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Computational screening of slime mold-derived compounds against NF-κB-inducing kinase (NIK) for potential breast cancer therapy

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A B S T R A C T

Breast cancer remains a major global health challenge, particularly due to therapeutic resistance driven by complex molecular mechanisms, including dysregulation of kinase-mediated signaling pathways. One critical target is nuclear factor kappa-light-chain-enhancer of activated B cells inducing kinase, which plays an essential role in tumor progression, inflammation, and resistance to treatment. This study aimed to identify potential natural inhibitors derived from slime mold metabolites using a comprehensive in silico approach. Molecular docking, pharmacokinetic prediction, toxicity assessment, and biological activity analysis were conducted to evaluate two compounds, Cribrarione A and Fuligorubin A, in comparison with a reference drug. The docking results demonstrated that Cribrarione A exhibited strong binding affinity with a binding energy of −8.3 kcal/mol, approaching that of the reference compound (−9.5 kcal/mol), while Fuligorubin A showed moderate affinity (−8.0 kcal/mol). All compounds occupied the catalytic pocket and interacted with key amino acid residues associated with kinase activity. Pharmacokinetic analysis indicated that all compounds met drug-likeness criteria and exhibited favorable absorption profiles with no predicted hepatotoxicity or mutagenicity. Furthermore, biological activity prediction revealed that Cribrarione A has promising anticancer potential through mechanisms involving the induction of apoptosis and the suppression of inflammatory signaling pathways. Overall, these findings suggest that slime mold-derived metabolites, particularly Cribrarione A, may represent a promising computational lead candidate for further experimental investigation targeting kinase-mediated breast cancer pathways, although further experimental validation is necessary.

Keywords: breast cancer, molecular docking; NF-κB inducing kinase (NIK); slime mold metabolites; virtual screening

1. INTRODUCTION

Breast cancer (BC) is a complex disease that primarily affects women; it accounts for about one-third of all cancers in women and approximately 15% of cancer-related deaths and represents a global health challenge (Xiong et al., 2025; Rizka et al., 2022). Lifestyle factors can influence the onset or progression of breast cancer in an individual. It has been established that 5% to 10% of breast cancer cases can be attributed to genetic mutations and family history, while 20% to 30% of breast cancer cases can be attributed to modifiable factors (Obeagu, 2024). Several significant hurdles, including debilitating side effects, the intrinsic complexity of the disease pathology, and the emergence of clinical drug resistance, compound the management of breast cancer (Breek *et al.*, 2025; Chopra *et al.*, 2023).

Drug resistance in breast cancer is a multifaceted phenomenon governed by diverse mechanisms, encompassing the tumor microenvironment as well as genetic and epigenetic alterations (Wu *et al.*, 2025). Specifically, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)-Inducing Kinase (NIK) has emerged as a pivotal protein contributing to therapeutic obstacles, notably in the development of chemotherapy resistance and the failure of endocrine-based treatments (Pavitra *et al.*, 2023). Activation of NF-κB was through the canonical pathway and the non-canonical pathway (Tokumasu *et al.*, 2025a). Through a non-canonical

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pathway, NIK plays a role in NF-κB protein activation and promotes breast cancer (Tegowski and Baldwin, 2018; Hayashi *et al.*, 2023; Tokumasu *et al.*, 2025b). Targeting this protein holds significant therapeutic potential, especially in overcoming challenges in breast cancer treatment by focusing on the ATP pocket of the protein (Anderson *et al.*, 2023). In addition, there is no specific drug for targeting NIK in breast cancer therapy (Wei wang *et al.*, 2016).

In recent years, natural products have gained increasing attention as potential sources of novel anticancer agents. Slime molds have been identified as organisms with significant therapeutic potential; their secondary metabolites are reported to exhibit potent antibacterial, antiviral, and antineoplastic activities (Tafakori, 2021; Dowsett, 2013). To address this gap, this study selects Fuligorubin A and Cribrarione A against breast cancer targets. Fuligorubin A is a common slime mold pigment, offering a sustainable biomass supply advantage for drug discovery (Steglich, 1989). Conversely, Cribrarione A is a rare naphthoquinone derivative, a chemical class well-documented for its potent anti-breast cancer activity (Naoe et al., 2003; Kumar et al., 2025). However, the potential of slime mold compounds has not been extensively explored.

