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Synthesis, Characterization, Biological Activity, and Molecular Docking Study of Some New Sulfamethoxazole Derivatives.

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Abstract

In this paper, new Sulfamethoxazole derivatives were studied in order to improve the treatment efficiency of this medicinal compound. Six compounds of Schiff bases were prepared via an intermediate reaction of Mannich bases. Two derivatives of thiadiazine heterocyclic compound were prepared as well. Characterization and the stereo conformations of the synthesized compounds were determined using ^{1}H-NMR, ^{13}C-NMR, and FT-IR techniques, in addition to elemental analysis and melting point measurements. The biological activity of the produced compounds against five types of bacteria including (*Staphylococcus aureus Escherichia coli, Klebsiella pneumonia Salmonella,* and *Proteus*) was investigated. The obtained results showed that biological activities against bacteria vary from high activity to not active. Moreover, (PyRx) software was utilized for the calculation of the binding affinity (kcal/mol) for the prepared compounds with proteins FYV (*S. aureus*), 4H2M (*E. coli*), 6P4T (*Salmonella*). The highest linking values with proteins were found to be (-9.4) with 4H2M and (-7.8) with 6P4T, whereas the lowest values were found (-5.3) with FYV. On the other hand, the results revealed that amino acids located around the prepared compound, which were linked through hydrogen bonding or charged and (aryne-aryne) hydrophobic interactions were also determined. In addition, the three dimensions' shape, which explains the linkage way between proteins and the synthesized compounds, was stated. By recognizing the characteristic features of amino acids, which surround these compounds, the electronic densities of the compounds were also reported.

Keywords: Bacteria, Insilico, Mannich bases, Molecular docking, Sulfamethoxazole.

Introduction

Sulfamethoxazole (Sulf), 4-amino-N-(5-methylisoxazol-3-yl) benzene sulfonamide is a drug derivative of the sulfonamide compound. It is exploited as an inhibitor for the growth of various sorts of bacteria including *E. coli, Klebsiella, Enterobacter, Morganella morganii, Proteus mirabilis, and Proteus Vulgari.* Sulfamethoxazole works together with trimethoprim to prevent folic acid formation, which stops the growth and reproduction of bacteria[1,2]**.** These therapeutic drugs have made significant contributions to increase average human life expectancy[3,4]. Chemists have a significant role in improving drug industry by exploiting novel methods to prepare original physiologically active compounds[5]. In recent years, researchers have carried out many works for synthesizing various sulfamethoxazole derivatives. These derivatives have been widely used in clinical

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medication as a pharmacological agent with a wide range of biological applications such as anti-cancer [3], antiviral agents[4], antifungal[5], herbicidal activities[6], mycobacterial[7,] and anti-tubercular [8]. The aim of the present work was to improve the efficiency of sulfamethoxazole via the synthesis of new sulfamethoxazole derivatives by exploiting the appropriate procedures to prepare physiologically active compounds. One of these is the Mannich reaction, which is a condensation reaction of different compounds. The Mannich reaction involved the condensation of aldehyde, amine, and compounds that have H-activity. For many years, The Mannich reaction has been an essential method for yielding molecules with desirable pharmacological characteristics[9,10]. The significant applications of these produced compounds have withdrawn researchers' attention accordingly; this led to extending their efforts in doing much research in this field of knowledge[11]. The scientific reports indicated that sulfonamides incorporated into Mannich bases have been displayed as remarkably effective antibacterial agents, and are less toxic than the parent sulfonamide[12-14]. On the other hand, both series of heterocyclic ring thiadiazine and of Schiff bases compounds are designed; and synthesized . The development of drugs is a process that aims to design safe and effective medications to improve life's quality and to reduce suffering to a minimum. Computational drug design methods minimize time and the cost needed for the drug designing process in comparison to traditional drug discovery methods [15-17]. Aims of this study to design safe and effective new Sulfamethoxazole derivatives and study molecular docking performed by using the PyRx software, which is an important tool for gaining an understanding of the binding interactions between a– ligand-protein then preparation of compounds and application in the laboratory.

Materials and Methods

Write Sulfamethoxazole was acquired from SDI in Iraq. All reagents and solvents were obtained from Sigma Aldrich, Germany. All the solvents used were purified before use. The Veego VMP-PM apparatus was utilized to measure melting points. To observe the reaction progress, a thin layer chromatogram (TLC) was carried out exploiting Merck silica gel 60 F254 and visualization by UV light, and the solvent used was ethyl acetate: benzene (1:3). Shimadzu 8400 S, Japan, was used to record the FT-IR spectra. ^{1}H-^{13}CNMR spectroscopic measurements were carried out using a 400 MHz NMR spectrophotometer at the College of Sciences, University of Basra. Micro elemental analysis CHN at the University of Tehran, Iran.

General procedure for the synthesis of Mannich bases (a, b).

To a solution of sulfamethoxazole (10 mmol) in absolute ethanol (10 mL), (10 mmol) of formalin was added directly. The acetophenone or piceol was then added drop by drop[18]. After that, the reaction mixture was stirred for 2 hours at room temperature. The reaction progress was monitored by TLC, using a mixture of (1:3) ethyl acetate and benzene. The resulting crude solids were recrystallized from ethanol, and then the obtained product was filtered and dried.

N-(5-methylisoxazol-3-yl)-4-((3-oxo-3-phenylpropyl) amino) benzene sulfonamide. a.

The physical data were given in Table 1. Yield: 83%, R_f = 0.36; MP. 110-111°C; FTIR (KBr) (cm^{-1}). 1374 (C-N), 1634(C=O), 3157-3046 (CH, Ar-H), 3383(NH); ^{1}H- NMR (DMSO, 400 MHz), δ (ppm): 2.25 (s, 3H, CH_3), 2.59 (m, 2H, -CH_2C=O), 3.43 (m, 2H, CH_2NH), 4. 55 (s, 1H, NH), 6.11(s, 1H, CH, oxazole), 6.61-7.98 (m, 9H, Ar-H), 10.97 (s, 1H, -$NHSO_2$); ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 198(C=O), 31.8 (CH_2), 26.5(CH_2NH), 12.1(CH_3), 96 and 170 (carbon in oxazole ring), 112-137.4 (aromatic carbon), 198.3 (carbonyl). Elemental Analysis: Calc: C, 59.21; H,4.97; N, 10.90. Found: C, 60.01; H, 4.91; N, 10.93.

4-((3-(4-hydroxyphenyl)-3-oxopropyl) amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide. **b.**

The physical data were given in Table 2. Yield =88%, R_f = 0.52; Mp.162-163 °C; FT-IR: 2936cm^{-1}(Aliphatic carbon), 3626cm^{-1}(OH) ^{1}H- NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.28 (s, 3H, CH_3), 3.53(m, 2H, CH_2C=O), 4.01(s, 2H, CH_2NH), 6.05(s, 1H, NH), 6.37(s, 1H, CH in oxazole), 6.7-7.77(m, 9H, Ar-H), 9.1(s, 1H, OH). ^{13}C-NMR (DMSO, 400 MHz), δ (ppm): 45.31(CH_2), 39.5 (CH_2NH), 17.25 (CH_3) ,92.01and 95 (two carbons in oxazole), 191.5

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(C=O), 114-139 (aromatic carbons). Elemental Analysis: Calc: C, 56.85; H, 4.77; N, 10.47; found: C,57.01; H,4.71; N,11.01.

General procedure for reduction of ketones 1a, 1b without additional solvent.

(Clemmensen reduction without Hg)

To a mixture of ketones (a & b) (1 mmol) and zinc dust (3 mmol), a mixture of 20 mL of concentrated HCl and 20 mL of distilled water was added. The obtained mixture was then refluxed overnight. The reaction progress was monitored by a thin layer of chromatography (TLC). At the end of the reaction, the mixture was extracted with CH_2Cl_2. The solvent was eliminated via the evaporator, and the residue was purified by re-crystallization.

General procedure for preparation of compounds (2a, 2b)

To a solution of compounds (1a &1b) (1 mmol) in DMF (20 mL), chloroacetyl chloride (3 ml, 3 mmol) was added dropwise. The reaction mixtures were refluxed for 8 hours. Then, the produced mixture was cooled, filtered, dried, and recrystallized from ethanol. Tables. 1 and 2 show the spectroscopic measurements data (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of compounds 2a and 2

General procedure for preparation of compounds (3a and 3b)

A mixture of (2 ml, 2 mmol), 99.5% Hydrazine hydrate with (1 mmol) compounds (2a and 2b) were refluxed for 6 hours. The reaction was monitored by TLC. The produced precipitate was collected, washed, and recrystallized from ethanol. Tables. 1 and 2 show the spectroscopic measurements data (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of compounds 3a and 3b

General procedure for preparation of compounds Schiff bases ($3a_i$-$3b_{ii}$)

To a stirred solution of aldehyde derivatives (5mmol) in ethanol (10 mL) for 25 min at room temperature, a few drops of GAA were added. (5 mmol) of compound 2a or 2b in ethanol (10 mL) was added dropwise, and the mixture was refluxed for 4 hours. The development of the reaction was followed by TLC with an eluent solution of ethyl acetate: benzene (1:3) mixture. Subsequently, the mixture was evaporated under reduced pressure to remove solvents. The precipitate was filtered and recrystallized. The reactions yielded compounds 3ai-3bii. The produced compounds were dried at 70 ^{o}C, and then the melting point was measured. Tables 1 and 2 show the spectroscopic measurement data (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of compounds $3a_i$-$3b_{ii}$.

