2024, 21(7): 2289-2307
https://doi.org/10.21123/bsj.2023.8553
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
Baghdad Science Journal

Molecular Docking, Synthesis and Evaluation for Antioxidant and Antibacterial Activity of New Oxazepane and Benzoxazepine Derivatives

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Received 09/02/2023, Revised 22/05/2023, Accepted 24/05/2023, Published Online First 25/12/2023, Published 1/7/2024

Abstract

In the field of molecular simulations, molecular docking is a method that can determine the optimal and preferred orientation of a certain molecule related to another when they are coupled to create a stable complex. The strength of the association, or binding affinity, between two molecules can be predicted using knowledge of their preferred orientation. In this study, a series of prepared compounds were evaluated for their binding modes, potential interactions, and target binding locations. Some derivatives 1,3-oxazepane, and 1,3-benzoxazepine were prepared from three Schiff bases compounds (1S-3S). The compounds (1S-3S) were reacted with succinic anhydride and phthalic anhydride to obtain derivatives of 1,3- oxazepane and 1,3-benzoxazepine (1B-3C). The characterization of prepared compounds was achieved by methods of elemental analysis, FT-IR, ^{1}H, and ^{13}C-NMR spectral analysis. The antibacterial activity of the compounds (1B-3C) was recorded against some isolated bacteria including gram-negative (*Staphylococcus aureus*), and gram-positive *(E.coli*) in parallel with Amoxicillin as a regular drug. Compounds (1B-3C) exhibited good values as antibacterial spreading from middling to perfect against the bacteria strains. Moreover, the antioxidant activity of the synthesized compounds (1B-3C) was evaluated using 2,2-diphenyl-1-picrylhydrazyl. The results showed that compounds have the highest values as radical scavenging.

Keywords: Antioxidant, Benzoxazepine, Biological, Docking, Oxazepane.

Introduction

Heterocycles play a significant role in the drug industry. The side groups are essential constituents for living cells and depend on aromatic heterocycles[1]. Oxazepine and oxazepane are hetero seven-membered rings consisting of oxygen and nitrogen atoms[1,2]. In 1864, Hago Schiff was the first to report Schiff bases (SBs), which are commonly synthesized by the condensation of a primary amine with a carbonyl compound [3,4]. The SBs are also well-known as imines and azomethine compounds. The SBs compounds have an azomethine group with the general formula of ($R_1HC=NR_2$). Where: R1 and R2 are aryl[5], alkyl[6], cycloalkyl[7], or heterocyclic groups[8]. For along time, the synthesis of 1,3-oxazepane and 1,3-oxazepine rings was based on two classical types of reactions. The first reaction is valence-bond isomerization which is carried out via irradiation of aryl pyridine N-oxides, which results in a ring

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https://doi.org/10.21123/bsj.2023.8553
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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expansion to 1,3-oxazepine derivatives[9]. The second reaction is enamine condensation which is done by irradiation of enamine derivative to produce 2,3,6-trihydric-5- methoxy carbonyl-2,3,4-triphenyl-1,4-oxazepam-7-one[10,11].

Recently, oxazepine and oxazepane derivatives were prepared in different ways. Hameed (2012) has synthesized many new oxazepine and oxazepane derivatives through the addition reaction of Schiff base to maleic anhydride using microwave power[12]. Moreover, Yousif reacted Schiff bases with phthalic anhydride to give1,3- oxazepine derivatives[13]. Oxazepine and its derivatives have many important biological pharmacological activities[14] such as enzyme inhibitors[15], anti-depressant and psychoactive drug[16]. Amoxapine is a group of drugs was called tricyclic antidepressants[17], which are used for treating symptoms of depression, anxiety, and agitation. Xin-Hua Liu et al. synthesized eight novel oxazepine derivatives to be screened for anticancer activity. 4-amino antipyrine is a commercially important aromatic amine used mainly for drug production, which is an essential compound used as an antibiotic in veterinary medicine[18]. This compound is commonly utilized as a starting material for the preparation of 1,3-oxazepine and 1,3-oxazepane heterocyclic compounds and their analogus[19].

In this paper, novel 1,3-oxazepine and 1,3-oxazepane heterocyclic compounds were developed and synthesized by combining cyclo anhydride with Schiff bases. On the other hand, molecular docking as a virtual screening method was utilized to screen our collection of prepared compounds, and then test them as an antioxidant and antibacterial agent.

The molecular docking was performed by applying the blind docking mode of the PyRx software[20-23], which is an important tool for gaining an understanding of the binding interactions between a ligand (prepared compound) and target receptors (mainly, a protein) [24-26]. In order to predict the inhibition of the target proteins corresponding to bacteria as shown in Fig. 1.

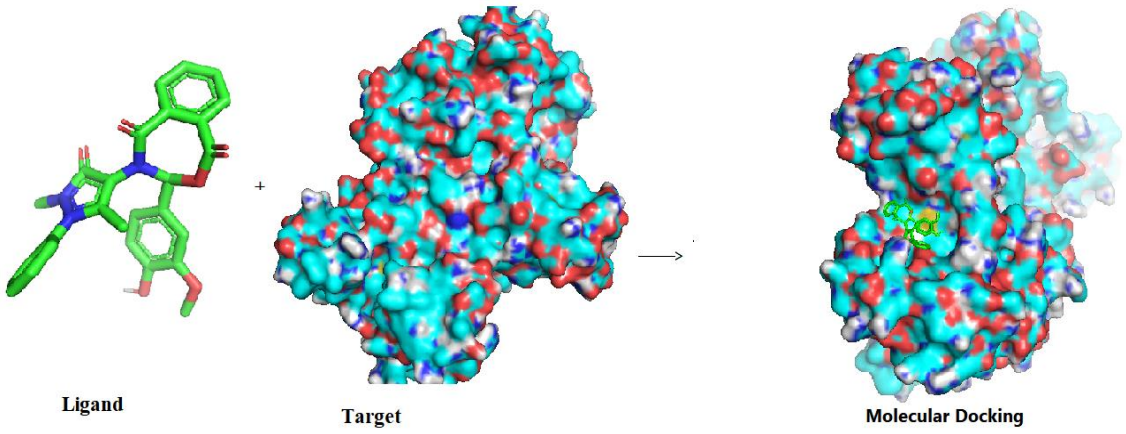

Figure 1. Docking of ligand and target.

Materials and Methods

All chemicals were used with high purity and supplied by Fluka, Sigma-Aldrich, and B.D.H. companies. NMR spectra were recorded using Bruker spectrometers operating (400 MH_Z) with DMSO-d_6 at the university of Basra. The chemical shifts are reported in ppm relative to tetramethylsilane. The FT- IR spectra were recorded using a Shimadzu spectrometer. Micro elemental analysis CHN at the University of Tehran, Iran. The biological activities of the prepared compounds (1B-3C) were screened out by a good diffusion method in agar medium in the biology laboratory at the College of Science.

In silico studies

Molecular docking is a method that studies interactions of the binding between ligands within the targeted protein. To support the antibacterial activity of newly synthesized heterocyclic compounds, two types of proteins were used PDB-

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ID 4H2M (undecaprenyl diphosphate synthase) from E. coli and PDB –ID 3FYV (Descriptor Dihydrofolate reductase) from *S. aureus* are obtained from the Protein Data Bank (www.pdb.org). The synthesized compounds displayed interactions with the binding affinities with target proteins in emulation via the PyRx program[26,27]. The structures of compounds (1B-1C) were drawn with Chem3D15.0. Their geometry optimization was performed using the MMFF94 method in the program and saved in pdp format. Proteins without water molecules were chosen for the evaluation of heterocyclic compound derivatives. Upon simulation, the outcomes were studied to locate the maximum power of active antibacterial inhibitors by visualizing different interactions of a ligand with the active side and were used program BIOVIA\Discovery Studio 2021 in that.

Synthesis of compounds

Synthesis of 4-((4-hydroxy-3-methoxy benzylidene) amino)-2,5-dimethyl-1-phenyl-1,2-dihydro-3H-pyrazol-3-one (1S).

To a stirred solution of vanillin (5mmol) in ethanol (10 mL) at room temperature, a few drops of glacial acetic acid (GAA) were added. 4-amino antipyrine (5 mmol) was then slowly added. The resultant mixture was stirred for 10 min using a microwave (300W). The development of the reaction was followed by the thin layer chromatography (TLC) technique using an ethyl acetate: benzene (1:4) mixture. Subsequently, the solution was evaporated under reduced pressure to remove the ethanol. The precipitate was filtered, and recrystallized to give compound 1S. The prepared compound was dried at 70°C, then the melting point was measured.

The physical data of 1S were given in Table 2. Yield =72%, m.p.= 210 °C. FT-IR:1622 cm^{-1} (C=N). ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm): 2.2 (s, 3H, CH_3), 2.9 (s, 3H, N -CH_3), 3.5 (s, 3H, O-CH_3), 6.9-7.6 (m, 8H, Ar-H), 8.9(s, 1H, CH=N imine), 9.8 (s, 1H, O-H). ^{13}C-NMR (DMSO-d_6 400MHz) δ (ppm):12.7 (CH_3), 34.2 (N-CH_3), 54.3 (OCH_3), 112 - 144.5 (Aromatic C), 158 (N=CH), 168.4 (C=O).

