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Synthesis and Characterisation a new 1,2,4-Triazole Carbohydrate

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Abstract. In this study, new alditol derivatives containing two triazole rings at the two terminal primary carbon atoms have synthesized starting from D-glucitol. In order to obtain these derivatives, it was required to protect the hydroxyl group at C1 and C6 position of the glucitol by converting them to 1,6-di-O-benzoyl-D-glucitol, followed by the protection of the remaining hydroxyl group.

Treatment of 1,6-di-O-benzoyl-D-glucitol with benzaldehyde in present of zinc chloride as catalyst afforded 1,6-di-O-benzoyl-2,4:3,5-di-O-benzylidene, then the two benzoate groups were removed using sodium methoxide to give 2,4:3,5-di-O-benzylidene-D-glucitol. Oxidation of 2,4:3,5-di-O-benzylidene-D-glucitol with alkaline permanganate gave 1,4:3,5-di-O-benzylidene-D-glucaric acid. This was converted to corresponding acid chloride using thionyl chloride, and then treated with semicarbazide to afford the semicarbazide derivative. This undergoes intramolecular cyclization with base to give the triazolyl derivative. All derivatives were confirmed with the help of infrared spectra (IR), and nuclear magnetic resonance for proton ¹HNMR and carbon ¹³CNMR spectroscopy.

Keywords: Oxidation, triazole, D-glucitol, semicarbazide, spectroscopy



1. Introduction.

The 1,2,3-triazole compounds and their biological effects brought a lot of attention and became an attractive aims in organic chemistry synthesis.^[1] The synthetic molecules that contains 1,2,3-triazole ring have shown pharmacological effects such as anti-bacterial, herbicidal, fungicidal and anti-allergic.^[2, 3] Recently, some literatures have reported the synthesis the triazoles compounds tethered to many carbohydrates, which have been shown biological activity towards anti-tubercular activity,^[4] anti-trypanosomal agents,^[2] inhibitors of α -lucosidases,^[3] HIV reverse transcriptase inhibitors and anti-tumor agents.^[1, 5] Additionally, carbohydrates bearing a 1,2,3-triazoles group have been tested as potential inhibitors of fucosyltransferases and glycosidases, and study model for substrate specificity of β -1,2-mannosyltransferases as well. The crucial role of the triazole core can be referred to the fact that they are stable hydrolytically and are almost difficult to undergo oxidation and reduction. Recent studies have implied that 1,2,3-triazole moiety is capable to form hydrogen bonding and dipole interactions and this may favour the tethered to biomolecular targets and might lead to enhance their solubility.

1,2,4-Triazole derivatives are an important compounds which possess pharmacological activities, such as anti-convulsant,^[6] anti-cancer,^[7] anti-inflammatory,^[8] diuretic, antimicrobial, hypoglycemic and anti-fungal.^[9] Now a day, synthesis compounds containing triazole ring have received considerable researcher attention. Some medications having 1,2,4-triazoles along with their applications are below (I-IV). In this work, we report the synthesis of carbohydrates that containing 1,2,3-triazoles moiety.

