Research Article

Synthesis, Characterization, X-Ray Crystallography, and Antileishmanial Activities of N-Linked and O-Linked Glycopyranosides

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Novel N-linked **5a–e** and O-linked glycopyranosides **7a–e** were synthesized in high yield from commercially available L-tartaric acid containing two asymmetric centers and C₂ axis of symmetry. The compound L-tartaric acid was completely protected and then partially hydrolyzed to get the monoester, which upon treatment with different amino and hydroxyl derivatives of glycopyranosides gave the desired amides and esters. The synthesized derivatives were purified by chromatography and characterized by spectroanalytical techniques. The structure of compound **7c** in the series was supported by X-ray analysis. Leishmanicidal activities of compounds **5a–e** and **7a–e** were investigated which showed moderate to good activities.

1. Introduction

Leishmania has long been known to human beings especially in African and Indian populations since the mid eighteenth century [1–3]. In 1903, Leishman and Donovan discovered the protozoan in spleen tissues of patients in India, which is now known as *Leishmania donovani* [4, 5]. Nicolle and Comte reported infection by *Leishmania* in dogs in 1908 [6]. Leishmaniasis is a vector-borne disease carried by sand fly and caused by protozoa of the genus *Leishmania*. Recent reports confirm that people in about 88 countries are affected by *Leishmania* and 350 million are at risk, and more or less 2 million new cases are reported each year [7]. In spite of the socioeconomical significance of this tropical infectious

disease, the discovery of new potential drugs against it is underway [8, 9].

Glycolipid and glycoprotein oligosaccharides present on cell surfaces are known to play an important role in various biological processes, that is, cellular recognition, adhesion, tumor metastasis, and cell growth regulation [10]. One major class of glycoprotein oligosaccharides consists of N-oligosaccharides linked to asparagine by an amide bond [11, 12]. Amides are usually prepared by thermolysis of carboxylic acids with amines, by coupling of carboxylic acids and amines in the presence of a coupling reagent [13] or by prior conversion of the carboxylic acid into a more electrophilic derivative [14]. The concept to add a chiral aglycone moiety such as tartaric acid to prepare glycosides is an active area

of research. L-tartaric acid is cheap and readily available starting material; it has two chiral centers with two carboxylic acid groups which can be easily derivatized. Derivatives of tartaric acid containing ester and amide linkages have promisingly useful biological applications, for example, anti-inflammatory, antifungal, thrombin inhibitors, antimicrobial, and β -secretase inhibitory activities [15–20].

Hence, glyco derivatives of tartaric acid have potential as curative agents for various infectious diseases. Herein, we report an efficient and scalable synthesis of *N*-linked (**5a–e**) and *O*-linked glycopyranosides (**7a–e**) through anomeric *N*- and *O*-acylation, respectively, using commercially available L-tartaric acid as a starting material.

2. Experimental

All chemicals were of highest purity available and used as supplied. D-glucose, D-mannose, D-galactose, D-glucosamine, and D-galactosamine hydrochloride were purchased from Fluka and Sigma Aldrich. Dry solvents like methanol, dichloromethane, chloroform, and *n*-hexane were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from anhydrous engineering (University of Bristol, UK) based on Grubbs' design. Reactions under anhydrous conditions were carried out under nitrogen gas using three-way stopcock and rubber septa.

Liquid reagents, solutions, or solvents were added via syringe or cannula through rubber septa. Solid reagents were added via Schlenk type adapters. All reactions were monitored by TLC on Kieselgel 60 F254 (Merck); ethyl acetate/*n*-hexane and methanol/chloroform were used as eluent. Chromatograms were detected under UV light ($\lambda_{\max}$ 254 and 365 nm) and by charring with 10% sulfuric acid in ethanol, ninhydrin, and vanillin, respectively. Column chromatography was performed using silica gel [Merck, 230–400 mesh (40–63 μ m)]. Extracts were concentrated under reduced pressure using both rotary evaporator (bath temperature up to 40°C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate and a high vacuum line at room temperature. Melting points were determined in degree Celsius (°C) using Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS 66 (FT-IR), Nicolet 205 FT-IR; Nicolet 360 smart orbit (ATR); Thermo Scientific Nicolet 6700 FT-IR and Shimadzu Fourier Transform Infrared Spectrophotometer Model 270. Solid samples were taken in KBr pellets and oils were used in NaCl cells for recording their spectra. ^1H NMR spectra were recorded on an NMR Bruker apparatus at 300 MHz and Varian 400 MHz INOVA instrument. ^{13}C NMR spectra were recorded on NMR Bruker apparatus at 75 MHz and Varian 100 MHz INOVA instrument. Chemical shifts are quoted in parts per million from SiMe_4 or residual solvent proton signals and coupling constants (*J*) given in Hertz. Multiplicities are abbreviated as b (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or combinations thereof. Positive ion Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) mass spectra were recorded using an HP-MALDI instrument using gentisic acid

as matrix material. Optical rotations were measured on an ATAGO, AP-100 Automatic polarimeter. Single crystal X-ray diffraction data were collected on a Bruker Smart APEX II, CCD detector diffractometer [21]. Data reductions were performed using the SAINT program. The structures were solved by direct methods [22] and refined by full-matrix least squares on F^2 by using the SHELXTL-PC package [23]. The figures were plotted with the aid of ORTEP program [24].

2.1. General Procedure for the Synthesis of *N*-Linked Glycopyranosides (5a–e**).** In a round bottom flask (100 mL), monoester **1** (0.61 g, 3 mmol), EDC (0.74 g, 3 mmol $\times$ 1.3 eq.), and catalytic amount of DMAP were placed under nitrogen. CH_2Cl_2 (30 mL) was added as a solvent. After 30 min glycopyranosyl amine **4a–e** (3 mmol) was added and the mixture was stirred for 18 h. The byproduct urea was removed by extraction of the reaction mixture with ethyl acetate or chloroform and water (30 mL $\times$ 2). The crude product was purified by column chromatography using ethyl acetate : hexane (3 : 7) as eluent.

