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Research Article

Computational Docking Studies of Phenyl Acetic Acid Derivatives with Biological Targets, DNA, Protein and Enzyme

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Abstract

Phenyl acetic acid (PAA) is a well-known biomolecule used in antibiotics and drugs. To elucidate the binding modes of PAA and its derivatives with DNA, Pim kinase protein, and urease enzymes, molecular docking studies were conducted. The results revealed that PAA and its derivatives intercalate with DNA, disrupting its structure and potentially affecting replication, transcription, and repair processes. The 3-chloro-PAA showed the highest docking score (-7.809) and significant polar interactions with DNA residues. For Pim kinase, the compounds exhibited polar interactions with key residues, with 2-propyl PAA demonstrating notable inhibitory effects. Similarly, PAA derivatives interacted effectively with urease enzymes, with the 4-propyl-PAA showing a strong docking score (-8.5250). Overall, the meta-substituted PAAs exhibited superior binding interactions compared to ortho and para-substituted derivatives, suggesting their potential as effective inhibitors for these biological targets.

Keywords: PAA derivatives, Molecular docking, DNA interaction, Pim kinase inhibition, Urease enzyme inhibition.

1. Introduction

PAA (Phenyl acetic acid) and its derivatives are gaining significant attention in various scientific fields. They are used widely in pharmaceuticals, agrochemicals, fragrances, and polymers. This versatility makes PAA derivatives essential in modern industries. PAA is a simple aromatic carboxylic acid that acts as a backbone for numerous compounds, each with unique characteristics. Its chemical structure includes a phenyl group linked to a carboxylic acid, allowing for easy modification This facilitates the synthesis of a diverse range of derivatives with tailored properties [1].

Recent studies highlight the significance of computational techniques like molecular docking in drug discovery, particularly for understanding the interaction between small molecules, such as PAA, and biological targets. Molecular docking plays a crucial role in predicting how drug candidates bind to proteins, which is essential for determining their binding modes, affinity, and specificity[2], enzymes, and other biomolecular targets[3]. A review of structure-based virtual screening highlighted the increasing application of docking in early drug discovery, specifically its success in identifying novel compounds with potential therapeutic effects[4]. PAA, due to its structural simplicity as an aromatic carboxylic acid, has shown promising binding potential in these simulations, aiding in the design of new derivatives for pharmaceutical applications [5, 6].

PAA is indeed an important biomolecule in the manufacturing of various antibiotics. It serves as a precursor in the synthesis of β-lactam antibiotics, including penicillin and cephalosporins. The production processes often involve using PAA in enzyme-catalyzed reactions, which help enhance the efficiency and yield of antibiotic formulations. Recent studies highlight its utility in both synthetic and biotechnological applications for antibiotic

production [1, 7]. PAA is also used as inhibitor for pesticides, aromatized ,eco-friendly corrosion and biomedical application [8]. Phenolic compounds, known for their diverse biological activities, exhibit significant free radical scavenging properties. They play a crucial role in combating oxidative stress, which is linked to various diseases, including cancer. Recent studies have highlighted the potential of phenolic compounds, particularly phenyl acetate derivatives, in modulating cellular mechanisms and exhibiting anticancer effects. These compounds' antioxidant properties are attributed to their structural characteristics, including hydroxyl groups, which enhance their reactivity with free radicals [9]. Recent research indicates that PAA is naturally present in various organisms, including fungi, bacteria, and plants. For example, PAA functions as an auxin in plants, playing a role in growth and development processes such as cell expansion and lateral root induction. Studies show its accumulation in various plants, including species like *Arabidopsis*, where PAA levels often exceed those of indole-3-acetic acid (IAA), a more studied auxin[10-13]. PAA plays an important role in maintaining normal cellular and root growth [14].

Pim kinases are frequently upregulated in various human cancers, including solid tumors and hematological malignancies. These kinases are implicated in creating an immunosuppressive tumor microenvironment, which can promote cancer progression by facilitating immune evasion[15, 16]. There is ongoing interest in developing inhibitors that target Pim kinases, given their association with cancer survival and proliferation[17].

Enzyme inhibition is central to modern pharmaceutical research, particularly in drug discovery, as inhibitors can block enzymes critical to disease progression. These inhibitors are widely used in treating conditions like cancer, cardiovascular diseases, and neurodegenerative disorders such as Alzheimer's disease. Recent research emphasizes the importance of developing more selective and potent enzyme inhibitors. Enzyme inhibitors not only offer therapeutic benefits but are also pivotal in the development of treatments targeting complex biochemical pathways involved in multiple diseases [18, 19]. Recent research highlights how enzyme inhibitors have been pivotal in areas like oncology, with inhibitors targeting mutations like KRAS, which are involved in cancer progression[20-23].

