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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2022, Vol. 38, No.(5):
Pg. 1104-1109

Synthesis of Azoles in Water by Copper(I)-Catalyzed Prepared by Arc Thermal Plasma Process and a molecular Docking Study Against COVID-19

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http://dx.doi.org/10.13005/ojc/380503

(Received: July 06, 2022; Accepted: September 15, 2022)

ABSTRACT

Huisgen's 1,3-dipolar cycloadditions in water of 6-azidohexan-1-ol dotted with terminal alkynes and catalyzed with copper nanoparticles, offering access to 1,2,3-triazoles 1,4-disubstituted. The SARS-CoV-2 coronavirus epidemic is still spreading at a fast rate worldwide. The core protease (Mpro) is a gorgeous mark for anti-COVID-19 agents. Click chemistry synthesis, catalyzed using nanoparticles, has been used to prepare the 1,2,3-triazole motif. The high docking score of the newly synthesized triazole are, may be, attributed to the presence of hydrogen bonds together with many interactions between the ligands and the active amino acid residue of the receptor. The comparison of the interactions of Taribavirin and Ribavirin drug with triazole in the largest pocket of 7JWY is also presented. Further interesting comparative docking analyses were performed. The results of this study suggest that triazole 3d may be considered for further investigation as one of the possible therapeutic agents for COVID-19.

Keywords: Click chemistry, Arc Thermal Plasma, Triazole, Taribavirin; Ribavirin, Covid-19, Docking.

INTRODUCTION

Click chemistry is an organic procedure presented in 2001 by Sharpless, hghlighting cycloaddition, producing rapidly and consistently products via the connection of minor units together.[1] Huisgen 1,3-dipolar copper catalyst reaction[2] between alkynes and azides has possibly developed the greatest current ligation reaction that has been extensively practical in numerous fields such as drug discovery and polymer, material science, etc.[3] The progress of copper catalytic classifications for

Huisgen 1,3-dipolar copper catalyst reactions has taken abundantly considered Furthermore, most of the described catalyst copper types were synthesized in situ by reduction of Cu(II)/Cu(0), Cu(II) salts by comproportionating, or oxidation of metal Cu(0).[4,5] Recently, the Cu_2O nanoparticles catalyzed organic reaction has attracted considerable attention.[6]

We expect that nanoparticles of Cu_2O strength have the performance as a novel catalytic structure for 1,3-dipolar reactions under aerobic conditions in water due to their essential characteristics, for example, simplistic surface functionality, elevated surface areas, and greater stability than bulk of cuprous oxide.[7] Triazole derivatives are imperative heterocycles that contain nitrogen atoms and have been extensively used in agronomic and medicinal production. Many preparation methods for this product type have been established. Previously, these heterocycles were classically synthesized by creating a combination of 1,5-disubstituted- and 1,4-disubstituted triazoles *via* a thermal 1,3-dipolar reaction of alkynes and azides.[8] The present economic and health apprehensions of the whole world owing to coronavirus have attracted numerous groups of researchers to discovery vaccine and/or treatment for this rapid dispersal contagion.[9] The outbreak of this original 2019-CoV, or coronavirus has posed a considerable test to the global scientific research public later. The World Health Organization cannot make available the flying broadcast of COVID-19.[10] Nitrogen-containing heterocyclic have revealed real antiviral activities. As examples, Taribavirin and Ribavirin are well known as nucleosides with a triazole structure and are the most largely agreed upon antiviral medications. They have been methodically tested against herpes simplex virus, human immunodeficiency virus, simplex virus, influenza virus, hepatitis C virus, and respiratory syncytial.[11]

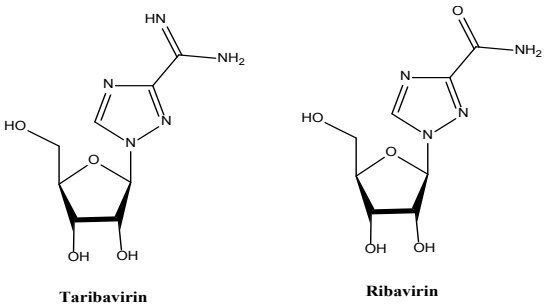


Fig. 1. Chemical structures of Taribavirin and Ribavirin

The above results encouraged us to conduct a study on the reactions of 6-azidohexan-1-ol and alkynes in the presence of copper nanoparticles to prepare 1,2,3-triazole derivatives.