General procedure for preparation of compounds (4a and 4b)

To a solution of compounds (3a and 3b) (1 mmol) in ethanol (20 ml), (2.73g, 1 mmol) of p-chloro phenyl isocyanate was added dropwise and refluxed for 6 hrs. The reaction was monitored with TLC. The produced mixture was filtered, dried, and re-crystallized from ethanol. Tables 1 and 2 show the spectroscopic measurement data (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of compounds 4a and 4b.

General procedure for preparation of compounds (5a and 5b)

A small amount of compound (4a or 4b) (1 mmol) was mixed carefully with ethyl acetoacetate (1mmol) and ethanol (15 mL) was mixed carefully. The mixture was refluxed for 3 hours. The produced mixture was concentrated and cooled with crushed ice to form a precipitate. The formed precipitate was then filtered, dried, and re-crystallized from ethanol. Tables 1 and 2 show the spectroscopic measurements data (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of compounds 5a and 5b.

Antimicrobial activity

The diffusion plates technique in disc-agar was utilized for testing compound efficacy against five strains of bacteria (*Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Salmonella, and Proteus*), which were obtained from the research laboratory, College of Science, Wasit University. These bacteria strains were grown in an incubator at 37 ^{o}C for 24 hrs. The inhibition zoom mm) was exploited to determine antibacterial activity after incubating the sample for 24 hours. On the other hand, three different doses of the synthesized chemicals were prepared by diluting them in dimethyl sulfoxide (DMSO) with concentrations of [50, 100, and 200 g/mL]. The biological activity of these doses was compared to Sulfamethoxazole activity. Whatman (no.3), filter paper discs (mm), were impregnated with 20 ml of each of the prepared diluted solvents, and the discs were stored at room temperature. Muller Hinton

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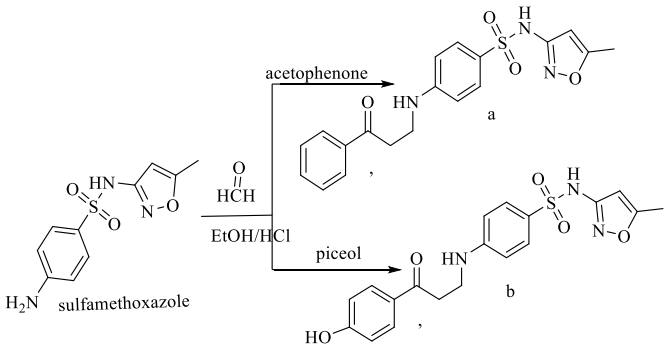
agar was covered with discs containing both natural and synthetic ingredients[19, 20].

Results and Discussion

Newly synthesized derivatives of sulfamethoxazole are presented in Schemes 1and 2. FT-IR frequencies of Schiff bases, mannich bases, and the new heterocyclic compounds are shown in Table1. FT-IR spectra of (a and b) compounds showed sharp peaks appearing at 1374 and 1385cm^{-1}, which are assigned to the presence of (-C-N-) groups in structures of compounds (a and b), respectively. These spectra also show the appearance of a single sharp peak (instead of double sharp peaks of NH_2 groups) at 3383, 3401 cm^{-1},which indicates the existence of just (N-H) groups in structures of a and b compounds, respectively. Moreover, the (C-H) aliphatic peaks are located between 2980 and 2700 cm^{-1}, which refers to the formation of the CH_2-CH_2-NH. FT-IR spectra of Schiff base ($3a_i$-$3b_{ii}$) show the absorption of azomethine (CH=N) groups listed in Table 1 On the other hand, FT-IR spectra of compounds (5a and 5b) show the disappearance of ν(-$NHNH_2$), and (CH_2) groups, that considered good proof of the formation of thiadiazine ring in compounds (5a and 5b). Table 1 shows all important vibrational for new compounds[21]. ^{1}H-NMR spectrums of compounds (a, $3b_{ii}$), show important characteristics of chemical shifts (DMSO, δppm) as listed in Table 3. ^{1}H NMR spectrum of compound a shows a signal at δ2.25 ppm due to (3H) in methyl group(CH_3), chemical shift seen at δ2.59 ppm due to (2H) in the CH_2C=O group[22]. A chemical shift was noticed at δ3.43 ppm due to (2H) in the CH_2NH group[22]. A signal appeared at δ 6.11 ppm due to (1H) of the oxazole ring and the region at δ 6.61-7.59 ppm due to aromatic protons, while a signal is assigned to a group ($NHCH_2$) at δ 4.86 ppm. The spectrum also shows a signal at δ 10.97 ppm belongs to (SO_2NH) as seen in Fig. 1. Fig. 3 shows the spectrum to ^{1}H-NMR of compound 5b as listed in Table 3. The ^{13}C-NMR spectrum of compound (a) is shown in Fig. 2, which displays signals of aromatic carbons at 111-136 ppm (aromatic carbons). Signals appeared at 26.9, and 19.3 ppm were assigned to (CH_2) groups, and signals were seen at 11.7 ppm due to (CH_3) group, and 96 ppm belonged to (HC=) group in heterocyclic. All signals of ^{13}C NMR of compounds are shown in Table 3. It displayed signals attributed to compound 5a that attached to thiadiazine moiety, (CH_3)group attached to is oxazole ring, for two-CH- groups of thiadiazine ring as shown in Table 4.



Scheme 1. Synthesis Mannich bases a and b.

Table 1. A comparison of experimental vibrational frequencies data (a-5b).

No.	υ (OH)	υNH	υC-H Hetro	C-H Aromatic	C-H Alpha.	υC-N	Others.
a	_	3383	3157	3111-3046	2971-2928	1677	C=O(1634),S-N(961)
$3a_i$	-	3331	3132	3073-3002	2965-2915	1593	C=O(1735)
$3a_{ii}$	-	3362	3142	3111-3008	2985-2926	1610	C=O(1712)
5a	-	3324	3131	3080-3002	2945-2915	1539	S-C(1165)
b	3526	3382	3154	3054	2936	1626	C-N934
3b	3541	3267	3171	3123-3019	2954	1604	C=O(1702),NH_2(3412)
$3b_i$	3528	3263	3155	3134-3001	2943	1604	C=O(1712)
$3b_{ii}$	3546	3245	3175	3094-3002	2935	1643	C=O(1732)
5b	3534	3415	3112	3088-3013	2939	1547	S-C(1143)SO_2 (1373)

