DOI: https://doi.org/10.31351/vol35iss1pp166-178

ADME Study, Molecular Docking, Synthesis, Characterization, and Preliminary Antimicrobial Activity Evaluation of New Glycine Derivatives of Sulfonamide

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Received 12/11/2024, Accepted 17/6/2025, Published 29/3/2026

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Abstract

Novel glycine-based sulfonamide derivatives were synthesized. This study presents the newly synthesized compounds (**G1-6**) that exhibit promising DHPS inhibition activities, designed through a molecular docking analysis targeting the *Yersinia pestis* DHPS protein (PDB ID: 5JQ9). The molecular docked compounds were subsequently subjected to an ADME study to evaluate their pharmacokinetic properties. This work started with the synthesis of the glycine methyl ester HCl salt (compound **I**) through the activation of the carboxylate functionality of glycine with thionyl chloride ($SOCl_2$), followed by esterification with methanol, and the synthesis of 4-acetamidobenzene sulfonyl chloride (compound **II**) from acetanilide, the reaction of the latter two intermediates using the triethyl amine (TEA) as base and neutralizing agent in the dichloromethane (DCM) led to the synthesis of a sulfonamide-containing compound (compound **III**). This compound was then reacted with $NH_2NH_2.H_2O$ (Hydrazine hydrate) to give the compound **IV**(Hydrazide), which furthermore reacted with various aldehydes using glacial acetic acid as a catalyst to provide the final target compounds **G1-6**. The identification of the newly synthesized compounds was carried out using ATR-FTIR (Infrared spectroscopy) and ^{1}HNMR (Proton nuclear magnetic resonance). By using the diffusion method, the antimicrobial effect of the final products was tested in vitro against two Gram-positive bacteria, *Staphylococcus aureus* and *Streptococcus pneumoniae*; two Gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli*; and one fungus, *Candida albicans* compared with the standard antimicrobial agents, sulfamethoxazole, sulfadiazine, and fluconazole. In general, all synthesized compounds have moderate to high antimicrobial activity, but compounds G5 and G6 with the highest activity had zone inhibition (**ZI**) ranging from 16 to 21 mm.
Keywords: Antimicrobial, Glycine, Molecular docking, Sulfonamide, Zone of Inhibition

Introduction

Numerous commonly prescribed medications contain the principal sulfonamide moiety ($R-SO_2NH_2$), including diuretics, carbonic anhydrase inhibitors, antiepileptics, the antipsychotic sulpiride, and cyclooxygenase-2 (COX-2) inhibitors [1,2]. Sulfonamide antimicrobials agents constitute a crucial category of synthetic antibiotics that have profoundly impacted the management of bacterial infections since their inception in the early 20th century [3]. Sulfonamides were originally identified in the 1900s and were significant in the late 1930s as the inaugural efficient chemotherapeutic medicines against several bacterial infections. Sulfonamides were initially identified by Domagk in 1935. He was researching a red azo dye, prontosil, and demonstrated its therapeutic efficacy on mice afflicted with β-hemolytic streptococci. Subsequently, the demonstration of prontosil activity which functions as a prodrug that is metabolized into an active sulfanilamide *in vivo* [4,5]. The mechanism of action of these agents principally entails the competitive suppression of dihydropteroate synthetase (DHPS), an enzyme essential for bacterial folic acid production. Sulfonamides, via imitating para-aminobenzoic acid (PABA), inhibit folate formation, which is an important for nucleic acid building and bacterial proliferation, thereby exhibiting bacteriostatic properties [6,7] .

Although historically significant, the therapeutic efficacy of sulfonamides has been undermined by the rise of bacterial resistance and the advent of more potent antibiotics. Target modification and enzymatic degradation are examples of resistance mechanisms that have reduced their efficacy against certain infections [8]. Antimicrobial-susceptible bacteria may acquire additional genetic material from resistant strains via transduction, transformation, or conjugation, with transposons often aiding in the integration of multiple resistance genes into the host genome or plasmids. [9] Figure (1) summarizes antibacterial resistance.

How to cite ADME Study, Molecular Docking, Synthesis, Characterization, and Preliminary Antimicrobial Activity Evaluation of New Glycine Derivatives of Sulfonamide. ***Iraqi J Pharm Sci,***

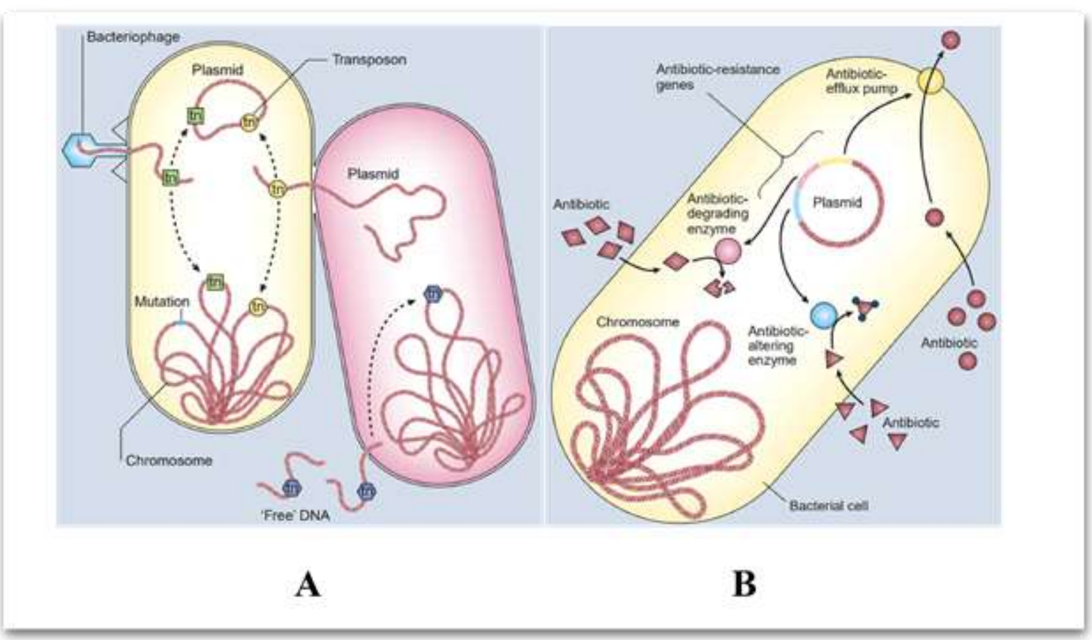


Figure 1. Antibacterial resistance A) acquisition of resistance genes B) mechanisms of resistance [8]

Sulfonamides are now typically reserved for specific indications, including the management of infections in immunocompromised individuals and urinary tract infections, when other therapies may prove ineffective [10].

Sulfonamides are divided into antibacterial (which contain aryl amine at position N4 and nitrogen- containing heterocyclic five or six-membered ring at position N1) and nonantibacterial (which lack either of structural moieties with expect for two antiviral agent amprenavir and its prodrug (fosamprenavir) [11-13].

