Synthesis, Biological Activity, and Docking Studies of New Heterocyclic Derivatives

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Abstract

Novel sulfonamides with a 1,2,3-triazole ring have been created, and their structures have been identified by spectrum analysis (1HNMR, 13CNMR and FT-IR). The antibacterial properties of produced compounds were tested in vitro against medically significant gram (+) bacterial strains (S. aureus) and gram (-) bacterial strains (E. coli). MIC values (g/mL) and zone of inhibitions were used to determine antibacterial activity (mm). Compounds 1b, 1c, and 1d were shown to have good potent action against S. aureus and E. coli at the minimum inhibitory concentration (MIC, M), and their activity increased as the concentration of manufactured target compounds increased.

1. Introduction

Sulfonamides are a class of medications that includes antibacterial [1–3], anti-inflammatory [4], insulin-releasing [5,6], antidiabetic [7,8], and anticancer [9,10] compounds. Sulfa medicines, which contain the sulfonamide functional group and have a wide range of biological actions, have transformed medical science [11]. Sulfonamides block folic acid, a crucial molecule for bacterial DNA and RNA synthesis; a lack of tetrahydrofolate reduces the generation of new DNA and RNA, causing the bacteria to decay. The proper growth of microorganisms is hampered by bacteria's incorrect conversion of sulfonamide to p-amino benzoic acid for folic acid production. Sulfonamides are also effectively used in agriculture for antibacterial activities as a result of these actions [12, 13]. Drugs with a sulfonamide functional group have been shown to block carbonic anhydrases enzyme, and these enzyme inhibitors have also been described as possible antiglaucoma, anticancer (as substituted heterocyclic and aromatic sulfonamides), diuretics, and antiobesity medicines [14]. Sulfonamides are commonly utilized in human and veterinary medicine [15], especially when other antibiotics are not tolerated by humans. Many sulfonamide derivatives have been reported for agricultural use due to their antifungal [16–18] and herbicidal [19] properties. To combat current drug-resistant infections, innovative antibacterial medicines with distinct modes of action and mechanisms are becoming increasingly popular. When harmful organisms (fungus, bacteria, and mold) are exposed to or treated therapeutically with common antibiotic medicati ons materials, new species emerge as a result of conjugation, transduction, mutation, or transformation. Researchers are paying more attention to the synthesis of novel sulfonamides because of their previous success in medicinal chemistry and pharmaceutical field. We developed a pure 1,4-disubsituted-1,2,3-triazole with antibacterial activity via a copper catalyzed azide-alkyne click chemistry reaction because of the unique structural qualities of 1,2,3-triazole heterocycles that attached with Sulfonamides moiety as well as their biological relevance (Cu-AAC). The chemical structures were determined using Fourier-transform infrared spectroscopy (FTIR) and 1D-NMR spectrum data. Synthetic compounds were also screened for antibacterial activity against two types of bacteria [Gram (-) and Gram (+) microorganisms].

Experimental

Chemicals utilized in this study were analytical grade, obtained from many companies BDH (UK), E-Merck (Germany), and commercial sources, and were synthesized without additional purification. The NMR data (300 MHz for ^{1}H NMR and 75 MHz for ^{13}CNMR and used DMSO-d6 as solvent) spectra were recorded using a Bruker and NMR spectrometer. Whereas IR spectra were recorded using an Alpha IR spectrometer (FTIR-ATR). On a percolated TLC silica plate, the purification and advancement of the produced compounds were validated (Merck, Germany).

General procedures of synthesis

Synthesis of 4-azido-N-(pyrimidin-2-yl) benzene- sulfonamide (compound a) [20]

In a mixture of distilled water and Hydrochloric acid

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in a ratio of (1:2.5) mL, (16.9mmol, 4.25 g) of sulfadiazine is dissolved, and then the mixture cooled with a salt-ice bath to a temperature of 0 °C. During this, an aqueous solution of sodium nitrite was prepared (16.9mmol, 1.171 g) and it is also cooled to 0 °C , after which a nitrite solution is added to sulfadiazine solution a drop by drop where after several additions the color of the solution turned to a yellow-green color, after completing the addition the solution is left for stirring for 45 min during this an aqueous solution of sodium azide was prepared (2eq, 2.207 g), after which the sodium azide solution was added in batches where bubbles were observed during the addition. After the completion of the addition of the solution is left for stirring for 2hrs. The sediment that is formed is filtered and washed several times with distilled water.

