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Design, Synthesis, And Antimicrobial Evaluation Of Some Glycine-Barbiturate-1,2,3-Triazole Hybrids

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ABSTRACT

Synthesis new glycine-barbiturate derivatives as probable antibacterialand antifungal agents was prepared, and identified by some analytical techniques such as FTIR, and NMRspectroscopy. The targetglycine-barbiturate-1,2,3-triazole compounds were testedin vitro against two types of bacterial strains (Bacillus subtilis, Staphylococcus epidermidis, Escherichia coliand Pseudomonas aeruginosa) and two fungal strains (Aspergillus niger and Candida albicans). The obtainedresults of biological activities exhibited that some of the evaluatedglycine derivatives showed higher activities than the control drugs.

Keywords: Glycine, Barbiturate, Antibacterial activity, Click reaction,1,2,3-Triazole.

INTRODUCTION

Multidrug-resistant bacteria and fungi are a disturbing and re-emerging microbial plague that is becoming a high public health anxiety around the world [1,2]. Many microorganism species that appear to be responsible for infectious diseases are once more causing losshuman life every year due to a lack of an efficient medications treatment [3]. As a result, the prepared and development of new compounds and molecules with increased bioactivity is critical [4]. In this context, structural bonding has established as one of the most effective synthetic approaches for creating efficient antibacterial agents with a

different mechanism of act and structural modification to increase their attached affinity and action [5].The fusion of two or more entities biologically active pharmacophoric pieces into a single structural material with established attachment and effectiveness in comparing to the parent pharmaceutical drugs [6].Based on its great yields, selectivity, and wide range, the Cu(I)-catalyzed alkyne-azide reaction yielding 1,4-disubstituted triazoles ring has been widely explored [7-9].This chemical reaction so named ‘‘click chemistry or click reaction” has also been investigated in medication development, chemical bio science, materials science in addition to in pharmaceutical applications [10,11].1,2,3-triazoles derivatives with 1,4-disubstituted got a lot of attention due to their broad spectrum of biological potential and pharmaceutical chemistry such as anticancer [12–14], antibacterial [15–17], ant tubercular [18–22], anti-oxidant activity [23], anti-inflammatory [24], in light of the importance of triazole moieties as previously stated, we developed, synthesized, and tested various glycine-barbiturate-1,2,3-triazole hybrids (1a,2a,3a) for antibacterial activity.

EXPERIMENTALND METHODS

General

All chemicals were obtained from commercial companies and used as such. The reactions progress was monitored by TLC plated, (ALUGRAMS, IL G/UV254) and development under Ultraviolet lamp. FTIR spectra were analyzed on a SHIMAZDU IR AFFINITY-I FTIR. NMR spectra were measured on Bruker device 400 MHz spectrometer.

synthesis ofglycine-barbiturate-1,2,3-triazole hybrids[25]

Propargylglycine (2 mmol) and barbiturate azides[26] (1 mmol) were put in to anddissolved in(10 mL) of DMF and equivalent amount of CuCland sodium ascorbate were added to the solution and heated it for 8h to 10 h at 70 ºC and reaction progresswas followed by TLC plate. The reaction contentswere filtered, andthe product was washed with chloroform three times (3X30 mL). The organic layer waswashed with water two times, thendried and brine over anhydrous Mg_2SO_4. The organic layer was removed and recrystallizedfrom chloroform: ethanol (2:5) to yield the target pure 1,2,3-triazoles(1a,2a,3a).

3,3'-(((5,5-diethyl-2,4,6-trioxodihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene))bis(1H-1,2,3-triazole-1,4-diyl))bis(2-aminopropanoic acid) (1a): White powder; Yield 81%; mp 104–106 ºC; Chemical formula: $C_{20}H_{28}N_{10}O_7$, IR (KBr /cm^{-1}): 3445(OH str, carboxyl group), 3325(NH_2 str, amine group), 3112(C-H str, triazolering), 1731 (C=O str, carboxyl group), 1674 (C=O str, pyrimidine ring), ^{1}H NMR, δ 12.31 (2H, s, carboxylic protonts), 7.51 (2H, s, triazole ring), 5.17(2H, s, H_2C-N, methylene protons attached

pyrimidine ring), 4.33 (4H, t, J = 6.8, 5.8 Hz, methyl proton of glycine), 3.65 (4H, d, J = 12.4 Hz, H_2C-N, methylene protons attached triazole ring), 1.98 (4H, q, J = 7.3 Hz, methylene protons attached pyrimidine ring), 0.89 (6H, t, J = 7.2 Hz, methyl protons); ^{13}C NMR, δ 193.21, 171.84, 152.56, 143.35, 122.81, 56.72, 53.98, 51.08, 28.74, 26.23, 10.08.

