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Click Synthesis and Spectral Characterization of a 1,2,3-Triazole Conjugated Pyrrole-2,5-dione Scaffold

Uday Mishra[1], Saheban Khan[2], Vinod Kumar[3], Nitesh Kumar[4], Ram Kumar[5]

[1, 2, 5]University Department of Chemistry, B.R.A. Bihar University, Muzaffarpur-842002, Bihar, India

[3]Department of Chemistry, M.J.K. College, (B.R.A. Bihar University, Muzaffarpur), Bettiah-845438, Bihar, India (Corresponding Author)

[4]Department of Chemistry, S.N.S. College, (B.R.A. Bihar University, Muzaffarpur), Motihari-845401, Bihar, India

Abstract: ***This study presents the synthesis and characterization of a novel 1,2,3-triazole conjugated pyrrole-2,5-dione compound via copper-catalyzed azide-alkyne cycloaddition (click chemistry). The synthetic route involves the reaction of benzyl azide with a pyrrole-2,5-dione-derived alkyne under mild conditions, yielding the target compound in excellent purity and yield (92 percent). The final product was comprehensively characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry, confirming its structural integrity. The reported methodology contributes to the development of bioactive heterocyclic scaffolds with potential pharmaceutical relevance.***

Keywords: Click chemistry, 1,2,3-triazole, pyrrole-2,5-dione, copper catalysis, heterocyclic scaffold

1. Introduction

In the development of novel bioactive scaffolds, heterocyclic chemistry plays a unique role. Heterocyclic chemistry has long history in the area of medicinal chemistry, because of its huge applications in drug design and discovery.[1] Nitrogen-, sulfur-, and oxygen-containing heterocyclic scaffolds play a unique role in biological applications.[2] Among the heterocyclic compounds, the N-containing azoles, which have five-membered ring are key structural components in many biologically active natural products.[3] Azoles such as triazole, tetrazole, imidazole, and others form the core structures of many biologically active compounds. These azoles demonstrate a diverse range of biological activities such as antiviral, antimalarial, antibacterial, anticancer, anti-inflammatory and antituberculosis attributes.[4] Amongst azoles, triazoles are particularly significant heterocyclic compounds due to their outstanding pharmacological properties.[5] Triazole exist in two isomeric forms i.e. 1, 2, 3-triazole and 1, 2, 4-triazole as shown in **figure 1**, Triazoles interact readily with enzymes, proteins and receptors in organisms to afford an extensive range of biological activities such as antioxidant[6], antitubercular[7], antimicrobial[8], anti-urease[6], anticonvulsant[9], anti proliferative[10], antiviral[11], anti-inflammatory[12], antidiabetic[13], and antimalarial activities[14]. Itraconazole, Voriconazole and Fluconazole are extensively used as antifungal drugs, Ribavirin used as an antiviral drug for the treatment of hepatitis. Rizatriptan is widely used as an antimigraine agent, Letrozole, Anastrozole, Talazoparib and Vorozole are extensively effective anticancer drugs. In 2008, Rufinamide has been approved by the FDA for the treatment of pediatric epilepsy. Maraviroc is widely used as an anti-HIV drug and Tazobactam is mainly used as antibiotic therapy. [15] Some common 1,2,3-triazole and 1,2,4-triazole based drugs are shown in **figure 2** and **3**.

