



Synthesis of Novel Glycosyl Imidazolidine-2,4,5-Trione Derivatives

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A series of glycosyl imidazolidine-2,4,5-trione derivatives were achieved by condensing per-*O*-acetylated glucosamine, triphosgene, amines and oxalyl chloride. The convenient and efficient method afforded the desired products with good to excellent yields and the described compounds were prepared for the first time in this work. Satisfactory IR, ¹H NMR, ¹³C NMR, ESI-MS spectra were obtained for all compounds described.

Keywords: Per-*O*-acetylated glucosamine, Imidazolidine-2,4,5-trione, Glycosyl imidazolidine-2,4,5-trione derivatives.

INTRODUCTION

Imidazolidine-2,4,5-trione and their derivatives are important heterocyclic compounds in organic and medicinal chemistry due to their broad spectrum of biological activity including antitumor¹, inhibition of aldose reductase², suppression of thymidine phosphorylase³. Even some special derivatives of imidazolidine-2,4,5-trione showed an interesting property as highly thermally stable polymers⁴ containing the unit of imidazolidine-2,4,5-trione with improved chemical resistance in organic solvents. Simultaneously, D-glucosamine and its N-substituted derivatives are found in numerous biologically active molecules⁵ such as cell surface N-glycoproteins, proteoglycans, glycosylphosphatidylinositol (GPI) anchors, glycosphingolipids, lipopolysaccharides and chitin/chitosan⁶. Since derivatives of imidazolidine-2,4,5-trione and D-glucosamine and its N-substituted derivatives showed diverse ranges of biological properties, compounds containing both imidazolidine-2,4,5-trione and glycosyl would provide novel leading structures for medicinal research. A careful literature survey revealed that imidazolidine-2,4,5-trione and its derivatives have rarely been studied due to synthetic difficulty and low yield in the past. To the best of our knowledge, the synthesis of compounds containing both imidazolidine-2,4,5-trione and glycosyl have not been investigated. As a part of our program directed at the design and synthesis of carbonyl compounds⁷, here we report a convenient and practical protocol for the synthesis of glycosyl imidazolidine-2,4,5-trione derivatives *via* the reactions of per-*O*-acetylated glucosamine, triphosgene, amines and oxalyl chloride under basic condition (**Scheme-I**).

These novel compounds contained with specific structural units were expected to exhibit biological activity in the future. The structures of products have also been fully characterized by IR, ¹H NMR ¹³C NMR and ESI-MS.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Oxalyl chloride was purchased from Alpha Aesar Chemicals Co. Ltd. (Tianjin, China) while triphosgene and amines were purchased from AladdinTM Chemicals Co. Ltd. (Shanghai, China). Melting points are uncorrected. IR spectra were taken on a FTIR-Tensor 27 spectrometer in KBr pellets and reported in cm⁻¹. ¹H NMR (¹³C NMR) spectra were measured on a Bruker ACF 300 MHz spectrometer using TMS as an internal standard and CDCl₃-*d*₆ as solvent. J values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS (ESI) was determined by using Agilent 6540 Q-TOF mass spectrometer.

Procedure for reaction of 1 with 2: To a vigorously stirred solution of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochloride **1** (1.8 mmol) in CH₂Cl₂ (18 mL) and saturated aqueous solution of NaHCO₃ (18 mL) was added in triphosgene (0.66 mmol) in an ice bath to composite glycosyl isocyanate. After this period, the TLC analysis of the mixture showed the reaction to be completed. Then the organic layer was separated, washed with water, dried over MgSO₄ and filtered. At last, amines **2** (2 mmol) in CH₂Cl₂ was slowly added dropwise to the separated organic layer at room temperature. Determining the reaction of raw materials completely, removing

the solvent, crude products isolated by filtration was purified to obtain glycosyl ureas by column chromatography (silica gel 200-300 mesh, petroleum ether/EtOAc = 2:1).

General procedure for synthesis of glycosyl imidazolidine-2,4,5-triones (3): A solution of glycosyl ureas obtained from the reaction of compounds **1** with **2** was stirred in CH₂Cl₂ was slowly added dropwise to the mixture of oxalyl chloride in CH₂Cl₂, then refluxing. When the TLC analysis of the mixture showed the reaction to be completed, removing the solvent, purifying crude products by column chromatography (silica gel 200-300 mesh, petroleum ether/EtOAc = 3:1), giving the desired products **3**.