Figure 2. general structure of sulfonamide [13]

Antimicrobial sulfonamides are among the most prevalent triggers of drug reactions, after beta-lactams (penicillins and cephalosporins). Hypersensitivity reactions may range from mild reactions like rash and fever, sometimes accompanied by hepatitis, hemolytic anemia, and/or lymphadenopathy, to severe ones like toxic epidermal necrolysis and Stevens-Johnson syndrome [14].

Hypersensitivity reactions to antimicrobial sulfonamides are associated with their structural features, which include N4 aryl amine (an aromatic amine) and an N1 five- or six-membered heterocyclic ring (or even an N1 aromatic ring, as seen in the antileprotic agent Dapsone). These characteristics are absent in non-antimicrobial sulfonamides, such as the diuretics furosemide and thiazide derivatives, as well as the antidiabetic sulfonylureas, among others [15].

Materials and Methods

Materials and instruments

The chemical store of College of Pharmacy, University of Baghdad provided all starting chemicals, solvents, and reagents which were used in the work. A digital melting point device (Stuart SMP30) utilized for melting points determination. The assessment for the purification of the synthetic compounds and the monitoring of the reactions was performed using the TLC (Thin layer chromatography). A Bruker, Germany NMR Spectrometer, 400 MHz (at the University of Basra, College of Education for Pure Sciences) was employed for recording ^{1}HNMR spectra, utilizing DMSO (Dimethyl-sulfoxide) as the solvent and TMS (Tetramethyl silane) as an internal standard. At the College of Pharmacy, University of Baghdad, ATR-FTIR spectra were obtained utilizing a FTIR Spectrometer (Shimadzu, Japan).

In silico studies

Molecular docking

The Glide program (which was integrated with Schrodinger's licensed Maestro software version 13.0135) used for conduction of the molecular docking findings. The synthesized target compounds were compared with the standard medications (sulfamethoxazole and sulfadiazine), the Protein Data Bank employed for obtaining the complex protein structure of *Yersinia pestis* DHPS with pterine-sulfa conjugate (PDB ID: 5JQ9). The

Protein Preparation Wizard (Within Schrodinger, New York, NY, 2021), was utilized to prepare the protein by filling in missing loops, adding hydrogen atoms, removing water molecules not involved in interactions (more than 5 Å from the active site), and eliminating non-essential atoms. The grid of the receptor was constructed utilizing the co-crystallized ligand that engaged with the protein. The used bounding box measures 12 Å [16].

The ligands were assessed using the DHPS (PDB ID: 5JQ9) ligand binding geometries and potential energy computations. A Grid-based Ligand Docking used for ranking the target ligands using G score (The glide scoring function) to examine of the interactions of the receptor with the ligands. Extra expression XP's default docking option, which imposed a constraint of 10 poses was used. The validation of the docking studies of the target protein active site done by redocking of the co-crystallized ligand into the binding active site [17].

ADME studies

The pharmacokinetic properties (Absorption, Distribution, Metabolism and Excretion, ADME) assessed by using the Qikprobe software within the Schrodinger Maestro for the Ligand-based ADME prediction. The approach is entering the Qikprobe panel to enter all items from the docking compounds project table (choosing the fast mode for ADME analysis), there after the QikProp run in the fast processing [18].

Chemical synthesis

Synthesis of glycine methyl ester HCL (methyl 2-aminoacetate HCL) (compound I):

The suspension of glycine (30.26mmol, 2.27gm in 50ml of methanol) in 250 ml round flask was cooled down to 0 ˚C then the $SOCl_2$ 1.2 eq (36.32 mmol, 2.6 ml) added dropwise for 5min after complete addition , the obtained mixture solution was stirred at 40 ºC for 3 hours, then refluxed for 3 hours, then allow to cooled down to RT , the solvent evaporated several times to get rid the excess of the $SOCl_2$, after that the 25 ml of the methanol added to the obtained crude product, and cooled down in an ice bath to 0 ºC, then the addition of the 100 ml of diethyl ether done by using of a glass rod for stirring, the obtained white color crystalline ppt. vacuumed, and washed by the mixture of the diethyl ether: methanol (5:1) and dried to get pure glycine methyl ester hydrochloride [19].

Glycine methyl ester HCL (methyl 2-aminoacetate HCL) (compound I)

White crystals, m.p.= 127-131ºC, yield=89%, R_f = 0.52 in solvent system = Ethanol: Water, 9:1, ATR-FTIR (ν =cm^{-1}): 3217-2800 (for NH bond str. of NH_4^+ salt, broad band), 1739 (for str. of C=O group of ester), 1624 (for NH bond bend. of NH_4^+ salt), 1242,1141(for C−O−C Asym. and sym. str. added to CN bond str.).

Synthesis of 4 - acetamidobenzenesulfonyl chloride, compound II:

To 250 ml Erlenmeyer flask, acetanilide (37.03mmol, 5gm) was added, the flask fixed on ice bath that is maintained at 10–15 °C equipped on magnetic stirrer, the chlorosulfonic acid (224.88 mmol, 15 ml) was measured into small separatory funnel .Then the acid was poured in one go into the flask with stirring, that was left 10-15 min get rid further fume while the temperature was maintained below 20 ºC that hasten the dissolution of solid to complete . After that the first reaction has passed, the cooling bath was removed. In order to finish the reaction, the mixture was heated in a water bath for 10 -20 min. at a temperature between 70 and 80 ºC while stirring to stopping the evolution of the gas.

Then the mixture was cooled below RT and then it was poured onto 300 gm of crushed ice. The precipitate that was formed is crude product of 4-acetamidobenzene sulfonyl chloride. By using vacuum filtration, the crude product collected and washed by cooled water, and was pressed using clean cork to be use immediately for further step [19].

4-acetamidobenzenesulfonyl chloride (compound II)

Powder of an off white color, m.p.=143-146ºC, the yield = 64%, R_f = 0.50 in the solvent system (Chloroform: Ethyl acetate,1:1), ATR-FTIR (ν=cm^{-1}): 3302 (for str. of NH bond of 2º amide),3051and 3005 (for str. CH bond of the Ar. ring), 2939 and 2866 (for Asym. and sym. str. C−H of CH_3 group),1678 (for str. of C=O of 2º amide group),1581-1492 (for str. of C=C of Ar. ring overlap with NH bond ben. of 2º amide) and 1365 and1161 (for Asym. and sym. str. of -SO_2- group).

Synthesis of methyl ((4-acetamidophenyl) sulfonyl) glycinate, compound III:

The suspension of the compound **I** (16 mmol, 2gm in 20 ml of DCM) in round flask putted in a salty ice bath with 0 ºC, then TEA (32 mmol, 4.44 ml) was added gradually. The mixture stirred for 20 min., then the suspension of the compound **II** (16 mmol, 3.73 in 20 ml of DCM) was added to the reaction mixture and stirred for 40 min. After that the mixture was stirred for 4 hr. at RT. To get compound **III,** the reaction solution was extracted three times using 20 ml of distilled water, the organic layer evaporated, then the yielded gummy product was decantated using diethyl ether and dried by vacuum filtration [20].

