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RESEARCH ARTICLE

Design, Synthesis, Structural Elucidation and Spectroscopic Studies of Novel 1,4-Disubstituted 1,2,3-Triazole Derivative f or Pharmaceutical Applications

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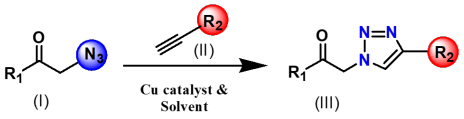
Abstract

Objectives: This study aims to explore the synthesis of the title derivatives, focusing on their biological activities and potential applications in drug discovery. The goal is to develop an efficient synthetic route, optimize the reaction conditions, and investigate the structural integrity of the synthesized compound for further therapeutic application. **Methods:** The synthesis of triazole derivatives through the copper-catalyzed (CuAAC) azide-alkyne cycloaddition reaction, employing sodium ascorbate as the base and dichloromethane as the solvent. Thin-layer chromatography (TLC) was used to monitor reaction completion, and the products were purified via column chromatography. **Findings:** The reaction provided good yields, and the synthesized triazole derivatives were confirmed to have the desired structure through detailed spectroscopic analysis. The purity and integrity of the compounds were verified using TLC, crystallization, and recrystallization techniques. The synthesized compound was characterized using infrared (IR), (NMR) nuclear magnetic resonance spectroscopy, HRMS-high-resolution mass spectrometry. **Novelty:** This research presents a novel pathway for producing 1,2,3-triazole derivatives with potential bioactive properties. The method utilizes a click chemistry approach for selective functionalization, offering a robust framework for designing new scaffolds for drug discovery. The novelty lies in the structural design and optimization of triazole derivatives, which hold significant promise for medicinal chemistry and pharmacology. The study also paves the way for future investigations into the SAR-structure-activity relationships and pharmaceutical applications of these compounds.



Keywords: Spectroscopy; Triazole; Crystal Growth; Click Chemistry; Heterocyclic Compound

1 Introduction

Triazoles are biologically active heterocyclic compounds with the molecular formula $C_2H_3N_3$. It includes 2 carbon and 3 nitrogen atoms in its 5-membered structure. The two isomers are 1,2,3 & 1,2,4 triazoles. The 1,2,3-triazole derivatives are mainly focused on screening the compounds for studying structure-activity relationships[1]. This research presents a novel synthetic pathway for producing 1,2,3-triazole derivatives with potential bioactive properties. The method utilizes a click chemistry approach for selective functionalization, offering a robust framework for designing new scaffolds for drug discovery[2]. The Sharpless concept of click reactions consists of reactants and reagents in simple reaction conditions and purification processes[3]. These compounds have significant interest due to their wide-range activities in the medicinal field, including antimicrobial, anticancer, and antiviral properties[4]. However, the synthesis often relies on multi-step procedures that are time-consuming and may lack regioselectivity[5]. While CuAAC has emerged as a prominent method for constructing 1,2,3-triazoles with high efficiency, challenges persist regarding scalability, substrate scope, and functional group compatibility[6]. Existing approaches, though efficient in certain aspects, have limitations like difficulty in achieving diverse functionalization and challenges in producing suitable derivatives for biological evaluation[7]. One significant research gap lies in the insufficient exploration of structure-activity relationships (SARs), optimal bioactivity studies, and the lack of robust methodologies for scalable and precise applicability in drug discovery[8]. These inadequacies underline the need for innovative synthetic strategies. To bridge these gaps, this study introduces a streamlined, click chemistry-based strategy for the synthesis of 1,2,3 isomeric form of triazole derivatives with enhanced functionalization.[9] It also addresses the limitations of existing methods by enabling regioselectivity and scalable synthesis. It has advantages over conventional techniques by offering broader substrate compatibility and facilitating the generation of derivatives tailored for SAR studies. Preliminary results validate the efficacy of the approach, demonstrating the production of the derivatives and highlighting the potential of the proposed methodology. Further investigations focus on expanding the scope and conducting detailed biological evaluations to explore the therapeutic potential of the derivatives[10]. The diverse synthetic potential and significant biological properties of heterocyclic compounds offer chemists valuable tools to innovate, strategize, and explore new methodologies for drug discovery. With a wealth of research continually expanding over time, the study of triazoles remains a vibrant and promising area in chemical science[11]. This scientific research aims to provide an overview of a logical investigative approach to the chemical development of heterocyclic compounds[12].