1-Phenyl-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3a): White solid, m.p. 98-100 °C; IR (KBr, ν_{max}, cm⁻¹): 2964, 1732, 1597, 1502, 1403, 1216, 1038; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.62-7.43 (m, 2H, ArH), 7.37 (d, *J* = 7.9 Hz, 2H, ArH), 6.15 (d, *J* = 8.8 Hz, 1H, H1), 5.84-5.61 (m, 1H, H3), 5.01 (t, *J* = 9.4 Hz, 1H, H4), 4.26 (ddd, *J* = 19.6, 17.9, 10.4 Hz, 3H, H5, H6, H6'), 4.02 (dd, *J* = 12.3, 4.5 Hz, 1H, H2), 2 (4s, 12H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 171.24, 170.95, 169.66, 169.21, 156.28, 154.76, 152.33, 129.75, 126.26, 89.78, 72.70, 71.02, 67.75, 61.48, 55.38, 21.23, 21.04, 20.90, 20.84, 14.51; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂Na: 543.1221, found 543.1226.

1-(4-Chlorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3b): Yellow solid, m.p. 95-96 °C; IR (KBr, ν_{max}, cm⁻¹): 2958, 1746, 1597, 1535, 1496, 1405, 1221, 1077; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.63 (d, *J* = 8.7 Hz, 2H, ArH), 7.39 (d, *J* = 8.7 Hz, 2H, ArH), 6.11 (d, *J* = 8.9 Hz, 1H, H1), 5.73 (m, 1H, H3), 4.99 (m, 1H, H4), 4.36-4.08 (m, 3H, H5, H6, H6'), 4.01 (d, *J* = 11.1 Hz, 1H, H2), 1.97 (4s, 12H, Ac); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 170.82, 170.53, 170.11, 169.59, 156.95, 152.97, 134.20, 130.08, 129.09, 89.20, 72.21, 69.21, 62.02, 53.99, 21.81, 21.60, 21.28, 21.20; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂NaCl: 577.0832, found 577.0833.

1-(3-Chlorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3c): Yellow solid, m.p. 92-94 °C; IR (KBr, ν_{max}, cm⁻¹): 2960, 1748, 1594, 1484, 1402, 1219, 1078; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.67-7.54 (m, 2H, ArH), 7.45 (s, 1H, ArH), 7.41-7.29 (m, 1H, ArH), 6.12 (d, *J* = 8.9 Hz, 1H, H1), 5.76 (m, 1H, H3), 5.01 (m, 1H, H4), 4.39-4.12 (m, 3H, H5, H6, H6'), 4.03 (d, *J* = 11 Hz, 1H, H2), 1.99 (4s, 12H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 171.44, 171.01, 169.65, 169.25, 155.95, 154.33, 135.36, 130.79, 129.97, 126.40, 124.35, 89.81, 72.80, 71.19, 67.61, 61.47, 55.56, 21.30, 21.11, 20.96, 20.90; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂NaCl: 577.0832, found 577.0834.

1-(2-Chlorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3d): Yellow solid, m.p. 93-95 °C; IR (KBr, ν_{max}, cm⁻¹): 2960, 1746, 1593, 1493, 1404, 1217, 1037; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.80-7.66 (m, 1H, ArH), 7.66-7.45 (m, 3H, ArH), 6.26-6.15 (d, *J* = 8.9 Hz, 1H, H1), 5.78-5.63 (m, 1H, H3), 5.14-4.95 (m, 1H, H4), 4.41-4.29 (m, 1H, H6), 4.29-4.15 (m, 2H, H5, H6'), 4.10-3.96 (m, 1H, H2), 2.10-1.87 (m, 12H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 170.99, 169.82, 169.69, 156.04, 154.33,

151.39, 132.77 132.23, 130.96, 130.42, 128.49, 127.37, 89.48, 72.76, 70.45, 67.90, 61.48, 55.32, 21.16, 21.08, 20.93, 20.86; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂NaCl: 577.0832, found 577.0830.