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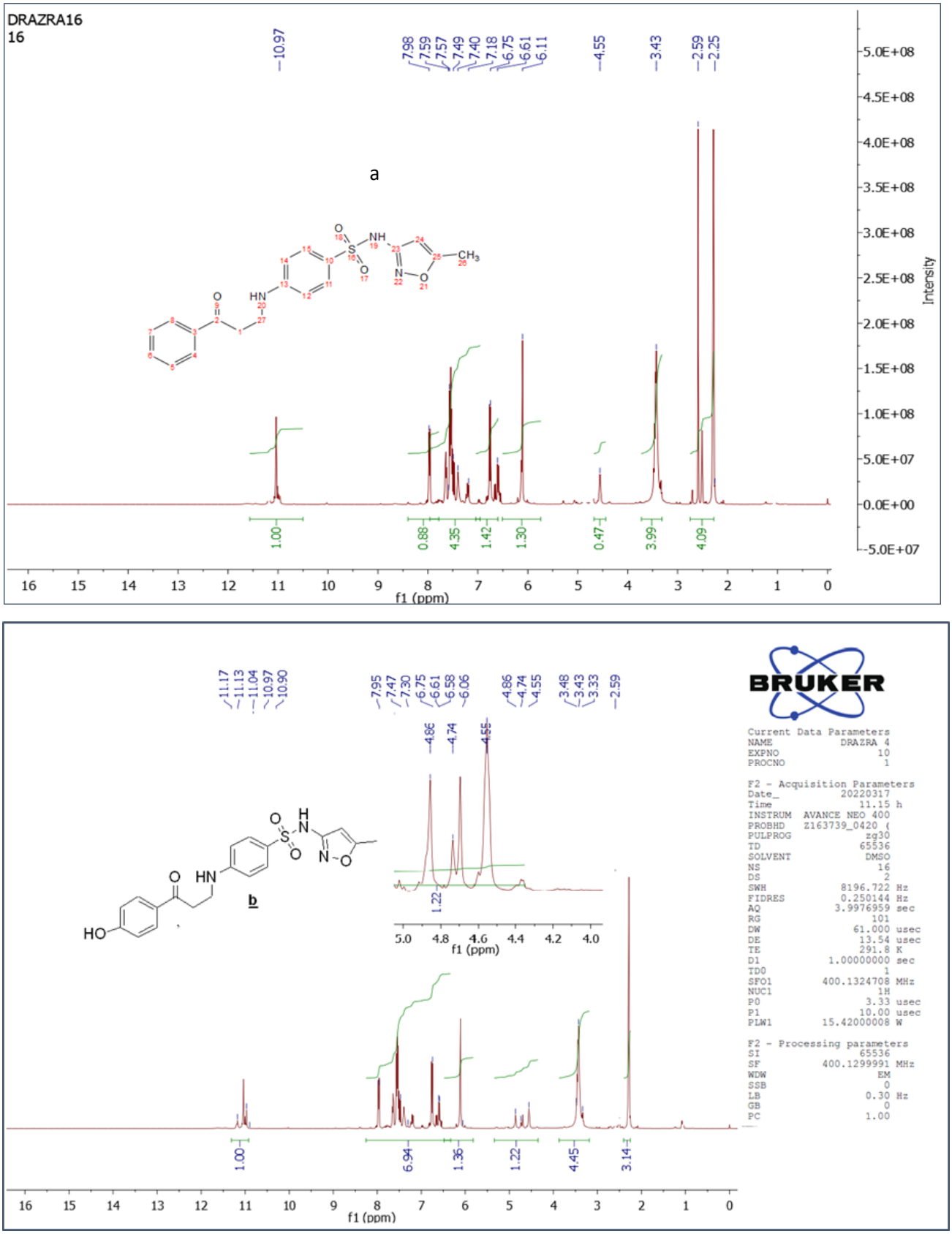

Figure 1. 1H NMR spectrum of compounds a and b.

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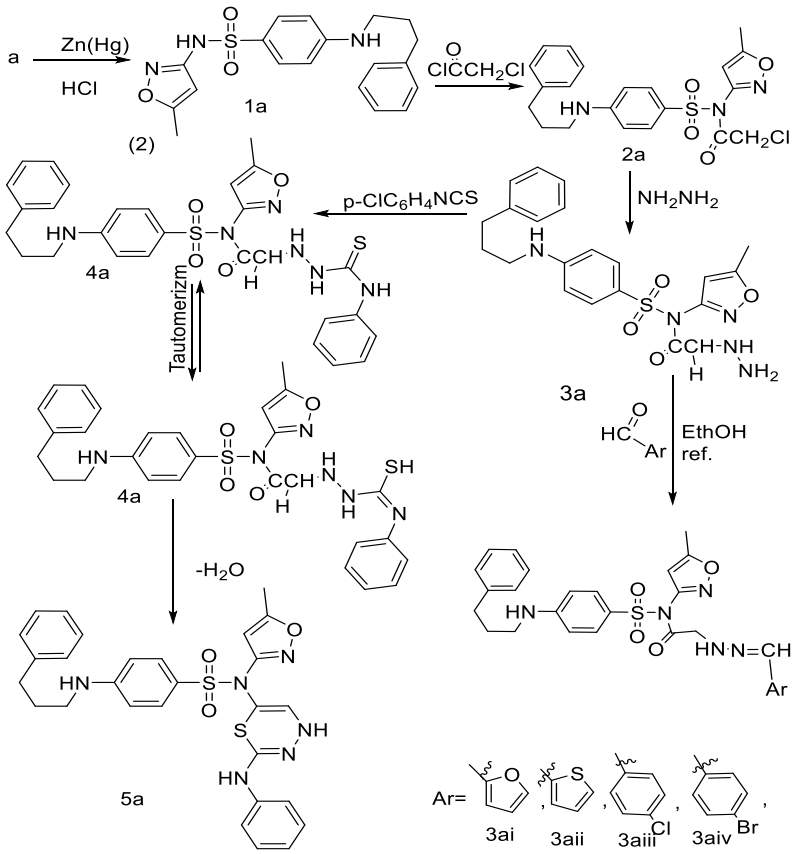

Scheme 2. Synthesis s sulfamethoxazole derivative of Schiff bases 3ai-3aiv and thiadiazine 5a

Table 2. ^{1}H and ^{13}C-NMR spectral data (δppm) for selected prepared compounds(1a-5b).

No.	Name	H-NMR	^{13}C-NMR
1a	N-(5-methylisoxazol-3-yl)-4-((3-phenylpropyl)amino) benzene sulfonamide.	2.3(s, 3H, CH_3), 1.9 (m, 2H,CH_2) , 3.52(t,2H, CH_2-NH), 3.21 (t,2H, CH_2-Ar), 7.24-7.81(m,9H,Ar-H).	17.21 (-CH_3), 39.1,33.5 and 46.7(3CH_2), 113.5-141(aromatic-carbon).
5a	N-(5-methylisoxazol-3-yl)-N-(2-(phenylamino)-4H-1,3,4-thiadiazin-6-yl)-4-((3-phenylpropyl)amino) benzene sulfonamide.	2.61 (s, 3H, CH_3), 2.03 (m, 2H, CH_2), 5.54 (s, 1H, C-H thiadiazine), 6.67-7.51 (m, 14H, Ar-H), 9.13(s, 1H,NH-Ph), 10.61(s, 1H, NH thiadiazine).	12.7 (-CH_3), 48.5(-CH_2NH). 119-147 (aromatic carbon). 157 (Carbon in thiadiazine).
3a$_{i}$	2-(2-(furan-2-ylmethylene) hydrazinyl)-N-(5-methyl isoxazol-3-yl)-N-((4-((3-phenylpropyl)amino) phenyl) sulfonyl)acetamide	2.12 (s, 3H, CH_3), 2.01 (m, 2H, CH_2), 3.91(t, 2H, CH_2-NH), 3.1 (t, 2H,CH_2-Ar), 8.14 (s, 1H, CH=N).	14.8(-CH_3),29-44.3(4CH_2). 110.2-131.6(aromatic carbon). 147, 149.1(furan). 173.4(carbonyl(C=O)).
3a$_{ii}$	N-(5-methylisoxazol-3-yl)-N-((4-((3-phenylpropyl) amino)phenyl)sulfonyl)-2-(2-(thiophen-2ylmethylene) hydrazinyl)acetamide	2.52 (s, 3H, CH_3), 2.01 (m, 2H, CH_2), 3.26 (t,2H, CH_2-NH), 2. 3(t, 2H,CH_2-Ar), 8.53 (s, 1H, CH=N).	17.4(-CH_3). 29.3-44.2(4CH_2). 112.1-129.4(aromatic carbon). 170.3 (carbonyl(C=O)).
3a$_{iii}$	2-(2-(4-chlorobenzylidene) hydrazinyl)-N-(5-methyl isoxazol-3-yl)-N-((4-((3-phenylpropyl)amino) phenyl)sulfonyl)acetamide	2.01(s, 3H, CH_3), 1.91 (m, 2H, CH_2), 3.43 (t,2H, CH_2-NH), 2. 61(t, 2H,CH_2-Ar), 8.01 (s, 1H, CH=N).	16-47.2 (aliphatic carbon), 119-134 (aromatic carbon). 176.1 (carbonyl(C=O)).
3a$_{iv}$	2-(2-(4-bromobenzylidene) hydrazinyl)-N-(5-methyl	2.41(s, 3H, CH_3), 2.17 (m, 2H, CH_2), 3.71 (t,2H, CH_2-NH), 7.35-7.78(m, 13H,CH_2-Ar),	19.3-42.5(aliphatic carbon), 110-137.6(aromatic carbon).