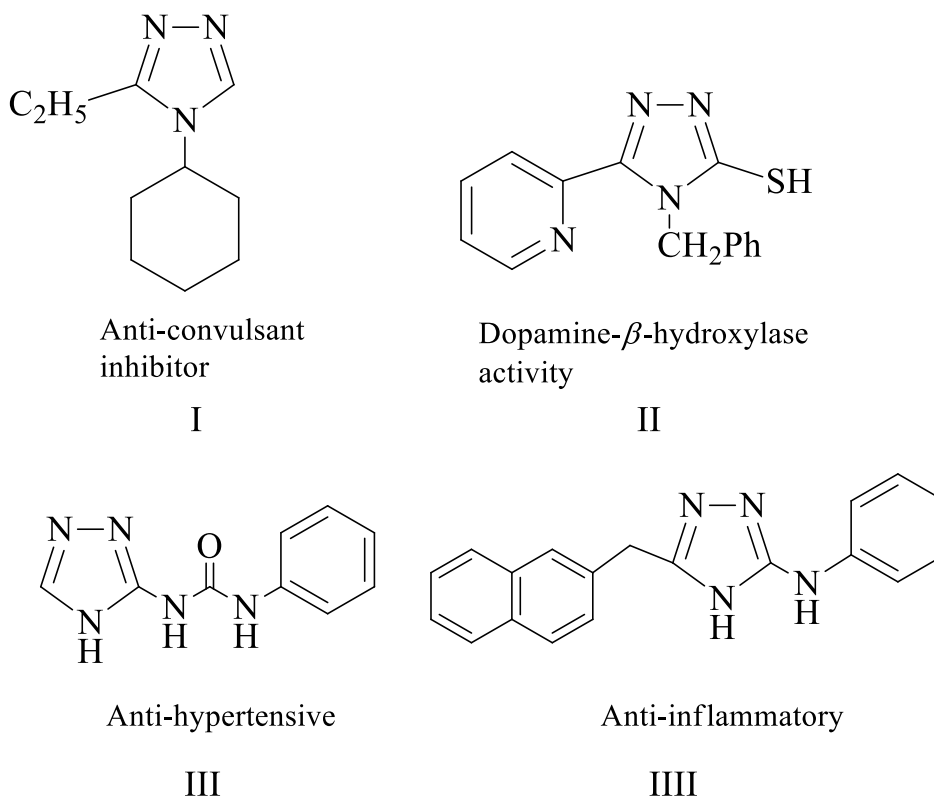


Figure 1 Some medications having 1,2,4-triazoles

2. Experimental.

2.1 Chemical and Apparatus

The following compounds were used: Sorbitol, Benzaldehyde, benzoyl chloride, semicarbazide and thionyl chloride were bought from their sources and used with no further purification. Solvents were purified and dried in the laboratory using standard methods. All other reagents were purchased from commercial sources and were of analytical grade. IR spectra have recorded using KBr disc in (FT-IR 8400S) Shimadzu spectrophotometer in the range from 4000 to 500 cm^{-1} region. All the ^1H and ^{13}C NMR were obtained using Bruker Am300 13MHz.

Melting points of the synthesized compounds were determined using electro-thermal Stuart melting Point apparatus. The TLC plates (MERCK, 60F) was

used to follow the development of the reaction and purity of the formed compounds, compounds were visualized by using KMNO₄ solution.

2.2 Procedures.

(2*R*,3*R*,4*R*,5*S*)-2,3,4,5-tetrahydroxyhexane-1,6-diyl dibenzoate **2**

Dry D-glucitol **1** (50 g, 274 mmol) was dissolved in 250 mL of pyridine and stirring at 55-60 °C. The reaction mixture was cooled to 6-8 °C, then, was followed by addition of benzoyl chloride (62 mL, 552 mmol) dropwise. Then this was left in the fridge overnight. The next step was to add the mixture to ice. Extraction from chloroform (3 × 50 mL), dried (MgSO₄), the solvent was evaporated under vacuum. Crystallization from EtOH gave **2** in 42% yield, m.p. 140-143 °C, *R_f* 0.48 [benzene–EtOH (8:2)]; IR ν_{max} (film)/cm⁻¹ 3460–3375 (O–H), 2935 (C–H), 1700 (C=O), 1600 (C=C).

((2*S*,4*R*,4*aR*,8*aR*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxine-4,8-diyl)bis(methylene) dibenzoate **3**

Benzaldehyde (66 mL) was added to a mixture of 1,6-di-O-Benzoyl-D-glucitol **2** (20 g, 50 mmol) and dry ZnCl₂ (5.0 g, 36 mmol). This was left for 24 h under stirrer at room temperature. Then, cooled H₂O (400 mL) was added to the reaction mixture, after 30 min water layer was separated and petroleum ether was added to the dense layer under stirring. This was left overnight in the fridge; the obtained precipitate was filtered and crystallized from EtOH. Compound **3** was obtained in 78% yield, m.p. 203-205 °C, *R_f* 0.66 [benzene–EtOH (9.5:0.5)]; IR ν_{max} (film)/cm⁻¹ 2935 (C–H), 1720 (C=O), 1600 (C=C).

