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In Silico Molecular Docking of N-Bromonicotinamide and N-Bromoisonicotinamide with Proteins 1HD2 and 2CDU

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Abstract: The fundamental step for drug discovery is the understanding of the protein-ligand interaction in innumerous pharmaceutical enterprises. The integration of computational and experimental process can reduce the time and cost for the advancement of novel medications. Molecular docking is one of the modern drug designing strategies, which explore the competence of a ligand by computing the minimum binding energy. Docking is utilized in virtual screening of enormous databases of compounds for hit identification and assessing the impact of chemical modifications during lead optimization. In the present study, *In silico* N-bromonicotinamide and N-bromoisonicotinamide molecular docking with 1HD2 and 2CDU proteins have been carried out. *In silico* molecular docking is one of the most powerful techniques to discover novel ligand for proteins of known structure and thus play a key role in structure-based drugs. Hence, *in silico* molecular docking has been carried out to analyze the binding properties of Peroxiredoxin 5 and water-forming NAD(P)H oxidase from *Lactobacillus sanfranciscensis* with N-bromonicotinamide and N-bromoisonicotinamide. The docking studies confirmed the antioxidant activity of N-bromonicotinamide and N-bromoisonicotinamide and thereby activation of target protein Peroxiredoxin 5 (1HD2) and water-forming NAD(P)H oxidase from *Lactobacillus sanfranciscensis* (2CDU) through the binding interactions.

Keywords: Protein-ligand, N-bromonicotinamide, N-bromoisonicotinamide, Molecular docking, Drug designing, *Lactobacillus sanfranciscensis*

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Introduction

Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall

system is minimized (Rohs *et al*., 2005; Guedes *et al*., 2014).

Molecular docking is a method to identify the architecture of compounds generated by two or more distinct molecules computationally. The objective of docking studies is to anticipate the desired three-dimensional structures. Docking, in and of itself, generates only suitable incentive structures (Shoichet *et al*., 2002; Seeliger and de Groot, 2010; Agarwal *et al*., 2015). These possibilities are sorted using scoring functions to determine, which structures are most likely to be present in nature. Docking study outlines the state of the art in several computational elements of molecular docking-based virtual screening of a library of small compounds (Gschwend *et al*., 1996; Lamb and Jorgensen, 1997). It is the process of arranging molecules in the most advantageous way for interaction with a receptor (Holt *et al*., 2008; Mehrotra *et al*., 2013; Agarwal *et al*., 2014; Ferreira *et al*., 2015). It is a phenomenon observed within moments in a cell when molecules are bonded together to form a sustainable complex (Elokely and Doerksen, 2013).

In the present study, N-bromonicotinamide and N-bromoisonicotinamide have been docked against Peroxiredoxin 5 (1HD2) and water-forming NAD(P)H oxidase from *Lactobacillus sanfranciscensis* (2CDU).

Materials and Methods

Employing AutodockVina 1.1.2, molecular docking experiments were performed to examine the interaction and mechanism of binding among the compounds N-bromonicotinamide and N-bromoisonicotinamide with the proteins1HD2, 1CDU. For the purpose of antioxidant screening, the Protein Data Bank's Human Peroxiredoxin 5's (PDB ID: 1HD2) crystal structure and the crystal structure of water-forming NAD(P)H oxidase from *Lactobacillus sanfranciscensis* have been retrieved. ChemDraw Ultra 12.0 and Chem3D Pro 12.0 software were used to create the 3D structures of the substances, N-bromonicotinamide and N-bromoisonicotinamide. Utilizing the AutoDock Tools 1.5.6 software package, the input files for AutodockVina were produced. The size x, y, z was 16, 16, 16 of the 1HD2 protein search grid were identified as center x: 7.657, center y: 42.687, and center z: 27.705 with spacing of 1.0. The size x, y, z was 20, 20, 24 of the 1CDU protein search grid were identified as center x: 0.755, center y: 7.447, and center z: 51.264 with spacing of 1.0. The value for exhaustiveness has been set to 8. For Vina docking, the other parameters were left at their default values and unmentioned. The best-scoring molecule was the one with the lowest binding affinity value, and the data has been visually assessed with the use of the Discovery studio 2019 application.

