chemistry proceedings

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Synthesis, Characterization of Some New Triazole Derivatives from Piprazene Via Click Chemistry: Molecular Docking and Biological activity Studies †

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† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

This study involved the synthesis of a series of novel triazole derivatives based on piperazine (2-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyrimidine) via click chemistry. The reaction was monitored using thin-layer chromatography (TLC). All newly synthesized piperazine derivatives (**1**–**5**) were characterized by Fourier-transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), and carbon-13 nuclear magnetic resonance (^{13}C-NMR). The biological activity of the compounds was tested against two microbial strains: one Gram-positiveand (Staphylococcus aureus) and author Gram-negative (Escherichia coli), bacterium. The antibacterial activity of the compounds **5a**–**d** was determined, and the derivatives showed excellent efficacy at a specific concentration. Additionally, the antioxidant activity was evaluated using the (Phosphomolybdate) method, revealing that the derivatives exhibited significant antioxidant activity compared to ascorbic acid at a certain concentration, with compound **3** showing the highest antioxidant potential. Molecular docking studies of the synthesized piperazine derivatives were also conducted against the 2X08 protein. The docking results showed varying binding affinities among the compounds, with compound **3** displaying the highest inhibitory effect, correlating with the biological assay results.

Keywords: antioxidant; click chemistry; piperazine; triazole; molecular docking

Academic Editor(s): Name

Published: date

Citation: Abdul-Reada, N.A.; Youssef, N.H. Synthesis, Characterization of Some New Triazole Derivatives from Piprazene Via Click Chemistry: Molecular Docking and Biological activity Studies. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

1. Introduction

Nitrogen-containing heterocyclic compounds (N-heterocyclic compounds) are widely distributed in nature and play essential roles in numerous physiologically important substances, such as vitamins, nucleic acids, drugs, dyes, and agrochemicals. These compounds have become extensively recognized in the rapidly evolving fields of organic and medicinal chemistry, as well as in the pharmaceutical industry [1–7]. The significance of 1,2,3-triazoles has emerged as essential "linkers" in the development of novel hybrid and conjugated compounds with evaluated biological activities, demonstrating broad potential in medical applications including anticancer, antimicrobial, antitubercular, antiviral, antidiabetic, and antimalarial activities [8], in addition to potential neuroprotective effects [9]. Synthetic approaches for these derivatives have significantly advanced,

focusing on improving reaction efficiency, enhancing yields, and adhering to green chemistry principles. Modern strategies, such as Click Chemistry, have facilitated the design of diverse derivatives with enhanced biological activity, and the interdisciplinary nature of this field has promoted collaboration among organic chemists, biochemists, and pharmaceutical scientists to better understand the relationship between chemical structure and biological activity [10,11]. Given the difficulty biological systems face in forming five-membered rings containing three adjacent nitrogen atoms, the development of synthetic methodologies for these derivatives is of critical importance [12,13]. Click Chemistry, particularly copper-catalyzed azide-alkyne cycloaddition (CuAAC), provides high selectivity and efficiency in the production of 1,2,3-triazole derivatives with significant pharmaceutical and biological relevance. The triazole ring is characterized by its ability to coordinate with the iron atom in the heme group of the CYP enzyme [14], and its heterocyclic structures can form multiple weak non-covalent interactions with receptors and enzymes in biological systems [15]. These intrinsic properties make triazole compounds highly significant in medicinal chemistry, serving as effective chromophores with high pharmaceutical value, which has attracted the attention of researchers across disciplines including organic chemistry, agriculture, supramolecular chemistry, medicinal chemistry, polymer chemistry, and materials science [16]. Among clinically approved drugs, triazole derivatives are incorporated into a wide range of highly effective pharmaceuticals, including antibacterial, antifungal, antiviral, anti-inflammatory, anticoagulant, antitubercular, antidiabetic, antioxidant, and anticancer agents [17]. In this research, we synthesized a new series of triazole derivatives and then evaluated in vitro as antimicrobial and antioxidant agents.