1-(4-Bromophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3e): Yellow solid, m.p. 100-102 °C; IR (KBr, ν_{max}, cm⁻¹): 2967, 1746, 1606, 1513, 1409, 1224, 1037; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.78 (d, *J* = 8.6 Hz, 2H, ArH), 7.34 (d, *J* = 8.6 Hz, 2H, ArH), 6.12 (d, *J* = 8.9 Hz, 1H, H1), 5.91-5.51 (m, 1H, H3), 5.01 (m, 1H, H4), 4.42-4.11 (m, 3H, H5, H6, H6'), 4.03 (d, *J* = 11.4 Hz, 1H, H2), 1.99 (4s, 12H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 171.42, 170.99, 169.64, 169.24, 156.01, 154.39, 133.01, 128.83, 127.68, 123.64, 89.81, 72.80, 71.17, 67.63, 61.47, 55.52, 21.28, 21.09, 20.95, 20.89; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂NaBr: 621.0327, found 621.0330.

1-(4-Fluorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3f): White solid, m.p. 98-100 °C; IR (KBr, ν_{max}, cm⁻¹): 2960, 1748, 1596, 1503, 1404, 1218, 1038; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.41 (d, *J* = 6.8 Hz, 4H, ArH), 6.13 (d, *J* = 8.9 Hz, 1H, H1), 5.75 (m, 1H, H3), 5.01 (m, 1H, H4), 4.40-4.11 (m, 3H, H5, H6, H6'), 4.10-3.91 (m, 1H, H2), 1.99 (4s, 12H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 171.37, 170.98, 169.65, 169.26, 164.54, 161.22, 156.15, 154.69, 152.23, 128.32, 125.67, 117.06, 116.76, 89.79, 72.74, 71.12, 67.66, 61.46, 55.46, 21.24, 21.04, 20.91, 20.85; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₄N₂O₁₂NaF: 561.1127, found 561.1131.

1-(2,4-Dichlorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3g): Pale yellow solid, m.p. 93-95 °C; IR (KBr, ν_{max}, cm⁻¹): 2961, 1743, 1610, 1516, 1407, 1218, 1035; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.95 (m, 1H, ArH), 7.75-7.62 (m, 1H, ArH), 7.60-7.45 (m, 1H, ArH), 6.25 (d, *J* = 8.9 Hz, 0.56 H, H1), 6.12 (d, *J* = 8.5 Hz, 0.44 H, H1), 5.73 (m, 1H, H3), 5.16-4.90 (m, 1H, H4), 4.41-4.30 (m, 1H, H6), 4.23 (m, 2H, H5, H6'), 4.03 (d, *J* = 11.7 Hz, 1H, H2), 2.16-1.75 (m, 12 H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 170.97, 169.68, 155.77, 153.98, 151.15, 137.80, 133.74, 131.28, 131.10, 131, 130.92, 128.88, 125.97, 89.52, 72.89, 70.60, 68, 67.66, 61.49, 55.55, 21.16, 21.08, 20.93, 20.87; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₂N₂O₁₂NaCl₂: 611.0442, found 611.0446.

1-(3-Chloro-4-fluorophenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3h): Pale white solid, m.p. 92-94 °C; IR (KBr, ν_{max}, cm⁻¹): 2960, 1750, 1587, 1498, 1406, 1216, 1050; ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 7.75-7.51 (m, 2H, ArH), 7.40 (m, 1H, ArH), 6.10 (d, *J* = 8.9 Hz, 1H, H1), 5.74 (m, 1H, H3), 4.99 (m, 1H, H4), 4.40-4.10 (m, 3H, H5, H6, H6'), 4.01 (d, *J* = 10.8 Hz, 1H, H2), 2.09-1.82 (4s, 12 H, Ac); ¹³C NMR (CDCl₃-*d*₆, 75 MHz) δ: 171.56, 171.03, 169.64, 169.28, 160.20, 156.85, 155.86, 154.32, 151.89, 128.74, 126.28, 122.61, 122.36, 117.87, 117.57, 89.82, 72.83, 71.22, 67.61, 61.50, 55.63, 21.27, 21.07, 20.93, 20.88; ESI-MS (*m/z*): Calcd. for [M + Na]⁺ C₂₃H₂₂N₂O₁₂NaClF: 595.0738, found 595.0742.