Methyl ((4-acetamidophenyl) sulfonyl) glycinate (compound III)

Pale yellow powder, m.p.= 143-146 ºC, the yield =74%, R_f = 0.22 in the solvent system (Chloroform: Ethyl acetate,1:1), ATR-FTIR (ν =cm^{-1}): 3317 (for str. of N−H of 2º sulfonamide), 3232 (for str. of N−H of 2º amide), 2989 (for str. of C−H of Ar. ring), 2939 (for str. of C−H Asym. of CH_3 group), 1735 (for str. of C=O of ester), 1670 (for str. of C=O of 2º amide), 1597and1531 (for str. of C=C of Ar. ring overlap with NH bond ben. of 2º amide)

and 1330 and1157 (for Asym. and sym. str. of -SO_2- group).

Synthesis of N-(4-(N (2 -hydrazineyl- 2-oxoethyl) sulfamoyl) phenyl) acetamide, compound IV:

To a 100 ml round flask, the mixture of the compound III (6.984 mmol, 2 g) in 20 ml of ethanol was added with hydrazine hydrate 80% (69.84 mmol, 3.35 ml) and was stirred for 8 hours at 80 ºC. The reaction mixture was cooled down to RT, the filtered ppt. was washed with distilled water and recrystallized from ethanol [21].

N-(4-(N (2 -hydrazineyl- 2-oxoethyl) sulfamoyl) phenyl) acetamide (compound IV)

White powder, m.p.= 194-198ºC, the yield = 58%, R_f = 0.27 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3344 and 3325 (for N−H Asym. and sym. str. of 1º amine of hydrazide),3128 (for str. of N−H of 2º sulfonamide overlapped with N−H str. of 2º amide), 3116 and 3059 (for str. of C−H of Ar. ring), 2854 (for str. of C−H Asym. of CH_3 group), 1662 (for str. of C=O of 2º amide), 1589 and 1516 (for str. of C=C str. of Ar. ring overlap with NH bond ben. of 2º amide) and 1315 and 1153 (for Asym. and sym. str. of -SO_2- group).

Synthesis of the final compounds, the compounds G1- 6:

The glacial acetic added acid as few drops to the aldehyde solutions in absolute ethanol (1.746 mmol): benzaldehyde (0.176 ml) , 4-OCH_3 benzaldehyde (0.263ml) ,4-OH benzaldehyde and 3-OH benzaldehyde (0.213 gm), 4-chlorobenzaldehyde (2.44 gm) and 4-hydroxy-3-methoxy benzaldehyde (0.265 gm) . Each one of the previous solutions was added separately to the mixture of compound **IV** (1.746 mmol, 0.5 gm) in 10 ml of absolute ethanol putted in 100ml round flask. Then reflux of the reaction mixtures done during 3-8 hr. and cool down to the RT, the yielded compounds were filtered and washed by cold distilled water and recrystallized from ethanol [22].

(E)-N-(4-(N-(2-(2-benzylidenehydrazineyl)-2-oxoethyl) sulfamoyl) phenyl) acetamide (compound G1)

Powder of white color, m.p.= 229-232, the yield=84%, R_f = 0.8 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3278 (for str. of NH bond of 2º sulfonamide), 3255 and 3182 (for str. of N−H of 2º amide), 3051 (for str. of C−H str. of Ar. ring), 3001 (for str. asym. of C−H of CH_3 group), 1674 (for C=O str. of 2º amide), 1593 (for str. of C=N of imine), 1535 and1500 (for str. of C=C of Ar. ring) and 1315 and 1153 (for asym. and sym. str. of -SO_2- group).^{1}HNMR : 400 MHz, DMSO, δ (ppm) 11.47 (s, 1H, -NH- of -NHCO-CH_3), 11.39 (s, 1H, -NH-CO), 10.31 (s, 1H, -$NHSO_2$-), 8.14 (s, 1H , -CH=N-), 7.95 (q, 2H , Ar.), 7.68 – 7.59 (m, 4H, Ar-SO_2), 7.41 (t, 3H, Ar.), 4.04 (s, 2H , -CH_2-), 2.08 (s, 3H, CH_3-CO-).

(E)- N - (4 - (N - (2 - (2-(4-methoxybenzylidene) hydrazineyl)- 2- oxoethyl) sulfamoyl) phenyl) acetamide (compound G2)

Powder of white color, m.p. ºC= 202-206, the yield=76%, R_f = 0.74 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3290 (for NH bond str. of 2º sulfonamide), 3186 (for str. of N−H of 2º amide), 3092 and 3039 (for str. of C−H of Ar. ring), 2962 and 2843 (for asym. str. C−H of -CH_3 and -CH_2 group), 1674 and 1662 (for str. C=O of 2º amide), 1608 (for str. of C=N of imine), 1573 and 1512 (for str. of C=C of Ar. ring) ,1327 and 1153 (for Asym. and sym. str. of -SO_2- group) and 1026 and 1253 (for C-O str. of -OCH_3 group). ^{1}HNMR : 400 MHz, DMSO, δ 11.34 (s, 1H, -NH of -NHCO-CH_3), 11.25 (s, 1H, -NHCO), 10.32 (s, 1H, -$NHSO_2$-), 8.08 (s, 1H , - CH=N-), 7.96 – 7.85 (m, 2H , Ar.), 7.73 – 7.48 (m, 4H, Ar-SO_2), 6.98 – 6.93 (m, 2H, Ar.), 4.00 (s, 2H , - CH_2-), 3.78 (s, 3H, -Ar-OCH_3), 2.08 (s, 3H, CH_3-CO).

(E)-N-(4-(N-(2-(2-(4-hydroxybenzylidene) hydrazineyl)-2-oxoethyl) sulfamoyl) phenyl) acetamide (compound G3)

Powder of white color, m.p. ºC= 268-273, the yield=87%, R_f = 0.82 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3309 (for str. of NH bond of 2º sulfonamide), 3240 and 3190 (for str. of N−H of 2º amide), 3062 (for str. of C−H of aromatic ring), 3062x3309 (for str. of O−H of -Ar-OH group broad band) , 1678 (for str. of C=O of 2º amide), 1658 (for str. of C=N of imine), 1600-1531 (for str. of C=C of Ar. ring) , 1350 and 1165 (for Asym. and sym. str. of -SO_2- group). ^{1}HNMR : 400 MHz, DMSO, δ (ppm) 11.26 (s, 1H, -NH of -NHCO-CH3), 11.17 (s, 1H, -NH-C=O), 10.31 (s, 1H, -NHSO2-),9.92 (s, 1H, -OH), 8.02 (s, 1H , -CH=N-), 7.87 (t, 2H , Ar.), 7.73 – 7.19 (m, 4H, Ar-SO2), 6.80 (t, 2H, Ar.), 4.00 (s, 2H , -CH_2-), 2.08 (s, 3H, CH_3-CO).

