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# Computational Calculation and Molecular Docking of Aeroplysinin-1 As Antibacterial

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**Abstract**

Aeroplysinin-1 is naturally found from marine sponges as an anti-bacterial compound. Computational calculation and molecular docking were performed for aeroplysinin. Aeroplysinin as an inhibitor has optimized in the gas phase using DFT with 6-31G(d) functional. The structure from geometry optimization of aeroplysinin-1is, not in one plane. The interaction of aeroplysinin-1 with two different DNA gyrase from E. *Coli* and S. *Aureus*. In this research,aeroplysinin-1 can inhibit the protein with the free binding energy of about -5.7 kcal/mol and -6.35 kcal/mol, respectively, for E. *Coli* and S. *Aureus*. The dominant molecular interaction is the hydrogen bond.

*Keywords: Aeroplysinin-1, DFT, Antibacterial, DNA Gyrase,* E. *Coli,* S. *Aureus.*

## INTRODUCTION

Sponges are aquatic animals that function as filters. One type of sponge that is promising for the health sector is Aplysina and Lanthella. Both of these sponges produce a secondary metabolite known as aeroplysinin-1. Aeroplysinin-1 is delivered when spongy tissue is damaged (Lira et al., 2011). Aeroplysinin has many health benefits. The two-dimension structure of Aeroplysinin-1 is shown in Figure 1.

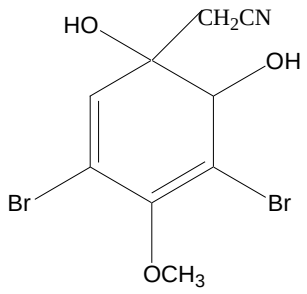


Figure1. Structure of aeroplysinin-1

Aeroplysinin-1 can act as an antiviral. Aeroplysinin-1 can inhibit proteins from HIV-1 in the process of replicating its cell(Gómez-Archila, Díaz, & Rugeles, 2014). Aeroplysinin-1 also can act as an anti-inflammatory. Aeroplysinin-1 can inhibit cyclooxygenase-2protein expression levels in endothelial cells and human monocyte cells (Martínez-Poveda et al., 2013). Apart from being an antiviral and anti-inflammatory, aeroplysinin-1 can act as an antibacterial. Aeroplysinin-1 has potency for growth inhibition against bacteria, such as *Staphylococcus aureus* (García-Vilas, Martínez-Poveda, Quesada, & Medina, 2016).

The potency of a molecule can be known through computational calculations. Muliadi, et al (2021) have performed computational calculations on myristicin derivatives and determined their properties as antioxidant compounds by QSAR (Muliadi, Basimin, & Jayali, 2021). The properties of aeroplysinin-1 can be found by computational calculation. Aerolysinin-1 has been computed computationally by Nieto-Ortega et al. (2011) using the B3LYP functional DFT theory and the cc-pvDz basis set. The explanation of this calculation is only about the conformations of this compound. The other explanation is also about the Raman spectra of each conformation are.

The potential of the compound in its use as pharmacology, for example, antibacterial, can be done by molecular docking. Gasperzs and Sohilait (2019) have carried out the mangosteen molecule's molecular docking to the alpha-amylase protein from the human pancreas. They get that mangosteen can inhibit alpha-amylase from preventing diabetes(Gaspersz & Sohilait, 2019). In the same year, the study of Quantitative Structure-Activity Relationship (QSAR) of pyrazoline analogs, designing the new potential compounds as antiamoebic and study the interactions between the new compounds and the drugs target by molecular docking approach has been published (Kilo, Aman, Sabihi, & Kilo, 2019).

Molecular docking to find out compounds that have the potential to inhibit DNA gyrase from S. *aureus* was done. Acar et al. (2020) have performed the docking of benzamide derivatives with DNA gyrase protein from S.*aureus*. The result was found that the synthesized benzamide derivatives were able to inhibit DNA gyrase from *S. aureus* (Acar et al., 2020a). There is no molecular docking of aeroplysinin-1 as antibacterial, antiviral, or anti-inflammation. So, this research is about computational calculation using DFT theory with functional B3LYP/6-31G(d) and molecular docking of the optimized structure of aeroplysinin-1 with DNA gyrase from*E.coli*. and *S.aureus.*

