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Research Article

The synthesis and assessment of the pharmacological potential of novel heterocyclic 1,2,3-triazoline scaffolds and its relation to biological diversity

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Abstract

A novel sulfamethoxazole containing a 1,2,3-triazoline moiety (designated as 1t, 2t, and 3t) was synthesized in the present investigation using a design-driven synthetic approach. The identification of the chemical structures of the synthesized products was accomplished through analytical techniques such as NMR, IR, and spectral analyses. The obtained results were in complete agreement with the assigned structures. The bacterial strains employed in this study included Staphylococcus aureus and Escherichia coli, and all final products were assessed for their antibacterial properties. The minimum inhibitory concentration (MIC) values were verified, revealing noticeable antibacterial activity for the prepared compound. These compounds could potentially serve as a promising starting point in the quest for new antibacterial medications.

Keywords: Sulfamethoxazole, 1,2,3-Triazoline ring, Docking, Click chemistry, Antibacterial activity

Introduction

Antibiotic resistance emerges when bacteria and fungi acquire the capability to overcome drugs

specifically designed to eliminate them (Cantas et al., 2013; Kuehn, 2013). This implies that the pathogens are not eradicated and instead multiply, resulting in infections that are more difficult to treat and, in some cases, incurable (Bassetti & Righi, 2013; Zhang et al., 2006). A global public health concern, antibiotic resistance is responsible for roughly 5 million fatalities in 2019 and at least 1.27 million deaths worldwide (Cueto, 2023). Over 35,000 individuals pass away as a result of the more than 2.8 million antimicrobial-resistant diseases that take place annually in the US (Cueto, 2023; Kothayer et al., 2013). Compounds of 1,2,3-triazoline are organic substances characterized by a five-membered ring comprising three nitrogen atoms and two carbon atoms. The ring is formed by connecting one carbon atom to two adjacent nitrogen atoms (Lauria et al., 2014). This chemical structural arrangement gives the organic compound its name: "1,2,3" refers to the positions of the nitrogen atoms in the ring (Kuntala et al., 2015). 1,2,3-Triazoline compounds have been studied for their potential applications in medicinal chemistry, agrochemicals, and materials science (Dofe et al., 2017). They possess diverse biological activities, such as antitumor, antimicrobial, antiviral (El-Sabbagh et al., 2009; Faria et al., 2017; Puneeth et al., 2016; Rashad et al., 2010; Sharma et al., 2011), antileshmanial (Bekhit et al., 2015; Yang et al., 2018), and anti-inflammatory properties (Bekhit et al., 2005; Bekhit & Abdel-Aziem, 2004). Due to their distinct structural characteristics, these compounds show great potential as candidates for drug discovery and advancement (Strzelecka & Świątek, 2021). Developing efficient synthetic strategies and exploring the structure-activity relationships of 1,2,3-triazoline compounds continue to be active areas of research (Zoidis et al., 2021). Their versatile nature and wide range of applications make them an intriguing subject for scientists working in various fields of chemistry (Kumari et al., 2021). In our work, we developed novel compounds with 1,2,3-triazole effective groups, and derivatives based on sulfamethoxazole, and also evaluated their biological antibacterial activity.

Experimental

All chemicals and organic solvents were used with the highest analytical status and were acquired commercially from Fluka, Sigma-Aldrich and commercially sourced. At the University of Kufa, Faculty of Science, infrared spectra were captured utilizing the Fourier-transform infrared Bruker ALPHA FT-IR instrument. At the Iranian Mashed University, NMR spectra in DMSO-d6 were recorded at 75 MHz for ^{13}C NMR and 300 MHz for ^{1}H NMR. The new compounds were determined melting points by using the Electro-Thermal Melting Point Apparatus from the United Kingdom.

Synthesis of 4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide (compound 1) (Salman et al., 2019)

Sulfamethoxazole (16.9 mmol) is dissolved in a solution comprising distilled water and hydrochloric acid in a 1:2.5 mL ratio. The mixture is then cooled to 0 °C using a salt-ice bath. Concurrently, a sodium nitrite aqueous solution (16.9 mmol) is prepared and also cooled to 0 °C. The nitrite solution is slowly added dropwise to the sulfamethoxazole solution upon reaching the desired temperature. Following this addition, the solution is stirred for 45 minutes, during which an aqueous solution of sodium azide (20 mmol) is prepared. Upon completion of the stirring period, the mixture is allowed to stir for an additional two hours. The resulting precipitate is filtered and meticulously washed with distilled water.