Synthesis of 2-((4-amino-2,5-dimethyl-1-phenyl-1,2-dihydro-3H-pyrazol-3-ylidene) amino)-3 -(4-hydroxy phenyl) propionic acid (2S)

To a stirred solution of 4-amino antipyrine 5mmol in ethanol 15 mL, a few drops of GAA were added at room temperature. Tyrosine (5 mmol) was then slowly added. The resultant mixture was stirred for 10 min using a microwave (300W). The development of the reaction was followed by the TLC using ethyl acetate: benzene (1:4) mixture. Subsequently, the solution was evaporated under reduced pressure to remove ethanol. The precipitate was filtered, and recrystallized to give compound 2S. The prepared compound was dried at 70°C, then the melting point was measured.

The physical data were given in Table 2. Yield =78%, m p.= 126 °C. FT-IR: 1619cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.19 (s, 3H, CH_3), 3.15 (s, 1H, N-CH_3), 2.87 (2H, CH_2-Ar), 4.8 (t, 2H, N=CH), 6.8 (d, 2H, Ar-H),7.01 (d, 2H, Ar-H),7.35-7.64 (m,5H, Ar-H), 9.43 (s, 1H, Ar-OH). ^{13}CNMR (DMSO-d_6, 400 MHz) δ (ppm):11.3 (pyrazole-CH_3), 29 (CH_2), 78.6(CH_2-N), 150.4 (C=N),154 (C-OH), 112.7-143.2 (aromatic C), 179.2 (COOH).

Synthesis of 2-((4-hydroxy-3-methoxy benzylidene) amino)-3-phenylpropanoic acid (3S).

To a stirred solution of vanillin (5mmol) in ethanol 10 mL, a few drops of GAA were added at room temperature. Tyrosine (5 mmol) was then slowly added. The resultant mixture was stirred for 7min using a microwave (300W). After completing the reaction, the precipitate was filtered and recrystallized by ethanol to give a compound (3S). The prepared compounds were dried at 70 °C. Physical data were listed in Table 2. Yield = 88%, m.p.= 185 °C, FT-IR: 1676 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.4 (s, 3H, CH_3), 2.4 (2H, CH_2-Ar), (6.7-7.6) (m, 3H and 5H, two Ar-H), 9.1 (s, 2H, HC=N), 10. 9 (d, 1H, COOH). ^{13}CNMR (DMSO-d_6, 400 MHz) δ (ppm): 56.9 (CH_3O), 68.6 (CH), 129.4-149 (aromatic C), 164.1 (CH=N), 184.1 (COOH).

General Procedure for the preparation of 1,3-oxazepane (1B-3B).

Stirred solution of SBs (1S–3S) (5 mmol) were dissolved respectively in 10 mL of dry THF at 66 °C using an oil bath. Succinic anhydride (5 mmol) was slowly added and left to reflux for 4h. The

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https://doi.org/10.21123/bsj.2023.8553
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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solution was evaporated under reduced pressure to remove the ethanol. The precipitate was filtered, and recrystallized to give compounds (1B-3B). Physical properties are shown in Table 3.

3-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(4-hydroxy-3-methoxyphenyl)-1,3-oxazepane-4,7-dione (1B). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.8 (s, 3H, CH_3 in pyrazole), 2.7 and 2.9 (t, 3H, $2CH_2$, oxazepane), (s, 3H, CH_3), 3.18 (N-CH_3) in imidazole, 3.8 (s, 3H,OCH_3), 6.3 - 7.6 (m, 8H, Ar-H), 8.7(s, 1H, O-CH-N),9.5 (OH). ^{13}C-NMR (DMSO-d_6, 400 MHz) δ (ppm):184.9, 173.3 (C=O, oxazepane), 159.5- 123.8 (aromatic C), 91(CH_2, oxazepane), 31.9-33.6 (two groups CH_2).

2-(4-amino-1,3-dimethyl-7,10-dioxo-2-phenyl-6-oxa-1,2,11-triazaspiro[4.6]undec-3-en-11-yl)-3-(4-hydroxyphenyl)propanoic acid (2B).^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.3 (s, 3H, CH_3) in pyrazole , t, 2.66 ppm, and t, 2.90 (CH_2, oxazepane), 2.76 (s, 3H, N -CH_3),), 6.8 -7.6 (m, 9H, Aromatic), 6.21 (t, 2H, CH_2 aliphatic), 12(s, 1H, COO-H).^{13}C-NMR (DMSO-d_6, 400 MHz) δ (ppm): 170 and 163 (2 C=O, oxazepane), 51.5(CH_2 COOH),158.4(C-OH); 113.5-136.1(Aromatic C),173.7 (COOH). The ^{1}H-NMR spectrum of compound (2B) in DMSO –d_6 is given in Fig. 8.

2-(2-(4-hydroxy-3-methoxyphenyl)-4,7-dioxo-1,3-oxazepan-3-yl)-3-phenylpropanoicacid (3B). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.8 and 2.8 (t, CH_2, ring oxazepane), 3.4 (m, 2H, CH_2 aliphatic), 4.6 (m, CH_2COOH), 6.6 (s, CH, oxazepane), (6.8-7.5) (m, 8H, Ar-H), 9.5(s, OH, phenol) 11.4 ppm (s, 1H, COO-H).^{13}CNMR (DMSO-d^6, 400 MHz) δ (ppm): 27.2-39.8 (CH_2, oxazepane), 88.5 (C-N, oxazepane), 114-146 (aromatic C), 170.4, 173 (C=O, oxazepane), 175.9 (COOH).

General Procedure for the preparation of 1,3-benzoxazepine. SBs (1S–3S) (2mmol) were dissolved in 10 mL dry DMF at 120°C using an oil bath. Phthalic anhydride (2mmol) was slowly added and left to reflux for 4 h. After completing the reaction, the solution was evaporated under reduced pressure to remove DMF. The crude product was recrystallized utilizing benzene. The physical properties were shown in Table 3.

4-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(4-hydroxy-3-methoxy phenyl)-3,4-dihydrobenzo[e][1,3] oxazepine-1,5-dione(1C). ^{1}H-NMR (DMSO-d6, 400 MHz) δ (ppm): 2.5 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3);6.9-8.3 (m, 12H, Ar-H), 7.9 (s, 1H, CH-N, oxazepine). ^{13}C-NMR (DMSO-d_6, 400 MHz) δ (ppm): 95.2 (C-N), 174,173.7 (2C=O , oxazepine), 111.8-148.3(aromatic C).

2-(4-amino-2,5-dimethyl-1,5-dioxo-1-phenyl-1,1,2,5-tetrahydro-4H-spiro[benzo[e][1,3]oxazepine-3,3'-pyrazole]-4-yl)-3-phenyl propanoic acid. The reaction did not give the product.

2-(3-(4-hydroxy-3-methoxyphenyl)-1,5-dioxo-1,5-dihydrobenzo[e] [1,3] oxazepin-4(3H)-yl)-3-phenyl propanoic acid (3C). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.64 (s,3H, CH_3),3.24(s, 3H, N-CH_3), 3.74 (s, 3H, OCH_3), 6.83-7.56 (m, 12H, Ar-H), 8.59(s, 1H, CH-N), 9.21 (s, H, O-H), 8.28 (s, 1H, CH-N), 12.68 (s, H, COOH). ^{13}C-NMR (DMSO-d_6,400 MHz) δ (ppm): 17.3(CH_3), 29.27 (N-CH_3), 64.33(O-CH_3), 74.01 (C-N), 170.8 &174.03 (2C=O, oxazepine), 111 -150 (aromatic C).

Antibacterial Activity Test

The test of antibacterial activity was screened for all synthesized compounds (1B-3C) against two kinds of bacteria (*S. aureus and E. coli*) using the agar diffusion method[28]. In the test of sensitivity, two types of bacteria colonies were transferred to nutrient agar and incubated at 37^{o}C for 12 h. The dilute normal saline solution was then transferred 0.1 mL from the bacterial suspension to the nutrient agar and spread on the surface of the dish, and then left for about 30 min. The DMSO was used as a solvent for all these compounds. Also, the zone inhibition was measured in mm units and repeated three times, then the measurement rate was taken[29-31]. The amoxicillin of antibiotic was used as a reference to inhibit the bacteria of the two species.

Antioxidant Test

According to the method described by Lu et al, (2013) [31]. The activity of free radical scavenging against the radicals of sample DPPH was studied for all Oxazepane and Oxazepine compounds. About (1

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https://doi.org/10.21123/bsj.2023.8553
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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mg/mL) of the stock solution of the tested compounds was diluted to (100 and 500 µg/mL) as a final concentration. The sample fluid was applied to a minimum of 50µM DPPH methanolic fluid (3.8mL) (0.1 mL each) at room temperature (RT), then left for 30 min in darkness. The absorbance has been recorded at a wavelength of 517 nm, and antioxidant activity can be determined. Inhibition of DPPH (1%) was calculated using the following relationship 1:

DPPH radical scavenging activity (%)= (**Abs** $_{Control}$ - **Abs** sample X 100)/ (Abs control) …… 1

Where: **Abs** control =Absorbance DPPH radical (1%).