4-azido-N-(pyrimidin-2-yl)benzenesulfonamide (a): Product **a** was obtained as a white solid. (yield97%) melting point: 223-225 °C (TLC: ethylacetate:n-hexane 2.5:1, R_f : 0.66), FTIR data (cm^{-1}): 3250(NH group), 3038(C-H aromatic), 2117(-N_3 group), 1577, 1493 (C=C aromatic), 1329(asy SO_2), 1161(sy SO_2), 945(S-N), 835(C-S), ^{1}H-NMR δ: 11.87 (s, 1H, Ar-SO_2-NH-), 8.51-7.03(7H, "aromatic protons").

Synthesis of (prop-2-yn-1-yloxy) derivatives (1-3t) [21]

To (0.01mol) from the phenol derivatives (3-hydroxyquinoline, 4-Hydroxycoumarin, and 2-bromo-5-hydroxybenzaldehyde) dissolved in acetone, 2-4 equivalents of anhydrous potassium carbonate K_2CO_3 were added, and cooling the reaction below 15°C, 2.7-1.2 equivalent of 3-Bromo-1-propyne solution is added in small quantities and in batches, after which the reaction was left under refluxed, the completion of the reaction was monitored using TLC. The solvent is removed under reduced pressure. The residue is dissolved in distilled water, and extraction is accomplished by adding ethyl acetate twice. Anhydrous magnesium sulfate was used to dry the organic layer. To obtain the desired product, the organic solvent is removed by using rotatory evaporator, and purified by Colum chromatography technique (3:2) using a mixture of organic solvents hexane and ethyl acetate as the eluent.

3-(prop-2-yn-1-yloxy)quinoline (1t): obtained as a brawn crystal, (yield 88%), melting point: 127-129°C, (R_f: 0.84), FTIR data (cm^{-1}): 3251(≡C-H), 3104(C-H aromatic), 2923(C-H aliphatic), 2121 (C≡C group), 1587(C=C aromatic), 1239(C-O aromatic), 1012(C-O aliphatic), ^{1}H-NMR δ: 8.24 (d, 2H, Ar-), 7.20 (d, 2H, Ar-), 4.99 (d, 2H, O-CH_2-C≡C), 3.70 (s, 1H, -C≡C-H).

4-(but-3-yn-1-yloxy)-2H-chromen-2-one (2t): Product **2t** was obtained as a yellow solid. (yield84%), melting point: 68-70 °C, (R_f: 0.81), FTIR data (cm^{-1}): 3245(≡C-H), 3078(C-H aromatic), 2982, 2927(C-H aliphatic), 2111(C≡C group), 1726(C=O), 1587,1509(C=C aromatic), 1264(C-O aromatic), 1005(C-O aliphatic), ^{1}H-NMR δ: 7.56 (d, 1H, Ar-), 7.42 (s, 1H, Ar-), 7.23 (d, 1H, Ar-), 4.94 (s, 2H, O-CH_2-C≡C), 3.84 (s, 3H, O-CH_3), 3.65 (s, 1H, C≡C-H).

2-bromo-5-(prop-2-yn-1-yloxy)benzaldehyde (3t) : Product **3t** was obtained as pale yellow powder. (yield 82%), melting point: 79-81°C, (R_f: 0.83), FTIR data (cm^{-1}): 3200(≡C-H), 2922(C-H aliphatic), 2113(C≡C group), 1155(C-N aliphatic), ^{1}H-NMR δ: 9.85 (s, 1H, -CHO), 7.56 (d, 1H, Ar-), 7.42 (s, 1H, Ar-), 7.23 (d, 1H, Ar-), 4.94 (s, 2H, O-CH_2-C≡C), 3.65 (s, 1H, C≡C-H).