4-azido-N-(5-methylisoxazol-3-yl)benzenesulfonamide (1): It was prepared as a powder, slight yellow; mp 93-95 ºC; 88% yield; FTIR data, ν (cm^{-1}) 3242(N-H of sulfonamide), 3077(C-H, aromatic ring), 2986, 2842(C-H, aliphatic), 2103(azide group, N_3), 1344(asy SO_2) , 1169(sy SO_2), 1686(alkene groupC=C), ^{1}H NMR: δ 2.32 (s, 3H, -CH_3), 6.16 (s, 1H, C-H-oxazole ring), 7.90–7.32 (m, 4H, Aromatic-H), 11.48 (s, 1H, N-H), ^{13}CNMR: δ 169.15, 156.74, 146.04, 136.61, 129.75, 119.16, 96.83, 12.54.

Synthesis of 1, 2, 3-Triazoline compounds (1t, 2t, and 3t) (Salman et al., 2019)

After a brief period, 17 mL of DMF containing 0.54 mmol (1.2 equiv) of compound 1, involving double bond derivatives such as malic anhydride, cinnamic acid, and acrylamide, is introduced. The catalyst comprises monovalent pentahydrated copper sulfate and sodium ascorbate in a 5% mol and 10% mol ratio, respectively. Upon completion of the reaction, determined by TLC (n-hexane:ethyl acetate:methanol 1:2:0.35), the temperature is elevated to 50 °C. The solvent is evaporated using a rotary evaporator, and the resulting product is rinsed with distilled water. For recrystallization, a mixture of glacial acetic acid and acetone (2:3) is employed.

4-(4,6-dioxo-3a,4,6,6a-tetrahydro-1H-furo[3,4-d][1,2,3]triazol-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (1t): Product **1t** was obtained as a white powder. (yield 79 %), melting point: 188-190 ºC, (R_f: 0.41), FT-IR data (cm^{-1}): 3041(C-H aromatic ring), 2994(C-H asy aliphatic), 2852(C-H sy aliphatic), 1772(C=O carbonyl group), 1586(C=C aromatic ring), 1333(asy SO_2), 1166(sy SO_2), 923(S-N), NMR: ^{1}H NMR: δ11.36 (s, 1H, N-H, sulfonamide), 7.84

–7.12 (m, Aromatic protons), 6.09 (s, 1H, C-H-oxazole ring), 5.49(d, J = 7.5 Hz, 1H, triazoline ring), 5.13 (d, J = 7.4 Hz, 1H, triazoline ring), 2.31 (s, 3H, -CH_3).

1-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4-phenyl-4,5-dihydro-1H-1,2,3-triazole-5-carboxylic acid (2t): Product **2t** was obtained as a white powder. (yield83%), melting point: 211-213 ^oC, (R_f: 0.39), FT-IR data (cm^{-1}): 3088(C-H aromatic), 2983(asy C-H aliphatic), 2879(sy C-H aliphatic) ,1732(C=O group), 1586(C=C aromatic), 1381(N=N group), 1333 (asy SO_2 group), 1267(N-N group), 1166(sy SO_2), 923(S-N), 812(C-S), ^{1}H-NMR: δ 12.37(s, 1H, COOH), 11.34 (s, 1H, N-H, sulfonamide), 7.79–7.06 (m, Aromatic protons), 6.09(s, 1H, C-H-oxazole ring), 5.42(d, J = 7.5 Hz, 1H, triazoline ring), 5.39 (d, J = 7.4 Hz, 1H, triazoline ring), 2.32 (s, 3H, -CH_3).

