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![Elaeagnus latifolia](image)

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Phan Tu Quy, Nguyen Thi Thanh Hai, Tran Thi Ai My, Thanh Q. Bui, Tran Thai Hoa, Nguyen Vinh Phu, Huynh Thi Phuong Loan, Nguyen Thi Ai Nhung
A theoretical study on inhibitability of silver(I) N-heterocyclic carbene and dimer silver(I) N-heterocyclic carbene complexes against Phytophthora capsici and Fusarium sporotrichioides in Piper nigrum L.

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Abstract

Phytophthora capsici and yellow disease caused by Fusarium sporotrichioides. The inhibitability of silver-carbene Ag-NHC and di-silver-carbene Di-Ag-NHC complexes on protein 6KD3 in Phytophthora capsici and protein 1JFA in Fusarium sporotrichioides was theoretically investigated using molecular docking simulation. The results reveal that both Ag-NHC and Di-Ag-NHC performing strong inhibitory effects towards both proteins. Docking score energy values regarding [Ag-NHC]-6KD3 and [Di-Ag-NHC]-6KD3 are -11.2 and -11.7 kcal.mol⁻¹. The corresponding figures for [Ag-NHC]-1JFA and [Di-Ag-NHC]-1JFA are -11.1 and -13.4 kcal.mol⁻¹. Also, analysis on hydrogen bonding, interaction distance, and van der Waals interactions formed in the inhibitory systems indicates good site-site binding between amino acids of the targeted proteins and the carbene molecules. This study introduces Ag-NHC and Di-Ag-NHC complexes as potential candidates for prevention of infection caused by Phytophthora capsici and Fusarium sporotrichioides, thus mitigate the impacts on the production of black pepper.

Keywords. Silver-carbene, Phytophthora capsici, Fusarium sporotrichioides, docking simulation, inhibition.

1. INTRODUCTION

Black pepper (Piper nigrum L.; Piperaceae) is well-known as the "King of spices" in many culinary cultures. It is mainly grown in pantropical areas, especially Southern India and Southeast Asia. Vietnam is one of the world's largest peppercorn exporters given its market share making up 58 % of the global export value. However, the plant is highly susceptible to a variety of infectious diseases. The most seriously affected ones are foot rot and yellow disease which either able to result in reduced yields or even complete crop loss. According to folk experiences, the former is described as "quick death disease" while the latter is depicted as "slow death disease", named after their impact rate developed on the host plants. Foot rot, or phytophthora foot rot, is acknowledged as the most common and highest destructive disease to black pepper by invariably leading to low productivity. In Vietnam, agricultural reports indicate that the disease can infect and spread rapidly on the plants, responsible for ca. 2 % of annual yield loss. The disease cause has been determined due to the spread of a polycyclic oomycete soil-borne plant pathogen Phytophthora capsici, whose symptoms are also observed on root, foliar and fruit of many other vegetables. The plants are expected to die within 2-3 weeks after the infection as they are ineffective in either absorbing or transporting water and nutrients by damaged phloem and xylem in their roots. Eventually, the leaves wilt and the plants die quickly. The yellow disease is also considered as the most dangerous disturbance to black pepper stemming from a fungal plant pathogen Fusarium sporotrichioides. The infection symptoms include yellowing of foliage and root rot, leading to either flaccidity or death of the affected plants. In Vietnam, farmers report that black pepper vines often grow for four months before typical symptoms of infection occur. After that, leaf discoloration and plant defoliation are expected. In severe cases, the infection might lead to root death, thus further leading to the death of the vines. Both foot rot and yellow disease are difficult to be treated. Systemic fungicides, such as metalaxyl, phosphonates and...
ningnanmycin, have been widely used for the control of the diseases. However, consistently applications of a certain fungicide are more likely to result in chemical resistance. Therefore, it is necessary to develop an alternative targeting to specific structures in the fungi. The targeting might mitigate the resistance of the fungi to other broad-spectrum antifungal drugs.