1-(*p*-Tolyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3i): White solid, m.p. 89-91 °C; IR (KBr, ν_{max}, cm⁻¹): 2960, 1738, 1517,

1406, 1217, 1038; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 7.35 (d, $J = 8.3$ Hz, 2H, ArH), 7.24 (d, $J = 8.3$ Hz, 2H, ArH), 6.14 (d, $J = 8.9$ Hz, 1H, H1), 5.89-5.50 (m, 1H, H3), 5.01 (m, 1H, H4), 4.25 (m, 3H, H5, H6, H6'), 4.11-3.94 (m, 1H, H2), 2.36 (s, 3H, CH₃), 1.99 (4s, 12H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.19, 170.93, 169.67, 169.22, 156.39, 154.92, 152.47, 139.95, 130.36, 127.20, 126.13, 89.78, 72.63, 70.98, 67.75, 61.43, 55.31, 21.53, 21.21, 21.02, 20.88, 20.82; ESI-MS (m/z): calcd for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{12}\text{Na}$: 557.1378, found 557.1382.

1-(*m*-Tolyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3j): White solid, m.p. 90-91 °C; IR (KBr, ν_{max} , cm^{-1}): 2960, 1738, 1610, 1494, 1403, 1218, 1038; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 7.43 (m, 1H, ArH), 7.30 (d, $J = 7.4$ Hz, 1H, ArH), 7.16 (d, $J = 8$ Hz, 2H, ArH), 6.14 (d, $J = 8.8$ Hz, 1H, H1), 5.74 (m, 1H, H3), 5.01 (m, 1H, H4), 4.37-4.12 (m, 3H, H5, H6, H6'), 4.09-3.92 (m, 1H, H2), 2.37 (s, 3H, CH₃), 2 (4s, 12H, Ac). ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.24, 170.94, 169.65, 169.17, 156.33, 154.83, 152.37, 139.98, 130.57, 129.58, 126.80, 123.37, 89.82, 72.71, 71.06, 67.75, 61.48, 55.38, 21.64, 21.22, 21.03, 20.89, 20.83; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{12}\text{Na}$: 557.1378, found 557.1381.

1-(*o*-Tolyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3k): White solid, m.p. 90-92 °C; IR (KBr, ν_{max} , cm^{-1}): 2961, 1744, 1498, 1403, 1218, 1038; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 7.34 (m, 4H, ArH), 6.23 (d, $J = 9$ Hz, 1H, H1), 6.06 (d, $J = 8.1$ Hz, 1H, H1), 5.88-5.73 (m, 1H, H3), 5.72-5.56 (m, 1H, H3), 5.02 (m, 1H, H4), 4.27 (m, 3H, H5, H6, H6'), 4.11-3.96 (m, 1H, H2), 2.16 (d, $J = 13.4$ Hz, 3H, CH₃), 2.09-1.87 (m, 12H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 170.99, 169.65, 169.22, 169.09, 156.48, 154.87, 152.23, 136.32, 131.81, 130.81, 128.38, 127.51, 89.79, 72.80, 70.99, 67.83, 67.65, 61.51, 55.55, 21.18, 21.06, 20.92, 20.85, 17.86; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{12}\text{Na}$: 557.1378, found 557.1382.

1-(4-Methoxyphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3l): White solid, m.p. 89-91 °C; IR (KBr, ν_{max} , cm^{-1}): 2961, 1731, 1608, 1497, 1397, 1212, 1036; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 7.27 (d, $J = 8.8$ Hz, 2H, ArH), 7.09 (d, $J = 8.9$ Hz, 2H, ArH), 6.14 (d, $J = 8.8$ Hz, 1H, H1), 5.84-5.52 (m, 1H, H3), 5.01 (m, 1H, H4), 4.38-4.11 (m, 3H, H5, H6, H6'), 4.03 (d, $J = 11.2$ Hz, 1H, H2), 3.80 (s, 3H, CH₃O), 2 (4s, 12H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.29, 170.98, 169.65, 169.15, 160.43, 156.38, 155.02, 127.73, 122.22, 115.03, 89.84, 72.79, 71.15, 67.72, 61.50, 55.91, 55.40, 21.26, 21.07, 20.93, 20.87; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{13}\text{Na}$: 573.1327, found 573.1332.

