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Research Article

HIGHLY ENANTIOSELECTIVE SYNTHETIC ROUTES FOR GLUCOSE CONJUGATED 1,2,3-TRIAZOLES

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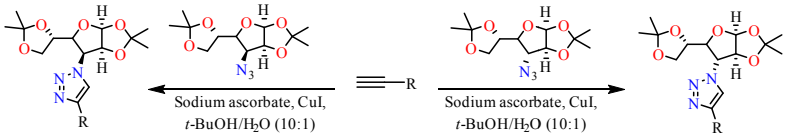
A B S T R A C T

A concise enantioselective synthetic routes to two new series of bis(dioxolane)-glucose derived 1,2,3-triazole derivatives have been developed. The enantiomeric precursors, bis(dioxolane)-glucose azide required for the synthesis are synthesized from the same precursor bis(dioxolane)-glucose. Various alkynes and enantiomeric azides undergo intermolecular [3+2] cycloaddition in the presence of Cu-catalyst, to give enantiomeric 1,2,3-triazoles at ambient temperature with good to excellent yield in respective synthetic routes.



INTRODUCTION

Carbohydrates conjugated with heterocyclic compounds such as pyrroles (Legler, 1999; Panday *et al*., 2000). imidazoles (Tschamber *et al*., Terinek and Vasella,2005; M. Terinek and A. Vasella, 2005). Tetrazoles (Kru¨lle *et al*., 1997; Heightman *et al*., 1996; Pandayand Vasella. 2000) and triazoles (Davis *et al*., 1999$_a$; Davis *et al*., 1999$_b$) are biologically attractive motifs, because they are potent glycosidase inhibitors. In particular, 1,2,3-triazole derivatives are emerging as potential pharmacophores (Bourne *et al*., 2004;Alvarez *et al*., 1994;Velazquez *et al*., 1998). On the other hand, combination of both carbohydrate and 1,2,3-triazole structures has led to the flouring field of conjugates that are powerful pharmacophores (Dedola *et al*., 2007; Leoneti etal., 2010; Dondoni, 2007). Besides, sugar derived 1,2,3-triazoles are also regarded as important precursors to analogues of some alkaloid antibiotics (Heightman and Vasella, 1999; Tezuka *et al*., 2000; Flessner and Wong, 2000), glycose phosphorylase (Bokor *et al*., 2010) and antitubercular activity (Singh *et al*., 2008). Triazoles are synthesized by the cycloaddition of alkynes with azides catalyzed by Copper, which is called as Click chemistry coined of carbohydrates with proteins of target receptors are important in biological systems, since it increases the binding ability of ligands (Agre *et al*., 2016; Mishra *et al*., 2003; Ferreira *et al*., 2010). Besides, they increases the solubility of therapeutically active heterocyclic compounds in biological systems, which increases the penetration through biological membranes. Some biologically important sugar conjugates are given in Figure 1.

Recently, we have developed new synthetic methods for the synthesis of biologically important heterocyclic compounds (Lingaraju *et al*., 2012; Rajeev et. al., 2017; Ashwini *et al*., 2015; Swaroop *et al*., 2020; Rajeev *et al*., 2020; Kiran *et al*., 2020). We have reported 1-(3-benzisoxazolyl)-4-aryl-1,2,3-triazoles by Click chemistry as anticancer agents, which inhibited histone deacetylases by inducing p21 and tubulin acetylation (Ashwini *et al*., 2015). In addition, a base induced click reaction is also reported for the synthesis of thiazoles from our laboratory (Lingaraju *et al*., 2012). In continuation of this work, we herein report enantioselective routes for the synthesis of 4-(substituted)-1-5-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1*H*-1,2,3-triazoles *via* click reactions by copper catalyst.