Results and Discussion

The AutodockVina software was used to examine the docking behaviour of the substances, N-bromonicotinamide and N-bromoisonicotinamide with proteins1HD2 and 2CDU. The compounds, N-bromoisonicotinamide, exhibited equipotent binding affinity (-3.8 kcal/mol) to the 1HD2 protein than the N-bromonicotinamide, which has a binding affinity of (-3.7 kcal/mol). Protein-ligand bonding was stable because of hydrogen bonding, and the ideal bond distance between the H-donor and H-acceptor atoms was less than 3.5. The inhibitor drugs have hydrogen bond distances in their respective proteins that were less than 3.5, which indicated strong hydrogen bonding. In hydrogen bonding interactions, the amino acid residue Thr44 (bond lengths: 2.05) and Cys47 (bond lengths: 3.56) were implicated. N-bromoisonicotinamide compound and receptor 1HD2 created two hydrogen bonds. In hydrogen bonding interactions, the amino acid residue Thr44 (bond lengths: 2.01), cys47 (bond lengths: 2.99) were implicated. Hydrophobic interactions involved the amino acid residues Gly46, Thr147 and Leu149. With the receptor 1HD2, N-bromonicotinamide, created three hydrogen bonds. In hydrogen bonding interactions, the amino acid residue Thr44 (bond lengths: 1.99, 3.40) and Cys47 (bond lengths: 3.03) were