((2*S*,4*R*,4*aR*,8*aR*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxine-4,8-diyl)dimethanol **4**

To compound **3** (10 g, 10.0 mmol) in EtOH (30 mL), sodium methoxide (17 mL, 1 M)(freshly prepared) was added at 0 °C, then, the solution was stirred till suspension obtained. This was poured to cooled water. The resulting compound was crystalized from chloroform to give **4** white crystals 82% yield, m.p. 214-216 °C, R_f 0.67 [benzene–EtOH (6:4)]; IR ν_{max} (film)/cm⁻¹ 3355–3300 (O–H), 2935 (C–H), 1585 (C=C).

(4*aS*,6*S*,8*R*,8*aR*)-8-(hydroxymethyl)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxine-4-carboxylic acid **5**

Potassium hydroxide (1.73 g, 7.0 mmol) was added to a solution of KMnO₄ (4.8 g, 30.0 mmol). To this solution, compound **4** (8.0 g, 22.0 mmol) portionwise under stirring, then, the reaction mixture was slowly warmed to 60 °C over 2 h. Then an additional KMnO₄ (4.8 g, 30.0 mmol) was added, the reaction mixture was left overnight. Filtration, solvent evaporation, then was cooled to 0 °C, followed by acidification with diluted HCl to get pH 3. Extraction from CH₂Cl₂ (3 × 50 mL), the organic layers was dried using MgSO₄, filtered and concentrated. Crystallisation from EtOH gave **5** in 50% yield, m.p. 215-217 °C, R_f 0.43 [benzene–methanol (9:1)]; IR ν_{max} (film)/cm⁻¹ 3420–3300 (O–H), 2920 (C–H), 1710 (C=O), 1600 (C=C). ¹H NMR (400 MHz, DMSO) δ = 10.4 (2H, s, OH), 7.8–7.4 (10H, m, ArH), 7.3 (1H, s, CH), 6.8 (1H, s, CH), 5.8 (1H, s, CH), 5.6 (1H, s, CH); ¹³C NMR (101 MHz, DMSO) δ = 173.9 (C), 172.6 (C), 128.0 (CH), 125.4(CH), 80.4 (C), 73.2 (CH), 72.2 (CH), 67.1 (CH), 66.7 (CH).

(2*R*,4*S*,4*aS*,8*aS*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxine-4,8-dicarbonyl dichloride**6**

Distilled thionyl chloride (18 mL) and compound **5** (6.0 g, 15.5 mmol) was refluxed in water bath for 2 h. The temperature was cooled down in ice bath, filtered, dried Na₂SO₄ and crystallised from ethylacetate to give **6** in 80% yield, m.p. 209-211 °C, *R_f* 0.38 [benzene–MeOH (7:3)]; IR ν_{max} (film)/cm⁻¹ 2920 (C–H), 1750 (C=O), 1600 (C=C), 709 (C–Cl). ¹H NMR (400 MHz, DMSO) δ = 8.5–7.8 (10H, s, ArH), 7.2–6.5 (4H, m, CH), 5.6 (1H, s, CH), 5.3 (1H, s, CH); ¹³C NMR (101 MHz, DMSO) δ = 163.1 (C), 157.5 (C), 128.0 (CH), 125.5 (CH), 80.4 (CH), 73.2 (CH), 67.1 (CH), 66.7 (CH).