2. Experimental Section

The chemical material used in this study were purchased from TCI and Merck company. Fourier-transform infrared (FTIR) spectra were recorded in the range of 4000–400 cm^{-1} using the KBr disk method on a SHIMADZU FTIR-8400S spectrometer. NMR spectra were measured on Bruker AMX 400 and 100 instruments respectively using DMSO-d_6 as a solvent and TMS as a reference. Elemental analyses were performed using a Vario EL elemental analyzer (Elementar Analysensysteme GmbH, Germany).

*2.1. General Method of the Proparation Compounds (**3**) [18]*

Synthesis of 2-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyrimidine **3**

2_(piperazin_1_yl)pyrimidine (10 mmol, 1.91 gm) dissolved in 25 mL of DMF taken in a round-bottom flask with the addition of potassium carbonate (15 mmol, 1.65 gm). Stir the mixture for 15 min, then slowly add Propargyl bromide (10 mmol, 0.91 mL) in a round-bottom flask, and stir the mixture for 24 h at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, cool the mixture, pour it over ice water, and separate the organic layer from the aqueous layer using a separating funnel by 3 × 15 mL of chloroform. The mixture was then dried by $MgSO_4$ and filtered. The solvent was removed under vacuum. It was completed. Yield 73%, mp 216–218 °C. IR spectrum (KBr), ν, cm^{-1}: 3324 (C-H_{Ar}), 1568 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.15 (CH), 6.55–8.39 m (3H, H_{Ar}), 3.67–3.76 (8H, $H_{Piperazine}$). ^{13}C NMR spectrum, δC, ppm: 79.50 (CH=CH_2), 76.24 (CH_2), 51.81, 46.80 ($C_{Piperazine}$), 110.55–158.44 (C_{Ar}).

*2.2. General Procedure to Synthesize Compound (**5**,**7**,**9**,**11**) [19]*

In a 100 mL round-bottomed flask with two holes connected to a condenser, (4 mmol) of the Propargyl bromide derivative was dissolved with 2 mmol of one of the organic azide compounds, respectively, in 20 mL of DMSO as a solvent, in the presence of aqueous as a catalyst. The mixture of cupric sulfate (0.1 mmol) and sodium ascorbate (0.2 mmol)

was elevated. The reaction continued for 12–16 h (monitored using TLC). The spots were detected using iodine after the reaction was completed by cooling the mixture and pouring it onto ice or cold water. The organic layer was extracted using a separating funnel using chloroform. It was then dried with anhydrous magnesium sulfate, filtered, and the excess solvent was removed by distillation under vacuum pressure.

2-(4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)pyrimidine(5). Yield 80%, Orange liquid,. IR spectrum (KBr), ν, cm^{-1}: 1449 (N=N) 1587 (C=N), 3297 (C-H_{Ar}), 1H NMR spectrum, δ, ppm: , (H, CH_2), 3.74, (2.76–3.16 -8H, Piperazine). m (H_{Ar}), 6.59–8.49 (1H, CH=N), 8.49 s 13C NMR spectrum, δC, ppm: 110.25–150.16 (C_{Ar}), 158.45 (C-N), 161.65 (C=N), 43.58, 46.60 (C Piperazine). Anal. calculated for: C, 55.73; H, 4.95; N, 30.58. Found: C, 56.7; H, 5.85; N, 29.59.

2-(4-((1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)pyrimidine 7. Yield 77%, Light brown liquid,. IR spectrum (KBr), ν, cm^{-1}: 1448 (N=N) 1675 (C=N), 3297 (C-H_{Ar}). ^{1}H NMR spectrum, δ, ppm: 3.34–3.80 (t, 8H, Piperazine). 3.16 (d, 2H, CH2), 6.59–8.49 (d, 4H, H_{Ar}), 8.49 (s, 1H, CH=N). ^{13}C NMR spectrum, δC, ppm: 40.93 (C Piperazine), 43.76110.61, 158.50 (C_{Ar}), 158.39 (C-N), 161.67 (C=N). Anal. calculated for: C, 64.46; H, 6.31; N, 29.23. Found: C, 63.9; H, 5.55; N, 28.76.

