https://doi.org/10.48047/AFJBS.6.Si3.2024.3324-3334

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Molecular Docking studies of Some Schiff Base Compounds

Hanan A.Abdalla. Khalid[1], ,Hana Faraj Saeid[1]. Somaia.M.Abdalla Elsheikhi[1]Taffaha A. Arhouma[2], Zainab S. Habiel[3] ,Ashraf A. Abulsalam[4]HamadM A. Hasan[5]

[1]Department of Chemistry, Faculty of pharmacy, Omar Al-Mukhtar University, Al-Beyda, Libya

[2]Department of Chemistry, Faculty of Arts and Sciences, Derna University, Al-Qubah, Libya

[3]Department of Chemistry, Faculty of Science, University of Derna, Libya.

[4]Department of Pharmaceutical Sciences, Faculty of health sciences, Sirte University, Sirte, Libya

[5]Department of Chemistry, Faculty of Science, Omar Al-Mukhtar University, Al-Beyda, Libya

Hamad.dr@omu.edu.ly , hanan.abdalkrim@omu.edu.ly , somia.elsheikhi@omu.edu.ly

Article Info
Volume6, Issue Si3, 2024
Received: 30 May2024
Accepted: 29 June 2024
doi:
10.48047/AFJBS.6.Si3.2024.3324-3334

Abstract

Molecular docking simulation is a powerful computational technique used in drug discovery and molecular biology. It involves the prediction of interactions between small chemical compounds, such as potential drugs, and their target macromolecules, such as proteins or nucleic acids. By employing various algorithms and scoring functions, molecular docking simulations can identify potential binding sites, determine binding affinities, and suggest optimal ligand orientations within the binding site.In recent years, the integration of molecular docking simulation with Schiff base studies has provided valuable insights into the design and optimization of novel therapeutic agents. Such simulations help in understanding the binding mode, binding affinity, and interactions between Schiff base derivatives and biological targets. Additionally, the computational predictions obtained from molecular docking simulations serve as a useful tool for guiding the synthesis and evaluation of Schiff base compounds produced from the reactions between (4-dimethyl amino benzaldehyde) ten different amino acids: (Tryptophan, Phenylalanine, Asparagine, Glycine, Tyrosine, Arginine, Glutamine, Methionine, Valine and Threonine) using AutoDock Vina.In conclusion, four compounds showed lower free energy of binding (FEB) and interactions with the essential amino acids in the binding pocket. Molecular docking results recorded that four of the examined compounds could be a potent inhibitor of

Staphylococcus aureus and help discover a new potent antibacterial inhibitor.This multidisciplinary approach enables efficient screening and optimization of compounds, paving the way for the development of effective treatments for various diseases.
Keywords: Schiff base, Amino acids,Molecular docking, Biological activities, Autodock Vina.

Introduction:

Schiff bases, on the other hand, are versatile organic compounds characterized by the presence of an imine functional group (-C=N-). They have garnered significant attention in medicinal chemistry due to their diverse pharmacological activities, including antimicrobial, anticancer, and antioxidant properties. Schiff bases offer a wide range of structural modifications, making them promising candidates for drug design and development.Schiff's bases are a type of chemical substance that is widely used. (Arulmurugan *et al*., 2010) . The azomethine group, with the generic formula RHC = N-R1, is the major structural hallmark of these compounds, with R and R1 being alkyl, aryl, cyclo alkyl, or heterocyclic groups.A Schiff's base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C = O) is substituted with an amine or azomethine group. Schiff's bases have also been demonstrated to have antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, and antipyretic properties, among others (Hasan et al., 2021). The presence of an amine group in these compounds has been proven necessary for their biological actions (Salimon *et al*., 2010). Because of their vast range of industrial applications, Schiff's bases are important chemicals (Li *et al*., 2003).This work aims to useMolecular docking simulation for some Schiff base synthesized compounds usingAutoDock Vina.

