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One-pot synthesis of new triazole-sucrose derivatives via click chemistry and evaluation of their antitubercular activity

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Abstract: Readily prepared copper nanoparticles are an effective catalyst for 1,3-dipolar cycloaddition of carbohydrate azide and a variety of alkynes that furnishes the corresponding 1,2,3-triazole-sucrose derivatives in excellent yields. Products were screened for their antimycobacterial activity against *Mycobacterium tuberculosis H37Rv* strain. Two compounds, **3b**,**c**, demonstrate significant growth inhibitory activity against the bacterial strain with a MIC of 3.125 mg/mL. The presence of an amide group on the 1,2,3-triazole ring enhances the inhibition activity of the molecules. The active compounds are not toxic to a normal cell line which signifies the lack of general cellular toxicity of these compounds.

Keywords: carbohydrates; copper nanoparticles; cycloaddition; heterogeneous catalysis; *Mycobacterium tuberculosis*; triazoles.

Introduction

Tuberculosis caused by *Mycobacterium tuberculosis* still remains the leading cause of worldwide deaths among infectious diseases. The World Health Organization reported that more than one-third of the world's population was infected with tuberculosis, which resulted in an estimated 1.5 million deaths worldwide in 2013 [1]. The long duration of therapy generally is due to the nonconformity of the treatment and to the extensively drug-resistant tuberculosis, which is highly lethal, extremely expensive and complicated to treat, posing new challenges for the prevention, treatment and control of tuberculosis [2].

Ferreria and coworkers [3] have reported that 1,4-disubstituted 1,2,3-triazole derivatives **A** and **B** (Figure 1) exhibit good inhibitory activities against MTB H37Rv. Similarly, 1,2,3-triazoles **C** show inhibitory activities against H37Rv [4].

The catalyzed azide-alkyne cycloaddition reaction has found extensive application in the preparation of carbohydrate derivatives [5]. This method, developed by Meldal [6] and Sharpless [7], has became an important tool in organic synthesis due to a regioselective formation of 1,4-disubstituted 1,2,3-triazoles [8]. Moreover, the use of water as a solvent makes this reaction very attractive [9]. Recently, significant attention also has been paid to the use of copper nanoparticles (CuNPs) as catalysts in 'CuAAC' reactions in the synthesis of 1,2,3-triazoles. However, most of these reactions require organic solvents and high loading of CuNPs [10–12]. We wish to present herein the applicability of a copper nanoparticles for the click synthesis of new 1,2,3-triazole derivatives of carbohydrates in water.

Results and discussion

The cycloaddition of 1-prop-2-ynyl-pyrrolidine-2,5-dione **1a** with carbohydrate azide **2** [13] in acetonitrile afforded the desired triazole **3a** under copper catalysis conditions (Scheme 1). The CuNPs was prepared by reducing $CuSO_4$ with hydrazine according to literature procedures [14, 15]. The use of CuNPs and CuBr gave similar results. Then, the replacement of acetonitrile by water as a solvent substantially affected the yield (80%) of the reaction catalyzed by CuNPs which was completed (TLC) within 15 min, while the CuBr catalyzed reaction gave **3a** in 60% yield under similar conditions. Encouraged by the efficiency of the reaction protocol described above, the scope of the

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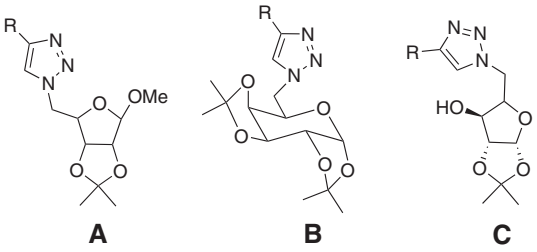


Figure 1 1,2,3-Triazoles A–C with antitubercular activity.

reaction was examined with alkynes **1b–e**. Corresponding triazoles **3b–e** were obtained in good yields.

