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Research article

Molecular docking studies of novel dihydro Pyrimidine derivatives as potential antibacterial agents

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ABSTRACT

A new compound of dihydropyrimidine derivatives was designed and predicted to have antibacterial effect. Synthesis of dihydropyrimidine derivatives could be carried out by reaction between Chalcone and thiourea to form dihydropyrimidine. It is incorporated with benzimidazole heterocycle. This study evaluated the mechanism of dihydropyrimidine derivatives in inhibition of DNAG with molecular docking. Docking was performed on the receptor file DNAG (PDB ID: 4DUH) using Auto Dock 1.5.6 program and visualized by Discovery Studio. The docking score of ligand standard, ciprofloxacin and dihydropyrimidine derivatives APUS17, APUS 20, APUS 9, APUS14 towards 4DUH were -8.0, -8.12, -12.1,-11.82, -10.96,-10.1 Kcal/mol respectively. From that derivatives having electron withdrawing group show highest binding affinity and having electron donating group show moderate binding affinity.

Keywords: Molecular Docking, Auto Dock, DNA gyrase, Dihydropyrimidine

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INTRODUCTION

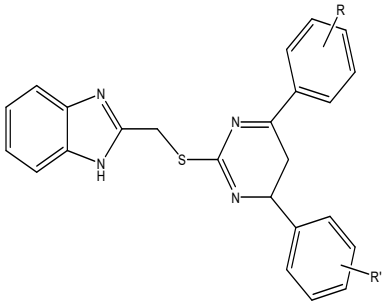
Molecular docking is a theoretical approach aiming to accurately predict the binding of macromolecules and a small ligand. In this aspect, we employed docking analysis to predict the docking models of the tested compounds in the binding pocket of bacterial proteins DNA gyrase subunit B that are known targets for some antibiotics.

The molecular-docking study was used to determine the binding modes of tested compounds against (DNAG) which are important targets for the development of antibacterial agents to gain perspective into the mechanism of action of the tested compounds. Based on their key roles in the formation of bacterial cells, these targets have been selected, so targeting this 4DUH proteins provides perceived benefits in killing bacteria. Using Auto Dock 1.5.6 to reflect the position and orientation of the ligand found in the crystal structure.

MATERIALS AND METHODS

Auto Dock 1.5.6 was used to perform all docking simulations. A set of new dihydro pyrimidine derivatives as antibacterial agents were subjected to docking with DNA gyrase subunit b (PDB ID : 4DUH). From the Protein Data Bank (RCSB) (rcsb.org/pdb). To carry out in silico studies, the 2D structures of the synthesized ligands APUS1 –APUS21 were drawn and converted to energy minimized 3D structures in the pdb file format. By removing the water molecule and cofactors, the target protein file was prepared by leaving the associated residue with protein by using Auto Dock 1.5.6). Preparation of target protein file Auto Dock 1.5.6 tool has been done, Docking simulations for the compounds APUS 1 – APUS 21 were performed against the 4DUH protein, and finally Discovery Studio Visualizer was used to visualize docking results [1-8].

Figure 1: Molecular Structure



2-((4-substituted phenyl-6- substituted phenyl-4,5-dihydropyrimidin-2-ylthio)methyl)-1H-benzoimidazole

Table 1: Sample Code

Sample code	R	R'
APUS1	H	H
APUS2	H	4-Cl
APUS3	H	2-Cl
APUS4	H	4-NO2
APUS5	H	2-NO2
APUS6	H	3-NO2
APUS7	H	4-OH
APUS8	H	2-OH
APUS9	H	4-CH3
APUS10	4-Cl	H
APUS11	4-OCH3	H
APUS12	3-NO2	H
APUS13	4-NH2	H
APUS14	3-NH2	H
APUS15	4-F	H
APUS16	3-Br	H
APUS17	4-Br	H
APUS18	4-OCH3	4-Cl
APUS19	4-Br	3-NO2
APUS20	3-NO2	4-OH
APUS21	4-F	4-CH3