3,3'-(((5-ethyl-2,4,6-trioxo-5-phenyldihydropyrimidine-1,3(2H,4H)-diyl)bis(methylene)) bis(1H-1,2,3-triazole-1,4-diyl))bis(2-aminopropanoic acid) (2a): White powder; Yield 84%; mp 145–147 ºC; Chemical formula: $C_{24}H_{28}N_{10}O_7$, IR (KBr /cm^{-1}): 3466(OH str, carboxyl group), 3338(NH_2 str, amine group), 3132(C-H str, triazolering), 1725 (C=O str, carboxyl group), 1664 (C=O str, pyrimidine ring), ^{1}H NMR, δ 12.25 (2H, s, carboxylic protonts), 7.61 (2H, s, triazole ring), 7.32–7.21(5H, m, ph-H), 5.23(4H, s, H_2C-N, methylene protons attached pyrimidine ring), 4.45(2H, t, J = 6.8, 5.8 Hz, methyl proton of glycine), 3.62(4H, d, J = 12.4 Hz, H_2C-N, methylene protons attached triazole ring), 1.92 (2H, q, J = 7.3 Hz, methylene protons attached pyrimidine ring), 0.87(3H, t, J = 7.2 Hz, methyl protons); ^{13}CNMR, δ 192.24, 169.53, 152.87, 142.78, 133.23, 128.35, 127.74, 126.33, 121.87, 62.18, 54.89, 53.78, 30.15, 28.98, 9.69.

3,3'-(((5-ethyl-2,4,6-trioxo-5-phenyldihydropyrimidine-1,3(2H,4H)-diyl)bis(2-oxoethane-2,1-diyl))bis(1H-1,2,3-triazole-1,4-diyl))bis(2-aminopropanoic acid) (3a): White powder; Yield 77%; mp 129–131 ºC; Chemical formula: $C_{26}H_{28}N_{10}O_9$, IR (KBr /cm^{-1}): 3468(OH str, carboxyl group), 3348(NH_2 str, amine group), 3125(C-H str, triazolering), 1721 (C=O str, carboxyl group), 1662 (C=O str, pyrimidine ring), ^{1}H NMR, δ 12.34 (2H, s, carboxylic protonts), 7.63 (2H, s, triazole ring), 7.34–7.22(5H, m, ph-H), 5.11(4H, s, H_2C-C=O, acetyl protons), 4.45(2H, t, J = 6.8, 5.8 Hz, methyl proton of glycine), 3.62(4H, d, J = 12.4 Hz, H_2C-N, methylene protons attached triazole ring), 1.94 (2H, q, J = 7.3 Hz, methylene protons attached pyrimidine ring), 0.3(3H, t, J = 7.2 Hz, methyl protons); ^{13}C NMR, δ 191.38, 169.31, 165.89, 152.16, 143.40, 133.41, 128.38, 127.87, 126.35, 123.21, 63.85, 54.38, 53.78, 30.57, 27.87, 9.97.

Antimicrobial activity assay [27,28]

