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*Full Length Article*

# Molecular Docking and ADMET Analysis of Bioactive Compounds from *Aspergillus nomius* NC06 Against Plasmepsin Protein: Antimalarial Activity

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## Abstract

The development of new antimalarial drugs is urgently needed. The marine sponge-derived fungus *Aspergillus nomius* NC06 is known to have bioactive compounds including aspergillicin A, oxisterigmatocystine J, oxisterigmatocystine K and oxisterigmatocystine L. In this study, we performed a virtual screening of bioactive compounds from *A. nomius* NC06 by molecular docking and adsorption, distribution, metabolism, excretion and toxicity analysis against plasmepsin I, IV and V proteins to observe their antimalarial activity. Plasmepsin protein is considered an important drug target due to its essential role in protein export. The results showed that aspergillicin A had the potential to inhibit Plms I, IV and V proteins, with the highest negative binding affinity values at -10.0, -10.3 and -10.7 kcal $moL^{-1}$, respectively. The binding affinity was supported by the formation of hydrogen bonds and hydrophobic interactions. In addition, artemisinin as a positive control has a binding affinity of about -7.4 kcal $moL^{-1}$, suggesting that the compounds isolated from the marine sponge have the potential to combat malaria and could be developed as lead compounds for anti-malarial therapy.

**Keywords:** Aspergillicin A; Binding affinity; Fungal compounds; Marine sponge; Oxisterigmatocystine

## Introduction

Malaria is an infectious disease caused by infection with the protozoan parasite *Plasmodium*, which is transmitted by the female *Anopheles gambiae* mosquito (Faust and Dobson 2015; Makungu *et al.* 2017). Tropical and subtropical regions such as Africa, South Asia, Central, and South America are the most common areas of malaria distribution. According to the WHO (2022), there were 241 million cases of malaria in 2020, with the African region accounting for the largest share of malaria cases.

Today, the global control and elimination of malaria caused by *Plasmodium falciparum* and *Plasmodium vivax* is threatened by the use of chloroquine and artemisinin-based combination therapies (ACTs), as resistance has emerged. This highlights the need for a new treatment with a new lead drug that is more effective than ACT. Natural products have played an important role in the development of drugs to suppress the resistance rate of *P. falciparum*. Studies on the efficacy of natural products have consistently shown their potential as antimalarial agents against *P. falciparum*, such as placortin, which was isolated from the marine sponge *Plakortis simplex* and is a potential antimalarial agent with an $IC_{50}$ value of 0.39 $\mu M$ against *P. falciparum* (Duru *et al.* 2016; Lei *et al.* 2020).

A fungus *Xylaria* sp. BCC 21097, which is isolated from *Licuala spinosa* produces a compound 1α-10α-Epoxy-7α-hydroxyeremophil-11-en-12,8-$\beta$-olide. This compound

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belongs to a sesquiterpenoid group which is active against *P. falciparum* with a mechanism related to the epoxide structure of the compound (Isaka *et al.* 2010). Niu *et al.* (2021) also reported that ethyl acetate extract of the fungus *Purpureocillium lilacinum* can inhibit *P. falciparum* transmission to mosquitoes. The isolated active compound of *Purpureocillium lilacinum* namely 3-amino-7,9-dihydroxy-1-methyl-6H-benzo[c]chromen-6-one or pulixin, prevented FREP1 from binding to *P. falciparum*-infected cell lysate and pulixin also inhibited the proliferation of asexual-stage *P. falciparum.*