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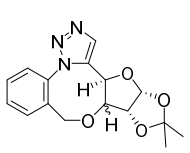
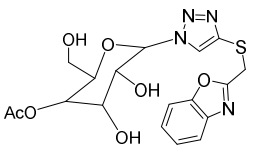


Benzolactum mimic of carbohydrate



Exhibitted potential anti inflamatoryactivity

Fig 1. Selected carbohydrate derived triazoles

MATERIALS AND METHODS

General

The starting materials were commercially available and used as receivedwithout further purification. Reactions were monitoredby TLC and visualized under UV light. Melting points were melting points were determined on Selaco melting point apparatus and are uncorrected. NMR spectra were recorded on Brucker NMR spectrometer. Tetramethyl silane was used as reference and DMSO-d_6 as solvent. HRMS spectra were recorded using Agilant Mass spectrometer. IR spectra were recorded on shimadzu IR spectrometer.

General procedure for the synthesis of (3)

A mixture **2** (35 g) and sodium azide (18.4 g) in DMF (400 mL) was heated to 150°C for 10 h. The reaction mixture was cooled to room temperature and then added EtOAc (500 mL). The mixture was washed with water (500 mL), brine (500 mL), dried and concentrated under vaccum. The crude was passed through silica gel to get the product **3** as colorless liquid. ^{1}H NMR (DMSO, 400 MHz) δ 1.28 (6H, s), 1.35 (3H, s), 1.44 (3H, s), 3.58 (1H, q, *J*=4.8, 4.8 Hz), 3.80 (1H, q, *J*=5.2, 3.2 Hz), 3.90 (1H, q, *J*=6, 3.6 Hz), 4.06 (1H, q, *J*=6.8, 1.6 Hz), 4.13 (1H, q, *J*=6.08, 6.08 Hz), 4.77 (1H, t, *J*=4.2 Hz), 5.76 (1H, d, *J*=3.68 Hz); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.6, 61.8, 66.4, 75.7, 77.6, 80.7, 104.2, 109.4, 112.5; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{12}H_{19}N_3O_5$: 285.1325; Found: 285.1325. HPLC = 99.35%.

(3aR,6aS)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(3aH)-one (4)

To a solution of diacetone-D-Glucose (50 g, 1.92 mol) in dry CH_2Cl_2 (650 mL), PDC (43.4 g, 1.15 mol) was added and acetic anhydride (65 mL) and heated to 45°C for 1 h. The reaction mixture was concentrated under vacuum and crude was residue purified by column chromatography over silica gel to give the product **5** as yellow liquid (47g). ^{1}H NMR (DMSO, 400 MHz) δ 1.16 (3H, s), 1.22 (3H, s), 1.36 (3H, s), 1.41 (3H, s), 1.89 (1H, s), 3.83 (1H, t, *J*=3.45 Hz), 3.95 (1H, q, *J*=7.05 Hz, 1.38 Hz), 4.24-4.30 (1H, m), 4.53 (2H, t, *J*=2.96 Hz), 6.07 (1H, d, *J*=4.47 Hz), 11.95 (1H, s). ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.6, 64.8, 68.2, 77.9, 80.5, 107.7, 118.5, 119.5, 203.6; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{12}H_{19}O_6$: 259.1182; Found: 259.1183.

(3aR,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (5)

To a stirred solution of compound **5** (50g, 1.94 mol) in 80% MeOH:H_2O, $NaBH_4$ (50.2 g) was added in portions at 0°C and then allowed to stir at room temperature for 1 h. The reaction mixture was concentrated under vacuum, and the residue was extracted with EtOAc (500 mL). The organic layer was washed with water (500 mL), brine (500 mL) dried and concentrated to give compound as white solid (43g). ^{1}H NMR (DMSO, 400 MHz) δ 1.22 (6H, s), 1.32 (3H, s), 1.44 (3H, s), 3.33-3.86 (3H, m), 3.93 (1H, t, *J*=7.56 Hz), 4.21-4.24 (1H, m), 4.46 (1H, t, *J*=4.12 Hz), 5.11 (1H, d, *J*=7.12 Hz), 5.66 (1H, d, 3.6 Hz); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.6, 67.0, 75.0, 75.8, 80.0, 84.2, 109.6, 119.5, 121.9; Anal. Calcd. for $C_{12}H_{21}O_6$:261.1338; Found: 261.1339. [α]= +33.79^o / C=1.054 / T=23°C.