1-(3-Methoxyphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3m): White solid, m.p. 91-93 °C; IR (KBr, ν_{max} , cm^{-1}): 2958, 1746, 1603, 1508, 1467, 1405, 1216, 1040; ^1H NMR (CDCl₃- d_6 , 300 MHz) δ : 7.41 (t, 1H, ArH), 7.05-6.84 (m, 3H, ArH), 6.44 (d, $J = 8.8$ Hz, 1H, H1), 5.70 (t, 1H, H3), 5.25 (t, 1H, H4), 4.50-4.26 (m, 2H, H6, 5), 4.13 (d, $J = 12.2$ Hz, 1H, H6'), 3.97 (d, $J = 8.1$ Hz, 1H, H2), 3.84 (s, 3H, CH₃O), 2.21-1.89 (4s, 12 H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.24, 170.96, 169.67, 169.21, 160.48, 156.24, 154.71, 152.23,

130.63, 118.38, 115.30, 112.25, 89.77, 72.68, 71.03, 67.74, 61.47, 55.83, 55.37, 21.23, 21.04, 20.90, 20.84; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{13}\text{Na}$: 573.1327, found 573.1332.

1-(2-Methoxyphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3n): White solid, m.p. 90-93 °C; IR (KBr, ν_{max} , cm^{-1}): 2946, 1745, 1600, 1508, 1465, 1404, 1221, 1039; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 7.52 (dd, $J = 10.9, 4.9$ Hz, 1H, ArH), 7.27 (m, 2H, ArH), 7.14-7.02 (m, 1H, ArH), 6.27 (d, $J = 8.9$ Hz, 0.58H, H1), 6.20 (d, $J = 8.9$ Hz, 0.40 H, H1), 5.80-5.62 (m, 1H, H3), 5.13-4.97 (m, 1H, H4), 4.38-4.12 (m, 3H, H5, H6, H6'), 4.04 (m, 1H, H2), 3.77 (s, 3H, CH₃O), 2.13-1.90 (m, 12H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 170.98, 169.72, 168.81, 156.39, 155.06, 151.96, 132.19, 129.69, 129.53, 121.39, 118.01, 112.65, 89.62, 72.97, 70.53, 68.24, 67.88, 61.58, 56.31, 55.15, 21.15, 21.08, 20.94, 20.85, 20.79; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_{13}\text{Na}$: 573.1327, found 573.1331.

1-(3,4,5-Trimethoxyphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3o): White solid, m.p. 99-101 °C; IR (KBr, ν_{max} , cm^{-1}): 2946, 2837, 1742, 1600, 1508, 1465, 1406, 1232, 1038; ^1H NMR (CDCl₃- d_6 , 300 MHz) δ : 6.63 (s, 2H, ArH), 6.44 (d, $J = 8.7$ Hz, 1H, H1), 5.70 (t, 1H, H3), 5.26 (dd, $J = 16.3, 6.5$ Hz, 1H, H4), 4.48-4.27 (m, 2H, H5, H6), 4.13 (d, $J = 12.6$ Hz, 1H, H6'), 4.02-3.76 (m, 10 H, H2, 3CH₃O), 2.08 (4s, 12 H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.39, 170.95, 169.60, 169.11, 156.14, 154.81, 153.94, 152.31, 139.02, 125.12, 104, 89.85, 72.87, 71.26, 67.69, 61.53, 61.24, 56.63, 55.54, 21.24, 21.05, 20.91; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_{15}\text{Na}$: 633.1538, found 633.1537.

1-(2,5-Dimethoxyphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3p): White solid, m.p. 97-99 °C; IR (KBr, ν_{max} , cm^{-1}): 2961, 2842, 1747, 1593, 1513, 1465, 1400, 1228, 1038; ^1H NMR (CDCl₃- d_6 , 300 MHz) δ : 7.06-6.89 (m, 2H, ArH), 6.80 (m, 1H, ArH), 6.41 (d, $J = 8.8$ Hz, 1H, H1), 5.88-5.61 (m, 1H, H3), 5.21 (m, 1H, H4), 4.51-4.25 (m, 2H, H5, H6), 4.11 (m, 1H, H6'), 4.03-3.88 (m, 1H, H2), 3.83-3.70 (m, 6H, 2CH₃O), 2.19-1.91 (m, 12 H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 170.94, 169.74, 168.86, 156.36, 154.98, 153.89, 151.86 (s, 1H), 149.19, 118.33, 117.19, 115.19, 113.60, 89.56, 72.85, 70.46, 68.26, 67.89, 61.54, 56.78, 56.20, 55.12 (s, 2H), 21.12, 21.04, 20.90, 20.82, 20.75; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_{14}\text{Na}$: 603.1433, found 603.1437.