Synthesis of 1,2,3-triazoles derivatives (1b-d) [22]

(1.2eq) From compounds **1t**, **2t** and **3t** to (0.54mmol, 0.149g) from compound **a** dissolved in 17mLDMF after the mixture remained on stirring for 10 minutes added (5mol%) from $CuSO_4.5H_2O$ and (10mol%) sodium ascorbate, after which the reaction is left for stirring at laboratory temperature, after the completion of the reaction(as indicated by TLC, ethylacetate:n-hexane:methanol 2:1:0.35),the solvent was removed using a rotary evaporator, then the sediment was washed with distilled water several times, after which the mixture was purified by recrystallization using glacial acetic acid and ethanol (1:3) .

N-(pyrimidin-2-yl)-4-(4-((quinolin-3-yloxy)methyl)-1H-1,2,3-triazol-1-yl)benzene sulfonamide (1b): Product **1b** was obtained as a white solid. (yield80%), melting point: 318-320 °C, (R_f: 0.41). FT-IR data (cm^{-1}): 3151(C-H triazole), 3107(C-H aromatic), 1592(C=C aromatic), 1252(C-O aromatic), 1099(S=O str), 1020(C-O aliphatic), 964(S-N), 838(C-S), NMR data: ^{1}H-NMR δ: 9.10 (s, 1H, triazole ring), 8.53-6.97 (aromatic protons), 5.43 (s, 2H, -O-CH_2-).^{13}C-NMR δ: 157.53, 156.40, 151.01, 148.63, 144.44, 140.15, 139.49, 137.51, 129.85, 129.56, 129.40, 129.11, 128.05, 126.53, 119.66, 117.90, 114.58, 112.74, 57.96. 164.00, 157.49, 155.55, 147.40, 141.81, 139.43, 137.18, 130.28, 124.54, 119.51, 114.78, 113.72, 59.46.

4-(4-(((6-methoxy-2-oxo-2H-chromen-4-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (1c): Product **1c** was obtained as a white solid. (yield83%), melting point: 276-278 °C, (R_f: 0.39), FTIR data(cm^{-1}): 3137(C-H triazole), 3083(C-H aromatic), 2955(C-H aliphatic), 1729(C=O carbonyl), 1586(C=C aromatic), 1259(C-O aromatic), 1087(S=O str), 1024(C-O aliphatic), 969(S-N), 860(C-S), ^{1}H-NMR δ: 11.25 (s, 1H, -NH-), 8.59 (s, 1H, triazole ring), 8.49-6.90(aromatic protons), 5.38 (s, 2H, -O-CH_2-), 3.82(s, 3H, -O-CH_3), **^{13}C-NMR** δ: 163.29, 163.00, 157.53, 156.45, 154.70, 149.90, 148.65, 139.51, 137.51, 129.70, 122.30, 119.66, 118.69, 117.07, 112.95, 112.74, 109.12, 91.72, 57.81, 55.81.

4-(4-((4-bromo-3-formylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (1d): Product **1d** was obtained as a white-yellow solid. (yield80%), melting point 321-323 °C, (R_f: 0.42), FTIR data (cm^{-1}): 3146(C-H triazole), 3050(C-H aromatic), 2815, 2734(C-H aldehyde "FERMI doublet"), 1688(C=O aldehyde), 1590(C=C

aromatic), 1247(C-O aromatic), 1091(S=O str), 1021(C-O aliphatic), 964(S-N), 835(C-S), ^{1}H-NMR δ: 11.32 (s, 1H, -NH-), 9.98 (s, 1H, CHO), 8.66,(s, 1H, triazole ring), 8.56-6.98 (aromatic protons), 5.41 (s, 2H, -O-CH_2-),13C NMR δ: 191.65, 158.08, 157.58, 156.45, 148.78, 139.51, 137.51, 136.47, 133.56, 129.70, 120.84, 120.17, 119.66, 117.90, 113.78, 112.75, 58.11, 40.74, 40.52, 40.21, 39.65, 39.41, 39.14.