2.2. (2*R*,3*R*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate **5a.** Yield: 72%. Colorless oil [α]_D²⁵ = 12.5. (IR ν cm^{-1}): 3347 (NH), 2955 (CH), 1742 (COOCH₃), 1701 (CONH), 1299 (C–O–C). ^1H NMR (400 MHz, CDCl_3): δ (ppm): 7.18 (d, *J* = 9.3 Hz, NH), 5.23, 5.18, 5.05, 4.96 (pseudo t, *J* $\sim$ 9.2 Hz in each, CH), 4.65 (d, *J* = 5.4 Hz, CH), 4.59 (d, *J* = 5.4 Hz, CH), 4.30 (dd, *J* = 12.5, 3.6 Hz, CH), 4.21 (ddd, *J* = 10.4, 3.6, 2.1 Hz, CH), 3.95 (dd, *J* = 12.5, 2.1 Hz, CH), 3.75 (s, OCH₃), 1.94, 1.92, 1.91, 1.89 (s, CH₃), 1.56 (s, CH₃), 1.50 (s, CH₃). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 171.2 (CONH), 170.7 (COOCH₃), 170.0, 169.9, 169.5, 169.2 (CO), 113.3 (qt C), 81.8 (CH), 76.3 (CH), 75.2 (CH), 73.3, 72.5, 70.0, 67.8 (CH), 61.2 (CH), 52.4 (OCH₃), 25.9, (CH₃), 25.2 (CH₃), 20.2, 20.1 (3), (CH₃). HRMS-ESI for $\text{C}_{22}\text{H}_{31}\text{NO}_{14}$ Na: $[\text{M} + \text{Na}]^+$ calcd: 556.1745, found: 556.1621. Anal. Calc. For $\text{C}_{22}\text{H}_{31}\text{NO}_{14}$: C, 49.53; H, 5.86; N, 2.63; O, 41.99 Found C, 49.43; H, 5.56; N, 2.78; O, 42.10.

2.3. (2*R*,3*R*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate **5b.** Yield: 69%. Colorless oil [α]_D²⁵ = 13.3. (IR ν cm^{-1}): 3337 (NH), 2925 (CH), 1732 (COOCH₃), 1703 (CONH), 1292 (C–O–C). ^1H NMR (400 MHz, CDCl_3): δ (ppm): 7.47 (d, *J* = 9.3 Hz, NH), 5.34, 5.31, 5.24 (pseudo t, *J* = 10.0, Hz in each, CH), 4.95 (t, *J* = 3.9 Hz, CH), 4.93 (d, *J* = 5.5 Hz, CH), 4.80 (d, *J* = 5.5 Hz, CH), 4.28 (dd, *J* = 12.4, 3.5 Hz, CH), 4.10 (ddd, *J* = 10.3, 3.6, 2.1 Hz, CH), 3.95 (dd, *J* = 12.4, 3.5 Hz, CH), 3.77 (s, OCH₃), 2.34, 2.23, 2.13, 1.99 (s, CH₃), 1.52 (s, CH₃), 1.46 (s, CH₃). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 172.2 (CONH), 170.9 (COOCH₃), 170.1, 169.6, 169.3, 169.1 (CO), 114.3 (qt C), 81.4 (CH), 76.5 (CH), 75.1 (CH), 73.1, 72.3, 70.1, 67.9 (CH), 61.8 (CH), 52.9 (OCH₃), 25.5 (CH₃), 25.1 (CH₃), 20.1, 20.0 (3) (CH₃). HRMS-ESI for $\text{C}_{22}\text{H}_{31}\text{NO}_{14}$ Na: $[\text{M} + \text{Na}]^+$ calcd: 556.1745, found: 556.1627. Anal. Calc. For $\text{C}_{22}\text{H}_{31}\text{NO}_{14}$: C,

49.53; H, 5.86; N, 2.63; O, 41.99 Found C, 49.43; H, 5.56; N, 2.78; O, 42.10.

2.4. (2*R*,3*R*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate **5c**. Yield: 65%. Colorless oil $[\alpha]_D^{25} = 27.1$. (IR ν cm⁻¹): 3339 (NH), 2928 (CH), 1736 (COOCH₃), 1700 (CONH), 1290 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.37 (d, $J = 9.3$ Hz, NH), 5.42, 5.40, 5.36 (pseudo t, $J \sim 6.5$ Hz in each, CH), 4.98 (t, $J = 11.9$ Hz, CH), 4.97 (d, $J = 5.6$ Hz, CH), 4.90 (d, $J = 5.6$ Hz, CH), 4.48 (dd, $J = 12.7, 3.4$ Hz, CH), 4.12 (ddd, $J = 10.4, 3.6, 2.1$ Hz, CH), 3.92 (dd, $J = 12.4, 3.5$ Hz, CH), 3.84 (s, OCH₃), 2.11, 2.10, 2.09, 1.99 (s, CH₃), 1.54 (s, CH₃), 1.48 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 171.8 (CONH), 170.2 (COOCH₃), 170.3, 169.5, 169.4, 169.2 (CO), 114.2 (qt C), 81.5 (CH), 76.1 (CH), 75.2 (CH), 73.3, 72.2, 70.1, 67.5 (CH), 61.9 (CH), 52.5 (OCH₃), 26.5 (CH₃), 25.7 (CH₃), 20.4, 19.5 (3) (CH₃). HRMS-ESI for C₂₂H₃₁NO₁₄ Na: [M + Na]⁺ calcd: 556.1745, found: 556.1643. Anal. Calc. For C₂₂H₃₁NO₁₄: C, 49.53; H, 5.86; N, 2.63; O, 41.99 Found C, 49.43; H, 5.56; N, 2.78; O, 42.10.

