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Synthesis of carbohydrate-substituted isoxazoles and evaluation of their antitubercular activity

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Abstract: Eight new sugar-substituted isoxazoles were synthesized by a 1,3-dipolar cycloaddition reaction of aromatic nitrile oxides with carbohydrate-substituted alkynes. Products were screened for antimycobacterial activity against the *Mycobacterium tuberculosis H37Rv* strain. Four compounds, **5e–h**, significantly inhibit growth of the bacterial strain with a minimum inhibitory concentration (MIC) of 3.125 μg/mL.

Keywords: aromatic nitrile oxides; 1,3-dipolar cycloaddition; isoxazole; *Mycobacterium tuberculosis*; propargyl *O*-glycoside.

Introduction

1,3-Dipolar cycloaddition is one of the most useful reactions for the synthesis of heterocyclic compounds [1]. Over the years, nitrile oxides have become important building blocks in organic synthesis. 1,3-Dipolar reactions of alkynes with nitrile oxides have been used to prepare isoxazoles [2]. Isoxazole derivatives represent an important class of biologically active heterocycles in drug discovery. They are clinically effective as antimicrobial, antibacterial, anticonvulsant, anticancer, antifungal, antiviral and antitubercular agents [3–12]. The synthesis of artificial enzymes containing isoxazole moieties is a dynamic area of research [13, 14]. Moreover, isoxazole derivatives have found applications as dyes, corrosion inhibitors and agrochemicals [15]. Many isoxazole derivatives have been synthesized to date [16–18]. Previously, we developed an efficient method for the synthesis of enantiopure isoxazoline derivatives based on the [3+2] cycloaddition between aromatic nitrile oxides and pyrrol-2-ones [19, 20]. In this paper, we report that chiral isoxazoles can be obtained by the [3+2] cycloaddition of aromatic nitrile oxides with propargyl *O*-glycoside derivatives, thereby providing a new synthetic route to carbohydrate-isoxazole conjugates.

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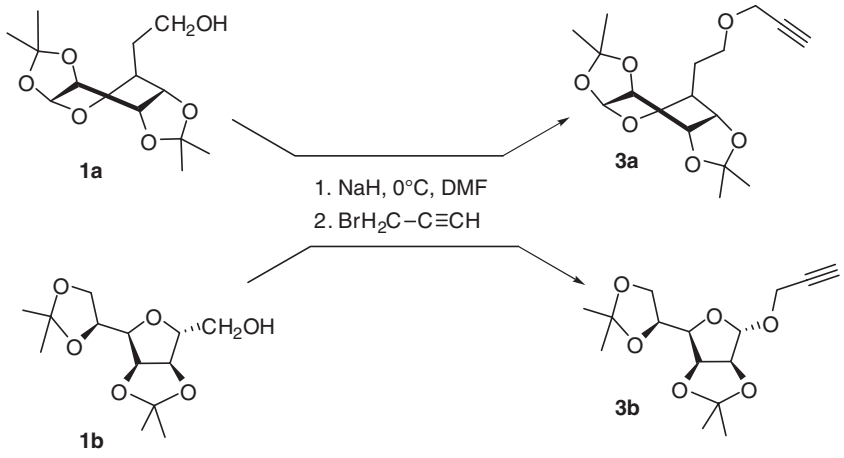
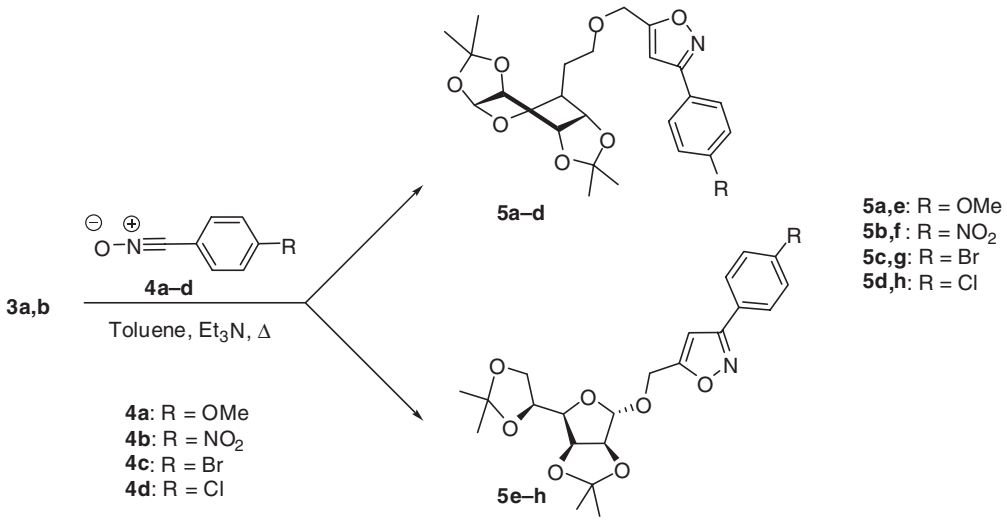
Results and discussion

