RESEARCH ARTICLE

Synthesis, Characterization and Anti-bacterial Study of N-substituted 1,2,4-Triazole Derived from L-Allose

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ABSTRACT

This work focused on synthesizing new carbohydrates tethered to triazole rings at both primary carbon atoms derived from L-allose. Oxidation of allose 4 gave aldaric acid of allose 5. The hydroxyl group's protection at C2 to C5 position of aldaric acid of allose was carried out using acetic anhydride. Acetylation of both carboxylic groups with the thionyl chloride gave 1,6-dichloro tetraacetate 7. Treatment of compound 7 with semicarbazide gave the corresponding semicarbazide derivative 8. Then, this was subjected to intramolecular cyclization with KOH to give the 1,2,4-triazole derivatives 9. The triazoles ring were fully alkylated with different alkyl chloride to give the desired products 10a-d. The synthesized compounds were confirmed using infrared (IR), and NMR spectroscopy.

Keywords: Acetylation, Aldaric acid, L-allose, Spectroscopy.

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Conflict of interest: None

INTRODUCTION

Compounds containing 1,2,4-triazoles ring are very important in the pharmaceutical industry, and because of that, synthetic organic chemists are more interested in designing and synthesizing new compounds containing triazoles ring moiety.[1,2] Many compounds containing triazoles ring show a very interesting pharmacological effect towards the treatment of several types of diseases, such as anti-fungal, anti-bacterial, anti-HIV, anti-cancer, and anti-allergic.[3,4] In the last decade, several literatures have been reported the synthesis of new carbohydrates derivatives containing triazoles ring; these compounds have exhibited an important pharmacological activity such as anti-trypanosomal agents,[3,4] anti-tubercular, inhibitors of α-lucosidases[5] and antitumor agents.[4] The five-member ring framework of the 1,2,4-triazole can be readily synthesized in a good yield, the relationship between the molecule chemical structure and its biological activity called the structure-activity relationship (SAR), so, the 1,2,4-triazoles compounds have good effects and potency.[6,7] Based on this, azoles can be used as anti-fungal 1, anti-inflammatory 2, and anti-diabetic 3 and have a significant pharmacological effect Figure 1.[8]

This paper describes the synthesis of new molecules derived from carbohydrate that attached to 1,2,4-triazole ring and testing their biological activity against some species of bacteria.

Experimental

Synthesis of 2,3,4,5-tetraacetoxy-6-chloro-6-oxohexanoic acid 5

To compound 1 (1.0 g, 5.55 mmol) in dilute HNO_3 (150 mL) (6 mL of acid in 44 mL water). The reaction mixture was heated in the water bath to reduce the volume to 50 mL. Filtration and dry gave compound 5 as a white precipitate in 65% yield. m.p 207–210°C, R_f 0.40 (CH_2Cl_2:MeOH 9:1); IR cm^{-1} 3400–3300 (OH), 1720 (C=O).

2,3,4,5-tetraacetoxyhexanedioic acid 6

Compound 5 (0.5 g, 2.19 mmol) was added acetic anhydride (25 mL), and con. H_2SO_4 (0.5 mL), then the mixture was heated to obtain-suspend solution. The mixture was cooled to room temperature, the addition of cold water gave 6 in 77% yield as white participate. m.p 255-258 °C, R_f 0.45 (CH_2Cl_2: MeOH 8:2); IR cm^{-1} 3500–3400 (OH), 1752 (C=O), 1725 (C=O).

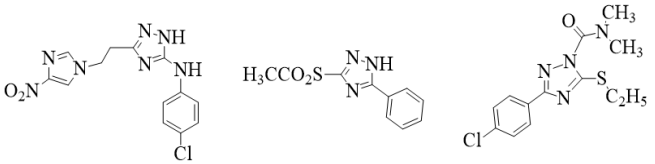

Figure 1: Some drugs containing triazoles

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1,6-dichloro-1,6-dioxohexane-2,3,4,5-tetrayl tetraacetate 7

A mixture of compound 6 (0.5 g, 1.32 mmol) and thionyl chloride (2.64 mmol) was refluxed. After 2 hours, the reaction mixture allow to cool to room temperature, filtration, recrystallization from ethyl acetate gave compound 7 in 82% yield as solid. m.p 170-172 °C, R_f 0.35 (CH_2Cl_2: MeOH 9.5:0.5); IR v_{max} (cm^{-1}) 1775 (C=O), 1752 (C=O).

