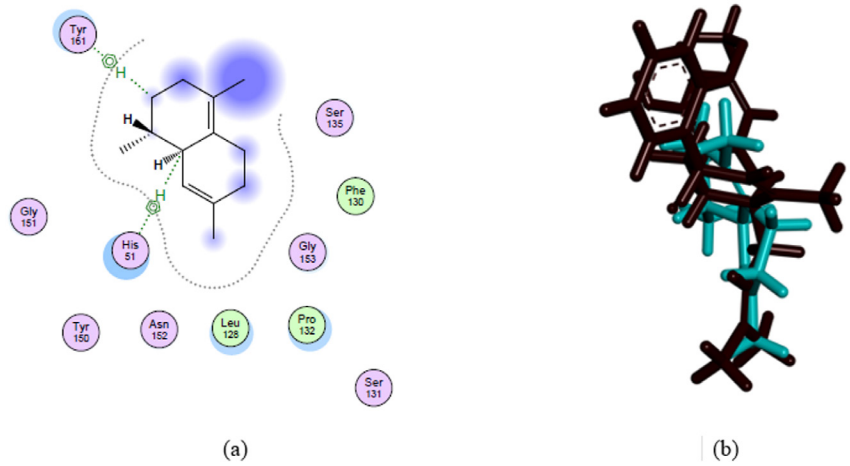


Figure 5. Visualization of (a) spatial arrangement of compound **3** (b) superimposition of compound **1** (blue) and panduratin A (brown)

DFT calculation

The gas-phase structures of compound **3** and panduratin A were optimized using Density Functional Theory (DFT) with the B3LYP approach and the 6-31 G basis set[19], implemented through the Gaussian program. The chemical stabilities of these compounds were assessed using the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO)[21,22]. Energy gap and chemical reactivity descriptors were determined using the DFT/B3LYP/6-31G method, and the results are presented in Table 2. Figure 6 illustrates the HOMO and LUMO of compound **3** and panduratin A.

Table 2. DFT calculation

Compound	Energy (au)	Structure Electronic		Energy gap
		HOMO	LUMO	
Senyawa 3	-507.44	-0.21	-0.02	-0.24
Panduratin A	-130.97	-0.22	-0.04	-0.26

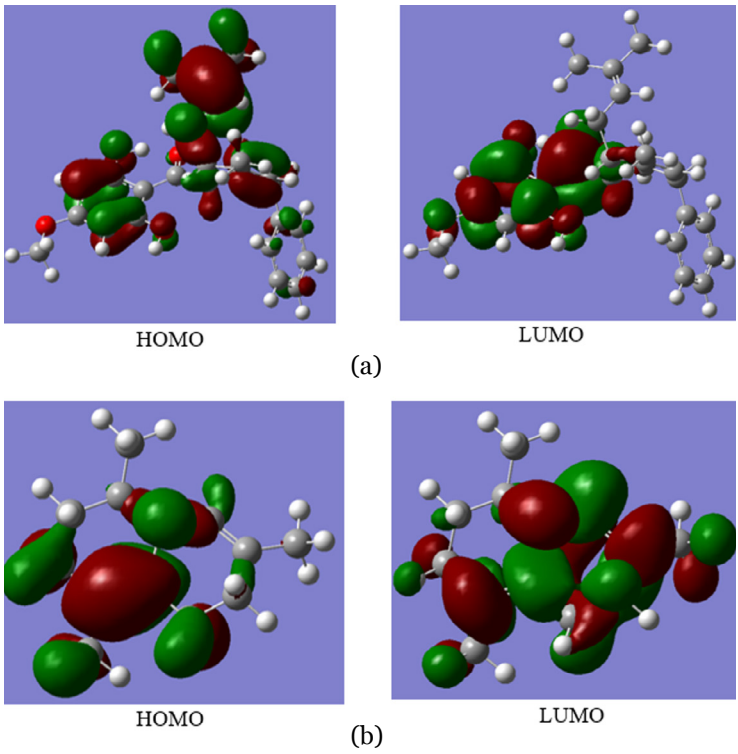


Figure 6. HOMO and LUMO for (a) compound **3** and (b) panduratin

Drug-likeness and ADMET properties

In order for a molecule to be considered a potential drug candidate, it must possess appropriate pharmacokinetics and safety properties[23]. Additionally, it should exhibit the necessary biological action. Compound **3** as determined by ADME analysis has a molecular weight of 176.30 kcal/mol, but it has no hydrogen bond donors or acceptors. This compound has a lipophilicity value of 3.57, which indicates optimal lipophilicity and enables to achieve good bioavailability when administered orally. Table 3 depicts the ADME analysis for compound **3**.