Materials:

All chemicals used in this study were laboratory grade, including: (4-dimethyl amino benzaldehyde)and different types of amino acids, including (Tryptophan, Phenylalanine, Asparagine, Glycine, Tyrosine, Arginine, Glutamine, Methionine, Valine and Threonine) in addition to some solvents and solutions:KOH,C_2H_5OH and CH_3COOH.

Synthesis of Schiff bases:

The amino acid Schiff bases were prepared as follows: KOH (20 mmol) was dissolved in methanol (50 cm^3), and (10 mmol) of each of the selected amino acids was added. The mixture was stirred magnetically at room temperature; when the mixture became homogeneous, a solution of 4-dimethyl amino benzaldehyde (10 mmol) in ethanol (50 cm^3) was added. After two minutes, the solution was evaporated to 20% of its original volume, and (1 ml) of CH_3COOH was added immediately. After two hours, yellow crystals appeared.The crystals were filtered and washed with ethanol,(Hasan et al., 2021).They were recrystallized from hot methanol to give yellow crystals. Synthesized compounds are taken numbers of (1-10) according to the reaction between the 4-dimethyl amino benzaldehyde and the selected amino acids of (Tryptophan, Phenylalanine, Asparagine, Glycine, Tyrosine, Arginine, Glutamine, Methionine, Valine and Threonine), respectively.