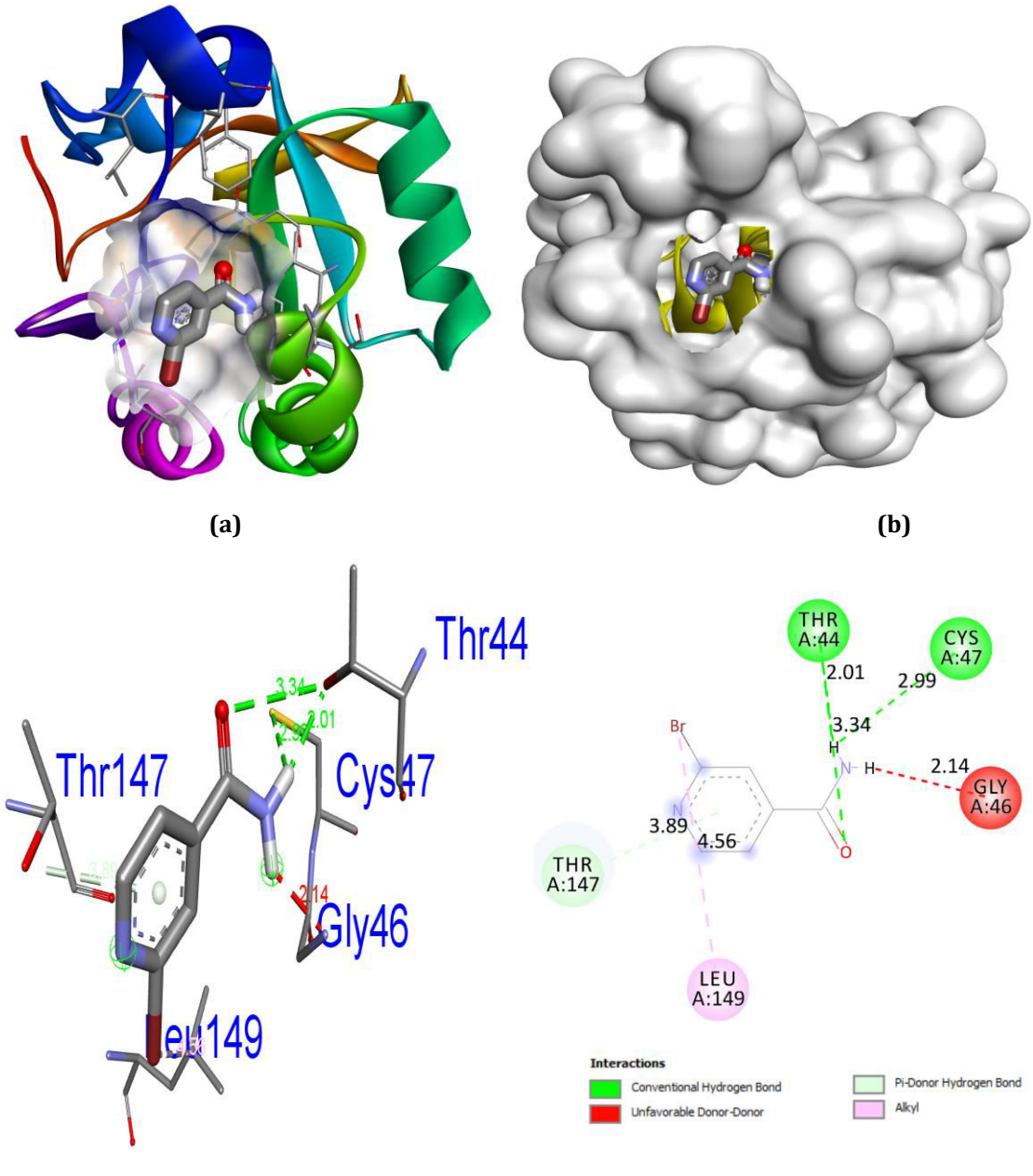

Fig. 1: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of compound N-bromoisonicotinamide within the binding site of 1HD2 protein.

implicated. Hydrophobic interactions involved the amino acid residues Gly46, Thr147 and Leu149.

Figures 1 and 2 demonstrate, respectively, the hydrogen bonding and hydrophobic interactions of amino acid residues in 1HD2 protein with substances N-bromoisonicotinamide and N-bromonicotinamide. The N-bromonicotinamide, which has a binding affinity of (-4.8 kcal/mol). N-bromoisonicotinamide compound and receptor 1HD2 does not create any hydrogen bond. Hydrophobic interactions involved the amino acid residues Asp179, Lys213, Val214 and Ile243. With the receptor 2CDU, N-bromonicotinamide, created two hydrogen bonds. In hydrogen bonding interactions, the amino acid residue Ile178 (bond length: 2.21) and Asp179 (bond length: 3.06) were implicated. Hydrophobic interactions involved the amino acid residues Pro120, Lys213 and Ile243.