## METHODOLOGY

The structure of aeroplysinin-1 was built in z-matrix format. The geometry was optimized using DFT/B3LYP with a 6-31G(d) basis set. The optimized structure is converted from .log to .pdb format using Open Babel (O'Boyle et al., 2011). The DNA gyrase from *E. coli* and *S.aureus* structure were taken from the protein data bank website www.rscb.org (PDB ID 1KZN and 3G7B) (Acar et al., 2020b; Priyanka, Singh, Ekta, & Katiyar, 2017)

The validation method is used, which we are redocking the original/native ligand to the active site of DNA gyrase. Redocking was performed using clorobiocin and gentamicin as native ligand. Clorobiocin for The DNA gyrase from *E. coli* and gentaciminfor The DNA gyrase from*S.aureus.* When the results of the RMSD value of not more than 2 Å, it indicates the redocking is done. The main parameters for docking are free binding energy (ΔG), ligand efficiency, constant inhibitor (Ki), and hydrogen bonds formed.

## RESULTS AND DISCUSSION

The results discussed in this article are optimized geometry, atomic charge distribution, HOMO-LUMO distribution, binding energy, and intermolecular interactions between ligand and proteins. The description of the results and discussion in this study is as follows:

### Optimized Geometry

Optimized Geometry is obtained from geometry optimization. The main aim is to get a stable geometry of aeroplysinin-1 before doing molecular docking. The optimized geometry of aeroplysinin-1 is not in one plane (non-planar). The non-planar structure is caused by the absence of one double bond from the missing benzene ring. The loss of one double bond in the benzene ring is due to four substituents that bind one of the carbon atoms that have a double bond. The optimized geometry of aeroplysinin-1 is shown in Figure 2.

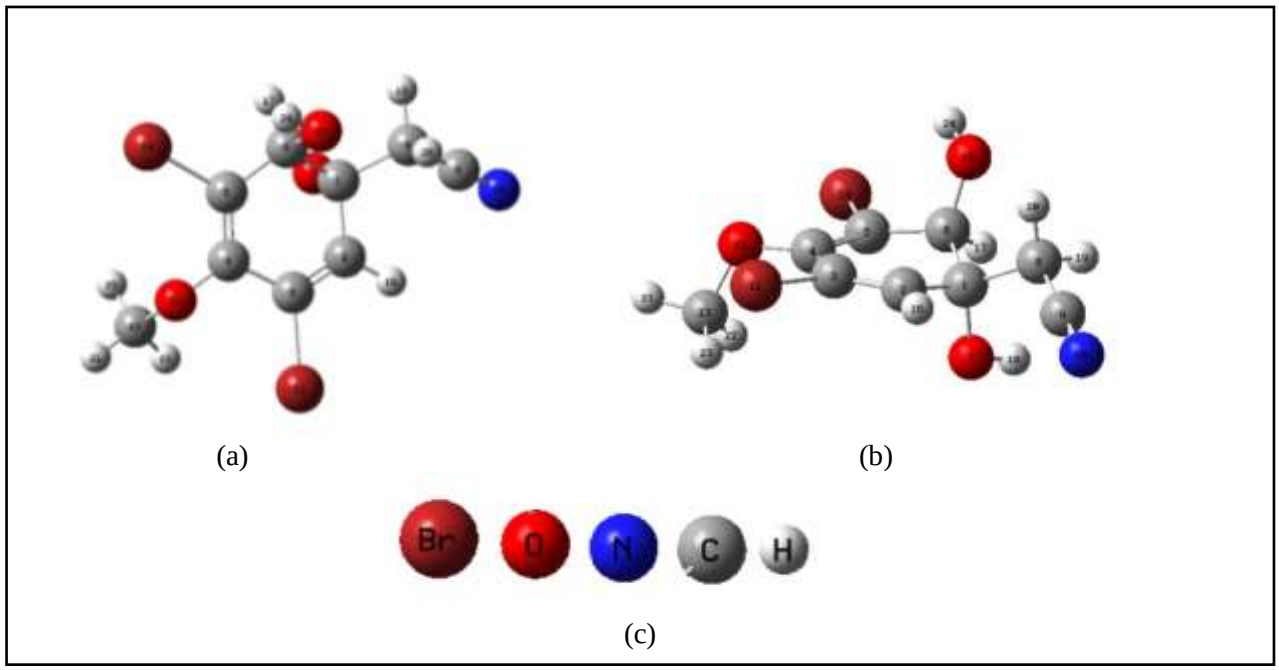


Figure 2. Optimized geometry of aeroplysinin-1, front look (a) and side look (b)