EXPERIMENTAL

General procedures

Before use all solvents were subjected to distillation. Chromatography was performed with silica gel, and the plate silica gel F254 was used for preparative TLC. The characterization of all the prepared heterocycles was established using NMR proton (300 MHz) and NMR carbon (75 MHz). The NMR solvent is DMSO-d6, and HRMS spectrometric studies were performed using Thermo Finnigan apparatus. For Fourier transformed infrared spectroscopy (FT-IR), samples were pressed into KBr pellets, and successively analyzed using a Bio-Rad FTS600 infrared spectrometer.

General Method of cycloaddition reaction of terminal alkynes and azides using Cu_2O-NPs as a catalyst

A solution of of alkyne 2 (1.0 mole), azide 1 (1.0 mole) and copper nanoparticles in water (20 mL), was stirred for 36 h at 30˚C. The obtained reaction combination was separated through a celite cloth in order to eliminate the Cu_2O-NP. The water was removed under reduced pressure. Generally, the obtained heterocycles were of appropriate purity.

(1-(6-hydroxyhexyl)-1H-1,2,3-triazol-4-yl)methyl-benzoate (3a)

Yield 85%, m.p. 134-135°C, yellow solid. R_f=0.15 (cyclohexane/AcOEt 2:8). ^{1}H NMR (δ, ppm): 7.59 (1H, s), 7.34-7.55 (5H, m), 5.63 (2H, s), 4.70 (s, 1H), 4.35-4.37 (2H, m), 3.34-3.37 (2H, m), 1.84-1.87 (2H, m), 1.39-1.41 (2H, m), 1.31-1.35 (2H, m), 1.24-1.27 (m, 2H). ^{13}C NMR (δ, ppm): 165.9, 146.9, 131.3, 129.4, 129.7, 113.1, 111.4, 62.9, 60.5, 49.4, 32.4, 29.8, 25.6, 24.8. HRMS calculated for $C_{16}H_{21}N_3O_3$ $[M+H]^+$ m/z 304.1661, found 304.1658.

(1-(6-hydroxyhexyl)-1H-1,2,3-triazol-4-yl)methyl 4-methylbenzoate (3b)

Yield 85%. m.p. 144-145°C, white solid., R_f=0.17 (cyclohexane/AcOEt 2:8). ^{1}H NMR (δ, ppm): 8.24 and 8.33 (d, 4H, *J* = 9Hz), 7.56 (s, 1H), 5.64 (2H, s), 4.71 (1H, s), 4.34-4.38 (2H, m), 3.33-3.36

(2H, m), 2.41 (3H, s), 1.83-1.86 (2H, m), 1.37-1.40 (2H, m), 1.30-1.35 (2H, m), 1.23-1.28 (2H, m). ^{13}C NMR (δ, ppm): 165.6, 146.8, 142.4, 129.6, 129.4, 127.1, 123.4, 62.8, 60.4, 49.5, 32.3, 29.9, 25.5, 24.7, 21.3. HRMS calculated for $C_{17}H_{23}N_3O_3$ $[M+H]^+$ m/z 318.1818, found 318.1815.

(1-(6-hydroxyhexyl)-1H-1,2,3-triazol-4-yl)methyl4 -methoxybenzoate (3c)

Yield 90%, m. p. = 110-111°C, white solid., R_f=0.21 (cyclohexane/AcOEt 2:8). ^{1}H NMR (δ, ppm): 8.03 and 6.89 (d, 4H, *J* = 9Hz), 7.54 (1H, s), 5.66 (2H, s), 4.69 (1H, s), 4.36-4.33 (2H, m), 3.85 (3H, s), 3.37-3.32 (2H, m), 1.87-1.82 (2H, m), 1.41-1.36 (2H, m), 1.37-1.31 (2H, m), 1.27-1.24 (2H, m). ^{13}C NMR (δ, ppm): 165.8, 163.6, 146.7, 130.4, 129.7, 122.9, 113.4, 62.9, 60.3, 55.5, 49.4, 32.4, 29.8, 25.4, 24.6. HRMS calculated for $C_{17}H_{23}N_3O_4$ $[M+H]^+$ m/z 334.1767, found 334.1770.