Furthermore, modern advancements in computational methods have accelerated the discovery and optimization of enzyme inhibitors. Techniques like deep learning models have been applied to predict drug-target interactions more accurately, improving the design of enzyme inhibitors with greater efficacy and specificity[24].

2. Methodology

The three-dimensional (3D) structures of phenyl acetic acid derivatives were generated using the Molecular Operating Environment (MOE-2016) software. Hydrogen atoms were added to phenyl acetic acid and its derivatives through 3D protonation, followed by energy minimization using the same software. The crystal structures of human DNA, human pim kinase protein, and human urease enzyme were obtained from the Protein Data Bank (PDB IDs: 1BNA, 3RO2, and 4UBP) via www.rcsb.org/pdb. Before molecular docking, all water molecules were removed from the crystal structures using MOE-2016 (www.chemcomp.com). Protonation and energy minimization of the DNA, pim kinase, and urease enzyme were also performed with MOE using default parameters. These prepared PDB files were then docked with phenyl acetic acid and its derivatives, applying MOE's default parameters: rescoring with London dG, placement via Triangle Matcher, and generating ten conformations per ligand. For further analysis, the top-ranked conformation of each compound was selected.

3. Results and discussion

3.1 Discussion of DNA

To investigate how phenylacetic acid (PAA) and its derivatives interact with DNA, molecular docking studies were performed. The results revealed that all compounds bind to DNA primarily through intercalation, meaning the compounds insert themselves between the DNA base pairs. The hydrophobicity of the phenyl ring in PAA enables favorable interactions with the hydrophobic core of the DNA helix, facilitating its insertion. Once inserted, PAA disrupts the regular stacking of the DNA base pairs, pushing them apart, which can interfere with key biological

processes such as replication, transcription, and DNA repair. Additionally, PAA intercalation may block the binding of DNA-associated proteins, enzymes, or transcription factors, potentially altering gene expression, inducing DNA damage, or impairing DNA-related functions. These effects depend on factors like PAA concentration, DNA sequence, and biological context, with outcomes ranging from mutations to interference with DNA repair mechanisms.

Among the studied compounds, 3-chlorophenylacetic acid (docking score = -7.809) showed the most potent inhibitory activity. This compound exhibited eight polar interactions with the DNA, including interactions between the chlorine, oxygen, and benzene ring of the ligand and the active site residues (DT 8 DG 16, DA 18, DG 10) of the DNA (Figure 1, 2 (a)). The interactions included two hydrogen acceptors, two hydrogen donors, and four pi-H interactions, indicating a strong binding affinity. The chlorine atom in the 3-chloro derivative interacts with the DT residue of DNA, and the electron-withdrawing nature of chlorine enhances the binding due to the inductive effect, though resonance stabilizes the benzene ring, minimizing deactivation[3].

The 3-methoxyphenylacetic acid derivative (docking score = -7.029) formed eight interactions—six hydrogen acceptors and two pi-H interactions—with DNA residues (DT 19, DC 9, DG 10). The methoxy group donates electrons to the benzene ring, increasing electron density and enhancing the interaction with DNA (b). The 3-nitrophenylacetic acid derivative (docking score = -7.428) showed six hydrogen acceptor interactions between the ligand's oxygen and DNA residues (DG 10, DG 16, DC 15). The electron-withdrawing nature of the nitro group deactivates the benzene ring, reducing the interaction potential with DNA (c).

The 3-hydroxyphenylacetic acid compound (docking score = -7.388) formed six interactions—four hydrogen acceptors and two pi-H interactions—with DNA residues (DT 19, DC 9, DG 10). The hydroxyl group donates electrons, making the benzene ring more electron-rich and enhancing its interactions with DNA (d).