1-(Naphthalen-1-yl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3q): Yellow solid, m.p. 114-116 °C; IR (KBr, ν_{max} , cm^{-1}): 2961, 1748, 1600, 1512, 1470, 1406, 1223, 1037; ^1H NMR (DMSO- d_6 , 300 MHz) δ : 8.23-7.89 (m, 3H, ArH), 7.72-7.49 (m, 4H, ArH), 6.24 (d, $J = 8.8$ Hz, 1H, H1), 5.93-5.82 (m, 1H, H3), 5.72 (m, 1H, H3), 5.01 (m, 1H, H4), 4.43-4.11 (m, 3H, H5, H6, H6'), 4.03 (d, $J = 11.8$ Hz, 1H, H2), 2.12-1.91 (m, 12H, Ac); ^{13}C NMR (CDCl₃- d_6 , 75 MHz) δ : 171.69, 171.36, 170.98, 169.65, 169.41, 169.19, 156.59, 156.53, 155.56, 155.38, 134.73, 131.42, 129.79, 129.07, 128.15, 127.33, 127.07, 126.93, 126.03, 125.66, 121.84, 90.08, 72.79, 71.41, 67.76, 67.59, 61.51, 55.78, 21.30, 21.08, 21.01, 20.94; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+ \text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_{12}\text{Na}$: 593.1378, found 593.1383.

1-[4-(Ethoxyl)phenyl]-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3r): White solid, m.p. 95-97 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 2982, 1743, 1609, 1514, 1478, 1408, 1217, 1041; ^1H NMR (CDCl_3 - d_6 , 300 MHz) δ : 7.28 (d, J = 9.6 Hz, 2H, ArH), 6.98 (m, 2H, ArH), 6.40 (d, J = 8.8 Hz, H1), 5.77-5.61 (m, H3), 5.24 (m, H4), 4.38 (m, 2H, H5, H6), 4.14-3.90 (m, 4H, H6', H2, CH₂), 2.10 (d, J = 2.2 Hz, 6H, Ac), 2.05 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.42 (m, 3H, CH₃); ^{13}C NMR (CDCl_3 - d_6 , 75 MHz) δ : 171.29, 170.96, 169.60, 169.05, 159.85, 154.98, 127.66, 121.99, 115.51, 89.89, 72.92, 71.23, 67.75, 64.18, 61.57, 55.47, 21.25, 21.07, 20.93, 20.86, 15.03; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+$ $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_{13}\text{Na}$: 587.1484, found 587.1488.

1-(3-Chloro-4-methylphenyl)-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-trione (3s): Yellow solid, m.p. 106-108 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 2960, 1747, 1574, 1500, 1407, 1217, 1052; ^1H NMR (CDCl_3 - d_6 , 300 MHz) δ : 7.43 (s, 1H, ArH), 7.36 (d, J = 8.2 Hz, 1H, ArH), 7.31-7.15 (m, 1H, ArH), 6.40 (d, J = 8.8 Hz, 1H, H1), 5.78-5.54 (m, 1H, H3), 5.37-5.07 (m, 1H, H4), 4.38 (m, 2H, H5, H6), 4.16-4.04 (m, 1H, H6'), 3.97 (d, J = 8.2 Hz, 1H, H2), 2.42 (s, 3H, CH₃), 2.11 (d, J = 2.4 Hz, 6H, Ac), 2.06 (s, 3H, Ac), 2 (s, 3H, Ac); ^{13}C NMR (CDCl_3 - d_6 , 75 MHz) δ : 171.42, 170.96, 169.58, 169.08, 155.99, 154.43, 138.21, 135.34, 131.82, 126.72, 124.35, 89.84, 72.94, 71.27, 67.69, 61.55, 55.61, 21.26, 21.08, 20.93, 20.86, 20.30; ESI-MS (m/z): Calcd. for $[\text{M} + \text{Na}]^+$ $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_{12}\text{NaCl}$: 591.0988, found 591.0993.

RESULTS AND DISCUSSION

On the basis of our previous experience, glycosyl imidazolidine-2,4,5-triones were synthesized by treatment of per-*O*-acetylated glucosamine **1** and excess of triphosgene initially, then processed with amines **2** to composite glycosyl isocyanate⁸ and the reaction was carried out in dichloromethane at room temperature. After that, the glycosyl isocyanate purified for closed-loop reaction with oxalyl chloride in dichloromethane at refluxing. Furthermore, the best reaction conditions are summarized in **Scheme-I**.