2 Methodology

2.1 Materials and methods

Chemicals purchased from Sigma Ald. Chem. Co. The reaction completion confirms using (TLC) Thin Layer Chromatography on 0.25 mm silica gel plates (Merck 60 F254) using a different solvent system. Proton and carbon NMR spectra were recorded using $CDCl_3$ solvent in Bruker AMX-400 spectrometer operating at 400 MHz. These reactions are characterized by their ability to selectively form carbon-heteroatom bonds, enabling precision in chemical synthesis. Click approach (H.C.Kolb et al., 2001) provides a robust framework for designing reactions that are both practical and

versatile, making it highly relevant for my new research in exploring novel catalytic pathways and bioactive molecule synthesis[13,14]. Heterocyclic compounds have many different functional groups, which play an essential role in the aromatic ring structure of triazole systems[15]. Copper-mediated reaction leads to the formation of the title compound. Our research focuses its prominence on quantitative functionalization and reaction-facilitating framework of triazole-based structures for the pivotal development of new scaffolds in molecular modeling.

2.2 General protocol of the synthesis

The triazole derivative was prepared from azide compound (100mg, 0.426mmol) treated with 10mL dichloromethane and started stirring. 2-methyl-3-butyn-2-ol (1.1eq) with $CuSO_4$ (5eq) & Na-L-ascorbate (10eq) added at room temperature (2Hrs) stirring. Thin layer chromatography was checked for the total reaction completion. The reaction mixture was extracted using DCM (dichloromethane) (40 mL×3) & washed with EtOAc (50 mL), brine (50 mL) and dried using sodium sulfate, and evaporated under reduced pressure. Column chromatography purification depends on the compound polarity. Filtered and dried, the final product was obtained.

Table 1. Table of contents used for the synthetic reaction

Sl. No	Reactants	Equiv.	Quantity	Mol. Weight	Mol/ mmol
1	2-methyl-3-butyn-2-ol	1.1	100 mg	84.12	0.000469
2	Na-L-ascorbate	10.0	843 mg	198.11	0.00426
3	$CuSO_4.5H_2O$	5.0	531 mg	249.68	0.00213

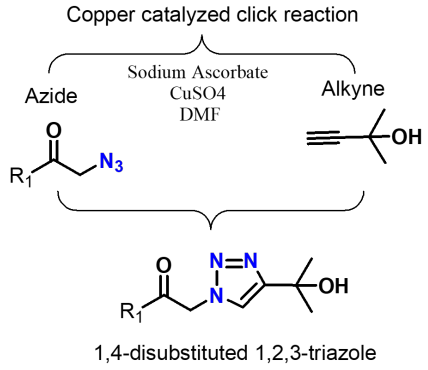


Fig 1. Preparative route of the 1,2,3-Triazole derivative using Cu catalyst

3 Result and discussion

3.1 Thin layer chromatography (TLC)

TLC technique analyzes the purity of organic compounds by separating them from inorganic components. Mobile phase solvents used: E- Ethyl acetate, H- Hexane. Analysis under normal pressure and room temperature.

3.2 Crystallization

The reaction was cooled, neutralized, filtered, and dried to obtain the compound. Colorless crystals were obtained by recrystallization from the EtOH and EtOAc solvent mixture using slow evaporation. The reaction was utilized to obtain the final product as a triazole derivative at 1,2,3 nitrogen positions. The final product synthesis used the cycloaddition of terminal alkynes and azide compounds under mild aerobic conditions with sodium ascorbate as the base and DMF solvent. Purification and recrystallization were carried out under particular conditions. It was then kept for slow evaporation in a test tube for crystal growth[16]. It took around one month for the crystal to form, and the microscopic view under a polarized microscope is as shown below. The quality of the crystals was not good for the diffraction pattern and for the collection of intensity data[17].