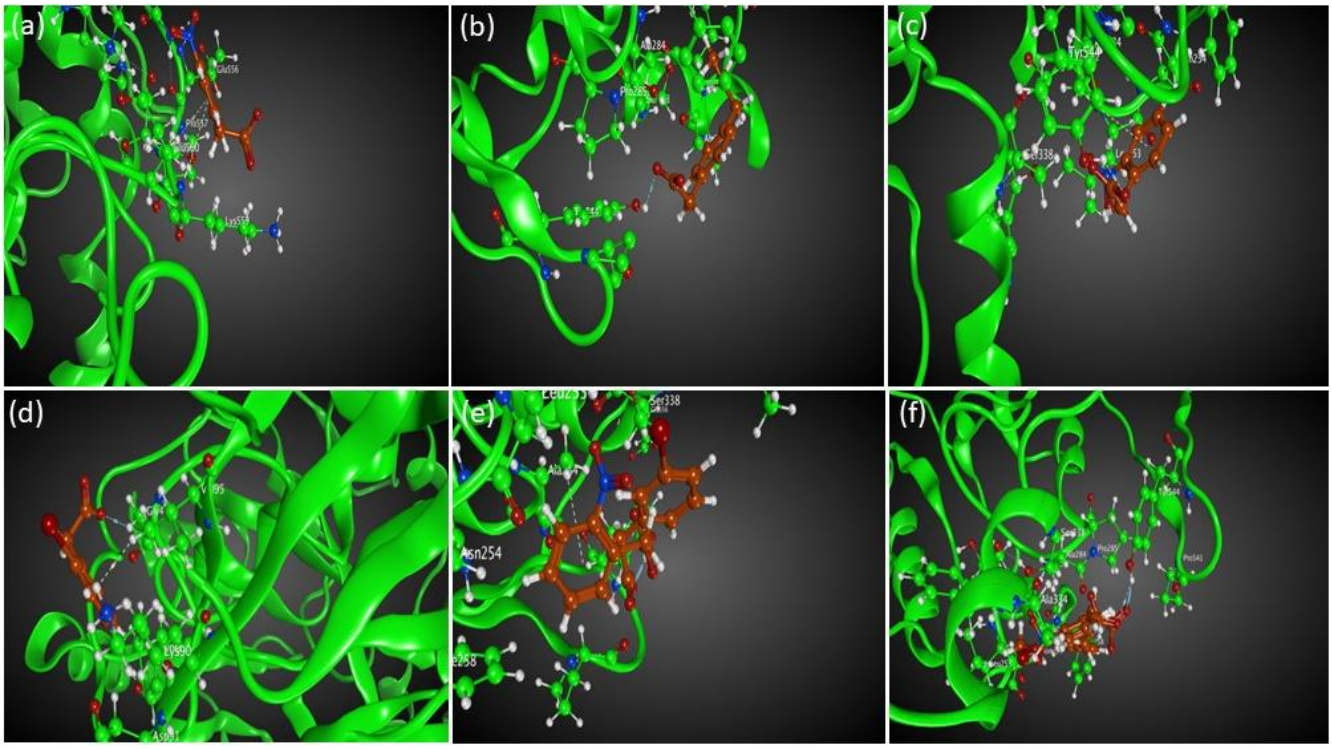

Figure 1. Three-dimension structures of DNA with PAA derivatives. (a) 3-Chloro-PAA, (b) 3-Methoxy-PAA, (c) 3-Nitro-PAA, (d) 3-Hydroxy-PAA, (e) 4-Nitro-PAA and (f) 3-Ethyl-PAA.