Uridine phosphorylase (UP) is an important enzyme in mammals and some microbes, which participate in the pathways of pyrimidine ribonucleosides degradation and salvage. It catalyzes the reversible phosphorylytic cleavage of uridine and deoxyuridine to uracil and ribose- or deoxyribose-1-phosphate, thus enabling the recycling of endogenous or exogenous-supplied pyrimidines. The biosynthesis of purine and pyrimidine nucleotides is imperative as they are critical substrates for the growth and replication of DNA and RNA. Therefore, if the enzyme can be inhibited, the host intracellular metabolism could be inactivated and its death ensues. Besides, the crystal structure of uridine phosphorylase from the oomycete pathogen Phytophthora capsici was characterized by Yang et al. and its structure data was archived under the number 6KD3 in Worldwide Protein Data Bank (DOI: 10.2210/pdb6KD3/pdb).

Figure 1A shows the structure of protein 6KD3 of Phytophthora capsici.

Trichodiene synthase (TS) is a sesquiterpene cyclase that catalyzes the formation of trichodiene, thus participating in terpenoid biosynthesis. The terpenoids are a large and diverse class of organic compounds making up ca. 60 % of known natural products. They are found in almost all living organisms, including plants, animals, microbes, insects, plant pathogens, and endophytes. In particular, fungal terpenoids were demonstrated playing as important characteristics of fungal adaption to inhabited ecosystems and their gene duplication. This leads to an implication that fungal infectiousness could be mitigated by prohibiting terpenoid production of the fungi. The approach is highly practicable with sufficient inhibition of the related-fungal trichodiene synthase. Furthermore, the X-ray crystal structure of trichodiene synthase from Fusarium sporotrichioides has been determined by Rynkiewicz et al. and its structure data was archived under the number 1JFA in Worldwide Protein Data Bank (DOI: 10.2210/pdb1JFA/pdb). Figure 1B illustrates the structure of protein 1JFA of Fusarium sporotrichioides.

Divalent carbon compounds have been highly interested since the discovery of stable nucleophilic N-heterocyclic carbenes (NHCs) by Arduengo in 1991. NHCs constitute promising alternatives to tertiary phosphines. They were demonstrated easily prepared and functionalized. Besides, strong metal-ligand interactions are conducive to the stability of multimetallic structures. Arduengo et al. also successfully synthesized the first NHC-Ag(I) and isolated free NHC. Moreover, silver–NHC complexes were reported not only exhibiting both antibiotic and anticancer properties but also holding many other promising applications in medical treatment. In 2004, Youngs et al. reported the experimental use of silver NHCs as antimicrobial agents. In addition, more recent studies proposed a structure-anticancer activity correlation of NHC-silver(I) complexes. The obtained results suggested significant enhancement of in biological applicability, especially in clinical therapy, if the metal-ligand coordination was formed.
Free-state carbenes are electrophilic but they become nucleophilic in an N-heterocyclic-coordinated system. N-heterocyclic carbenes (NHCs) are highly able to form complex structures with most main-group metals, transition metals, and rare earth elements. The synthesizability and applicability of NHC-Ag(I) complexes interest significant attention from scientists in comparison to other metal compounds in their family. A study revealed that two silver(I) complexes, namely, silver(I) 2,6-bis(ethanolimidazolemethyl)pyridine hydroxide and silver(I)2,6-bis(propanolimidazolemethyl)pyridine hydroxide exhibited better antimicrobial activity than AgNO$_3$ against Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. The synthesis of NHC–silver complexes derived from 1-benzyl-3-tert-butylimidazole and their antimicrobial evaluation were carried out by Ghosh's research group. More recently, Gurbuz et al. reported effective antimicrobial activity of new imidazolidin-2-ylidene silver complexes against a variety of bacteria and fungi.