Antibacterial Study

Disk diffusion method [23]

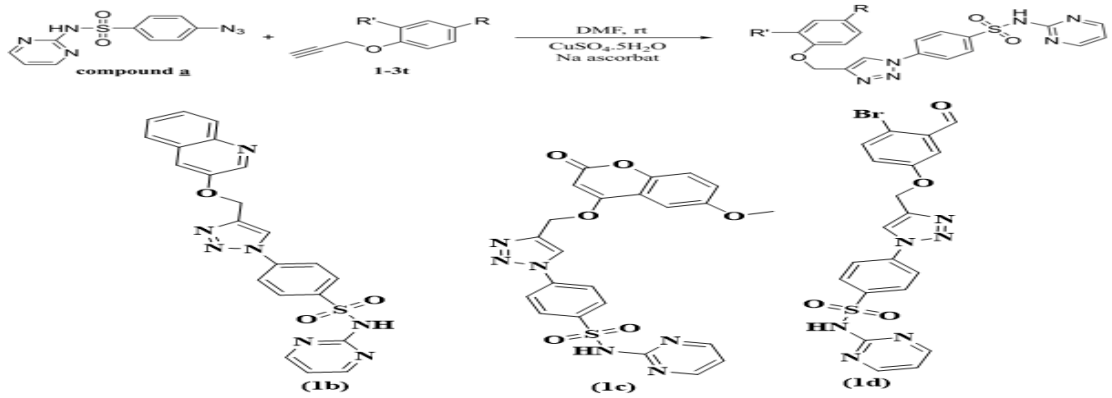
Two strains of *Staph aureus and E. coli* have been chosen. Bacterium is used for all experiments, and grown in Muller Hinton agar. All types of bacteria have been grown at 36 hrs and have been incubated at 37 °C. After serial optimization to reach $1.5x10^{-8}$ bacteria per ml, it is used spectrophotometry experiment to compare the OD_{600} with viable count (CFU). It is around OD_{600} 0.4 equal $1x10^8$.Different concentrations have been prepared as following (25, 50, 100, 150 & 200) µM in (DMSO) of all prepared heterocyclic in our study, added separately to the wells on the plates that already have bacterial growth. The plates were incubated for 24 h to test the anti-bacterial effects; a ruler is used to measure the inhibition zone to the nearest millimeter (mm).

Docking Study Assay

The protein structure was improved before the docking process using Molecular Operating Environment (MOE) by deleting irrelevant structures and crystallographic water molecules. The protein's structure was further improved by mending the backbone, side chains, and termini. The protein was also given hydrogen atoms.

2. Results and Discussion

A series of three sulfonamides containing 1,2,3-triazole ring were synthesized through 1,3-dipolar cycloaddition reaction. The end products were obtained by reacting 4-azido-N-(pyrimidin-2-yl) benzene- sulfonamide (compound a) and (prop-2-yn-1-yloxy) derivatives (1t-3t) in the presence of $CuSO_4.5H_2O$ and sodium ascorbate as catalyst with continuous stirring. The reaction conditions are detailed in the experimental section, and the (δ 163.25-109.12 ppm) sulfonamide synthetic pathway is shown in Scheme 1. The synthesized compounds were characterized by FT-IR; the characteristics band at 3250 cm^{-1} of N-H amide stretching, 3038 cm^{-1} of C-H aromatic, 2117 cm^{-1} of azide group, 1577, 1493 cm^{-1} of (C=C aromatic), 1329 cm^{-1}, 1161 cm^{-1} of (asy SO_2) and (sy SO_2) respectively for compound (a) reveals the formation of azido sulfonamide. Whereas the characteristics band at 3251-3200 cm^{-1} of (≡C-H), 3104-3078 cm^{-1} of (C-H aromatic), 2121-2111 $cm^{-1}$of (C≡C group) and 1587-1509 cm^{-1} of (C=C aromatic) for compound (a) reveals the formation of (prop-2-yn-1-yloxy) derivatives (1t-3t). Finally, the characteristics band at 3151-3137 $cm^{-1}$of (C-H triazole ring), 3107-3050 $cm^{-1}$of (C-H aromatic), 1592-1586 $cm^{-1}$of (C=C aromatic) for compound (a) reveals the formation of target compounds and other stretching vibrations bands at 2815, 2734 of cm^{-1} (C-H aldehyde "FERMI doublet"), 1688 cm^{-1} (C=O aldehyde), in compound (1d). The structures of all prepared sulfonamide derivatives were also identified by ^{1}HNMR and ^{13}CNMR by dissolving in DMSO-d6. ^{1}HNMR spectra of the first compound (a) showed a singlet signal at δ 11.87 ppm of (-SO_2-NH-) corresponds to NH group of sulfonamide in azido sulfonamide, while a signal at *δ* 8.51-7.03 assigned to aromatic protons. ^{1}HNMR spectra of (prop-2-yn-1-yloxy) derivatives (1t-3t) showed a specific singlet signal at *δ* 3.70-3.65 ppm due to acetylic protons(-C≡C-H) and δ 4.99-4.94 ppm of methylene protons (O-CH_2-C≡C), and other singlet signal at δ 9.85 ppm and 3.84 ppm assigned to aldehyde proton and methyl protons in methoxy group respectively. Whereas ^{1}HNMR spectra of the end derivatives (1b,1c and 1d) showed a singlet signal at δ 11.25-11.32 ppm of (-SO_2-NH-) corresponds to NH group of sulfonamide in 1,2,3-triazole sulfonamide derivatives, while a singlet signal at *δ* 9.10-8.59 ppm assigned to 1,2,3-triazole ring protons. The aromatic protons showed multiple signals at δ 8.56-6.90 ppm. The value of methylene protons (-O-CH_2-triazole ring) was shifting to down field at δ 5.41-5.38 ppm because attached to the triazole ring. Also, ^{13}C-NMR spectra of the end derivatives (1b,1c and 1d) showed the signals, (*δ* 120.84-119.66, & *δ* 144.44-139.51ppm) to triazole ring carbon atoms, and the aromatic carbon's signals in the range