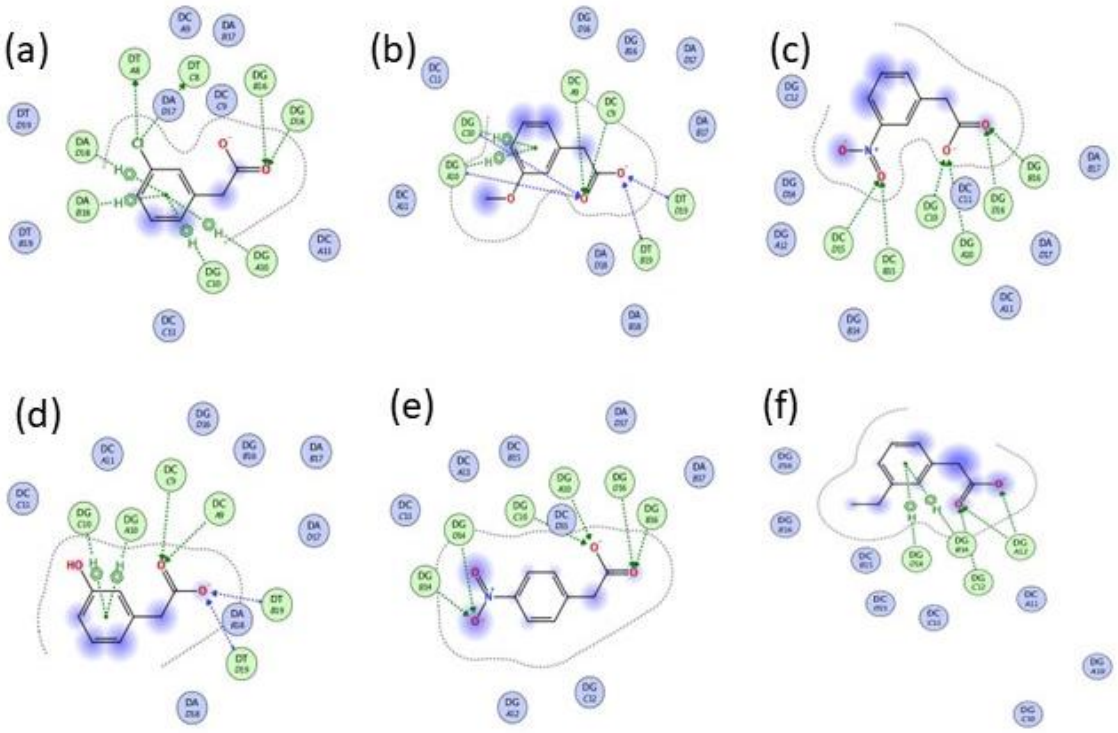

Figure 2. Two-dimension structures of DNA with PAA derivatives. (a) 3-Chloro-PAA, (b) 3-Methoxy-PAA, (c) 3-Nitro-PAA, (d) 3-Hydroxy-PAA, (e) 4-Nitro-PAA and (f) 3-Ethyl-PAA.

Similarly, the 4-nitrophenylacetic acid derivative (docking score = -7.417) exhibited six hydrogen acceptor interactions with DNA residues (DG 10, DG 16, DG 14), demonstrating electron-withdrawing properties like the 3-nitro derivative (e). The 3-ethylphenylacetic acid compound (docking score = -6.499) formed five interactions, including three hydrogen acceptors and two pi-H interactions with DNA residues (DG 14). The ethyl group donates electrons to the benzene ring, enhancing interaction possibilities on the ring and the compound overall (f). Several other phenylacetic acid derivatives, including 3-fluoro, 4-propyl, 4-iodo, 4-chloro, 3-propyl, 4-bromo, 4-methyl, 4-hydroxy, and 3-methyl compounds, displayed four interactions with the active residues of DNA. These derivatives showed moderate levels of interaction with DNA. Their respective docking scores were recorded as follows: -7.519, -7.197, -7.136, -7.056, -6.899, -6.877, -6.763, -6.643, and -6.372. The remaining phenylacetic acid derivatives, including 2-hydroxy, 4-ethyl, 4-methoxy, 3-iodo, 3-bromo, 2-iodo, 2-bromo, 2-nitro, 2-chloro, 2-fluoro, 1-PAA, 2-methoxy, 4-fluoro, 2-ethyl, 2-methyl, and 2-propyl, exhibited weaker interactions compared to the previously discussed derivatives. However, the best docking poses still demonstrated key binding features, primarily due to interactions involving different functional groups of the derivatives.

From the analysis, it is evident that phenylacetic acid derivatives with meta-directing substituents tend to have stronger interactions and greater inhibitory potential than those with ortho or para substituents. This suggests that meta-directing groups contribute more effectively to binding and inhibition, leading to more promising results.

3.2 Discussion of pim kinase protein

The interaction between phenylacetic acid (PAA) and Pim kinase protein is an intriguing area of study. Pim kinases are a group of serine/threonine kinases that play key roles in several cellular functions, including cell growth, survival, differentiation, and programmed cell death. Abnormal activity of Pim kinases has been associated with the development and progression of

various cancers and other diseases, making them potential targets for therapeutic interventions.

Pim kinases typically have a kinase domain responsible for binding ATP and facilitating catalytic activity. PAA is a small aromatic compound composed of a phenyl ring and a carboxylic acid group. The phenyl ring of PAA might interact with the hydrophobic regions of the ATP-binding site, while the carboxyl group could form hydrogen bonds with nearby polar or charged residues. By disrupting ATP binding and interfering with substrate recognition, PAA may inhibit Pim kinase activity. It could also compete with ATP for binding to the kinase domain or induce structural changes that diminish the kinase's function. Computational techniques like molecular docking are commonly used to predict how PAA might bind to the Pim kinase protein. These methods simulate interactions between PAA and the target protein to identify possible binding sites and assess the strength of these interactions.

Molecular docking was performed to investigate the binding modes of phenylacetic acid (PAA) and its derivatives with Pim kinase. The docking results indicated that all the compounds interacted with the Pim kinase protein through polar interactions which was the primary interaction type observed. For example, 2-propylacetic acid (PAA) achieved a docking score of -6.577 and formed three key interactions with the active site residues of Pim kinase (TYR 1993, TRP 319). These included one hydrogen-bond acceptor interaction and two hydrogen-pi interactions. The propyl group, acting as an electron donor, enhanced the ligand's activity, resulting in the inhibition of Pim kinase (Figure: 3, 4 (a)).