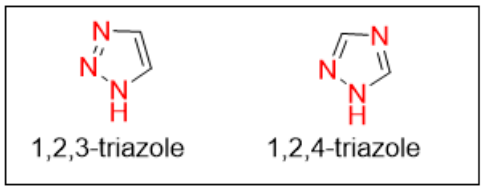


Figure 1: Two isomeric forms of triazole

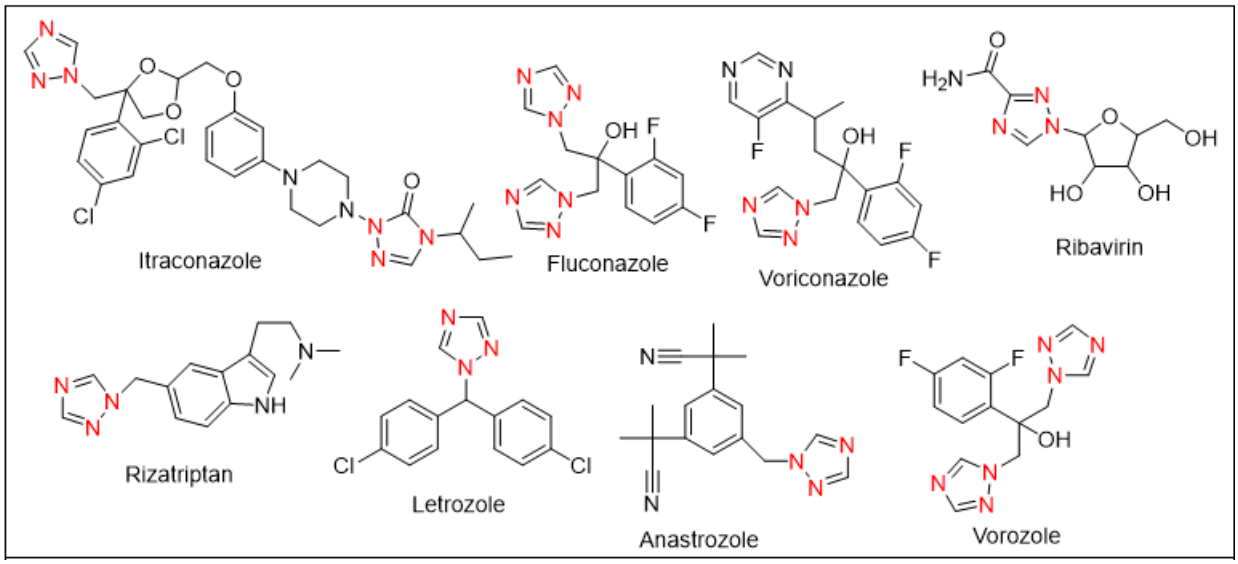


Figure 2: Drug carrying 1,2,4-triazole.

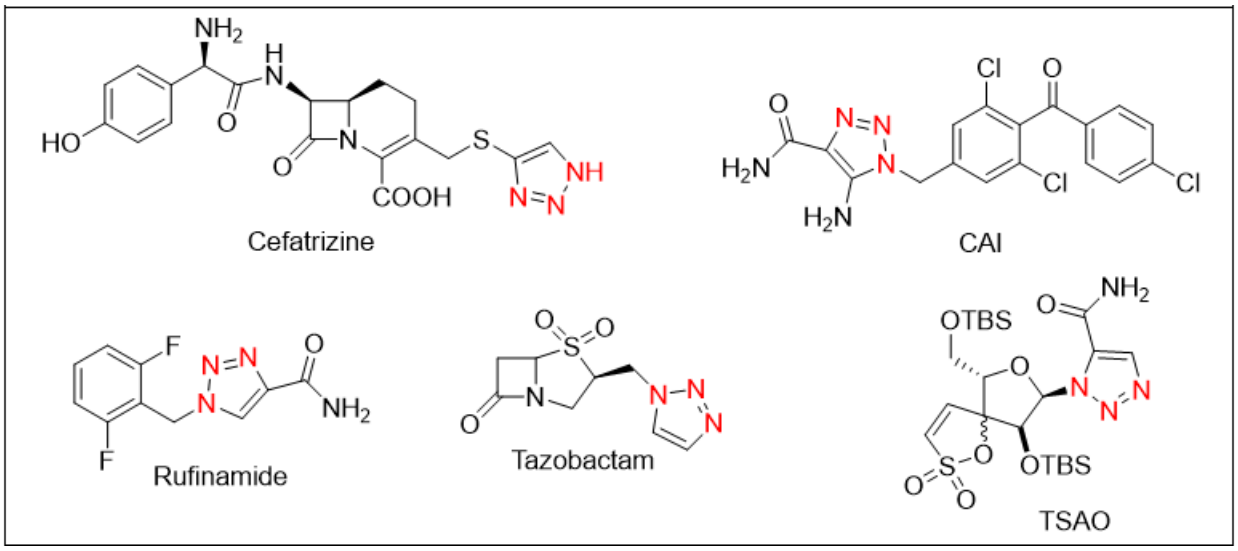
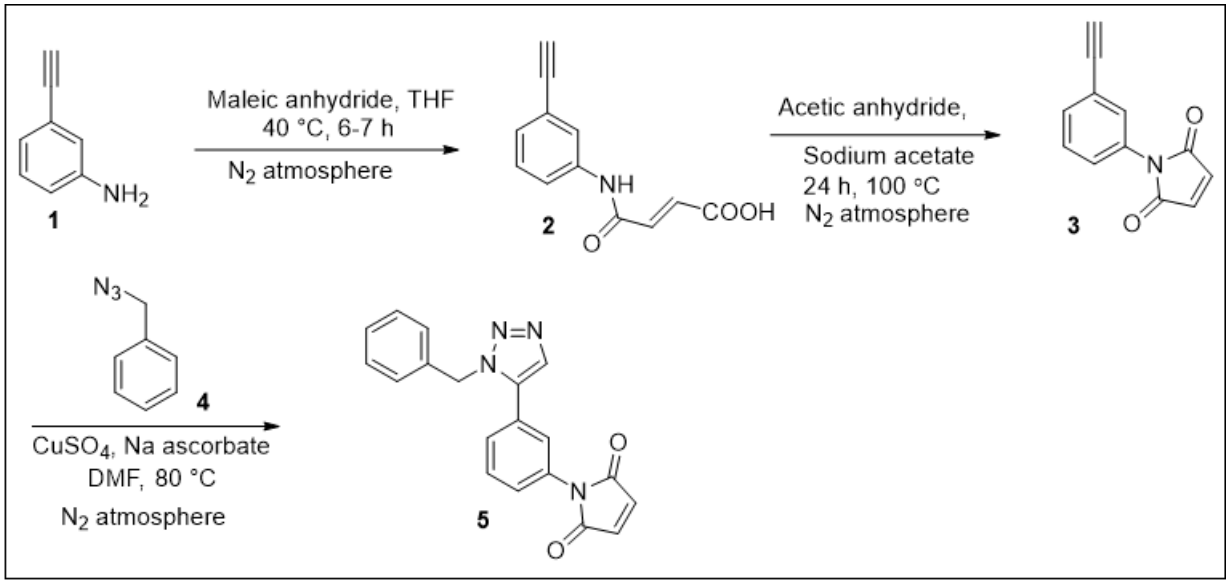