Scheme 1. Synthesis new sulfonamides attached to 1,2,3-triazole derivatives 1b, 1c and 1d

Antibacterial activity

Synthesized compounds were also screened for their antibacterial activities against Gram negative bacterial *E. coli* and gram positive *S. aureus* for their antibacterial efficacy by a diffusion method in a Mueller-Hinton agar medium and using ciprofloxacin as reference antibacterial agent. Among the bacterial strains, we found approximately the tested compounds are highly active tested bacteria, while compound **1d** has a high activity against *Staphylococcus aureus*.

Table 1: The produced compounds 1b, 1c and 1d each have a minimum inhibitory concentration (MIC) of g/mL

Com. NO	Gram-negative bacteria					Gram-positive bacteria				
	E. coli					*S. aureus*				
	25 µM	50 µM	100 µM	150 µM	200 µM	25 µM	50 µM	100 µM	150 µM	µM200
1b	40	55	70	85	95	40	55	70	85	95
1c	40	55	70	85	95	40	55	70	85	95
1d	35	50	60	75	90	35	50	60	75	90
Ciprofloxacin	50	70	80	95	105	50	70	80	95	105

Antibacterial study of the prepared heterocyclic

The antibacterial effectiveness of the produced heterocyclic compounds was examined using Gram-negative Escherichia coli and Gram-positive Staphylococcus aureus bacteria in a Mueller-Hinton agar medium using a diffusion method. The inhibition zones were assessed after 24 hours of incubation. We found approximately the tested compounds are highly active against Gram-positive bacteria than Gram-negative bacteria, while compound **1d** has a high activity against *Staphylococcus aureus*.