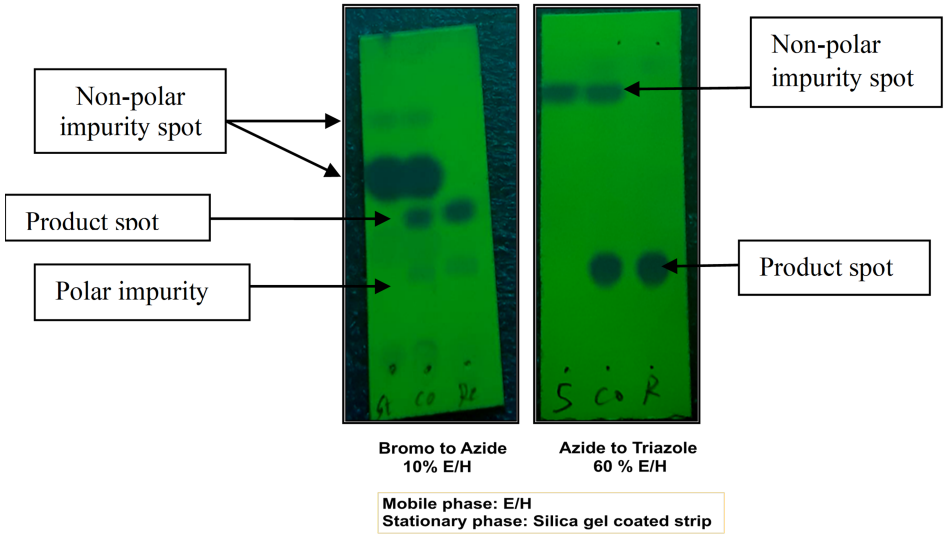


Fig 2. TLC of the reaction

The purification process involves workup, separation, evaporation, wash-up, filtration, and distillation using different solvents to obtain the crystalline nature of the product. As a future direction, we plan to synthesize novel triazole variants [18]. Crystallization of the compound at room temperature through slow evaporation technique for crystallographic studies.

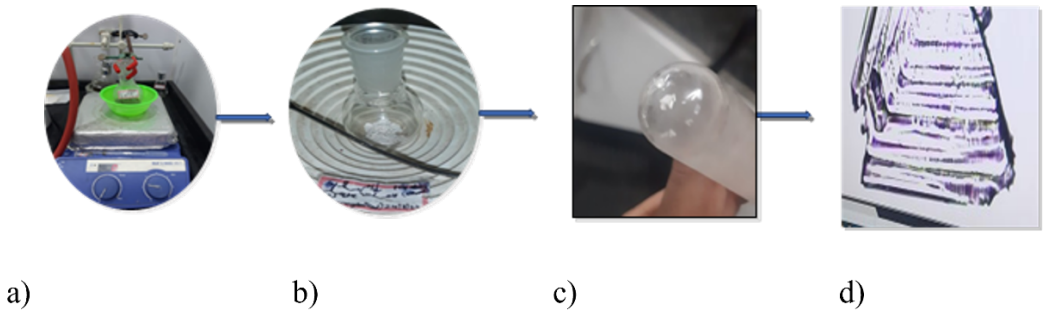


Fig 3. a) Reaction b) Final product c) Crystallization d) Crystal microscopic view

3.3 Spectral data of the structure

2-{2-[4-(1-Hydroxy-1-methyl-ethyl)-[1,2,3]triazol-1-yl]-acetylamino}-benzoic acid methyl ester

Triazole compound was obtained via cycloaddition reaction between al (alkyne) and az (azide) for 2 hrs as a white solid. Yield: 48.56%

3.4 Structure analysis

Regioselective formation of title compound derivative confirmed by obtained data and analytical techniques such as IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra [19]. According to the IR spectrum data of the compound, the observed peak at 3502cm^{-1} indicates the presence of the N-H group. From IR spectra, the stretching vibration band between C=O can be identified [20]. Ketones are expected to possess carbonyl stretching vibrations in the range of 1715-1680 cm^{-1}. C=O vibrations were detected by Ushakumari et al. [21] as a strong band at 1653 cm^{-1}. The C=O stretching mode at 1638 cm^{-1} was reported by Chidan Kumar et al. [22] . The C=O stretching bands in our investigations are seen at 1677.81 cm^{-1}. The C-O stretching vibration appears between 1300 and 1000 cm^{-1} in the FTIR spectrum. Ushakumari et al. [21] observed a C-O stretching band at 1249 cm^{-1}, whereas Arjunan et al. [23] discovered one at 1220 and 1225 cm^{-1}. We found a very strong band at 1258.88 cm^{-1} as a result of our analysis.