(1-(6-hydroxyhexyl)-1H-1,2,3-triazol-4-yl)methyl4 -nitrobenzoate (3d)

Yield 75%, m.p. = 153-154, °C, white solid., R_f=0.18 (cyclohexane/AcOEt 2:8). ^{1}H NMR (δ, ppm): 7.95 and 7.23 (d, 4H, *J* = 7.8Hz), 7.52 (1H, s), 5.64 (2H, s), 4.68 (1H, s), 4.37-4.33 (2H, m), 3.37-3.33 (2H, m), 1.87-1.83 (2H, m), 1.42-1.37 (2H, m), 1.34-1.30 (2H, m),1.28-1.24 (2H, m). ^{13}C NMR (δ, ppm): 165.9, 163.5, 147.6, 136.9, 131.4, 129.6, 123.4, 62.8, 60.6, 49.3, 32.5, 29.7, 25.3, 24.7. HRMS calculated for $C_{16}H_{20}N_4O_5$ $[M+H]^+$ m/z 349.1512, found 349.1510.

Docking

MOE. 2015.10 software was used to establish the docking studies[15] using the crystal building of Covid protein [PDB ID: 7JWY].[16] Chem-drawn ultra-version was used to reproduce all these molecular structures, and then all products were used in molecular format in order to expose these documents in MOE later to building research, and these were protonated 3D with minimized energy complete MOE, using default parameters. All minimizations were established using MOE with a RMSD ramp of 0.01 kcal/mol/A with Amber99 force field and programmed control of the partial charges. The modeled structures of triazoles and remdesivir are 3D protonated and later the minimization of energy was achieved using the MOE software through default parameters as declared above. Docking settings were established as follows: Amber99 force field for consequence the refinement, triangle Matchmaker location was selected to control positions, the London ΔG recording occupation was practical for rescoring and consequence improvement, and buildings have been further sophisticated with a refinement of the rigid receiver. The resultant docking positions were produced in a database, which was organized according to the ending score function, which is the score of the preceding step that was not zeroed.

RESULTS AND DISCUSSION

Chemistry

Copper nanoparticles were prepared by the plasma arc discharge technique under an air atmosphere and nitrogen gas. The experimental method is shown in Fig. 2. The voltage of the arc was attuned by touching the distance between the two electrodes. In order to produce copper nanoparticles, the cavity was expatriated up to an improper pressure of 1.8×10^{-4} mbar and then backboned complete with nitrogen gas up to 1 atm.

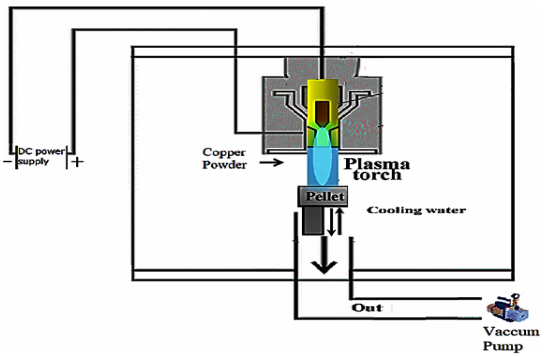
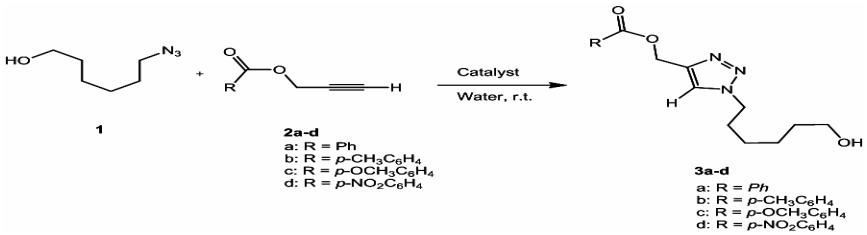


Fig. 2. Representation illustration of plasma arc discharge system

The average particle size of the CuNPs was obtained at around 65nm and they were of spherical shape[12,13]. The syntheses of the triazoles **3a-d** are exposed in Scheme 1. Novel triazole derivatives **3a-d** were synthesized *via* the Click Chemistry reaction of alkynes **2a-d** and 6-azidohexan-1-ol **1** in the presence of copper nanoparticles.[11] The 1,3-dipolar cycloaddition was successfully reacted at room temperature in water to give the single regioisomer **3a-d**.



Scheme 1. Formation of triazoles derivatives 3a-d using the 1,3-dipolar reaction

The FT-IR spectra of all the prepared triazole **3a-d** displayed absorption bands corresponding to the azo group (N=N) ranging from 1515 to 1520 cm^{-1}. The confirmation of the obtention of the heterocycle was established by the existence of absorption band in the range of 1640-1650 cm^{-1} relative to vinylic proton in the triazole cycle. The chemical shifts of vinylic protons contained in products **3a-d** have ranged from 7.45 to 7.59ppm. The ^{13}C-NMR of triazole **3a-d** presented vinylic carbon peaks at 131.3–131.9ppm and 146.4–146.9ppm.