1,6-bis(2-carbamoylhydrazinyl)-1,6-dioxohexane-2,3,4,5-tetrayl tetraacetate 8

To compound 7 (0.5 g, 1.20 mmol) in EtOH (20 mL), semicarbazide HCl (2.40 mmol) and $NaHCO_3$ (2.4 mmol) was added, then the mixture was refluxed for 24 hours. Filtration, solvent evaporation, water was added and extracted from chloroform (3 × 50 mL). The combined organic layer was dried, recrystallization from EtOH gave compound 8 in 70% as solid; m.p 170-173 °C, R_f 0.50 (CH_2Cl_2: MeOH 9.7: 0.3); IR v_{max} (cm^{-1}) 3400-3300 (N–H), 2900 (C–H), 1680 (C=O), 1720 (C=O). ^{1}H NMR (400 MHz, DMSO) δ = 7.9 (2H, s, NH), 6.1 (6H, s, NH), 5.6-5.4 (2H, m, CH), 2.3 (12H, s, CH_3), ^{13}C NMR (101 MHz, DMSO) δ = 174.2 (C), 173.1 (C), 163.1 (C), 81.1 (CH), 72.1 (CH), 24.0 (CH_3), 20.0 (CH_3).

1,2,3,4-tetrahydroxybutane-1,4-diyl)bis(1H-1,2,4-triazol-5(4H)-one) 9

To compound 8 (0.5 g, 1.01 mmol), was added sodium hydroxide 10% (25 mL), then, the mixture was heated under reflux overnight. Filtration, neutralization with CH_3COOH obtained white precipitate, recrystallization from ether gave compound 9 in 73% yield as solid, m.p. 145-142°C, R_f 0.62 [CH_2Cl_2–MeOH (8:2)]; IR v_{max}(cm^{-1}) 3390-3385 (OH), 3280 (N–H), 2920 (C–H), 1680 (C=O), 1668 (C=N). ^{1}H NMR (400 MHz, DMSO) δ = 12.3 (2H, s, NH), 8.0 (2H, s, NH), 5.6-5.4 (2H, m, CH), 2.7 (6H, s, CH_3), 2.4 (6H, s, CH_3). ^{13}C NMR (101 MHz, DMSO) δ = 173.28 (C), 172.7 (C), 163.5 (C), 137.8 (C), 75.1 (CH), 72.3 (CH), 20.5 (CH_3).

General *N-alkylation* Procedure

Synthesis of 10a-d

To compound 9 (0.5 g, 1.73 mmol) and NaOH (0.14 g, 3.46 mmol) in DMF (10 mL), was added (6.94 mmol) of benzyl chloride, 4-(chloromethyl) aniline, 1-chloro-4-(chloromethyl) benzene, and 1-ethyl-4-nitrobenzene dropwise and the reaction left string at room temperature. After 2–5 hours, solid were filtered, washed with water, dried, and recrystallized from EtOH given products.

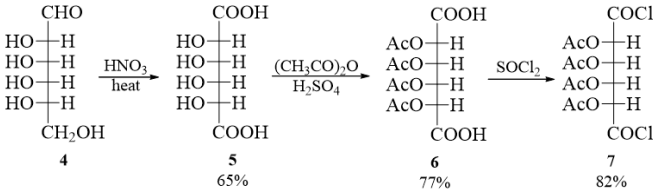
RESULT AND DISCUSSION

To obtain targeted molecules, the work starts with the oxidation of L-allose 4 using nitric acid to give aldaric acid of allose 5. The IR spectra of the resulted compound show band at 1725 cm^{-1} which belongs to the carbonyl groups of carboxylic acid and the aldehyde C-H peak, was disappeared, confirming product 5. The next step is to protect the OH groups on C2 to C5; this was carried out using acetic anhydride in the presence of sulfuric acid to give compound 6. The desired compound 6 was confirmed using IR spectroscopy; the ester group's carbonyl's absorption band appeared at 1752 cm^{-1}. Dichloride compound 7 was obtained in good yield by treating compound 6 with thionyl chloride under reflux; the TLC plate was used to follow the completion of the reaction (Scheme 1). The product was confirmed using IR spectroscopy. However, the peak at 1725 cm^{-1} and the OH peak has disappeared, and the band at 1775 cm^{-1} appeared instead and is referred to as the carbonyl group of acid chloride and band.