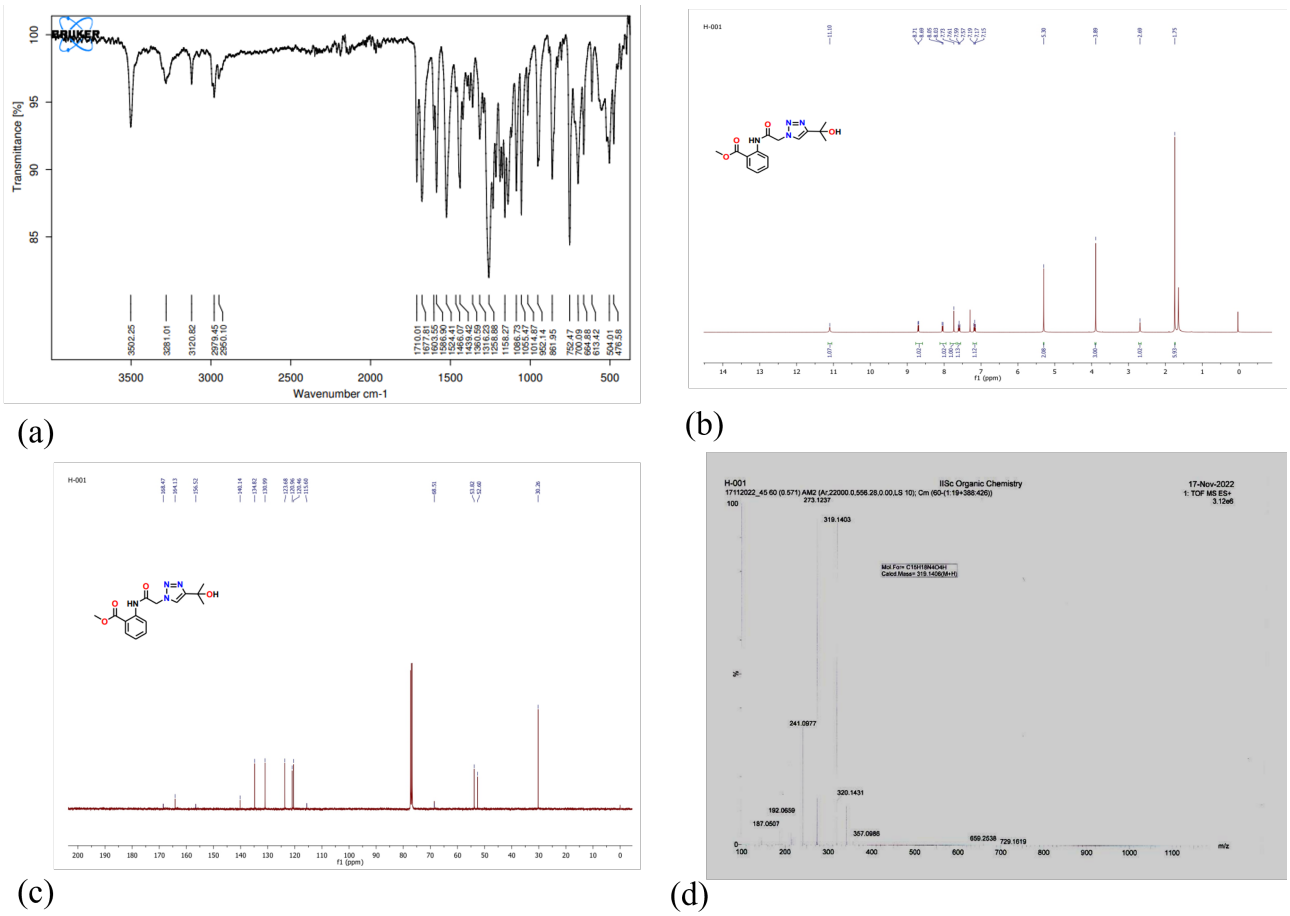


Fig 4. a)IR (KBr, νmax, cm^{-1}): 3502.25 (-N-H), 1710.01 (-C=O), 1677.81 (-C=C-triazole), 1524.41 (-CH_3), 1466.07 (-CH_2), 1360.59 (-CH_3) 1258.88 (-CH_3) b) ^{1}H NMR (400 MHz, $CDCl_3$ Solvent): δ 11.10 (1H, s, NH), 8.70 (1H, d, J = 8.0 Hz, ArH), 8.04 (1H, d, J = 8.0 Hz, ArH), 7.73 (1H, s, triazole-H), 7.59 (1H, t, J = 8.0 Hz, ArH), 7.17 (1H, t, J = 8.0 Hz, ArH), 5.30 (2H, s, CH_2), 3.89 (3H, s, CH_3), 2.69 (1H, s, OH), 1.75 (6H, s, CH_3(2)) c) ^{13}C-NMR (100MHz, $CDCl_3$ Solvent): 168.47, 164.13, 156.52, 140.14, 134.82, 130.99, 123.68, 120.96, 120.46, 115.60, 68.51, 53.82, 52.60, 30.26 d) HRMS: m/z calculatedfor [M+H]$^+$ [$C_{15}H_{18}N_4O_4$+ H]$^+$ = 319.1406

At 1300-1000 cm^{-1}, the C-H in-plane bending vibrations manifest as a range of intensities, from strong to mild. Aditya et al.[24] discovered strong bands at 1331 and 1181 cm^{-1}, whereas, in our reports, it is between 1360.59 and 1014.87 cm^{-1}. The coupled C-H out-of-plane bending vibrations are often detected between 1000 and 750 cm^{-1} [25]. In the current investigation, it is observed at 952.14, 861.95 and 752.47 cm^{-1}, respectively. The vibrations recorded agree well with the literature data. In the ^{1}H NMR spectrum of the compound, the signal at 1.75 ppm indicates the two methyl groups (-CH_3) present on the triazole ring, and signals at 5.30, 3.89, 2.69 ppm are methylene (-CH_2), methoxy (-O-CH_3) & O-H group. In addition to this, the signal appearing at 7.73 ppm shows ring triazole formation. Sathya et al.[26] found a singlet signal at 8.05 ppm for triazole proton, respectively. A singlet peak at 3.69 ppm indicates methoxy protons on the phenyl ring, and a doublet at 1.24 ppm is attributed to methyl protons. Similarly, Riddima et al.[27] found a signal at 7.67 ppm corresponding to the 1,2,3-triazole ring as a sharp peak. The triazole-ring structure confirmation is thus successfully demonstrated by the results, which is consistent with the data analysis. Usually, the chemical shift values are typically between 7.49 and 8.14 ppm for the formation of the titled compound derivative. As for carbon atoms, the