Similarly, 4-nitro PAA, with a docking score of -6.1534, displayed three interactions with active site residues TYR 1993 and PHE 1992, comprising two hydrogen-bond acceptor interactions and one pi-hydrogen interaction. The nitro group, attached to the para position of the benzene ring, displayed activating properties due to its electron-withdrawing characteristics, leading to the inhibition of Pim kinase (**b**).

In the case of 3-iodo PAA, a docking score of -5.5008 was obtained, and the compound exhibited three interactions with TYR 1993 and TRP 319. These included one hydrogen-bond acceptor, one pi-hydrogen interaction, and one hydrogen-pi interaction. The iodine group, being an electron-withdrawing substituent, increased susceptibility to nucleophilic attack. However, due to the resonance effect, the benzene ring remained stabilized, allowing these interactions to contribute to Pim kinase inhibition (**c**).

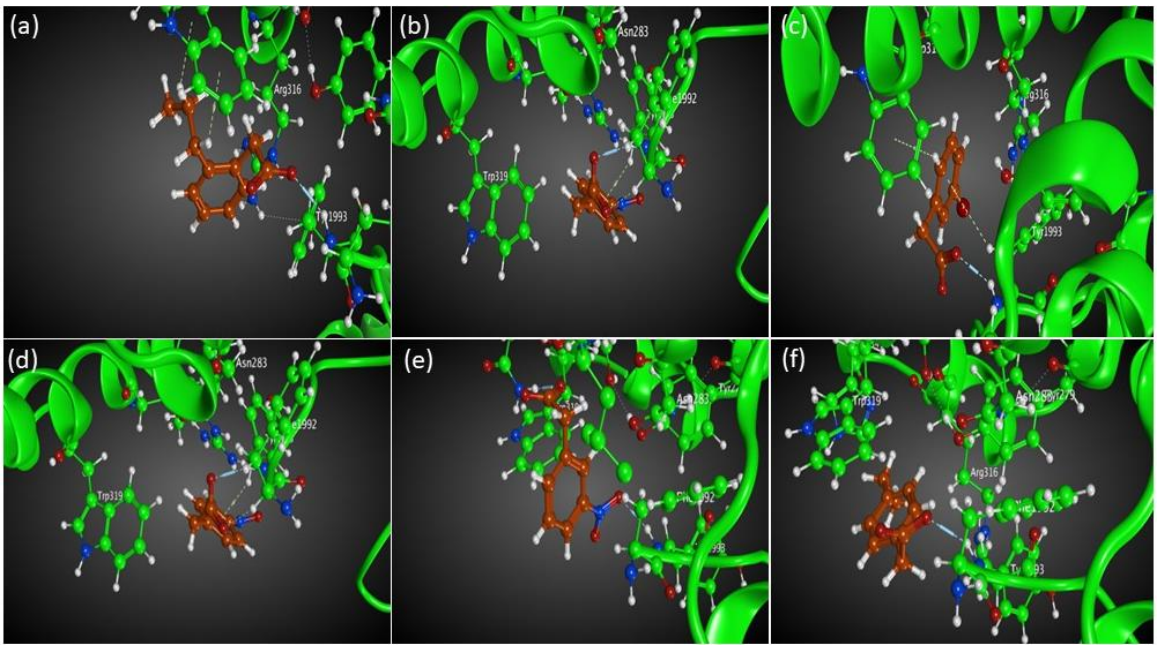

Figure 3. Three-dimension structures Pim kinase protein with (a) 4-Propyl-PAA, (b) 4-Nitro-PAA, (c) 3-Iodo-PAA, (d) 3-Hydroxy-PAA, (e) 3-Nitro-PAA and (f) 4-Ethyl-PAA.