In this context, bioinformatic study through in silico approaches such as molecular docking and virtual screening offer efficient strategies to evaluate ligand–target interactions and predict binding affinity at the molecular level (Maciejewska-Turska et al., 2025). Therefore, by utilizing docking-based and virtual screening, this research can predict the binding modes of slime mold-derived ligands and their properties to identify insights into their potential as therapeutic candidates for anti-breast cancer agent (Roney and Mohd Aluwi, 2024).

2. MATERIAL AND METHODS

This study, conducted between February and March 2026, employed a comprehensive in-silico framework encompassing molecular docking, toxicity prediction, and ADME profiling. The investigation targeted the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)-Inducing Kinase (NIK), utilizing the crystal structure from the Protein Data Bank (PDB ID: 4DN5) (https://www.rcsb.org/structure/4DN5). The ligands analyzed were secondary metabolites derived from slime molds, specifically Cribrarione A (CID: 10084919) and Fuligorubin A (CID: 76183973) (https://pubchem.ncbi.nlm.nih.gov/). Ribociclib (CID: 44134847) was selected as the control due to its established clinical efficacy in cancer therapy (Hortobagyi *et al.*, 2021), particularly as no specialized inhibitors currently exist for the specific targeting of the NIK protein (Lukas et al., 2025).

2.1 Protein and Ligand Preparation

The 3D protein structure was downloaded from the PDB and prepared by removing unnecessary parts of the protein using Biovia Discovery Studio 2025 (Dassault Systèmes, 2025), adding polar hydrogens, and converting it to the pdbqt format. For the ligand (compound), the 3D structure was downloaded from PubChem, energy-minimized using Open Babel software integrated with software PyRx, and then converted to pdbqt (O'Boyle *et al.*, 2011).

2.2 Molecular docking

Molecular docking was performed through AutodockVina 1.2.0 (Trott and Olson, 2010; Eberhardt *et al.*, 2021), with coordinate center_x = -7.82, center_y = 27.32, center_z = -3.29 and grid box size size_x = 15.63, size_y = 24.63, size_z = 14.62. Docking position was determined based on the ATP pocket in the NF-κB protein (Liu *et al.*, 2012). The validation process was conducted by re-docking the native ligand (APT) into the binding site of the protein, followed by evaluation of the resulting poses through comparison of the root mean square deviation (RMSD) values with the experimentally determined structure (Martis and Téletchéa, 2025). To provide additional insight into the predicted binding strength and ligand affinity, the inhibition constant (Ki) was estimated using the following thermodynamic relationship.

$$K_i = e^{\frac{\Delta G}{RT}} \quad (1)$$

Where ΔG is the binding free energy (cal/mol), R is the universal gas constant (1.987 cal/mol·K), and T is the absolute temperature (298.15 K) (Elfita *et al.*, 2023; Aziz *et al.*, 2022).

2.3 Molecular dynamics (MD) simulations

The structural flexibility of the complexes was analyzed through root-mean-square fluctuations (RMSF) using coarse-grained MD simulations on the CABS-Flex 3.0 server (Wróblewski *et al.*, 2025). The protocol involved 50+ cycles and 50 trajectory frames at 10 ns per frame, with a global distance constraint weight of 1.0. Detailed configuration and default settings strictly adhered to the framework published by Kuriata and colleagues (Wróblewski *et al.*, 2025; Sen and Karati, 2026).

2.4 Visualization and Interaction Analysis

Visualization and analysis of the interactions resulting from the molecular docking process were performed using Biovia Discovery Studio 2025. This process provides insight into the interactions formed between the ligand and the protein (Baroroh *et al.*, 2023).