2,2'-((2*R*,4*S*,4*aS*,8*aS*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxine-4,8-dicarbonyl)bis(hydrazinecarboxamide) **7**

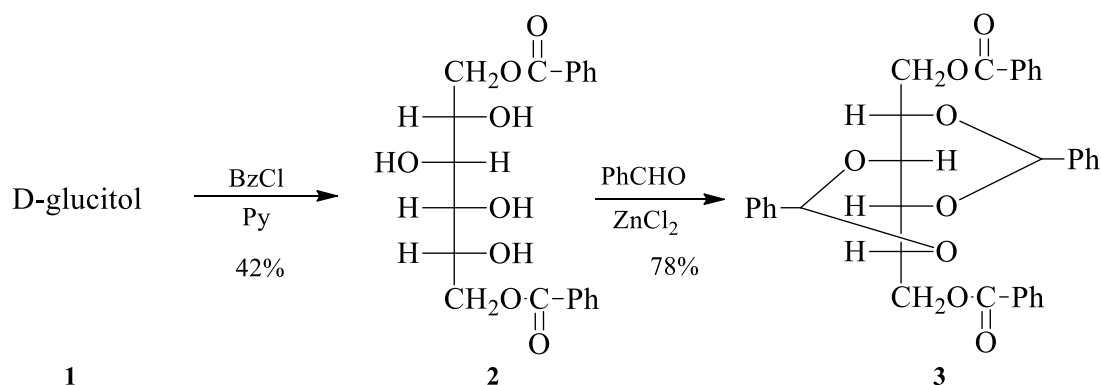
Semicarbazide salt (2.5 g, 24.0 mmol) was added to sodium bicarbonate (5%). Then, 20 mL of the prepared solution was added to a solution of compound **6** (5 g, 0.012 mol) in C₂H₅OH. Then, was refluxed for 24 h, filtered and water (50 mL) was added to the obtained solution. Extraction from CH₃Cl (3 × 50 mL), organic layers was dried MgSO₄, solvent was evaporated to give grey solid, recrystallized from EtOH gave **7** in 53% yield, m.p. 166-168 °C, *R_f* 0.33 [benzene–MeOH (9.9:0.1)]; IR ν_{max} (film)/cm⁻¹ 2920 (C–H), 1750 (C=O), 1600 (C=C). ¹H NMR (400 MHz, DMSO) δ = 8.5–7.8 (10H, s, ArH), 7.2–6.5 (4H, m, CH), 5.6 (3.1 (C), 128.0 (CH), 125.5 (CH), 80.4 (CH), 73.2 (CH), 72.2 (CH), 67.1 (CH), 66.7 (CH).

5,5'-((2*S*,4*R*,4*aR*,8*aR*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-d][1,3]dioxine-4,8-diyl)bis(4*H*-1,2,4-triazol-3-ol)8or 3,3'-((2*S*,4*R*,4*aR*,8*aR*)-2,6-diphenyltetrahydro-[1,3]dioxino[5,4-d][1,3]dioxine-4,8-diyl)bis(1*H*-1,2,4-triazol-5(4*H*)-one) 9