Table 1. Atomic charge distribution of aeroplysinin-1

| Molecule | Atomic charge | | | | | |
|---|---|---|---|---|---|---|
| | N10 | Br11 | O12 | C13 | Br14 | O15 |
| Aeroplysinin-1 | -0.475 | -0.086 | -0.496 | -0.219 | -0.097 | -0.626 |

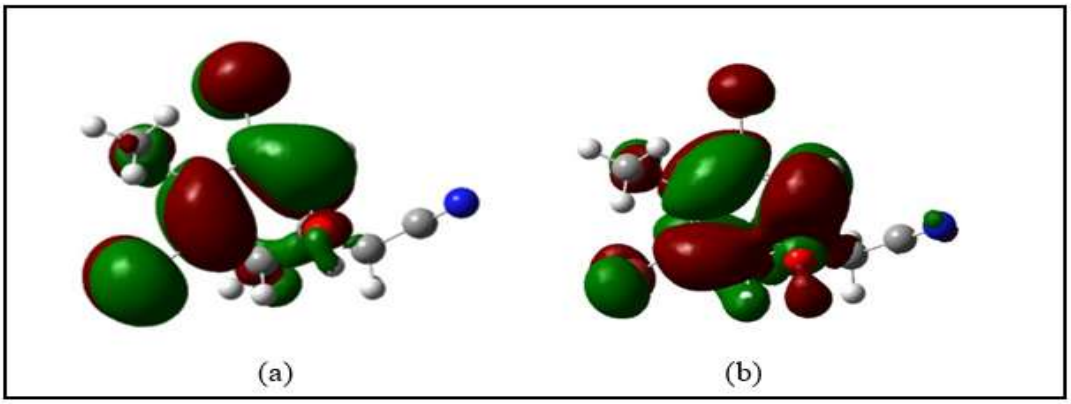


Figure 3. HOMO Distribution(a) and LUMO Distribution in Aeropysinin-1

Table 2. Data from molecular docking of aeroplysinin-1

| Protein | Binding Affinity | Ligan efficiency | Inhibitor Constant |
|---|---|---|---|
| 1KZN - native | -9.00 kcal/mol | -0.18 | 252.69 nM |
| 1KZN – aeroplysinin-1 | -5.7kcal/mol | -0.38 | 66.89 uM |
| 3G7B- native | -8.50 kcal/mol | -0.29 | 590.30 nM |
| 3G7B – aeroplysinin-1 | -6.35kcal/mol | -0.42 | 22.09 uM |

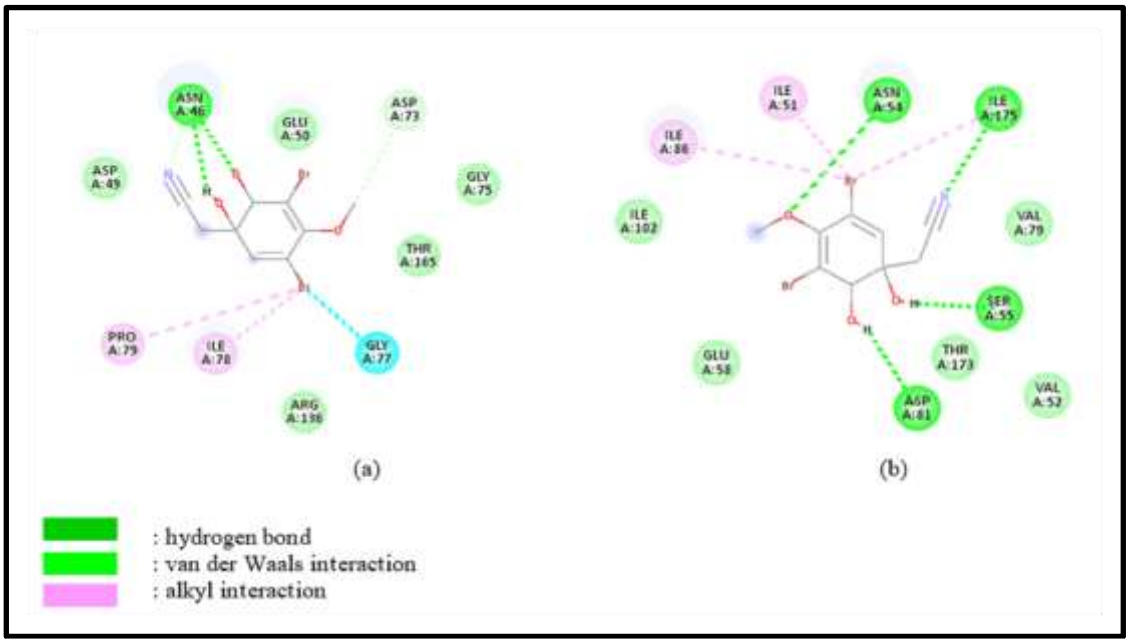


Figure 4. Intermolecular interaction between aerolysinin-1 with DNA Gyrase from (a) E.Coli (a) and (b) S. Aureus