Figure 3: Drug carrying 1,2,3-triazole.

By considering the increasing demand of triazole-carrying scaffolds with significant biological attributes. Herein, we synthesized a pyrrole 2,4-dione based triazole compound via copper- catalyzed click reaction between pyrrol-2,4-dione alkyne and benzyl azide in good yield. The purpose of this study is to synthesize a novel 1,2,3-triazole conjugated pyrrole-2,5-dione compound using click chemistry and to characterize its structure using spectroscopic techniques for potential bioactive applications. This work contributes to the expanding field of bioactive heterocyclic compounds by providing a novel scaffold that can be further explored for therapeutic properties such as antimicrobial or anticancer activity.

2. Result and Discussion

The desired compound **5** i.e. 1,2,3-triazole conjugated pyrrol-2,5-dione has been synthesized via cupper-catalyzed cycloaddition reaction between key precursor alkyne **3** and azide **5** as shown in **scheme 1.** Firstly, 3-Ethynylaniline **1** (1.0 equivalent) was treated with maleic anhydride (1.0 equivalent) in tetrahydrofuran solvent at 40 °C for 6-7 h to yield the intermediate **2** in good yield. The alkyne precursor **3** was synthesized from intermediate **2** with acetic anhydride under basic medium. The key azide precursor **4** was obtained from benzyl bromide in one step by the reaction of benzyl bromide with sodium azide in quantitative yield. Lastly, the desired product **5** was achieved by the treatment of alkyne precursor **3** and azide precursor **4** via click chemistry with copper sulphate and sodium ascorbate in N, N-dimethylformamide solvent at 80 °C in 92% yield.



Scheme 1: Synthesis of triazole conjugate pyrrole-2,5-dione.

3. Experimental Section

The IR spectrum was recorded using a Perkin-Elmer model 2000 FT-IR spectrometer with KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Jeol alpha-400 spectrometer at 400 and 100.6MHz, respectively, using TMS as internal standard. The chemical shift values are on δ scale. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solvent. HR-ESI-TOF-MS analyses were recorded on a Micro TOF instrument from Bruker Daltonics, Bremen on ESI positive mode. Analytical TLCs were performed on precoated Merck silica-gel 60F254 plates; the spots were detected under UV light. Silica gel (100-200 mesh) was used for column chromatography. Chemicals were obtained from commercial suppliers and were used without any further purification.

4. Methods

(a) Synthesis of compound (E)-4-((3-ethynylphenyl) amino)-4-oxobut-2-enoic acid (2)

In a 100 mL round bottom flask compound **1** (1.0 equivalent) was dissolved in anhydrous tetrahydrofuran (THF) at 40 °C temperature followed by the addition of maleic anhydride (1.0 equivalent) along with stirring for 6-7 hour at nitrogen atmosphere. The progress of reaction was monitored by thin layer chromatography (methanol: chloroform, 1:20). On completion of the reaction, the solvent was evaporated under reduced pressure. The solid residue thus obtained was rinsed with petroleum ether and dried over the high vacuum to yield the intermediate **2** with 90 % as a solid scaffold.