RESULTS AND DISCUSSION

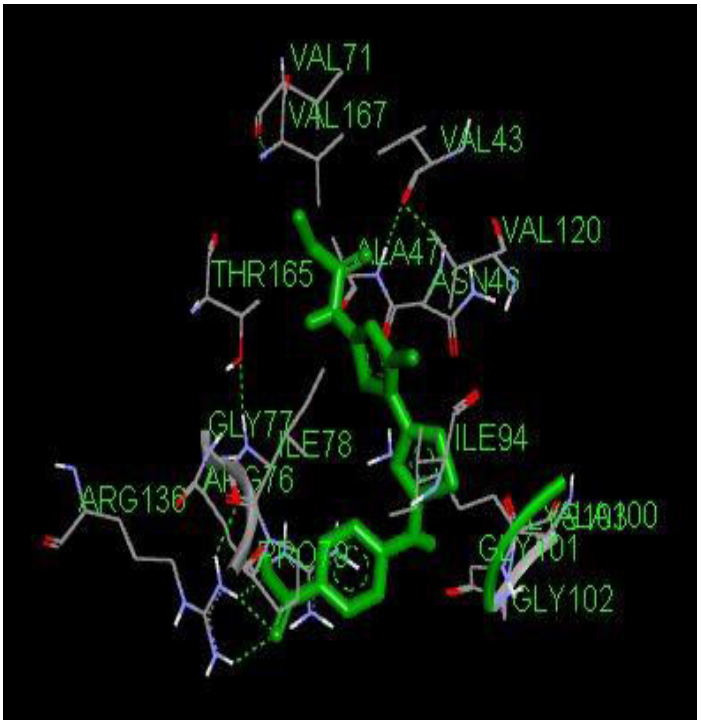
In –silico Analysis

In –silico docking standard, dihydropyrimidine derivatives, ciprofloxacin into the 4DUH binding pocket result in the docking score were showed in table-1. Figure-1 is showing the results of visualization of standard and tested compound APUS17 and table-2 was showed interaction between standard, tested compounds, ciprofloxacin towards amino acid residues of DNA gyrase. The docking score represents the binding affinity of ligand to the target protein. The docking of 4DUH target with compounds using docking procedure revealed that all the computationally predicted lowest energy complexes are stabilized by intermolecular hydrogen bonds and stacking interactions. Docking score of Dihydropyrimidine derivatives was lower than ciprofloxacin as antibacterial drugs. The results were obtained at in silico screening have shown that it represents the best step to get an accurate result in a short time and saving manner.

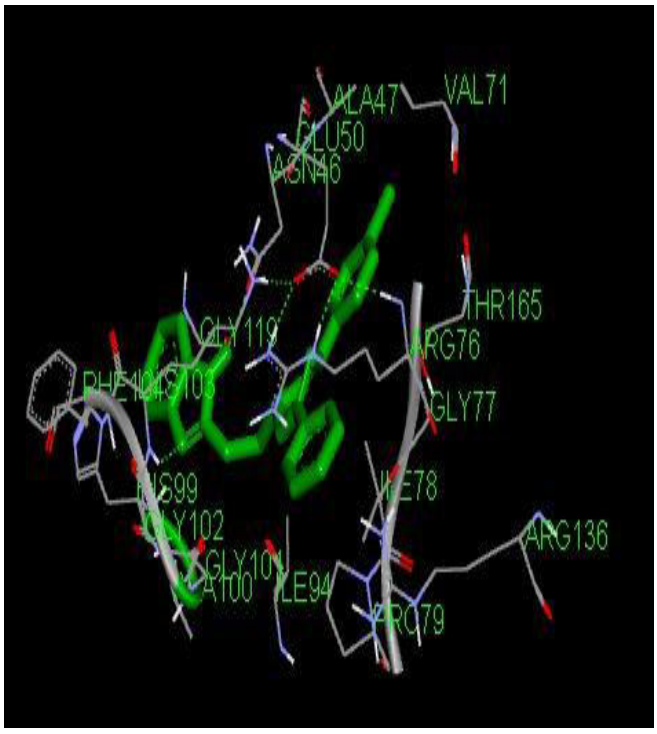
Table 2: The results of molecular docking of synthesized compounds against DNAG with protein 4DUH

PDB Code	Compounds	Binding Energy (kcal/mol)
4DUH	APUS1	-9.69
4DUH	APUS2	-10.91
4DUH	APUS3	-10.78
4DUH	APUS4	-11.78
4DUH	APUS5	-10.66
4DUH	APUS6	-10.88
4DUH	APUS7	-10.44
4DUH	APUS8	-10.04
4DUH	APUS9	-10.96
4DUH	APUS10	-10.58
4DUH	APUS11	-8.17
4DUH	APUS12	-11.65
4DUH	APUS13	-10.32
4DUH	APUS14	-10.1
4DUH	APUS15	-10.25
4DUH	APUS16	-10.54
4DUH	APUS17	-12.1
4DUH	APUS18	-10.74
4DUH	APUS19	-11.7
4DUH	APUS20	-11.82
4DUH	APUS21	-10.91
4DUH	Standard	-8.12
4DUH	Ciprofloxacin	-8.0