The propargyl *O*-glycosides **3a,b** were synthesized beginning with alcohols, **1** (Scheme 1). Etherification of **1** using propargyl bromide in the presence of sodium hydride at 0°C generated the corresponding ether in a good yield [21]. The synthetic method to obtain the target isoxazoles **5a–h** is shown in Scheme 2. The 1,3-dipolar cycloaddition of the propargyl *O*-glycoside derivatives **3a,b** with aromatic nitrile oxides **4a–d** at 110°C in toluene for 2 h furnished compounds **5a–h**. The 1,3-dipolar cycloaddition between the propargyl *O*-glycoside derivatives **3** and aromatic nitrile oxides **4** gave cycloadducts **5** as single regioisomers [22]. The structures of the new isoxazoles **5a–h** were established from their elemental analyses using Fourier transform infrared (FT-IR) and ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra. The IR spectra of all isoxazoles have a peak at 1635–1645 cm^{-1}, which is related to the C=N stretching of the isoxazole ring.

The structures of new isoxazoles **5a–h** were by analysis of the ^{1}H NMR and ^{13}C NMR spectra. The relevant data are presented under the Experimental section. In particular, the ^{1}H NMR spectrum of **5a** shows that the sugar ring is strongly distorted from the regular conformation because of the presence of two fused five-membered isopropylidene rings. Thus, unusual coupling constant values of 2.4 and 7.8 Hz are observed between *trans* (H-8a, H-8b)- and *cis* (H-8a, H-5a)-coupled protons, respectively. In the heteronuclear multiple quantum coherence spectrum of **5a**, the apparent singlet at 6.55 ppm correlates with the carbon C4′ (101.1 ppm), whereas it does not correlate with the carbon C5′ at 161.1 ppm. In the heteronuclear multiple



Scheme 1



Scheme 2

bond correlation (HMBC), the atom H4′ is correlated with C3′ and C-aromatic (Figure 1).

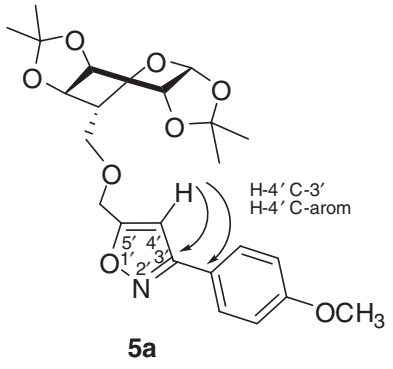


Figure 1 HMBC correlations of H-4′ in compound **5a**.

All the products **5a–h** were screened against *Mycobacterium tuberculosis H37RV* (ATCC27294) using agar dilution method [23]. Their antimycobacterial activity was evaluated in terms of minimum inhibitory concentration (MIC) values. Four compounds, **5e–h**, are potent antitubercular agents with an MIC of 3.125 μg/mL. The MIC of those compounds is comparable with the MIC value of the standard drug, ethambutol. Compounds **5a–d** show a moderate inhibitory activity with MIC of 12.5 μg/mL.