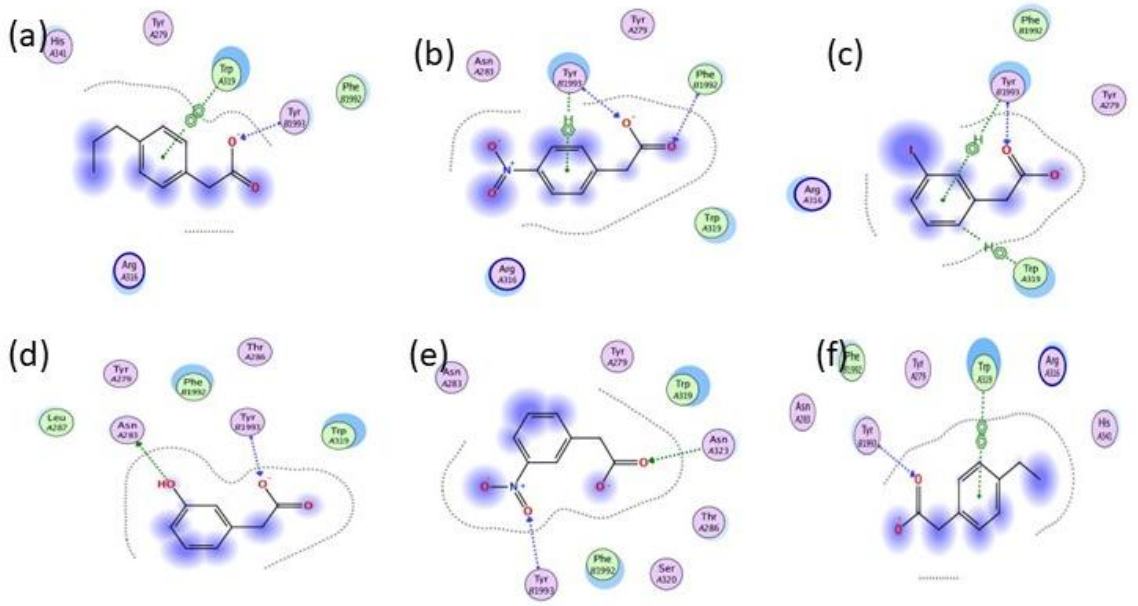

Figure 4: Two-dimension structures Pim kinase protein with (a) 4-Propyl-PAA, (b) 4-Nitro-PAA, (c) 3-Iodo-PAA, (d) 3-Hydroxy-PAA, (e) 3-Nitro-PAA and (f) 4-Ethyl-PAA.

Certain derivatives of phenylacetic acid exhibit intermediate interaction modes with Pim kinase protein, leading to moderate inhibition. These derivatives include 4-ethyl, 3-nitro, 3-bromo, 4-propyl, 2-nitro, 2-iodo, 4-methoxy, 2-methoxy, 4-bromo, 2-bromo, 2-hydroxy, 3-ethyl, 3-methyl, 4-iodo, 4-fluoro, 3-fluoro, 4-chloro, 3-propyl, 3-methoxy, 2-fluoro, 3-chloro, 2-ethyl, and 2-methyl. Their respective docking scores are as follows: -6.7603, -6.5761, -6.5400, -6.5127, -6.3269, -6.3096, -6.2719, -6.2524, -6.2413, -6.1898, -6.1328, -6.1309, -6.1307, -6.111, -6.0765, -6.0414, -6.0333, -6.0201, -5.9853, -5.8917, -5.8818, -5.7702, and -5.6591. Each of these compounds shows two distinct interactions with Pim kinase. In contrast, the remaining compounds, including 2-chloro, 4-hydroxy, 4-methyl, and simple phenylacetic acid, only demonstrate a single interaction with the protein.

3.3 Discussion of urease enzymes

Urease enzymes are metalloenzymes with a nickel-based active site that catalyzes the breakdown of urea into ammonia and carbon dioxide. In contrast, PAA is an aromatic carboxylic acid characterized by a phenyl ring and a carboxyl group. The carboxyl group in PAA can interact with urease residues in the active site through hydrogen bonds or electrostatic forces. PAA may inhibit urease activity by binding to the active site, thereby blocking the substrate from accessing or participating in the catalytic process.

This inhibition could be either reversible or irreversible, depending on the strength and nature of the interactions between PAA and the urease enzyme. Urease inhibition is significant due to its role in various biological processes and its potential for therapeutic applications. When PAA binds to urease, it may induce structural changes in the enzyme, which can affect its stability, substrate affinity, or allosteric regulation. Such conformational alterations could impact urease's activity and its related physiological functions, such as nitrogen metabolism, urea recycling, and pH regulation.

Computational tools, like molecular docking, are used to predict how PAA might bind to urease. These methods simulate interactions between PAA and urease to identify potential binding sites and evaluate the strength of these interactions. Docking analyses of the most favorable conformations have shown that the ligands consistently interact within the enzyme's active site through nitrogen, oxygen, halogen atoms, and pi systems. The ligands bind to the backbone of the enzyme using hydrogen bonds and pi-H interactions. Different synthesized

compounds, with varied electron-rich groups, exhibited similar binding patterns within the active site, although halogen-substituted derivatives displayed slightly altered binding potentials depending on the position and type of substituent.