To investigate the scope of this reaction, various glycosyl imidazolidine-2,4,5-trione derivatives were employed under the optimized reaction conditions and a series of new 1-substituted

-3-(1,3,4,6-tetra-*O*-acetyl-2-deoxy- β -D-glucopyranos-2-yl)imidazolidine-2,4,5-triones were synthesized in good to excellent yields. The results are given in Table-1.

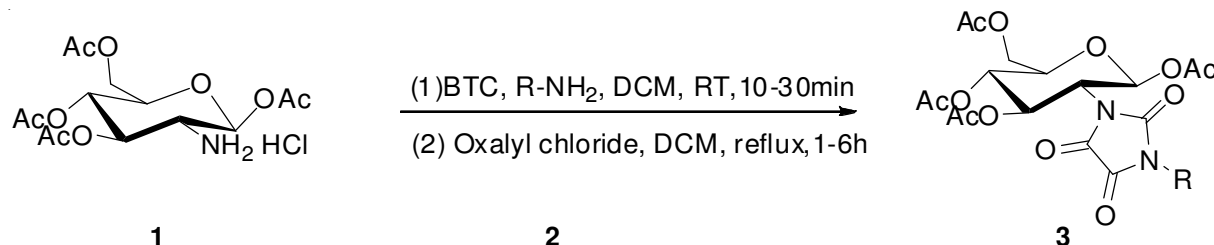
TABLE-1
CLOSED-LOOP REACTION WITH
OXALYL CHLORIDE TO SYNTHESIZE **3**

Compound	R	Yield (%)
3a	C ₆ H ₅	85
3b	4-Cl-C ₆ H ₄	87
3c	3-Cl-C ₆ H ₄	82
3d	2-Cl-C ₆ H ₄	77
3e	4-Br-C ₆ H ₄	80
3f	4-F-C ₆ H ₄	65
3g	2,4-di-Cl-C ₆ H ₃	75
3h	3-Cl-4-F-C ₆ H ₃	59
3i	4-Me-C ₆ H ₄	86
3j	3-Me-C ₆ H ₄	85
3k	2-Me-C ₆ H ₄	81
3l	4-CH ₃ O-C ₆ H ₄	86
3m	3-CH ₃ O-C ₆ H ₄	88
3n	2-CH ₃ O-C ₆ H ₄	73
3o	3,4,5-tri-MeO-C ₆ H ₂	80
3p	3,5-di-MeO-C ₆ H ₃	76
3q	Naphthalen-1-yl	80
3r	4-C ₂ H ₅ O-C ₆ H ₄	86
3s	3-Cl-4-Me-C ₆ H ₃	83

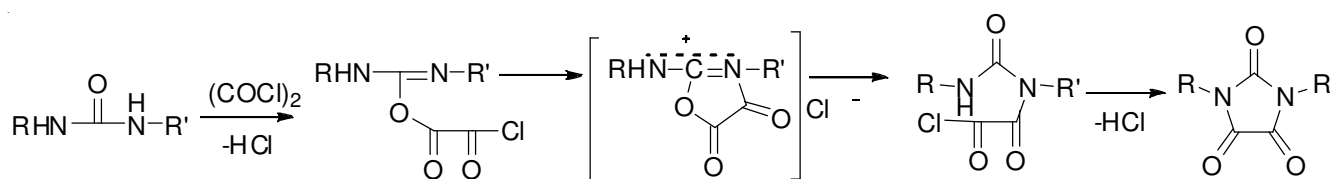
As shown in Table-1, we premeditated amines with electron-withdrawing groups or electron-donating groups. The reaction was detected by means of the TLC analysis of the mixture and determined by the reaction of raw materials completely. It is found that all amines containing either electron-withdrawing group, electron-donating group or can be smoothly converted to the desired products with satisfactory yields under the analogous conditions. It is noteworthy that the present reaction was accomplished under mild conditions and the method is operationally simple with satisfactory yields. For a more in-depth study of the reaction, a plausible mechanistic pathway⁹ to products **3** is illustrated in **Scheme-II**.