Conclusion

New sugar-isoxazole conjugates were obtained regio- and stereoselectively by the [3+2] cycloaddition of aromatic nitrile oxides with propargyl *O*-glycoside derivatives. The antimycobacterial activity of these compounds is

significant; hence, they could potentially serve as antitubercular agents.

Experimental

IR spectra were recorded in KBr pellets on a Perkin-Elmer IR-197 spectrometer. Mass spectra were recorded in the electrospray ionization (ESI) mode. NMR spectra were obtained in $CDCl_3$ on a Bruker AC 300 spectrometer operating at 300 MHz for ^1H and at 75 MHz for ^{13}C. Melting points were recorded in open capillaries and are uncorrected. Optical rotations were measured at 589 nm. Thin-layer chromatography (TLC) was performed on precoated plates (0.2 mm, silica gel 60 F254). All solvents were distilled and purified as necessary.

General procedure for the synthesis of propargyl *O*-glycosides 3a,b

NaH (29 mg, 1.2 mmol) was added to a solution of protected sugar **2** (300 mg, 1.15 mmol) in dry DMF (10 mL) at 0°C. The mixture was stirred for 20 min and then treated slowly with propargyl bromide (0.77 mL, 8.6 mmol) in toluene followed by stirring at 0°C for 20 min and then at room temperature for 12 h. Then, the mixture was cooled to 0°C, treated with MeOH (20 mL) and concentrated under reduced pressure. The residue was suspended in water (30 mL) and extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a brown oil of **3a,b**, which was purified by silica gel chromatography eluting with hexanes/EtOAc (3:1).

(3aR, 8bR, 8aS, 5aS, 5R)-2,2,7,7-Tetramethyl-5-prop-2-ynyloxymethyltetrahydro-bis[1,3]dioxolo[4,5-*b*;4′,5′-*d*]pyran (3a) Yellow solid; mp 50–51°C; Rf = 0.5 (cyclohexane/AcOEt, 3:7); yield 64%; IR: υ_{max} 3280 cm^{-1} ; ^1H NMR: δ 5.55 (d, J_{H3a-8b} = 5.1 Hz, 1H, H_{3a}), 4.62 (dd, J_{H8a-8b} = 2.4 Hz, J_{H8a-5a} = 5.7 Hz, 1H, H_{8a}), 4.33 (dd, J_{H8a-8b} = 2.4 Hz, $J_{H8b-H3a}$ = 5.1 Hz, 1H, H_{8b}), 4.28 (dd, $J_{H8a-H5a}$ = 5.7 Hz, J_{H5a-H5} = 2.1 Hz, 1H, H_{5a}), 4.23 (m, 2H, $H_{3''}$), 4.02 (m, 1H, H_5), 3.80 (m, 2H, $H_{4''}$), 2.44 (t, J_{H3-1} = 2.4 Hz, 1H, $H_{1''}$), 1.54, 1.45, 1.34, 1.33 (s, 3H, CH_3); ^{13}C NMR: δ 109.3, 108.5, 96.3, 79.6, 74.5, 71.2, 71.7, 70.5, 68.7, 66.7, 58.5, 26.0, 25.9, 24.9, 24.4. HRMS. Calcd for $C_{15}H_{22}O_6$: *m/z* 298.1416. Found: *m/z* 298.1416. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39, H, 7.43. Found: C, 60.37, H, 7.45.

4-(2′,2′-Dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-6-prop-2-ynyloxy-tetrahydro-furo[3,4-*d*][1,3]dioxole (3b) Yellow oil, Rf = 0.6 (cyclohexane/AcOEt, 3:7); yield 70%; IR: υ_{max} 3300 cm^{-1} ; ^1H NMR: δ 5.11 (s, 1H, H_6), 4.71 (dd, J_{H3a-6a} = 6 Hz, J_{H3a-4} = 3.6 Hz, 1H, H_{3a}), 4.55 (d, J_{H6a-3a} = 6 Hz, 1H, H_{6a}), 4.31 (m, 1H, $H_{4'}$), 4.21 (d, 2H, $J_{H3''-1''}$ = 2.1 Hz, $H_{3''}$), 3.98 (m, 1H, $H_{5'}$), 3.87 (m, 1H, H4), 2.42 (t, $J_{H1''-3''}$ = 2.1 Hz, 1H, $H_{1''}$), 1.40, 1.38, 1.31, 1.26 (s, 3H, CH_3); ^{13}C NMR: δ 112.1, 108.6, 104.3, 84.4, 80.0, 78.9, 74.2, 72.4, 66.2, 53.5, 26.3, 25.3, 24.6, 23.9. HRMS. Calcd for $C_{15}H_{22}O_6$: *m/z* 298.1416. Found: *m/z* 298.1413. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39, H, 7.43. Found: C, 60.41, H, 7.40.