In the docking analysis, the compound 3-Nitro PAA (docking score = -4.8088) showed three key interactions with urease: one hydrogen bond as a hydrogen acceptor and two pi-H interactions with active residues GLN387, VAL558, and LYS559, as illustrated in Figures 5 and 6(a). The nitro group attached to the benzene ring exhibits electron-withdrawing properties due to the presence of two oxygen atoms bonded to nitrogen, which pulls electrons away from the nitrogen. This electron deficiency causes the nitrogen to withdraw electrons from the benzene ring, leading to its deactivation. However, the resonance effect stabilizes the ring, reducing the deactivation, allowing interactions to occur on the ring.

The compound 4-Propyl PAA (docking score = -8.5250) displayed two hydrogen acceptor interactions with LYS48 urease residues, where the two oxygen atoms of the ligand participated in bonding with nitrogen from LYS48, as seen in Figure 6(b). Similarly, the compound 2-Nitro PAA (docking score = -6.2316) exhibited two interactions: one with oxygen and another with the benzene ring of the ligand, interacting with TYR544 and ALA284 urease residues, as shown in Figure 6(c). The mechanism of interaction here mirrors that of 3-Nitro PAA, where the nitro group leads to electron withdrawal from the ring, although resonance effects mitigate ring deactivation.

The 2-Iodo PAA compound (docking score = -4.0950) demonstrated hydrogen acceptor and pi-H interactions between the oxygen and benzene ring of the ligand and the active site residues GLY430 and VAL95, respectively, as seen in Figure 6(d). The iodo group, being an electron-withdrawing substituent, makes the benzene ring more susceptible to nucleophilic reactions. In this case, the inductive effect surpasses the resonance effect, making ring deactivation more pronounced. However, due to resonance stabilization, the molecule maintains some stability. The iodo group's ability to enhance the molecule's polarizability through its inductive effect contributes to strong interaction modes, as seen in Figures 6(e) and 6(f).

The other phenylacetic acid derivatives also demonstrated favorable interaction modes, including compounds such as 3-Iodo, 3-Methoxy, 2-Methoxy, 3-Methyl, 3-Ethyl, 2-Ethyl, 2-Bromo, 3-Propyl, 3-Chloro, 2-Propyl, and 4-Methoxy. Their respective docking scores are as follows: -6.8039, -6.7693, -6.6577, -6.5836, -6.5823, -6.0678, -6.0241, -5.9074, -5.9009, -5.8128, and -4.2684. Based on these docking scores and interaction modes, it can be concluded that phenylacetic acid and its derivatives are effective inhibitors of urease enzymes.