The molecular pathway of antimalarial compound inhibits the plasmodium such *P. falciparum* and *P. vivax* can interfere the plasmepsin protein. This protein is responsible as renovation cellular process of *Plasmodium.* Plasmepsin I, IV and V are the main enzymes in the life cycle of malaria parasites which are found in food vacuoles and will work by degrading hemoglobin to be used as an energy source. Their functions are strikingly multifaceted, ranging from hemoglobin degradation to secretory organelle protein processing for egress, invasion, and effector export (Nasamu *et al*. 2020). Methanol extracts of leaves of *Albizia adinochepala* showed the antimalarial activity which able to inhibit plasmepsin protein. The compound budmunchiamines L4 and L5, alkaloid compounds from stem bark of *A. adinochepala* displayed antimalarial activity against plasmepsin protein with $IC_{50}$ value 14 and 15 $\mu M$, respectively (Trieu *et al.* 2011; Ovenden *et al.* 2002). *Aspergillus* spp. is known to possess a number of bioactive compounds (Javaid *et al.* 2014; Khan and Javaid 2021, 2022). Several compounds such as aspertenol B, oxisterigmatocystins E, F, G, H and demethylsterigmatocystin-1-(4-O-methyl)-$\beta$-Larabinopyranose that isolated form *Aspergillus* have potential as anti-plasmodial activity against *P. falciparum* with $IC_{50}$ values 4.39–23.9 $\mu M$ (Jittra *et al*. 2012; Rajachan *et al*. 2017; Liu *et al*. 2018).

However, there are not many studies that report the form of interaction between active compounds isolated from *Aspergillus* and amino acid residues in the parasite proteins plasmepsin I, IV and V that cause malaria. Hence, this study was carried out to explore antimalarial activity observed by *in silico* from the new cytotoxic compounds of marine sponge-derived fungus *Aspergillus nomius* NC06, namely oxisterigmatocystine J-L, and known compound, aspergillicin A, against plasmepsin I, IV and V protein.

## Materials and Methods

### Experimental details and treatments

**Experimental material:** *In silico* analysis were done by using protein plasmepsin I (PMI) from *P. falciparum* (ID 3QRV), plasmepsin IV from *P. falciparum* (ID 5I70) and plasmepsin V from *P. vivax* (ID 6C4G). These proteins obtained from PDB https://www.rcsb.org/, along with the control ligands artemisinin. The bioactive compounds of *A. nomius* NC06 (*i.e*., aspergillicin A, oxisterigmatocystine J, oxisterigmatocystine K and oxisterigmatocystine L) were obtained from PubChem https://pubchem.ncbi.nlm.nih.gov/. The software used during *in silico* process were PyRx software, 4096 MB RAM Memory, Acer TravelMate P633-M Laptop Open Babel GUI, PyMOL, Discovery Studio Visualizer and Intel(R) Core™ i5-3230M CPU @ 2.60 GHz (4 CPUs).

### Pharmacokinetics analysis

All test ligands (aspergillicin A, oxisterigmatocystine J, oxisterigmatocystine K and oxisterigmatocystine L) were evaluated for their pharmacokinetic properties based on Lipinski's rule. The SMILES codes of each ligand are entered on the web www.swissadme.ch and drug-likeness data was obtained for each compound.

### Molecular docking analysis

Molecular docking was performed on bioactive compounds from *A. nomius* NC06 with protein targets plasmepsin I (PMI) from P. falciparum (ID 3QRV), plasmepsin IV from *P. falciparum* (ID 5I70) and plasmepsin V from *P. vivax* (ID 6C4G), which each a resolution of 2.5Å as a receptor using PyRx software. The protein targets as receptor were obtained from https://www.rcsb.org. The test ligands used were obtained from bioactive compound of *A. nomius* NC06 and control ligand was artemisinin. The ligands' 3D structure was downloaded in. sdf format from PubChem at https://pubchem.ncbi.nlm.nih.go. Then, the Discovery Studio Visualizer (DSV) program is used to convert it into.pdb format. The C chain structure was extracted from the intact structure and saved in the *.pdbqt format in order to prepare the receptor. Following storage, the natural ligand was extracted from the enzyme chain C structure and the water molecules were eliminated. Next, the file was stored under the *.pdbqt extension. Blinded docking is the form of docking that is used in the PyRx software to carry out the molecular docking procedure. Following the completion of docking, the binding affinity (kcal/moL) value and the outcomes of many docking modes were collected. Furthermore, DSV was used to display the docking results in two dimensions.

### Toxicity and bioavailability analysis

Using an online toxicity test tool available at http://tox.charite.de/protox_II/, the test ligands with the best binding affinity were assessed for toxicity predictions one by one (Banerjee *et al*. 2018). A program available at http://www.swissadme.ch/ was used to assess the bioavailability (ADME) of ligands that demonstrated non-toxic findings (Daina *et al*. 2017).