Figure2: 3D interaction of standard and tested compound APUS17 with 4 DUH Protein

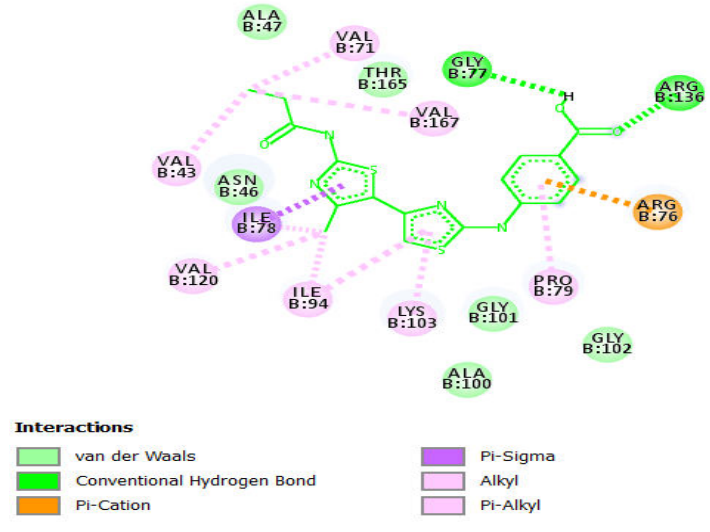
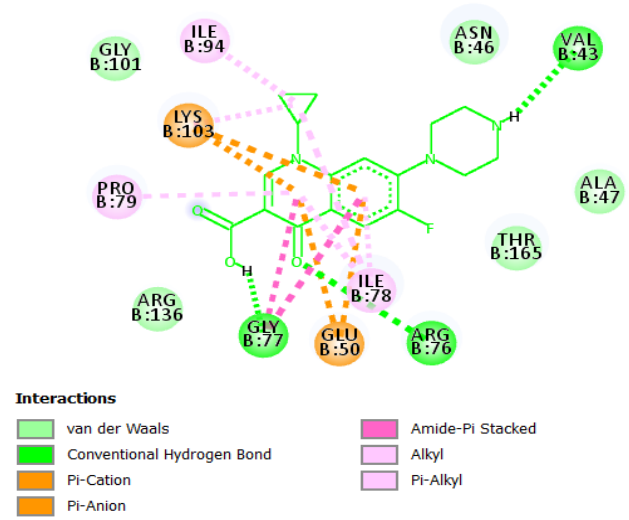
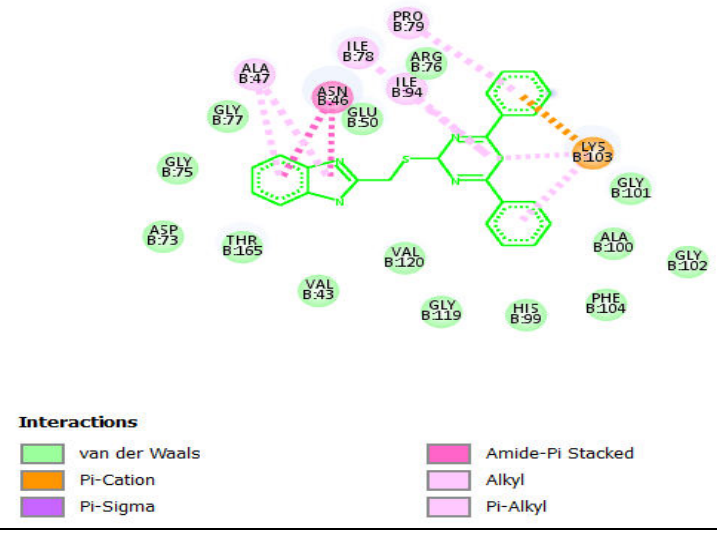