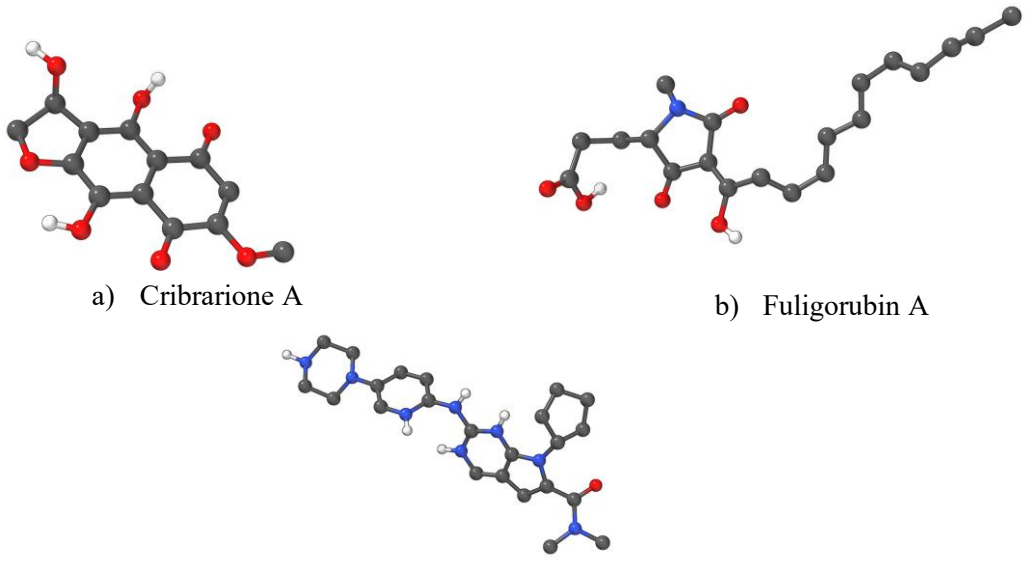
2.5 Pharmacokinetic, Toxicity, and QSAR Analysis

Pharmacokinetic properties were evaluated using pkCSM (https://biosig.lab.uq.edu.au/pkcsm/), with a specific focus on Lipinski's Rule of Druglikeness, human intestinal absorption (HIA), and drug suitability to assess the potential of candidate ligands as orally active drugs (Pires *et al.*, 2015). Toxicity predictions were performed using ProTox 3.0 to estimate the likelihood of adverse effects, including hepatotoxicity and mutagenicity (Banerjee et al., 2012). Additionally, QSAR analysis was performed using Way2Drug (https://way2drug.com/PassOnline/) to establish correlations between molecular descriptors and biological activity, thereby enabling the prediction of inhibitory potential and the identification of relevant structural features (Filimonov et al., 2014).

3. Results and Discussion

3.1 Molecular Docking Analysis

Molecular docking was performed to evaluate the binding energy and interaction through a pythchemical compound from slime mold and drug control (Ribociclib) (Figure 1). The method was validated by performing redocking of ATP as a native ligand of the protein structure, followed by molecular docking using a model derived from a slime mold.



a) Cribrarione A b) Fuligorubin A

c) Ribociclib (Control)

Figure 1. Compound structure from Slime Mold Cribrarione A and Fuligorubin A, Ribociclib (control drug)

The validation results based on redocking showed an RMSD value of 1.9 Å. An RMSD ≤ 2.0 Å indicates that the docking protocol can reliably reproduce the native binding orientation, confirming the validity of the docking method for further analysis (Llop-Peiró *et al.*, 2024), as shown in Figure 2. The native ligand was extracted from the crystal structure of NIK and prepared using Open Babel in PyRx. Molecular docking was performed using

AutoDock Vina with an exhaustiveness value of 8 and 10 generated poses for each ligand. The first pose with the lowest binding energy was selected for further analysis, while the receptor was treated as rigid during docking.

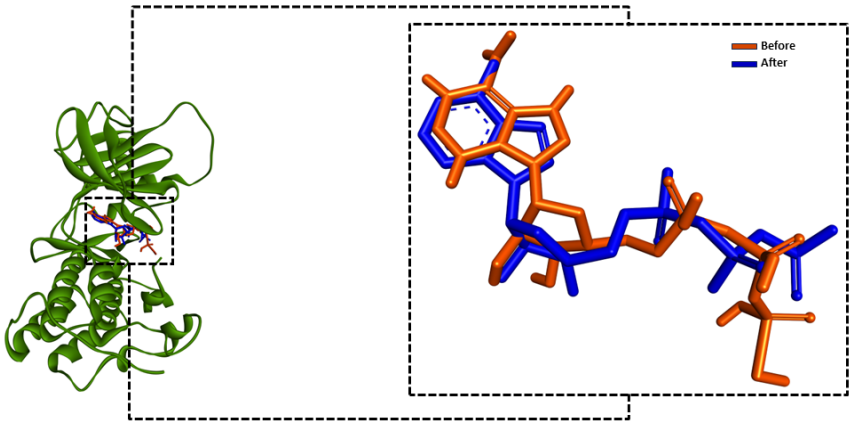


Figure 2. Native ligand (ATP) redocking in NF-κB, showing pose comparison before (orange) and after (blue)