2.5. (2*R*,3*S*,5*R*,6*R*)-5-Acetamido-2-(acetoxymethyl)-6-((4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)tetrahydro-2*H*-pyran-3,4-diyl Diacetate **5d**. Yield: 67%. Gel like. $[\alpha]_D^{25} = 43.3$. (IR ν cm⁻¹): 3343 (NH), 2948 (CH), 1746 (COOCH₃), 1710 (CONH), 1293 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.69 (d, $J = 9.5$ Hz, NH), 7.57 (d, $J = 9.3$ Hz, NH), 5.43 (t, $J = 10.0$ Hz, 1H), 5.41-5.32 (m, CH), 5.37, 4.99 (pseudo t, $J \sim 10.0$ Hz in each, CH), 4.96 (d, $J = 5.5$ Hz, CH), 4.94 (d, $J = 5.5$ Hz, CH), 4.44 (dd, $J = 12.7, 3.4$ Hz, CH), 4.22 (ddd, $J = 10.4, 3.6, 2.1$ Hz, CH), 3.91 (dd, $J = 12.4, 3.5$ Hz, CH), 3.86 (s, OCH₃), 2.21, 2.20, 2.19, 2.13 (s, CH₃), 1.57 (s, CH₃), 1.49 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 172.8 (CONH), 171.2 (COOCH₃), 170.2, 169.8, 169.5, 169.1 (CO), 114.1 (qt C), 81.8 (CH), 76.1 (CH), 75.3 (CH), 73.2, 72.1, 70.0, 67.8 (CH), 61.4 (CH), 52.2 (OCH₃), 26.2 (CH₃), 25.8 (CH₃), 20.3, 19.3 (3) (CH₃). HRMS-ESI for C₂₂H₃₂N₂O₁₃ Na: [M + Na]⁺ calcd: 555.1904, found: 555.1619. Anal. Calc. For C₂₂H₃₂N₂O₁₃: C, 49.62; H, 6.06; N, 5.26; O, 39.06 Found C, 49.32; H, 6.16; N, 5.21; O, 39.16.

2.6. (2*R*,3*S*,5*R*,6*R*)-5-Acetamido-2-(acetoxymethyl)-6-((4*R*,5*R*)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)tetrahydro-2*H*-pyran-3,4-diyl Diacetate **5e**. Yield: 68%. Gel like. $[\alpha]_D^{25} = 47.1$. (IR ν cm⁻¹): 3341 (NH), 2942 (CH), 1745 (COOCH₃), 1711 (CONH), 1290 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.67 (d, $J = 9.6$ Hz, NH), 7.55 (d, $J = 9.3$ Hz, NH), 5.41 (t, $J = 10.8$ Hz, CH), 5.40 (m, CH), 5.38, 4.97 (pseudo t, $J \sim 6.9$ Hz in each, CH), 4.93 (d, $J = 5.6$ Hz, CH), 4.91 (d, $J = 5.5$ Hz, CH), 4.41 (dd, $J = 12.7, 3.4$ Hz, CH), 4.21 (ddd, $J = 10.4, 3.6, 2.1$ Hz, CH), 3.90 (dd, $J = 12.4, 3.5$ Hz, CH), 3.83 (s, OCH₃), 2.23, 2.22, 2.20, 2.16 (s, CH₃), 1.56 (s, CH₃), 1.46 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 172.2 (CONH), 171.3 (COOCH₃), 170.5, 169.5, 169.2, 169.1 (CO), 113.4 (qt C), 81.6 (CH), 76.4 (CH), 75.2 (CH), 73.4,

72.3, 70.1, 67.3, (CH), 62.4 (CH), 53.2 (OCH₃), 26.2 (CH₃), 25.7 (CH₃), 20.7, 19.5 (3) (CH₃). HRMS-ESI for C₂₂H₃₁NO₁₄ Na: [M + Na]⁺ calcd: 555.1904, found: 555.1719. Anal. Calc. For C₂₂H₃₂N₂O₁₃: C, 49.62; H, 6.06; N, 5.26; O, 39.06 Found C, 49.32; H, 6.16; N, 5.21; O, 39.16.

2.7. General Procedure for the Synthesis of O-Linked Glycopyranosides (**7a-e**). Hydrazinium acetate (1.10 g, 12 mmol) was added to a stirred solution of anomeric mixture of acetylated monosaccharides **1a-e** (3.12 g, 8 mmol) in DMF (40 mL). The reaction mixture was heated at 55°C for 30 min under a nitrogen atmosphere. After completion, the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (40 mL $\times$ 3). The combined organic layers were washed with water and brine (40 $\times$ 2), dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the crude product was used without further purification. To the resulting hemiacetal (1.04 g, 3 mmol), monoester **1** (0.61 g, 3 mmol), EDC (0.74 g, 3 mmol $\times$ 1.3 eq.), and catalytic amount of DMAP were added under nitrogen with CH₂Cl₂ (30 mL). The reaction mixture was stirred for 18 h; the byproduct urea was removed by extraction of the reaction mixture with ethyl acetate or chloroform and water (30 mL $\times$ 3). The crude product was purified by column chromatography using ethyl acetate: n-hexane (3 : 7) as eluent.