(3aR,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl methanesulfonate (6)

To a stirred solution of diacetone-D-Glucose (20g, 1.02 mol) in pyridine (80 mL) was added methane sulfonyl chloride (16.2 mL) at 0°C and allowed to stir at room temperature for 12 h. The reaction mixture was poured in to ice and filtered off the solid. The solid was washed repeatedly with water and dried under suction to give the compound **7** as white solid (20.5 g).

^{1}H NMR (DMSO, 400 MHz) δ 1.21 (6H, s), 1.16 (3H, s), 1.44 (3H, s), 3.62-3.87 (2H, m), 4.02 (m, 2H), 4.16 (1H, s), 5.25 (s, 1H), 6.26 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.6, 67.0, 75.0, 78.4, 84.0, 85.4, 109.6, 119.5, 121.9; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{13}H_{23}O_8S$: 339.1114; Found: 339.1116.

(3aR,6S,6aR)-6-Azido-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (8)

A mixture of compound **7** (20 g) and sodium azide (12.3 g) in DMF (220 mL) was heated to 150°C for 10 h. The reaction mixture was cooled to RT and then added EtOAc. The mixture was washed with water (250 mL), brine (250 mL), dried and concentrated under vacuum. The crude was passed through silica gel to give the product as colorless liquid. ^{1}H NMR (DMSO, 400 MHz) δ 1.25 (3H, s), 1.27 (3H, s), 1.40 (3H, s), 3.79 (1H, q, *J*=5.32, 3.04 Hz), 4.01 (1H, q, *J*=3.12, 4.92 Hz), 4.06 (1H, q, *J*=6.2, 2.2 Hz), 4.14 (1H, m), 4.25 (1H, d, *J*=3.12 Hz), 5.83 (1H, d, *J*=3.6 Hz): ^{13}C NMR (DMSO, 100 MHz) δ 25.6, 26.4, 26.8, 27.0, 66.0, 67.1, 73.0, 80.2, 83.2, 104.9, 109.1, 111.8: HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{12}H_{20}N_3O_5$:286.1403; Found: 286.1403.

General procedure for the preparation of glucose conjugate 1,2,3-triazoles 9a-g

To a mixture of **3** (1 mmol) in isopropropyl alcohol (2 mL), was added different alkynes **8** (1.1 mmol), sodium ascorbate (1 mmol) and CuI (0.2 mmol) was added and stirred the reaction mixture at room temperature for 8 h. Filtered the solid product and washed with excess water and dried under vacuum to give crude product which was purified by column chromatography.

2-(1-((3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)cyclopentanol (9a)

^{1}H NMR (DMSO, 400 MHz) δ 1.15 (3H, s), 1.16 (3H, s), 1.25 (3H, s), 1.53 (3H, s), 1.66-1.68 (2H, m), 1.79-1.85 (4H, m), 1.91-1.97 (2H, m), 3.49 (1H, q, *J*=5.6, 2.8 Hz), 3.95 (1H, q, *J*=6.8, 2.0 Hz), 4.15 (1H, t, *J*=6.0 Hz), 4.56 (1H, q, *J*=4.8, 5.2 Hz), 5.91 (1H, d, *J*=3.6 Hz), 7.89 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 23.7, 23.8, 25.4, 26.8, 62.3, 65.6, 75.6, 77.6, 77.9, 79.5, 104.5, 113.0, 121.9, 154.7; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{19}H_{30}N_3O_6$:396.2135; Found: 396.2135.