## Results

### Active compounds of marine sponge-derived fungus

The marine sponge-derived fungus *A. nomius* NC06 contained 4 active compounds, namely aspergilicin A, oxisterigmatocystin J, oxisterigmatocystin K and oxisterigmatocystin L and was used as tested ligands. The detailed structure of the tested ligands and protein target can be found in Table 1 and 2, respectively.

### Pharmacokinetic drug-likeness Lipinski's rules

The analysis of the test ligand for the Lipinski's rule parameters is presented in Table 3. Based on the result that oxisterigmatocystin J-L were fulfilled to Lipinski's rule (drug-like compound) same as artemisinin as antimalarial drug.

### Antimalarial activity of bioactive compound from *A. nomius* NC06

Table 4 shows the potential of *A. nomius* NC06 bioactive compounds, i.*e*., Aspergillicin A, Oxisterigmatocystine J, Oxisterigmatocystine K and Oxisterigmatocystine L as antimalarial. The binding affinities of Oxisterigmatocystine J, Oxisterigmatocystine K and Oxisterigmatocystine L as novel compounds presented a greater energy than the positive control, Artemisinin, through all types of Plms protein.

### 2D Visualization

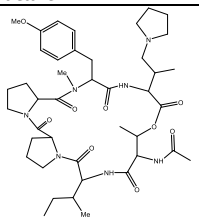
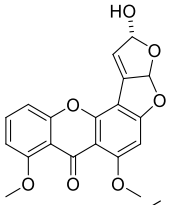
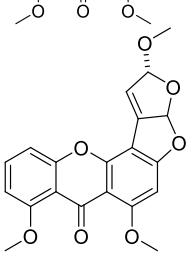
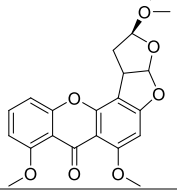
The lower binding affinity value of the ligands to the Plms protein becomes clearer through a 2D visualization. The visualization of interaction between aspergillicin A, oxisterigmatocystine J and artemisinin (control ligands) to Plms I protein is shown in Fig. 1. The visualization of interactions between the same ligands to Plms IV protein and Plms V protein are shown in Fig. 2 and 3, respectively.

The number of amino acid residues bound to the artemisinin, as a control positive ligand, is the different when compared with bioactive compound *A. nomius* NC06, against to the Plms I, IV and V as target proteins (Table 5–7).

## Discussion

Bioactive compounds from *A. nomnius* NC06 can be docked to protein receptors. A ligand is classified as drug-like if it meets the following criteria molecular weight of less than 500 g/moL to facilitate membrane crossing, a Log P value of less than 5 to reduce toxicity when crossing blood vessels, a number of hydrogen bond donors, hydrogen bond acceptors of 5 and 10, respectively, which are related to biological activity and a polar surface area (PSA) of less than 140 Å, which is related to the permeability of the drug

**Table 1:** Bioactive compounds of *A. nomius* NC06

| Name | Role | Structure |
|---|---|---|
| aspergillicin A | Test Ligand |  |
| Oxisterigmatocystine J | Test Ligand |  |
| Oxisterigmatocystine K | Test Ligand |  |
| Oxisterigmatocystine L | Test Ligand |  |

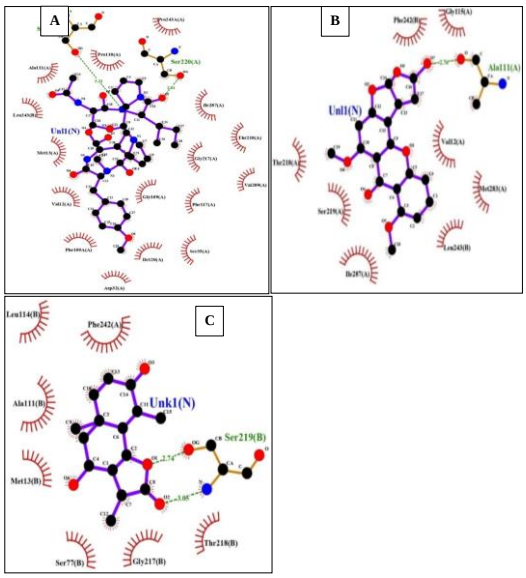
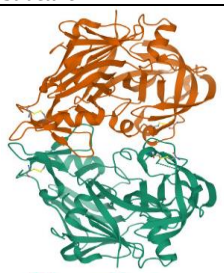
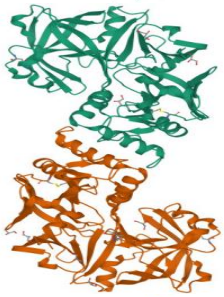
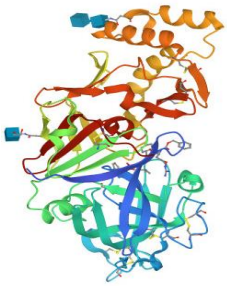