signal at 123.4 and 124.5 ppm indicates –CH group, 142.3 and 143.7 ppm for the quaternary carbon. In ^{13}C NMR data, 30.26 ppm indicates methyl carbon, and the signal at 68.51, 53.82, and 30.26 ppm indicates the presence of three methylene groups, respectively. Furthermore, peaks 164.13 and 168.47 ppm indicate the carbon carbonyl group. The mass spectra calculated [M+1] for the compound is at 318.1328, and [M+1] observed in the mass spectrum is at 319.1406, confirming the successful synthesis of the compound and the spectroscopic data provided.

4 Conclusion

The successful synthesis of the title 1,4-disubstituted-1,2,3-triazole derivative using a click reaction approach from commercially available materials via an efficient synthetic pathway facilitates the exploration of structure-activity relationships. The obtained product was successfully purified using the chromatography technique, and the reaction resulted in good yields. The synthesized 1,2,3-triazole derivative was confirmed through various analytical techniques and spectroscopic investigations. The IR spectrum showed characteristic peaks for functional groups, such as N-H (3502 cm^{-1}), C=O (1677.81 cm^{-1}), and C-O stretching (1258.88 cm^{-1}), consistent with literature values. NMR chemical shifts confirmed the number of protons and the number of carbon atoms for structural integrity, indicating the triazole ring formation. HRMS confirmed the molecular structure by examining the fragmentation of molecules within the sample, providing the purity of the compound. Collectively, these results validate the regioselective formation and molecular stability of the synthesized compound, aligning well with the reported data in the literature.

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Declaration of interests

This research was performed using Solution State NMR Spectrometer 13C 1H 400 MHz & HRMS analysis of the sample performed using analytical services, Dept. of organic chemistry, through I-STEM web portal, funded by the office PSA, Govt. of India, and located at Indian Institute of Science (IISc), Bengaluru.

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