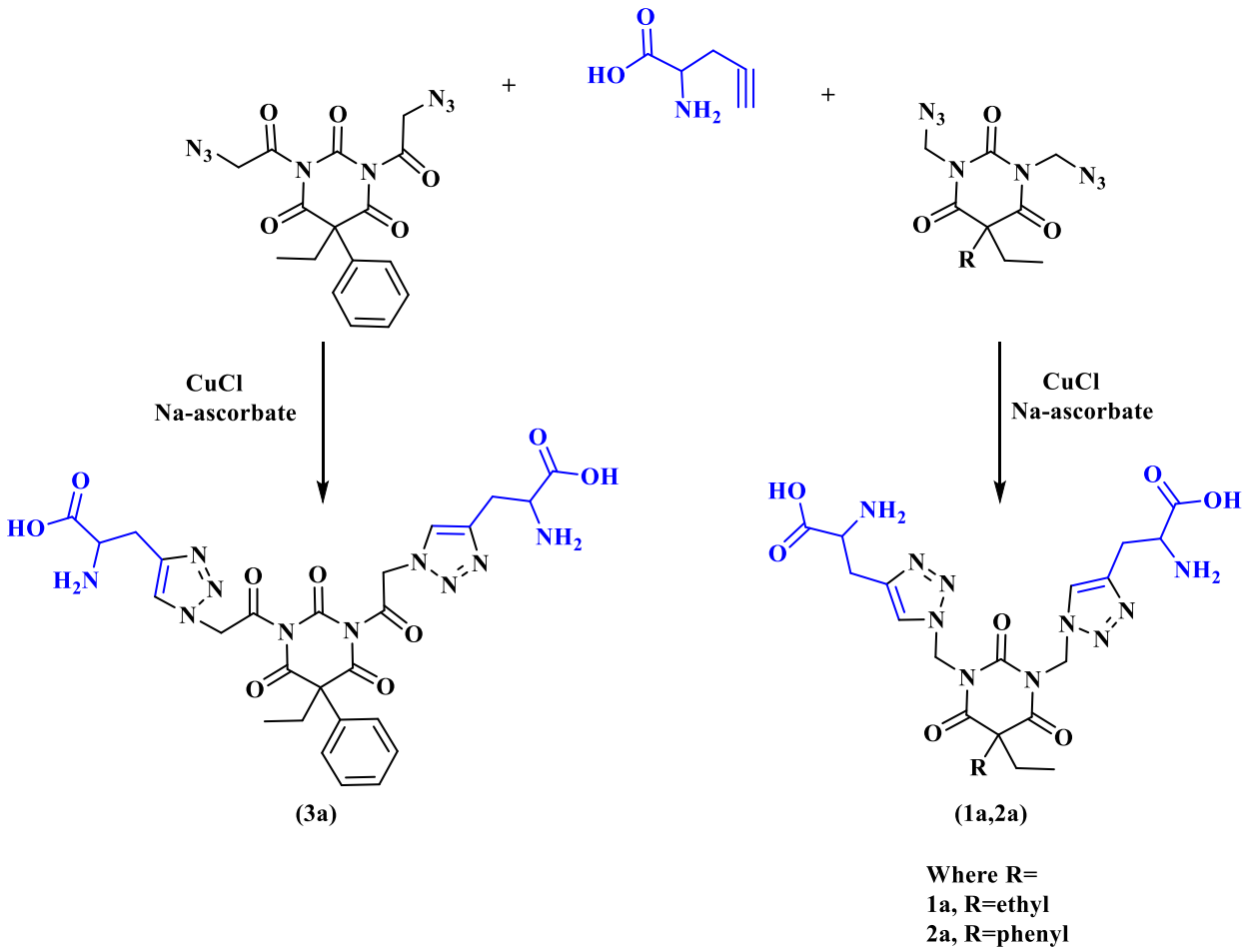
All the target compounds (1a,2a,3a) were tested against two types of bacteria the Gram-positive bacteria strains (Staphylococcus epidermidis MTCC 6880and Bacillus subtilis MTCC 441) and two Gramnegative bacteria (Escherichia coli MTCC 16521and Pseudomonas aeruginosa MTCC 424) and two type of fungal strains viaAspergillus niger (MTCC 8189and Candida albicans (MTCC 227)). The MICs of the synthesized 1,2,3-triazole derivatives assays were conducted by the susceptibility procedure of micro dilution. Ciprofloxacin has been used as an antibacterialwhereas fluconazole has been used as an antifungal reference agent. Dissolved in dimethyl sulfoxied (DMSO) at a concentration of 300 µg / mL,

the research compounds ciprofloxacin and fluconazole; Then, they were diluted in the culture mediumand dilution with prepared solution (100, 50, 25, 12.5 and 6.25 µg / mL). The tubes were then incubated for fungi and bacteria at 36 ºC for 48hours, and 24 hours respectively. The compounds' minimal inhibitory concentrations (MICs, µg / mL) were reported as the lowest concentration of each chemical derivative in turbidity-free tubes of inoculated fungi / bacteria.

RESULTS AND DISCUSSION

Synthesis

In a single step, novel heterocyclic compounds (1,2,3-triazole) including glycine and barbiturate derivatives were synthesized. (**Scheme 1**). Using 2-aminopent-4-ynoic acid and barbiturate derivatives with an azide moiety as a starting materials, in the existence of Cu(I) and sodium ascorbatein DMF at 70 ^{o}C, firstly glycine with a terminal alkyne was treated to copper(I)-catalyzed and then added barbiturate-azide derivatives to create glycine-barbiturate-triazoles hybrids in good yield.On the other hand, barbiturate azide compounds were synthesized depending on the reported methods [25,26].All of the synthesized products' structures were determined using FTIR, ^{1}H NMR, and ^{13}C NMR data.



Scheme 1. Synthesis 1,2,3-triazole derivatives

FTIR data

The appearance of a distinctive band at 3112, 3132, 3125 cm^{-1} in the FTIR analysis of synthesized 1,2,3-triazole (1a,2a,3a) evidenced the preparation of 1,2,3-triazolecompounds. The synthesized1,2,3-triazole compounds(1a,2a,3a) showed two absorption peaks in the region 1674,1664,1662 cm^{-1} and 3445, 3466, 3468 cm^{-1}that were due to the carbonyl group stretching vibrations in pyrimidine ring and amine group that overlap with carboxylic group, respectively. On the other hand, IR spectrum of glycine-barbiturate-triazoles, disappearance bands in the triple bond region due to propargylglycine were due to alkyne moiety, whereas disappearance bands at 2121 cm^{-1} were due to azide group in barbiturate azides [26].