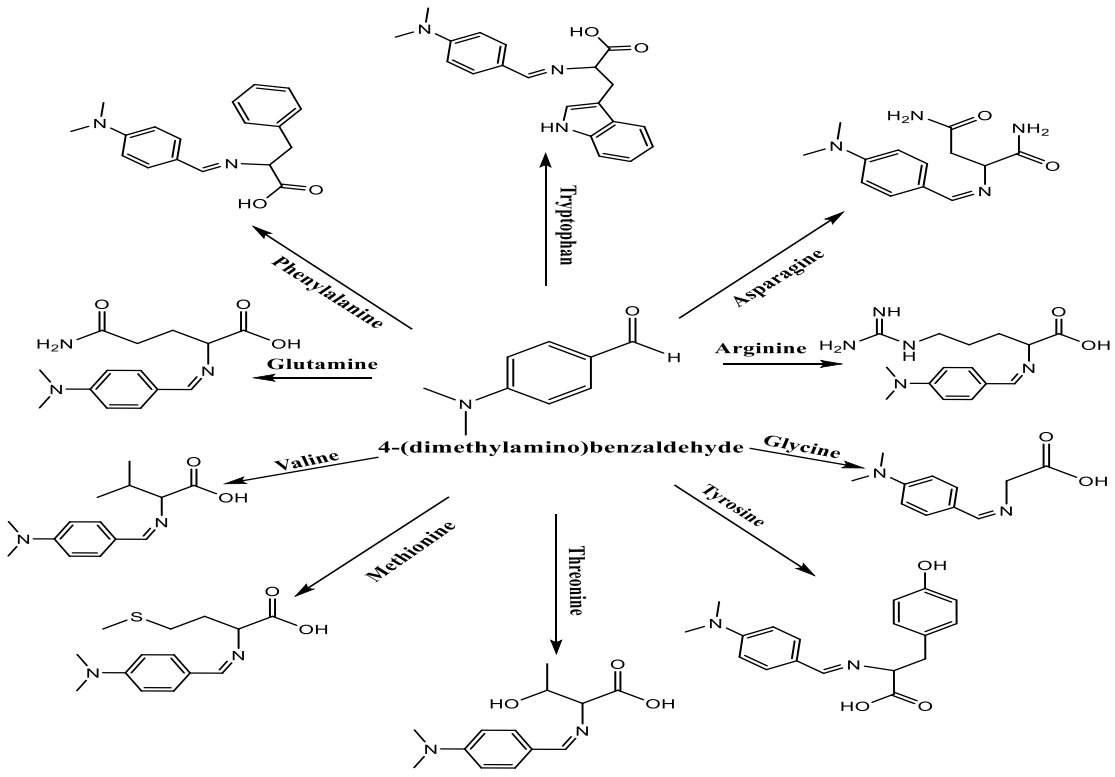
Molecular docking

Molecular docking was performed for the ten synthesis compounds using Autodock Vina (Trott and Olson, 2010). The compounds were built using Marvensketch and followed by energy minimization using Hyperchem 8(Coleman and Arumainayagam, 1998), then saved to pdb format. The crystal structure of *Staphylococcus aureus* (PDB: 1JIJ) was obtained from Protein Data Bank with (PDB ID: 1JIJ) (Qiu et al., 2001). Proteins were edited using AutoDockTools (ADT) by removing unwanted water molecules and Herero atoms, adding

all hydrogen atoms, computing Gasteiger and adding Kollman charge. A grid box of 60 × 60 × 60 points, with a spacing of 0.375A˚ and located at the centre of the active site. Discovery Studio Visualizer 2016 (Systèmes, 2016) was used to visualize the docking results and Ligplot (Laskowski and Swindells, 2011).

Results and Discussion

The proposal of reactions between amino acids and were given in Scheme 1 as following :



Scheme 1.The proposal reactions between benzaldehyde **and studied amino acids**

I.R Characterization of synthesized compounds:
I.R data were given in the Tables (1&2).

Table(1): IR spectra of4-(Di methylamino) benzaldehyde with (Trptophan , Phenylalanine, Asparagine, Glycine, Tyrosine) Schiff base compounds:

Compounds / Groups	Schiff base (1)	Schiff base (2)	Schiff base (3)	Schiff base (4)	Schiff base (5)
OH	3400	3410	3880	3970	3320
C=O	1710	1640	1620	1725	1610
C=N	1590	1580	1540	1575	1580
C = C	1440	1450	1410	1400	1430
CH_3	1360	1380	1365	1380	1350
CH_2	1410	1400	1405	1370	1420
CH(Aromatic)	3150	3100	3050	3210	3115
CH(Aliphatic)	2890	2820	2720	2830	2825
C-C	850	875	900	890	820

Table(2): IR spectra of4-(Di methylamino) benzaldehyde with (Arginine, Glutamine, Methionine, Valine and Threonine) Schiff base compounds:

Compounds / Groups	Schiff base (6)	Schiff base (7)	Schiff base (8)	Schiff base (9)	Schiff base (10)
OH	3290	3390	3300	3280	3310
C=O	1620	1640	1615	1710	1630
C=N	1530	1580	1570	1540	1560
C = C	1420	1390	1380	1390	1410
CH_3	1315	1310	1295	1380	1360
CH_2	1400	1425	1400	1410	1405
CH(Aromatic)	3185	2920	2910	2960	2950
CH(Aliphatic)	2885	2710	2740	2710	2700
C-C	890	880	870	790	875

Prepared compounds showed bands in the range of (3290 - 3410 cm^{-1}) assigned to OH Group, (Que *et al* ., 1999).The presence of (C=N) bands for all prepared compounds indicates to produce of Schiff base of reactions by (NH_2 and C=O) groups , and appeared at (1590 , 1580 ,1575, 1580, 1530, 1575 , 1570, 1540 and 1560 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine, Tyrosine , Arginine, Glutamine, Methionine , Valine and Threonine) with 4-(Di methylamino) benzaldehyde , respectively.(Hasan et al., 2021)The (– C=O) bands for all the prepared compounds, indicates to presence of carboxylic acid group of amino acids , These bands are recorded at

(1710, 1640 , 1620 , 1725 , 1610, 1620, 1640 , 1615, 1710 and 1630 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine, Tyrosine , Arginine, Glutamine, Methionine , Valine and Threonine) with 4-(Di methylamino) benzaldehyde , respectively. The relative variations of C=O positions of this band are suggesting to coordination through oxygen atom of hydroxyl group (Hamad et al., 2019).The (CH) aromatic bands are recorded in all Schiff base compounds and located at (3150,3100 , 3030, 3210, 3115, 3185, 2920 , 2910, 2960 and 2950 cm^{-1}) for the reactions of the amino acids of (Trptophan ,Phenylalanine, Asparagine, Glycine, Tyrosine , Arginine, Glutamine, Methionine,Valine and Threonine)with 4-(Di methylamino) benzaldehyde , respectively assigned to benzene ring of 4-(Di methylamino) benzaldehyde.The (NH_2)band appear at 3300 Cm^{-1}in Schiff base compounds which containing additional NH_2 group as basic amino acids (Asparagine , Arginine and Glutamine), the (NH) Schiff base bands located at 1500cm^{-1}.