1-(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)-4,5-dihydro-1H-1,2,3-triazole-4-carboxamide (3t): Product **3t** was obtained as a white-yellow solid. (yield80%), melting point 241-243^oC, (R_f: 0.41), FTIR data (cm^{-1}): 3274 (NH_2),3120(C-H aromatic), 29٧9(asy C-H aliphatic), 2843(sy C-H aliphatic), 1665 (C=O group), 1580 (C=C aromatic), 1421 (N=N group), 1330(asy SO_2 group), 1241(N-N group), 1158(sy SO_2), 956(S-N), 827(C-S), ^{1}H-NMR: 11.38 (s, 1H, -NH-), 7.78–7.09 (m, 4H, aromatic protons), 7.18 (m, 2H amine protons), 6.09 (s, 1H, C-H-sulfamethoxazole ring), 4.49-4.39 (m, 3H, protons of triazoline ring), 2.31 (s, 3H, -CH_3).

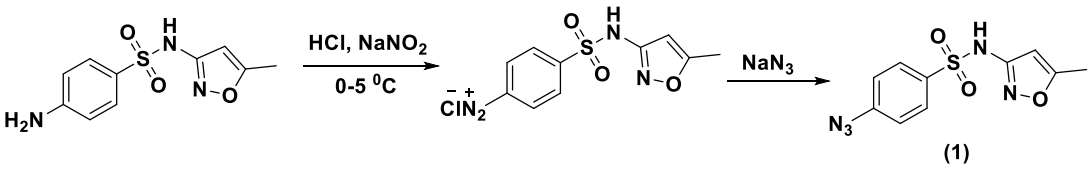
Antibacterial Study

Disk diffusion method

Two strains of *Staph aureus and E. coli* have been chosen. The 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 $1x10^8$. Various concentrations (12.5, 25, 50, and 100 µM) of all the prepared heterocyclic compounds in our investigation were individually prepared in DMSO and added to wells on plates containing existing bacterial growth. The plates were then incubated for 24 hours to assess the antibacterial effects. The inhibition zone was measured using a ruler, recorded to the nearest millimeter (mm) (Radhi et al., 2019).

Results and Discussion

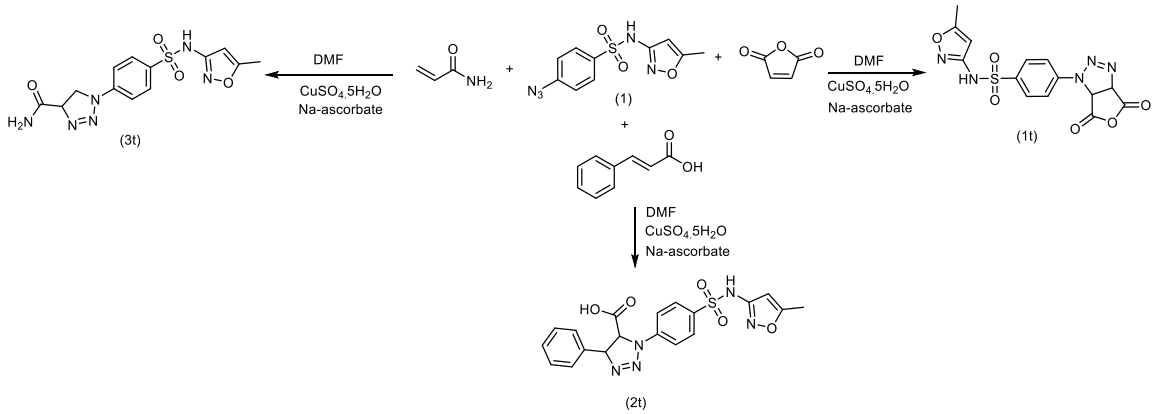
The sulfonamide group is a significant structural center that has a wide range of pharmacological activities in many approved drugs for a variety of diseases (Huisgen & Ugi, 1956) that allowed us to focus on the structural modification of one of the sulfonamides, sulfamethoxazole. Structural modification on sulfadiazine was done by introducing very important heterocyclic units, such as 1,2,3-triazole. The heterocyclic derivatives have been prepared using simple, high-yielded reactions and uncomplicated purification steps. The azide derivative of the sulfamethoxazole is formed by first forming the sulfamethoxazole diazonium ion, then proceeding with the reaction via an azide attack on the diazonium ion, as suggested by Huisgen and Ugi. (Scheme 1) Because nitrogen is very stable and is lost as a gas, and the amine group (-NH_2) of the sulfadiazine is linked to the benzene ring, which contains the electron-withdrawing group (-SO_2-), this provides a strong driving force for the reaction to occur with high yield. Following the conclusion of the reaction steps, the resulting precipitate is rinsed multiple times with distilled water and subsequently dried. One evidence for obtaining the azide derivative is the appearance of the azide group (-N_3) band in the FT-IR spectrum (2103cm^{-1}), with the complete disappearance of the N-H stretching primary amine group's band frequency (3242cm^{-1}) in comparison with the original sulfamethoxazole spectrum.