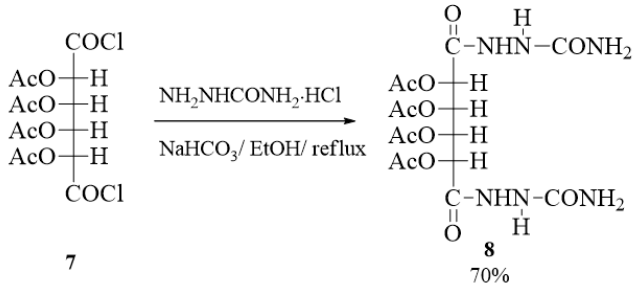
Condensation of two equivalents of semicarbazide hydrochloride with one equivalent of 1,6-dichloro tetraacetate 7 yielded 1,6-bis(2-carbamoylhydrazinyl) tetraacetate 8 in 70% (Scheme 2). The IR spectra show there are bands for the carbonyl group at 1690 and 1985 cm^{-1}, and the NH_2 band at 3440-3410 cm^{-1} with no band at 910 cm^{-1} for C-Cl.

Now, with compound 8 become possible to test the intramolecular cyclization towards the formation of the 1,3,4-triazole ring. To do so, compound 8 was heated with potassium hydroxide 10% to give 1,4-bis(1H-1,2,4-triazol-5(4H)-one tetraacetate 9 in 75% yield (Scheme 3). The IR spectra shows there are peaks at 3550-3500 cm^{-1} for the OH groups, 3410 cm^{-1} for NH and carbonyl groups bands at 1690 cm^{-1} and band at 1668 for (C=N), with no NH_2 bands at 3500-3520 cm^{-1} and band at 910 cm^{-1} for C-Cl.

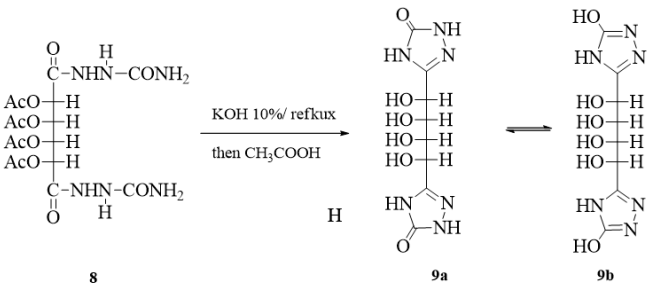
Nitrogen alkylation[9] with different electrophiles such as benzyl chloride, 4-(chloromethyl) aniline, 1-chloro-4-(chloromethyl) benzene, and 1-ethyl-4-nitrobenzene gave compounds 10a, 10b, 10c and 10d alternatively in good yields



Scheme 1: Preparation of dichloride compound



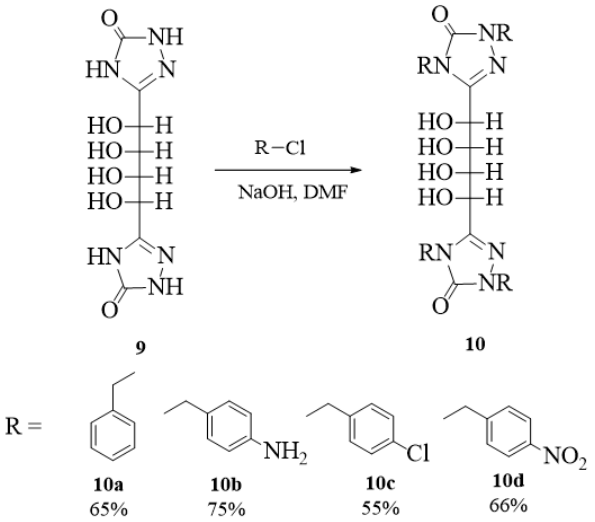
Scheme 2: Condensation reaction with semicarbazide



Scheme 3: Intramolecular cyclization reaction

Table 1: Describe the results, clearly, the compounds exhibited moderate to good inhibition in the range of 1.5 µg/mL to 18 µg/mL.