4-(4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid 9. Yield 78%, Orange liquid,. IR spectrum (KBr), ν, cm^{-1}: 1500 (N=N) 1577 (C=N), 3363 (C-H_{Ar}). ^{1}H NMR spectrum, δ, ppm: 2.84–3.48 (t, 8H, Piperazine), 3.17 (s, H, CH2), 6.60–8.41 (d, 4H, H_{Ar}), 8.42 (s, 1H, CH=N), 10.01 (s, 1H, S-OH). ^{13}C NMR spectrum, δC, ppm: 46.93, 51.42 (C- Piperazine), 110.35–141.55 (C_{Ar}), 161.74 (C-N), 164.44 (C=N). Anal. calculated for: C, 59.17; H, 5.24; N, 26.83. Found: C, 58.9; H, 5.1; N, 28.87.

1,4-bis(4-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzene 11. Yield 74%, Orange liquid,. IR spectrum (KBr), ν, cm^{-1}: 1500 (N=N) 1604 (C=N), 3139 (C-H_{Ar}). ^{1}H NMR spectrum, δ, ppm: 3.44 (H, CH_2), 2.84–3.48 (t, 8H, H- Piperazine). 6.61 (s, 1H, CH triazole), 6.58–8.06 (HAr), 8.34 (s, 1H, CH=N). ^{13}C NMR spectrum, δC, ppm: 43.58, 46.63 (C- Piperazine), 110.51, 158.51 (CAr), 161.64 (C-N). Anal. calculated for: C, , 59.56; H, 5.71; N, 34.73. Found: C, 58.8; H, 4.80; N, 35.06.

2.3. Phosphomolybdate Assay (Total Antioxidant Capacity) [20]

The total antioxidant capacity of the fractions was evaluated using the phosphomolybdate assay, with ascorbic acid (vitamin C) serving as the standard reference. For the assay, 1 mL of the sample solution was mixed with a reagent solution containing 28 mM sodium phosphate, 4 M ammonium molybdate, and 0.6 M sulfuric acid. The reaction mixtures were then incubated in tightly sealed tubes at 95 °C for 90 min in a water bath. After incubation, the samples were allowed to cool to room temperature. Absorbance was measured at 765 nm against a reagent blank. A standard calibration curve was constructed using ascorbic acid under the same experimental conditions, with the reagent solution mixed with an equivalent volume of solvent. The antioxidant activity was calculated using the following equation:

Antioxidant activity (%) = [(Absorbance of control − Absorbance of sample)/Absorbance of control] × 100

2.4. Antibacterial Activity [21]

The bacterial strain *Escherichia coli* and the fungal strain *Candida albicans* were used in this study to evaluate antimicrobial activity. The sensitivity of these microorganisms to the tested compounds was determined using the well diffusion method. Muller-Hinton agar medium was prepared according to the manufacturer's instructions, poured into Petri dishes, and allowed to solidify. Once solidified, five wells of 6 mm diameter were

aseptically created in the agar using a sterile cork borer, ensuring sufficient spacing between wells to prevent overlapping of inhibition zones. A bacterial suspension (1 mL) was uniformly spread over the surface of the agar plates using a sterile cotton swab within a laminar flow hood. The inoculated plates were then left to stand for approximately 30 min to allow for absorption. Subsequently, 0.1 mL of the test compounds at concentrations of 250 μM and 200 μM were added into the respective wells. One well was reserved as a control and received an equal volume of solvent without the test compound. Each plate thus contained wells with varying concentrations to assess the antimicrobial efficacy of the compounds