1-(3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(3-methoxyphenyl)-1H-1,2,3-triazole (9b)

^{1}H NMR (DMSO, 400MHz) δ 1.17 (3H, s), 1.18 (3H, s), 1.25 (3H, s), 1.57 (3H, s), 3.38 (1H, br), 3.81 (3H, br), 4.00 (1H, br), 4.24 (1H, br), 4.71 (1H, br), 4.89 (1H, br), 5.22 (1H, br), 5.96 (1H, br), 6.91 (1H, br), 7.3-7.43 (3H, m), 8.69 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.3, 26.4, 26.7, 26.8, 55.6, 62.7, 65.8, 75.7, 77.4, 79.5, 104.7, 109.4, 110.9, 113.0, 113.9, 117.9, 122.8, 130.5, 132.5, 146.2, 160.1; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{21}H_{28}N_3O_6$: 418.1978; Found: 418.1980.

3-(1-((3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)phenol (9c)

^{1}H NMR (DMSO, 400MHz) δ 1.14-1.23 (9H, m), 1.55 (3H, s), 3.31 (1H, br), 3.60 (1H, br), 3.98 (1H, br), 4.22 (1H, br), 4.64 (1H, br), 4.87 (1H, br), 5.22 (1H, br), 5.93 (1H, br), 7.39-7.47 (2H, m), 7.83-7.92 (2H, m), 8.79 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.3, 26.4, 26.7, 26.82, 62.8, 65.9, 75.8, 77.5, 79.5, 104.7, 109.4, 113.11, 123.3, 124.1, 125.2, 128.1, 131.4, 133.5, 134.2, 145.0; HRMS (ESI) $[M+H]^+$ Anal. Cald. for $C_{20}H_{26}N_3O_6$: 404.1822; Found: 404.1822.

4-([1,1'-Biphenyl]-4-yl)-1-((3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazole (9d)

^{1}H NMR (DMSO, 400 MHz) δ 1.09-1.24 (9H, m), 1.57 (3H, s), 3.61 (1H, t, *J*=7.2 Hz), 3.99 (1H, t, *J*=10.36 Hz), 4.23 (1H, d, *J*=7.4 Hz), 4.69 (1H, q, *J*=6.28, 6.08 Hz), 4.89 (1H, br), 5.24 (1H, q, *J*=6.52, 6.64 Hz), 5.95 (1H, d, *J*=7.4 Hz); ^{13}C NMR (DMSO, 100 MHz) δ 25.3, 26.4, 26.81, 65.8, 75.8, 104.7, 109.4, 113.1, 126.1, 127.0, 127.6, 129.4, 139.9; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{26}H_{30}N_3O_5$: 464.2185; Found: 464.2187.

4-(1-((3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)aniline (9e)

^{1}H NMR (DMSO, 400MHz) δ 1.18-1.25 (9H, m), 1.56 (3H, s), 3.55 (1H, br), 3.98 (1H, br), 4.24 (1H, br), 4.70 (1H, br), 4.75 (1H, br), 4.87 (1H, br), 5.16 (2H, br), 5.94 (1H, br), 6.61 (1H, br), 7.51 (1H, br), 8.34 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.4, 26.4, 26.8, 26.8, 65.5, 75.6, 77.3, 79.56, 104.6, 109.4, 113.0, 126.6; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{20}H_{27}N_4O_5$: 403.1981; Found: 403.1983.

1-((3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(2-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (9f)

^{1}H NMR (DMSO, 400 MHz) δ 1.14 (3H, s), 1.16 (3H, s), 1.25 (3H, s), 1.52 (3H, s), 3.48 (1H, br), 3.97 (1H, br), 4.21 (1H, br), 4.63 (1H, br), 4.90 (1H, br), 5.20 (1H, br), 7.62-7.86 (4H, m), 8.32 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.4, 26.3, 26.6, 26.8, 62.6, 65.9, 75.7, 77.8, 79.3, 104.7, 109.4, 113.0, 124.8, 126.8, 129.3, 129.7, 132.2, 133.1, 143.4; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{21}H_{25}F_3N_3O_5$: 456.1746; Found: 456.1748.