The binding energy of the compound from slime mold shows Cribrarione A has the lowest score (Table 1), -8.3 kcal/mol, with rmsd 0.4 Å and inhibition constant 0.82 µM. Fuligorubin A -8.0 kcal/mol with rmsd 1.3 Å and inhibition constant 1.35 µM. In addition, Ribociclib has shown the lowest binding score, -9.5 kcal/mol, among all tested compounds from the slime mold, with rmsd 0.6 Å and inhibition constant 0.11 µM. The lowest binding energy indicates that bonding occurs easily and that the interaction between the protein and the compound is stable, as shown by all compounds (Vaidyanathan *et al.*, 2023), while the rmsd value ranges from 0.6 to 1.3 Å, indicating that the predicted ligand orientation closely aligns with the reference pose or crystallographic structure. This indicates that the docking protocol showed acceptable reliability in reproducing ligand–receptor interactions (Llop-Peiró *et al.*, 2024). Overall, compounds showed low inhibition constant values ranging from 0.11 to 1.35 µM, indicating the ligand strongly binds with the protein (Aziz *et al.*, 2022). Binding affinity predictions and inhibition constantly suggest potential interaction with the active site, although actual inhibitory activity requires experimental validation

Table 1. Binding energy, RMSD values, and inhibition constants of Ribociclib (control) and selected natural compounds (Cribrarione A and Fuligorubin A) against NIK protein

Protein	Compound	Binding Energy (kcal/mol)	RMSD (Å)	Inhibition Constant (µM)
NIK	Ribociclib (Control)	-9.5	0.6	0.11
	Cribrarione A	-8.3	0.4	0.82
	Fuligorubin A	-8.0	1.3	1.35

3.2 Molecular Dynamics (MD) Simulation Analysis

The RMSF analysis showed that most residues in the NIK–ligand complexes exhibited fluctuation values below 3 Å, with several active site regions remaining below 2 Å during the simulation at ATP binding pocket (Figure 3), indicating relatively stable structural behavior (Fajar *et al.*, 2020). These results are consistent with the docking interaction analysis, where all tested compounds interacted with important residues within the ATP-binding pocket of NIK, including Lys429, Asn520, Asp515, and Asp534. Cribrarione A formed hydrogen bonds with Asn520 and Cys533, while Fuligorubin A interacted with Lys429 and several hydrophobic residues around the binding pocket. Ribociclib also maintained interactions with catalytic residues Asp515 and Asp534. Overall, the interaction profiles

within the active site may contribute to maintaining the stability of the protein–ligand complexes during the simulation.

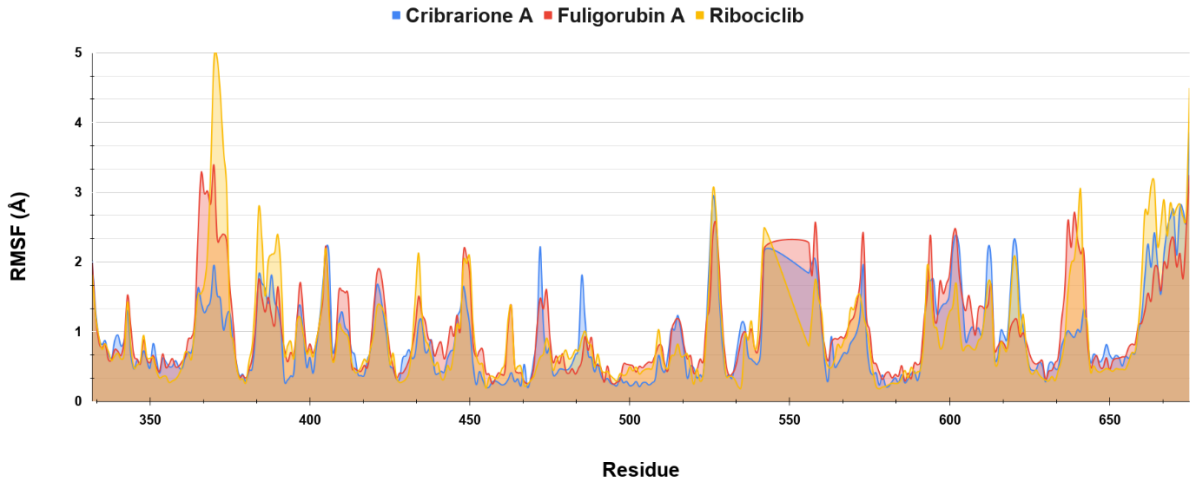


Figure 3. Root Mean Square Fluctuation (RMSF) profile of the NF-κB-inducing kinase (NIK) residues in complex with Cribrarione A, Fuligorubin A, and Ribociclib obtained from CABS-flex 3.0 simulation. The RMSF values represent the fluctuation behavior of amino acid residues during the simulation and were used to evaluate the relative structural flexibility and stability of each protein–ligand complex