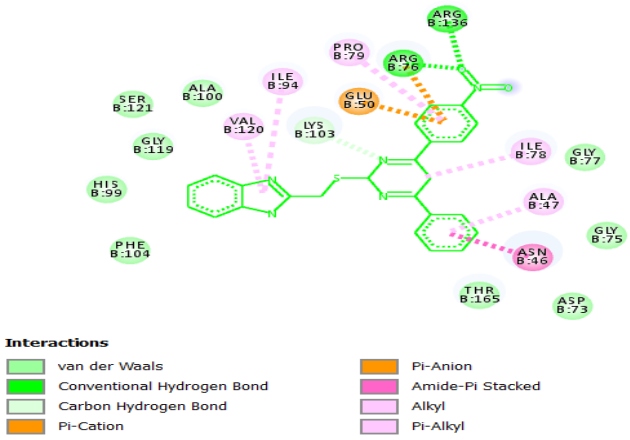
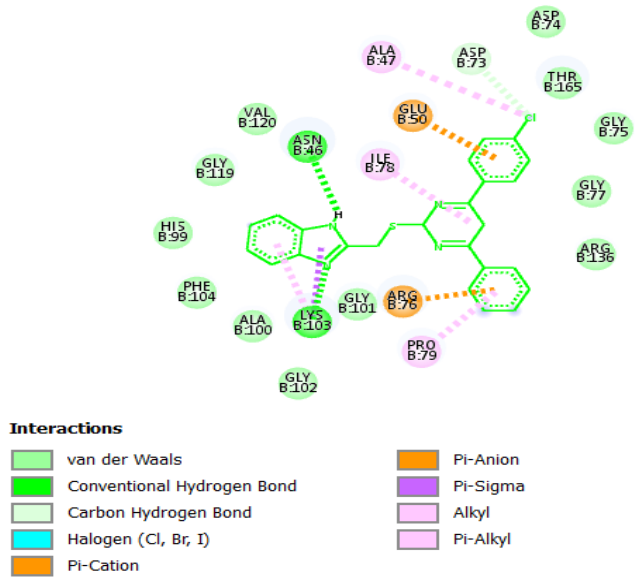
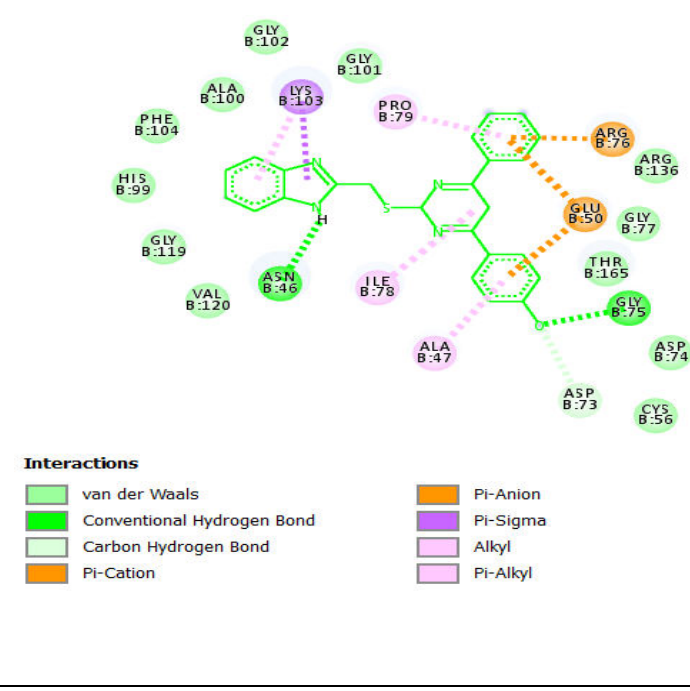
Standard