**Fig. 1:** The 2D visualization of aspergillicin A (**A**), oxisterigmatocystine J (**B**) and artemisinin (**C**) to Plms I protein

(Lipinski 2004; Giménez *et al.* 2010; Yadav and Khan 2013). Since aspergillicin A has a molecular weight of 740.89 g $mol^{-1}$, this compound does not fulfil the Lipinski rule. However, this Lipinski rule refers to orally

**Table 2:** Protein target structure of malarial

| Name | Role | Structure |
|---|---|---|
| Plasmepsin I (ID 3QRV) | Protein Target |  |
| Plasmepsin IV (ID 5I70) | Protein Target |  |
| Plasmepsin V (ID 6C4G) | Protein Target |  |

administered drugs where the criteria facilitate the penetration of the compound into the membrane (Chagas 2018).

Bioactive compounds from natural products can be used as lead medicinal agents, *e.g.*, as antimalarials. Preliminary testing for antimalarial activity is done by *in silico* testing, which involves molecular docking to the binding site of a protein or enzyme. There are several proteins that we can use as a target for the malaria test. For this study, the plasmepsin protein was used as a target for malaria activity. The plasmepsin I (PMI) of *P. falciparum* (ID 3QRV), plasmepsin IV of *P. falciparum* (ID 5I70) and plasmepsin V of *P. vivax* (ID 6C4G). Aspartylproteases and plasmepsins (Plms) of malaria pathogens are potential targets for antimalarial drug discovery as they are expressed during several life stages of the parasite (Liu 2017).

Grid box is used to determine the attachment area of the tested compound. The obtained grid box indicates that the two types of ligands will attach to the dimensions (Å) X 68.8366, Y 65.8079 and Z 61.4372 as well as the center positions X 15.6063, Y 7.5107 and Z 19.3297. The RMSD value of 0 Å was observed in the case of re-docking between the receptor and its natural ligand. Since the average RMSD value obtained is less than 2Å, this molecular docking validation is considered valid or

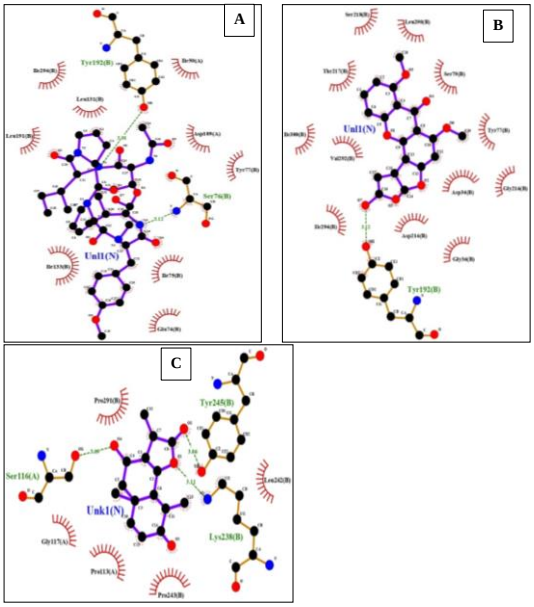



**Fig. 2:** The 2D visualization of aspergillicin A (A), oxisterigmatocystine J (B) and artemisinin (C) to Plms IV protein