Abs $_{sample}$ = Absorbance in the presence of the samples of the prepared compounds.

The values obtained are compared with ascorbic acid.

Results and Discussion

The molecular docking was carried out on all synthesized compounds (1B-3C) in order to anticipate the closeness to target proteins obtained from two categories of bacteria. These proteins are 4H2M obtained from bacterial *E. coli* and 3FYV obtained from bacterial *S. aureus*. Analysis of the docking results demonstrated that all derivatives have the ability to inhabit the different sites of 4H2M & 3FYV binding pockets with perfect docking interaction scores, as shown in Table 1. Furthermore, docking studies of oxazepine and oxazepane derivatives revealed their ability as antibacterial agents.

All compounds (1B-3C) consist of aromatic rings, showing remarkable hydrophobic interactions with the amino acids in a protein. These compounds are ranked according to their binding energy, and a check of each molecule's total interactions with the binding site was effectively performed by counting the total number of H-bonds.

Docking studies of the prepared compounds 1B–3C, towards the 4H2M receptor. The outcomes attained are listed in Table 1. and Figs. 2 and 3 which revealed that the docked ligands are involved in many interesting hydrogen bonds and hydrophobic interactions which demonstrate a good protein inhibition of prepared compounds. As a detailed docking of all compounds, it can be noted that compound 1B which contains in its structure an oxazepane ring that formed a conventional H-bond with (4H2M in *E. coil*) LEU; A8:85 and MET;A:86 via the carbonyl group and three hydrogen bonds with ASN;A:144, TYR;A:145, and TYR;A:68 via hydroxyl groups. Furthermore, it is importance as an inhibitor is perceptible through many hydrophobic interactions such as: Pi-cation and pi-Alkyl with HIS; A:43, Pi-Pi stacked with ALA; A:69, Pi-Pi stacked with LEUA85 HISA:43, and MET; A:86, Carbon H-bond with ALA; A:142 in 4H2M (E-coil) On the other hand, compound 1B is linked mainly with protein 3FYV by the three H-bonds displayed with residues: LEU; A; 24, SER; A:49, and HIS; A:23 inhibitors are perceptible through hydrophobic interactions such as Pi-Sigma via HIS; A:49. Furthermore, compound 2B bonded mainly with protein 4H2M by four H-bonds via two H-bonds with CYS A: 182, One -H-bond with GLY; A: 111, ARGA: 108, and ILE; A: 109. Furthermore, it is an inhibitor through hydrophobic interactions such as Pi-Pi T-shaped with HIS; A:184.

The compounds 1C, and 3C that consist of benzoxazepine rings, showed docking results with 4H2M without hydrogen bonds in 1C, but three H-bonds in compound 3C by the OH and C=O groups; In case of the compound 3C, which showed three H-bonds with ASN;A:144(two H-bonds), SER;A:71, in addition to other hydrophobic interactions as Pi-Doner, Pi-sulfur with GLU(128), and Unfavorable Doner-Doner with MET 183. Furthermore, compound 1C with 3FVY showed the same types of interactions: three H-bonds via the NH and CO groups with amino acids: ARG; A:12, and TYR; A:126. Also, Pi-alkyl with VAI; A:112, Carbon H-bond with LEU; 10. The compound 3C displayed a single H-bond with LYS; A:140 in addition to other hydrophobic bonds as pi -Alkyl with LEU; A: 34, LYS; A:3, 3 and LYS; A: 29. Some of the above results are more significant than those given by the control drug Amoxicillin which only formed three H bonds with (3FYV) in ALA; A:7, ASP; A:27 and THR; A:46. Alkyl with SER; A:49, PHE;A: 92, VAL; A: 31, and LEU; A:28. On the other hand,

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P-ISSN: 2078-8665 - E-ISSN: 2411-7986
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drug Amoxicillin given good docking results with protein 4H2M, E-coil) is shown Fig. 4.

Results showed that most of our compounds exhibit an interesting antibacterial (binding affinity= −6.3 to −7.8 kcal/mol) compared to the relocked amoxicillin (binding affinity= -6.8 kcal/mol). The values of the energy of the complexes (target - protein) resulting from these interactions are referred to as the lower energy, more stable complex, and better activity. The compounds (1B, 1C, and 3C) which hold oxazepane and Benzoxazepine exhibited the lowest energy value 7.8 (kcal/ mol) followed by 2B and 3B with an energy value of 7.4 and 7.7 (kcal/ mol) respectively.

Table 1. Binding affinity (kcal/mol) with bacteria proteins and hydrophobic contacts (from molecular docking) in ligands (1B-3C).

No.	B.P.	BindingAffinity (kcal/mol)	H- bond contacts	Bond length (Aº)	Type of bond
1B	4H2M (E. coli)	-7.4	ALA;A:142	2	Conventional H-bond
			TYR*;A:145	2.28	Conventional H-bond
			TYR*,A:68	2.62	Conventional H-bond
			ALA,A:69	2.9	Conventional H-bond
			HIS,A:43	2.4	Conventional H-bond
			ASN*,A:144	4.5	Pi-Alkyl
			LEU*.A:85	4.25	Pi-Alkyl
			MET*,A:86	4.05	Pi-Alkyl
				4.32	Pi-Pi Stacked
				3.65	Carbon
				3.89	Pi-Cation
				3.59	Pi-Sigma
1B	3FYV (S.aureus)	-7.8	LEU*;24	2.68	Conventional H-bond
			SER*;49	2.89	Conventional H-bond
			HIS*;23	2.13	Conventional H-bond
				3.59	Pi-Sigma
				3.65	carbon
2B	4H2M (E.coli)	-7.4	HIS; A;:184	2.18	Conventional H-bond
			CYS**;A:182	2.08	Conventional H-bond
			GLY*; A:11	2.67	Conventional H-bond
			ARG;A;:108	2.07	Conventional H-bond
			ILE*;A:109	3.51	Conventional H-bond
				2.18	Conventional H-bond
				4.99	Pi-Alkyl
				4.53	Alkyl
				5.19	Pi-Pi T-shaped
2B	3FYV (S.aureus)	-6.6	GLY*:72	2.75	Conventional H- bond
			ASN:59	2.49	Conventional H-bond
			ARG*.:57	2.08	Conventional H-bond
			ASP:74	2.56	Conventional H-bond
			ARG:58	4.72	Pi-Pi Stacked
			HIS*.:38	3.23	Carbon
				2.98	Pi-doner
			MET*, A:86	2.75	Conventional H-bond
			ASN, A:144	2.49	Conventional H-bond
			TYR**,A:145	2.08	Conventional H-bond
				2.56	Conventional H-bond

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3B	4H2M	-7.7	ALA, A:69	4.41	Pi-Alkyl
	(E. coli)		HIS, A:43	4.72	Pi-Pi Stacked
			PHE, A;89	3.23	Carbon
			SER*, A;71	4.44	Pi-Cation
			PHE, A:71	2.98	Pi-Doner
		-	LEU:2	2.86	Conventional H-bond
			LEU:85	2.01	Conventional H-bond
			ILE:82	4.17	Pi-alkyl
3B	3FYV	-6.6	GLY*.:87	3.52	Carbon
	(S. aureus)		VAL*.:89	5.35	Amide-Pi Stacked
			TYR:83	3.72	Pi-Pi Stacked
				5.17	Pi-pi T-shaped
				3.72	Pi-Doner,Pi-sulfur
			ILE,A:109	4.29	Alkyl
1C	4H2M	-7.8	GLU,A:128	2.60	Doner-Doner
	(E. coli)		TRP,A:149	3.45	Carbon
			CYS,A:182	3.55	Pi-Anion
			MET, A:183	3.45	Carbon
				3.38	Pi-Sigma
				2.26	Conventional H-bond
			VAL :112	2.59	Conventional H-bond
1C	3FYV	-6.3	LEU :10	1.82	Conventional H-bond
	(S.aureus)		ARG* :12	2.93	Conventional H-bond
			TYR* :126	5.27	Pi-alkyl
				3.38	Pi – Sigma
				3.66	Carbon
				2.22	Conventional H-bond
			SER*; A:71	2.09	Conventional H-bond
3C	4H2M	-7.8	LEU; A:85	2.56	Conventional H-bond
	(E. coli)		MET;A:86	4.13	Pi-Alkyl
			ALA;A:142	3.65	Carbon
			ALA; A:69	3.79	Cation
			ASN**;A:144	3.38	Pi-Sigma
				3.82	Pi-Sigma
				1.96	Conventional H- bond
			LYS*:140	5.50	Pi-alkyl
3C	3FYV	-7.0	LYS:33	5.06	Pi-Alkyl
	(S.aureus)		LYS-29	5.47	Pi-Alkyl
			ASN:26	3.37	Pi – Sigma
			LYS:33	3.58	Carbon
				3.83	Alkyl
		-6.8	TYR**B:68	2.55	Conventional H-bond
			TYR*B:145	2.25	Conventional H-bond
Amoxicillin	4H2M		ASN* B:203	2.7	Conventional H-bond
	(E. coli)		TYRA:211	2.14	Conventional H-bond
			PHE B:70	2.00	Conventional H-bond
			SER* B:71	2.24	Conventional H-bond
			MET* B:86	2.09	Pi-Alkyl
			LEU B:85	4.81	Pi-Alkyl
			GLU* B:73		
			ALA* A:7	2.79	Conventional H-bond
	3FYV	-8.4	ASP*A:27	2.82	Conventional H-bond
	(S.aureus)		THR*A46	2.72	Conventional H-bond