1-((3aS,5S,6R,6aS)-5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(thiophen-3-yl)-1H-1,2,3-triazole (9g)

^{1}H NMR (DMSO, 400MHz) δ 1.15-1.23 (9H, m), 1.54 (3H, s), 3.58 (1H, t, *J*=7.48 Hz), 3.97 (1H, t, *J*=9.76 Hz), 4.21 (1H, d, *J*=5.5 Hz), 4.64 (1H, br), 4.87 (1H, br), 5.93 (1H, br), 7.51 (1H, d, *J*=4.41 Hz), 7.63 (1H, br), 7.84 (1H, br), 8.51 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.3, 26.4, 26.8, 26.8, 62.6, 65.8, 75.7, 77.5, 79.5, 104.6, 109.4, 113.0, 121.2, 122.2, 126.3, 127.6, 132.5; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{18}H_{24}N_3O_5S$: 394.1437; Found: 394.1439.

General procedure for preparation of glucose conjugate 1,2,3-triazoles (10a-g)

To a mixture of azide scaffold (1 mmol) in IPA, was added different alkynes (1.1 mmol), sodium ascorbate (1 mmol) and CuI (0.2 mmol) was added and stirred the reaction mixture at RT for 8h.Filtered the solid product and washed with excess water and dried under vacuum to give crude product which was purified by column chromatography.

2-(1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)cyclopentanol (10a)

^{1}H (DMSO, 400 MHz) δ 1.15 (3H, s), 1.31 (3H, s), 1.33 (3H, s), 1.50 (3H, s), 1.68 (2H, br), 1.81-1.83 (4H, m), 1.91-1.97 (2H, m), 3.25-3.30 (1H, q, *J*=6.0, 7.24 Hz), 3.51-3.58 (2H, m), 4.32 (1H, q, *J*=3.76, 3.52 Hz), 5.06 (2H, d, *J*=1.96 Hz), 5.30 (1H, d, *J*=3.8 Hz), 6.16 (1H, d, *J*=3.64 Hz), 7.82 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 23.7, 25.6, 26.4, 27.0, 64.9, 65.9, 72.8, 80.0, 83.7, 105.9, 109.0, 112.9, 154.7; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{19}H_{30}N_3O_6$:396.2135; Found: 396.2135.

1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(3-methoxyphenyl)-1H-1,2,3-triazole (10b)

^{1}H (DMSO, 400 MHz) δ 1.13 (3H, s), 1.33 (3H, s), 1.36 (3H, s), 1.52 (3H, s), 3.33 (1H, t, *J*=3.48 Hz), 3.68 (2H, d, *J*=5.68 Hz), 3.82 (3H, s), 4.35 (1H, t, *J*=4.08 Hz), 5.11 (1H, d, *J*=3.44 Hz), 5.31 (1H, d, *J*=3.6 Hz), 6.25 (1H, d, *J*=3.4 Hz), 6.93 (1H, q, *J*=2.4, 5.76 Hz), 7.36-7.46 (3H, m), 8.51 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.4, 27.0, 27.1, 55.6, 65.4, 66.3, 72.5, 79.9, 83.7, 105.8, 109.2, 111.0, 112.2, 114.2, 118.1, 123.0, 130.6, 132.1, 146.5, 160.2; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{21}H_{28}N_3O_6$: 418.1978; Found: 418.1980.

3-(1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)phenol (10c)

^{1}H (DMSO, 400 MHz) δ 1.12 (3H, s), 1.32 (3H, s), 1.34 (3H, s), 1.51 (3H, s), 3.32-3.34 (1H, m), 3.67 (2H, d, *J*=5.6 Hz), 4.35 (1H, q, *J*=3.6, 4 Hz), 5.10 (1H, d, *J*=3.6 Hz), 5.31 (1H, d, *J*=3.6 Hz), 7.39-7.51 (2H, m), 7.84-7.94 (2H, m), 8.60 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.4, 27.0, 27.1, 65.5, 66.3, 72.5, 79.9, 83.7, 105.8, 109.2, 112.2, 123.6, 124.2, 125.4, 128.3, 131.4, 132.9, 134.2, 145.3; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{20}H_{26}N_3O_6$: 404.1822; Found: 404.1822.