All the target molecules **3b–e** were screened against *M. tuberculosis H37RV* (ATCC27294) using agar dilution method [16]. Their antimycobacterial activity was evaluated in terms of minimum inhibitory concentration (MIC) values. The MIC values of these compounds are in the range of 3.125–25 mg/mL. As can be seen from Figure 2, compounds **3a–c** show potent anti-tubercular activity with MIC of 3.125 µg/mL each. The MIC values of these three compounds are comparable with that of the standard drug, ethambutol. Compound **3e** shows moderate inhibition activity with MIC of 12.5 mg/mL.

Conclusion

The 1,3-dipolar cycloaddition reaction, the so-called click reaction, between a terminal alkyne and a carbohydrate azide is catalyzed by copper nanoparticles. Water works well as a green solvent for this reaction.

Experimental

Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). All anhydrous reactions were performed

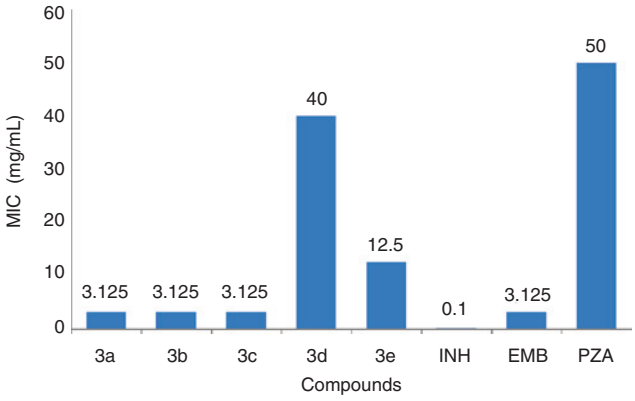


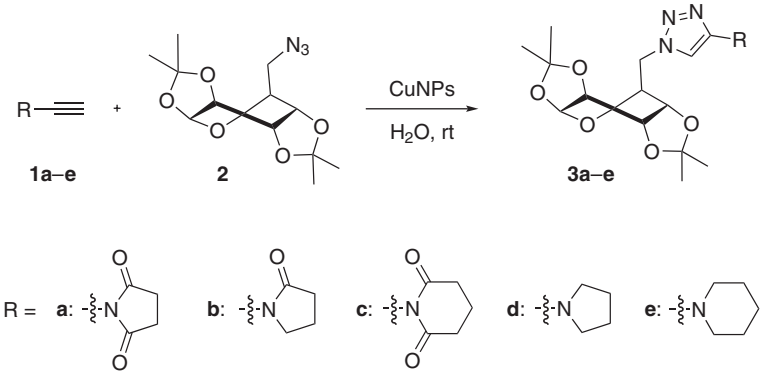
Figure 2 The antitubercular activity of **3a–e** against *M. tuberculosis H37RV* (INH: isoniazid; EMB: ethambutol; PZA: pyrazinamide).

under nitrogen using anhydrous solvents. NMR spectra were obtained on a Bruker AC 300 spectrometer operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Melting points were determined on a Buchi-510 capillary melting point apparatus. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS). The spectra were recorded in $CDCl_3$ as solvent at room temperature. Elemental analysis was recorded on a Perkin-Elmer 240B microanalyzer. Mass spectra were recorded on a Finnigan LCQ DECA XP plus spectrometer.

Synthesis of triazoles 3

To a solution azide **1** (160 mg, 0.5 mmol, 1 eq) in acetonitrile (12 mL) was added alkyne **2** (0.88 mmol), $CuSO_4{\cdot}5H_2O$ (12 mg, 0.05 mmol) and hydrazine hydrate (25 mg, 0.5 mmol). The mixture was microwave-irradiated at 100 W for 5 min. Reaction was monitored by TLC. After completion of the reaction, the mixture was passed through a celite pad and the filtrate was concentrated under a reduced pressure. The residue of **3** was purified on a silica gel column eluting with ethyl acetate.