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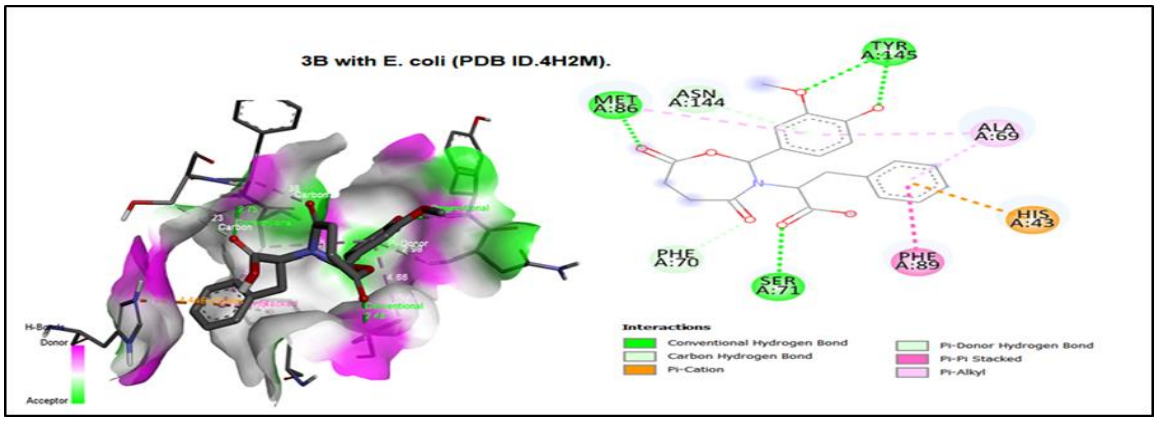
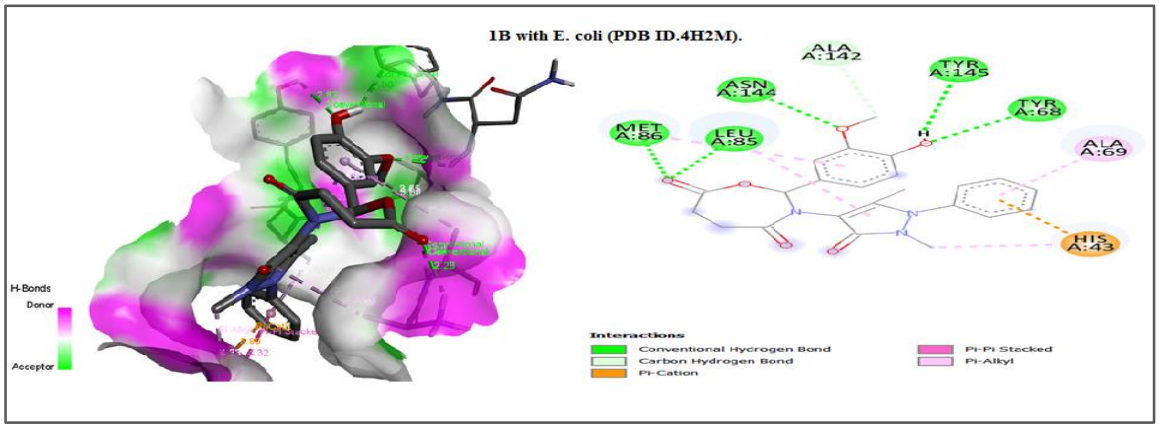
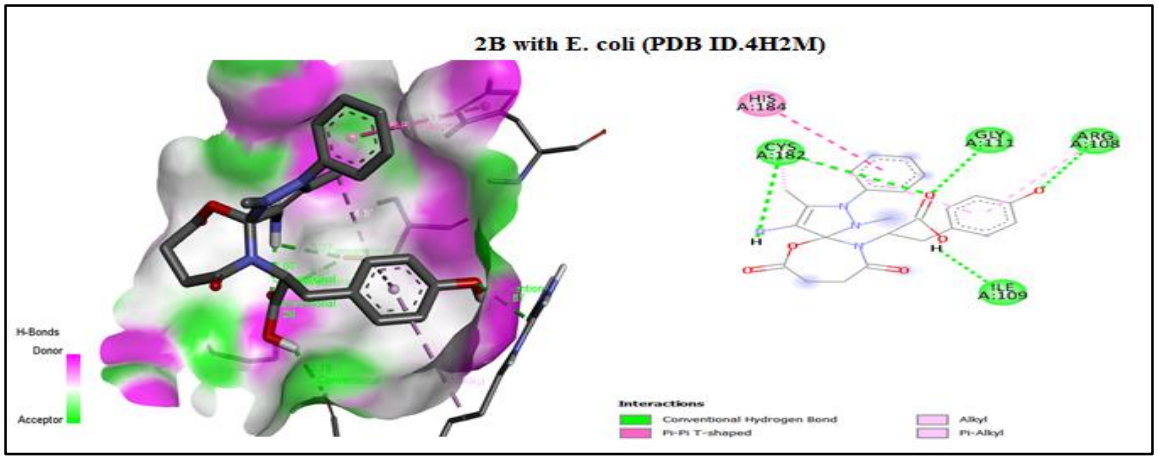
Am	SER A:49	2.8	Pi-Alkyl
oxic	PHEA:92	2.61	Doner-Doner
illin	VAL A:31		

Amoxicillin: Reference drug; *:1H-bond; **: 2H-bonds; ***:3H-bonds.







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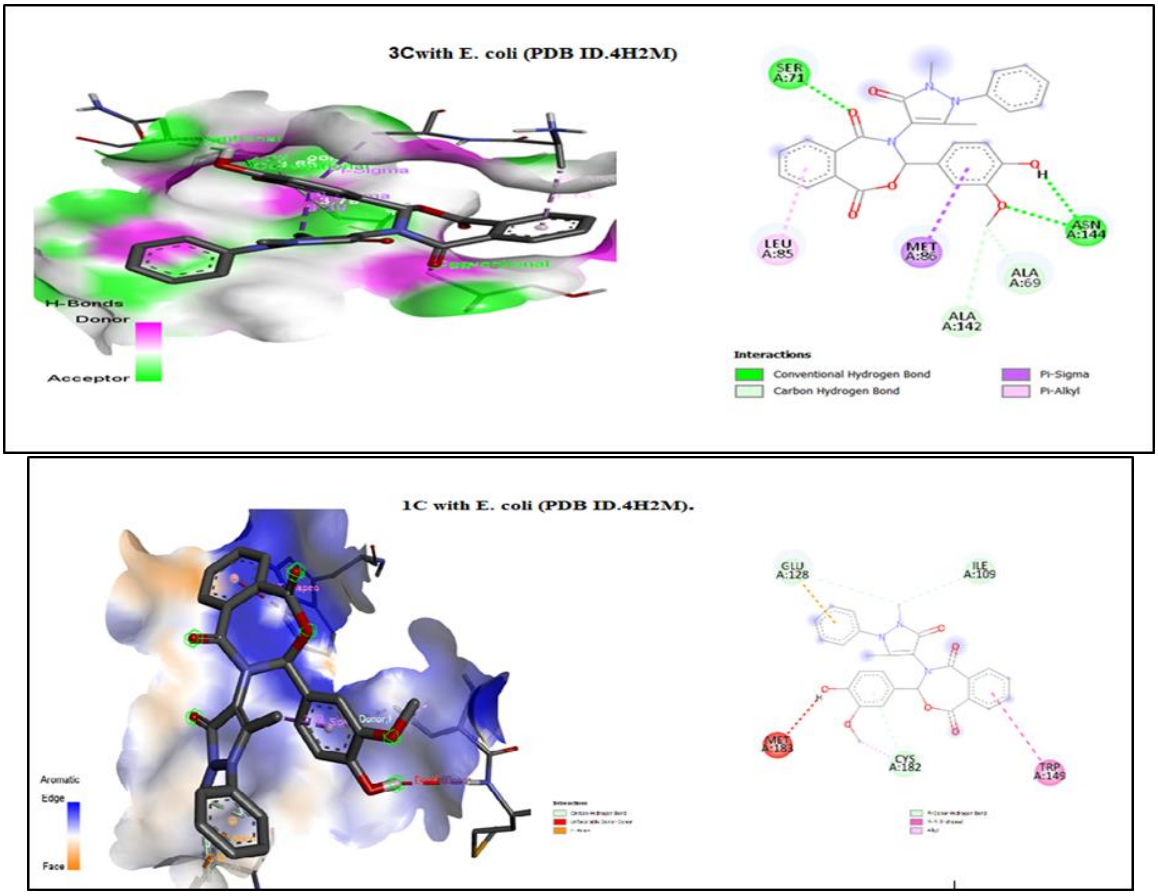
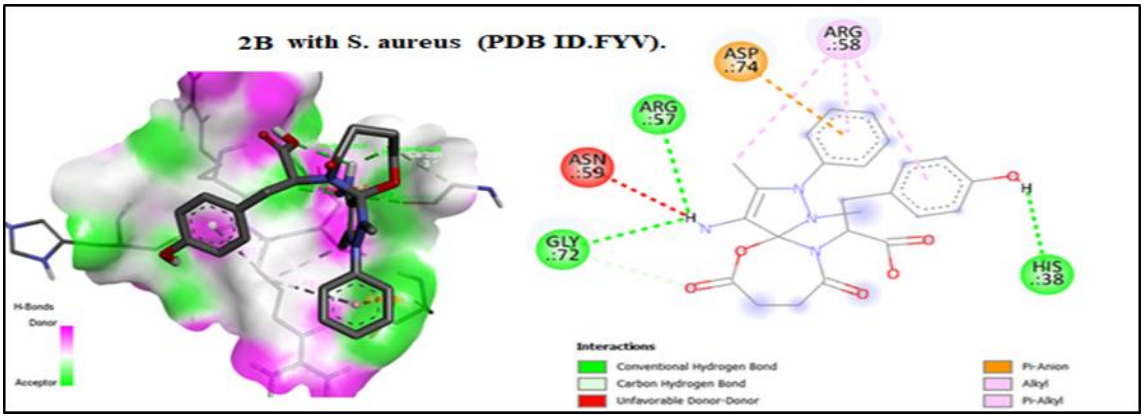