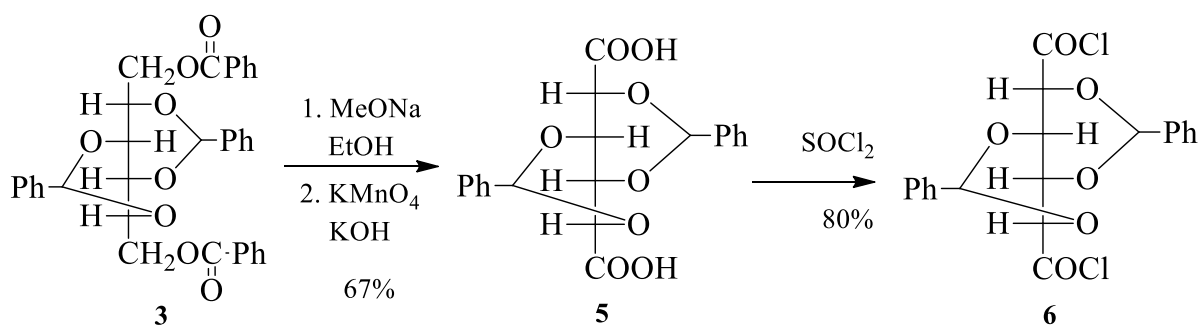
Sodium hydroxide (10%, 25 mL) was added to compound **7**, then, was heated under reflux for 24 h. Filtration, followed by neutralized by acetic acid, white precipitate was obtained, and crystallization from (petroleum–ether) gave compound **8** in 73% yield, m.p. 143-141 °C, R_f 0.62 [benzene–EtOH (8:2)]; IR $\nu_{max}(\text{film})/\text{cm}^{-1}$ 3500–3300 (NH and OH), 2920 (C–H), 1700 (C=O), 1967 (C=O), 1676 (C=N), 1600 (C=C). ^1H NMR (400 MHz, DMSO) δ = 10.9 (1H, s, NH), 9.5 (1H, s, OH), 8.5–7.2 (10H, s, ArH), 7.2–6.5 (4H, m, CH), 5.4 (1H, s, CH), 5.2 (1H, s, CH); ^{13}C NMR (101 MHz, DMSO) δ = 163.1 (C), 157.5 (C), 145.1 (CH), 137.9 (CH), 128.0 (CH), 125.5 (CH), 80.4 (CH), 73.2 (CH), 72.2 (CH), 67.3 (CH), 66.7 (CH), 25.3 (CH).

3. Result and Discussion.

The aim of our study is to synthesize an compound **7** that contains two 1,2,4-triazol rings derived from glucitol. To do this, protection of the two primary hydroxyl groups at positions 1 and 6 of compound **1** was carried out using two equivalents of benzoyl chloride.^[10] This was characterized by FTIR as the peak 1700 cm^{-1} belong to carbonyl group and peak at 1600 cm^{-1} which is indicate the existence of aromatic (C=C). Then, the remaining hydroxyl groups in compound **2** at positions (2,4) and (3,5) were protected using benzaldehyde, which was catalysed using dry zinc chloride to form compound **3** (scheme 1). FTIR shows that the hydroxyl peak was disappeared in the spectrum.

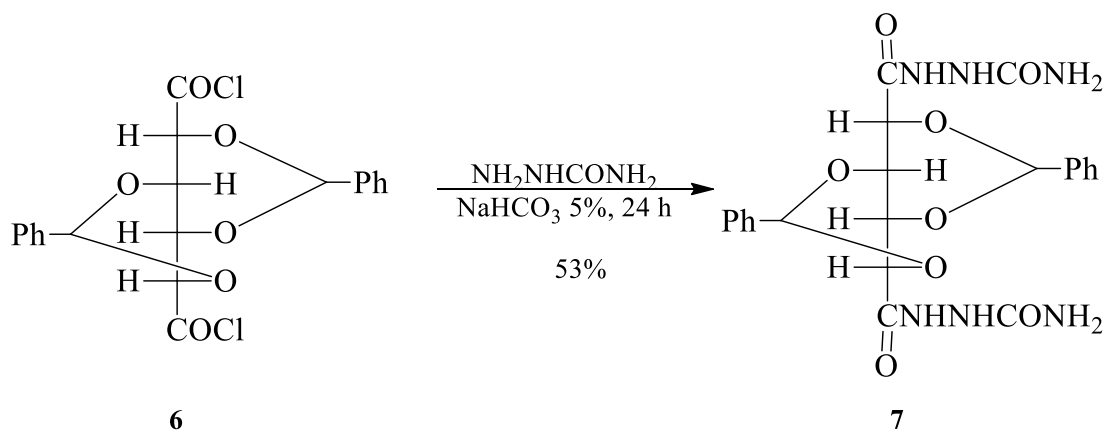
**Scheme 1**

Deprotection of two hydroxyl groups at positions 1 and 6 in **3** was carried out using sodium methoxide in $\text{C}_2\text{H}_5\text{OH}$ to give compound **4** in very good yield; this will allow oxidizing the both hydroxyl groups. The product was confirmed by FTIR spectrum, since the peaks belong to the aromatic ring and carbonyl groups were disappeared, the OH peak appeared instead. The oxidation step to form the dicarboxylic compound **5** was successfully done using potassium permanganate in alkaline medium to give **5** in 82% yield (scheme 2).