3.3 Binding Interaction Analysis (Ligand-Protein Interaction)

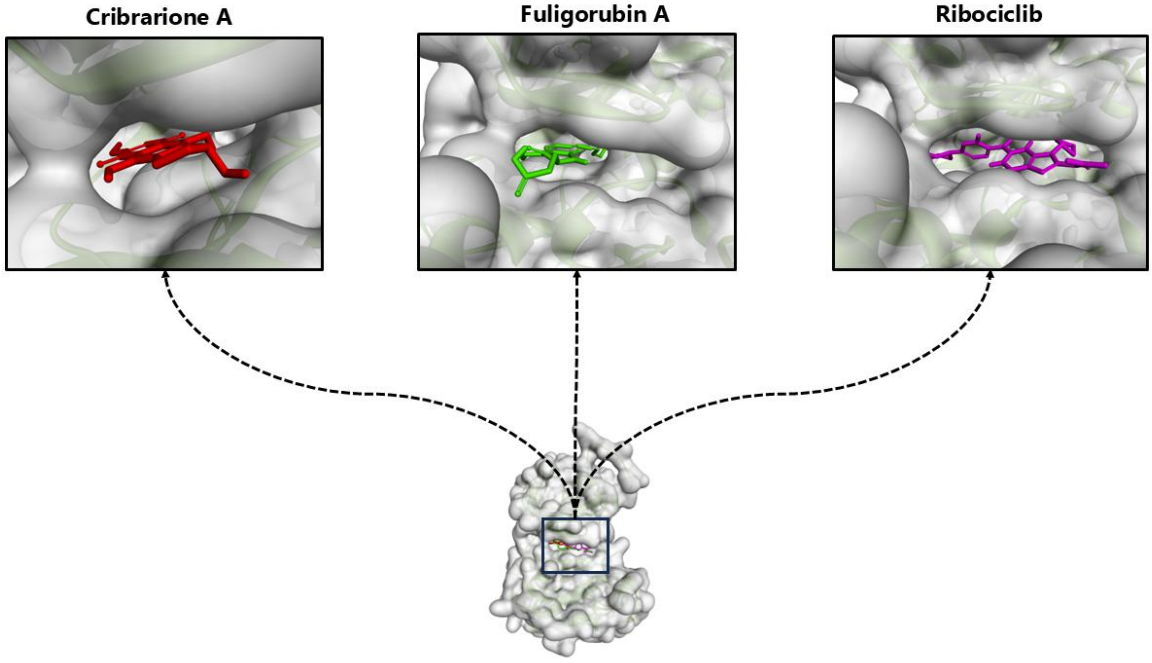


Figure 4. Docking visualization of Cribrarione A (red), Fuligorubin A (green), and Ribociclib (purple) within the ATP-binding pocket of the NF-κB protein, highlighting their relative orientations and binding positions.

All tested compounds were successfully docked into the ATP-binding pocket of the NF-κB-inducing kinase (NIK), as shown in Figure 3, indicating proper binding orientation within the active site. This pocket contains key catalytic residues such as Lys429, Asn520, Asp515, and Asp534 that are essential for kinase activity (Liu *et al.*, 2012). Cribrarione A formed hydrogen bonds with Asn520 and Cys533, along with hydrophobic interactions with

Leu406, Val414, and Leu522, suggesting its role in stabilizing the binding pocket (Figure 4a). Fuligorubin A exhibited broader interactions, including contact with Lys429 through hydrophobic interaction, indicating potential interference with ATP positioning (Figure 4b), while another hydrophobic interaction with Val414, Cys44, Leu455, Ile467, Met469, Leu522, and Cys533. Meanwhile, Ribociclib showed electrostatic interactions with Asp515 and Asp534, which are critical residues in catalysis (Figure 4c), while hydrogen interactions with Ser410 and Leu472, and then hydrophobic interactions with Phe411. Overall, the interaction patterns indicate that both natural compounds and the reference ligand bind within the active site and may inhibit NIK activity by disrupting ATP binding and catalytic function.