(E)-N-(4-(N-(2- (2-(3-hydroxybenzylidene) hydrazineyl) -2- oxoethyl) sulfamoyl) phenyl) acetamide (compound G4)

Powder of white color, m.p. ºC=219-223, the yield=73%, Rf = 0.8 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3317 (for str. of NH bond of 2º sulfonamide), 3282 and 3190 (for str. of N−H of 2º amide), 3140 (for str. of C−H of aromatic ring), 3317 (for str. of O−H of -Ar-OH group), 3000 (for str. of C-H of Ar. ring), 1670 (for str. of CO of 2º amide), 1590 (for str. of C=N of imine), 1577-1496 (for str. of C=C of Ar. ring) , 1315 and 1153 (for Asym. and

sym. str. of $-SO_2-$ group). ^{1}HNMR : 400 MHz, DMSO, δ (ppm) 11.41 (s, 1H, -NH of $-NHCO-CH_3$), 11.34 (s, 1H, -NHCO), 10.32 (s, 1H, -NHSO2-),9.65 (s, 1H, -OH), 8.06 (s, 1H , - CH=N-), 7.84 (s, 1H , Ar.), 7.41 – 7.05 (m, 4H, $Ar-SO_2$), 7.02 – 6.73 (s, 3H, Ar.), 4.03 (s, 2H , $- CH_2-$), 2.09 (s, 3H, CH_3-CO).

(E) - N- (4 - (N - (2 - (2 - (4 -chloro-benzylidene) hydrazineyl)-2-oxoethyl) sulfamoyl) phenyl) acetamide (compound G5)

Powder of white color, m.p. ºC= 235-238, the yield=74%, R_f = 0.76 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3410 (for NH bond str. of 2º sulfonamide), 3294 and 3201 (for str. of N−H of 2º amide), 3101 (for str. of C−H of aromatic ring), 2978-2862(for str. of C−H of CH2 group and CH_3 group) , 1685 (for str. of C=O of 2º amide), 1589 (for str. of C=N of imine), 1519 and 1496 (for str. of C=C of Ar. ring) , 1135 and 1157 (for Asym. and sym. str. of $-SO_2-$ group). ^{1}HNMR : 400 MHz, DMSO, δ (ppm) 11.52 (s, 1H, -NH of $-NHCO-CH_3$), 11.45 (s, 1H, -NHC=O), 10.31 (s, 1H, $-NHSO_2-$),8.13 (s, 1H , -CH=N-), 7.94 (t, 2H , Ar.), 7.70 – 7.61 (m, 4H, $Ar-SO_2$), 7.47 (t, 2H, Ar.), 4.03 (s, 2H , $- CH_2-$), 2.08 (s, 3H, CH_3-CO).

(E) – N - (4 - (N - (2- (2 - (4 - hydroxy-3-methoxybenzylidene) hydrazineyl)-2-oxoethyl) sulfamoyl) phenyl) acetamide (compound G6)

Powder of white color, m.p. ºC=235-238, the yield=74%, R_f = 0.76 in the solvent system (Methanol: Ethyl acetate, 6:4), ATR-FTIR (v =cm^{-1}): 3352 ((for OH bond str. of Ar-OH group), 3286 (for str. of NH bond of 2º sulfonamide), 3194 (for str. of N−H of 2º amide), 3086 and 3113 (for str. of C−H of aromatic ring), 2974-2843 (for str. of C−H of CH_2 group and CH_3 group) , 1685 (for str. of CO of 2º amide), 1589 (for str. of C=N of imine), 1527 and1469 (for str. of C=C of Ar. ring) , 1369 and 1161 (for Asym. and sym. str. of $-SO_2-$ group). ^{1}HNMR : 400 MHz, DMSO, δ (ppm) 11.30 (s, 1H, -NH of $-NHCO-CH_3$), 11.18 (s, 1H, -NHCO), 10.31 (s, 1H, $-NHSO_2-$),9.52 (s, 1H, -OH), 8.01 (s, 1H , -CH=N-), .97 – 7.21 (m, 4H, $Ar-SO_2$), 7.16 (s, 1H, Ar.), 7.01 (d, J = 8.2 Hz, 1H, Ar.), 6.80 (d, J = 8.2 Hz, 1H, Ar.), 3.98 (s, 2H , $-CH_2-$),3.80 (s, 3H, -Ar-OCH_3), 2.08 (s, 3H, CH_3-CO).

Antimicrobial assessment

The minimum bactericidal concentration (MBC), the minimum fungicidal concentration (MFC) ,the minimum inhibitory concentration (MIC) and zone of inhibition (ZI) were done using the broth dilution method and the agar diffusion method, and they were used to evaluate the antimicrobial activity of target compounds against four bacteria , *S. aureus*, *S. pneumoniae*, *P. aeruginosa,* and *E. coli* as well as against one fungus *C. albicans*. For MBC and MIC testing, the stock solution of the target compounds and reference drugs (sulfamethoxazole, sulfadiazine, and fluconazole) of 10 mg /ml was used to prepare different concentrations from 10 to1000 mcg/ml. The zone inhibition was measured utilizing the resulted MIC by using the agar diffusion method. The final compounds were solubilized by DMSO, and the later was used as a negative control [23].

Sensitivity Assessment

The above samples diluted by utilizing Muller–Hinton broth as diluent and were putted on a microtiter plate. Except for the negative control, all wells of the plate were inoculated for18-20 hr. at 37 ºC with 20 µl of bacterial suspension that was eq. to McFarland standard no. 0.5 (1.5 x 10^8 CFU/ml). After that 20 µl of resazurin (which was previously produced by dissolving 0.015 g of resazurin in 100ml of distilled water and stored at 4 ºC after its preparation) [107] was putted onto each well and then the plate incubated for 2hr. to observe color changes. By visual detection the sub-MIC (the lowest concentration at which the color of resazurin changed from blue to pink) was established [24,25].

The agar diffusion method was done by distributing of the bacterial suspension (0.1 ml) on the surface of nutrient agar and incubated for 24 hr. at 37 ºC. Then from single colony, the bacterial suspension was prepared eq. to McFarland standard no. 0.5 (1.5 x 10^8 CFU/ml). the spreading of this suspension on the Mueller – Hinton agar medium was done by using a sterile cotton swab and left for 10 min. the wells with 5 mm were made on this agar (4 well per plate). After that the tested compounds (80 µl) were added to each well and then the incubation done at 37 ºC for 24 hr. for bacterial isolates and at 30 ºC for 72 hr. for fungal isolate. After completion this periods the diameter of inhibition zones was measured in mm [26].

Statistical analysis

To assess the difference between the data acquired from the target compounds and the reference controls, a two-way ANOVA test was used. The software IBM SPSS Statistics 25 was used for difference analysis.