	Antibacterial activity (MIC in microgram/mL)			
Sample	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*
9	3.12	2.5	3.12	4.12
10a	10.0	11.0	12.5	18.0
10b	8.0	12.0	13.0	10.0
10c	1.5	1.6	1.6	2.0
10d	4.0	2.0	2.5	3.0
Erythromycin	2.0	3.0	2.0	1.0
DMSO	-	-	-	-



Scheme 4: *N-alkylation* reaction

(Scheme 4). In the IR spectra there was a peak for carbonyl group at 1985 cm^{-1} and no NH band at 3410 cm^{-1}. Furthermore, each compound 10a, 10b, 10c, and 10d has the characteristic band on IR spectrum indicates that the desired product was obtained.

Anti-bacterial activity

The big challenging problem is the treatment of infectious diseases because of important factors, including the resistance to bacteria therapy. The biological effect of the synthesized compound has screened against gram –ve and gram +ve. As shown in Table 1, some compounds showed moderate to good anti-bacterial activity compared with reference drugs.

The newly synthesized compounds 9 and 10a-d have screened its anti-bacterial activity against; B. subtilis, S. aureus, E. coli and P. aeruginosa, erythromycin was the reference drug in term of minimum inhibitory concentration (MIC).

CONCLUSION

The oxidation, protection, and deprotection of the allose compound were carried out successfully; this was followed by the acylation and amide formation to obtain the key step compound. Cyclization reaction to form the hetero ring was done with good yield. *N-alkylation* then using deferent alkyl halide gave the target compound a moderate to good anti-bacterial effects.

REFERENCES

1. Hu Y, Li C-Y, Wang X-M, Yang Y-H, Zhu H-L. 1, 3, 4-Thiadiazole: synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry. Chemical reviews. 2014;114(10):5572-5610.
2. Dheer D, Singh V, Shankar R. Medicinal attributes of 1, 2, 3-triazoles: Current developments. Bioorganic Chemistry. 2017;71:30-54.
3. Genin MJ, Allwine DA, Anderson DJ, Barbachyn MR, Emmert DE, Garmon SA, et al. Substituent effects on the antibacterial activity of nitrogen− carbon-linked (Azolylphenyl) oxazolidinones with expanded activity against the fastidious gram-negative organisms haemophilus i nfluenzae and moraxella c atarrhalis. Journal of Medicinal Chemistry. 2000;43(5):953-970.
4. Ferreira MdL, Souza MVd, Wardell SM, Wardell JL, Vasconcelos TR, Ferreira VF, et al. Synthesis and antitubercular evaluation of new bis-1, 2, 3-triazoles derived from D-mannitol. Journal of Carbohydrate Chemistry. 2010;29(6):265-274.
5. Carvalho I, Andrade P, Campo VL, Guedes PM, Sesti-Costa R, Silva JS, et al. 'Click chemistry'synthesis of a library of 1, 2, 3-triazole-substituted galactose derivatives and their evaluation against Trypanosoma cruzi and its cell surface trans-sialidase. Bioorganic & medicinal chemistry. 2010;18(7):2412-2427.
6. Cao X, Sun Z, Cao Y, Wang R, Cai T, Chu W, et al. Design, synthesis, and structure–activity relationship studies of novel fused heterocycles-linked triazoles with good activity and water solubility. Journal of medicinal chemistry. 2014;57(9):3687-3706.
7. Patil BS, Krishnamurthy G, Lokesh M, Shashikumar N, Naik HB, Latthe PR, et al. Synthesis of some novel 1, 2, 4-triazole and 1, 3, 4-oxadiazole derivatives of biological interest. Medicinal Chemistry Research. 2013;22(7):3341-3349.
8. Zimmermann LA, de Moraes MH, da Rosa R, de Melo EB, Paula FR, Schenkel EP, et al. Synthesis and SAR of new isoxazole-triazole bis-heterocyclic compounds as analogues of natural lignans with antiparasitic activity. Bioorganic & medicinal chemistry. 2018;26(17):4850-4862.
9. Kharb R, Sharma PC, Yar MS. Pharmacological significance of triazole scaffold. Journal of Enzyme Inhibition and Medicinal Chemistry. 2011;26(1):1-21.
10. Katritzky AR, Kuzmierkiewicz W, Greenhill JV. An improved method for the N-alkylation of benzotriazole and 1, 2, 4-triazole. Reel Trav Chim Pays-Bas. 1991;110:369-373.