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	isoxazol-3-yl)-N-((4-((3-phenylpropyl)amino) phenyl)sulfonyl)acetamide	8.51 (s, 1H, CH=N).	171.3(carbonyl(C=O)).
2b	4-((3-(4-hydroxyphenyl) propyl)amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide	2.1(s, 3H, CH_3), 1.87 (m, 2H, $CH_2\underline{CH_2}$-CH), 3.81 (t, 2H, CH_2-NH), 2.91 (t, 2H,CH_2-Ar), 7.03-7.48 (m, 8H, H-Ar), 9.3(s, 1H, OH-Ar)	19.3(-CH_3), 35.2, 37.51 and 49.1(3CH_2). 112.6-143(aromatic carbon).
5b	4-((3-(4-hydroxyphenyl) propyl)amino)-N-(5-methyl isoxazol-3-yl)-N-(2-(phenyl amino)-4H-1,3,4-thiadiazin-6-yl)benzene sulfonamide.	2.36 (s, 3H, CH_3), 5.39 (s, 1H, C-H thiadiazine), 6.55-7.56 (m, 13H, Ar-H), 9.05 (s, 1H, OH-Ar), 10.29 (s, 1H, NH-Ph), 10. 9 (s, 1H, NH thiadiazine).	18-49.2 (aliphatic carbon), 119.1-150(aromatic carbon). 156 (Carbon in thiadiazine).
3b$_i$	2-(2-(furan-2-yl methylene) hydrazinyl)-N-((4-((3-(4-hydroxyphenyl)propyl) amino)phenyl)sulfonyl)-N-(5-methylisoxazol-3-yl) acetamide.	2.6 (s, 3H, CH_3), 1.93 (m, 2H, CH_2), 3.72(t, 2H, CH_2-NH), 3.48 (t, 2H,CH_2-Ar), 6.8-7.65(m, 8H, H-Ar) , 7.83(d, 1H, furan), 8.42(s, 1H, CH=N)	13.61(-CH_3). 26.1, and 39.7 (3CH_2). 114-136 (aromatic-carbon). 146,143.6(furan). 177.1(carbonyl(C=O)).
3b$_{ii}$	N-((4-((3-(4-hydroxy phenyl)propyl)amino) phenyl)sulfonyl)-N-(5-methylisoxazol-3-yl)-2-(2-(thiophen-2-ylmethylene) hydrazinyl) acetamide	2.42 (s, 3H, CH_3), 16.8 (m, 2H, CH_2), 3.41(t, 2H, CH_2-NH),2.47 (t, 2H,CH_2-Ar), 8.63 (s, 1H, CH=N).	17.8(-CH_3), 26.5, 35.1, and 42.3(3CH_2). 116-137(aromatic carbon). 176.1(carbonyl(C=O)).

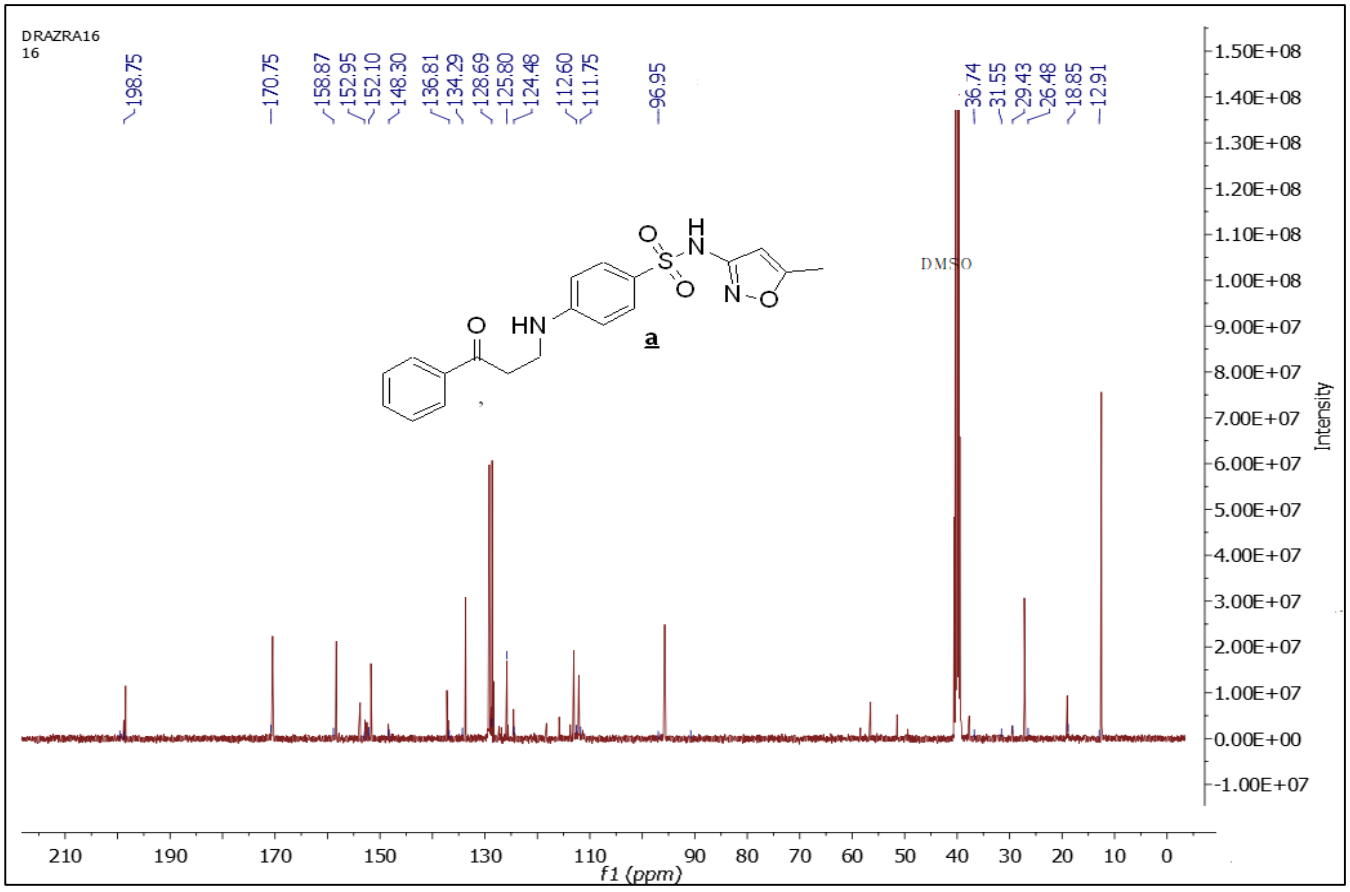

Figure 2. ^{13}C-NMR spectrum of compound a.

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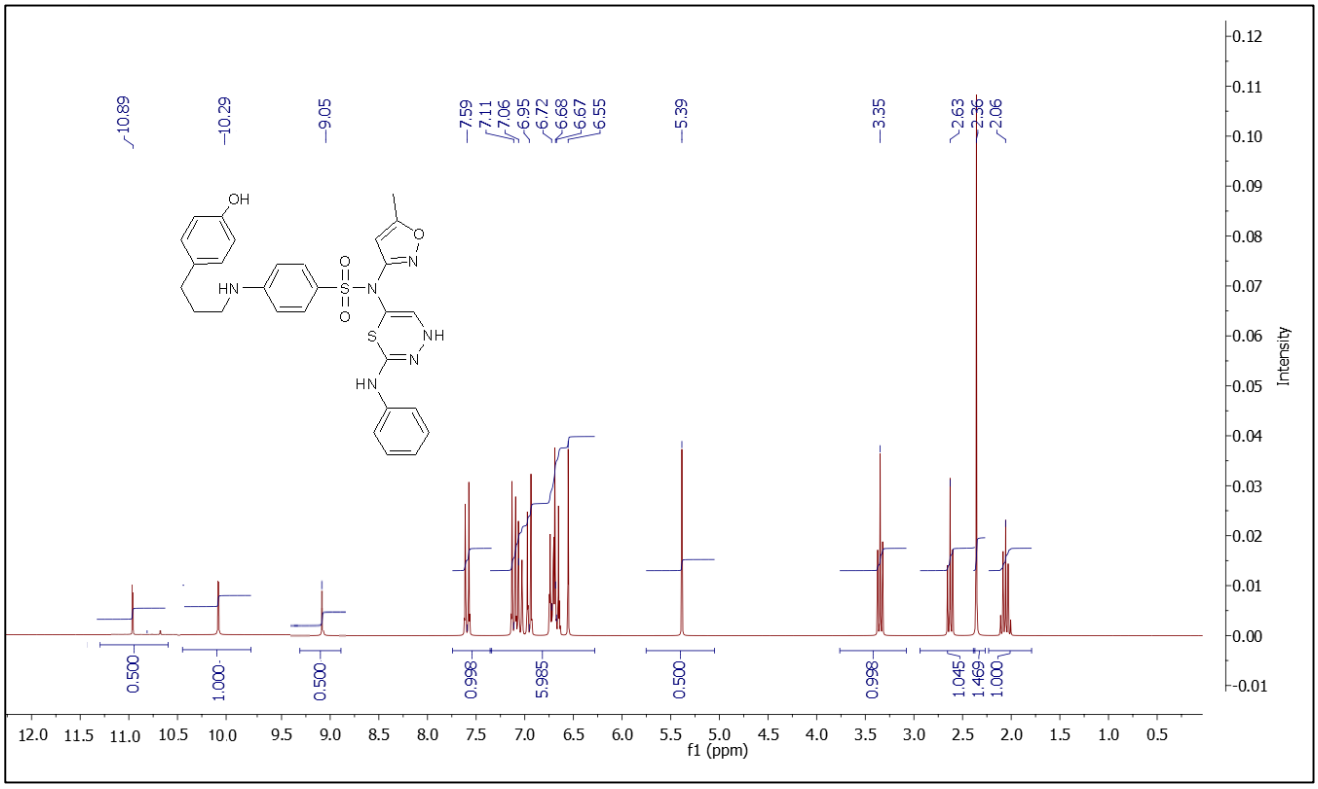

Figure 3. ^{1}H-NMR spectrum of compound 5b.