![Figure 2: Molecular structure of the studied complexes: (a) silver-carbene Ag-NHC and (b) di-silver-carbene Di-Ag-NHC](image)

This research includes theoretical calculations of bonding properties of silver-carbene complexes using density functional theory (DFT) and further predictions on their inhibitability developed by molecular docking simulation (MDS). Firstly, the structures of silver-carbene Ag-NHC, di-silver-carbene Di-Ag-NHC, and free carbene ligand NHC were optimized using BP86/def2-SVP level of theory. Then, the inhibitory effects of the carbene complexes on protein 6KD3 and protein 1JFA were investigated. The results are evaluated by analysis of obtained docking score (DS) energy, calculated root-mean-square deviation (RMSD), and associated van de Waals (VDW) interactions. To the best of our knowledge, there is no experimental and theoretical information reported about the prevention of foot rot and yellow disease on black pepper related to carbene complexes.

2. METHODOLOGY

Firstly, quantum chemical calculations were implemented on the studied ligands Ag-NHC and Di-Ag-NHC. Geometry optimization and vibrational frequency calculations were carried out for their neutral states without symmetry constraints using Gaussian 09 at the level of theory BP86/def2-SVP. Zero-point energy (ZPE) was obtained using frequency analysis at the same functional level and all minima were characterized to have zero imaginary frequency. This was for determination of the molecular structures being global minimum on potential energy surface (PES). A small-core quasi-relativistic effective core potential (ECP) was applied for silver atoms. Single-point energy at the BP86/def2-SVP level optimized geometries was calculated with an application of the frozen-core approximation for non-valence-shell electrons. The same functional geometry optimizations at the larger def2-TZVPP basis set were carried out. The resolution of identity (RI) approximation was used for all structure optimizations with appropriate auxiliary basis sets. The energies of the highest occupied molecular orbital ($E_{HOMO}$) and lowest unoccupied molecular orbital ($E_{LUMO}$) were calculated using NBO 5.1 available in Gaussian 09. According to DFT-Koopman's theorem, electron affinity (A) and ionization potential (I) of a molecule are in direct correlation with $E_{HOMO}$ and $E_{LUMO}$, i.e. $I = E_{HOMO}$ and $A = E_{LUMO}$. Therefore, the energy gap $\Delta E = E_{LUMO} - E_{HOMO}$ of an organic complex might be a good indicator for its inhibitability towards the surface of silver elements. Besides, electron affinity (A) and ionization potential (I) can yield electronegativity ($\chi$) following the equation $\chi = (I + A)/2$. In principle, electronegativity ($\chi$) derived for an N electron system is defined as its negative chemical potential ($\gamma$) and is determinable from total electronic energy ($E$) and an external potential $\nu(r)$. This is expressed by the differential equation: $\chi = -\gamma = -(\partial E/\partial N)|_{N}$. Secondly, molecular docking simulation was investigated using software MOE 2015.10. The structural information of the proteins (6KD3 and 1JFA), two potential complexes (Ag-NHC and Di-Ag-NHC) had been needed before the interaction between the ligands and the targeted proteins were
simulated. The corresponding inhibitability was evaluated by analyzing a set of output data. This includes molecular configuration of the complexes, docking score (DS) energy, root-mean-square deviation (RMSD) value, interaction types, and relative ligand-protein distance. In a typical procedure, molecular docking simulation follows 2 steps.\cite{56-59}

a) Protein and ligand preparation: Structures of protein 6KD3 (DOI: 10.2210/pdb6KD3/pdb) and protein 1JFA (DOI: 10.2210/pdb1JFA/pdb) are available at Worldwide Protein Data Bank. Quickprep tool was applied to plot their molecular structures and 3D protonation. The active zones of the proteins were identified based on the ligand position within a radius of 4.5 Å from important amino acids. The data of the protein structures were saved in format *.pdb. The potential complexes were structurally optimized via Conjugate Gradient for the minimum energy; termination for energy change 0.0001 kcal.mol\(^{-1}\); max iterations 1000; and Gasteiger-Huckel charges. Intermolecular interaction was performed on system MOE 2015.10. Finally, the obtained information on was saved in format *.sdf.