2.8. (4*R*,5*R*)-4-Methyl-5-((2*S*,3*R*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7a**. Yield: 72%. Colorless oil $[\alpha]_D^{25} = 26.5$. (IR ν cm⁻¹): 2991 (CH), 1742 (CO), 1366 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 6.45 (d, $J = 4.0$ Hz, 1H, H-1 $^\alpha$), 5.56 (d, $J = 8.0$ Hz, 1H, H-1 $^\beta$), 5.48, 5.45, 4.93 (pseudo t, $J \sim 9.8$ Hz in each, CH), 4.91 (d, $J = 6.3$ Hz, CH), 4.88 (d, $J = 6.3$ Hz, CH), 4.32 (dd, $J = 12.5, 3.6$ Hz, CH), 4.12 (ddd, $J = 10.4, 3.6, 2.1$ Hz, CH), 3.93 (dd, $J = 12.5, 2.1$ Hz, CH), 3.86 (s, OCH₃), 2.19, 2.17, 2.12, 2.04 (s, CH₃), 1.55 (s, CH₃), 1.46 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 172.6 (COOCH₃), 171.2, 169.5, 169.3, 169.0 (CO), 113.4 (qt C), 92.3 (CH), 92.1 (CH), 76.3 (CH), 75.4 (CH), 74.2, 73.3, 72.1, 70.3 (CH), 56.6 (CH), 53.4 (OCH₃), 26.6 (CH₃), 25.9 (CH₃), 20.3 (2), 19.8, 19.3 (CH₃). HRMS-ESI for C₂₂H₃₀O₁₅ Na: [M + Na]⁺ calcd: 557.1585, found: 557.1452. Anal. Calc. For C₂₂H₃₀O₁₅: C, 49.44; H, 5.66; O, 44.90 Found C, 49.39; H, 5.70; O, 44.81.

2.9. (4*R*,5*R*)-4-Methyl-5-((2*S*,3*R*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7b**. Yield: 74%. Colorless gel $[\alpha]_D^{25} = 21.6$. (IR ν cm⁻¹): 2993 (CH), 1744 (CO), 1361 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 6.47 (d, $J = 3.9$ Hz, 1H, H-1 $^\alpha$), 5.53 (d, $J = 8.3$ Hz, 1H, H-1 $^\beta$), 5.47, 4.93 (pseudo t, $J \sim 6.9$ Hz in each, CH), 5.50 (t, $J = 8.9$ Hz, CH), 4.94 (d, $J = 6.3$ Hz, CH), 4.88 (d, $J = 6.3$ Hz, CH), 4.27 (dd, $J = 12.5, 3.6$ Hz, CH), 4.14 (ddd, $J = 10.4, 3.6, 2.1$ Hz, CH), 3.96 (dd, $J = 12.5, 2.1$ Hz, CH), 3.86 (s, OCH₃), 2.19, 2.17, 2.12, 2.04 (s, CH₃), 1.55 (s, CH₃), 1.45 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 172.3 (COOCH₃), 171.7, 169.4, 169.3, 169.1 (CO), 113.3 (qt C), 92.7 (CH), 92.4 (CH), 76.2 (CH), 75.6 (CH), 74.4, 73.5,

72.2, 70.2, (CH), 56.5 (CH), 53.2 (OCH₃), 25.6 (CH₃), 24.9 (CH₃), 20.6 (2), 19.7, 19.5 (CH₃). HRMS-ESI for C₂₂H₃₀O₁₅ Na: [M + Na]⁺ calcd: 557.1585, found: 557.1466. Anal. Calc. For C₂₂H₃₀O₁₅: C, 49.44; H, 5.66; O, 44.90 Found C, 49.39; H, 5.70; O, 44.81.

2.10. (4*R*,5*R*)-4-Methyl-5-((2*R*,3*R*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7c**. Yield: 70%. White foam m.p = 151–153°C. [α]_D²⁵ = 17.3. (IR ν cm⁻¹): 2995 (CH), 1745 (CO), 1336 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 6.42 (d, *J* = 3.7 Hz, 1H, H-1^α), 5.51 (d, *J* = 4.0 Hz, 1H, H-1^β), 5.46, 5.43 (pseudo t, *J* ~ 5.6 Hz in each, CH), 4.96 (t, *J* = 9.8 Hz, CH), 4.93 (d, *J* = 5.3 Hz, CH), 4.89 (d, *J* = 5.3 Hz, CH), 4.26 (dd, *J* = 12.5, 3.6 Hz, CH), 4.13 (ddd, *J* = 10.4, 3.6, 2.1 Hz, CH), 3.93 (dd, *J* = 12.5, 2.1 Hz, CH), 3.76 (s, OCH₃), 2.15, 2.14, 2.12, 2.11 (s, CH₃), 1.56 (s, CH₃), 1.46 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 171.3 (COOCH₃), 170.7, 169.6, 169.3, 169.1 (CO), 113.4 (qt C), 92.4 (CH), 92.1 (CH), 76.1 (CH), 75.6 (CH), 74.2, 73.2, 72.1, 70.5 (CH), 56.7 (CH), 53.3 (OCH₃), 26.6 (CH₃), 25.8 (CH₃), 20.2 (2), 19.8, 19.4 (CH₃). HRMS-ESI for C₂₂H₃₀O₁₅ Na: [M + Na]⁺ calcd: 557.1585, found: 557.1475. Anal. Calc. For C₂₂H₃₀O₁₅: C, 49.44; H, 5.66; O, 44.90 Found C, 49.39; H, 5.70; O, 44.88.