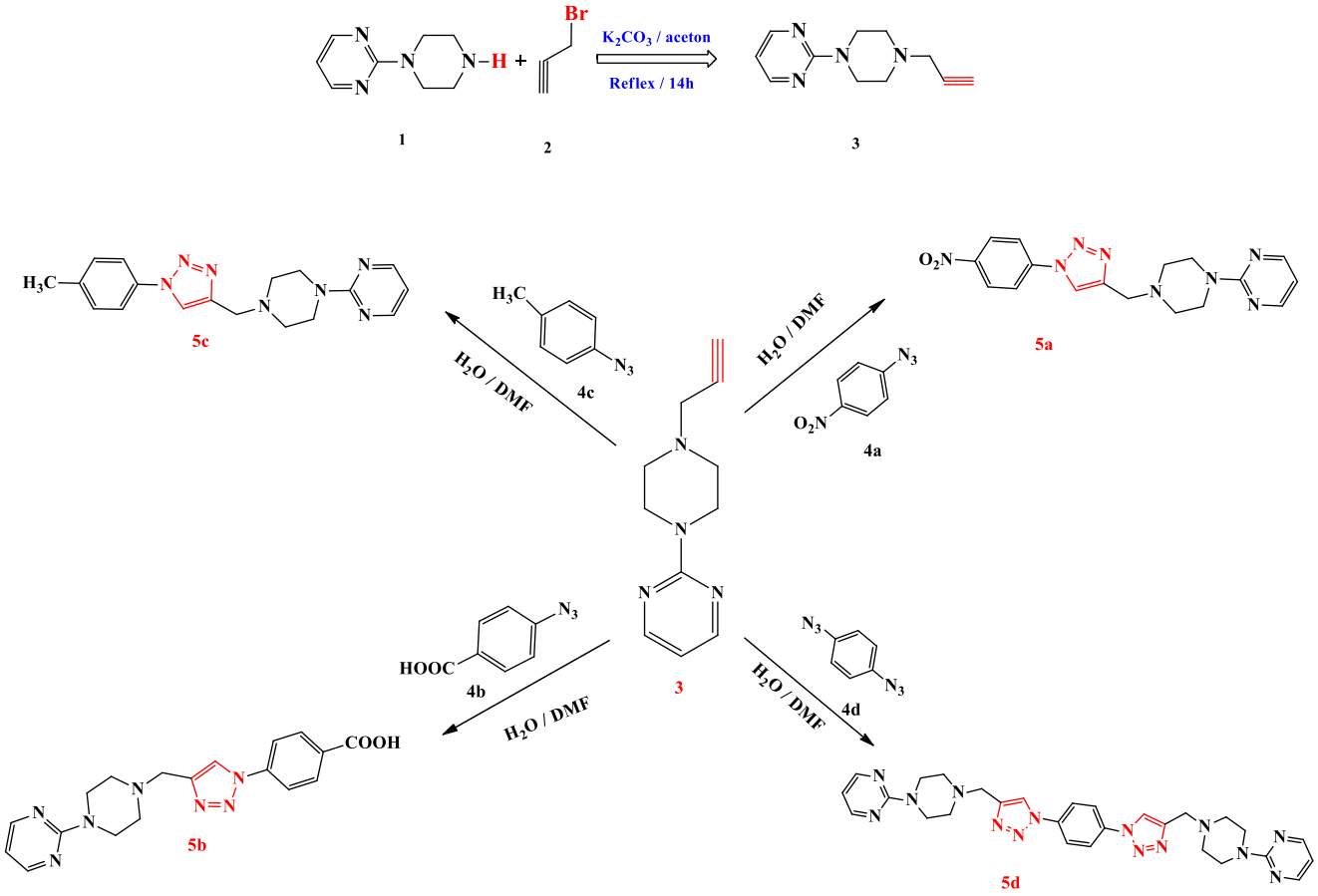
2.5. Molecular Docking Analysis [22]

The molecular docking investigation was conducted using the MOE docking tool, version 0.8. The Protein Data Bank was used to obtain the target protein, which is the cytochrome c peroxidase enzyme (PDB ID: 2X08). We used Chem Draw Ultra to create a two-dimensional model of Trizole compounds **5a–d**, and then used MOE to transform it into a three-dimensional model. The energy was minimized for the compounds and the target protein by the MOE.

3. Results and Discussion

3.1. Chemistry

The new Triazoline compounds **5a–d** have been synthesized with good yields via some common reactions. The derivative **3** was synthesized via reaction 2-(piperazin-1-yl)pyrimidine **1** with allyl bromide **2** in presence of K_2CO_3 and acetone as solvent. Next, the derivative 3 was entered into cycloaddition reaction with some of the aromatic azides **4a–d** in presence of both ascorbate sodium and hydrated copper sulfate as catalysts. Triazoline compounds **5a–d** have been formed according to the cycloaddition 1,3-dipolar mechanism which leads to formation a five-membered rings as exhibited in Scheme 1. The synthesized compounds' structures were spectroscopically characterized by (IR, ^{1}H NMR and ^{13}C NMR) in addition to micro-elements analysis. The spectroscopic data obtained were included in the experimental section.