Scheme 1. Synthesis of (compound 1)

Also, from the ^{1}H-NMR the complete disappearance of the signal of the primary amine group's proton of the sulfamethoxazole (Pájaro et al., 2017), the found of a signal of the sulfonamide group's proton(11.48 ppm), and signals of aromatic protons of the benzene ring and pyrimidine ring at the range (7.90-7.32 ppm), whereas a singlate signal at 6.16 ppm and 2.32 ppm due to C-H-sulfamethoxazole ring and methyl group that attached sulfamethoxazole ring respectively. On the other hand, the ^{13}C-NMR (Fig. 3.3) showed signals at (146.04, 136.61, 129.75, 119.16 ppm) due to carbons of aromatic ring and signals at (169.15, 156.74 ppm) due to C5 and C3 in sulfamethoxazole ring respectively, such signs show the product structur. We believe that making the modification of the sulfamethoxazole compound by adding the

heterocyclic unit 1,2,3-triazoline, known for its importance in medicinal chemistry, will lead us to obtain compounds that have a good bioactivity. Utilizing the copper(I)-catalyzed azide-alkyne cycloaddition reaction, 1,4-disubstituted 1,2,3-triazoles were synthesized from sulfamethoxazole. Copper sulfate pentahydrate and sodium ascorbate were employed as catalysts for the reaction, as illustrated in Scheme 2.



Scheme 2. The preparation of 1,4 sub. 1,2,3-triazoline Derivatives

The commonly employed, reliable, and straightforward technique of copper-catalyzed azide-alkyne cycloaddition (CuAAC) facilitates the formation of covalent bonds between building blocks featuring diverse functional groups. Its mechanism entails multiple steps that include the formation of coordination complexes with copper (I) (Hein & Fokin, 2010). The characteristic of this type of reaction is the high yield ratio and simple conditions that it needs in addition to non-chromatographic purification methods (where we used recrystallization). Through the FT-IR spectra (Figs. 3.4, 3.5 & 3.6) a distinctive indication of the preparation of derivatives (**1t**, **2t** & **3t**) was the first of which was the disappearance of the azide group ($-N_3$) of the compound (**1**) in the range (2103 cm^{-1}) and appearance new band at (1772 cm^{-1}) in compound (1t) due to carbonyl group in malic anhydride, whereas, at new band at (3443 cm^{-1}) in compound (2t) due to carboxylic group of cinnamic acid. Finally, the band of the amine group in acryl amide at (3223 cm^{-1}). The ^{1}H-NMR (Fig. 3.8) of the product **2t** shows a good indication of its structure, the presence of the most important signal at (12.37 ppm) assgiande to carboxylic proton and signal at (11.34 ppm) that is due to the (N-H) sulfonamide proton, also a signal at (6.08 ppm) that is to oxazole ring proton, in addition of aromatic hydrogen signals (7.79-7.06 ppm). Where the doulate signals at (5.42 ppm) are due to the protons of the 1,2,3-triazoline ring and the singlate signal at (2.32 ppm) assgiande to methyl protons that attached oxazole ring. The ^{1}H-NMR (Fig. 3.9) of the product **3t** shows a

good indication of its structure, the presence of the most important signal at (7.18 ppm) assgiande to amine proton in acryl amide and signal at (11.38 ppm) that is due to the (N-H) sulfonamide proton, also a signal at (6.09 ppm) that is to oxazole ring proton, in addition of aromatic hydrogen signals (7.78-7.09 ppm). Where the multiplate signals at (4.49-4.39 ppm) are due to the protons of the 1,2,3-triazoline ring and the singlate signal at (2.31ppm) assgiande to methyl protons that attached oxazole ring.