2.11. (4*R*,5*R*)-4-((2*S*,3*R*,5*S*,6*R*)-3-Acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-5-methyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7d**. Yield: 67%. Colorless oil [α]_D²⁵ = 45.0. (IR ν cm⁻¹): 3342 (NH), 2981 (CH), 1739 (CO), 1360 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.87 (d, *J* = 9.5 Hz, NH), 6.49 (d, *J* = 3.7 Hz, 1H, H-1^α), 5.57 (d, *J* = 8.3 Hz, 1H, H-1^β), 5.46 (m, CH), 5.43, 4.96 (pseudo t, *J* ~ 7.4 Hz in each, CH), 4.94 (d, *J* = 6.3 Hz, CH), 4.83 (d, *J* = 6.3 Hz, CH), 4.37 (dd, *J* = 12.5, 3.6 Hz, CH), 4.23 (ddd, *J* = 10.4, 3.6, 2.1 Hz, CH), 3.93 (dd, *J* = 12.5, 2.1 Hz, CH), 3.87 (s, OCH₃), 2.13, 2.11, 2.10, 2.04 (s, CH₃), 1.57 (s, CH₃), 1.49 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm): 171.6 (COOCH₃), 170.3, 169.3, 169.2, 169.0 (CO), 113.6 (qt C), 92.6 (CH), 92.2 (CH), 76.2 (CH), 75.1 (CH), 74.5, 73.3, 72.6, 70.1 (CH), 57.9 (CH), 53.5 (OCH₃), 26.4 (CH₃), 25.6 (CH₃), 20.1 (2), 19.5, 19.2, (CH₃). HRMS-ESI for C₂₂H₃₁NO₁₄ Na: [M + Na]⁺ calcd: 556.1745, found: 556.1614. Anal. Calc. For C₂₂H₃₁NO₁₄: C, 49.53; H, 5.86; N, 2.63; O, 41.99 Found C, 49.55; H, 5.76; N, 2.60; O, 41.90.

2.12. (4*R*,5*R*)-4-((2*S*,3*R*,5*S*,6*R*)-3-Acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-5-methyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7e**. Yield: 63%. Colorless oil [α]_D²⁵ = 33.3. (IR ν cm⁻¹): 3348 (NH), 2990 (CH), 1741 (CO), 1356 (C-O-C). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.86 (d, *J* = 9.7 Hz, NH), 6.52 (d, *J* = 3.9 Hz, 1H, H-1^α), 5.67 (d, *J* = 8.7 Hz, 1H, H-1^β), 5.46 (m, CH), 5.43, 4.96 (pseudo t, *J* ~ 6.0 Hz in each, CH), 4.93 (d, *J* = 5.4 Hz, CH), 4.82 (d, *J* = 5.3 Hz, CH), 4.38 (dd, *J* = 12.5, 3.6 Hz, CH), 4.33 (ddd, *J* = 10.4, 3.6, 2.1 Hz, CH), 3.93 (dd, *J* = 12.5, 2.1 Hz, CH), 3.85 (s, OCH₃), 2.14, 2.12, 2.10, 2.06 (s, CH₃), 1.56 (s, CH₃), 1.46 (s, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ (ppm):

171.4 (COOCH₃), 170.3, 169.5, 169.4, 169.2 (CO), 114.4 (qt C), 93.4 (CH), 92.7 (CH), 76.3 (CH), 75.2 (CH), 74.5, 73.4, 72.6, 70.1 (CH), 58.7 (CH), 53.5 (OCH₃), 26.6 (CH₃), 25.6 (CH₃), 20.1 (2), 19.4, 19.1 (CH₃). HRMS-ESI for C₂₂H₃₁NO₁₄ Na: [M + Na]⁺ calcd: 556.1745, found: 556.1616. Anal. Calc. For C₂₂H₃₁NO₁₄: C, 49.53; H, 5.86; N, 2.63; O, 41.99 Found C, 49.55; H, 5.81; N, 2.60; O, 41.91.

3. Results and Discussion

As outlined in synthetic Schemes 1 and 2, our proposed strategy was to transform five different glycopyranoses to glycopyranosyl amines **4a–e** which would serve as nucleophiles. In sugars, the anomeric position is comparatively more reactive due to the presence of the endocyclic oxygen atom. Owing to its higher reactivity, microwave assisted Kochetkov amination was tried. The Kochetkov amination is used to introduce amino functionality at the anomeric position in unprotected sugars [25]. However, when glucose was reacted under microwave with Kochetkov reagents, that is, ammonium carbonate in DMSO, a mixture of amino and untreated glucose was obtained after prolonged lipophilization. In the case of glucosamine and galactosamine hydrochlorides, which already contain amino functionality, to ensure chemoselectivity in coupling with tartaric acid, a relative long route was adopted involving protecting the entire hydroxyl and amino functionalities on these sugars. Thus per acetylation [26], followed by anomeric bromination [27], azide formation [28] and reduction of azides afforded the target acetylated glycopyranosyl amines **4a–e**.

Following the same coupling procedure with increased time (Table 2), O-linked glycopyranosides **7a–e** were also prepared in 63–74% yields, starting from acetylated monosaccharides **1a–e**, Scheme 3.

It was observed that during per acetylation, a mixture of both α and β anomers is formed in a 3:1 ratio. In the bromination step, the thermodynamically more stable α anomer was obtained exclusively. In the resultant bromo analogue when left for longer time (two days), slight decomposition was observed. Therefore the product was used in the next step immediately. The reaction of bromide **3a** with sodium azide in DMF proceeded in low yield; however under sonication, the azide analogue was produced in excellent yield. The substitution involves inversion of configuration at the anomeric site and thus the α-glycopyranosyl bromide gave the corresponding β-glycopyranosyl azide. The azide intermediates were reduced immediately under catalytic hydrogenation in the next step. The hydrogenation reaction furnished the desired amines in quantitative yield, which were stable when completely dried under vacuum. Once a series of glycopyranosyl amines **4a–e** were generated, the next step was to synthesize the monoester **1** starting from commercially available L-tartaric acid. Both the hydroxyl and carboxyl groups were protected followed by partial hydrolysis with one equivalent of lithium hydroxide; however the yield was variable. By the use of a stronger base sodium hydroxide, the yield was improved. It is important to mention that the formation of monoester **1** from the diester does not depend

SCHEME 1: Reagents and conditions: (a) Ac_2O , pyridine, cat. DMAP, N_2 , r.t., overnight; (b) $HBr/AcOH$ (30%), CH_2Cl_2 , N_2 , r.t., 2 h; (c) NaN_3 , DMF, sonication, r.t., 15 min; (d) Pd/C (10%), H_2 , MeOH, 30 min; (e) EDC, CH_2Cl_2 , cat. DMAP, N_2 , r.t., 18 h.