Validation of docking protocol

We first validate the docking procedure before achieving a molecular docking screen of the synthesized compounds using AutoDock Vina. Then, the coordinated ligand was extracted from a crystallographic structure (PDB ID: 1JIJ) and re-docked into the same binding pocket. The results revealed a similarity between the ligand and crystallographic pose (RMSD = 0.84 Å, binding affinity −8.1 kcal/mol). These results confirmed that the AutoDock Vina docking parameters reproduced the expected binding mode Figure 1.

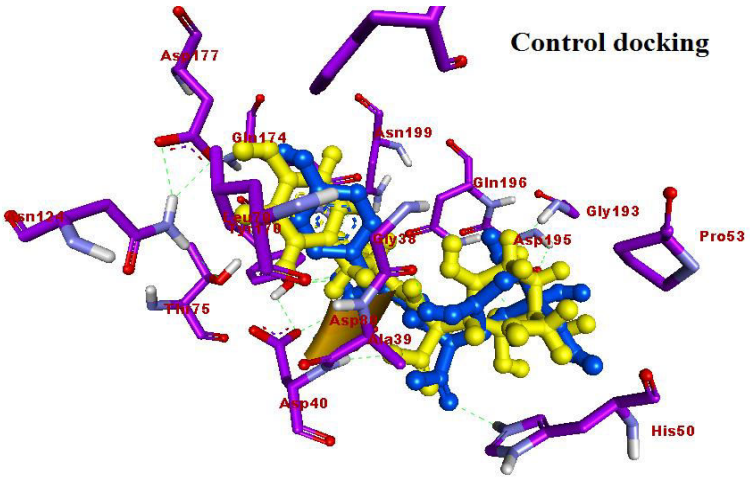


Figure (1):Superimposition of the docked and crystallographic poses (Blue and yellow, respectively for 1JIJ).

Using auto dock Vina, this study used molecular docking to evaluate the binding interactions between the synthesized compounds and the target protein.To gain structural and functional insight into the mechanism of inhibition, reliable conformations of the synthesized compounds within the active site were achieved.Originally, molecular docking simulation was performed for the ten synthesized compounds using Autodock Vina against the protein (PDB: 1JIJ). However, the obtained results revealed that the synthesized compounds, including (compounds 1 to-10) exhibited low binding energy against the target protein, as follows in Table 3.

Table (3): The value of FEB of synthesized compounds.

No	Compounds	AutoDock Vina FEB

		(kcal/mol)
Compound 1	2-((4-(dimethylamino)benzylidene)amino)-3-(1H-indol-3-yl)propanoic acid	-8.1
Compound 2	2-((4-(dimethylamino)benzylidene)amino)-3-phenylpropanoic acid	-8.8
Compound 3	2-((4-(dimethylamino)benzylidene)amino)succinamide	-7.5

No	Ligands	AutoDockVina (kcal/mol)	Residue	Type of interactions
Compound 4	2-((4-(dimethylamino)benzylidene)amino)acetic acid	-6.6		
Compound 5	2-((4-(dimethylamino)benzylidene)amino)-3-(4-hydroxyphenyl)propanoic acid	-8.6		
Compound 6	-2-((4-(dimethylamino)benzylidene)amino)-5-guanidinopentanoic acid	-9.2		
Compound 7	-5-amino-2-((4-(dimethylamino)benzylidene)amino)-5-oxopentanoic acid	-9.1		
Compound 8	2-((4-(dimethylamino)benzylidene)amino)-4-(methylthio)butanoic acid	-6.8		
Compound 9	2-((4-(dimethylamino)benzylidene)amino)-3-methylbutanoic acid	-7.3		
Compound 10	2-((4-(dimethylamino)benzylidene)amino)-3-hydroxybutanoic acid	-7.1		