General procedure for synthesis of isoxazoles 5a–h

A mixture of alkyne **3a,b** (0.33 mmol) and chloroxime **4a–d** (0.63 mmol) was dissolved in 10 mL of toluene and the mixture was stirred at 110°C. Then, a solution of triethylamine (0.39 mmol) in toluene (10 mL) was added dropwise. The resultant precipitate of triethylammonium chloride was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was subjected to a silica gel column chromatography eluting with hexanes/EtOAc (7:3) to afford compound **5a–h**.

(3aR, 8bR, 8aS, 5aS, 5R)-3′-(4-Methoxyphenyl)-5-(2,2,7,7-tetramethyltetrahydro-bis[1,3]dioxolo[4,5-*b*;4′,5′-*d*]pyran-5-ylmethoxymethyl)isoxazole (5a) Yellow oil; $[\alpha]_D^{22}$ = +55 (c 1, CH_2Cl_2); Rf = 0.15 (cyclohexane/AcOEt, 2:8); yield 72%; IR: υ_{max} 1640 cm^{-1}; ^1H NMR: δ 7.75–6.95 (AA′BB′, $J_{AA'BB'}$ = 8.7 Hz, 4H, H_{arom}), 6.55 (s, 1H, $H_{4'}$), 5.54 (d, J_{H3a-8b} = 5.1 Hz, 1H, H_{3a}), 4.64 (d, *J* = 8.7 Hz, 2H, $H_{6'}$), 4.59 (dd, J_{H8a-8b} = 2.4 Hz, J_{H8b-5a} = 7.8 Hz, 1H, H_{8a}), 4.31 (dd, J_{H8b-3a} = 5.1 Hz, J_{H8b-8a} = 2.4 Hz, 1H, H_{8b}), 4.25 (dd, J_{H5a-8a} = 7.8 Hz, J_{H5a-5} = 1.8 Hz, 1H, H_{5a}), 4.00 (m, 1H, H_5), 3.85 (s, 3H, CH_3), 3.69 (m, 2H, $H_{6''}$), 1.54, 1.43 (s, 3H, CH_3), 1.33 (s, 6H, CH_3); ^{13}C NMR: δ 169.1, 161.4, 160.5, 127.7, 121.1, 113.8, 108.6, 108.1, 101.1, 95.8, 70.6, 70.2, 70.0, 69.4, 66.5, 63.8, 54.8, 25.6, 25.5, 24.4, 23.9. HRMS. Calcd for $C_{23}H_{29}NO_8$: *m/z* 447.1893. Found: *m/z* 447.1890. Anal. Calcd for $C_{23}H_{29}NO_8$: C, 61.73, H, 6.53, N, 3.13. Found: C, 61.69, H, 6.50, N, 3.09.