Docking studies

The main purpose of this section is the fulfillment of a molecular docking study[14] of 1,2,3-triazoles **3a-d** in order to discover the vigorous location of the main protease of the coronavirus (7JWY) and to discover an antiviral agent for this epidemic (Figure 3).

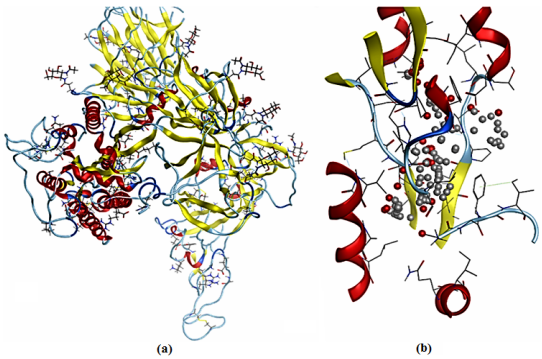


Fig. 3. Structures of protein 7JWY (A) and largest pocket 7JWY (B)

An accurate study was directed between the triazoles **3a-d**, Taribavirin, and Ribavirin approving antiviral drugs using 7JWY. The obtained results demonstrated that all designated inhibitors and drugs were in the concise of the board proteins. The docking score assesses the interaction consequences. The scoring value was exploiting in order to visualize the binding attraction of the target and ligand when they are docked. MOE was served to calculate the docking scores for the U. S. FDA-approved antiviral drug against 7JWY protease. In this work, the same restriction for calculating the docking scores for triazoles **3a-d** against 7JWY protease was used. Docking scores were noticed for the triazole **3a-d**, fluctuating from –5.2077 to –6.1612. However, the binding affinities of the approved antiviral drugs Taribavirin and Ribavirinwere –4.5353 and –4.1265 with 7JWY protease, respectively (Table 1).

Table 1: Docking Scores of triazoles 3a-d, Taribavirin and Ribavirin with proteins 7JWY

Trial N°	Drugs	S-Value
1	Triazole 3a	-5.4081
2	Triazole 3b	-5.6838
3	Triazole 3c	-5.2077
4	Triazole 3d	-6.1612
5	Taribavirin	-4.5353
6	Ribavirin	-4.1265

Triazoles, Taribavirin, and Ribavirin exhibited good interactions with protein 7JWY. The greatest effective ligand, triazole **3d** moorage with protein 7JWY, constitutes one H-arene bond interaction with the Phe338 dynamic amino acid residue and one acidic hydrogen bond, with the negative oxygen atom of the nitro group bonding of the aryl moiety of the ligand with Asp364 active amino acid residue. Cys336 and Asn343 were observed to develop a basic hydrogen bond with the oxygen atom of the ligand. All these interactions are shown in Fig. 4E, and in this case, the docking score was -6.1612.

The Taribavirin docking with protein 7JWY presents two acidic hydrogen interactions of two nitrogen atoms of the amino group with the Asp240 and Phe58 and basic hydrogen interactions between nitrogen of triazole cycles with Arg273 active amino

acid residue. All these interactions are shown in Fig. 4B, in this case the docking score was -4.5353.

The interactions observed in Ribavirin between protein 7JWY and Ser364 were observed to from an H-arene bond with the triazole cycle. Phe59 exhibited a two-hydrogen bond with the oxygen atoms. These interactions are shown in Figure 4C.

