Sys Rev Pharm 2020;11(12):1039-1041
A multifaceted review journal in the field of pharmacy

Synthesis, identification and study antibacterial activity of new 1,2,3-triazoles derived from resorcinol using click chemistry

Mohammed Hamza Heriz [1], Isam Mohammed turki[2],
Zeyad Kadhim oleiwi[1], Hayder Kadhim Abbas[1], Ibtihal Kareem Mahdi[3]

[1]Department of pharmaceutics and pharmaceutical chemistry, College of pharmacy-University of Alkafeel
[2]Department of community health, Technical institute of kufa -Al-Furat Al-Awsat Technical University
[3]Department of medical laboratories techniques, Altoosi university college
Corresponding Author: Zeyadkadhim@alkafeel.edu.iq

ABSTRACT

Background: Triazole has special importance in several fields such as, medicinal chemistry and drug research owing to the diversity of their biological activity from anti-inflammatory, anti-bacterial, anticancer, enzyme inhibition and many other activities, as well as to their structural features enable them to mimic various functional groups, which justifying their wide utilize as a bioisostere for development of totally new active molecule. So from of the above facts in this work we concerned with synthesis of new triazole derivatives from resorcinol using click chemistry and studying their antibacterial activity.

Materials and methods: first of all, in our procedure we do etherfication of both phenolic hydroxyl groups of resorcinol by reaction with propargyl bromide to get 1,3-bis[(prop-2-yn-1-yl) oxy] benzene, which in turn will be reacted with azide derived from aniline in the presence of copper sulphate pentahydrate as catalyst and sodium ascorbate as stabilizer, finally the desired products have been achieved.

Result and discussion: the synthesized compounds subjected to FT-IR spectrum, 1H NMR and 13C NMR study to confirm their structures, as well as biological study against some of gram positive and gram negative bacterial species by well diffusion method in nutrient medium agar, which show that all 3 compounds have antibacterial activity especially compound (II) has broad spectrum of activity then Compound (I) and compound (III) has more antibacterial activity against gram negative species.

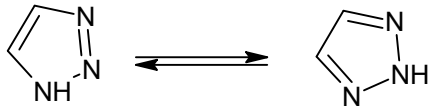
Conclusion: from above results of our work respecting the antibacterial activity of produced triazole compounds which show that these compounds have good activity, so more work in this field is required supported with our encouraging results.

Keywords: Antibacterial activity, bioisostere, 1,2,3-Triazoles, Resorcinol, Click .chemistry

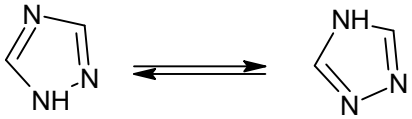
Correspondence:
Zeyad Kadhim oleiwi
1Department of pharmaceutics and pharmaceutical chemistry, College of pharmacy-University of Alkafeel
*Corresponding author: Zeyad Kadhim oleiwi email-address: Zeyadkadhim@alkafeel.edu.iq

INTRODUCTION

Nitrogenous heterocyclic compounds play a vital role in synthetic, agrochemical and pharmaceutical fields mainly 1,2,3-triazole and 1,2,4-triazole (1). Triazoles are an important class of five-membered ring heterocyclic compounds. They are grouped into two main types, the 1,2,3-triazoles which is V-triazoles (I) and 1,2,4-triazoles or S-triazoles (II) (2).



(I)



(II)

Triazole is a surprisingly stable structure compared to other organic compounds having three adjacent nitrogen atoms. V-triazoles have been studied extensively and still attract considerable attention due to their spread biological activities (3,4). Recently the take significant importance as a result of development of novel triazoles with antiviral, anticancer, antimicrobial and anti-inflammatory activities (5-10), like ibuprofen linked triazoles (10). Azoles anti-fungal such as miconazole, fluconazole and itraconazole, Enzyme inhibitors (4-6) like anstrazole which is a potent aromatase inhibitor and $GABA_A$ receptor positive allosteric modulator like Loreclezole considered a good example on drugs with triazole moiety. Anti-HIV, antiallergic, anticonvulsant, local anesthetic, antimalarial, antiviral, and antimycobacterial agents, potassium channel activators and many other active compounds in their way of clinical trials (7). 1,2,3-Triazole finds wide use in research as a bioisostere in drug analogue design as their structural features enable them to mimic various functional groups, which justifying their wide utilize as a bioisostere for new active molecules (11).