(3aR, 8bR, 8aS, 5aS, 5R)-3′-(4-Nitrophenyl)-5-(2,2,7,7-tetramethyltetrahydro-3a*H*-bis ([1,3]dioxolo) [4,5-*b*:4′,5′-*d*]pyran-5-yl)methoxy)methyl)isoxazole (5b) Yellow solid; mp 66–67°C; $[\alpha]_D^{22}$ = +52 (c 1, CH_2Cl_2), Rf = 0.18 (cyclohexane/AcOEt 2:8), yield (80%); IR: υ_{max} 1645 cm^{-1}; ^1H NMR: δ 8.25-7.89 (AA′BB′, $J_{AA'BB'}$ = 9 Hz, 4H, H_{arom}), 6.61 (s, 1H, $H_{4'}$), 5.46 (d, J_{H3a-8b} = 5.1 Hz, 1H, H_{3a}), 4.67 (d, *J* = 8.7 Hz, 2H, $H_{6'}$), 4.52 (dd, J_{H8a-8b} = 2.4 Hz, J_{H8a-5a} = 7.8 Hz, 1H, H_{8a}), 4.24 (dd, J_{H8b-3a} = 5.1 Hz, J_{H8b-8a} = 2.4 Hz, 1H, H_{8b}), 4.16 (dd, J_{H5a-8a} = 7.8 Hz, J_{H5a-5} = 2.1 Hz, 1H, H_{5a}), 3.95 (m, 1H, H_5), 3.65 (m, 2H, $H_{6''}$), 1.46, 1.36 (s, 3H, CH_3), 1.26 (s, 6H, CH_3); ^{13}C NMR: δ 171.1, 160.5, 148.7, 135.1, 127.6, 124.2, 109.4, 108.7, 101.1, 96.4, 71.2, 70.7, 70.5, 70.2, 67.1, 64.3, 26.1, 25.9, 24.9, 24.5. HRMS. Calcd for $C_{22}H_{26}N_2O_9$: *m/z* 462.1638. Found: *m/z* 462.1635. Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14, H, 5.67, N, 6.06. Found: C, 57.17, H, 5.64, N, 6.02.

(3aR, 8bR, 8aS, 5aS, 5R)-3′-(4-Bromophenyl)-5-(2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4′,5′-*d*]pyran-5-yl)methoxy)methyl)isoxazole (5c) Yellow oil; $[\alpha]_D^{22}$ = +77 (c 1, CH_2Cl_2); Rf = 0.34 (cyclohexane/AcOEt, 2:8); yield 75%; IR : υ_{max} 1640 cm^{-1} ; ^1H NMR: δ 7.69–7.57 (AA′BB′, $J_{AA'BB'}$ = 10.8 Hz, 4H, H_{arom}), 6.59 (s, 1H, $H_{4'}$), 5.54 (d, J_{H3a-8b} = 5.1 Hz, 1H, H_{3a}), 4.67 (d, *J* = 8.7 Hz, 2H, $H_{6'}$), 4.60 (dd, J_{H8a-8b} = 2.4 Hz, J_{H8a-5a} = 7.8 Hz, 1H, H_{8a}), 4.31 (dd, J_{H8b-3a} = 5.1 Hz, J_{H8b-8a} = 2.4 Hz, 1H, H_{8b}), 4.24 (dd, J_{H5a-8a} = 7.8 Hz, J_{H5a-5} = 2.1 Hz, 1H, H_{5a}), 4.01 (m, 1H, H_5), 3.70 (m, 2H, $H_{6''}$), 1.54, 1.44, 1.34, 1.26 (s, 3H, CH_3); ^{13}C NMR: δ 169.8, 160.9, 131.6, 127.8, 127.5, 123.7, 108.8, 108.1, 100.4, 95.8, 70.6, 70.2, 70.0, 69.5, 66.5, 63.8, 25.5, 25.4, 24.4, 23.9. HRMS. Calcd for $C_{22}H_{26}BrNO_7$: *m/z* 495.0893. Found: *m/z* 495.0890. Anal. Calcd for $C_{22}H_{26}BrNO_7$: C, 53.24, H, 5.28, N, 2.82. Found: C, 53.20, H, 5.25, N, 2.79.