Figure 2. Interaction model for the compounds (1B-3C) with E. coli (PDB ID.4H2M).



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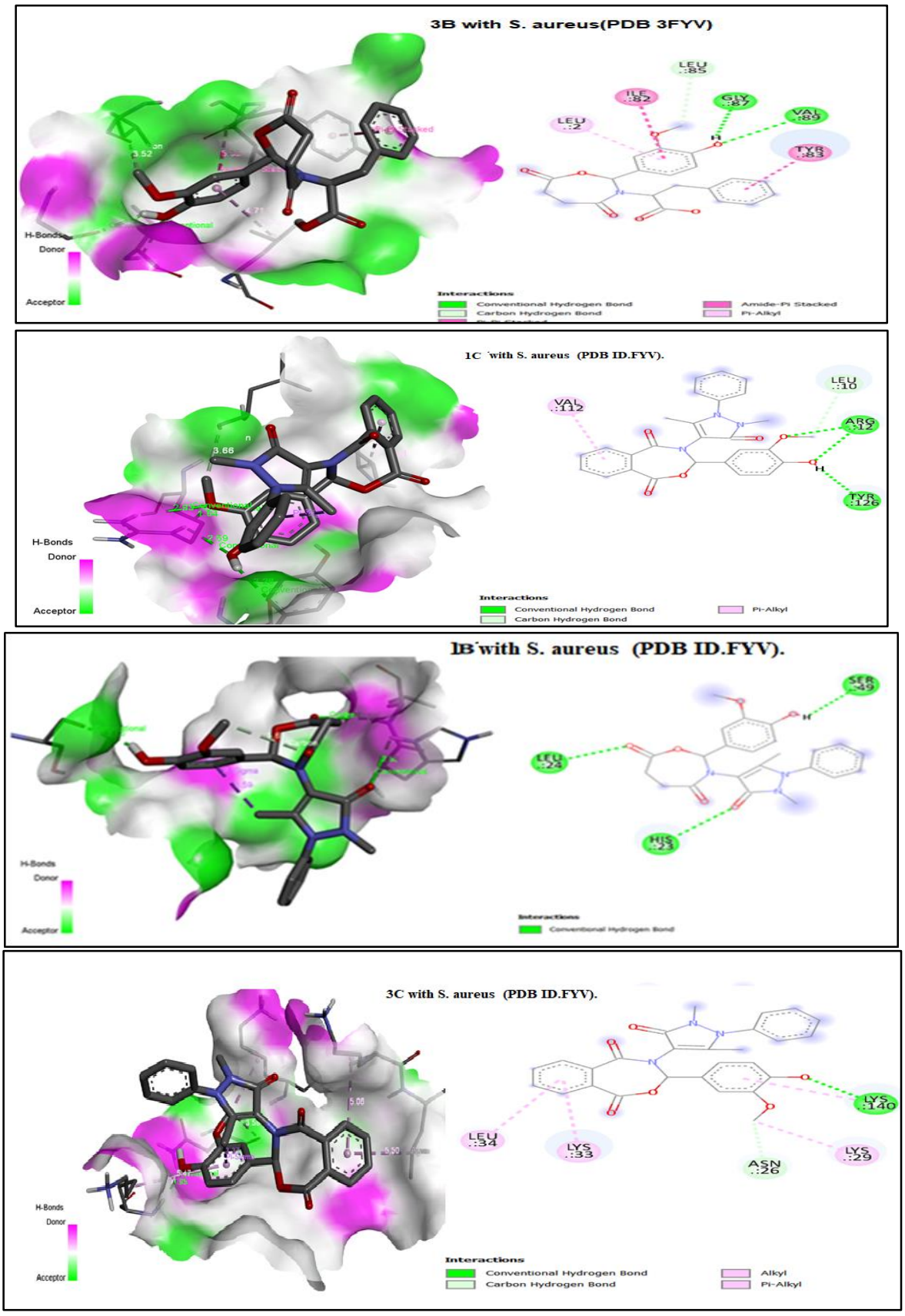

Figure 3. Interaction model for the compounds (1B-3C) with S. aureus ((PDB ID.3FYV).

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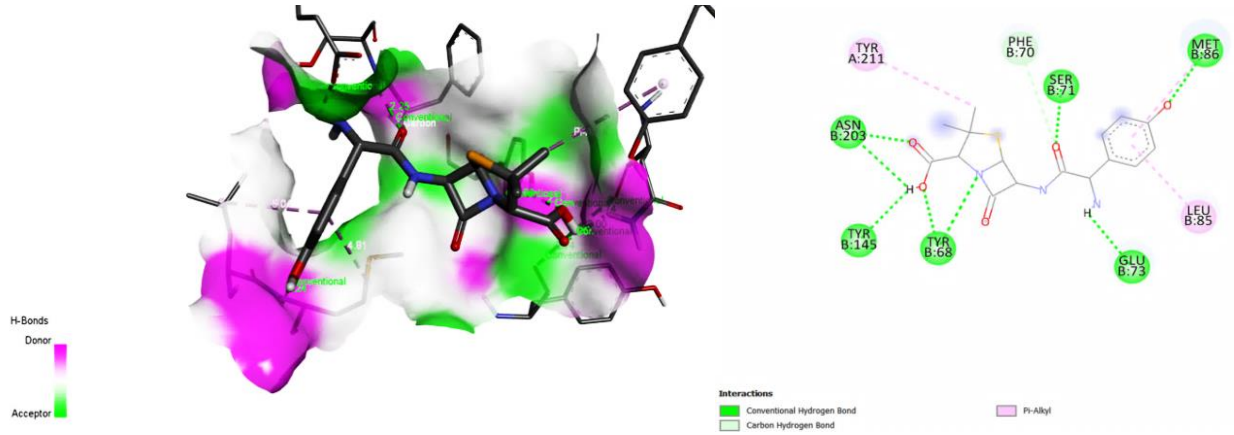


Figure 4. Interaction model for the Amoxicillin with E. coli (PDB, ID.4H2M).