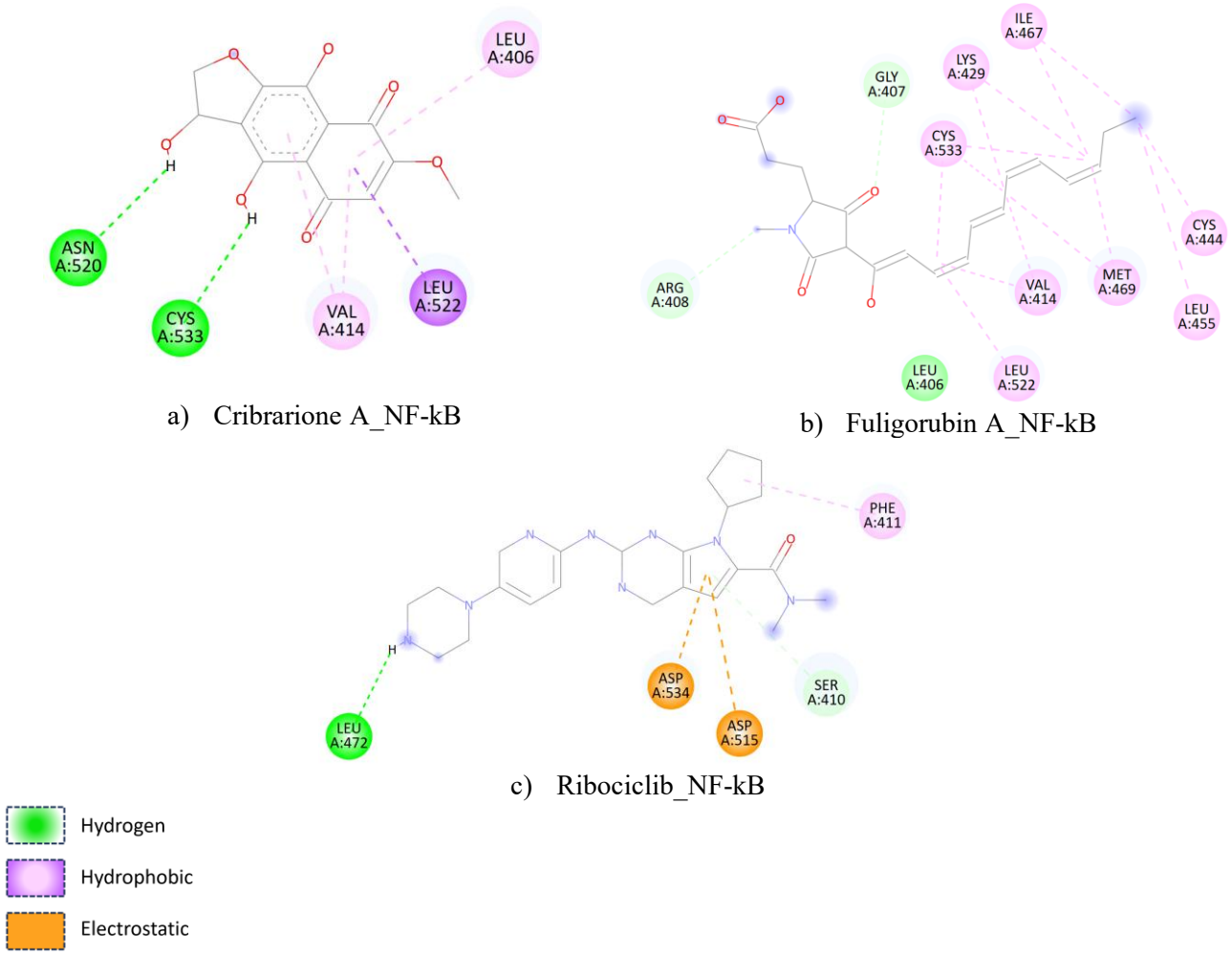


Figure 5. Molecular interaction diagrams of Cribrarione A (a), Fuligorubin A (b), and Ribociclib (c) within the NF-κB protein active site, showing hydrogen bonds (green), hydrophobic interactions (purple), and electrostatic interactions (orange) with key amino acid residues.