Generally, a protein-ligand complex with the lowest FEB is often considered a potential inhibitor. Therefore, according to the results displayed in Table 1, the four synthesized compounds that showed the lowest FEB (6,7,2,5 and 1) were considered the potential candidates. The molecular docking results exhibited minimum binding energy ranging from -9.2 to -6.6 kcal/mol. The interactions between the docked compounds and the target proteins were manually examined. The results showed extensive interactions with the essential amino acids at the binding pocket; it includes hydrogen bonding, Van der Waals, pi-pi T-shaped, Hydrophobic, Alkyl and electrostatic interactions, Table 4.

1	Compound 6	-9.2	Gln174, Asp177, Asn124	H-Bond
			Leu70, Gly38, Gln196, Gly139, Asp195, His50, Tyr170, Thr75,	van der Waals
			Tyr36, Tyr36, Asp40	Carbon H-Bond
			Ala39	Pi-Alkyl
2	Compound 7	-9.1	Asp40, Gly38, Gln174	H-Bond
			Thr75, Asn124, Tyr170, Leu70, His50, Pro53, Gly193, Tyr36, Asp177	van der Waals
			Gln196	Carbon H-Bond
			Asp195	Pi-Anion
			Ala39	Pi-Alkyl
3	Compound 2	-8.8	Gln196, Gln174, Gln174	H-Bond
			Asp 40, Tyr 170, Thr 75, Asn 124, Asp177, Tyr 36, Gly 38, Gly 139, Pro 53, His 50, Asn 199, Asp 80,	van der Waals
			Ala39,	Pi-Alkyl
			Leu70	P-sigma
			Asp 196	Carbon H-Bond
4	Compound 1	8. - 1	Asp 80, Gln 196	H-Bond
			Ala39, Asp 40, Tyr1 70, Gln174, Thr75, Asn 124, Asp 177, Tyr 36, Gly3 8, Gly1 39, Pro 53	van der Waals
			Leu 70	Pi-Alkyl
			His 50	Pi-Anion
			Asp 195	Pi-cation

Table (4): Details of binding interactions of the potential four synthesized compounds docked into the binding pocket.

The amino acids completely wrapped all four compounds. The analysis of the interactions between the four compounds and the essential amino acids revealed that those compounds are located deeply inside the binding pocket of the target protein in a similar shape to the coordinated ligand, meaning that they can bind strongly with amino acids (Figure 2).

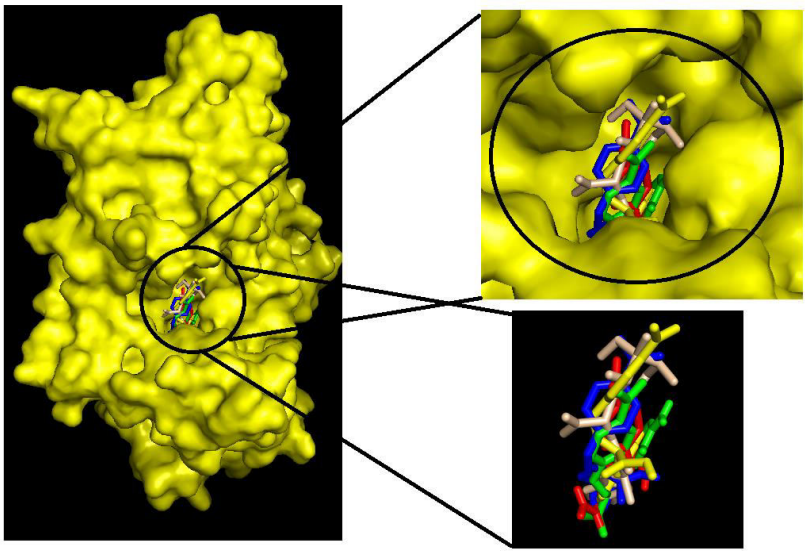


Figure (2) :Enfolding of the four synthesized compounds (1) Compound 6 (Green), (2) Compound 7(Red), (3) Compound1(yellow), (4) Compound2 (Blue) together with the coordinated 4-(dimethylamino)benzaldehyde (White) in the binding pocket.