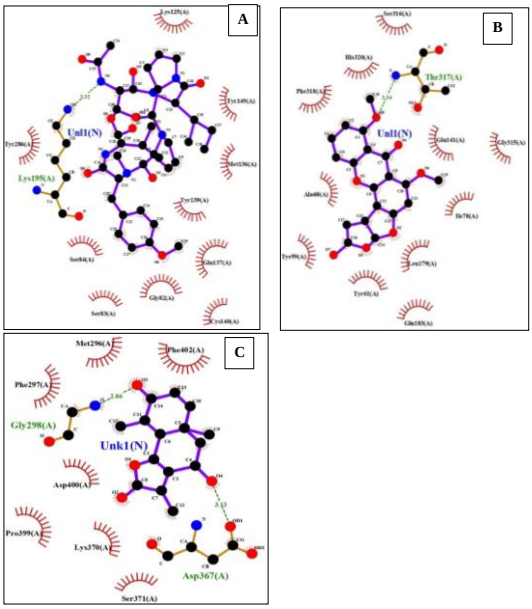



**Fig. 3:** The 2D visualization of aspergillicin A (A), oxisterigmatocystine J (B) and artemisinin (C) to Plms V protein

appropriate (Hernández-Santoyo *et al*. 2013; Toppo *et al*. 2021). Aspergillicin A is the more stable ligand to the Plms proteins, according to an *in silico* analysis of the activity of the marine sponge-derived fungus *A. nomius* NC06 to the Plms (I, IV and V) protein. The binding affinity of Aspergillicin A to the active sites of Plms I, Plms IV, and Plms V are -10.0, -10.3 and -10.7 kcal $moL^{-1}$, respectively.

**Table 3:** The test ligand characteristics with the Lipinski's rule parameters

| Ligand/Compound | Molecular Weight (g/mol) | Log P | Number of hydrogen bond donors | Number of hydrogen bond acceptor | Polar Surface Area (Å) |
|---|---|---|---|---|---|
| Aspergillicin A | 740.89 | 4.30 | 3 | 9 | 183.76 |
| Oxisterigmatocystine J | 354.31 | 2.50 | 1 | 7 | 87.36 |
| Oxisterigmatocystine K | 370.35 | 2.94 | 0 | 7 | 76.36 |
| Oxisterigmatocystine L | 370.35 | 2.88 | 0 | 7 | 76.36 |
| Artemisinin* | 282.33 | 1.39 | 0 | 5 | 53.99 |

**Table 4:** Binding affinity of active compound marine sponge-derived fungus

| Compound | Binding Affinity with Plms I (kcal $mol^{-1}$) | Binding Affinity with Plms IV (kcal $mol^{-1}$) | Binding Affinity with Plms V (kcal $mol^{-1}$) |
|---|---|---|---|
| Aspergillicin A | -10.0 | -10.3 | -10.7 |
| Oxisterigmatocystine J | -9.8 | -9.7 | -9.8 |
| Oxisterigmatocystine K | -9.6 | -9.5 | -9.7 |
| Oxisterigmatocystine L | -9.4 | -9.3 | -9.4 |
| Artemisinin* | -7.4 | -7.5 | -7.6 |

**Table 5:** Interaction type of active compound marine sponge-fungus derived Plms I complex

| Complex Compound | Interaction | Amino Acids Residues |
|---|---|---|
| [Aspergillicin A-Plms I] | Hydrogen | Ser219, Ser220 |
| | Hydrophobic | Ala111, Leu243, Met13, Val12, Phe109, Asp32, Ile120, Ser35, Gly109, Phe117, Val289, Gly217, Thr218, Ile287, Pro243, Pro110 |
| [Oxisterigmatocystine J-Plms I] | Hydrogen | Ala111 |
| | Hydrophobic | Thr218, Ser219, Ile287, Leu243, Met283, Val12, Gly115, Phe242 |
| [Oxisterigmatocystine K-Plms I] | Hydrophobic | Thr79, Tyr75, Ile48, Gly78, Val76, Glu109, Gly109, Asn74, Glu109B |
| [Oxisterigmatocystine L-Plms I] | Hydrogen | Ser77 |
| | Hydrophobic | Gly217, Phe117, Ile30, Val12, Ser219, Phe242, Leu243, Pro241, Ile287, Val76 |
| [Artemisinin-Plms I] | Hydrogen | Ser219 |
| | Hydrophobic | Thr218, Gly217, Ser77, Met13, Ala111, Leu114, Phe242 |