Table 3. CHN analysis data and physical properties of selected prepared compounds.

No.	Mol. Formulas	Yield (%)	MP. °C.	Color	Solvent re-cryst.	Calc. (Found)
1a	$C_{19}H_{21}N_3O_3S$	67	116	White	Ethanol	C,61.44(60.32); H, 5.709(5.60); N,11.31(10.64)
5a	$C_{28}H_{28}N_6O_3S_2$	68	153	Deep yellow	Ethanol	C,59.98(60.02); H,5.03(5.21); N, 14.99(14.77)
3a$_i$	$C_{26}H_{27}N_5O_5S$	43	139	yellow	Ethanol	C,59.87(59.7); H, 5.22(4.97); N, 13.43(13.07)
3a$_{ii}$	$C_{26}H_{27}N_5O_4S_2$	62	143	brown	Ethanol	C, 58.08(57.6); H, 5.06(4.86); N, 13.03(12.97).
3a$_{iii}$	$C_{28}H_{28}ClN_5O_4S$	67	181	Light yellow	Ethanol	C,59.41(59.03); H, 4.99(4.37); N, 12.37(11.79).
3a$_{vi}$	$C_{28}H_{28}BrN_5O_4S$	72	187	yellow	Ethanol	C,55.08(53.98);H,4.62(4.52); N, 11.47(11.04).
2b	$C_{19}H_{21}N_3O_4S$	57	174	White	Ethanol	C,58.90(58.63);H,5.46(4.98); N,10.85(10.17)
5b	$C_{28}H_{28}N_6O_4S_2$	71	206	Light brown	Ethanol	C,58.32(57.28); H, 4.89(4.01); N, 14.57(14.10)
3b$_i$	$C_{26}H_{27}N_5O_6S$	43	183	Deep brown	Ethanol	C,58.09(58.62);H,5.06(5.36); N,13.03(12.82).
3b$_{ii}$	$C_{26}H_{27}N_5O_5S_2$	54	191	Light yellow	Ethanol	C,56.40(57.07);H,4.92(5.03); N,12.65(12.12).

Antibacterial Activity

Table. 5 exhibits the outcome of antimicrobial activity versus three strains of Gram-positive bacteria (*Salmonella*, *Staphylococcus aureus, and Proteus*), and two strains of Gram-negative bacteria (*Escherichia coli and Klebsiella*) confronted with Sulfamethoxazole as the control. Outcomes of compounds a,b,5a,5b, 3a$_i$, 3a$_{ii}$, 3b$_i$, and 3b$_{ii}$ showed excellent bioactivity against *E. coli*, *staphylococcus*

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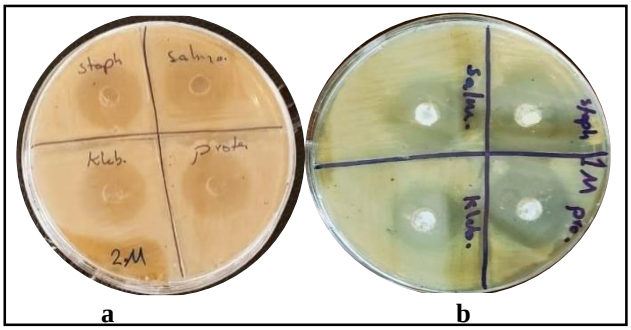
aureus, and *proteus* with a concentration of 3 $mg.ml^{-1}$. Also, compounds a, and be inhabited a good activity against *salmonella*[24]. In contrast, a weak action was noticed for a compound against *Klebsiella pneumonia* as shown in Table 4. Also, Fig.4. shows the inhibitory effects around each disc to compounds a and b.

Table 4. Shows Antibacterial action data.

No	10^{-3}	*E-coli*	*Klebsiella pneumoniae*	*Salmonella*	*Staphylococcus aureus*	*Proteus*
	1	10	-	6	6	8
a	2	14	6	8	8	14
	3	17	6	11	12	22
b	1	15	8	10	12	9
	2	19	10	10	16	17
	3	22	17	11	26	21
5a	1	27	10	6	6	8
	2	24	10	7	4	14
	3	26	14	10	25	27
5b	1	20	-	8	6	10
	2	24	9	7	10	18
	3	29	12	10	17	27
$3a_i$	1	14	17	17	-	12
	2	12	20	22	20	15
	3	12	21	21	19	20
$3a_{ii}$	1	4	-	11	6	-
	2	10	12	16	10	4
	3	14	14	19	12	8
3bi	1	12	10	14	4	-
	2	18	14	16	4	4
	3	22	18	21	8	10
$3b_{ii}$	1	8	6	10	-	7
	2	10	6	11	-	10
	3	12	7	14	4	18
(Sulf)	1	-	-	-	-	-
	Staphylococcus aureus			*Klebsiella pneumoniae*		
Amoxicillin	-			-		
Impenem	30			26		
Doxycycline	22			14		
Ampicillin	-			-		



a **b**

Figure 4. The inhibitory effects around each disc a and b.

Molecular Docking Study

Study silico was carried out on some synthesized compounds in order to foretell their closeness to bacterial protein 4H2M from *E. coli*, 3FYV from *S.aureus*, and 6P4T from Salmonella. Analysis of the docking demonstrates that some sulfamethoxazole derivatives displayed they inhabit the different domains of 4H2M, 3FYV, and 6P4T binding pockets with perfect docking interaction scores Table 5.

As explained in the empirical outcomes, these compounds a -5b showed activity toward bacteria, and the docking studies of Sulfamethoxazole derivatives uncovered their ability as antibacterial. All compounds (a-5b) have aromatic rings in their structures, which show remarkable hydrophobic interactions along with the amino acid in the protein. These compounds are ranked according to their binding energy, and a check of each

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molecule's total interactions with the binding site was effectively performed by counting the total number of H-bonds. As a detailed docking of all compounds, it can be noted that compound 5a contains in its structure a thiadiazin ring, which formed three conventional H-bond with (4H2M in E. coil) ALA; A:69, ASN: A:144, and TYR;A:145 via the amine groups. Furthermore, it is important as an inhibitor is perceptible through many hydrophobic interactions such as alkyl and Pi-Alkyl with HIS;A:43, MET;A:86, ALA:143 and PHE, A:89, Pi-Pi stacked with HIS, A:43, Pi-Sulfur with MET;A:25.

On the other hand, compound 5a is linked mainly with protein 3FYV by one H-bond with residues: ASN;A:26. Also, the occurrences of a perceptible inhibition through hydrophobic interactions such as Pi-Sigma via VAL.A:137, Alkyl and Pi-Alkyl with LYS;A:33, LYS;A:29, LEU;A:34 and HIS;A:30 . Additionally, compound 5b bonded mainly with protein 4H2M by eight H-bonds, with GLN; A: 157, GLN; A:153, GLY;A:111, GLU:A:185, and VAL;A:181. Furthermore, it is an inhibition took place through hydrophobic interactions such as Pi-Pi T-shaped with HIS;A:43. Whereas, compound 5b, consists of a thiadiazin ring, which showed docking results with 3FYV (*S.aureus*) via one H-bond in ASN:26.

The obtained results revealed that most of our compounds exhibit an interesting antibacterial activity (binding affinity= - 6.0 to -9.4 kcal/mol) compared to the referenced compound, sulfamethoxazole (binding affinity= -7.1 kcal/mol). Energy values of the complexes (target -protein) resulting from the interactions is referred to as the lower energy, more stable complex, and better activity. The compounds (a-5a), exhibited the lowest energy value -9.4 (kcal/ mol). In general, docking study indicates that compounds bonding with 3FYV is less than 4H2M, and this demonstrates the weak efficiency towards Gram-positive bacteria. Figs. 5-15 show the bonding of some compounds in proteins. Table 5 shows various interactions involved between receptors and compounds, types of bonding, and bond length.

Table 5. Binding affinity (kcal/mol) with bacteria protein and hydrophobic contacts (from molecular docking) in ligands a, a_i, a_{ii}, 5a, b, b_i, b_{ii}, and 5a.