Scheme 1. Experimental steps for synthesizing derivatives **5a–d.**

3.2. Antioxidant Activity Study

The total antioxidant capacity of the synthesized compounds **5a–d** was assessed using the phosphomolybdate method, ascorbic acid employed as a reference standard. The test works by measuring the reduction of molybdate (VI) ions to molybdenum (V) in the presence of an antioxidant. Generally, the results in Table 1 indicated that the synthesized compounds exhibited significant antioxidant activity, particularly at the highest concentration tested (250 µM). Notably, compounds **5a**, and **5c** demonstrated the strongest antioxidant effects compared to control. In contrast, compounds **5b** and **5d** showed relatively lower antioxidant activity at same concentrations, with a marked increase as the concentration increased. Furthermore, compounds **5a–d** exhibited varying degrees of activity, suggesting potential differences in their antioxidant mechanisms or structural features influencing their effectiveness.

Table 1. Results of phosphomolybdate assay of compounds **5a–d** at wavelength 765 nm and concentration 250 µM.

Sample ID	Conc. (µg/mL) Mean ± SD				
	250	**200**	**150**	**100**	**50**
5a	25.172 ± 0.501	18.581 ± 0.469	16.574 ± 0.689	13.241 ± 0.479	8.249 ± 0.259
5b	24.035 ± 0.417	19.642 ± 0.585	17.157 ± 0.417	12.129 ± 0.581	3.538 ± 0.647
5c	26.346 ± 0.196	24.028 ± 0.446	17.710 ± 0.401	14.756 ± 0.479	11.575 ± 0.665
5d	24.154 ± 0.234	21.985 ± 0.136	18.546 ± 0.228	15.541 ± 0.267	12.284 ± 0.163
Control	24.215 ± 0.145	23.141 ± 0.231	19.216 ± 0.291	15.150 ± 0.184	13.131 ± 0.115

3.3. Antibacterial Activity

The biological activity of the synthesized compounds was evaluated against *Escherichia coli* and *Staphylococcus aureus* using the agar well diffusion method. These microorganisms were selected due to their clinical relevance, their association with a wide range of infections, and their increasing resistance to conventional antimicrobial agents. As summarized in Table 2, the tested compounds demonstrated notable inhibitory effects against both bacterial and fungal strains across different concentrations. At a concentration of 500 μM, the compounds **5a**, **5b** and **5d** exhibited moderate to strong antimicrobial activity for *E. coli* and *S. aureus* in comparison to the standard drugs. Among all tested compounds, compounds **5a** and **5b** exhibited the most pronounced inhibitory effect against *S. aureus*. Other compounds displayed significant antimicrobial activity when evaluated relative to the reference drugs.

Table 2. Results of antimicrobial activity of derivatives **5a-d** on the two types of bacteria.

Staphylococcus aureus			***E. coli***		
	Inhibition Size (mm)			Inhibition Size (mm)	
No.	250 μg/mL	500 μg/mL	No.	250 μg/mL	500 μg/mL
5a	16	21	**5a**	13	16
5b	14	22	**5b**	14	17
5c	12	14	**5c**	11	15
5d	6	11	**5d**	17	20
Amoxicillin	21	25	Amoxicillin	20	22

3.4. Molecular Docking Study

To further explore their antioxidant potential, the synthesized compounds were subjected to molecular docking studies targeting the active site of the cytochrome c peroxidase enzyme (PDB ID: 2X08). The docking simulations yielded stable and energetically favorable binding conformations for all compounds. As shown in Table 3, the amide derivatives exhibited acceptable binding affinities, expressed in kcal/mol, indicating their potential interaction with the enzyme. Among the tested compounds, compound **5a**, **5c** and **5d** displayed particularly effective binding within the active site, engaging in multiple types of molecular interactions, including hydrogen bonding, hydrophobic contacts, and electrostatic interactions. These diverse interaction modes suggest a strong and specific binding capability. A comprehensive summary of the binding energies and interaction types is provided in Table 3, while the accompanying 2D and 3D docking visualizations depict the binding orientations and key interactions of compounds **5a–d** with the target protein, as show in Figures 1–4.