MATERIALS AND METHODS

Propargyl bromide solution, purum, ~80% in toluene (Sigma-Aldrich)
Resorcinol ACS reagent, ≥99.0% (Sigma-Aldrich)
Aniline (Parchem)

Experimental part:

Synthesis of propargyl aryl ether

2 mole of phenol derivative (Resorcinol) was dissolved in acetone (20 ml) and 2.6 mole of K_2CO_3 and 5 moles of propargyl bromide were added in a round bottom flask and reflux this mixture overnight. Follow up the completion of reaction by TLC analysis to reveal conversion of reactant completely, then cooling this

reaction mixture to room temp. and put off the reaction by addition of saturated solution of by NH_4Cl, this mixture of reaction was extracted three times by using diethyl ether then the organic phase were combined and then dried via usinig anhydrous $MgSO_4$ and its volume reduced by rotary evaporator.

Synthesis of azide derivatives

0.02 mole of aniline derivative dissolved in diluted solution of HCl (25 ml). The reaction mixture was cooled at (- 5 C°), then 1.5 mole of sodium nitrite in equal portion manner (4 times) was added dropwise to the reaction mixture with maintaining the reaction temperature at (- 5 C°) for about 10 minute.

1.7 mole of sodium azide was dissolved in 10 ml of water was added dropwise to the mixture at 0 C° and continue the reaction for about 10 minute at 0 C°.

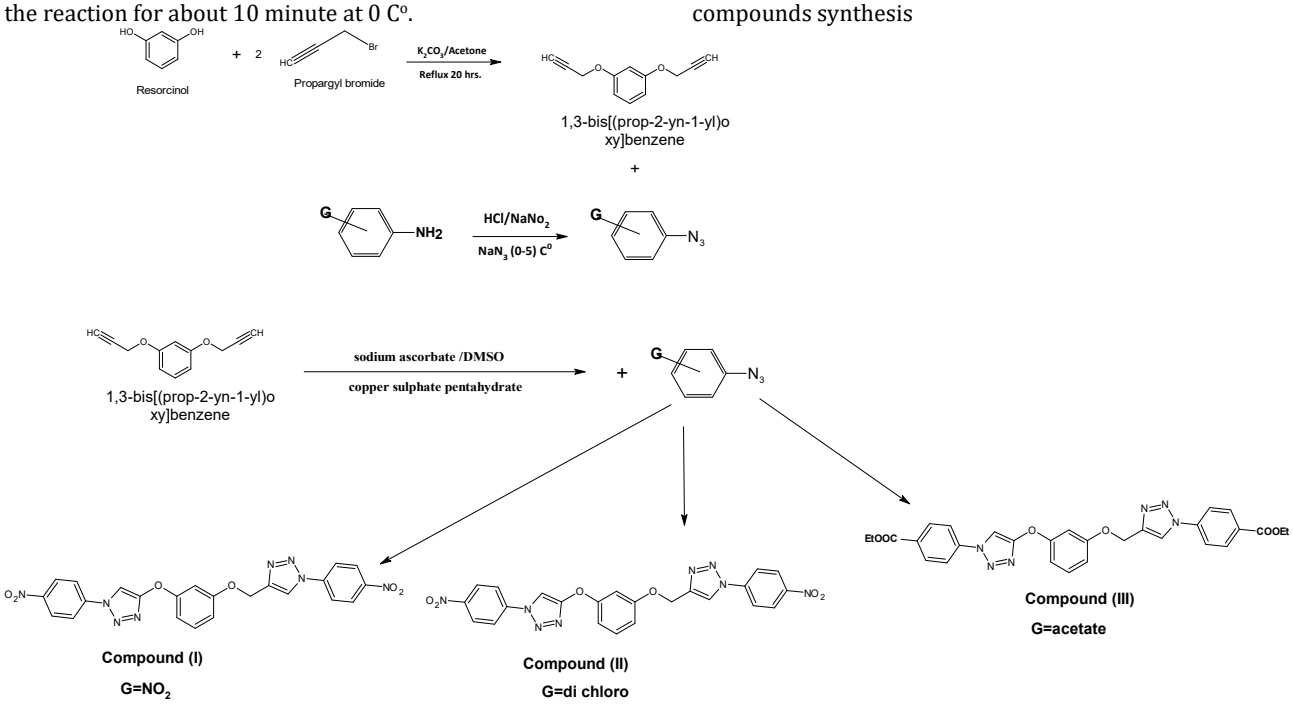
Synthesis of 1,2,3-triazole derivatives

3 mmole (0.894 g) of proparyl ether solution in 5 ml DMSO was added to 0.3 mmole (0.1107 g) sodium ascorbate suspension and 0.3 mmole (0.748 g) copper sulphate pentahydrate (CuSO4.5H2O) in about 4 ml of DMSO stirring this mixture for 10 min. then azide derivatives was added and heating the reaction mixture to 50 C° with continuous stirring for 24 hrs.