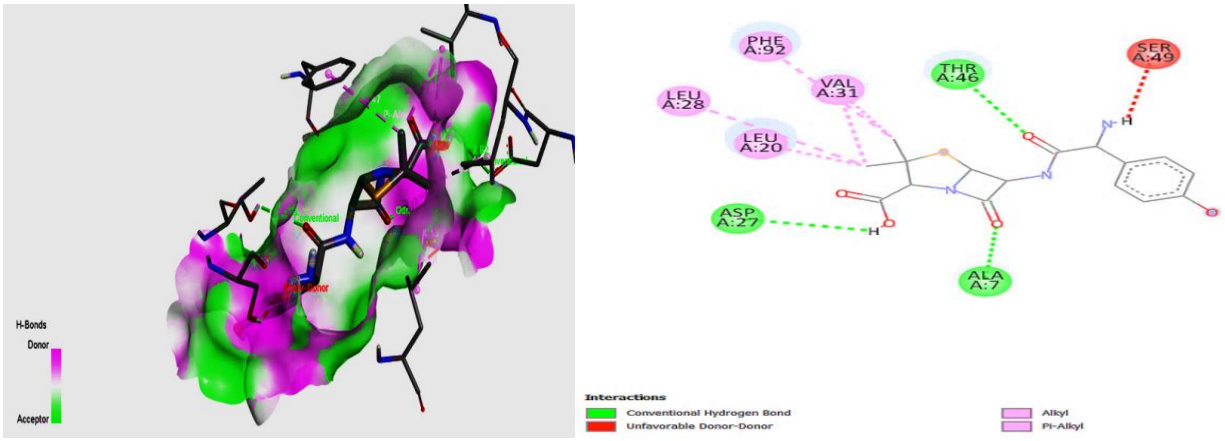
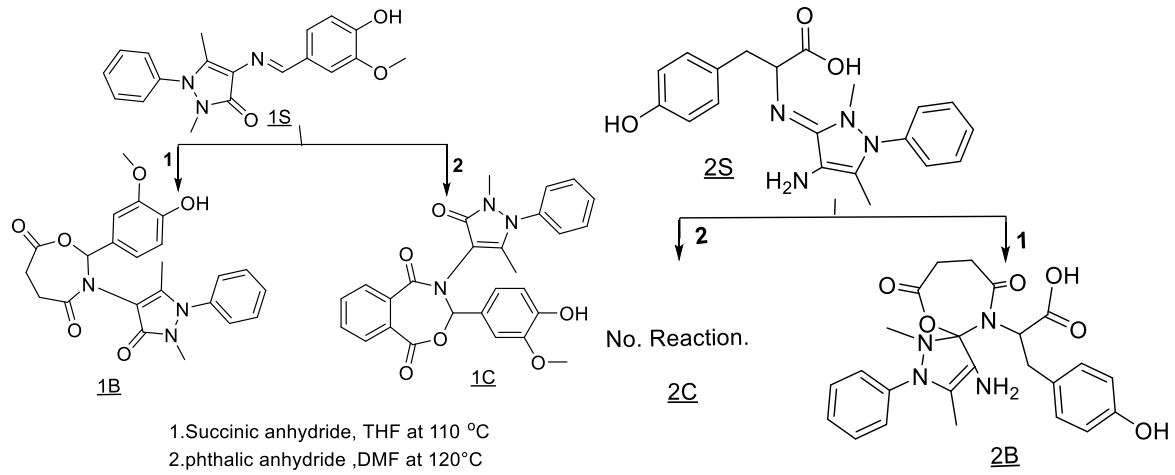


Figure 5 .Interaction model for the Amoxicillin with S. aureus ((PDB ID.3FYV).

Synthesis scheme 1 shows that oxazepine ring was obtained as a result of attacking the nitrogen atom in the imine group to the electrophilic group (Carbon of carbonyl group) in the anhydride. Heterocyclic (1,3-Oxazepane and 1,3-benzoxazepine) rings were characterized using identification methods including FTIR spectrum, melting point measurement,[1]H-NMR, and [13]C-NMR. Table 2 shows the chemical and physical data of the synthesized compounds, which in agreement with the calculated data obtained from the empirical formula of SBs and the hetero ring of each compound.



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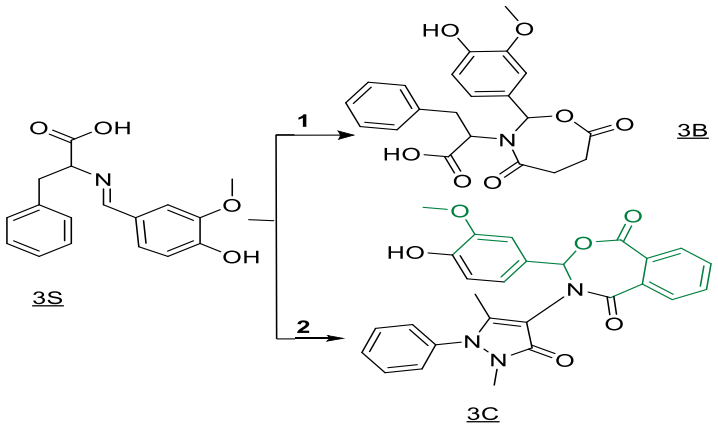

Scheme 1. Synthesis pathway of compounds1S-3C.

Spectroscopic study FT-IR spectrum.

The IR frequencies of SBs and the new heterocyclic compounds are reported in Table 2. The FT-IR spectra of SBs (1S-3S) show particular bands at 1622, 1619, and 1676 cm^{-1} respectively related to the absorption of azomethine (CH=N) groups[32]. These groups are not participating in 1,3- oxazepane or 1,3-oxazepine ring derivatives (1B-3C). The IR spectra of compounds 1B-3C show specific bands at 1703, 1791, and 1710 cm^{-1} respectively related to the absorption of C=O Lactam groups [32]. Figure 6. Shows the spectra of 3S. All compounds were characterized by FT-IR in Table 2; CHN analysis in Table 3, and the calculated data for the compounds (1B-3C) are consistent with the experimental data.

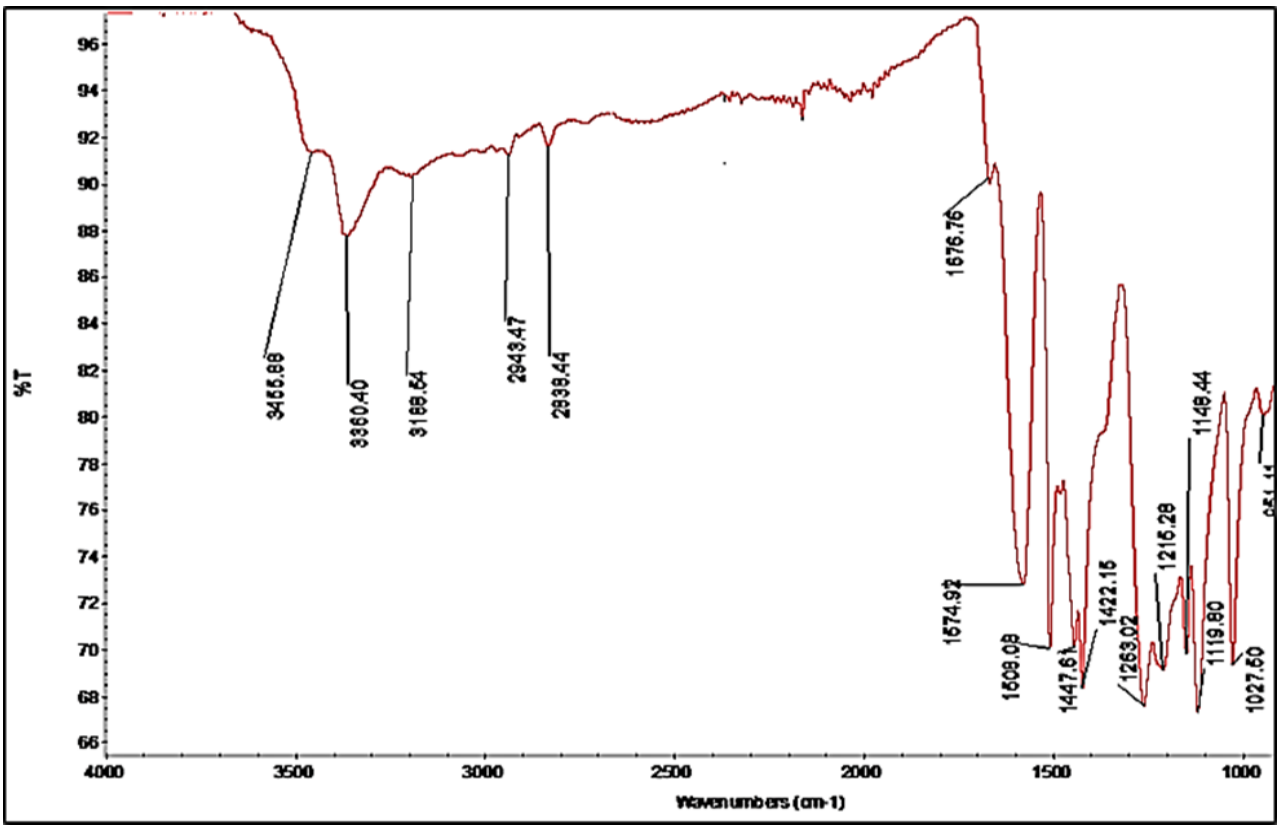

Figure 6. FTIR spectrum of compounds 3S.

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^{1}H-NMR Spectral Analysis

^{1}H-NMR spectrum of 1,3-Oxazepine (1B) in DMSO –d_6 is given in Fig. 7. The signals obtained at 6.8 - 7.6 (m, 8H, benzene), the signal at δ 2.27ppm (s, 3H, CH_3), at 2.7 ppm as shows the signal in a region of δ 2.97 ppm characteristic for the CH_2 in the ring of oxazepane, and 9.46 ppm (s, 1H, -OH). The ^{1}H-NMR spectrum of 1,3-Oxazepane (2B) in DMSO – d_6 is given in Fig. 8. The signal obtained at 2.3 (s, 3H, CH_3) in pyrazole, the signal at δ 2.76ppm (s, 3H, N -CH_3), the signals obtained at 6.8 -7.6 (m, 9H, benzene). All signals proton of compounds (1B-3C) are shown in the experimental part[23].