Table 3. ADME analysis

Compound	Cpd 3
Physicochemical properties	
Number of H-bond acceptors	0
Number of H-bond donors	0
Molecular weight (g/mol)	176.30
Number of heavy atoms	13
Number of aromatic Heavy atoms	0
Fraction Csp3	0.69
Number of rotable bonds	0
Molar refractivity	59.43
TPSA ($Å^2$)	0.00
Lipophilicity	
iLOGP	3.06
XLOGP3	3.01
WLOGP	4.09
MLOGP	4.11
SILICOS-IT	3.58
Consensus Log $P_{o/w}$	3.57
Water solubility	
ESOL	-2.83
Ali	-2.67
SILICOS-IT	-3.08
Pharmacokinetics	
GI absorption	Low
BBB permeation	Yes
Skin permeation Log K_p (cm/s)	-5.24

Veber and Muegge rules state that the maximum number of rotatable bonds in a molecule is 10 and 15, respectively. Compound **3** was examined using the Veber and Muegge criteria and was found to have a maximum of seven rotatable linkages. The aliphatic degree of a molecule is determined by the fraction of sp3 carbon atoms, which is also used to predict solubility. It is hypothesized that increasing saturation increases the clinical success rate 24, 25. In this study, Compound **3** had substantially higher degrees of saturation compared to the majority of other compounds studied, with a proportion of C sp3 of 0.69, which is higher than 0.25. Compound **3** had an XLOGP3 value of 3.01. PAIN analysis showed no alerts; in the Brenk analysis, only one alert was found, and no violations were observed in the lead-likeness analysis. The results indicated that the synthetic accessibility scores ranged from 1.60–4.55. The drug-like properties are presented in Table 4.

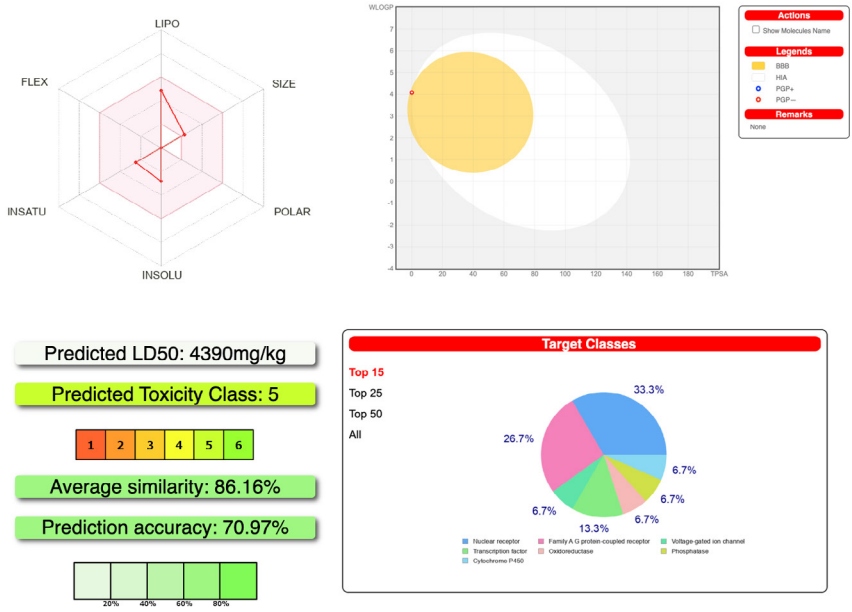
Table 4. Drug-likeness

Compound	Cpd 3
Drug-likeness	
Lipinski	Yes
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No
ABS	0.55
Medicinal chemistry	
PAINS (Alerts)	0
Brenk (alerts)	1
Leadlikeness	No (1)
Synthetic accessibility	3.94

Based on Pro-Tox II calculations, it appears that compound **3** falls into the five parameters used for predicting toxicity: size, lipophilicity, insolubility, insaturation, and flexibility. Furthermore, compound **3** was predicted to be an inhibitor of nuclear receptors, family A G protein-coupled receptors, and transcription factors with probabilities of 33.3%, 26.7%, and 13.3%, respectively. The toxicity model report in Figure 7 demonstrates that compound **3** affects only the aromatase target.

The BOILED-Egg method proved effective in predicting the permeability of the human blood-brain barrier (BBB) and gastrointestinal absorption based on polarity (topological polar surface area, TPSA) and lipophilicity (WLOGP).

In this study, compound **3** exhibited a WLOGP value of 4. Molecules were depicted as points in the yolk of boiled eggs. Molecules positioned in the white region (BOILED Egg's white) were expected to passively absorption through the gastrointestinal system, while points situated in the black region (BOILED Egg's black) were predicted to actively penetrate the BBB. P-glycoprotein is presumed to expel certain chemicals from the central nervous system, as indicated by the blue (PGP+) and red (PGP-) dots.



Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.78
Toxicity end points	Carcinogenicity	carcino	Inactive	0.68
Toxicity end points	Immunotoxicity	immuno	Inactive	0.58
Toxicity end points	Mutagenicity	mutagen	Inactive	0.65
Toxicity end points	Cytotoxicity	cyto	Inactive	0.72
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.91
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Active	0.56
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.81
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.90
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.90
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.88
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.99
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99

Figure 7. Toxicity results (middle left and bottom), prediction of drug (middle-right), BOILED-Egg model (top-right) together with the bioavailability radar

STATEMENT OF ETHICS

All the necessary ethical rules were followed while performing research.

CONFLICT OF INTEREST STATEMENTS

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

IS: Literature search, designing the study, data analysis and interpretation, manuscript drafting. MF: Designing the study, data analysis and interpretation, and manuscript editing. NF: Ideas and concept, data analysis and manuscript editing, review of manuscript.

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