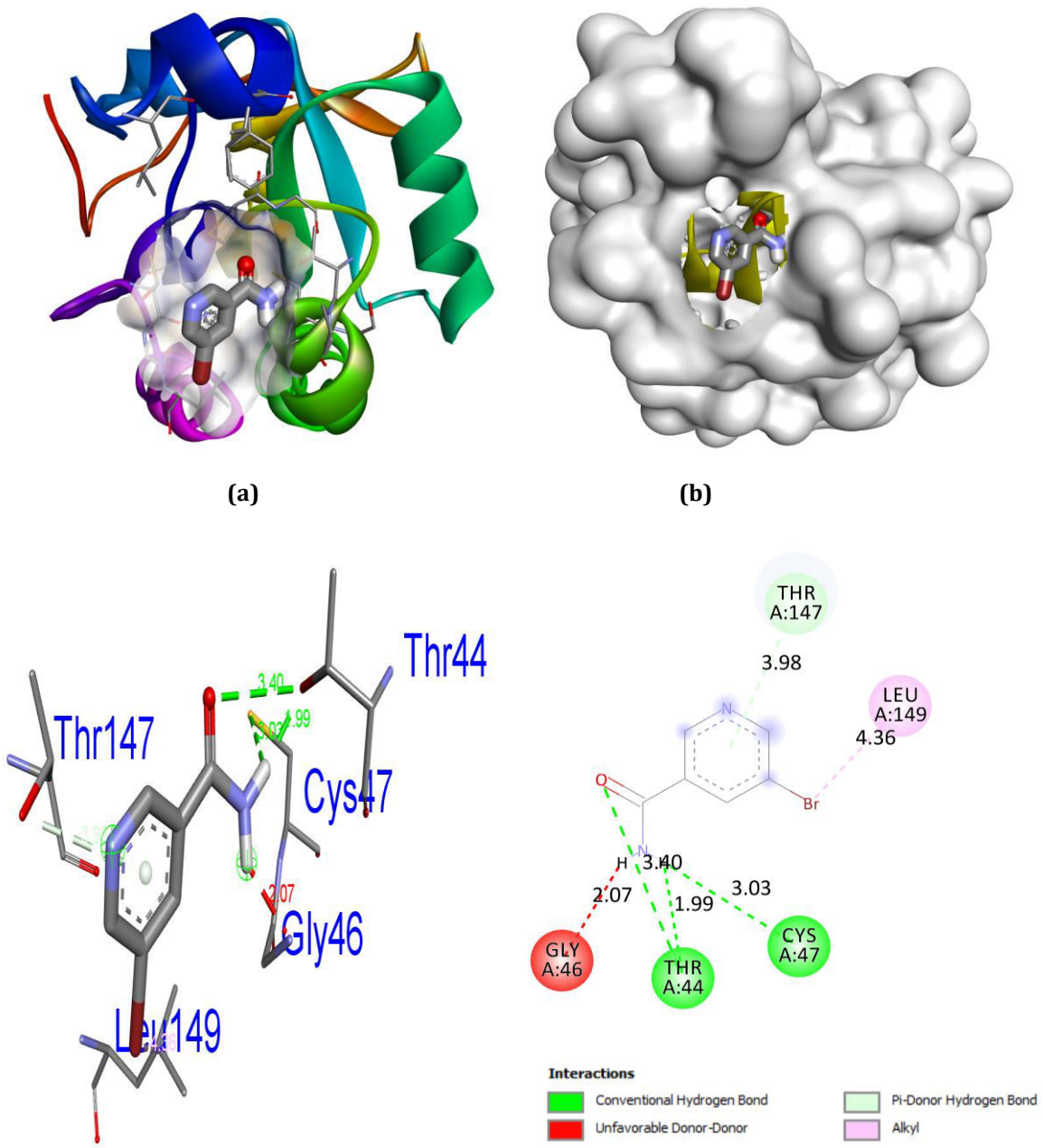

Fig. 2: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of compound N-bromonicotinamide within the binding site of 1HD2 protein.

Figures 3 and 4 demonstrates the hydrogen bonding and hydrophobic interactions of amino acid residues in 2CDU protein with substances N-bromonicotinamide and N-bromoisonicotinamide.

The findings demonstrate that the inhibitor drugs have a remarkable capacity to inhibit 2CDU protein than 1HD2 protein. Tables 1 and 2 provides summary of the findings.