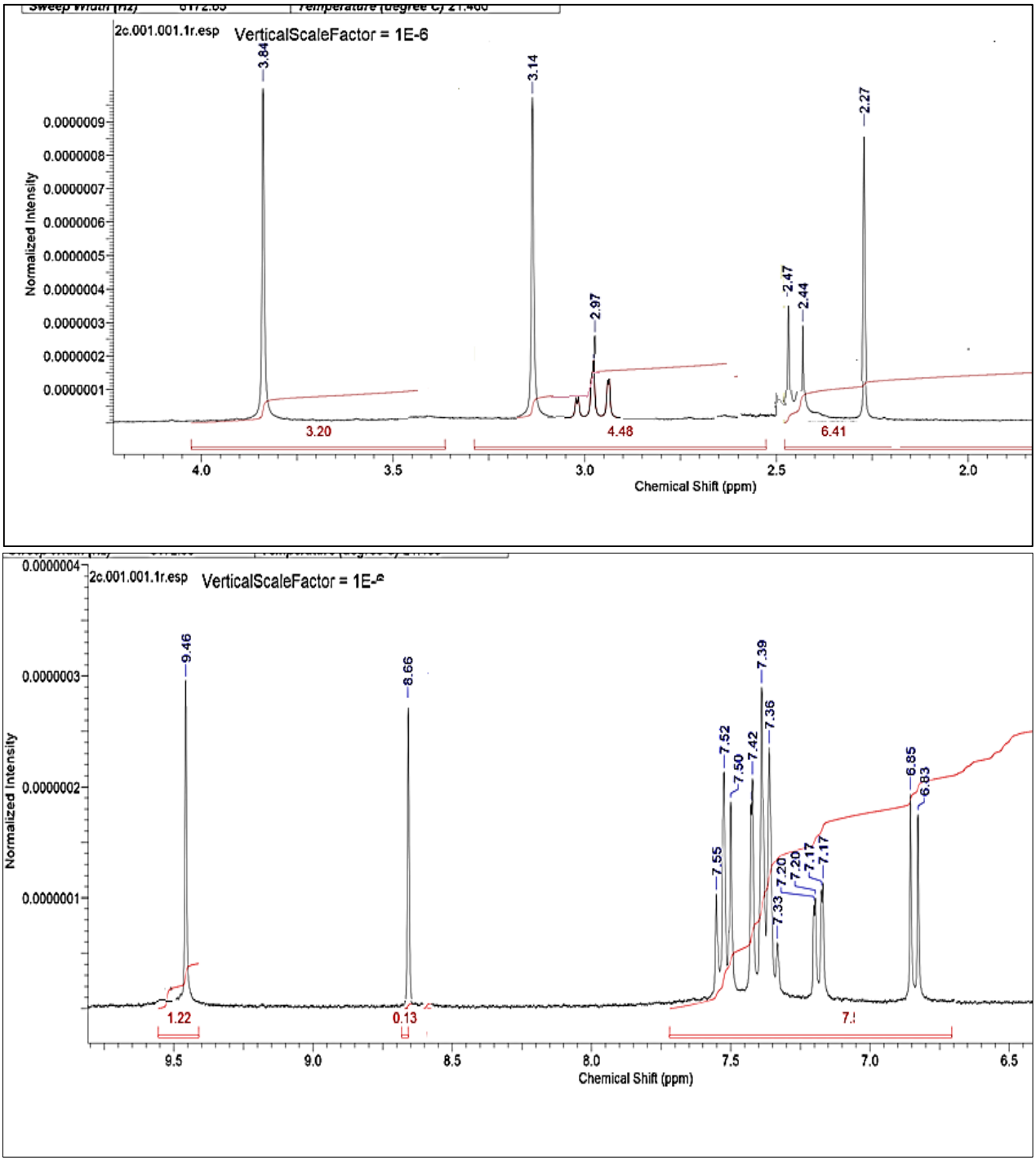

Figure 7. ^{1}H-NMR spectra of 1B.

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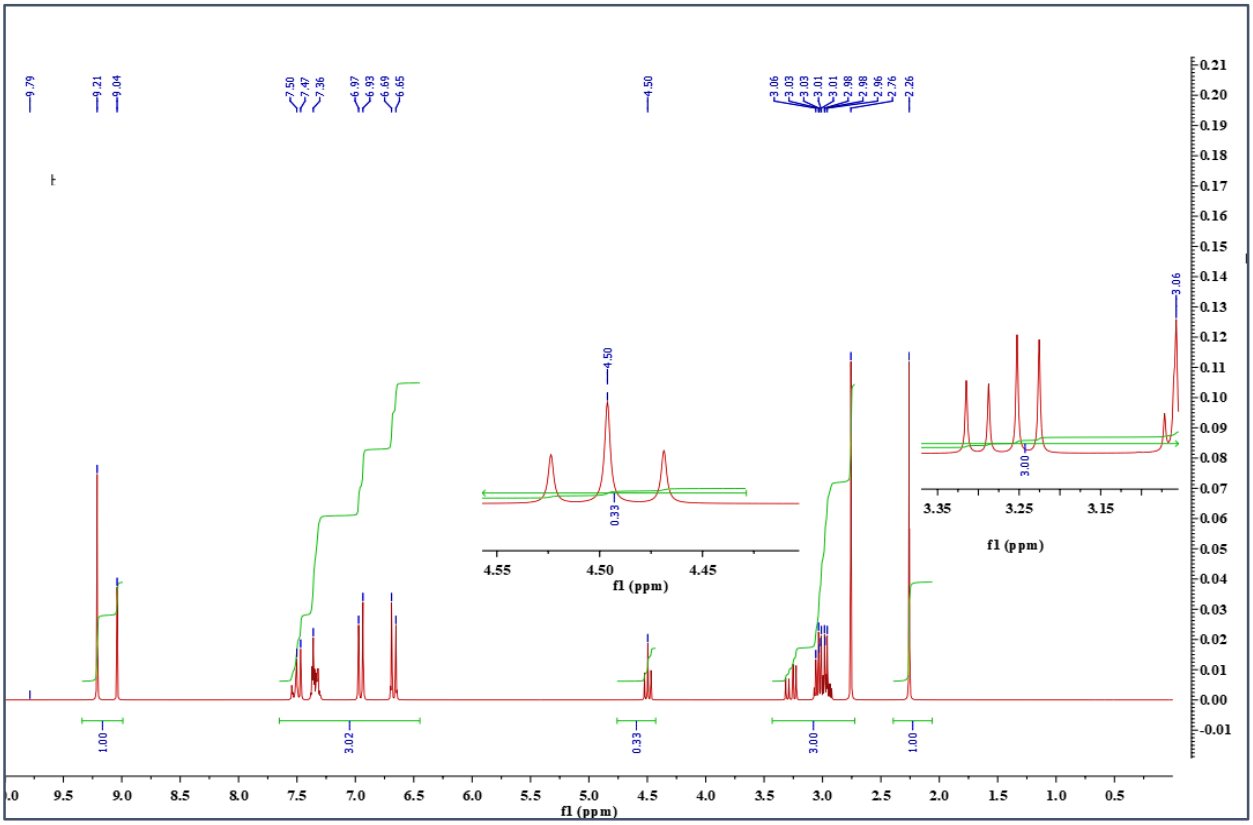

Figure8. ^{1}H-NMR spectra of 2B.

Table 2. FT-IR data of compounds (1S-3C).

Comp.	Ar-O-H	C-Hstr: Ar	(C-H Aliph)	C=Ostr.	(C=C,Ar)	C=N	Other
1S	3369	3061	2962	-	1578	1622	1730(C=O), 1486(N-CH_3)
2S	3310	3168	2949	-	1416-1463	1619	1729(C=O)
3S	3330	3180	2943	-	1478-1524	1676	-
1B	3160	3000.7	2930	1703	1573,1511	-	1484(N-CH_3), 1263(C-O)
2B	-	3210	2843	1791	1522	-	1288(C-O oxazepane)
3B	3356	3274	2953,2933	1633	1584-1487	-	1363(C-O oxazepane)
1C	3163	3105	2290,2792	1781	1514	-	1724(C=O),1282(C-O)
3C	3379	3101	2972	1710	1431-1590	-	1269(C-O)

Table 3. Characterization of the prepared compounds.

No.	M. W(g.mol^{-1})	Color	Yield(%)	%(Found)Calc.			m.p.(°C)
				C	H	N	
1S	337.3	yellow	82	(67.53)67.64	(5.49)5.68	(12.49)12.46	210
2S	350.4	white	78	(67.23)68.55	(5.97)6.33	(15.05)15.29	126
3S	299.3	yellow	88	(67.89)68.22	(5.49)5.72	(4.71) 4.68	185
1B	473.4	white	62	(63.68)63.15	(4. 9)5.30	(9.38) 9.61	165
2B	450.5	white	28	(63.78)63.99	(5.02)5.82	(12.76)11.44	191
3B	399.4	white	41	(63.54)63.14	(5.41)5.30	(3.29)3.51	187
1C	485.1	brown	34	(65.9)66.8	(4.76)4.78	(8.82)8.66	173
3C	680.7	green	78	(67.04)67.05	(5.21)5.33	(3.96)4.12	189

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^{13}C-NMR Spectral Analysis

The ^{13}C-NMR spectrum of 2B showed a diagonal signal of 170.2 and 173.04(two carbons, C=O ring oxazepane). While, the ^{13}C-NMR spectrum of compound 3C displays signals at 111 -150 ppm (Aromatic C) and diagonal signal at 170.8 ppm, and 174 ppm (two carbon of carbonyl C=O, and ring benzoxazepine). The spectrum of 3B showed a diagonal signal of 171 and 173(two carbons, C=O ring oxazepane), 175.9 (COOH), shown in Fig. 9.