1-((1-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrrolidine-2,5-dione (3a) Yield 80%; white solid; mp 76°C; $[\alpha]^{22}_{D}$ +45° (c 1, CH_2Cl_2); Rf 0.4 (AcOEt); ^{1}H NMR: δ 7.72 (s, 1H, H5), 5.49 (d, $J_{H3a\text{-}8b}$ = 4.8, 1H, H3a), 4.85–4.72 (m, 1H, H6), 4.63–53 (m, 2H, H8a, NCH), 4.43–4.92 (m, 2H, H8b, NCH), 4.16–4.14 (m, 2H,



Scheme 1

H5′, H5a), 2.73 (s, 4H, H7), 1.47 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR: δ 175.3 (CO), 140.7 (C4), 113.3 (C5), 108.9 (C_{isop}), 108.1 (C_{isop}), 95.3 (C3a), 70.3 (C5a), 69.9 (C8a), 69.5 (C8b), 66.2 (C5′), 49.5 (CNH), 32.8 (C6), 27.2 (C7), 25.0, 24.9, 23.9, 23.5 (CH_3). HRMS. Calcd for $C_{18}H_{24}N_4O_7$: *m/z* 408.1645. Found: *m/z* 408.1644. Anal. Calcd for $C_{18}H_{24}N_4O_7$: C, 52.94; H, 5.92; N, 13.72. Found: C, 52.92; H, 5.96; N, 13.70.

1-((1-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)pyrrolidin-2-one (3b) Yield 70%; white solid; mp 113°C; $[\alpha]^{22}_D$ +40° (c 1, CH_2Cl_2); Rf 0.3 (AcOEt); ^{1}H NMR: δ 7.61 (s, 1H, H5), 5.42 (d, $J_{H3a\text{-}8b}$ = 4.8, 1H, H3a), 4.57–4.48 (m, 3H, H8a, NCH, H6), 4.43–4.32 (m, 1H, NCH), 4.25 (dd, $J_{H8b\text{-}8a}$ = 2.4, $J_{H8b\text{-}3a}$ = 4.8, 1H, H8b), 4.11–4.08 (m, 2H, H5′, H5a), 3.38 (t, 2H, H7), 2.32 (t, $J_{H9\text{-}8}$ = 8.1, 2H, H9), 1.96–1.86 (m, 1H, H8), 1.41 (s, 3H, CH_3), 1.31(s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR: δ 174.7 (CO), 140.7 (C4), 123.7 (C5), 109.9 (C_{isop}), 109.0 (C_{isop}), 96.2 (C3a), 71.2 (C5a), 70.8 (C8a), 70.4 (C8b), 67.2 (C5′), 50.5 (CNH), 47.0 (C7), 37.8 (C6), 30.8 (C9), 25.9, 25.9, 24.8, 24.4 (CH_3), 17.8 (C8). HRMS. Calcd for $C_{18}H_{26}N_4O_6$: *m/z* 394.1852. Found: *m/z* 394.1855. Anal. Calcd for $C_{18}H_{26}N_4O_6$: C, 54.81; H, 6.64; N, 14.20. Found: C, 54.84; H, 6.68; N, 14.18.

1-((1-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperidine-2,6-dione (3c) Yield 75%; white solid; mp 147°C; $[\alpha]^{22}_D$ +71° (c 1, CH_2Cl_2); Rf 0.2 (cyclohexane/AcOEt 3:7); ^{1}H NMR: δ 7.69 (s, 1H, H5), 5.52 (d, $J_{H3a\text{-}H8b}$ = 5.1, 1H, H3a), 5.16–5.01 (m, 2H, H6), 4.65–4.55 (m, 2H, H8a, NCH), 4.42–4.34 (m, 1H, NCH), 4.31 (dd, $J_{H8b\text{-}8a}$ = 2.7, $J_{H8b\text{-}3a}$ = 5.1, 1H, H8b), 4.18–4.15 (m, 2H, H5′, H5a), 2.66 (t, $J_{H5\text{-}H6}$ = 6.6, 4H, H7), 1.97–1.93 (m, 2H, H8), 1.49 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR: δ 171.5 (CO), 142.6 (C4), 123.8 (C5), 109.4 (C_{isop}), 108.5 (C_{isop}), 95.7 (C3a), 70.6 (C5a), 70.2 (C8a), 69.5 (C8b), 66.6 (C5′), 49.9 (CNH), 33.9 (C6), 32.2 (C7), 29.2, 25.5, 24.4, 23.9 (CH_3), 16.5 (C8). HRMS. Calcd for $C_{19}H_{26}N_4O_7$: *m/z* 422.1802. Found: *m/z* 422.1804. Anal. Calcd for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20; N, 13.26. Found: C, 54.04; H, 6.17; N, 13.23.