No.	Type protein	Binding affinity	H-bond (Bond length (A^o))	Types of bond (Bond length(A^o))
a	4H2M (E. Coli)	-9.1	TYR A: 211(1.87). GUL A: 240(2.26).	Pi-pi T-shaped (5.23), Pi-cation(4.15) Carbon (3.72, 3.35), Pi-Alkyl(4.47), Pi-sigma (3.44), Doner-Doner (2.23).
	3FYV (S. aureus)	-8.9	THR-121(2.09). ASN-18(2.91).	Pi-pi stacked (3.86)(3.39), Pi-DonerAmide-Pi-stacked(4.23), Pi-Alkyl(5.08, 5.44, 4.09), Pi-Alkyl, Alkyl(3.84), Pi-Pi-T-shaped (5.08)
	6P4T (Salmonella)	-6.4	SERE94(2.13); ASP-E87(1.78). ARG-D90(2.17).	Pi-Sigma (3.55, 3.74, 3.79), Pi-Alkyl (4.93).
$3a_i$	4H2M (E.coli)	-7.9	TYR A:145(2,54). ASN A:144(2.36).	Pi-Alkyl(4.21, 4.6), Pi-anion (4.76), Pi -Pi-Stacked(5.94), carbon(3.49, 2.78), Pi-sulfur(5.57),Pi-sigma(5.61).
	3FYV (S. aureus)	-5.3	ASN X;18(2.32). SER X:49(2.55). GLN X:19(2.5)	Pi-Alkyl(4.78), Alkyl(4.50), Pi-Cation(3.59), Pi -Pi-Stacked(3.76).
	6P4T (Salmonella)	-7.2	LYS E:83(2.12) ARG E:90(2.32) ARG B:90(2.89) LYS B:83(2.61) ASP E:87(2.47).	Pi-Alkyl(4.83), Pi-anion(4.76), Pi -Pi-Stacked(3.37,4.84), Charge-Charge (4.78, 4.59).
	4H2M (E.coli)	-6.0	SERA:114(2.15). GLYA:111(3.01) GLN A:157(2.87).	Pi-Alkyl (4.01), Pi-Pi Stacked(3.91), Pi-Sulfur(5.51).

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$3a_{ii}$	3FYV (S. aureus)	-7.9	ASN X:26(2.04, 2.42)	Pi-Alkyl (5.23, 4.36)Pi-anion(4.83) Pi -Pi-Stacked(3.74, 4.03)Charge-charge(2.25, 3.86).
	6P4T (Salmonella)	-7.7	ASP E:87(2.02). LUS E:8(1.93). LYS A:83(2.25)	Pi-Alkyl (4.01), Pi-anion (3.45), Charge-charge(4.77).
	4H2M (E.coli)	-9.1	ALA A:69(2.86). ASN A:144(2.16) TYR A:14(2.46)	Alkyl(4.03),Carbon(3.64), Sulfur(5.62), Pi-Alkyl(4.87).
5a	3FYV (S. aureus)	-7.1	ASN:26(3.07)	Pi-Alkyl(5.16, 4.66, 5.04), Alkyl(4.02), Pi-sigma(3.76), Pi -Pi-Stacked(5.09).
	6P4T (Salmonella)	-7.9	TYR:91(2.61). ARG:90(2.49). ASP.:87(2.84).	Alkyl(4.4), Pi-Cation(4.59).
	4H2M (E.coli)	-7.6	TRP221(2.28) TYR68(2.32),ALA 69(2.1)	Pi-pi stacked (5.78), Pi-alkyl(4.41 4.45,4.08, 5.36), Amide-Pi stacked (4.17)
b			ASN144(2.73),KEU85(2.02)	Sulfur(5.64).
	3FYV (S. aureus)	-9.4	SER 49(2.13) LYS 45(2.15) PHE 92(2.02)	Pi-pi stacked(4.37),Pi-alkyl(5.19, 5.01, 4.58), Pi – Sigma(3.09), Carbon(3.57), Doner-Doner(2.01)
	6P4T (Salmonella)	-6.7	SER E;94(2.79) ARG E90(2.79) ARG-D90(2.46)	Pi-Alkyl (4.42, 4.82) Pi-Pi stacked(3.7), Pi-Cation(5.0)
	4H2M (E.coli)	-6.9	THR A:113(2.04) GLN A:153(1.84)	Pi-Alkyl(5.25, 5.01), Pi -Pi-Stacked(3.72), Carbon(3.64), Pi-sulfur(5.72) Pi-Cation(2.93).
3bi			GLY A:111(2.03) ILE A:109(2.29)	
	3FYV (S. aureus)	-6.6	ASN X:26 (2.39,1.84)	Pi-alkyl(4.79, 4.72), Pi – Pi Stacked Carbon(3.74), Pi-Cation (3.31), Pi-Doner (3.77), Charge-charge(3.93).
	6P4T (Salmonella)	-7.1	ARG D:90(2.3) LYS D:83(2.78), ASP C:87(2.82) LYS C:83(2.82)	Pi-Alkyl(4.91), Pi -Pi-Stacked(3.74), Carbon(3.43) Pi-Cation(3.86), Pi-anion(3.83).
	4H2M (E.coli)	-6.5	CYS A:182(2.13). GLN A:153(3.32)	Pi-pi stacked (3.74), Pi-Alkyl(4.22), Alkyl (4.63, 5.05), Carbon (3.46), Pi-Doner(2.63).
3bii			ILE A:109(3.0)	
	3FYV (S. aureus)	-6.2	ASN X:26(2.31, 2.71).	Pi-Alkyl (4.01, 4.45). Pi -Pi-Stacked(3.71).
	6P4T (Salmonella)	-7.8	LYS B:83(2.57) ARG B:90(2.67) ASP E:87(2.79)	Pi-Alkyl (5.08, 4.8, 5.19), Pi-Anion(4.17, 3.55), Charge-charge(4.53), Pi-Cation(2.64).
5b	4H2M (E.coli)	-7.2	GLN A:157(2.69) GLNA:153(2.62) GLY A:111 (2.93) GLU A:185(2.48) VAL A:181(2.64).	Pi-Alkyl (4.13), sulfur (5.12). Pi -Pi-Stacked(3.37), Carbon(3.46),
	3FYV (S. aureus)	-6.0	ASN X:26(2.31, 2.69).	Pi-pi stacked (5.01, 3.68), Pi-alkyl(5.01), Carbon(3.50), Pi-sulfur(5.59)
	6P4T (Salmonella)	-7.5	ASP A:87(2.4, 2.00)	Pi-Alkyl (4.10, 4.91). Pi-Pi stacked(3.68).

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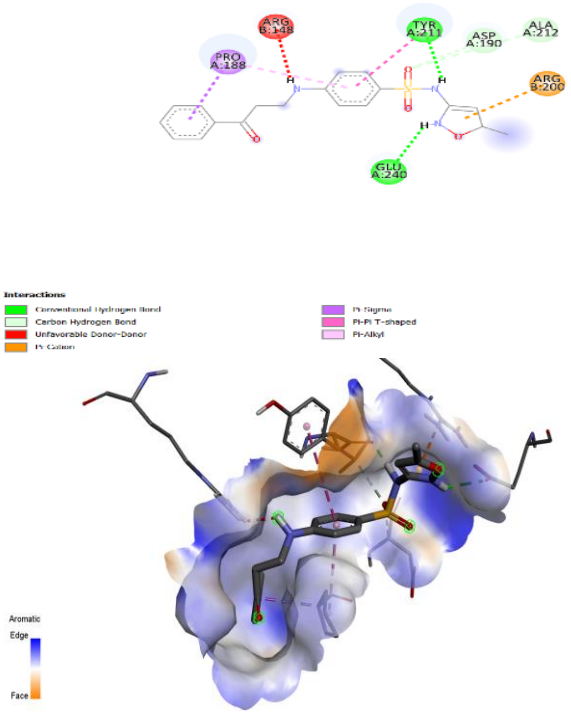

Figure 5. 3D and 2D Binding site interaction of compound a with E.coli (PDB ID.4H2M).

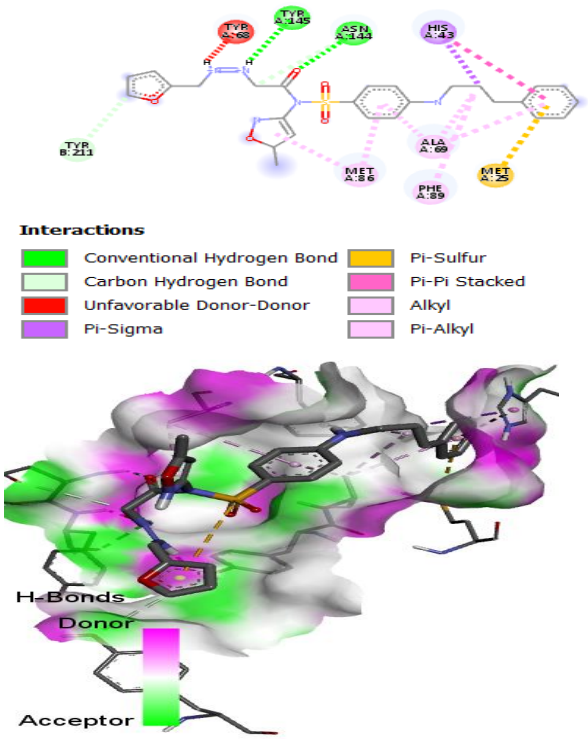

Figure 6. 3D and 2D Binding site interaction of compound 3ai with E. coli (PDB ID.4H2M).