Conclusion

In summary, we report a rapid and efficient protocol to synthesize a series of novel glycosyl imidazolidine-2,4,5-



Scheme-I: Synthesis of the compounds **3**



Scheme-II: Proposed mechanism for products **3**

triones in good to excellent yields. Additionally the J values of the pyranose ring are indicative of the preponderance of the 4C_1 conformations in solution. Also, the β configuration of the products was verified by the $J_{1,2}$ values around 8-9 Hz. Given the fact that imidazolidine-2,4,5-triones have exhibited biological activity, we anticipate that these new compounds described in the present report would be valuable in further pharmaceutical research.

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REFERENCES

1. E.J. Yu, Y. Lee, S.Y. Rha, T.S. Kim, H.C. Chung, B.K. Oh, W.I. Yang, S.H. Noh and H.-C. Jeung, *Mol. Cancer Res.*, **6**, 1554 (2008).
2. A. Ishii, T. Kotani, Y. Nagaki, Y. Shibayama, Y. Toyomaki, N. Okukado, K. Ienaga and K. Okamoto, *J. Med. Chem.*, **39**, 1924 (1996).
3. M. Rajabi, D. Mansell, S. Freeman and R.A. Bryce, *Eur. J. Med. Chem.*, **46**, 1165 (2011).
4. C. Gaina, V. Gaina and V. Cozan, *Eur. Polym. J.*, **37**, 79 (2001).
5. (a) N.S. Gandhi and R.L. Mancera, *Chem. Biol. Drug Des.*, **72**, 455 (2008); (b) M.G. Paulick and C.R. Bertozzi, *Biochemistry*, **47**, 6991 (2008); (c) L.-X. Wang and W. Huang, *Curr. Opin. Chem. Biol.*, **13**, 592 (2009); (d) C.E. Bryant, D.R. Spring, M. Gangloff and N.J. Gay, *Nat. Rev. Microbiol.*, **8**, 8 (2010); (e) S. Taube, M. Jiang and C.E. Wobus, *Viruses*, **2**, 1011 (2010); (f) L. Liu, C.S. Bennett and C.H. Wong, *Chem. Commun.*, **21**, (2006).
6. C. Tao, F. Liu, W. Liu, Y. Zhu, Y. Li, X. Liu and J. Zhao, *Tetrahedron Lett.*, **53**, 7093 (2012).
7. (a) W.W. Liu, Y.Q. Zhao, Y.Q. Pu, R.B. Xu and H.W. Hu, *Chin. J. Org. Chem.*, **25**, 838 (2005); (b) W.W. Liu, Y.Q. Zhao, R.B. Xu, L.J. Tang and H.W. Hu, *Chin. J. Chem.*, **24**, 1472 (2006); (c) W.W. Liu, L.J. Tang, Y.X. Zeng, L. Wang, Y.Q. Zhao, K.Q. Chen and Z.E. Lu, *Chin. J. Org. Chem.*, **27**, 1285 (2007); (d) W. Liu, Y. Zhao, S. Tu, T. He and H. Hu, *J. Heterocycl. Chem.*, **45**, 1311 (2008); (e) W.W. Liu, C.Z. Tao, L.J. Tang, J. Li, Y. Jin, Y.Q. Zhao and H.W. Hu, *J. Heterocycl. Chem.*, **48**, 361 (2011).
8. (a) Ó. López, S. Maza, I. Maya, J. Fuentes and J.G. Fernández-Bolaños, *Tetrahedron*, **61**, 9058 (2005); (b) Ó. López, E. Zafra, I. Maya, J. Fuentes, M.J. Diáñez, M.D. Estrada, S. Pérez-Garrido and J.G. Fernández-Bolaños, *Tetrahedron*, **64**, 11789 (2008); (c) O. López, S. Maza, V. Ulgar, I. Maya and J.G. Fernández-Bolaños, *Tetrahedron*, **65**, 2556 (2009); (d) I. Maya, Ó. López, S. Maza, J.G. Fernández-Bolaños and J. Fuentes, *Tetrahedron Lett.*, **44**, 8539 (2003); (e) P.F. Wdey, D.L. McMichael, J.M. Koert and V.H. Wiley, *J. Antibiotics*, **29**, 1218 (1976); (f) J.C. Jochims and A. Seeliger, *Tetrahedron*, **21**, 2611 (1965).
9. H. Ulrich and A.A.R. Sayigh, *J. Org. Chem.*, **30**, 2781 (1965).