Results and Discussion

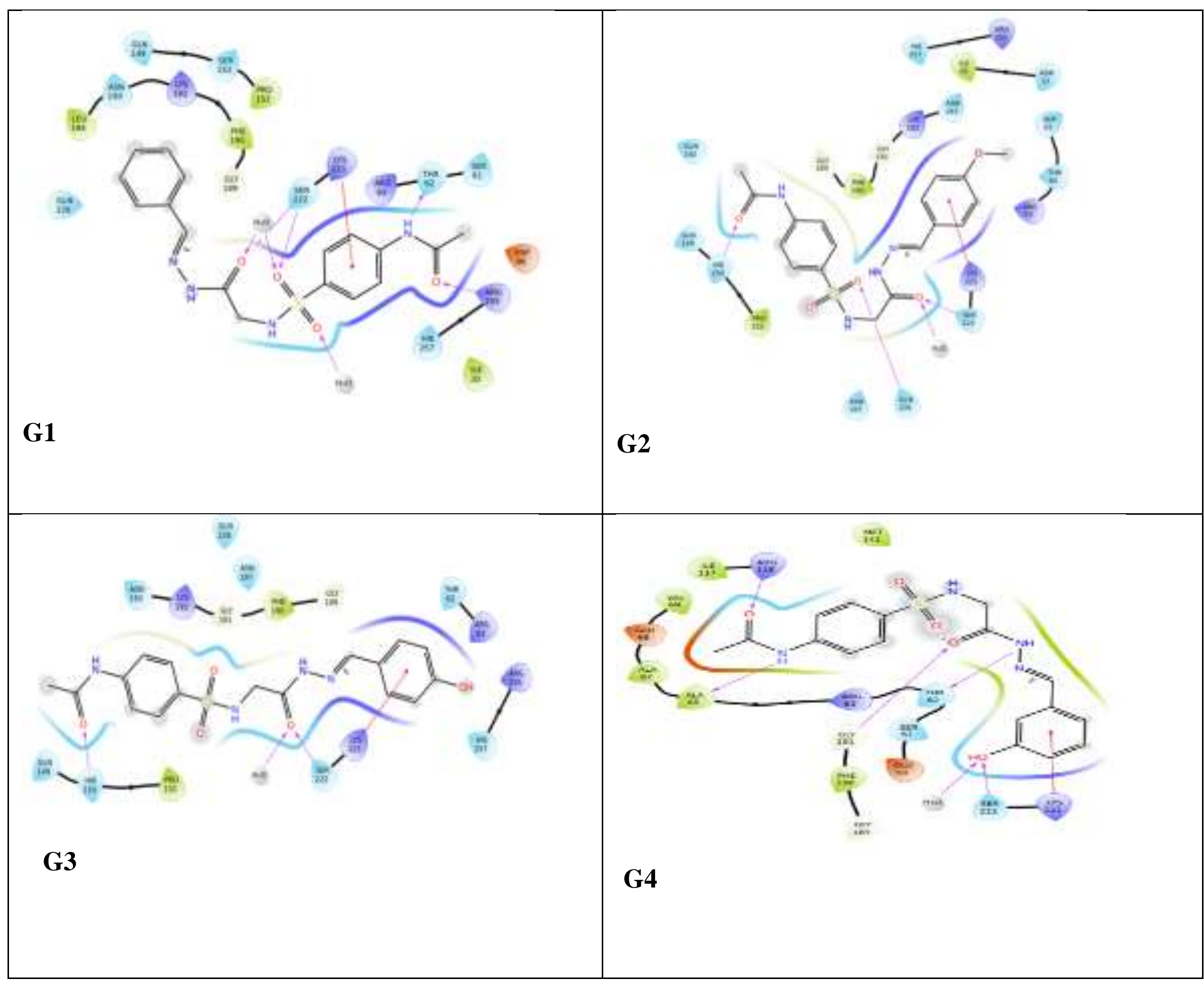
***In silico* studies**

Molecular docking results

The molecular docking findings, comprising docked ligands, binding mode, and binding free energy, were investigated to assess the interaction between target produced ligands and the amino acid residues of the protein Yersinia pestis DHPS (PDB ID: 5JQ9). Table 1 summarizes the docking findings.

Table 1. The docking score and the interactions of final compounds and standard drugs with DHPS (PDB ID: 5JQ9)

Compound	Docking score Kcal/mole	Type of interactions
G1	-5.848	Hydrogen bonding: Thr 62, Ser 222, Arg 255 Pi-cation: Lys 221
G2	-5.894	Hydrogen bonding: Hie 150, Ser 222, Gln 256 Pi-cation: Lys 221
G3	-5.987	Hydrogen bonding: Hie 150, Ser 222 Pi-cation: Lys 221
G4	-5.998	Hydrogen bonding: Thr 62, Ala 66, Arg 118, Gly 191, Ser 222 Pi-cation: Lys 221
G5	-5.177	Hydrogen bonding: Thr 62, Gly 189, Ser 222, Arg 256 Pi-cation: Lys 221 Pi-Pi stacking: Phe 190 Halogen bond: Arg 118
G6	-6.295	Hydrogen bonding: Arg 63, Hie 150, Ser 222 Pi-cation: Lys 221
sulfamethoxazole	-5.895	Hydrogen bonding: Glu 60, Arg 63, Asp 96, Arg 255, Hie 256 Salt bridge: Arg 63
Sulfadiazine	-5.712	Hydrogen bonding: Glu 60, Arg 63, Asp 96, Arg 255, Hie 257 Pi-cation: Lys 221 Pi-Pi stacking: Phe 190 Salt bridge: Arg 63