Compound (6)exhibited four hydrogen bonds with the amino acids Gln174, Asp177, and Asn124. Van der Waals interaction was displayed with amino acids Leu70, Gly38, Gln196, Gly139, Asp195, His50, Tyr170, and Thr75. Likewise, Carbon H-Bond was formed with amino acids Tyr36, Tyr36, and Asp40. In addition, Pi-alkyl interactions were formed with the amino acid Ala39.The compound (7) displayed three hydrogen bonds with residues Asp40, Gly38, and Gln174. Likewise, Van der Waals interactions were shown with the amino acids Thr75, Asn124, Tyr170, Leu70, His50, Pro53, Gly193, Tyr36, and Asp177; in addition, Pi-alkyl interactions were formed with Ala39, Carbon H-Bond also displayed with the Gln196 residue as well as Pi-Anion interaction showed with Asp195 (as showing in Figures 3, 4. Table 4).Compound 2displayed three hydrogen bonds with the amino acid residues Gln196, Gln174, Gln174, and Van der Waals; interactions were also noticed with amino acids Asp40, Tyr170, Thr75, Asn124, Asp177, Tyr36, Gly38, Gly139, Pro53, His50, Asn199, Asp80 at the binding pocket. P-sigma interaction was formed with Leu70, another Pi-alkyl interaction displayed with Ala39 and Carbon H-Bond exhibited with the amino acid Asp196 (as shown in Figure 3, 4. Table 4).Finally,compound 1 was found to show two hydrogen bonds with the amino acid residues Asp80 and Gln196,Van der Waals interaction formed with the resides Ala39, Asp40, Tyr170, Gln174, Thr75, Asn124, Asp177, Tyr36, Gly38, Gly139, Pro53, Alkyl with Leu70, Likewise, Pi-cationinteractions were noticed with Asp195as well as Pi-anion with His50 (as showing in Figures 3 and 4., Table 4).