4-([1,1'-Biphenyl]-4-yl)-1-((3aR,5S,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazole (10d)

^{1}H (DMSO, 400 MHz) δ 1.12 (3H, s), 1.21 (3H, s), 1.32 (3H, s), 1.51 (3H, s), 3.31-3.35 (1H, m), 3.66 (2H, d, *J*=7.48 Hz), 4.35 (1H, q, *J*=4.84, 5.48 Hz), 5.12 (1H, d, *J*=4.76 Hz), 5.32 (1H, d, *J*=4.92 Hz), 6.24 (1H, d, *J*=4.72 Hz), 7.36-7.39 (1H,

m), 7.44-7.49 (2H, m), 7.69-7.78 (4H, m), 7.95 (2H, d, *J*=10.96 Hz), 8.53 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.0, 26.0, 26.5, 26.6, 65.0, 65.8, 72.0, 79.5, 83.3, 105.4, 108.7, 111.7, 122.5, 125.8, 126.5, 127.2, 127.6, 128.98, 129.4, 139.5, 139.7, 145.8; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{26}H_{30}N_3O_5$: 464.2185; Found: 464.2187.

4-(1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-1H-1,2,3-triazol-4-yl)aniline (10e)

^{1}H (DMSO, 400 MHz) δ 1.11 (3H, s), 1.30 (3H, s), 1.33 (3H, s), 1.49 (3H, s), 3.61-3.64 (2H, m), 4.31 (1H, q, *J*=4.84, 5.4 Hz), 5.05 (1H, d, *J*=4.76 Hz), 5.23-5.24 (3H, m), 6.20 (2H, d, *J*=11.4 Hz), 7.48 (2H, d, *J*=11.28 Hz), 8.15 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.4, 27.0, 27.1, 65.2, 66.2, 72.5, 80.0, 83.8, 105.8, 109.1, 112.1, 114.4, 118.3, 120.6, 126.7, 147.6, 149.3; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{20}H_{27}N_4O_5$: 403.1981; Found: 403.1983.

1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(2-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (10f)

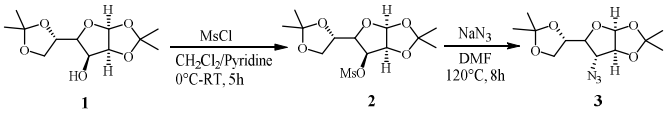
^{1}H (DMSO, 400 MHz) δ 1.12 (3H, s), 1.32 (3H, s), 1.33 (3H, s), 1.50 (3H, s), 3.21 (1H, br), 3.63-3.73 (2H, m), 4.32 (1H, q, *J*=5.04, 5.44 Hz), 5.17 (1H, d, *J*=4.76 Hz), 5.44 (1H, d, *J*=5.04 Hz), 6.19 (1H, d, *J*=4.72 Hz), 7.64-7.66 (1H, m), 7.75 (2H, t, *J*=8.72 Hz), 7.86 (1H, d, *J*=10.4 Hz), 8.24 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.3, 26.4, 26.9, 27.0, 65.2, 66.5, 72.4, 80.4, 83.6, 106.0, 109.2, 112.2, 125.9, 126.2, 126.7, 126.8, 127.2, 129.5, 132.3, 133.2, 143.3; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{21}H_{25}F_3N_3O_5$: 456.1746; Found: 456.1748.

1-((3aR,5S,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-(thiophen-3-yl)-1H-1,2,3-triazole (10g)