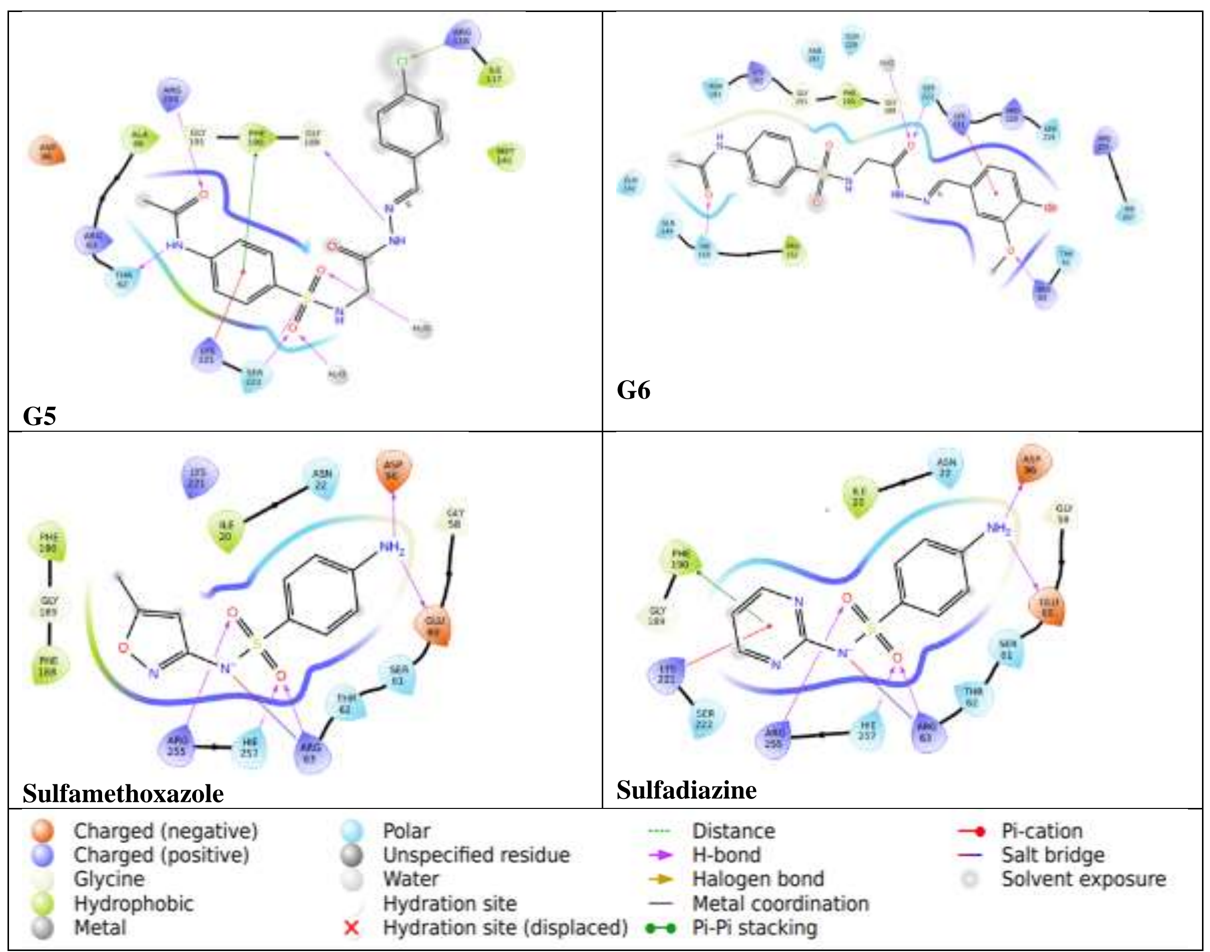


Figure 3. The 2D structures of docked compounds (target compounds and reference drugs) with DHPS enzyme

Based on the docking results of the target compounds and reference drugs with prepared protein DHPS (PDB ID: 5JQ9) which were mentioned in Table 1, The reference drugs (sulfamethoxazole and sulfadiazine) had docking score -5.895 (resulted from 3 H-bonding of sulfonyl group with Arg 63,Arg 255 and Hie 256, 2 H-bonding of the amino group with Glu 60 and Asp 96 , and Salt bridge between ionized nitrogen atom of sulfonamide group with Arg 63) and -5.712 (resulted from 3 H-bonding of sulfonyl group with Arg 63,Arg 255 and Hie 257, 2 H-bonding of the amino group with Glu 60 and Asp 96 , Pi-cation bond between diazine ring with Lys 221,Pi-Pi stacking bond between diazine ring with Phe 190 and Salt bridge between the ionized nitrogen atom of sulfonamide group with Arg 63) respectively.

The molecular docking scores for the synthesized compounds (which are ranges from strong affinity, the same or good affinity to slightly poor affinity in comparison with reference drugs) are clarified below:

For the compounds with strong affinity , **G6** scored -6.295 (reflecting from its interaction with the target protein as a 3 H-bonding of oxygen atoms of 2 amide group and methoxy group with Arg 63, Hie 150, and Ser 222 , and as a Pi-cation bond between one aromatic ring with Lys 221) , **G4** was scored -5.998 (reflecting from its interaction with target protein as 5 H-bonding of oxygen atoms of 2 amide group and nitrogen atoms of 2 amide group with Thr 62, Ala 66, Arg 118, Gly 191, Ser 222, and as Pi-cation bond between one aromatic ring with Lys 221) and **G3** was scored -5.987 (coming from its interaction as 2 H bonding of oxygen atoms of 2 amide group with Hie 150, Ser 222 and as a Pi-cation bond between acetamido benzene ring with Lys 221).

The compounds with the same or good affinity, **G2** scored -5.894 (resulting from its interactions as a 3 H bonding of oxygen atoms of 2 amide group and the oxygen of sulfonyl group ,and as pi-cation bond between one aromatic ring with Lys 221) , **G1** scored -5.848 (resulted from its interactions as a 3 H bonding of oxygen atom of sulfonyl group , of oxygen atom and nitrogen atom of acetamido group with Thr 62, Ser 222, Arg 255 and as a pi-cation bond between acetamido benzene ring with Lys 221) .

The reminder compound,**G5** with slightly poor affinity was scored -5.177 (resulted from its interactions as a 4 H bonding of oxygen atom of acetamido group , of oxygen atom of sulfonyl group , nitrogen atoms of acetamido group and amide group , as Pi-cation bond between aromatic ring with Lys 221, as pi-pi bond between aromatic ring with Phe 190 and as Halogen bond of chlorine atom with Arg 118).

Additionally, based on the molecular docking results above, the H-bonding with Ser 222 and the Pi-cation bond with Lys 221 are essential for the affinity of the final compounds to the target protein.

ADME prediction results

The ADME findings indicated that the target compounds adhere to the Lipinski rule of five, categorizing them as potential drug-like molecules. These drugs had favorable oral bioavailability while exhibiting less CNS penetration. Additionally, the QPPCaco model for the gut-blood barrier indicated that the final compounds exhibited permeability results ranging from acceptable to good (values >500 nm/sec are considered excellent, while values <25 are deemed bad) [27].

Ultimately, the analysis of the number of probable metabolic reactions (#Metab) indicated that all final compounds lack structural liability to participate in further metabolic processes such as aromatic hydroxyl oxidation, enol oxidation, and others (normal range 1-8) [28].

Table 2. Drug likeness characteristics for final compounds and reference drugs

Compound	Mol. MW	Rule Of Five	Human Oral Absorption	CNS	#Metab	Donor HB	Accpt HB	QPP Caco	% oral Absorp.
G1	374.41	0	3	-2	1	2.25	8.75	108.99	74.375
G2	404.44	0	3	-2	3	2.25	9.5	404.44	71.501
G3	390.41	0	2	-2	2	3.25	9.5	390.41	57.825
G4	390.41	0	2	-2	2	3.25	9.5	390.41	57.947
G5	408.85	0	3	-2	1	2.25	8.75	408.85	76.106
G6	420.43	0	2	-2	3	3.25	10.25	420.43	58.956
Sulfadiazine	250.27	0	3	-2	3	2.5	7.5	250.27	68.642
Sulfamethoxazole	253.27	0	3	-2	2	2.5	7	253.27	70.212

(HB donor ≤ 5, HB acceptor ≤ 10, molecular weight < 500, and log p < 5) are all included in the Lipinski Rule of Five (limit 0–3). (1=Low,2=Medium, or 3=high) was the range of the oral absorption. The scale for Prediction of CNS central nervous system activity ranged from a –2 (inactive) to +2 (active). The Primary Metabolites < 7 (Limit 0-3 accepted).Gut-blood barrier QPPCaco with scale of <25 poor permeability to >500 great. The scale of <25% poor to >80% high% for the oral absorption estimation.