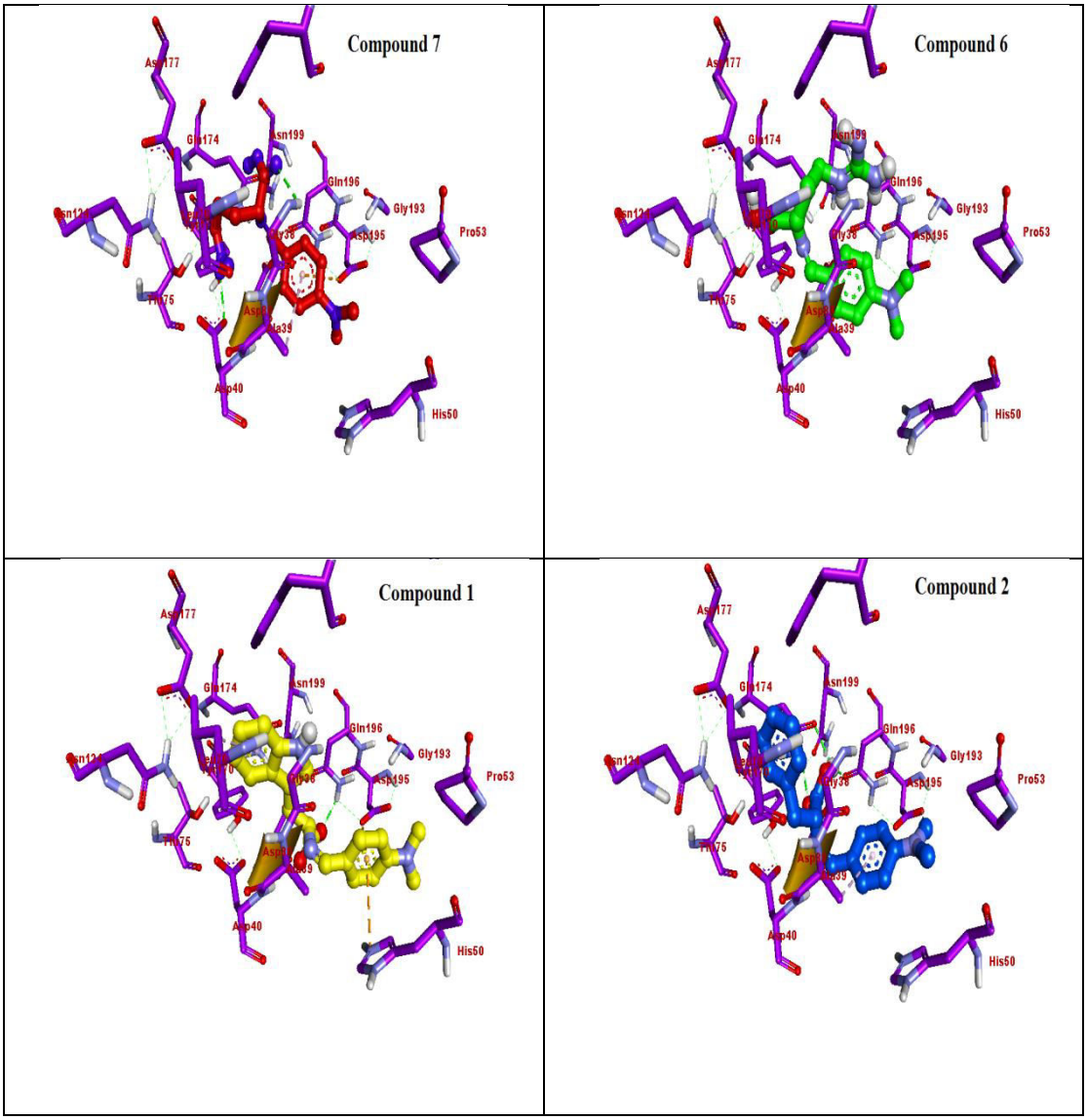


Figure (3). The (3D) three dimensional of the binding modes of the four compounds found at the binding pocket represented by stick structure (1) Compound 6 (Green), (2) Compound 7(Red), (3) Compound1(yellow), (4) Compound2 (Blue)