3.4 In Silico Assessment of Drug-Likeness, Absorption, and Toxicity Profiles

Comparison of several properties of the slime mold compound and drug control is shown in Table 2. Drug-likeness indicators are based on Lipinski's rules of five, including molecular weight (MW), hydrogen donor, hydrogen acceptor, and Log-P. All test and control compounds showed no violations of this rule; the compounds satisfy general drug-likeness criteria associated with oral bioavailability; furthermore, 90% of the drugs currently on the market do indeed comply with this rule. Overall, the tested compounds showed human intestinal absorption (HIA) ranges of 56.49–95.75% (Benet *et al.*, 2016), indicating that the tested compounds, including the control, exhibit good absorption in the human intestine (Hou *et al.*, 2007).

Table 2. Comparison of drug-likeness, absorption, and toxicity profiles of Ribociclib and candidate compounds

Compound	MW ≤ 500	H-Donor ≤ 5	H-Acceptor ≤ 10	Log-P ≤ 5	HIA (%)	LD50 mg/kg	Hepatoxicity	Ames Toxicity
Ribociclib (Control)	434.54	2	8	2.79	95.75	2500	Inactive 0.71	Inactive 0.51
Cribrarione A	278.21	3	7	0.43	71.22	600	Inactive 0.73	Inactive 0.50
Fuligorubin A	357.40	2	4	2.87	56.49	1000	Inactive 0.74	Inactive 0.73

The median lethal dose (LD50) ranges from 600 to 2500 mg/kg; Cribrarione A, with an LD50 of 600 mg/kg, is classified as Class IV—hazardous if swallowed. Similarly, Fuligorubin A, with an LD50 of 1000 mg/kg, is classified in the same category, while Ribociclib (Control) is classified as Class V with an LD50 of 2500 mg/kg. These results indicate that the toxicity observed in the tests is relatively low compared to classes below IV; however, caution is still warranted (Erhirhie *et al.*, 2018; Morris-Schaffer and McCoy, 2021). None of the tested compounds exhibited hepatotoxicity or Amest oxicity, as evidenced by the values presented in Table 2. A value approaching 1 indicates a higher probability of safety (Banerjee et al., 2012). The test compound showed no hepatotoxicity; these findings are favorable based on the in-silico profile; however, further experimental validation is required to confirm their safety. Previous studies have reported that chemotherapy is known to be more hepatotoxic than radiation-based treatments (Song *et al.*, 2025). Similarly, the compound exhibited no Ames toxicity, indicating that it has no potential to cause genetic mutations (Bębenek *et al.*, 2024; Akash *et al.*, 2022).