In the next day distilled water was added (30 ml) and extraction with ethyl acetate (30 ml) has been done for three times. The ethyl acetate layer then combined and washed with 20 ml of saturated NaCl for two times and dried over Na_2SO_4 and evaporated under vacuum.

RESULTS AND DISCUSSION

Scheme (I) represent the pathway used for the intended compounds synthesis



Scheme (I)

propargyl aryl ether

refluxing of phenol derivative like resorcinol with propargyl bromide overnight in acetone as a solvent system with potassium carbonate (K_2CO_3) have been lead to etherification of both resorcinol hydroxyl groups (12) to yield 1,3-bis[(prop-2-yn-1-yl) oxy] benzene, FT-IR identification of this compound reveal below data: 3292 due to (υ C–H acetylenic), 2123 due to (υ C=C acetylenic), 1595 due to (υ C=C aromatic), 3052 due to (υ C–H aromatic), 1257 due to (δ C–H aromatic).

Azide derivatives

reaction of diazonium salt of aniline or its derivatives with sodium azide will produce aryl azide which show the following peaks on FT-IR data sheet:

when (G1=NO_2) 3100 due to (υ C–H aromatic),2127 due to (υ N_3), 1579 due to (υ C=C aromatic), 1517 (υ O=N=O), 1286(δ C–H aromatic).

(G2= di chloro) 2120 due to (υ N_3),3111 due to (υ C–H aromatic), 1600 due to (υ C=C aromatic).

(G3=benzoate) 2123 due to (υ N3), 3111 due to (υ C–H aromatic),2983due to (υ C–H, CH3), 1600 due to(υ C=C aromatic),1716 due to (υ C=O of ester), 1278 due to (υ C–O of ester).

1,2,3-triazole derivatives

We use click chemistry to get the triazole derivatives. Which synthesized by reaction of acetylenic derivatives (propargylic ether) with azide derivatives in the presence in DMSO as solvent and using Cu(I) as catalyst. The following data represent FT-IR peacks, ^{1}H-NMR & ^{13}C-NMR spectrum of this compound:

i. FT-IR spectra at cm^{-1}: 3290 due to (υ C–H aromatic of triazole) , 3150 due to (υ C–H aromatic) ,1725 assigned to (υ C=C of triazole), 1596 assigned to (υ C=C aromatic), 1495 assigned to (υ O=N=O),1285 assigned to (δ C–H aromatic).

^{1}H NMR , 400 MHz, DMSO-*d6* δ: 5.2 ppm (2H, s, 2O-CH_2 of ether), 6.55- 8.25 ppm(m, Ar-H), 8.55ppm (2H, s, protons triazole rings), 9.20 ppm(1H, s, CH-NO2).

^{13}C NMR, 100MHz, DMSO-*d6* δ: 78.25ppm (assigned to carbons of OCH_2 of ether), 97.1ppm (assigned to carbon OCH_2-CH-OCH_2) , 104-160ppm (assigned to aromatic carbon in benzene and triazole ring).

ii. FT-IR spectra at cm^{-1}: 3190 due to(υ C–H of triazole ringe), 3157 due to(υ C–H aromatic), 1687 due to(υ C=C of triazole), 1597 assigned to (υ C=C aromatic).
^{1}H NMR, 400 MHz, DMSO-*d6* δ: 5.18ppm (2H, s, 2O-CH_2 of ether), 6.60-7.80ppm (m, Ar-H), 8.03ppm (2H, s, protons triazole rings), 8,75ppm (1H, s, CH-Cl).
^{13}C NMR spectrum, 100MHz, DMSO-*d6* δ: 78.25ppm (assigned to carbons of OCH_2 of ether), 97. 1ppm (assigned to carbon OCH_2-CH-OCH_2) , 109-158 160ppm (assigned to aromatic carbon in benzene and triazole ring).