b) Docking investigation and results analysis: The docking simulation parameters were set with number of poses 10, reserving for further inhibition analysis. The maximum number of solutions per iteration was 1000. The maximum number of solutions per fragmentation was 200. Docking score energy (DS) values was selected as the main indicator to evaluate binding capability between the ligands and the proteins. Ligand-protein visual simulation was modelled on 2D, 3D planes. The chemical interactions formed in the site-site distances between the ligands and important amino acids of 6KD3 and 1JFA were analyzed. Hydrogen bonds, ion bonds, \(\pi-\pi\) interactions, cation-\(\pi\) interactions, and van der Waals interactions were detected to gain information on hydrophilic, hydrophobic, and solvent interactions. Finally, the analysis allows reaching an implication on the inhibitory effects of potential complexes (Ag-NHC and Di-Ag-NHC) into protein 6KD3 of Phytophthora capsici fungi and protein 1JFA of Fusarium sporotrichoides fungi in Piper nigrum L.

3. RESULTS AND DISCUSSION

Optimized structures of Ag-NHC, mono-free ligand NHC, and Di-Ag-NHC are presented in Figure 3. They were obtained a computational calculation using density-functional theory (DFT) under BP86 functional and def2-SVP basis set program Gaussian09 was responsible for this.\cite{58} The main bond Ag-C in the silver-carbene adduct (Ag-NHC) registers 2.059 Å for its bonding length. This is highly consistent with a study carried out by Frenking et al. on a less bulky silver-carbene complex AgCl-NHC\(_{\text{H}}\)\cite{60}. The calculated value was 2.076 Å. In terms of di-silver-carbene structure (Di-Ag-NHC), Ag-Ag and Ag-N are the main bonds, linking two heterocyclic systems. The calculation reveals that Ag-Ag bonding length is 2.843 Å and the length of Ag-N bonds varies marginally, i.e., 2.088 – 2.090 Å. The optimized structures of the studied complexes seem to possess higher stability than the carbene adducts already reported.\cite{61}

![Figure 3: Optimized structures of (a) silver-carbene Ag-NHC, (b) free carbene ligand NHC, and (c) di-silver-carbene Di-Ag-NHC using BP86/def2-SVP level of theory. Bond lengths in Å and angles in degrees](image)

Intermolecular interaction is though in relation with frontier molecular orbitals, especially highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).\cite{62} The
former might infer the capability of electron donation while the latter is considered as a parameter for electron-accepting capability. The corresponding orbitals for the two carbene complexes (Ag-NHC and Di-Ag-NHC) are shown in Figure 4. Regarding Di-Ag-NHC, the electron density of its HOMO and LUMO are rather uniformly distributed over its molecular structure in the form of π-electron delocalized dimer rings. In contrast, Ag-NHC HOMO density is mainly distributed over its N-heterocyclic carbene ring whose attribute is the lone pairs of the central carbon atom and nitrogen atoms. This is followed by a spread to its phenyl groups located on either side. Meanwhile, the LUMO, filling the complementary space of the molecule, occupies the regions located by carbon 5-ring (C-heterocyclic) and two phenyl 6-rings. The significance of volume and density localized by these orbitals, exhibited in figure 4, implies that the studied complexes Ag-NHC and Di-Ag-NHC are considered excellent for intermolecular activities.\[61\]

The quantum chemical parameters related to molecular electronic structures of the studied complexes Ag-NHC and Di-Ag-NHC are presented in Table 1 for further analysis. They include HOMO energy ($E_{HOMO}$), LUMO energy ($E_{LUMO}$), the energy gap between HOMO and LUMO densities ($\Delta E_{\text{gap}}$ ($E_{\text{LUMO}}-E_{\text{HOMO}}$)), ionization potential ($I$), electron affinity ($A$), chemical potential ($\gamma$), and electronegativity ($\chi$). In particular, $E_{HOMO}$ quantifies electron-accepting capability while $E_{LUMO}$ value provides information on the capability of electron donation. To evaluate, either high HOMO energy density or low LUMO energy value of the ligand molecules is considered as a good binding indicator to targeted proteins. The reasoning is due to the fact that amino acids in polypeptide molecules were proposed and well demonstrated electronically conductive and polarizing.\[61,63\]