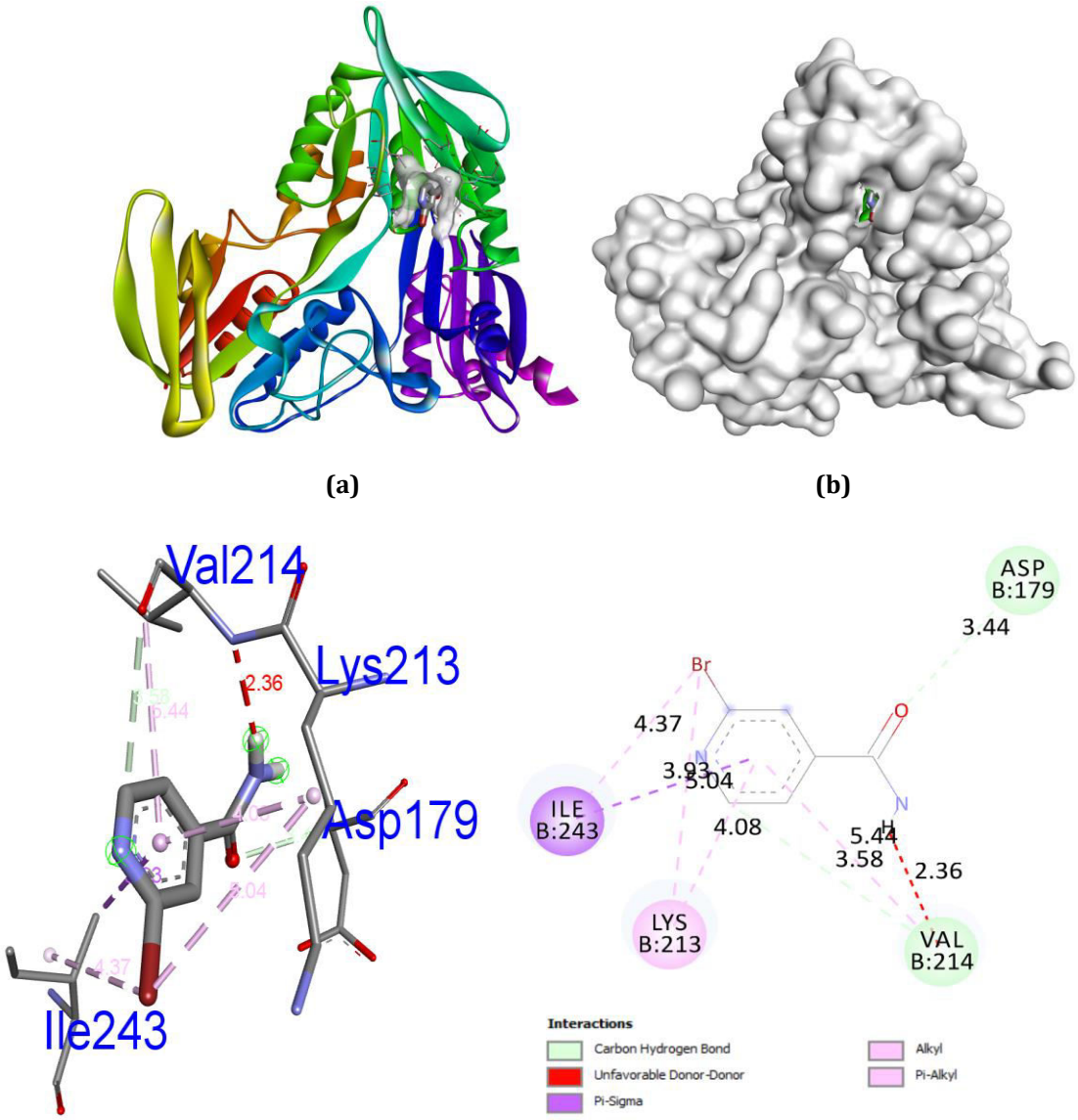

Fig. 3: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of compound N-bromoisonicotinamide within the binding site of 2CDU protein.

Table 1: Molecular docking interaction of compounds N-bromoisonicotinamide and N-bromonicotinamide against protein 1HD2

Proteins	**Compound Name**	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
1HD2	N-bromoisonicotinamide	-3.8	2	Thr44, Cys47
	N-bromonicotinamide	-3.7	3	Thr44, Cys47