^{1}H NMR data

In the ^{1}H NMR analysis of glycine-barbiturate-triazoles, a broad peak assigned carboxylic (OH) group appeared at 12.31,12.25,12.34 ppmwhich is made up of protons that can be exchanged with D_2O. A new

sharp peak and distinguishingsignal singlet at 7.51, 7.61, 7.63 ppmdue to (-CH proton)were found to have 1,2,3-triazole rings proton. On the other hand, one sharp singlet peak of (-CH_2) methylene protons (pyrimidine(-N-CH_2) at 5.17, 5.23, 5.11 ppmin (1a,2a,3a) compounds respectively, and one doublet signal at 3.65,3.62,3.62 ppm due to methylene attached 1,2,3-triazole ring in (1a,2a,3a) compounds respectively.

^{13}C NMR data

In the ^{13}C NMR analysis, new peaks and signals of 1C-5 and 1C-4 carbonatoms of the 1,2,3-triazole ring (1a,2a,3a) appeared at 122.81,121.87,123.21 ppm and 143.35,142.78,143.40 ppm respectively. The peaks appeared 193.21, 192.24, 191.38 ppm were due to carbon atoms of the carbonyl carboxylic group. Whereas new peaks appearedat 56.72, 54.89,54.38 and51.08, 53.78, 53.78 ppm two carbon atoms were discovered due to methylene groups that bind to the pyrimidine ring-N-CH_2 and carbon number four in the 1,2,3-triazole ring (C-4),((1a,3a,2a) respectively.

Antibacterial activity

The biological action of the target products (1a,2a,3a) was evaluated in vitro using a conventional dilution approach, [29] on two types of bacteria [Gram-positive bacteria strains (Bacillus subtilis MTCC 441and Staphylococcus epidermidis MTCC 6880) and two Gram negative (Pseudomonas aeruginosa MTCC 424 and Escherichia coli MTCC 16521) and two types of fungal strains via Aspergillus niger (MTCC 8189and Candida albicans (MTCC 227))]. Ciprofloxacin was used as control drug for antibacterial and Fluconazole as antifungal, respectively, zone inhibition and minimum inhibitory concentration (mic (MIC in M/mL) of the chemical values were investigated for antimicrobial activities and are listed in Table 1. It was found from the antibacterial showing results that most of the prepared compounds showedprobable antibacterial activity. The 1a and 2a compounds showed very strong activity against E. coli with MIC values of 0.0039 µM/mL and 0.0035 µM/mL, respectively this is superior to the standard drug Ciprofloxacin (MIC, 0.0049 µM/mL). The target compound 1a demonstrated exceptionally good behavior against B. Subtilis is stronger than the reference drug Ciprofloxacin (MIC, 0.0049 µM/mL), with a MIC value of 0.0021µM/mL. Whereas compound 3a demonstrated exceptionally good behavior against S. With MIC values of 0.0045 µM/mL and 0.0020 µM/mL, aureus and w P. aeuroginosa are greater than the superior to the standard drug Ciprofloxacin (MIC, 0.0049 µM/mL). On the other hand, compound 3a, was discovered to be the most active with a MIC value of 0.0089 and 0.0042 µM/mL against C. with the amide substituent on the pyrimidine ring. A. and Albicans. Niger and Niger, respectively.

TABLE 1: ANTIMICROBIAL RESULTS OF COMPOUNDS 1a,2a,3a (MIC in µM/mL).

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. epidermidis	B. subtilis	E. coli	P. aeuroginosa	A. niger	C. albicans
1a	0.0055	0.0021	0.0039	0.0097	0.0155	0.0074
2a	0.0065	0.0085	0.0035	0.0084	0.0094	0.0087
3a	0.0045	0.0071	0.0069	0.0020	0.0089	0.0042
Ciprofloxacin	0.0049	0.0049	0.0049	0.0049		
Fluconazole					0.0107	0.0065

CONCLUSION

In conclusion, the current study details the production of glycine-barbiturate-1,2,3-triazole hybrids (1a,2a,3a) for antibacterial activity, using click chemistry and their determination as antifungals and antibacterial agents. The principal procedures exposed that some of the synthesized compounds had bioactivities that were comparable to or significantly exceeded those of the control medicines. When compared to the other derivatives, all of the 1,2,3-triazole compounds containing phenobarbital showed greater efficacy.

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