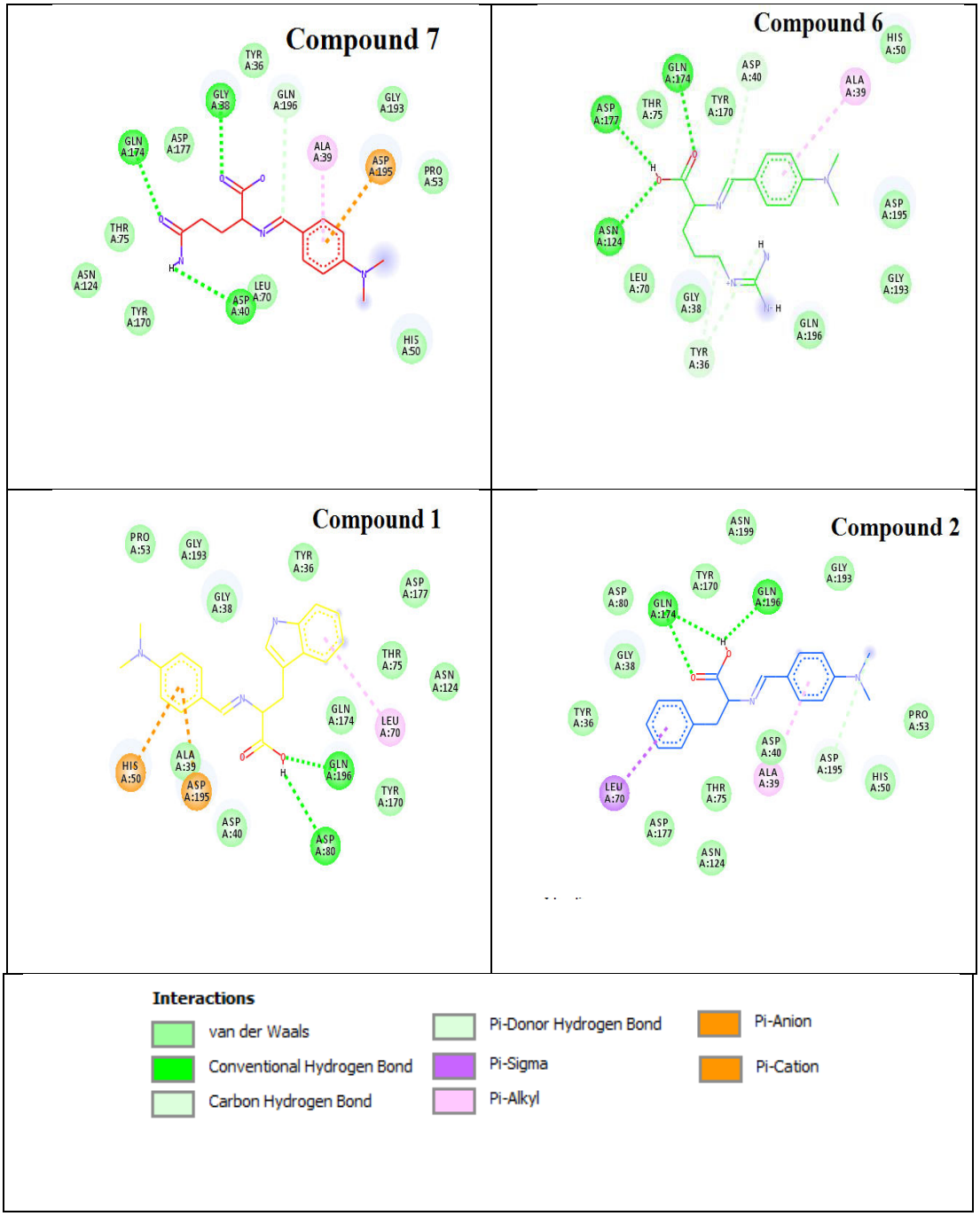


Figure (4): The (2D) three dimensional of the binding modes of the four compounds found at the binding (1) Compound 6 (Green), (2) Compound 7(Red), (3) Compound1(yellow), (4) Compound2 (Blue)

After performing molecular docking, the four synthesized compounds displayed a high affinity and excellent binding interactions with the essential amino acids at the binding pocket. Thus, these compounds could inhibit the target protein. This ability to interact with the target protein offers good advantages in inhibiting bacterial activity. Furthermore, these compounds exhibit an improvement over the coordinated ligand in the target protein in terms of amount, types of interactions and FEB that allow them to be a potential inhibitor for bacterial activity (Systèmes, 2016).

Conclusion

An important family of ligands that coordinate to metal ions via azomethine nitrogen and have been widely researched are Schiff bases, which are generated from an amino and carbonyl molecule. Several azomethines were reported to have remarkable antibacterial activity. The C=N linkage is necessary for biological activity in azomethine derivatives. Due to their structural diversity and preparative accessibility, Schiff base complexes are regarded as among the most significant stereochemical models in the main group and transition metal coordination chemistry. Encouraged by this discovery, several Schiff bases were created, described, and tested for their ability to antibacterial activity. *Insilico*molecular docking for the synthesized compounds displayed suitable interaction mode at the binding pocket;they confirmed that these potential compounds might be necessaryfor developing lead compounds to search for new antibacterial inhibitors. The synthesized Schiff base, could be further extended for its complex formation with different transition metal ions for enhanced biological activity.

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