Antibacterial study of the prepared heterocyclic

The antibacterial effectiveness of the prepared heterocyclic compounds was assessed using *Escherichia coli* as a Gram-negative and *Staphylococcus aureus* as a Gram-positive bacterium through a diffusion method on Mueller-Hinton agar medium. Following a 24-hour incubation period, the inhibition zones were gauged. It was observed that the tested compounds exhibited greater activity against Gram-positive bacteria compared to Gram-negative bacteria. Notably, compound 2t demonstrated high efficacy against both *Staphylococcus aureus* and *Escherichia coli*.

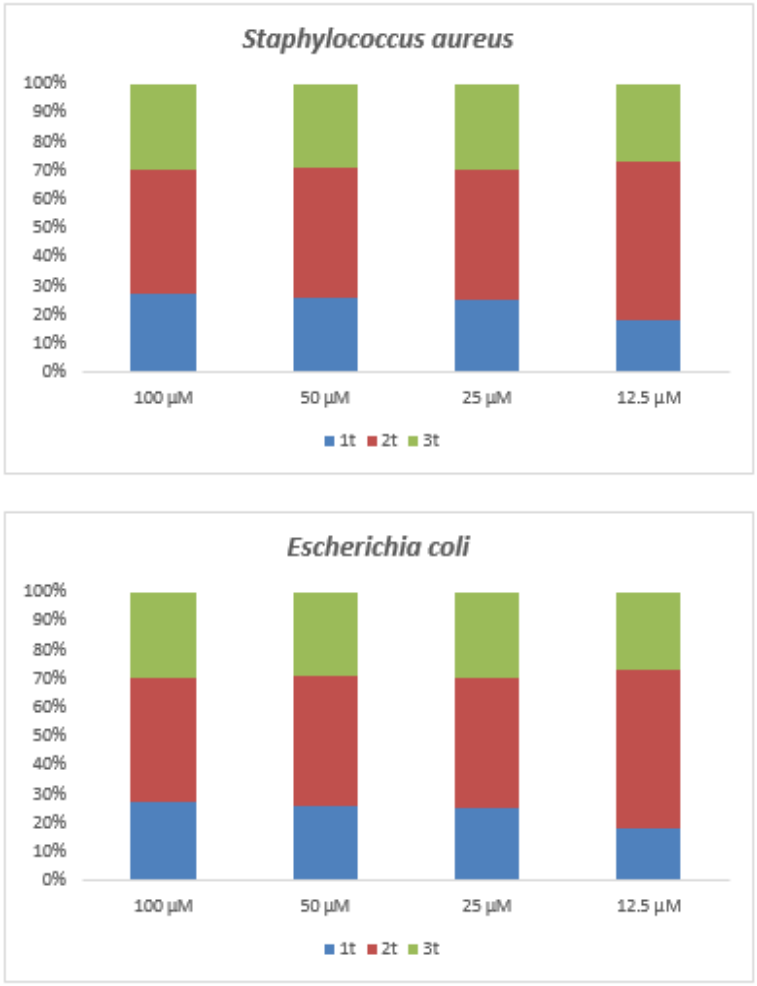


Fig. 1. Biological activity of the synthesized heterocyclic in this study

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. The study aimed to provide a good simulation of antibacterial activity of the prepared heterocyclic **1t**, **2t**and **3t**. 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 biomolecular 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 (Pájaro et al., 2017). In many cases, the missing data needs to be modeled and fixed before subsequent computational analyses can proceed. Using the 3D atomic coordinates of the receptor, the Site Finder phase aimed to identify putative active sites within the receptor. Because MOE uses no energy models, its Site Finder is a geometric method. Rather, the relative positions and accessibility of the receptor atoms are considered along with a generic classification of the chemical sort. The Site Finder approach relies on Alpha Shapes, which are generalized convex hulls constructed for this purpose (Attique et al., 2019). The MOE module was used to implement the docking procedure between the PDB co-crystals of Staphylococcus aureus and Escherichia coli (4h8e and 1ecl) and the selected synthesized chemical (1t, 2t, and 3t). Basic data was exported (Table 1), and Fig. 1-3 additionally includes images of docking complexes (interaction and surface maps).