The corresponding value for the carbene complexes $E_{HOMO}$ values obtained follows Ag-NHC < Di-Ag-NHC. Several studies demonstrated that $E_{HOMO}$ is well correlated with the inhibition\[61,64\] given the electron-donating ability of the inhibitor. The reports revealed a positive correlation, meaning that higher $E_{HOMO}$ value indicates a better electron donating tendency of an inhibitor to its acceptor molecule. A similar tendency is observed in consideration of $E_{LUMO}$ values by a narrower differential. However, $E_{LUMO}$ indicates the electron-accepting capacity of an inhibitor complex. This means a lower $E_{LUMO}$ value represents better electron accepting capability. Correspondingly, the HOMO energy values are -3.265 and -4.898 eV; whilst, the LUMO energy values are -2.721 and -3.374 eV.

Besides, energy gap ($\Delta E_{\text{gap}}$) value of Di-Ag-NHC (0.544 eV) is smaller than that of Ag-NHC (1.524 eV). According to previous reports, low gap-energy molecules are likely performing high polarization, thus conducive to chemical reactivity and inhibitory stability.\[61,63,64\] This can be explained that the electrons are easily transferred to the surface of the inhibitor molecule, ready for intermolecular activities. Also, electronegativity ($\chi$), or the chemical potential ($\gamma$) in a negative value, could be considered as a reliable inhibition indicator as it presents the tendency of attracting electrons. In detail, a higher electronegativity implies a stronger attraction of electrons towards the host molecule. The corresponding values for Ag-NHC and Di-Ag-NHC are 4.136 and 2.993, respectively.

The analysis on quantum properties of the carbene complexes suggests their promising applicability in physiological mediums. This preliminarily reveals their high practicability in the application of inactivating Phytophthora capsici and Fusarium sporotrichioides infecting Piper nigrum L. by carrying out investigations on their inhibitability towards the host important proteins, i.e. 6KD3 and 1JFA, respectively. In addition, the associated results for the two referenced pesticides (metalaxyl and nignannymycin) are shown.

Molecular docking simulation is used to investigate the interactions between the two carbene complexes with protein 6KD3 in Phytophthora capsici and protein 1JFA in Fusarium sporotrichioides. The schematic illustrations (2D and 3D modelling) for the former and the latter are exhibited in figures 5 and 6, respectively. These provide a visual view of the inhibitions including the crystal structure of targeted proteins and the relative positions of the docked ligands to their molecular

Table 1: Quantum chemical parameters of the complexes Ag-NHC and Di-Ag-NHC at the level of theory BP86/def2-TZVPP//BP86/def2-SVP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ag-NHC</th>
<th>Di-(Ag-NHC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{HOMO}}$ (eV)</td>
<td>-4.898</td>
<td>-3.265</td>
</tr>
<tr>
<td>$E_{\text{LUMO}}$ (eV)</td>
<td>-3.374</td>
<td>-2.721</td>
</tr>
<tr>
<td>$\Delta E_{\text{gap}}$ (LUMO-HOMO) (eV)</td>
<td>1.524</td>
<td>0.544</td>
</tr>
<tr>
<td>Ionization potential ($I$) (eV)</td>
<td>4.898</td>
<td>3.265</td>
</tr>
<tr>
<td>Electron affinity ($A$) (eV)</td>
<td>3.374</td>
<td>2.721</td>
</tr>
<tr>
<td>Chemical potential ($\gamma$) (eV)</td>
<td>-4.136</td>
<td>-2.993</td>
</tr>
<tr>
<td>Electronegativity ($\chi$) (eV)</td>
<td>4.136</td>
<td>2.993</td>
</tr>
</tbody>
</table>

Figure 5: Protein 6KD3 docked with silver-carbene Ag-NHC and di-silver-carbene Di-Ag-NHC. (A) Crystal structure of Phytophthora capsici protein 6KD3; 2D and 3D docking simulations between (B) Ag-NHC and (C) Di-Ag-NHC with protein 6KD3

Figure 6: Protein 1JFA docked with silver-carbene Ag-NHC and di-silver-carbene Di-Ag-NHC. (A) Crystal structure of Fusarium sporotrichioides protein 1JFA; 2D and 3D docking simulations between (B) Ag-NHC and (C) Di-Ag-NHC with protein 1JFA