SCHEME 2: Reagents and conditions: (a) MeOH, H^+ , reflux, 2 h, 2-methoxypropene, CSA, DMF, N_2 , r.t., overnight; (b) NaOH (1 eq), MeOH, r.t., 2 h.

on which ester group of the two is cleaved as both groups are homotopic and therefore monohydrolysis of any of these groups will lead to identical molecules. The same strategy was then used for all of the compounds in the series.

With glycopyranosyl amines and monoester in hand, it was decided to use coupling reagents to form peptides **5a–e**. Different coupling conditions were tried to generate the target amides, Table 1. DCC in the presence of a DMAP catalyst furnished the target amide in low yield. EDC when used in 1.3 equivalents for 12 h afforded the amides in good yield and the reaction was reproducible. Once coupling conditions were optimized, the same coupling conditions were used for the rest of the series to furnish the respective amides, Table 1.

The coupling reaction was high yielding and the compounds were purified by column chromatography. IR spectral data of the compounds **5a–e** exhibited the appearance of characteristic (NH) stretching bands in the range of $3347\text{--}3331\text{ cm}^{-1}$ and disappearance of NH_2 stretching. Two $C=O$ stretching bands ranging from 1742 to 1736 and 1701 to 1692 cm^{-1} were assigned to ester and amide, respectively. 1H NMR spectral data shows characteristic doublets for the NH protons in the range of $7.69\text{--}7.18\text{ ppm}$ with a coupling constant of $9.6\text{--}9.3\text{ Hz}$. The anomeric protons appeared as pseudotriplets in the range of $5.42\text{--}5.36\text{ ppm}$ with coupling constant of $12.2\text{--}6.5\text{ Hz}$ which confirms the formation of the β -anomer. In ^{13}C NMR spectra, peaks ranging from $172.8\text{--}171.2\text{ ppm}$ were assigned to $C=O$ (amide)

and $170.9\text{--}170.2\text{ ppm}$ to $C=O$ (ester), respectively. Elemental analysis of the glycopyranosyl amides **5a–e** confirmed the structures of the compounds. The exact mass of the compounds was confirmed by HRMS-ESI.

The anomeric acetyl group was hydrolyzed selectively using hydrazinium acetate, in DMF [29–31]; the resulting hemiacetal was washed with water and brine and used without further purification. To the crude hemiacetal, monoester was added using EDC as a coupling agent. When compound **6a** was coupled with monoester **1** using 1.3 eq. EDC, DMAP with increased reaction time afforded compound **7a** in 72% yield. Once the reaction conditions were optimized, the same conditions were used for the rest of the series to furnish the respective esters, Table 2.

The synthesized compounds were purified by column chromatography and characterized by spectroscopic techniques. IR spectral data of the compounds **7a–e** showed characteristic ($C=O$) stretching bands ranging from 1745 to 1739 cm^{-1} in addition to $C-O-C$ stretching in $1366\text{--}1356\text{ cm}^{-1}$. The NH stretching bands **7d–e** appeared in $3348\text{--}3342\text{ cm}^{-1}$. 1H NMR spectral data showed doublets **7d–e**, for the NH protons in the range of $7.87\text{--}7.86\text{ ppm}$ with coupling constant of $9.7\text{--}9.5\text{ Hz}$. Both α - and β -anomers were found to be 1:3 except compound **7c** where α and β ratio was 1:1 as confirmed by 1H NMR spectroscopy. The anomeric protons appeared as doublets in the range of $5.67\text{--}5.43\text{ ppm}$ with coupling constant of $8.3\text{--}8.0\text{ Hz}$ for the β -anomers

SCHEME 3: Reagents and conditions: (a) $\text{N}_2\text{H}_4/\text{AcOH}$ (1.5 eq.), DMF, 55°C , N_2 , 30 min; (b) EDC, CH_2Cl_2 , cat. DMAP, N_2 , rt, 18 h.

TABLE 1: Different coupling condition for amide synthesis.

Entry	Starting material		Reagents/conditions	Product (isolated yield%)
1	4a	HA	1.2 eq. DCC, cat. DMAP, CH_2Cl_2 , r.t., 8 h	46
2	4a	HA	1 eq. EDC, cat. DMAP, CH_2Cl_2 r.t., 8 h	36
3	4a	HA	1.1 eq. EDC, cat. DMAP, CH_2Cl_2 r.t., 12 h	70
4	4a	HA	1.3 eq. EDC, cat. DMAP, CH_2Cl_2 r.t., 12 h	76
5	5a	HA	1.3 eq. EDC, cat. DMAP, CH_2Cl_2 r.t., 12 h	61
6	6a	HA	1.3 eq. EDC, cat. DMAP, CH_2Cl_2 r.t., 18 h	79

and in 6.52–6.42 ppm with coupling constant of 4.0–3.7 Hz for the α -anomers, respectively. The coupling constant of anomeric hydrogen for mannopyranosyl **7c** was 4.0 Hz in both the anomers. Finally the synthesis of glycopyranosides was supported by one of the crystal structure for α -anomer, *O*-(2,3,4,6-tetra-*O*-acetyl- α -*D*-mannopyranosyl)-(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7c** by X-ray crystallography (Figure 1).