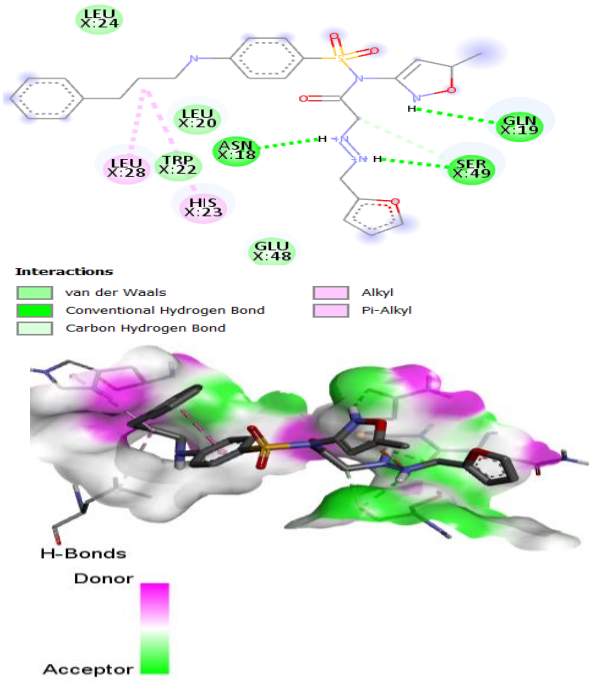

Figure 7. 3D and 2D Binding site interaction of compound 3ai with S. aureus (PDB ID.3FYV).

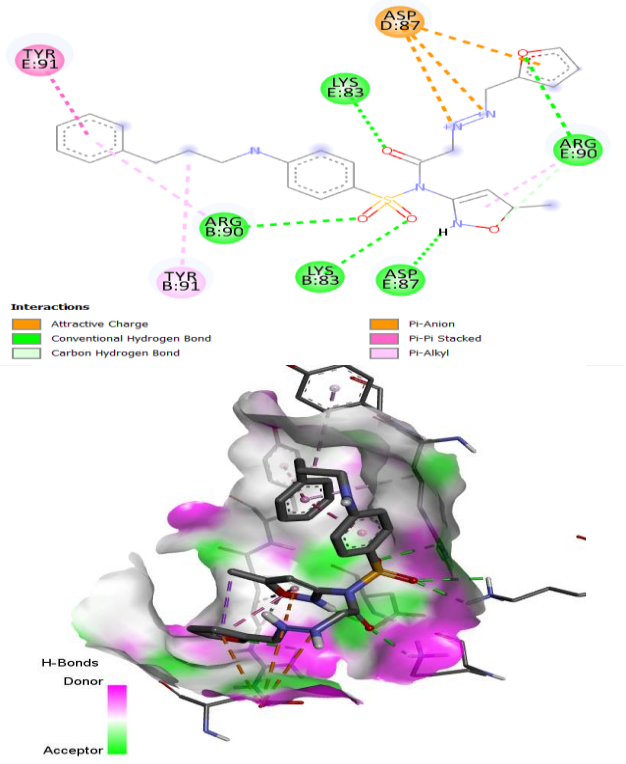

Figure 8. 3D and 2D Binding site interaction of compound 3ai with Salmonella (PDB ID.6P4T).

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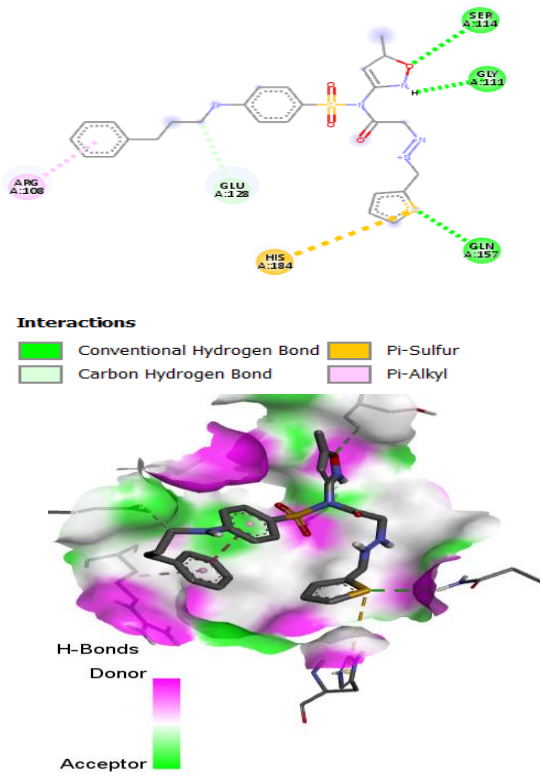

Figure 9. 3D and 2D Binding site interaction of compound 3a ii with E. coli (PDB ID.4H2M).

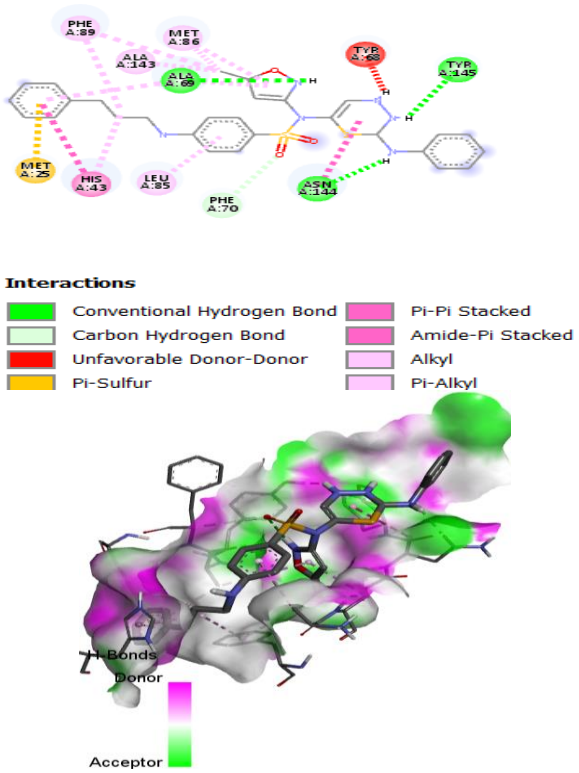

Figure 11. 3D and 2D Binding site interaction of compound 5a with E. coli (PDB ID.4H2M).

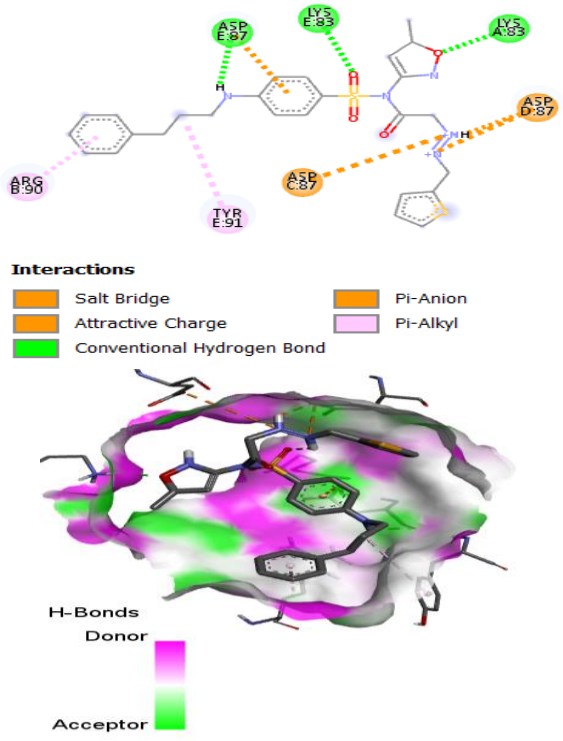

Figure 10. 3D and 2D Binding site interaction of compound 3aii with Salmonella (PDB ID.6P4T).