Table 1. Docking interaction parameters for effective synthesized 1t, 2tb & 3t ligands against 4h8e proteins

Protein	Compound docked	Receptor	Distance(Å)	E (Kcal/mol)	S (energy score)	rmsd_refine (Å)
4h8e	1t	TYR 218 , ARG248, ARG248	3.08, 2.99, 3.71	-2.0, -1.7, -0.6	-5.6195	0.9011

4h8e 4h8e 4h8e	2t	ARG 46, ARG 37, ARG 37, LYS 40 ARG46, ARG46, ARG 37, ARG 37, GLY 34, ARG 84, ILE 92	2.86, 2.89, 3.05, 3.96, 3.96, 2.86, 3.05, 3.69, 4.29, 3.84, 4.00	-6.7, -6.7, -2.3, -0.6, -0.6, -5.5, -4.2, -1.3, -0.7, -0.8, -0.6	-8.2022	1.1531
	3t	ASN 81, ARG 84, ARG 201	3.02, 2.97, 3.09	-1.7, -2.6, -1.2	-6.0543	1.9710

From the observation of docking results of the compound 1t, 2t and 3t with the chosen site of Staphylococcus *aureus* protein, shows the batter results as includes in (Table 1) where the docking score was (-5.6195, -8.2022, -6.0543). The root mean square divergence between the initial pose and the final stance was (0.9011, 1.1531, and 1.9710), respectively.

Table 2. docking interaction parameters for effective synthesized 1t, 2t & 3t ligands against 1ecl

Protein	**Compound docked**	**Receptor**	**Distance(Å)**	**E (Kcal/mol)**	**S (energy score)**	**rmsd_refine (Å)**
1ecl	1t	ASN 555, ASP 551	3.16, 3.74	-2.8, -0.6	-5.5201	1.2716
1ecl	2t	ARG173, ARG173, ARG173, ARG173, ARG173, ARG173, ARG173, TYR177	3.03, 3.45, 2.97, 3.03, 3.98,3.45, 2.97, 3.62	-6.8, -0.7, -8.2, -4.3, -0.5, -2.1, -4.7, -0.0	-7.0945	1.6132

1ecl	3t	ARG173, ARG173, ARG173, HIS 33	3.38,3.45,3.10, 3.60	-2.1, -0.7, -3.4, -0.9	-5.4265	0.7543

Whereas the observation of docking results of the compound 1t, 2t, and 3t with the chosen site of *Escherichia coli* protein, shows the batter results as included in Table (2) where the docking score was (-5.5201, -7.0945, -5.4265). Additionally, the difference in the root mean square between the first stance and the final pose was (1.2716, 1.6132, 0.7543). Basic data was exported (Table 2), and Figs. 3 and 4 display photographs of the docking complexes (interaction and surface maps).

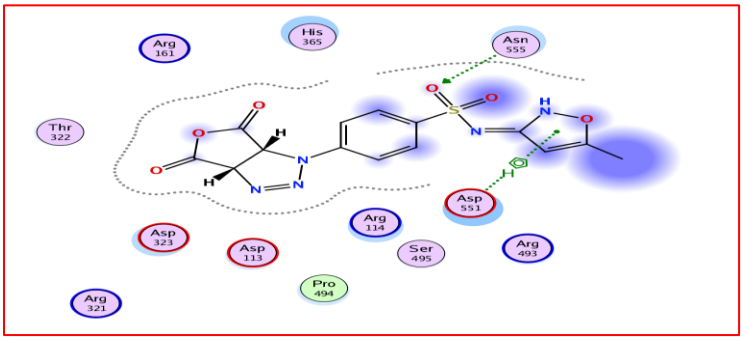


Fig. 2. 2D interaction graphs showing how the ligand 1t and the receptor 1ecl are coupled.

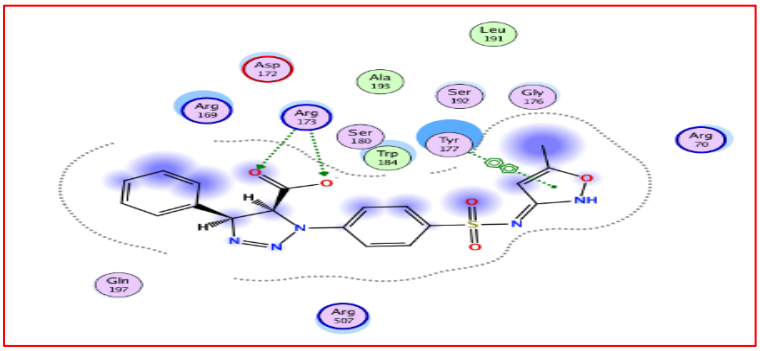


Fig. 3. 2D interaction graphs showing how the ligand 2t and the receptor 1ecl are coupled.