Crystal system = monoclinic. Torsion angles for compound **7c** are $\text{C5-O1-C1-O13} = -62.9(2)^\circ$, $\text{C5-O1-C1-C2} = 54.9(2)^\circ$, $\text{C15-O13-C1-O1} = -76.4(2)^\circ$, $\text{C15-O13-C1-C2} = 160.28(19)^\circ$, $\text{C13-O8-C2-C3} = -103.8(2)^\circ$, $\text{C13-O8-C2-C1} = 136.00(19)^\circ$, $\text{O1-C1-C2-O8} = 73.3(2)^\circ$, $\text{O13-C1-C2-O8} = -165.60(16)^\circ$, $\text{O1-C1-C2-C3} = -46.9(2)^\circ$, $\text{O13-C1-C2-C3} = 74.2(2)^\circ$, $\text{C11-O6-C3-C4} = -149.8(2)^\circ$, $\text{C11-O6-C3-C2} = 88.7(3)^\circ$, $\text{O8-C2-C3-O6} = 49.8(2)^\circ$, $\text{C1-C2-C3-O6} = 167.17(17)^\circ$, $\text{O8-C2-C3-C4} = -69.0(2)^\circ$, $\text{C1-C2-C3-C4} = 48.4(3)^\circ$, $\text{C9-O4-C4-C3} = -119.6(3)^\circ$, $\text{C9-O4-C4-C5} = 123.8(3)^\circ$, $\text{O6-C3-C4-O4} = 67.2(2)^\circ$, $\text{C2-C3-C4-O4} = -172.34(18)^\circ$, $\text{O6-C3-C4-C5} = -176.24(17)^\circ$, $\text{C2-C3-C4-C5} = -55.8(2)^\circ$, $\text{C1-O1-C5-C6} = 176.43(19)^\circ$, $\text{C1-O1-C5-C4} = -61.4(2)^\circ$, $\text{O4-C4-C5-O1} = 176.08(18)^\circ$, $\text{C3-C4-C5-O1} = 60.3(2)^\circ$, $\text{O4-C4-C5-C6} = -65.2(3)^\circ$, $\text{C3-C4-C5-C6} = 179.0(2)^\circ$, $\text{C7-O2-C6-C5} = -153.1(2)^\circ$, $\text{O1-C5-C6-O2} = -68.2(3)^\circ$, $\text{C4-C5-C6-O2} = 172.1(2)^\circ$, $\text{C6-O2-C7-O3} = 1.9(5)^\circ$, $\text{C6-O2-C7-C8} = -175.2(3)^\circ$, $\text{C4-O4-C9-O5} = -7.1(6)^\circ$, $\text{C4-O4-C9-C10} = 174.8(3)^\circ$, $\text{C3-O6-C11-O7} = 3.7(4)^\circ$, $\text{C3-O6-C11-C12} = -175.5(2)^\circ$, $\text{C2-O8-C13-O9} = 6.4(3)^\circ$, $\text{C2-O8-C13-C14} = -171.9(2)^\circ$, $\text{C1-O13-C15-O12} = -5.2(4)^\circ$, $\text{C1-O13-C15-C16} = 173.8(2)^\circ$, $\text{C19-O15-C16-C15} = 131.8(4)^\circ$, $\text{C19-O15-C16-C17} = 11.0(5)^\circ$, $\text{O12-C15-C16-O15} = -7.6(4)^\circ$, $\text{O13-C15-C16-O15} = 173.5(2)^\circ$, $\text{O12-C15-C16-C17} = 108.9(4)^\circ$, $\text{O13-C15-C16-C17} = -70.1(3)^\circ$, $\text{C19-O14-C17-C18} = 130.6(5)^\circ$, $\text{C19-O14-C17-C16} = 11.5(6)^\circ$, $\text{O15-C16-C17-O14} = -13.4(5)^\circ$, $\text{C15-C16-C17-O14} = -133.2(4)^\circ$, $\text{O15-C16-C17-C18} = -131.8(3)^\circ$, $\text{C15-C16-C17-C18} = 108.4(3)^\circ$, $\text{C22-O11-C18-O10} = -2.3(9)^\circ$, $\text{C22-O11-C18-C17} = 178.0(4)^\circ$, $\text{O14-C17-C18-O10} = -31.2(7)^\circ$, $\text{C16-C17-C18-O10} = 82.9(6)^\circ$, $\text{O14-C17-C18-O11} = 148.5(4)^\circ$, $\text{C16-C17-C18-O11} =$

FIGURE 1: Crystal structure of α -anomer, *O*-(2,3,4,6-tetra-*O*-acetyl- α -*D*-mannopyranosyl)-(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **7c**.

$-97.4(4)^\circ$, $\text{C17-O14-C19-O15} = -5.3(7)^\circ$, $\text{C17-O14-C19-C21} = 109.3(8)^\circ$, $\text{C17-O14-C19-C20} = -123.6(6)^\circ$, $\text{C16-O15-C19-O14} = -4.3(6)^\circ$, $\text{C16-O15-C19-C21} = -121.1(8)^\circ$, and $\text{C16-O15-C19-C20} = 113.7(6)^\circ$.

TABLE 2: Coupling conditions and isolated yield for **5a–e** and **7a–e**.

Entry	Starting material		Reagents/conditions	Product (isolated yield%)	$\alpha : \beta$ ratio	$[\alpha]_D^{25}$
1	4a	HA	1.3 eq. EDC, cat. DMAP, r.t., 12 h	72	0 : 1	12.5
2	4b	HA	1.3 eq. EDC, cat. DMAP, r.t., 12 h	69	0 : 1	13.3
3	4c	HA	1.3 eq. EDC, cat. DMAP, r.t., 12 h	65	0 : 1	27.1
4	4d	HA	1.3 eq. EDC, cat. DMAP, r.t., 12 h	67	0 : 1	43.3
5	4e	HA	1.3 eq. EDC, cat. DMAP, r.t., 12 h	68	0 : 1	47.1
6	6a	HA	1.3 eq. EDC, cat. DMAP, r.t., 18 h	72	1 : 3	26.5
7	6b	HA	1.3 eq. EDC, cat. DMAP, r.t., 18 h	74	1 : 3	21.6
8	6c	HA	1.3 eq. EDC, cat. DMAP, r.t., 18 h	70	1 : 1	17.3
9	6d	HA	1.3 eq. EDC, cat. DMAP, r.t., 18 h	67	1 : 3	45.0
10	6e	HA	1.3 eq. EDC, cat. DMAP, r.t., 18 h	63	1 : 3	33.3

c = 24 mg/2 mL in dichloromethane.