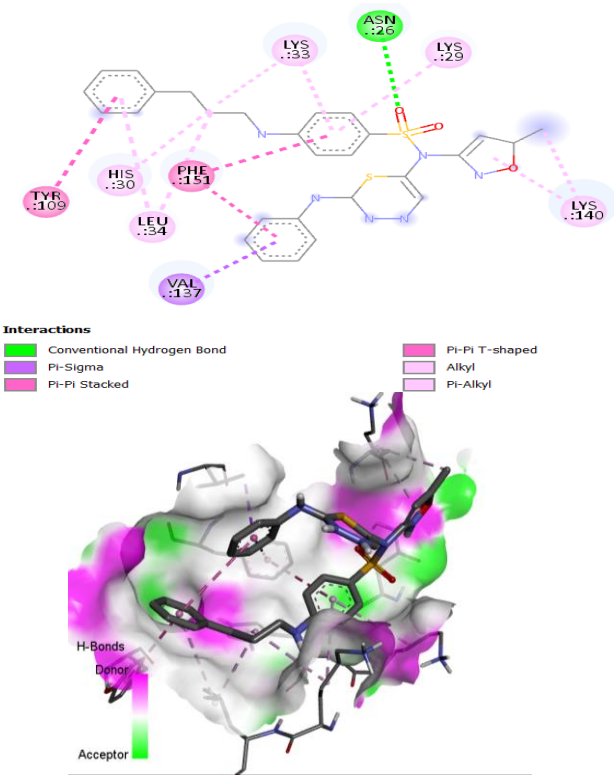

Figure 12. 3D and 2D Binding site interaction of compound 5a with S. aureus (PDB ID.3FYV).

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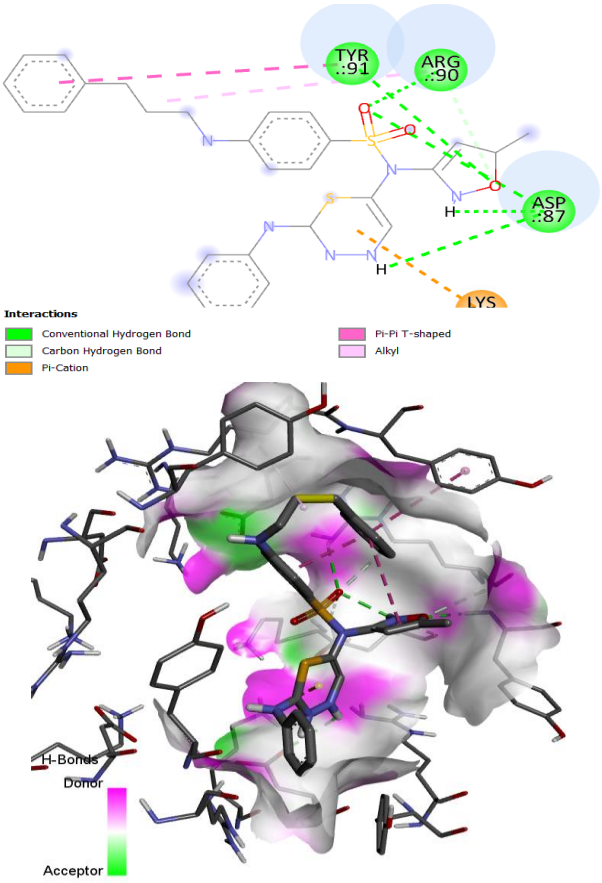

Figure 13. 3D and 2D Binding site interaction of compound 5a with Salmonella (PDB ID.6P4T).

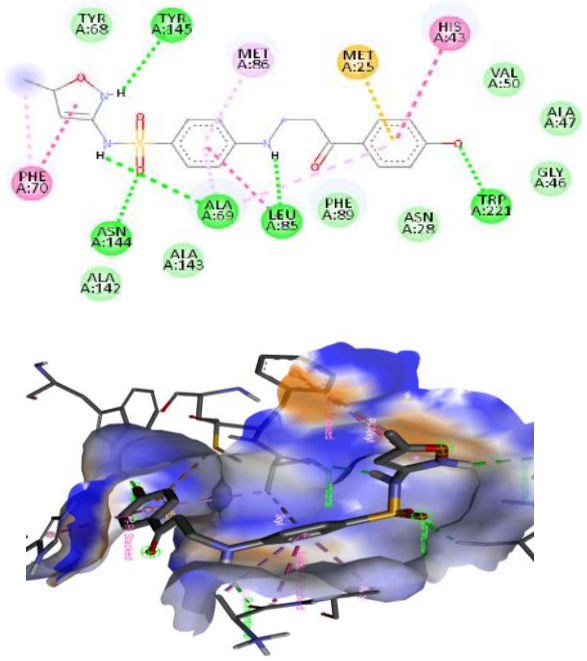

Figure 14. 3D and 2D Binding site interaction of compound b with E. coli (PDB ID.4H2M).

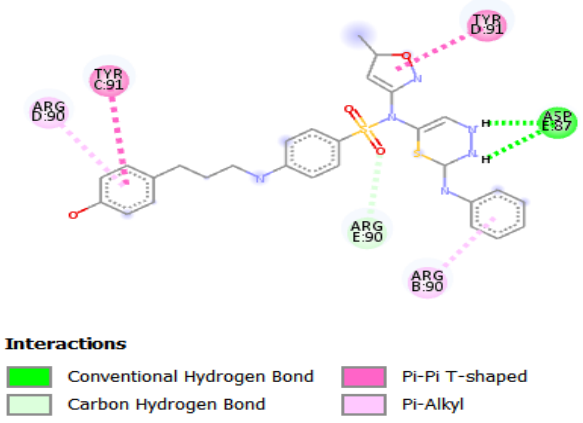

Figure 15. 2D Binding site interaction of compound 5b with Salmonella (PDB ID.6P4T).

Conclusion

A molecular docking study of Sulfamethoxazole derivatives compounds with proteins including 6P4T *(Salmonella)*, 4H2M *(E. coli)*, and 3FYV *(S. aureus)* revealed that compounds have good interactions in the favorable sites with proteins, which was explained by strong bond length, and the lowest binding energy with active sites of proteins. Moreover, it can be concluded that Mannich bases could be used in improving drugs through the designing and modification of more potent compounds. Therefore, Novel Mannich bases (a and b) have been synthesized via the reaction of sulfamethoxazole with acetophenone or piceol, and formaldehyde. Accordingly, modification of Mannich bases via reaction of Schiff bases. All compounds have been characterized by FT-IR, ^{1}H-^{13}C-NMR. The results of these investigations supported the suggested structure of all compounds. Compounds a-5b, are important chemicals that can be considered primary substances for drugs, especially when it is being antibacterial.

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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 Wasit.
- Ethics statement:
  No animal studies are present in the manuscript.
  No human studies are present in the manuscript.
  No potentially identified images or data are present in the manuscript.

Authors' Contribution Statement

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

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تحضير وتشخيص و ودراسة النشاط البيولوجي والالتحام الجزيئي لبعض مشتقات السلفاميثوكسازول الجديدة.

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الخلاصة

تضمنت الدراسة في هذا البحث تحضير مركبات كيميائية جديدة مشتقة من المركب الدوائي السلفاميثوكسازول بهدف تطوير فعاليته العلاجية. تم تحضير ستة مركبات من قواعد شيف بواسطة تفاعل قواعد مانخ، كما تم تحضير مشتقين للحلقة الغير متجانسة ثيادايازين. تشخيص المركبات المحضرة والتاكد من تركيبها تم باستخدام طيف الأشعة تحت الحمراء وطيف الرنين النووي المغناطيسي و تقنية تحليل العناصربالأضافة الى قياس درجات الاتصهار واللون. تم دراسة الفعالية البايلوجية للمركبات المحضرة وتأثيرهاعلى تثبيط خمسة انواع من البكتريا وهي المكورات العنقودية الذهبية، الإشريكية القولونية، الالتهاب الرئوي كليبسيلا، السالمونيلا، والبروتيوس. أظهرت نتائج الدراسة قيم متفاوتة للفعالية البايلوجية تتراوح بين القيمة العالية الى عدم الفعالية. تم استخدام برنامج (PyRx) لحساب طاقة الارتباط للمركبات مع بروتينات البكتيريا وهي بروتين (FYV) في المكورات العنقودية الذهبية وبروتين (4H2M) في الإشريكية القولونية، وبروتين (6P4T) في السالمونيلا، حيث تم حساب قيم طاقات الارتباط وكانت اعلى قيمة لها مع البروتين (4H2M) وكانت(9.1- كيلوكلري/مول) و مع البروتين (6P4T) كانت (7.8- كيلوكلري/مول) و اقل طاقة ارتباط وجدت مع البروتين (FYV) وكانت (5.3- كيلوكلري/مول). تم تحديد الحوامض الامينية المحيطة بالمركبات والتي ترتبط بهاغالبا بواسطة الاصرة الهيدروجينية اوبواسطة تاثرات هيدروفوبية نوع (شحنة-شحنة) او (ارين-ارين)، فضلًا على الحصول على شكل ثلاثي الابعاد لكيفية ترابط المركبات مع البروتينات. تم أيضا معرفة الكثافة الالكترونية للمركبات من خلال معرفة صفات الحوامض الامينية المحيط بالمركبات المحضرة .

الكلمات المفتاحية: البكتريا، الحاسوبية، قواعد مانخ ، الالتحام الجزيئي، سلفاميثوكسازول.