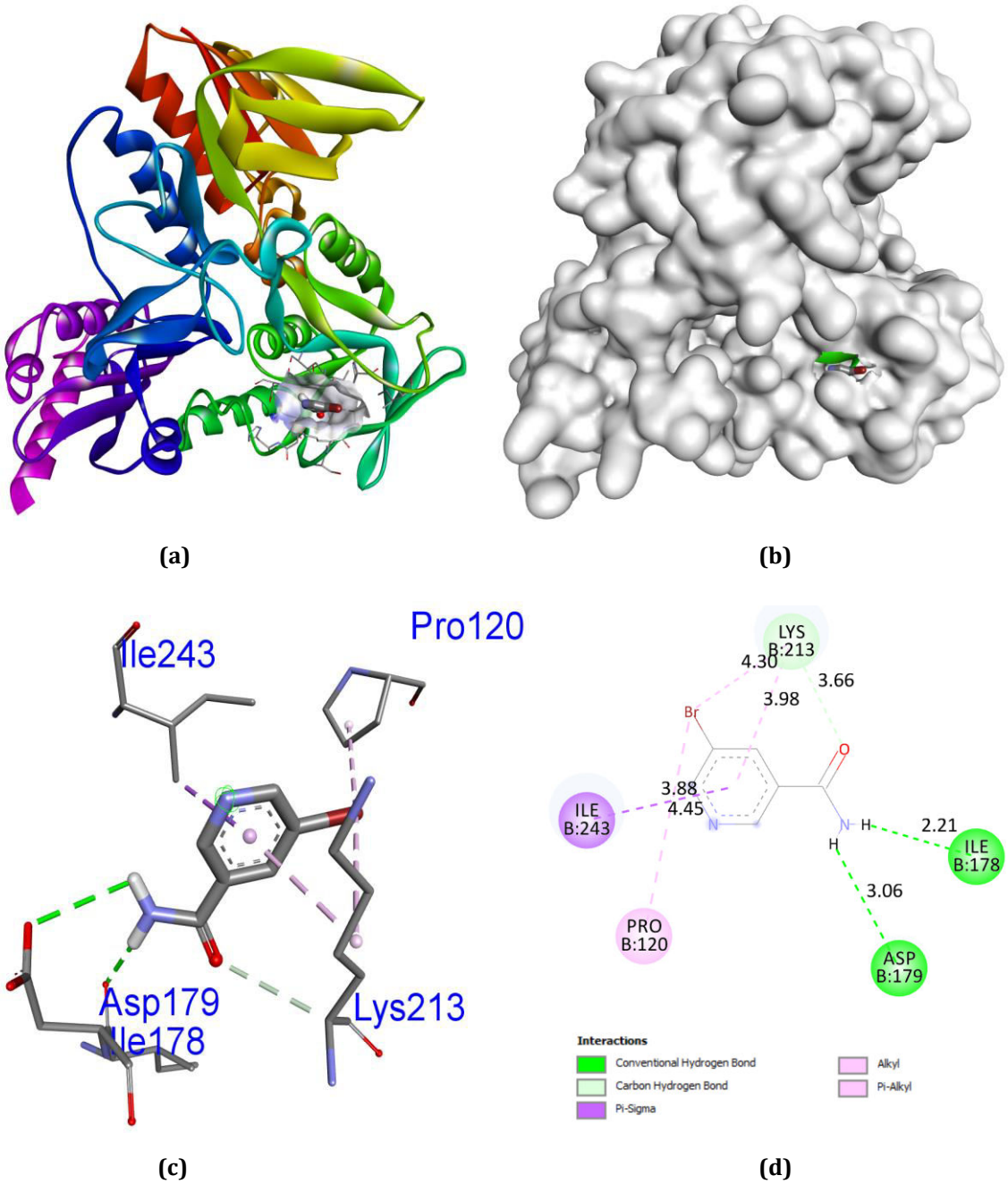

Fig. 4: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of control N-bromonicotinamide within the binding site of 2CDU protein.

Table 2: Molecular docking interaction of compounds N-bromoisonicotinamide and N-bromonicotinamide against protein 2CDU

Proteins	**Compound Name**	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
2CDU	N-bromoisonicotinamide	-5.1	-	-
	N-bromonicotinamide	-4.8	2	Ile178, Asp179

Conclusion

In silico molecular docking is a computational method that plays a critical role in drug discovery and development. By using computer programs to predict the binding affinity and orientation of small molecule ligands to protein targets, *in silico* molecular docking can rapidly screen large databases of compounds to identify potential drug candidates, saving time and resources compared to traditional experimental methods. It can also be used to study protein-protein interactions and the effects of mutations on protein-ligand interactions. However, it is important to note that *in silico* molecular docking is a theoretical approach and its predictions should always be validated by experimental data. Additionally, the accuracy of the results depends on the quality of the protein and ligand structures, as well as the algorithm and scoring function used. *In silico* molecular docking is just one tool in the arsenal of computational and experimental methods used in drug discovery, and it should be combined with other methods to maximize the chances of success in developing new therapies.

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