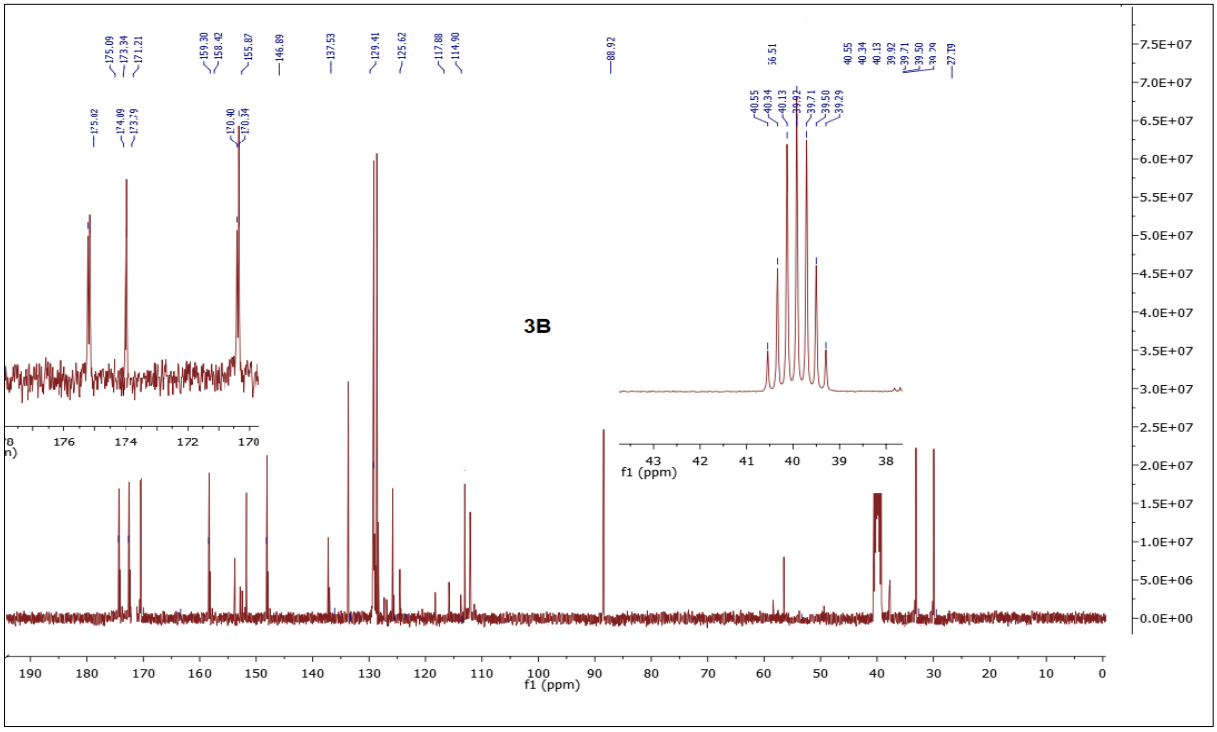

Figure 9. 1,3-Oxazepane ring ^{13}CNMR signals of 3B.

Antioxidant Activity.

The antioxidant activities s of compounds (1B -3C) are determined using DPPH free radical[33,34]. This method was based on the loss of the violet color of the DPPH radical after the reaction with tested samples. The activity of the heterocyclic compounds against ascorbic acid at various concentrations is presented in Table 4. The following points have been noticed.

Table 4. Antioxidant activity of compounds (1B-3C) by DPPH method.

Com. code	Concentration (µg /mL)	
	500	**100**
1B	90.01	17
1C	88.93	78.63
2B	81.53	34.23
3B	73.03	19.76
3C	45	15
Ascorbic acid	99.74	99.5

The results pointed to all compounds that have activity. The compounds 1B and 3C at a concentration of (100 µg/mL) and (500 µg/mL) were found to be a moderate activity, while (100 µg/mL) of 1C was found to be strong antioxidants.

Antibacterial activity

The prepared compounds (1B-3C) were examined for antibacterial activity against two types of bacteria (*S. aureus, and E. coli*) at the concentration of (10^{-7}-10^{-11} µm inhibition) by diffusion method in Mueller-Hinton agar medium[34-36]. After one day, a zone appeared around each disc. The test results are presented in Table 5. The inhibitory effects of the prepared oxazepine were significantly higher. Table 5 shows the antimicrobial activities of the (1B-3C) compounds. The DMSO was used as a control substance[37].

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Table 5. The antimicrobial activities of (1B-3C).

Comp. code	*S. aureus*			*E. coli*		
	1×10^{-7} µM	**1×10^{-9} µM**	**1×10^{-11} µM**	**1×10^{-7} µM**	**1×10^{-9} µM**	**1×10^{-11} µM**
1B	-	-	18	15	20	18
2B	12	17	16	15	11	7
3B	30	23	21	19	15	20
1C	12	-	-	10	-	-
3C	18	10	-	10	-	-
Amoxicillin	-	-	-	13	14	11
DMSO	-	-	-	-	-	-

Note: slight activity (5-10 mm), moderate activity (11-15mm), and high activity (< 15mm). (—): no activity.

Conclusion

The molecular docking study of oxazepine and oxazepane derivatives with proteins (4H2M and 3FYV) revealed that compounds have good interactions in a favorable pose with proteins, which was explained by the lowest binding energy, and strong bond length with active sites of proteins. Moreover, it can be concluded that some oxazepane and oxazepine derivatives could be used in the development of drugs through the design and modification of compounds to make them more potent. Thus, Novel Schiff's bases (SBs) have been synthesized by condensation of 4-amino antipyrine with tyrosine or vanillin. The oxazepane and oxazepine rings have been synthesized then by cyclo-addition reactions of the prepared SBs with anhydride. They have been characterized by elemental analysis CHN, FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The results of these investigations supported the suggested structures of all compounds. The heterocyclic [1B-3C] are important chemicals that can be considered a primary substance of the drugs, especially when they are antioxidants and antibacterial. However, the results of the present study were limited by applications. The author's aims to study these compounds in animals in the future.

Acknowledgment

The authors are thankful to the University of Waist for the help across work and study facilities.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Waist.

Authors' Contribution Statement

A. G. S. contributed to the design, the analysis of the results, and the writing of the manuscript. J. K. A. and Z. R. K. contributed to the implementation of the research, the analysis of the results, and writing of

the manuscript. All authors have read and agreed to the final draft of the manuscript.

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Baghdad Science Journal

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الالتحام الجزيئي في تحضير وتقييم النشاط كمضادات أكسدة ومضادات بكتيرية لمشتقات الاوكسازيبان و وبنزواوكسازيبين الجديدة

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الخلاصة

يعد الالتحام الجزيئي طريقة في مجال المحاكاة الجزيئية يمكن خلالها تحديد الاتجاه الأمثل والمفضل لارتباط جزيء معين بجزيء آخر عندما يكونان معقد مستقر. و من معرفة الالتحام يمكن التنبؤ بقوة الارتباط أو تقارب الارتباط المفضل بين الجزيئين. في هذه الدراسة ، تم تقييم سلسلة من المركبات المحضرة ومعرفة وضعيات الربط والتفاعلات المحتملة ومواقع الربط المستهدفة. حضرت بعض مشتقات 1، 3-أوكسازيبان و 3،1-بنزوكسازيبين من ثلاثة مركبات لقواعد شيف (3S-1S). تم تفاعل المركبات مع (3S-1S أنهيدريد السكسينيك و أنهيدريد الفثاليك للحصول على مشتقات 3،1- أوكسازيبان و 3،1-بنزوكسازيبين(3C-1B). شخصت المركبات المحضرة من خلال طرق تحليل العناصر و الاشعة تحت الحمراء FT-IR و وطيف الرنين النووي المغناطيسي ^{1}H-$^{13}CNMR$ تم تسجيل النشاط المضاد للبكتيريا للمركبات (1 B-3C) ضد بعض البكتيريا المعزولة بما في ذلك البكتيريا سالبة الجرام (المكورات العنقودية الذهبية) و موجبة الجرام (البكتريا القولونية) مع استخدام الاموكسيلين كدواء مرجع. أظهرت المركبات(1B-3C) قيمًا جيدة مثل فعاليتها من المتوسطة الى المرتفعة ضد سلالات البكتيريا المستخدمة. علاوة على ذلك ، تم تقييم النشاط المضاد للأكسدة للمركبات المصنعة (1B-3C) باستخدام 2،2-.ثنائي فنيل 1-1-بيكريل هدرازين و أظهرت النتائج أن المركبات لها أعلى القيم كقانص جذور حرة .

الكلمات المفتاحية: مضادات اكسدة، بنزواوكسازبين ،الفعالية، الارساء، الاوكسازبان.