The inhibitability of the ligands into proteins 6KD3 and 1JFA is evaluated by their corresponding values of docking score (DS) energy, root-mean-square deviation (RMSD), and associated van der Waals (VDW) interactions. These parameters are presented in table 2. It can be seen that both Ag-
NHC and Di-Ag-NHC perform strong inhibitory effects towards 6KD3 than metalaxyl, given the relative significance of their DS values (-11.2 and -11.7 kcal.mol\(^{-1}\), respectively). The former is derived from the VDW interactions with 17 different 6KD3 amino acids (Ser 90; His 32; Phe 211; Met 247; Arg 217; Leu 270; Ile 109; Gly 142; Arg 93; Ser 141; Thr 140; Phe 31; Ser 60; Glu 62; Arg 291; His 283; Leu 286) while the number of 6KD3 amino acids responsible for the interaction in the complex Di-Ag-NHC-6KD3 is 7 (His 283; Leu 286; Glu 62; Arg 63; Ser 90). The results imply that the inhibitability of the investigated compounds towards the protein 6KD3 accords with the order Di-Ag-NHC > Ag-NHC. This is followed by the corresponding figure for the complex formed by Di-Ag-NHC and 1JFA (-13.4 kcal.mol\(^{-1}\)). In detail, the number of their VDW interactions with the protein amino acids is not in noticeable difference, ca. 10 interactions formed by each. Otherwise, although creating 15 VDW interactions with 1JFA amino acids (Arg 304; Tyr 305; Lys 232; Glu 233; Asn 225; Asp 226; Asn 185; Arg 182; Glu 164; Ser 242; Gln 165; Ile 241; Asn167; Gln 240; Asp 239), Ag-NHC appears to form a weaker complex with the host protein since the calculated DS value is -11.1 kcal.mol\(^{-1}\), significantly lower than its bi-structural homologue. Therefore, the relative inhibitory effect on the protein 1JFA seems in good agreement with the order Di-Ag-NHC > Ag-NHC. In addition, the RMSD values of all simulated systems are smaller than 2 Å. This justifies the validation of molecular docking programs for all virtual investigations.\(^{[65]}\)

The insights of hydrogen bonds formed between the selected ligands and the host protein amino acids, resided within the distance of 5 Å, are also achieved. The information for protein 6KD3 is provided in table 3, while table 4 gives the corresponding figures for protein 1JFA. Inside the binding sites, Di-Ag-NHC forms 9 and 10 hydrogen bonds with protein 6KD3 and protein 1JFA, respectively. The interactions are mainly ionic formed between its nitrogen atoms and oxygen atoms of the proteins. In particular, Glu 290 is the contributor for all 7 ionic interactions in regard to 6KD3, while Asp 100, Glu 164, and Glu 233 are equally responsible for 9 ionic interactions created by 1JFA. The shortest interactions in each docking complex are 3.09 Å with the associated energy -3.9 kcal.mol\(^{-1}\) (Di-Ag-NHC-6KD3) and 2.86 Å with the bonding energy -5.5 kcal.mol\(^{-1}\) (Di-Ag-NHC-1JFA). Regarding the complexes of Ag-NHC and the proteins, their interaction type is rather varied. There are 4 hydrogen-type bonds formed in Ag-NHC-6KD3, including H-acceptor, metal, ionic, and π-H interactions. Meanwhile, Ag-NHC-1JFA consists of 6 hydrogen bonds, divided into three types: ionic, π-cation, and π-H interactions. Also, Ag-NHC heterocyclic rings play an important role in these interactions.