^{1}H (DMSO, 400 MHz) δ 1.12 (3H, s), 1.32 (3H, s), 1.34 (3H, s), 1.51 (3H, s), 3.31 (1H, s), 3.67 (2H, d, *J*=5.72 Hz), 4.33 (1H, q, *J*=3.76, 4.16 Hz), 5.09 (1H, d, *J*=3.6 Hz), 5.30 (1H, d, *J*=3.76 Hz), 6.21 (1H, d, *J*=3.2 Hz), 7.53 (1H, q, *J*=1.2, 3.8 Hz), 7.65 (1H, q, *J*=2.92, 2.04 Hz), 7.88 (1H, q, *J*=1.2, 1.72 Hz), 8.35 (1H, s); ^{13}C NMR (DMSO, 100 MHz) δ 25.5, 26.4, 27.0, 27.1, 65.3, 66.3, 66.3, 72.5, 79.9, 83.8, 105.8, 109.2, 112.2, 121.7, 122.6, 126.2, 127.7, 132.1, 143.5; HRMS (ESI) $[M+H]^+$ Anal. Calcd. for $C_{18}H_{24}N_3O_5S$: 394.1437; Found: 394.1439.

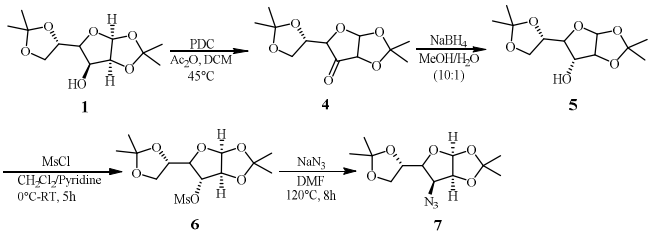
RESULTS AND DISCUSSION

The required substrate (3aS,6R,6aS)-6-azido-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole **3** was synthesized according to sequence of reactions given in Scheme 1. The (3aS,6S,6aS)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol **1** was mesylated with methanesulfonyl chlroride in dichloromethane in pyridine gave (3aS,6S,6aS)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl methanesulfonate **2**.Nucleophilic substitution of mesylate by azide by heating at 120°C in DMF gavethe required substrate **3**.



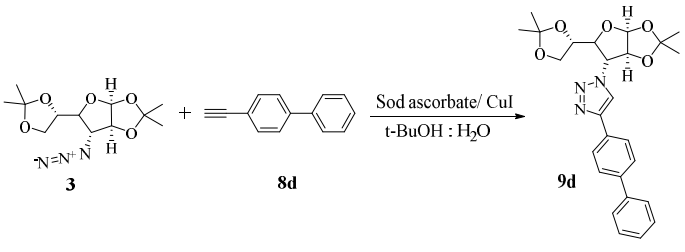
Scheme 1. Synthesis of (3aS,6R,6aS)-6-azido-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole **3**

The enantiomer of **3, 7** was synthesized as per Scheme 2. The **1** was oxidized with pyridinium dichromate to get ketone **4**, which was reduced with sodium borohydride. This, furnished a enantiomer of **1**, (3aR,6R,6aR)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol **5**. Mesylation of **5** formed an intermediate **6**, which upon nucleophilic substitution by azide afforded a enantiomer of **3**,(3aS,6S,6aS)-6-azido-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole **7**.



Scheme 2. Synthesis of (3aS,6R,6aS)-6-azido-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole **7**

In order to explore the optimal reaction conditions for the synthesis of glucosyl-1,2,3-triazoles, we considered [3+2] cycloaddition reaction of glycosyl azide **3** and biphenyl acetylene **8d** as a model reaction (Scheme 3, Table 1). Thus, reaction of **3** with biphenyl acetylene **8d**, in the presence of CuI (5 mol%) in a reducing atmosphere of sodium ascorbate (20 mol%) in *t*-BuOH:H_2O (10:1) at ambient temperature yielded traces of required triazole **9d** after 36 h (Table 1, entry 1). Increase in CuI quantity to 40 mol% at constant concentration of sodium ascorbate did not improve the yield (Table 1, entries 2-4). Further, increase in concentration of sodium ascorbate at constant CuI quantity gradually increased the yield and simultaneously reduced the reaction time (Table 1, entries 5-8). Thus, a maximum yield of product **9d** was obtained when 100 mol% of sodium ascorbate was used (Table 1, entry 8). Increase in catalyst concentration did not improve the yield (Table 1, entry 9).