(3aR, 8bR, 8aS, 5aS, 5R)-3′-(4-Chlorophenyl)-5-(2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-*b*:4′,5′-*d*]pyran-5-yl)methoxy)methyl)isoxazole (5d) Yellow oil, $[\alpha]_D^{22}$ = +89 (c 1, CH_2Cl_2); Rf = 0.47 (cyclohexane/AcOEt, 2:8; yield 78%; IR : υ_{max} 1645 cm^{-1} ; ^1H NMR: δ 7.67–7.33 (AA′BB′, $J_{AA'BB'}$ = 8.4 Hz, 4H, H_{arom}), 6.50 (s, 1H, $H_{4'}$), 5.46 (d, J_{H3a-8b} = 5.1 Hz, 1H, H_{3a}), 4.58 (d, *J* = 8.7 Hz, 2H, $H_{6'}$), 4.51 (dd, J_{H8a-8b} = 2.4 Hz, J_{H8a-5a} = 7.8 Hz, 1H, H_{8a}), 4.23 (dd, J_{H8b-3a} = 5.1 Hz, J_{H8b-8a} = 2.4 Hz, 1H, H_{8a}), 4.17 (dd, J_{H5a-8a} = 7.8 Hz, J_{H5a-5} = 1.8 Hz, 1H, H_{5a}), 3.94 (m, 1H, H_5), 3.64 (m, 2H, $H_{6''}$), 1.46, 1.36 (s, 3H, CH_3), 1.25 (s, 6H, CH_3); ^{13}C NMR: δ 169.7, 160.9, 135.50, 128.7, 127.6, 127.1, 108.9, 108.1, 100.4,

95.8, 70.6, 70.2, 70.0, 69.5, 66.5, 63.8, 25.6, 25.5, 24.4, 23.9. HRMS. Calcd for $C_{22}H_{26}ClNO_7$: *m/z* 451.1398. Found: *m/z* 451.1395. Anal. Calcd for $C_{22}H_{26}ClNO_7$: C, 58.47, H, 5.80, N, 3.10. Found: C, 58.45, H, 5.78, N, 3.08.

(3aS, 6aS, 4′S, 6′R, 4″S)-5-[6′-(2″,2″-Dimethyl-[1,3]dioxolan-4″-yl)-2′,2′-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4′-yloxymethyl]-3-(4-methoxyphenyl)isoxazole (5e) White solid; mp 113–114°C; $[\alpha]_D^{22}$ =+49 (c 1, CH_2Cl_2); Rf = 0.1 (cyclohexane/AcOEt, 2:8), yield 68%; IR: υ_{max} 1640 cm^{-1}; ^1H NMR: δ 7.75–6.95 (AA′BB′, $J_{AA'BB'}$ = 8.7 Hz, 4H, H_{arom}), 6.50 (s, 1H, H_4), 5.13 (s, 1H, $H_{4'}$), 4.82–4.62 (m, 4H, H_{3a}, H_{6a}, CH_2), 4.53–4.39 (m, 1H, $H_{4''}$), 4.14–4.01 (m, 3H, $H_{6''}$,$H_{6'}$), 3.85, 1.46, 1.45, 1.38, 1.33 (s, 3H, CH_3); ^{13}C NMR: δ 168.3, 161.5, 160.5, 127.7, 120.9, 113.8, 112.3, 108.7, 105.8, 100.6, 84.3, 80.3, 78.9, 72.5, 66.2, 59., 54.8, 29.1, 26.8, 26.3, 25.4. HRMS. Calcd for $C_{23}H_{29}NO_8$: *m/z* 447.1893. Found: *m/z* 447.1897. Anal. Calcd for $C_{23}H_{29}NO_8$: C, 61.73, H, 6.53, N, 3.13. Found: C, 61.69, H, 6.51, N, 3.10.

(3aS, 6aS, 4′S, 6′R, 4″S)-5-[6′-(2″,2″-Dimethyl-[1,3]dioxolan-4″-yl)-2′,2′-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4′-yloxymethyl]-3-(4-nitrophenyl)isoxazole (5f) White solid; mp 85–86°C, $[\alpha]_D^{22}$ =+93 (c 1, CH_2Cl_2), Rf = 0.3 (cyclohexane/AcOEt, 2:8), yield 77%; IR: υ_{max} 1635 cm^{-1}; ^1H NMR: δ 8.36–8.00 (AA′BB′, $J_{AA'BB'}$ = 8.7 Hz, 4H, H_{arom}), 6.67 (s, 1H, H_4), 5.15 (s, 1H, $H_{4'}$), 4.85–4.68 (m, 4H, H_{3a}, H_{6a}, CH_2), 4.47–4.41 (m, 1H, $H_{4''}$), 4.15–4.01 (m, 3H, $H_{6''}$,$H_{6'}$), 1.48, 1.46, 1.40, 1.35 (s, 3H, CH_3); ^{13}C NMR: δ 170.2, 160.7, 148.8, 134.9, 127.7, 124.2, 112.9, 109.2, 106.3, 101.4, 84.9, 80.8, 79.4, 73.1, 66.6, 59.7, 26.9, 25.8, 25.2, 24.5. HRMS. Calcd for $C_{22}H_{26}N_2O_9$: *m/z* 462.1638. Found: *m/z* 462.1634. Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14, H, 5.67, N, 6.06. Found: C, 57.10, H, 5.69, N, 6.05.