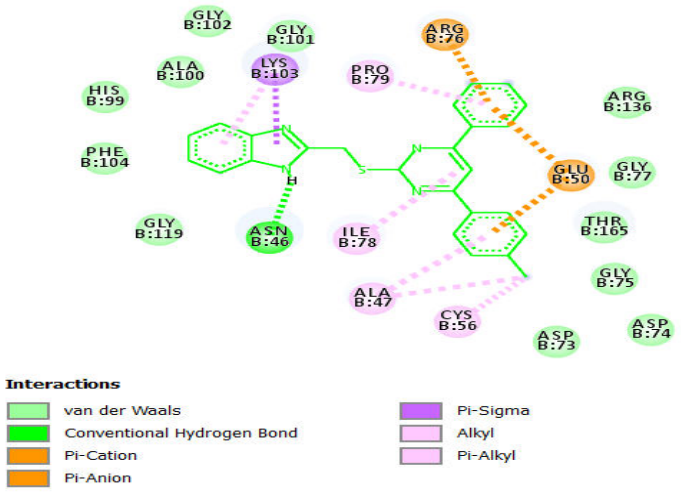
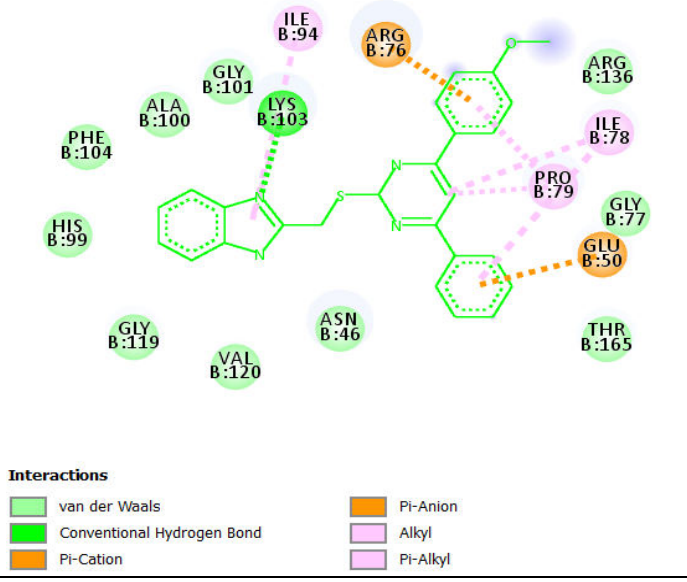
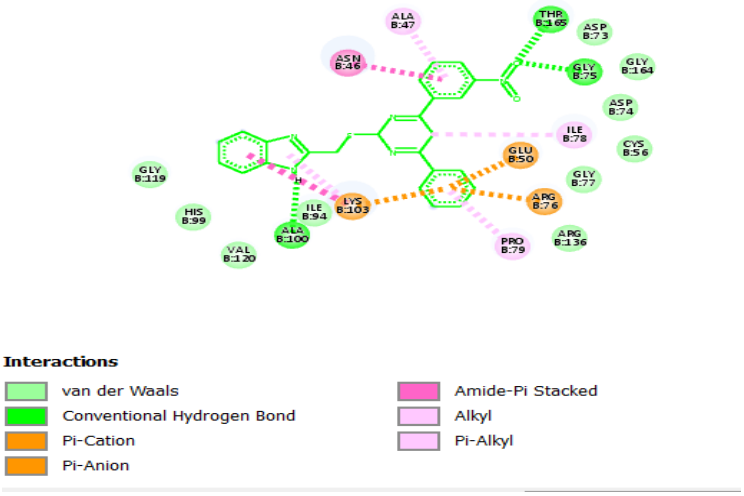