**Table 6:** Interaction type of active compound marine sponge-fungi derived Plms IV complex

| Complex Compound | Interaction | Amino Acids Residues |
|---|---|---|
| [aspergillicin A-Plms IV] | Hydrogen | Ser76, Tyr192 |
| | Hydrophobic | Ile133, Glu74, Ile75, Leu191, Leu131, Ile294, Ile50, Asp109, Tyr77 |
| [Oxisterigmatocystine J-Plms IV] | Hydrogen | Tyr192 |
| | Hydrophobic | Ile294, Val292, Ile300, Thr217, Ser218, Leu290, Ser79, Tyr77, Asp34, Gly216, Asp214, Gly36 |
| [Oxisterigmatocystine K-Plms IV] | Hydrophobic | Tyr192, Ile294, Ile300, Thr217, Val292, Ser79, Ser218, Gly216, Asp34, Gly36, Tyr77 |
| [Oxisterigmatocystine L-Plms IV] | Hydrophobic | Ile294, Gly36, Val292, Leu290, Thr217, Ser218, Ser79, Gly216, Asp34, Tyr77 Asp214, Tyr192, Ile300 |
| [Artemisinin-Plms IV] | Hydrogen | Ser116, Lys238, Tyr245 |
| | Hydrophobic | Gly117, Pro113, Pro243, Pro291, Leu242 |

**Table 7:** Interaction type of active compound marine sponge-fungi derived Plms V complex

| Complex Compound | Interaction | Amino Acids Residues |
|---|---|---|
| [aspergillicin A-Plms V] | Hydrogen | Lys195 |
| | Hydrophobic | Tyr286, Ser84, Ser83, Gly82, Cys140, Gln137, Tyr139, Met136, Tyr149, Lys125 |
| [Oxisterigmatocystine J-Plms V] | Hydrogen | Thr317 |
| | Hydrophobic | Ser316, His320, Phe318, Ala60, Tyr59, Tyr61, Gln183, Leu179, Ile78, Gly315, Glu141 |
| [Oxisterigmatocystine K-Plms V] | Hydrogen | Thr317 |
| | Hydrophobic | Ser316, His320, Phe318, Ala60, Tyr59, Tyr61, Gln183, Leu179, Ile78, Gly315, Glu141 |
| [Oxisterigmatocystine L-Plms V] | Hydrophobic | Ley398, Asp400, Phe297, Pro399, Lys370, Asp367, Ser371, Ser374, Gly397, Glu396 |
| [Artemisinin-Plms V] | Hydrogen | Gly298, Asp367 |
| | Hydrophobic | Ser37, Lys370, Pro399, Asp400, Phe297, Met296, Phe402 |

Furthermore, the ligands from *A. nomius* NC06 have a higher binding affinity value than control ligands, artemisinin, according to the data shown in Table 3. Stronger binding and greater inhibitory potential of the ligand to the target protein or enzyme are associated with lower binding affinity values of the ligand-receptor complex interaction (Toghueo *et al*. 2021; Toppo *et al*. 2021). Aspergillicin A is the compound that has the lowest affinity compared with others. It indicates that Aspergillicin A has the ability to bind all type of Plms and suggests to have anti-malarial properties. The bioactive compounds from fungal repeatedly show an antimalarial activity such us study of

Toghueo *et al*. (2021) reported that the endophytic extracts from *Aspergillus niger*, an endophytic fungus that grows on *Terminalia catappa*, may contain secondary metabolites that could be used to combat the malaria parasite. According to Martínez-Luis *et al*. (2012), *Aspergillus* sp. strain F1544, an endophytic fungus, exhibits strong anti-malarial activity against *P. falciparum*, with an $IC_{50}$ value of 5.4 $\mu$g $mL^{-1}$.