(3aS, 6aS, 4′S, 6′R, 4″S)-3-(4-Bromophenyl)-5-[6′-(2″,2″-dimethyl-[1,3]dioxolan-4″-yl)-2′,2′-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4′-yloxymethyl]isoxazole (5g) White solid; mp 115–116°C; $[\alpha]_D^{22}$ =+67 (c 1, CH_2Cl_2); Rf = 0.45 (cyclohexane/AcOEt, 2:8); yield 50%; IR: υ_{max} 1640 cm^{-1}; ^1H NMR: δ 7.71–7.59 (AA′BB′, $J_{AA'BB'}$ = 8.4 Hz, 4H, H_{arom}), 6.56 (s, 1H, H4), 5.14 (s, 1H, H4′), 4.83–4.66 (m, 4H, H_{3a}, H_{6a}, CH_2), 4.64–4.40 (m, 1H, $H_{4''}$), 4.15–4.01 (m, 3H, $H_{6''}$, $H_{6'}$), 1.49, 1.48, 1.40, 1.34 (s, 3H, CH_3); ^{13}C NMR: δ 169.3, 161.5, 132.15, 127.8, 127.7, 124.4, 112.8, 109.0, 106.2, 101.2, 84.8, 80.8, 79.4, 73.0, 63.9, 59.6, 26.9, 26.8, 25.9, 25.2. HRMS. Calcd for $C_{22}H_{26}BrNO_7$: *m/z* 495.0893. Found: *m/z* 495.0890. Anal. Calcd for $C_{22}H_{26}BrNO_7$: C, 53.24, H, 5.28, N, 2.82. Found: C, 53.20, H, 5.29, N, 2.84.

(3aS, 6aS, 4′S, 6′R, 4″S)-3-(4-Chlorophenyl)-5-[6′-(2″,2″-Dimethyl-[1,3]dioxolan-4″-yl)-2′,2′-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4′-yloxymethyl]isoxazole (5h) White solid; mp 108–109°C; $[\alpha]_D^{22}$ =+83 (c 1, CH_2Cl_2); Rf = 0.42 (cyclohexane/AcOEt, 2:8); yield 89%; IR: υ_{max} 1635 cm^{-1}; ^1H NMR: δ 7.77–7.43 (AA′BB′, $J_{AA'BB'}$ = 8.4 Hz, 4H, H_{arom}), 6.55 (s, 1H, H_4), 5.14 (s, 1H, $H_{4'}$), 4.84–4.66 (m, 4H, H_{3a}, H_{6a}, CH_2), 4.44-4.40 (m, 1H, $H_{4''}$), 4.15–4.01 (m, 3H, $H_{6''}$,$H_{6'}$), 1.48, 1.46, 1.40, 1.34 (s, 3H, CH_3); ^{13}C NMR: δ 169.3, 161.5, 136.1, 129.2, 128.1, 127.4, 112.8, 109.2, 106.2, 101.2, 85.0, 80.8, 79.4, 76.8, 66.7, 59.8, 26.8, 25.9, 25.0, 24.6. HRMS. Calcd for $C_{22}H_{26}ClNO_7$: *m/z* 451.1398. Found: *m/z* 451.1395. Anal. Calcd for $C_{22}H_{26}ClNO_7$: C, 58.47, H, 5.80, N, 3.10. Found: C, 58.44, H, 5.78, N, 3.13.

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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