Synthetic studies

The procedures for production of the synthesized target compounds and their intermediates demonstrated in the scheme1 steps can clarify as follows:

- Step 1: Synthesis of first intermediates, glycine methyl ester HCL salts involving esterification (protection) of carboxyl groups of two amino acid by their activation using thionyl chloride to produce acyl chloride that react with methanol to get compound I.
- Step 2: synthesis of second intermediate, 4-acetamidobenzene sulfonyl chloride, was done by reaction of acetanilide with chlorosulfonic acid to produce compound II that is used immediately in next step.
- Step 3: synthesis of sulfonamide by reaction of compound I with fishily prepared compound II separately in presence of TEA in DCM to get compound III.
- Step 4: synthesis of hydrazides by reaction compound III with hydrazine hydrate separately to produce compound IV.
- Step 5: synthesis of hydrazones or Schiff bases (the final products) by separately reaction of compound IV with ethanolic solutions of different aldehydes (benzaldehyde and some of its substituted analogues) by using glacial acetic acid as catalyst to produce the compounds G1-6.

Glycine — $SOCL_2$, MeOH; reflux ,40 ºC/3 hrs → Compound I

acetanilide + chlorosulfonic acids — Heat; w. B, 70 ºC, 20min → Compound **II**

Compound **II** — TEA, Stirring 4hrs at RT; Compound I → Compound **III**

Compound **III** — EtOH, $NH_2NH_2.H_2O$ 80%; Reflux 8-10 hrs → Compound **IV**

Compound **IV** — EtOH, glacial acetic acid; aldehyde, reflux80 ºC for 3-8 hrs → G1-G6

	R
G1	Ar-
G2	4-OCH3-Ar-
G3	4-OH-Ar-
G4	3-OH-Ar-
G5	4-CL-Ar-
G6	4-OH-3OCH3-Ar-

Scheme 1. The steps for the synthesis of the final products, compounds G1-6.

Interpretation of synthetic results

The compound **I** was demonstrated by the appearance of NH bond stretching (broad band), illustrating the formation of the salt of NH_4^+ ion at 3217 to 2800 cm^{-1} and C=O stretching (sharp band) at 1739 cm-1 for the ester formation. The compound **II** formation was indicated by the appearance of the band at 1365 and 1161 cm^{-1} for asymmetric and symmetric stretching of the $-SO_2-$ group. The compound **III** formation was demonstrated by the appearance of a band at 3317 cm^{-1} for NH bond stretching of 2° sulfonamide and a band at 1330 cm-1 and 1157 cm-1 for asymmetric and symmetric stretching of $-SO_2-$ group and band at 1735 cm^{-1} for C=O stretching of ester, The compound **IV** formation was clarified by the appearance of double bands at 3344 cm-1 and 3325 cm^{-1} for NH bond stretching of asymmetric and symmetric 1° amine of the hydrazide and the disappearance of the characteristic ester band.

The formation of the final products demonstrated by the disappearance of the bands for NH stretching of the 1° amine of hydrazide and the appearance of bands of NH bond stretching for 2° sulfonamide and NH bond stretching for 2° amide in the range at 3401 cm-1 to 31182 cm^{-1}. All final compounds have essentially identical signals in the ^1H NMR spectra for the protons of these functional groups, with varying chemical shifts as shown below:

- Singlet for the -NH proton of the acetamido group (at 11.47,11.34,11.26,11.41,11.52 and11.30 ppm for compounds **G1-G6,** respectively).
- Singlet for the -NH proton of amide group adjacent to imine group (at 11.39,11.25,11.17,11.34,11.45 and 11.18 ppm for compounds **G1-G6,** respectively).
- Singlet for 1 proton of -NH of sulfonamide (at 10.31,10.32,10.31,10.32,10.31and10.31 ppm for compounds **G1-G6,** respectively).
- Singlet for -CH=N- proton of imine group (at 8.14, 8.08,8.02,8.06,8.13 and 8.01 ppm for compounds **G1-G6,** respectively).

- Singlet for 2 protons of the $-CH_2$-group (at4.04,4.00,4.00,4.03,4.03 and 3.98 ppm for compounds **G1-G6,** respectively).
- Singlet for the $-CH_3$ protons of the acetamido group (at 2.08, 2.08,2.08,2.09,2.08 and 2.08 for compounds **G1-G6,** respectively).

Additionally, the appearance of the characteristic signals for compound **G2** singlet for the $-OCH_3$ group protons; for compounds **G3** and **G4**, singlet for the OH proton at 9.92 ppm and 9.65 ppm, respectively; for compound **G6** singlet for the OH proton at 9.52 ppm, and singlet for 3 protons of the $-OCH_3$ group attached to the aromatic ring.

Antimicrobial activity

The antimicrobial evaluation of the target compounds (**G1-6**) were determined using Mueller-Hinton agar medium. All these compounds were evaluated against *S. aureus* and *S. pneumonia* as a gram-positive bacterium, against *E. coli* and *P. aeruginosa* as a gram-negative bacterium and against *Candida albicans* as a fungus and Sulfamethoxazole and sulfadiazine were used as references for antibacterial effect, and fluconazole was used as a reference for antifungal effect, DMSO was utilized as solvent. The zone of inhibition demonstrated in Table (3) was measured by mm. The figure 4 showed the antimicrobial activity of tested compounds.

Table 3. The MIC findings for final compounds and compared reference drugs

Compounds	MIC (mm)				
	Gram positive bacteria		Gram negative bacteria		Fungi
	S. aureus	*S. pneumonia*	*E. coli*	*P. aeruginosa*	*Candida albicans*
	Conc.(mcg/ml)				
Sulfamethoxazole	250	500	500	500	-
Sulfadiazine	125	500	1000	1000	-
Fluconazole	-	-	-	-	250
DMSO	solvent and control				
G1	250	500	500	500	500
G2	500	1000	1000	1000	500
G3	500	500	1000	1000	500
G4	500	1000	1000	1000	1000
G5	1000	500	1000	1000	500
G6	250	500	500	500	250

The table 3. was shown the antimicrobial activities of target compounds in comperes with reference drugs represented as MIC values ranging from 250 to 1000 µg/ml

Table 4. The Zone of the inhibition of final compounds and their compared standards in mm

Isolate / Compound	S. aureus	S. Pneumonia	E. coli	P. aeruginosa	C. albicans	Mean	S. E.M	SD	p-value
G1	6	20	10	7	_	8.6	3.44	7.33	0.2
G2	7	20	15	7	_	9.8	3.44	7.79	0.2
G3	10	23	14	12	_	11.8	3.44	8.25	0.2
G4	15	24	16	13	_	13.6	3.44	8.67	0.2
G5	20	20	20	16	21	19.4	3.44	1.94	0.004
G6	20	19	19	16	21	19	3.44	1.87	0.0035
Sulfamethoxazole	34	35	35	31	_	27	3.44	15.18	0.008
Sulfadiazine	30	30	30	30	_	24	3.44	13.41	0.001
Fluconazole	_	_	_	_	32	6.4	3.44	14.31	0.001
DMSO	solvent and control								

The ranges of the zones of the inhibition for assessed compounds (> 15 mm highly inhibitory effect, from 15 -10 mm for moderate inhibitory effect, from 5-10 mm slightly inhibitory effect, and < 5 mm inactive) [29].