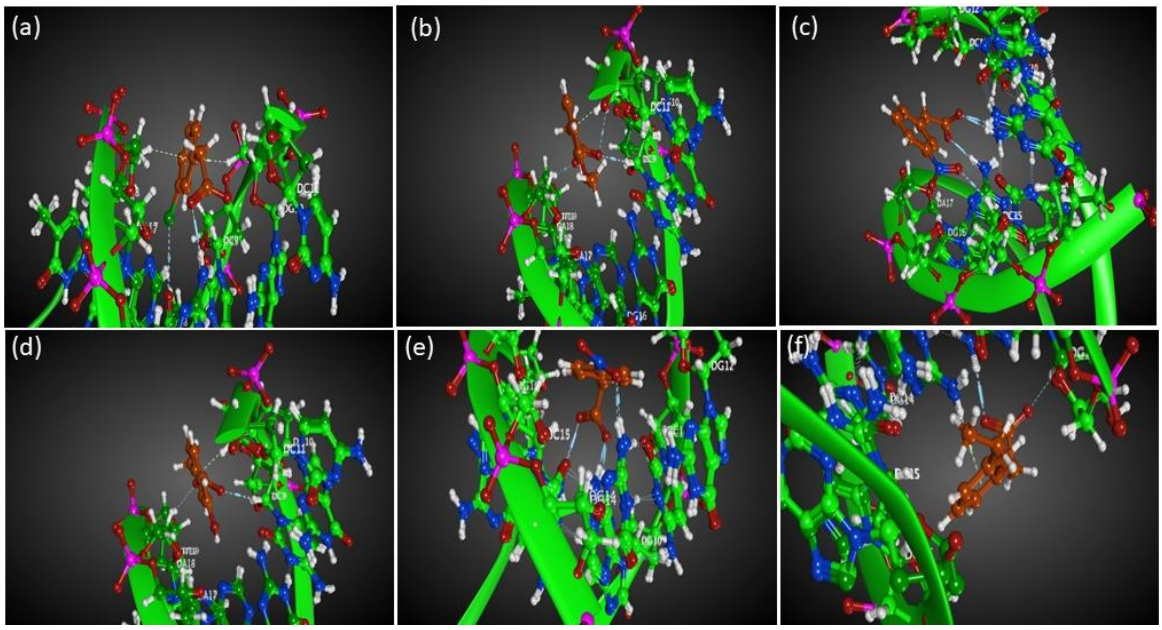

Figure 5. Three-dimension structures of Urease enzyme with (a) 3-Nitro-PAA, (b) 4-Propyl-PAA, (c) 2-Nitro-PAA, (d) 2-Iodo-PAA, (e) 3-Iodo-PAA and (f) 3-Methoxy-PAA.

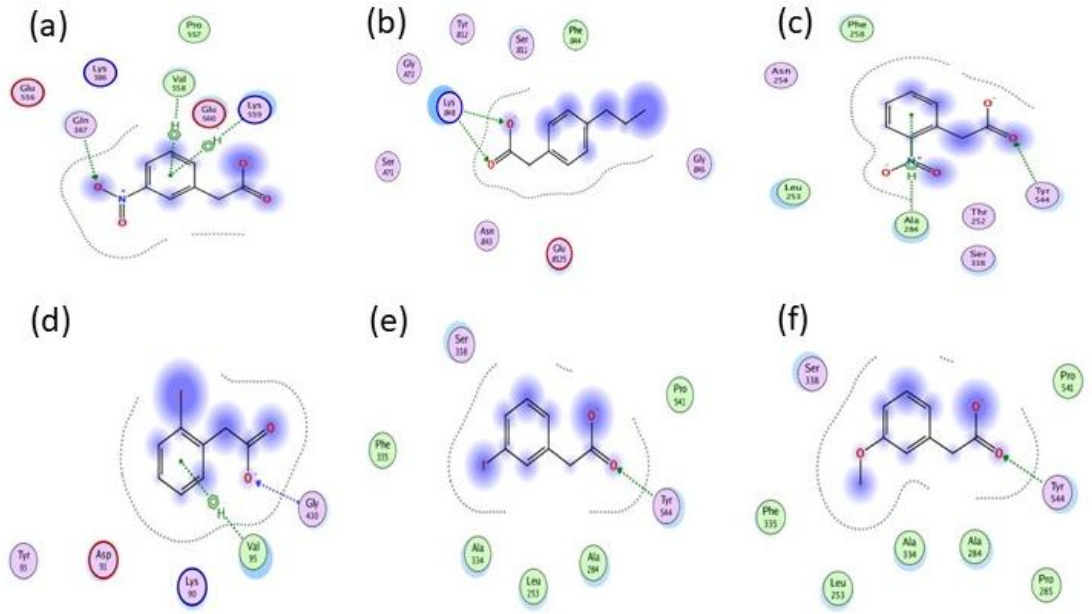

Figure 6. Two-dimension structures of Urease enzyme with (a) 3-Nitro-PAA, (b) 4-Propyl-PAA, (c) 2-Nitro-PAA, (d) 2-Iodo-PAA, (e) 3-Iodo-PAA and (f) 3-Methoxy-PAA.

4. Conclusion

In our present study we conclude that the molecular docking studies of PAA and its derivatives have demonstrated significant interactions with DNA, Pim kinase protein, and urease enzymes, indicating their potential as inhibitors. For DNA, PAA and its derivatives primarily bind through intercalation, with compounds like 3-chloro-PAA showing strong binding due to polar interactions and hydrophobic effects, potentially disrupting DNA replication and transcription. In the case of Pim kinase protein, PAA derivatives exhibit inhibitory interactions primarily through polar interactions, with compounds such as 2-propyl-PAA demonstrating notable inhibition by interacting with key active site residues. Similarly, for urease enzymes, PAA derivatives interact via hydrogen bonds and pi-H interactions, with compounds like 3-nitro-PAA showing effective binding. These findings highlight the versatility and efficacy of PAA derivatives in targeting multiple biological macromolecules, paving the way for further exploration of their therapeutic potential in treating diseases related to DNA, kinase proteins, and urease enzyme dysfunction.

Authors Contribution

Z.A. is solely responsible for the research, lab work, supervision, and manuscript preparation.

Conflicts of Interest

The author declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper..

Data Availability statement

The data presented in this study are available on request from the corresponding author.

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