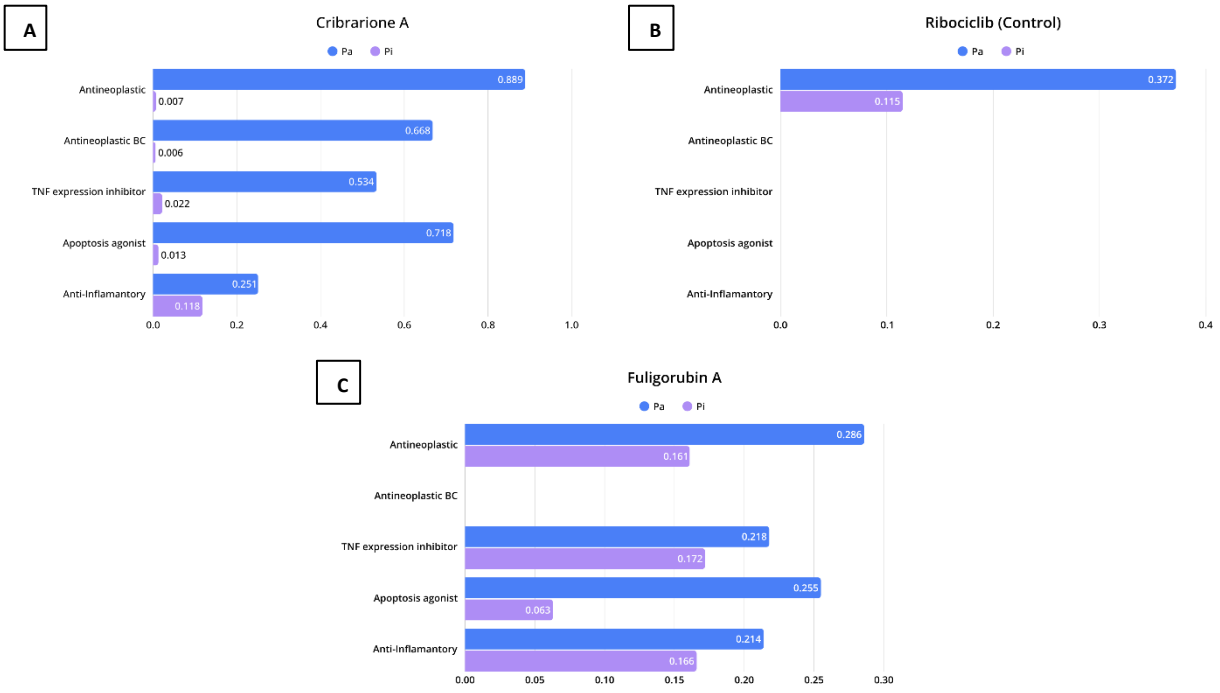


Figure 6. Predicted biological activities of Cribrarione A (A), Fuligorubin A (B), and Ribociclib (C) generated using Way2Drug, showing probability of activity (Pa, blue) and probability of inactivity (Pi, purple) across selected pharmacological categories

The Biological activities predicted through PASS prediction based on a structural model; therefore, the predicted biological activities in this study should be considered hypothesis-generating and require further experimental validation. The results indicate that Cribrarione A exhibits the most promising biological activity compared to Fuligorobin A and the reference compound Ribociclib. A compound is considered potentially biologically active when Pa > Pi, and highly reliable when Pa > 0.7 (Druzhilovskiy *et al.*, 2017; Ul Hassan *et al.*,

2022). In this study, Cribrarione A (Figure 4a) shows high Pa values for antineoplastic (0.844) and apoptosis agonist (0.718) activities, along with moderate TNF expression inhibitory activity (0.534), all with significantly lower Pi values. In contrast, Fuligurobin A (Figure 4b) presents low Pa values (<0.5) in all activity prediction, suggesting weak prediction, while Ribociclib (Figure 4c) shows moderate prediction due to limitations of PASS in capturing its specific mechanism as a CDK4/6 inhibitor. The predicted TNF expression inhibitory activity of Cribrarione A is highly relevant to NF-κB signaling, as TNF-α is a key upstream activator of NF-κB. Upon TNF binding to TNFR1, a signaling cascade involving TRADD, TRAF2, and IKK leads to NF-κB activation and transcription of pro-survival and inflammatory genes (Quickelberghe et al., 2018). Therefore, inhibition of TNF expression may suppress NF-κB activation and reduce tumor-promoting inflammation. This is supported by studies showing that bioactive compounds can predictively inhibit TNF-induced NF-κB activation and inflammatory cytokine production (Fariña *et al.*, 2023). Additionally, the apoptosis agonist activity of Cribrarione A aligns with the critical role of apoptosis induction in breast cancer therapy. Dysregulation of apoptosis pathways, including reduced activation of caspases and AIF1, contributes to tumor progression and poor prognosis in triple-negative breast cancer (TNBC). Increased expression of apoptotic markers such as caspase-3 and AIF1 has been associated with improved patient survival (Török *et al.*, 2025), highlighting apoptosis as an important therapeutic target. Since NF-κB suppresses apoptosis by upregulating anti-apoptotic genes, compounds that promote apoptosis while inhibiting NF-κB signaling, such as Cribrarione A, are particularly promising (Quickelberghe et al., 2018). Overall, results based on in silico prediction suggest Cribrarione A (Figure 4a) has strong potential as an anti-breast cancer agent by targeting the NIK protein through a non-canonical pathway in the NF-κB pathway mechanism, and through PASS prediction, several mechanisms of TNF inhibition, anti-inflammatory activity, and apoptosis induction, whereas Fuligurobin A (Figure 4b) shows weak activity by PASS prediction, and Ribociclib (Figure 4c) serves as a comparative control with a different mechanism of action.

4. CONCLUSION

This study demonstrates that slime mold-derived compounds, particularly Cribrarione A demonstrated favorable computational interaction profiles against NIK and may represent a promising candidate. Future studies are needed to validate the biological activity of Cribrarione A using in vitro assays, including cytotoxicity evaluation in breast cancer cell lines, apoptosis analysis, and investigation of NIK/NF-κB signaling inhibition.

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