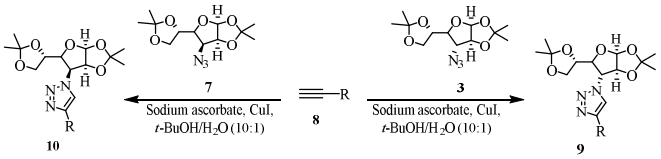
Scheme 3. Cycloaddition reaction of glycosyl azide **1** and biphenyl acetylene **2d**

Table 1 Optimization of reaction conditions for the synthesis of **9d**

Entry	Sodium ascorbate (mol %)	CuI (mol %)	Time (h)	Yield (%)
1	20	5	36	trace
2	20	10	21	trace
3	20	20	19	trace
4	20	40	14	trace
5	40	10	21	8%
6	60	10	19	21%

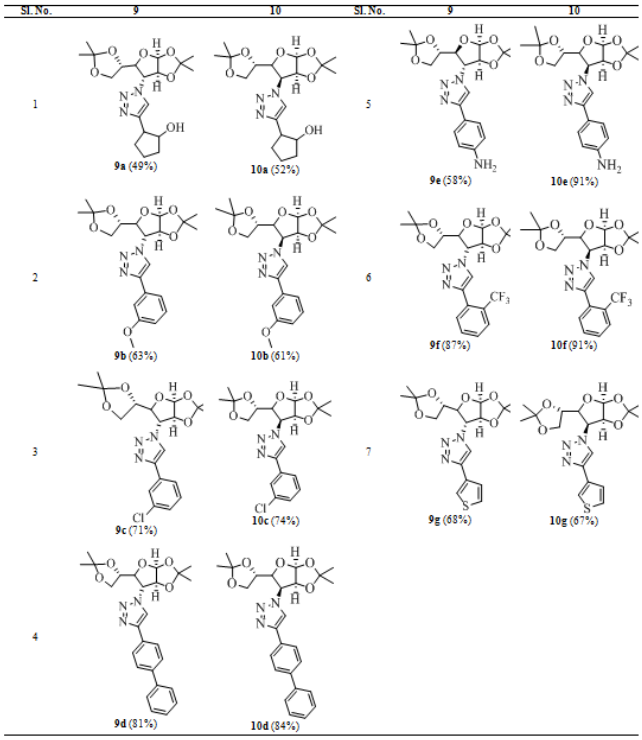
7	80	10	14	49%
8	**100**	**10**	**9**	**81%**
9	100	20	9	80%

After the optimization of reaction condition, we next explored the generality of the protocol for the synthesis triazoles by the cycloaddition of enantiomeric azides with alkynes (Scheme 4, Table 2). Thus, azide **3** undergo cycloaddition with various monosubstituted alkynes (cycloalkynes, aryl, biaryl and hetaryl) containing active functional groups like hydroxyl, methoxy, chloro, amino and trifluromethyl furnished respective triazoles **9a-g** in 49-87% yield (Table 2, entries 1-7). On the other hand, the enantiomeric triazoles **10a-g** were synthesized under the same reaction conditions in 52-91% yield by the cycloaddition of enantiomeric azide **7** with alkyne **8** (Table 2, entries 1-7). Thus, the reactions were successful with various alkynes bearing electron donating and withdrawing groups.



Scheme 4. Synthesis of enantiomeric glucosyl-triazoles

Table 2 Synthesis of triazole enantiomers



CONCLUSION

In conclusion, we have designed convenient protocols for highly enantioselective synthesis of 1-((3aR,5S,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3- d][1,3]dioxol-6-yl)-4-substituted-1*H*-1,2,3-triazoles and 1-((3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)-4-substituted- 1*H*-1,2,3-triazoles by adopting Huisgen cycloaddition of azido glucose derivatives (**3** and **7**) with different alkynes. Using these synthetic routes, enantiomeric glucosyl 1,2,3,-triazole epimers are smoothly prepared in good yield under green reaction conditions.

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Supplementary Material

Electronic supplementary material is given in this article

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