Molecular docking study

MOE was chosen from among a variety of available resources for docking because of its user-friendly graphical interface. It provides a clear graphical representation of the results by displaying the positions and interactions of ligand and receptor binding residues [24]. The study aimed to provide a good simulation of antibacterial activity of the prepared heterocyclic **1d**, **1b** and **3b**. Before starting the molecular docking process, there were several important steps that included preparing the ligand and correcting the structure of the protein, in addition to selecting the docking site on the protein. The purpose of preparing 3D macromolecular structures is to correct structures and to prepare macromolecular data for further computational analysis. At present, the primary source of 3D bio molecular structural data is X-ray crystallography. One major issue with macromolecular X-ray crystal structures is that of missing or poorly resolved atomic data. Areas that cannot be well-resolved may result in multiple models, alternate locations, or data being absent altogether [25]. In many cases, the missing data needs to be modeled and fixed before subsequent computational analyses can proceed. The goal of the Site Finder phase was to compute putative active sites in a receptor using the receptor's 3D atomic coordinates. Because no energy models are used, MOE's Site Finder is classified as a geometric method. Instead, the relative locations and accessibility of receptor atoms, as well as a basic classification of chemical kind, are taken into account. Alpha Shapes are a generalization of established convex hulls [26], and the Site Finder approach is based on them. The docking process was carried out using the MOE module between the selected produced compound (1d, 1c, and 1d) and (4h8e and 1ecl) PDB co-crystals of *Staphylococcus aureus* and *Escherichia coli*, respectively [27,28]. Basic data (Tables 2 and 3) as well as photos of docking complexes were exported, are presented as well in Figure 1 and 2. From the observation of docking results of the compound **1b, 1c and 1d** with the chosen site of Staphylococcus *aureus* protein, shows the batter results as includes in Table (3.1) where the docking score was (-6.9209, -8.0463, -7.9208) in addition to The root mean square deviation between the pose before refinement and the pose after refinement was (1.5396, 1.5179, 1.1869). Whereas the observation of docking results of the compound **1b, 1c and 1d** with the chosen site of *Escherichia coli* protein, shows the batter results as includes in Table (3.2) where the docking score was (-7.2941, -7.6163, -7.7.2919) in addition to The root mean square deviation between the pose before refinement and the pose after refinement was (1.0560, 1.18391, 1.1211).

Table 2. docking interaction parameters for effective synthesized 1d, 1b & 3b ligands against 4h8e protein

Compound docked	Receptor	Distance(Å)	E (Kcal/mol)	S(energy score)	rmsd_refine(Å)
1b	ARG84,	3.01	-3.1	-6.9209	1.5396
1c	ARG84,GLY34, ASP33, ASN35,HIS50.	3.02,3.21, 3.11,4.08, 3.35	-3.1, -2.9, -2. 3,-1.6, -3.4	-8.0463	1.5179
1d	ARG84,GLY34, ASP33, ARG201,SER209.	3.03,4.25, 3.12,3.01, 4.06	-1.9,-1.8, -2.7,-3.3, -1.8	-7.9208	1.1869

Table3.docking interaction parameters for effective synthesized 1b, 1c & 1b ligands against 1ecl protein					
Compound docked	Receptor	Distance(Å)	E (Kcal/mol)	S(energy score)	rmsd_refine(Å)
1b	ARG493, ARG114, ARG161	3.09,3.15, 3.16	-3.2, -1.8, -1.4	-7.2941	1.0560
1c	ARG161, ARG 114, ARG 158	3.02,3.12, 3.19	-3.4, -2.9, -2.5	-7.6163	1.1839
1d	ARG493, ASP323, HIS 365	3.43,4.45, 2.17	-0.9, -0.8, -3.1	-7.2919	1.1121