iii. FT-IR spectra at cm^{-1}:3210 assigned to (υ C–H aromatic of triazole), 3146 due to (υ C–H aromatic) , 1764 due to (υ C=O of ester), 1709 due to (υ C=C of triazole), 1603 due to (υ C=C aromatic),1285 due to (δ C–H aromatic).
^{1}H NMR, 400 MHz, DMSO-*d6* δ:.34-1.37 ppm (6H, m, 2CH3 of ethyl ester), 2.09 ppm (4H, m, 2CH_2 of ethyl ester), 5.24 ppm (2H, s, 2OCH_2 of ether), 6.30-7.27 ppm(m, Ar-H), 8.19 ppm (2H, S, triazole protons rings), 9.11ppm (1H,CH-COOEt).
^{13}C NMR spectrum, 100MHz, DMSO-*d6* δ: 25.30ppm (2C, CH3 of acetate), 39.32-40.35 ppm(2C ,CH_2 acetate),78.25ppm 25ppm (assigned to carbons of OCH_2 of ether),108.2697 ppm (assigned to carbon OCH_2-CH-OCH_2) ,111-149ppm (assigned to aromatic carbon in benzene and triazole ring).

Antibacterial activity

studying of the antibacterial activity of these prepared triazole derivatives against two types are gram positive and gram negative bacterial species by using well diffusion method in nutrient medium agar. Examination of (*Streptococcus Pneumonia, Staphylococcus aureus)* as Gram Positive bacteria and (*Escherichia Coli)* as Gram Negative one. The antibacterial activity of compounds determined by measuring zone of inhibition around disc of each compound after 24 hours' incubation. The following tablet will represent these results.

Bacterial Species	Compound (I)	Compound (II)	Compound (III)
Streptococcus Pneumonia	**+**	**+++**	**+**
Staphylococcus aureus	**+++**	**++**	**+**
Escherichia Coli	**+++**	**++**	**+++**

Compound (I) has good antibacterial activity against two types (*Staphylococcus aureus* and *Escherichia Coli)*, while compound (II) show good activity against all tested species specially against *Streptococcus Pneumonia*, finally third compound has good antibacterial activity against *Escherichia Coli*. Compound (I) can be considered as to has a broad spectrum of antibacterial activity.

REFERENCES

1. Anees Ahmad Siddiqui , Hamad M.I.Hasan, Mojahidul Islam *Der Pharmacia Lettre*, **2011**, 3(1): 228-236
2. K.T.POTTS ; The chemistry of 1,2,4-triazole,*Chem.Rev.* ,1961,61,2,87-127
3. Jagerovic, N.; Gómez de la Oliva, C.; Goya, P.; Dordal, A.; Cuberes, R. Eur. Pat. Appl. 0380 290, **2006**.
4. Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, 6, 2696–2718. doi:10.1002/asia.201100432
5. Jordão, A. K.; Ferreira, V. F.; Lima, E. S.; de Souza, M. C. B. V.; Carlos, E. C. L.; Castro, H. C.; Geraldo, R. B.;Rodrigues, C. R.; Almeida, M. C. B.; Cunha, A. C. *Bioorg. Med. Chem*. **2009**, 17, 3713–3719. doi:10.1016 /j.bmc.2009.03.053
6. Zeyad Kadhim Oleiwi, Synthesis and Characterization of Some New D-mannoseDerivatives Containing 1, 2, 3-Triazole Moiety and Screening Their Action as Urease Inhibitors, ***Journal of Global Pharma Technology*, 10 (11 S)169-179**(2018).
7. Vijaya Raghava Reddy, L.; Venkat Reddy, P.; Mishra, N. N.; Shukla, P. K.; Yadav, G.; Srivastava, R.; Shaw, A.K. *Carbohydr. Res.* **2010**, 345, 1515–1521. doi:10.1016 /j. carres.**2010**.03.031
8. Aher, N. G.; Pore, V. S.; Mishra, N. N.; Kumar, A.; Shukla, P. K.; Sharma, A.; Bhat, M. K. *Bioorg. Med. Chem.Lett*. **2009**, 19, 759–763. doi:10.1016 /j.bmcl. **2008**.12.026
9. Soltis, M. J.; Yeh, H. J.; Cole, K. A.; Whittaker, N.; Wersto, R. P.; Kohn, E. C. *Drug Metab. Dispos*. **1996**, 24, 799–806.
10. Kishore Kumar Angajala, Sunitha Vianala, Ramesh Macha, M Raghavender, Murali Krishna Thupurani, PJ Pathi, SpringerPlus.**2016**,5(1),423.doi:10.1186/s40064-016-2052-5
11. Elisa Bonandi, Michael S. Christodoulou, Gaia Fumagalli, Dario Perdicchia, Giulio Rastelli, Daniele Passarella. ***Drug Discovery Today*** 2017, 22 (10), 1572-1581. doi:10.1016/j.drudis.2017.05.014
12. Robert Smith, Karah Mason. ***Synthetic Page*** 838. doi: 10.1039/SP838.