TABLE 3: % inhibition of compounds **5a–e** and **7a–e** against *L. tropica leishmania*.

Compound	<i>L. tropica</i> ^a	Compound	<i>L. tropica</i> ^a
5a	0.65 ± 0.01	7a	1.35 ± 0.04
5b	0.68 ± 0.09	7b	0.73 ± 0.12
5c	0.81 ± 0.16	7c	0.63 ± 0.18
5d	0.68 ± 0.27	7d	0.77 ± 0.08
5e	0.89 ± 0.11	7e	0.66 ± 0.18
	Standard drug IC ₅₀	($\mu\text{g/mL} \pm \text{SD}$)	
	Amphotericin B	0.56 ± 0.20	

^aPercentage inhibition activity: 100 = (nonsignificant; 0.95–0.80 = low; 0.79–0.70 = moderate; 0.69–0.60 = good; below 0.59–0.56 = significant activity).

4. Material and Methods

4.1. Antileishmanial Activity. Antileishmanial activities of compounds **5a–e** and **7a–e** were assayed by Zhai et al.'s method (1999) [32] using a preestablished culture of *Leishmania*. Triple-N media slants were overlaid with 199 media for *leishmanial* growth. NNN medium was prepared by mixing 4 g of agar in 100 mL of distilled water. The mixture was then dissolved and sterilized by autoclaving at 121°C and then allowed to cool to 55°C. 15–20 mL of defibrinated sheep blood was aseptically added to the mixture with gentle rolling with glass beads; 1 ampoule of gentamicin was mixed in blood and mixed with the agar mixture. Slopes of culture medium were prepared by dispensing 2–3 mL of the blood agar mixture into sterile tubes that were then set in a slant position until the agar completely solidified. To prepare 199 medium different constituents were mixed in 1000 mL of distilled water. The pH was adjusted to 7.4 and medium was filtered, sterilized, and kept at 37°C for 24 h to check sterility. Preestablished culture of *Leishmania tropica* KWH23 was inoculated in 199 medium in Triple-N medium slants and incubated at 24°C for 6–7 days and the results are summarized in Table 3.

5. Results

All the synthesized *N*-linked **5a–e** and *O*-linked glycopyranosides **7a–e** were tested for their antileishmanial activity

using *Leishmania tropica* KWH23 promastigotes for *in vitro* screening. The results are shown in Table 3. Compounds **5a**, **5b**, and **5d** showed good activity while the compounds **5c** and **5e** exhibited low activity.

Among the synthesized *O*-linked glycopyranosides **7a–7e**, compounds **7c** and **7e** showed good activity; **7b** and **7d** showed moderate activity. Compound **7a** showed nonsignificant activity.

6. Conclusion

Most of the synthesized compounds **5a–e** and **7a–e** showed moderate to good activities against *Leishmania tropica* KWH23 promastigotes. Compounds **5a**, **5b**, and **5d** were the most active. Among the synthesized compounds, **7a–7e**, **7c**, and **7e** were more active than **7a**, **7b**, and **7d**. Drug resistance has been reported in various species of *Leishmania* against various antileishmanial drugs like antimonials, amphotericin B, pentamidine, miltefosine, and so forth. In this scenario these synthetic compounds may be further explored for research in medicinal chemistry and drug designing. These compounds may prove to be good candidates against leishmaniasis. A number of other new compounds can also be synthesized while following the same *N*- and *O*-acylation synthetic routes. Such compounds can act as valuable glycodrugs as many of the glycosides and their derivatives have been reported to be biologically active compounds.

Conflicts of Interest

The authors confirm that this article's content has no conflicts of interest.

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Supplementary Materials

Supplementary data include NMR (^1H and ^{13}C), IR, and MS spectra of the synthesized compounds (**5a–5d** and **7a–7e**). $^1\text{HNMR}$ of compound **5a**. $^{13}\text{CNMR}$ of compound **5a**. ESI-MS of compound **5a**. FT-IR of compound **5a**. $^1\text{HNMR}$ of compound **5b**. $^{13}\text{CNMR}$ of compound **5b**. ESI-MS of compound **5b**. $^1\text{HNMR}$ of compound **5c**. $^{13}\text{CNMR}$ of compound **5c**. $^1\text{HNMR}$ of compound **5d**. $^{13}\text{CNMR}$ of compound **5d**. ESI-MS of compound **5d**. $^1\text{HNMR}$ of compound **7a**. $^{13}\text{CNMR}$ of compound **7a**. ESI-MS of compound **7a**. $^1\text{HNMR}$ of compound **7b**. $^{13}\text{CNMR}$ of compound **7b**. ESI-MS of compound **7b**. ESI-MS of compound **7b** backup. $^1\text{HNMR}$ of compound **7c**, new. $^1\text{HNMR}$ of compound **7c**. $^{13}\text{CNMR}$ of compound **7c**. $^{13}\text{CNMR}$ of compound **7b**, new. ESI-MS of compound **7c**. Mass analysis of compound **7c**. $^1\text{HNMR}$ of compound **7d**. $^{13}\text{CNMR}$ of compound **7d**. ESI-MS of compound **7d**. Mass analysis of compound **7d**. $^1\text{HNMR}$ of compound **7e**. $^{13}\text{CNMR}$ of compound **7e**. (Supplementary Materials)

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