Table 5. ANOVA test (Two-way) for the zones of the inhibition of the tested compounds

Tests of Between-Subjects Effects					
Dependent Variable: YI					
Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2881.422[a]	12	240.119	2.844	.009
Intercept	10826.756	1	10826.756	128.231	.000
T	2060.844	8	257.606	3.051	.011
B	820.578	4	205.144	2.430	.068
Error	2701.822	32	84.432		
Total	16410.000	45			
Corrected Total	5583.244	44			
a. R Squared = .516 (Adjusted R Squared = .335)					

From the results shown in two Table 4, All final products had antimicrobial activity demonstrated as the values of the zones of the inhibition in table 5(higher, moderate, or low antimicrobial effect that varied for each microbial species) and the T variable that was clarified in Table 6, has a P value of 0,011 (that is, mean $P < 0.05$). There is a significance difference related to the effect on the dependent variable that represents the zone of the inhibition values.

The compounds **G5** and **G6** were show broad antimicrobial effect with higher zones of inhibition ranging from 16 to 21 mm (including their antifungal activity) , the compounds **G3** and **G4** were exhibited moderate to high antibacterial effect with the zones of the inhibition ranging from 10 to 24 mm , however, the compounds **G1** and **G2** approximately were exhibited the lowest results ranging from 6 to 20 mm of the zones of inhibition . Additionally, S. *pneumonia* and *E. coli* were the more sensitive bacteria for the activity of the final products. The antimicrobial effects of the final compounds are clarified in figures 13 and 14.

Figure 4 Antibacterial and antifungal activity for final compounds compared with standards drugs

Conclusion

The synthesis of series of glycine-based sulfonamide compounds **G1-G6** was done successfully. The compounds were designed by a molecular docking study targeting the *Yersinia pestis* DHPS protein (PDB ID: 5JQ9). Also, they were showed accepted pharmacokinetic properties using simulated ADME analysis.

The physical properties, including melting point and description, and ATR-FTIR and ^{1}H-NMR spectra, have been investigated for the identification and characterization of the synthesized compounds, and the findings corroborate their chemical structure.

The investigation of the antimicrobial effect demonstrated that all final products showed inhibitory effect based on their MIC values and zones of the inhibition. The compounds **G5** and **G6** had broad and high antimicrobial activity.

Acknowledgment

The authors express gratitude to the University of Baghdad, College of Pharmacy, and the Department of Pharmaceutical Chemistry for their cooperation and for the facilities provided to perform the study. My sincere gratitude to Assistant Professor Dr. Salema S. Salman for her invaluable assistance and support.

Conflicts of Interest

The authors of this article affirm that they are free from any personal or financial conflicts of interest that may have appeared to impact their work.

Funding

No financial assistance has been received by the authors.

Ethics Statements

The authors state that their work does not need to approve from the ethics committee.

Author Contribution

The research project was designed by both authors, and their contributions extended to the research approach, which they put into practice by preparing target compounds for FTIR and 1HNMR testing and interpreting the findings. In addition to performing and discussing antimicrobial tests, the authors carefully revised the whole study paper for clarity and scientific rigor.

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دراسة الحركية الدوائية والرسو الجزيئي والتخليق والتركيب والتوصيف والتقييم الأولي للنشاط المضاد للميكروبات لمشتقات الجلايسين الجديدة من السلفوناميد

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الخلاصة

تم تخليق مشتقات سلفوناميدات جديدة قائمة على الجلايسين. تعرض هذه الدراسة المركبات المُخلّقة حديثًا (**G1-6**) التي تُظهر أنشطة واعدة لتثبيط بروتين DHPS، والتي تم تصميمها من خلال تحليل الإرساء الجزيئي الذي يستهدف بروتين DHPS من يرسينيا الطاعونية (معرف PDB: 5JQ9). تم بعد ذلك إخضاع المركبات التي تم الرسو الجزيئي لها الى دراسة الامتصاص والتوزيع والايض والطرح (ADME) لتقييم خصائصها الحركية الدوائية. بدأ هذا العمل بتخليق ملح جلايسين ميثيل إستر الميثيل HCl (مركب **I**) من خلال تنشيط مجموعة الكاربوكسيل الوظيفية للجلايسين بأستخدام كلوريد الثيونيل($SOCl_2$) ثم الاسترة بالميثانول وتخليق ٤-أسيتاميدوبنزين سلفونيل كلوريد (مركب **II**) من الأسيتانيل ، أدى تفاعل المركبين الوسيطين الأخيرين باستخدام ثلاثي إيثيل أمين (TEA) كقاعدة وعامل معادل في ثنائي كلورو الميثان (DCM) إلى تخليق مركب يحتوي على السلفوناميد (مركب **III**). تفاعل هذا المركب بعد ذلك مع $NH_2NH_2.H_2O$ (هيدرات الهيدرازين) لإعطاء مركب **IV** (الهيدرازيد)، الذي تفاعل بعد ذلك مع العديد من الألدهيدات باستخدام حمض الأسيتيك الجليدي كمحفز لإعطاء المركبات المستهدفة النهائية **G1-6**. تم تحديد هذه المركبات باستخدام التحليل الطيفي ب ATR-FTIR (الأشعة تحت الحمراء) و ^{1}HNMR (الرنين المغناطيسي النووي). وباستخدام طريقة الانتشار الجيد، تم اختبار التأثير المضاد للميكروبات للنواتج النهائية في المختبر ضد اثنين من البكتيريا موجبة الجرام المكورات العنقودية الذهبية والمكورات العقدية الرئوية و نوعين من البكتيريا سالبة الجرام الزائفة الزنجارية والإشريكية القولونية وفطر واحد هو المبيضات البيضاء بالمقارنة مع الأدوية القياسية سلفاميثوكسازول وسلفاديازين وفلوكونازول. بشكل عام، جميع المركبات المُصنَّعة لها نشاط مضاد للميكروبات يتراوح بين متوسط إلى عالٍ، لكن المركبين **G5** و **G6** اللذين لهما أعلى نشاط كان لهما منطقة تثبيط (**ZI**) تتراوح بين ١٦ إلى ٢١ ملم.

الكلمات المفتاحية : مضادات الميكروبات، الجلايسين، الرسو الجزيئي، السلفوناميد، منطقة التثبيط