Table 2: Docking simulation results with docking score energy (DS), root-mean-square deviation (RMSD), and van der Waals (VDW) interactions of complexes Ag-NHC, Di-Ag-NHC with amino acids of proteins 6KD3 and 1JFA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Symbol (compound-protein)</th>
<th>DS (kcal.mol(^{-1}))</th>
<th>RMSD (Å)</th>
<th>VDW interaction with amino acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound – 6KD3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag-NHC</td>
<td>Ag-NHC-6KD3</td>
<td>-11.2</td>
<td>1.41</td>
<td>Ser 90; His 32; Phe 211; Met 247; Arg 217; Leu 270; Ile 109; Gly 142; Arg 93; Ser 141; Thr 140; Phe 31; Ser 60; Glu 62; Arg 291; His 283; Leu 286.</td>
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<tr>
<td>Di-Ag-NHC</td>
<td>Di-Ag-NHC-6KD3</td>
<td>-11.7</td>
<td>1.45</td>
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<tr>
<td>Compound – 1JFA</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ag-NHC</td>
<td>Ag-NHC-1JFA</td>
<td>-11.1</td>
<td>1.90</td>
<td>Arg 304; Tyr 305; Lys 232; Glu 233; Asn 225; Asp 226; Asn 185; Arg 182; Glu 164; Ser 242; Gln 165; Ile 241; Asn167; Gln 240; Asp 239;</td>
</tr>
<tr>
<td>Di-Ag-NHC</td>
<td>Di-Ag-NHC-1JFA</td>
<td>-13.4</td>
<td>0.90</td>
<td>Ser 229; Lys 232; Arg 182; Asn 225; Ser 242; Asp 239; Ile 241; Asn 185; Phe 157; Leu 97.</td>
</tr>
</tbody>
</table>
in its interaction with the targeted proteins, especially 1JFA with 4/6 interactions stemmed from either 5-ring or 6-ring. The shortest interactions in each inhibitory complex are 2.99 Å with the associated energy -1.2 kcal.mol\(^{-1}\) (Ag-NHC-6KD3) and 3.58 Å with the bonding energy -1.6 kcal.mol\(^{-1}\) (Ag-NHC-1JFA). Therefore, given either the number of hydrogen bonds or their bonding parameters (length and energy), the inhibitability of Di-Ag-NHC is predicted stronger than that of Ag-NHC. This is significant regardless of the targeted proteins.

**Table 3**: Molecular docking simulation results with critical interactions between the complexes Ag-NHC, Di-Ag-NHC, and the protein 6KD3: interaction and distance, site-site binding, energy, cation-π, π-π bonds, ionic interactions, and total hydrogen bonds

<table>
<thead>
<tr>
<th>Symbol (compound-protein)</th>
<th>Ligand</th>
<th>Protein</th>
<th>Interaction</th>
<th>Distance (Å)</th>
<th>Energy (kcal.mol(^{-1}))</th>
<th>Hydrogen bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag-NHC-6KD3</td>
<td>Cl</td>
<td>N Arg 63</td>
<td>H-acceptor</td>
<td>3.29</td>
<td>-0.8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Ag</td>
<td>O Glu 290</td>
<td>metal</td>
<td>2.99</td>
<td>-1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.67</td>
<td>-1.3</td>
<td></td>
</tr>
<tr>
<td>6-ring</td>
<td>N</td>
<td>Gln 287</td>
<td>π-H</td>
<td>3.43</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>O Gln 287</td>
<td>H-donor</td>
<td>3.35</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.28</td>
<td>-2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.31</td>
<td>-2.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.09</td>
<td>-3.9</td>
<td></td>
</tr>
<tr>
<td>Di-Ag-NHC-6KD3</td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.67</td>
<td>-1.3</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.65</td>
<td>-1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.17</td>
<td>-3.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 290</td>
<td>ionic</td>
<td>3.17</td>
<td>-3.4</td>
<td></td>
</tr>
<tr>
<td>5-ring</td>
<td>N</td>
<td>Gln 287</td>
<td>π-H</td>
<td>3.95</td>
<td>-1.8</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4**: Molecular docking simulation results with critical interactions between the complexes Ag-NHC, Di-Ag-NHC, and the protein 1JFA: interaction and distance, site-site binding, energy, cation-π, π-π bonds, ionic interactions, and total hydrogen bonds