The characteristics proton of compound **2** in ^{1}H-NMR spectroscopy appeared at δ 10.32 (broad, OH), 9.88–9.92(NH). 6.24 (doublet, CH=CH), 7.14-7.81 (aromatic hydrogen), 3.53 (singlet, ethynyl CH). ^{13}C-NMR appeared at δ 166.23(C=O), 121.27-135.34 (aromatic carbon), 136.23-138.21 (CH=CH), 81.23(terminal ethynyl CH). The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 3350 (NH), 1750 (acid, C=O), 3250 (C-OH) 3123 (aromatic, C-H), 1664 (C=C, stretching). HR-ESI-TOF-MS: *m/z* 216.0660 ([M+H]$^{+}$), calcd. for $[C_{12}H_9NO_3+H]^{+}$ 216.0661.

(b) Synthesis of compound 1-(3-ethynylphenyl)-1H-pyrrole-2,5-dione (3)

In a 100 mL round bottom flask, compound **2** (1.0 equivalent) was dissolved in a minimum amount of acetic anhydride and sodium acetate (1.0 equivalent) was added along with stirring at room temperature for 15 minutes. After 15 minutes, the reaction mixture was heated at 100 °C for 24 h under nitrogen environment and progress of the reaction was monitored by thin layer chromatography (methanol: chloroform, 1:20). On completion, the reaction was diluted with ethyl acetate and water (50 mL). Organic layer so obtained was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was then evaporated under reduced pressure to obtain the solid residue which was purified by silica gel column chromatography (methanol:chloroform, 1:49) to give the compound **3** as a light yellow solid in 83 % isolated yield. The characteristics proton of compound **3** in ^{1}H-NMR spectroscopy appeared at δ 7.82 (doublet, pyrrolidine CH), 7.76–7.14 (aromatic proton). 3.24 (singlet, ethynyl CH). ^{13}C-NMR appeared at δ 161. 21(C=O), 122.24-127.34 (aromatic carbon), 135.21 (CH=CH, pyrrolidine), 81.14 (terminal ethynyl CH). The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 1720 (cyclic amide, C=O), 3135 (aromatic, C-H), 2160 (ethynyl C-C, stretching), 3308 (ethynyl CH, stretching). HR-ESI-TOF-MS: *m/z* 198.0552 ([M+H]$^{+}$), calcd. for $[C_{12}H_7NO_2+H]^{+}$ 198.0555.

(c) Synthesis of compound 1, 2, 3-triazole conjugated pyrrole-2,5-dione (5)

In a 100 mL round bottom flask, compound **3** (1.0 equivalent) was dissolved in a 20 ml of anhydrous N, N-dimethylformamide then added benzyl azide **4** (1.0 equivalent) followed by calculated amount of copper sulphate and sodium ascorbate and stirred the reaction mixture at 80 ° for 3 h using nitrogen atmosphere and progress of the reaction was monitored by thin layer chromatography (methanol: chloroform, 1:20). On completion, the reaction was diluted with ethyl acetate and water (50 mL). Organic layer so obtained was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was then evaporated under reduced pressure to obtain the solid residue which was purified by silica gel column chromatography (methanol: chloroform, 1:30) to afford the

desired compound **5** as a solid in 92 % isolated yield. The characteristics proton of compound **5** in ^{1}H-NMR spectroscopy appeared at δ 8.24 (singlet, triazole CH), 7.82 (doublet, pyrrolidine CH). 7.32-7.53 (aromatic CH), 5.24 (singlet, benzyl C$\underline{H}_2$). ^{13}C-NMR appeared at δ 161. 32 (C=O), 129.72 (triazole, $\underline{C}$H), 140.21 (triazole $\underline{C}$) 134.78 ($\underline{C}$H=$\underline{C}$H, pyrrolidine), 127.21-133.14 (aromatic $\underline{C}$H). The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 1725 (cyclic amide, C=O), 3138 (aromatic, C-H). HR-ESI-TOF-MS: *m/z* 331.1192 ([M+H]$^{+}$), calcd. for [$C_{19}H_{14}N_4O_2$+H]$^{+}$ 331.1195.

5. Conclusion

In this work, we successfully synthesized a novel triazole-conjugated pyrrole-2,5-dione compound through copper-catalyzed click chemistry. The structure was verified through a suite of spectroscopic techniques, affirming its potential as a bioactive scaffold. Future research should explore its pharmacological properties and functional derivatives to further assess its applicability in medicinal chemistry.

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