A two-dimensional visualization helps to clarify whether the drug has a higher inhibitory power or a lower binding affinity value for the Plms protein. Fig. 1 illustrates that the control ligands (artemisinin), aspergillicin A, oxisterigmatocystine J interact with the Plms I protein. The 2D visualizations illustrated the interactions of the same ligands with the Plms IV and Plms V proteins, respectively. Different types of bonds can occur between the various types of amino acid residues in the receptor and the ligand, and varying distances between the various types of amino acid residues and the ligand will result in varying binding energies. Binding affinity of the ligand-receptor value is determined by the molecular interactions. Patrick (2001) states that every compound has electronegativity that determines the strength of its hydrophobic interactions, hydrogen bonds and ionic bonds. Stronger bonds are those with shorter bond distances (Drwal *et al*. 2014). The number of amino acid residues bound to the artemisinin, as a control positive ligand, is different when compared with bioactive compound A. nomius NC06, against to the Plms I, IV and V as target proteins. This finding indicates that the ligands bind to the Gly36, Tyr192, Ser215 and Ser218 are catalytic residues of Plms that have hydrophobic interaction, while the hydrogen bond between ligand and receptor binding can observe from residues of Asp34, Gly36 and Asp214. Amino acid residues Asp34 and Asp214 are the active sites of plasmepsin I, IV and V. Amino acid residues Asp34 and Asp214 coordinate water molecules. Where, Asp214 acts as a proton donor which then attacks the peptide bonds in hemoglobin, namely residues Phe33-Leu34 (Nasamu *et al*. 2020).

It is expected that compounds with the same biological activity as their native ligands will bind to the same amino acid residues. In the process of the ligand-target protein interaction, the hydrogen bonds created particular interactions that are significant (Hardoko *et al.* 2023; Whatin *et al*. 2023; Kartikaningsih *et al.* 2024). During the hemoglobin degradation process, the Asp34 and Asp214 residues work together to coordinate a water molecule that targets the Phe33-Leu34 peptide bond of the α-chain in host hemoglobin after Asp214 abstracts a proton. This bond will prevent Plms' substrate from binding to the enzyme's active site. The hemoglobin degradation process will be impeded as a result of the bioactive compounds from *A. nomius* NC06 inhibiting two catalytic dyads of Plms. According to Rifai *et al*. (2017), this binding disarms the enzyme, preventing it from catalyzing a reaction in the host hemoglobin degradation process. Although the anti-plasmodial mechanism of action of the *A. nomius* NC06's compounds were not investigated in this study, several previous studies have been proved that bioactive compounds isolated from marine sponge-derived fungus has anti-plasmodial activity through its ability to form DNA adduct and cause DNA damage appear to play a key role in anti-plasmodial pathways (Awuchi *et al.* 2022).

Aspergillicin A as potential antimalarial compound due to the binding affinity value against Plms. Based on the predicted of toxicity of this compound has $LD_{50}$ value of 1000 mg/kg and classified as class 4 of 6. Therefore, aspergillicin A, is not toxic compound to bodily organs. The bioavailability analysis of the compound was done after the toxicity of two possible compounds was established. Aspergillicin A exhibited a high category of human gastrointestinal (GI) absorption. It indicated that the substance could be easily absorbed by the organs of the digestive system, distributed precisely to the intended locations, metabolized by the body, and eliminated without endangering the organs (Drwal *et al*. 2014).

## Conclusion

Bioactive compounds from *A. nomius* NC06 such as aspergillicin A, Oxisterigmatocystine J, Oxisterigmatocystine K and Oxisterigmatocystine L proved potential antimalarial constituents. The results *in silico* showed that the most potent compound, aspergillicin A, had the potential to inhibit the plasmepsin I, IV and V proteins with the highest binding affinity through hydrogen bonds and hydrophobic interactions. As a potential compound, aspergillicin A met Lipinski's rules, exhibits a high category of human gastrointestinal (GI) absorption and is not potentially toxic to the body. These compounds need to be explored further to check its antimalarial activity by using *in vitro* and *in vivo* assay.

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## Author Contributions

MAA planned the experiments. HD and WEP conducted the experiments. DL, DEKP, HR and AC interpreted the results. MAA and HD made the write up and made illustrations.

## Conflicts of Interest

The authors declare no conflict of interest.

## Ethics Approval

There is no need ethics approval for this study.

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