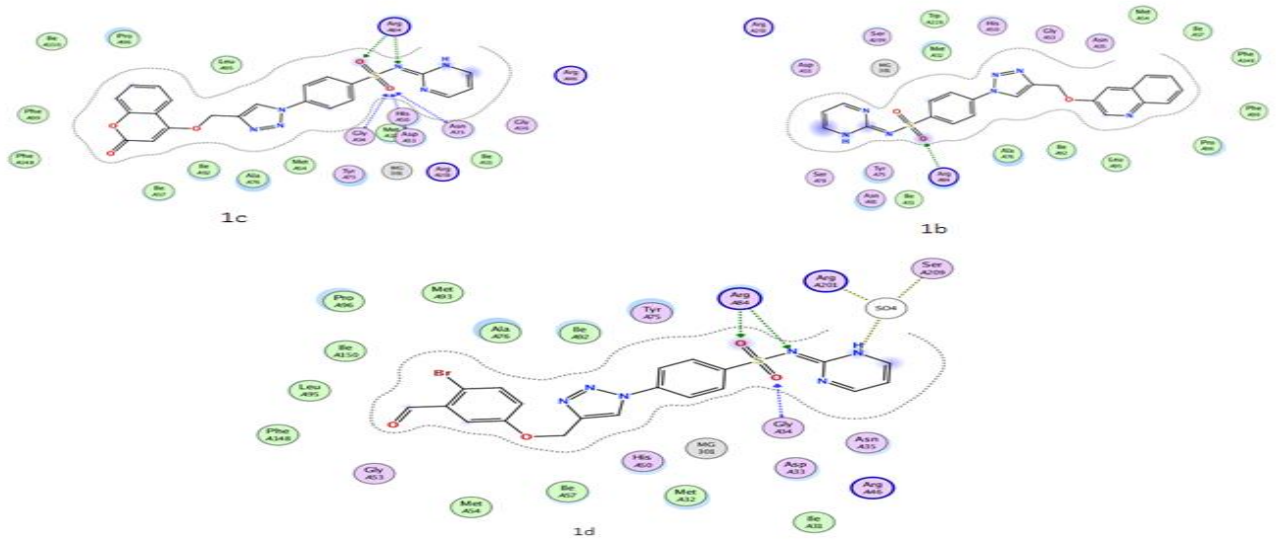


Figure 1. 2D interaction diagrams representing the docked conformation of ligand 1b,1c,1d against 4h8e

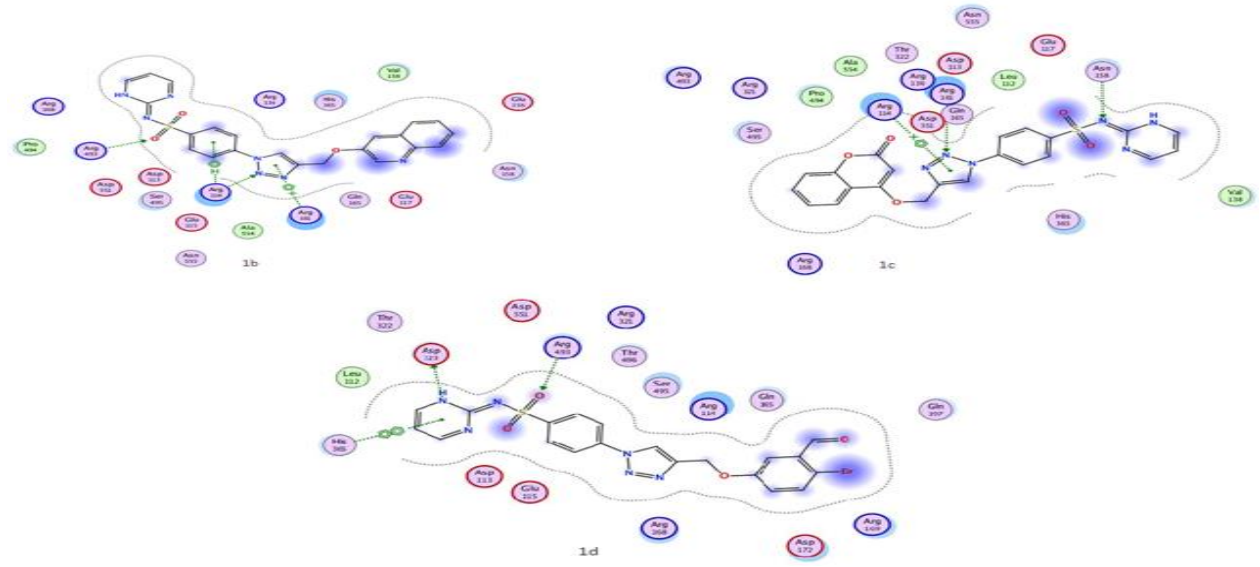


Figure .2 2D interaction diagrams representing the docked conformation of ligand 1b,1c, 1d against 1ecl

3. Conclusion

In conclusion, three novel sulfonamides were synthesized; the reactions conditions are easy and excellent yields of compounds were obtained and progress of reaction was monitored by TLC and their structures were confirmed by spectral analysis. All the synthesized compounds were evaluated for their antibacterial activities and the results of their bioassay indicated that the sulfonamides attached to 1,2,3-triazole ring showed antibacterial activities comparable to ciprofloxacin. The results confirmed that the compounds which are active against bacterial strains showed antibacterial activities after formation of sulfonamides.

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