Table 3. Molecular docking results for synthesized derivatives **5a–d**.

Com	S Score (Kcal/mol)	RMSD (Ă)	Atom of Compound	Atom of Receptor	Involved Receptor Residues	Type of Interaction Bond	Distance (Ă)	E (Kcal/mol)
5a	−9.38	1.71	C 1 C 8 6-ring 6-ring	NE2 NE2 ND1 5-ring	HIS 175 HIS 175 HIS 175 TRP 51	H-donor H-donor pi-cation pi-pi	3.35	−1.8
5b	−6.16	2.85	O 28 6-ring 6-ring	N ND1 5-ring	HIS 181 HIS181 TRP 51	H-accept pi-cation pi-pi	3.28	−0.5
5c	−12.70	2.49	N 10	NH2	ARG 48	H-accept	4.11	−1.3

			N 24 6-ring 6-ring	NH2 CA 5-ring	ARG 48 SER 81 TRP 51	H-accept pi-H pi-pi		
5d	−9.24	2.39	N 13 C 32 6-ring	NH2 5-ring CA	ARG 48 HIS 181 THR 180	H-accept H-pi pi-H	4.11	−1.3

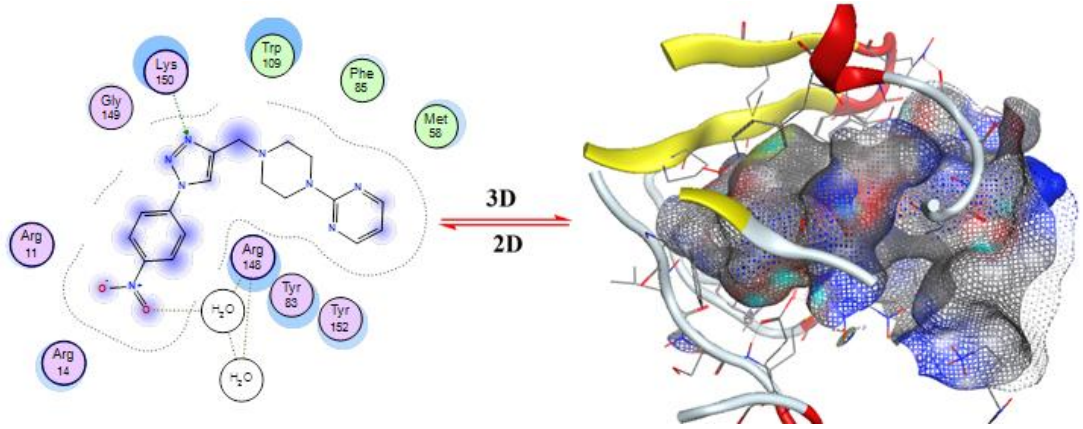


Figure 1. 2D and 3D conformations for simulation of compound **5a** with the 2X08 receptor.

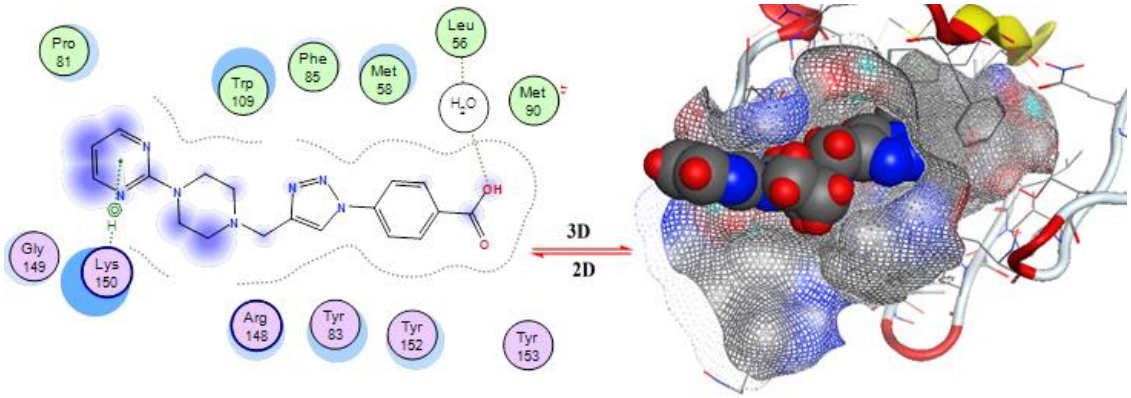


Figure 2. 2D and 3D conformations for simulation of compound **5b** with the 2X08 receptor**.**