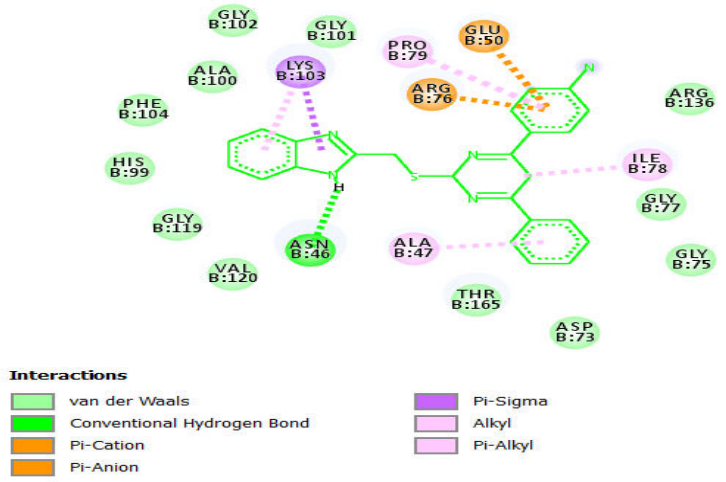
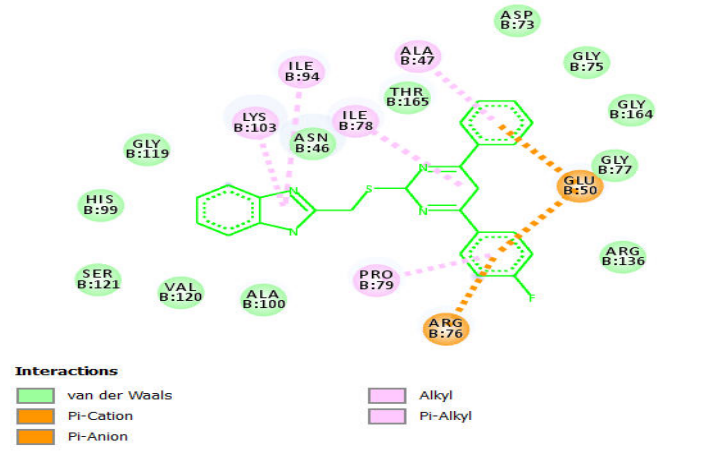
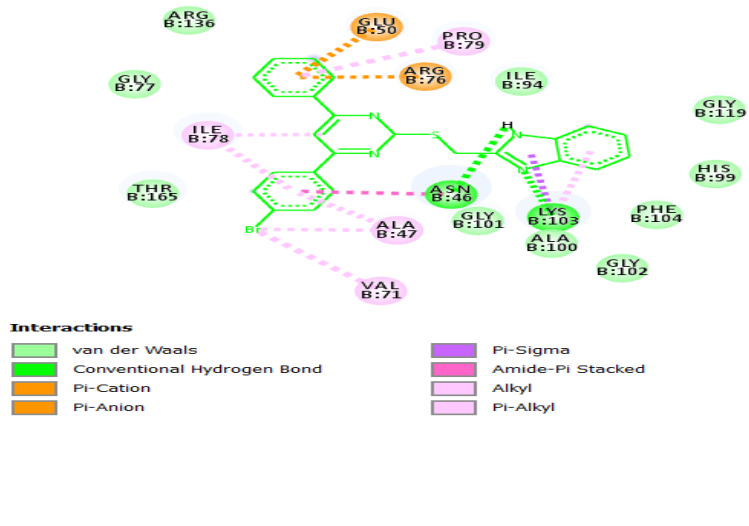
APUS17

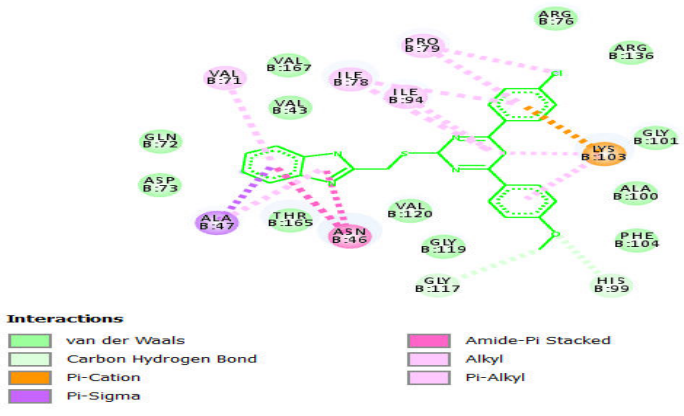
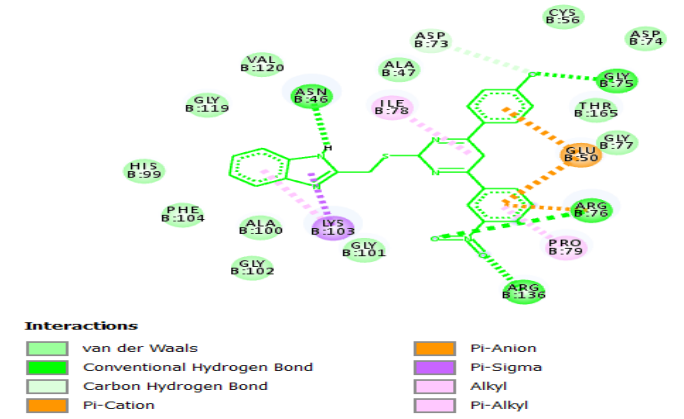
Table 3: 2D interactions of best conformer with DNA gyrase subunit B (DNAG) Receptor with 4 DUH Protein.

Compound	2D interaction on the active site of PDB
STANDARD	
CIPROFLOXACIN	
APUS1	

APUS4	
APUS2	
APUS7	

APUS9	
APUS11	
APUS12	

APUS13	
APUS15	
APUS17	

APUS18	
APUS20	

CONCLUSIONS

Based on the research, it can be concluded that electron withdrawing groups like NO_2, Cl, Br, F having higher activity and electron donating groups like CH_3, OCH_3, OH having moderate activity on binding to 4DUH than standard and ciprofloxacin. These compounds are the potential to develop as an antibacterial agent [9-11].

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