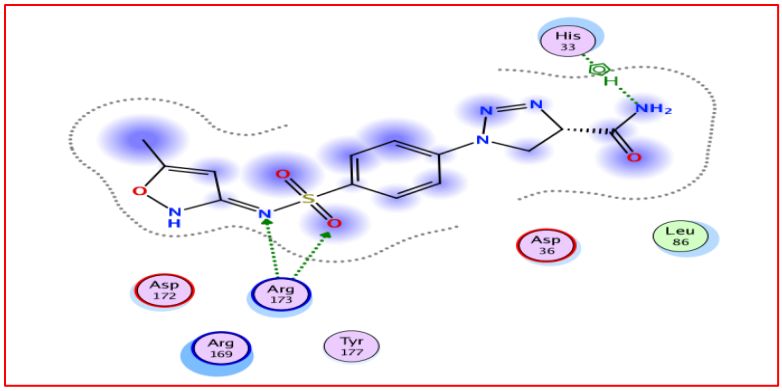


Fig. 4. 2D interaction graphs showing how the ligand 3t and the receptor 1ecl are coupled.

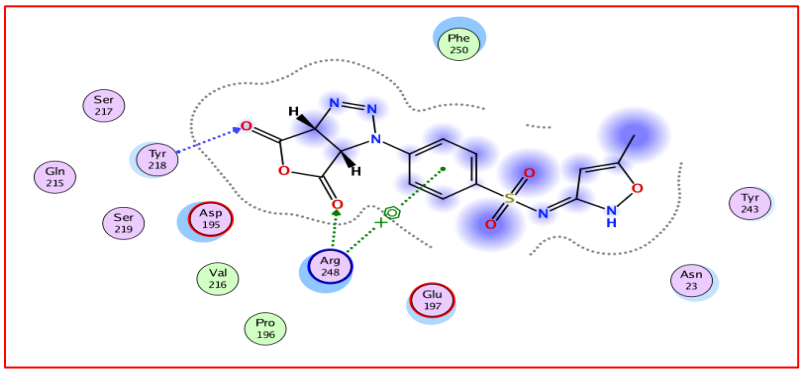


Fig. 5. 2D interaction graphs showing how the ligand 1t and the receptor 4h8e are coupled.

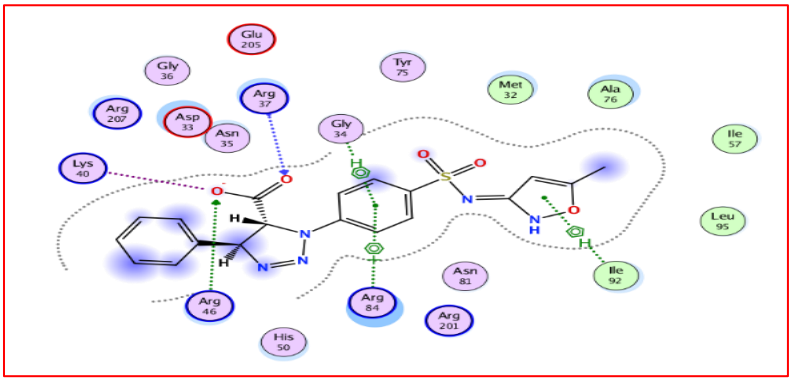


Fig. 6. 2D interaction graphs showing how the ligand 1t and the receptor 4h8e are coupled.

Conclusion

Successful syntheses of the 1,2,3-triazoline compound (1) have been made. To assess the impact of the substituent on the antibacterial, a pharmacological investigation was conducted. The newly synthesized 1,2,3-triazoline compounds with sulfamethoxazole demonstrated better antibacterial

activity. The outcomes of the anti-bacterial showing also showed that compound (2t), out of all the compounds, had the strongest antibacterial effect against the bacteria that were tested, but compounds (1t) and (3t) had only mild anti-bacterial effects.

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