**Atomic Charge Distribution**

Based on the molecular property that needs to be discussed is the distribution of atomic charge. It is necessary to know the atomic charge distribution in the molecule. The charge distribution explains the intermolecular interactions formed between the ligands and the protein at the molecular docking. Atomic charge distribution of aeroplysinin-1 can be seen in

Table 1. Based on table 1, there is something odd where bromide has a positive charge, while bromide has a large electronegativity. Still, when it bonds with other electronegative atoms, the negative charge becomes a positive charge.

**HOMO-LUMO Distribution**

View from HOMO and LUMO show how the distribution of molecular orbitals for the molecule. HOMO-LUMO distribution also can show how easy is the process of transferring electrons(Maahury, Male, & Martoprawiro, 2020). HOMO-LUMO distribution of aeroplysinin-1 is shown in Figure 3. Based on Figure 3, HOMO and LUMO of aeroplysinin-1 overlap each other. There is no HOMO or LUMO in the CN substituent.

**Binding Energy**

Molecular docking of aeroplysinin-1 to Protein DNA Gyrase of E.coli and S.aureus obtain one type of molecular interaction. The molecular interaction happens between aeroplysinin-1 and amino acid residue in 1KZN and 3G7B. The binding energy has been obtained from analysis. This analysis using the method of comparing Root Mean Square Distances (RMSD). The RMSD values compare to ligand native (clorobiocin and gentamicin). The data from molecular docking are shown in Table 2. Based on table 2, the bond affinity between aeroplysinin-1 to 1KZN and 3G7B show lower energy than the natives. On the other side, the ligan efficiency of aeroplysinin-1 is higher than the natives. Even though the binding energy value (bond affinity) is lower, it has a better efficiency in bonding. So, aeroplysinin-1 can inhibit the protein.

**Intermolecular interactions with amino acid residues**

The intermolecular interactions of ligan and protein can be analyzed when studying molecular docking. The intermolecular interaction between aeroplysinin-1and DNA gyrase from bacteria is dominated by a hydrogen bond. Interaction distance obtained from the interaction between ligand and amino acid in the active site has a bond length below 3 Å.

The intermolecular interactions between aeroplysinin-1 with amino acid residues in DNA gyrase from E.*coli* and S.*aureus* can be seen in Figure 4. Interaction between aeroplysinin-1 with 1KZN shows three kinds of interaction: hydrogen bond, van der Waals interaction, and alkyl interaction. Hydrogen bond formed between aeroplysinin-1 and 1KZN (E.*coli* DNA gyrase) occur with ASN46 (1.85 Å and 2.07 Å). There are two atoms (H and O) from aeroplysinin-1 that interact with ASN46. The other interactions are van der Waals interaction and alkyl interaction. The van der Waals interaction occurs between CN with ASN46 (2.99 Å); OH with ASP73 (5.47 Å). The alkyl interaction occurs between Br with PRO79 (5.08 Å) and ILE78 (4.73 Å).

Interaction between aeroplysinin-1 with 3G7B shows three kinds of interaction too: hydrogen bond, van der Waals interaction, and alkyl interaction Hydrogen bond formed between aeroplysinin-1 and 3G7B (S.*aureus* DNA gyrase) happen with SER55 (1.72 Å) and ASP81 (2.11 Å). There are four hydrogen bonds based on color, but two have a distance of more than 2 Å. So, there are only two hydrogen bonds.

## CONCLUSION

Based on computational calculations of aeroplysinin-1, the structure of aeroplysinin-1is not planar. This nonplanar is caused by many substituents bond to the benzene ring. The result of molecular docking shows that aeroplysinin-1 can inhibit the DNA gyrase of E.*coli*and S. *Aureus.* The molecular interactions that occur are hydrogen bond, van der Waals interaction, and alkyl interaction.

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