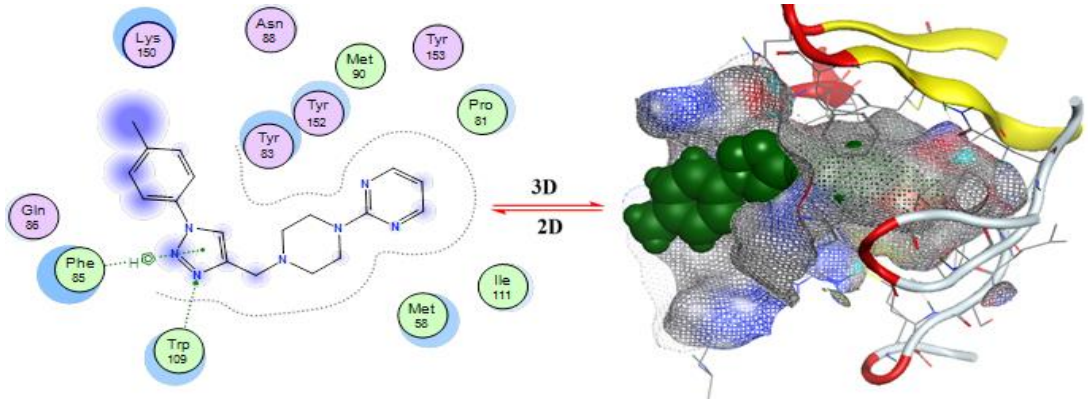


Figure 3. 2D and 3D conformations for simulation of compound **5c** with the 2X08 receptor.

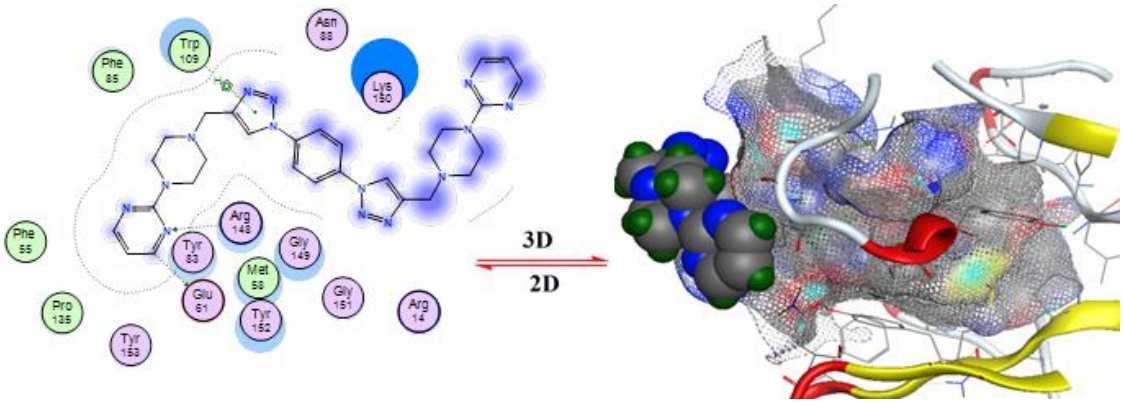


Figure 4. 2D and 3D conformations for simulation of compound **5d** with the 2X08 receptor.

4. Conclusions

In conclusion, the successful synthesis of novel triazole derivatives was achieved through the reaction of allyl bromide with a piperazine derivative in the presence of an organic azide. The synthesized compounds demonstrated promising results in molecular docking studies, showing favorable interactions with the cytochrome c peroxidase protein (PDB ID: 2X08), suggesting potential antioxidant activity. Among them, derivative **5c** exhibited a notably higher inhibition rate compared to ascorbic acid in the antioxidant biological activity assay. Furthermore, the biological evaluation of the synthesized compounds revealed appreciable antifungal and antibacterial properties, indicating their potential as multifunctional bioactive agents.

Author Contributions:.

Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

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