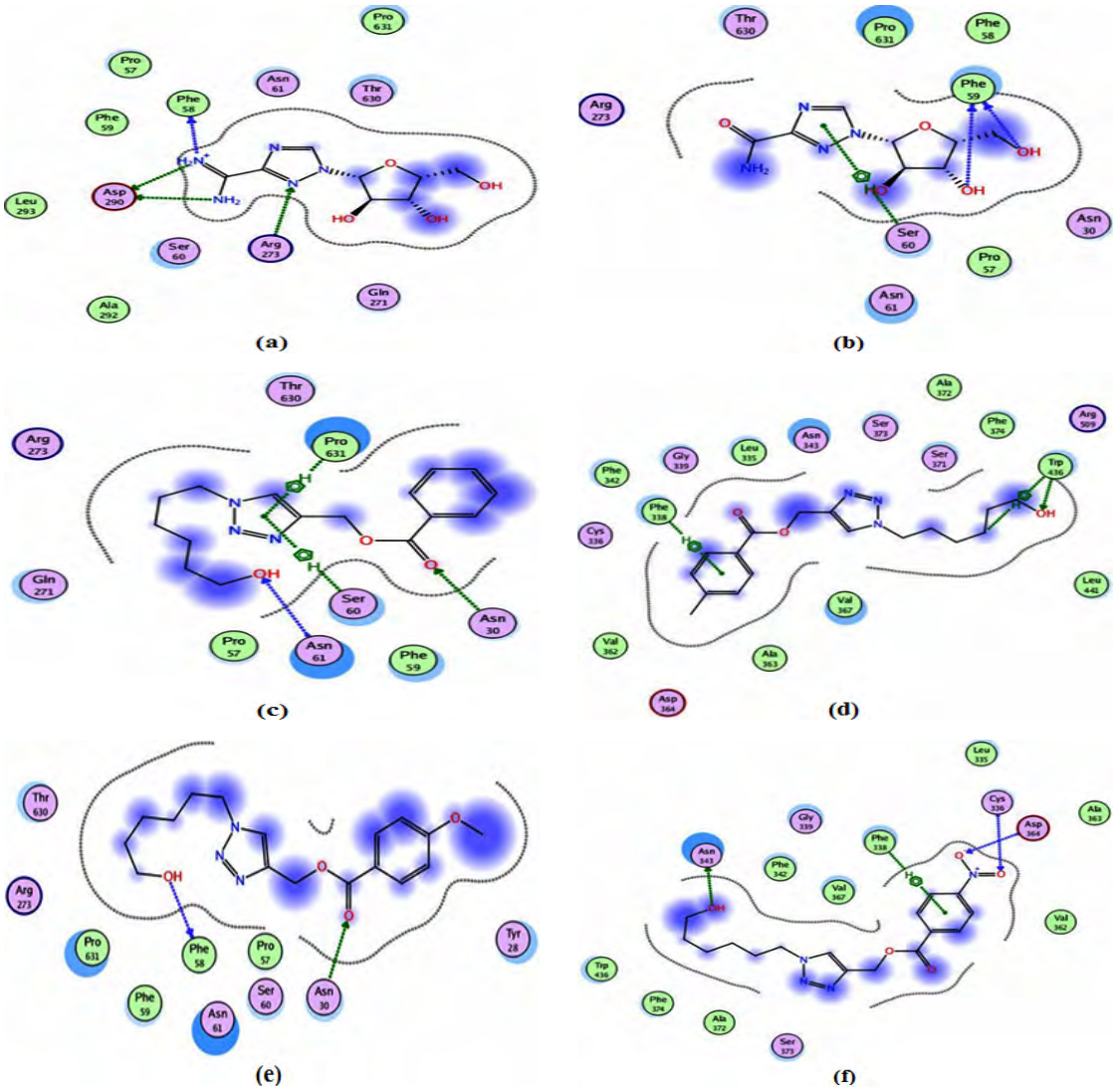


Fig. 4. (A) 2D interactions images of docking conformations of Taribavirin with the active proteins, (B) Interactions of Ribavirin and protein, (C) Interactions triazole 3a and protein, (D) Interactions triazole 3b and protein, (E) Interactions triazole 3c and protein, (F) Interactions triazole 3d and protein

CONCLUSION

An original group of 1,2,3-triazole derivatives were modeled and efficiently synthesized. Copper nanoparticles were prepared by the plasma arc discharge technique under un air atmosphere and nitrogen gas. The 1,2,3-triazole heterocycles **3a-d** were synthesized using the Click Chemistry of alkynes and 6-azidohexan-1-ol in the presence of copper nanoparticles. On the basis of the remarks of simulated showing realized via molecular moorage accomplished in order to detect new heterocycles that can be capable of predicament with protein constructions of coronavirus (PDB ID:7JWY), we hypothesized that the triazoles might assist in coronavirus medication detection. This is obviously displayed by the bond attraction attained for triazole **3d** representing a respectable binding strength against the coronavirus.

ACKNOWLEDGEMENT

This research was supported by the Deanship of Scientific Research, Imam Mohammad Ibn Saud Islamic University (IMSIU), Saudi Arabia, Grant No. (21-13-18-035).

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