**Scheme 2**

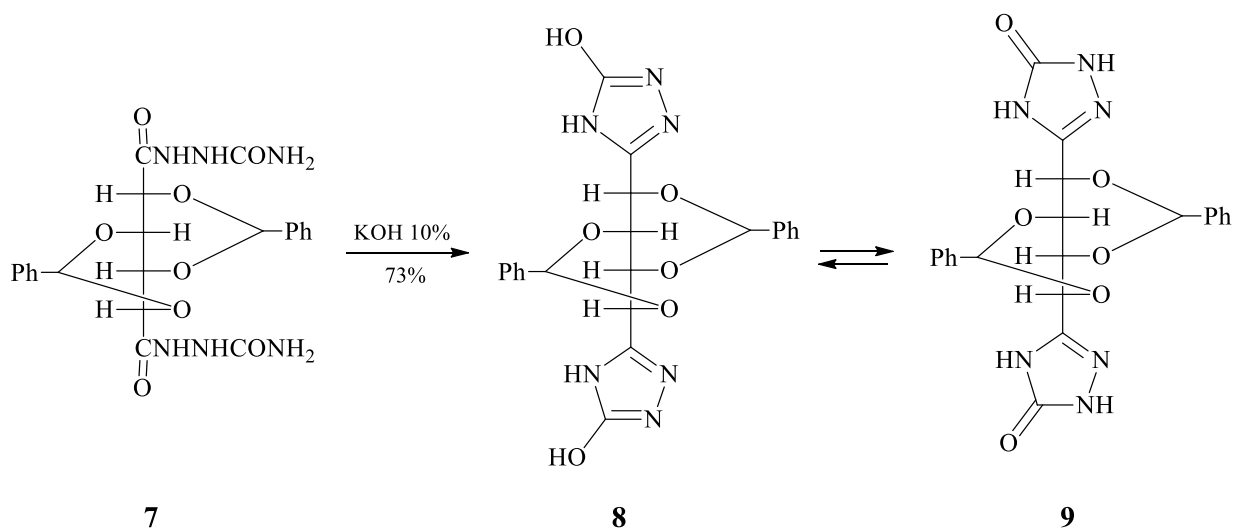
Compound **5** was treated with thionyl chloride under reflux to form compound **6**, the progress completion of the reaction was followed by TLC plate.^[11] The yield was very good, the FTIR and ^1H NMR spectrums show that the peak which belong to OH was disappeared, and the $\text{C}=\text{O}$ stretching peak observed at

1720 cm^{-1} , and peak at 709 cm^{-1} indicate the existing of C–Cl. The acid chloride compound **6** was treated with semicarbazide in alkaline media, heated under reflux for 24 hour, to give compound **7** in moderate yield (scheme 3). The peak at 709 cm^{-1} was disappeared IR spectrum and the broad band at 3400 cm^{-1} for the amine group was appeared. The ^{13}C NMR spectrum shows that there are two peaks at 163.12 and 168.40 ppm for carbonyl.



Scheme3

Having compound **7** in hand, become possible to test the cyclisation step to form compound **8** in the presence of base.^[12, 13] To do this, compound **7** was treated with 10% KOH solution; heating under reflux gave compound **8** and **9** (scheme 4).

**Scheme4**

4.Conclusion

In this work, we successfully synthesized a new 1,2,4-triazole containing carbohydrate, and was confirmed using ^1H and ^{13}C NMR spectroscopy. Hydroxyl group protection, deprotection and oxidation steps were in good yield. The triazole rings were synthesized in the last step easily through the cyclisation, condensation of compound hydrazinecarboxamide in alkali medium.

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