4-(Pyrrolidin-1-ylmethyl)-1-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl)-1*H*-1,2,3-triazole (3d) Yield 77%; white solid; mp 110°C; $[\alpha]^{22}_D$ +65° (c 1, CH_2Cl_2); Rf 0.05 (AcOEt); ^{1}H NMR: δ 7.67 (s, 1H, H5), 5.52 (d, $J_{H3a\text{-}H8b}$ = 5.1, 1H, H3a), 4.65–4.59 (m, 2H, H8a, NCH), 4.47–4.40 (m, 1H, NCH), 4.33 (dd, $J_{H8b\text{-}8a}$ = 2.4, $J_{H8b\text{-}3a}$ = 5.1, 1H, H8b), 4.19–4.15 (m, 2H, H5′, H5a), 3.82 (d, $J_{H6\text{-}H5}$ = 1.8, 2H, H6), 2.59–2.56 (m, 4H, H7), 1.83–1.77 (m, 4H, H8), 1.50 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR: δ 145.1 (C4), 123.5 (C5), 109.8 (C_{isop}), 109.0 (C_{isop}), 96.2 (C3a), 71.2 (C5a), 70.8 (C8a), 70.4 (C8b), 67.3 (C5′), 53.6 (C7), 50.5 (C6), 50.4 (CNH), 25.9, 25.9, 24.8, 24.4 (CH_3), 23.5 (C8). HRMS. Calcd for $C_{18}H_{28}N_4O_5$: *m/z* 308.2060. Found: *m/z* 308.2064. Anal. Calcd for $C_{18}H_{28}N_4O_5$: C, 56.83; H, 7.42; N, 14.73. Found: C, 56.87; H, 7.39; N, 14.69.

1-((1-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperidine 3e Yield 72%; white solid; mp 130°C; $[\alpha]^{22}_D$ +36° (c 1, CH_2Cl_2); Rf 0.1 (AcOEt); ^{1}H NMR: δ 7.69 (s, 1H, H5), 5.51 (d, $J_{H3a\text{-}H8b}$ = 4.8, 1H, H3a), 4.64–4.61 (m, 2H, H8a, NCH), 4.48–4.41 (m, 1H, NCH), 4.32 (dd, $J_{H8b\text{-}8a}$ = 2.4, $J_{H8b\text{-}3a}$ = 4.8, 1H, H8b), 4.18–4.16 (m, 2H, H5′, H5a), 2.47 (s, 2H, H6), 1.58–1.56 (m, 22H, H7, H8, H9, 4 CH_3); ^{13}C NMR: δ 144.5 (C4), 123.9 (C5), 109.8 (C_{isop}), 108.9 (C_{isop}), 96.2 (C3a), 71.2 (C5a), 70.8 (C8a), 70.5 (C8b), 67.4 (C5′), 53.2 (C6), 50.5 (NCH), 26.6, 24.8, 24.4 (CH_3), 29.6, 25.9, 24.1 (C7, C8, C9). HRMS. Calcd for $C_{19}H_{30}N_4O_5$: *m/z* 394.2216. Found: *m/z* 394.2219. Anal. Calcd for $C_{19}H_{30}N_4O_5$: C, 57.85; H, 7.67; N, 14.20. Found: C, 57.82; H, 7.72; N, 14.24.

Antitubercular studies

A standard methodology, recommended by the National Committee for Clinical Laboratory Standards, USA, for the determination of MIC, was used. The assays were conducted in triplicate.

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