<table>
<thead>
<tr>
<th>Symbol (compound-protein)</th>
<th>Ligand</th>
<th>Protein</th>
<th>Interaction</th>
<th>Distance (Å)</th>
<th>Energy (kcal.mol(^{-1}))</th>
<th>Hydrogen bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag-NHC-1JFA</td>
<td>N</td>
<td>O Asp 100</td>
<td>ionic</td>
<td>3.63</td>
<td>-1.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Asp 100</td>
<td>ionic</td>
<td>3.58</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>6-ring</td>
<td>N</td>
<td>Arg 62</td>
<td>π-cation</td>
<td>3.79</td>
<td>-1.5</td>
<td></td>
</tr>
<tr>
<td>5-ring</td>
<td>N</td>
<td>Arg 62</td>
<td>π-cation</td>
<td>4.39</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>6-ring</td>
<td>N</td>
<td>Arg 62</td>
<td>π-cation</td>
<td>4.69</td>
<td>-1.2</td>
<td></td>
</tr>
<tr>
<td>6-ring</td>
<td>C</td>
<td>Arg 238</td>
<td>π-H</td>
<td>4.31</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>O Asp 226</td>
<td>H-donor</td>
<td>3.04</td>
<td>-1.1</td>
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<tr>
<td></td>
<td>N</td>
<td>O Asp 100</td>
<td>ionic</td>
<td>3.25</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Asp 100</td>
<td>ionic</td>
<td>3.34</td>
<td>-2.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 164</td>
<td>ionic</td>
<td>3.58</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Asp 100</td>
<td>ionic</td>
<td>4.00</td>
<td>-0.5</td>
<td></td>
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<tr>
<td></td>
<td>N</td>
<td>O Glu 164</td>
<td>ionic</td>
<td>3.28</td>
<td>-2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 164</td>
<td>ionic</td>
<td>3.92</td>
<td>-0.7</td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 233</td>
<td>ionic</td>
<td>3.25</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 233</td>
<td>ionic</td>
<td>2.86</td>
<td>-5.5</td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>O Glu 233</td>
<td>ionic</td>
<td>3.58</td>
<td>-1.6</td>
<td></td>
</tr>
</tbody>
</table>

In summary, Di-Ag-NHC exhibits stronger inhibitory effects to both proteins 6KD3 and 1JFA than silver-carbene complex Ag-NHC. This can be explained by the facts that Di-Ag-NHC possesses a larger volume and a higher molecular mass, leading to a significant polarizability and strong binding capacity with amino acids of the protein. Therefore, the observations imply that there are likely a correlation between the bulkiness of the ligands and their inhibitability towards the protein structure.
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However, the preliminary judgement still requires more in-depth and systematic research for confirmation.

4. CONCLUSIONS

The study demonstrates promising inhibitability of the silver-carbene and di-silver-carbene complexes towards protein 6KD3 of Phytophthora capsici and protein 1JFA of Fusarium sporotrichioides. Di-silver-carbene complex Di-Ag-NHC exhibits stronger inhibitory effects to both proteins 6KD3 and 1JFA than silver-carbene complex Ag-NHC. The docking score energy values of carbene and di-carbene complexes regarding protein 6KD3 of Phytophthora capsici are -11.7 and -11.2 kcal.mol\(^{-1}\), respectively. The corresponding figures in regard to protein 1JFA of Fusarium sporotrichioides are -13.4 and -11.1 kcal.mol\(^{-1}\). The simulation also reveals that carbene and di-carbene complexes exhibit good site-site binding with protein 6KD3 and protein 1JFA. The root-mean-square deviation values are always lower than 2 \(\text{Å}\) calculated for any system. The results predicted by molecular docking simulation in this study preliminarily suggest that the carbene complexes are highly promising for further research on development of new agents to inhibit proteins 6KD3 (Phytophthora capsici) and 1JFA (Fusarium sporotrichioides) in particular. These might further open environment-advanced and molecular-effective alternatives to tackle the impacts of foot rot and yellow disease on black pepper in general.

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Conflict of interest. The authors declare no conflict of interest.

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A theoretical study on inhibitability of...