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Synthesis of 1′-β-D-glucopyranosyl-1,2,3-triazole-4,5-dimethanol-4,5-bis-(isopropylcarbamate) as potential antineoplastic agent

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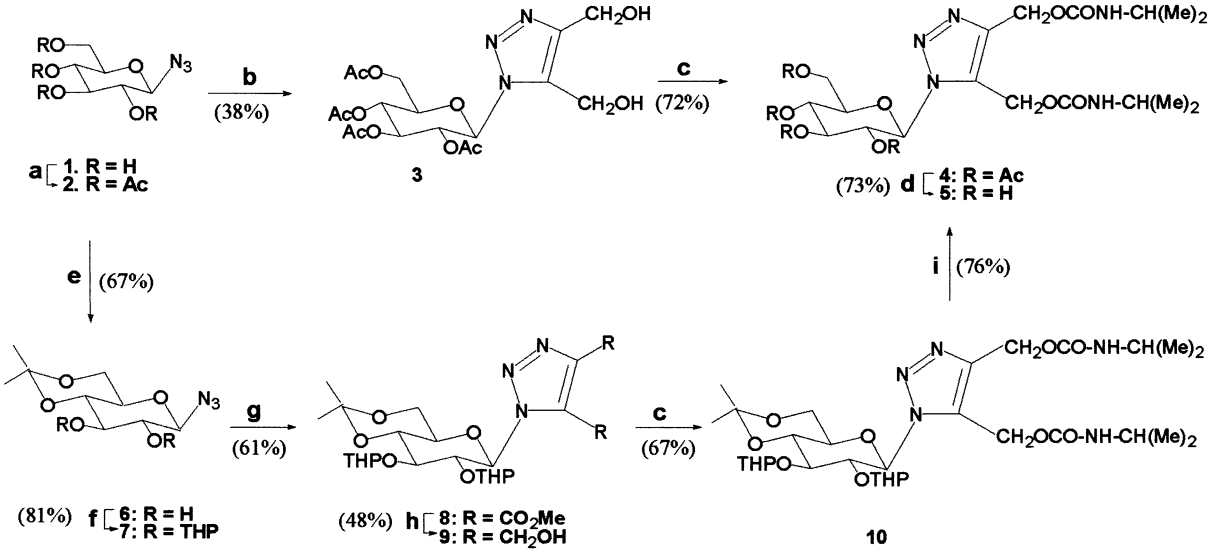
Abstract—The title compound **5** was prepared from the 1-β-D-azido-glucose **1** via four steps. Alternatively, **5** was synthesized from **1**, via acetalation, cycloaddition with acetylene derivative, reduction, then carbamoylation followed by an acid hydrolysis.

Recent studies showed that some carbamates, such as 5-aryl-2,3-dihydropyrrolo[2,1-*b*]thiazole-6,7-dimethanol-6,7-bis(isopropylcarbamates)[1] and the bis(carbamate) derivatives of 4,5-bis(hydroxymethyl)imidazoles[2] exhibited in vitro potential activity against HL-60 human leukemia and HT-29 human colon carcinoma cells as well as antineoplastic activities. These findings and in vitro antileukemic activity of 1-aryl-1,2,3-triazole-4,5-dimethanol-4,5-bis(isopropylcarbamates)[3] encouraged us to synthesize the nucleoside analogue as a potential antineoplastic agent.

The title compound 4,5-bis(carbamate) **5** was synthesized from the glucose azide **1** via two routes with



Scheme 1. *Reagents and conditions*: (a) AC_2O–pyr., rt, 24 h; (b) HOH_2C-C≡C-CH_2OH–toluene–pyr. 9:1, reflux, 18 h; (c) Me_2CHNCO, $Sn(Bu)_2(OAc)_2$, rt, 4 h; (d) K_2CO_3–MeOH, rt, 18 h; (e) Me_2CO–DMP–pTSA, rt, 30 min; (f) DHP-H^+, rt, 16 h; (g) MEO_2C-C≡C-CO_2Me, 80°C, 24 h; (h) LAH, dry ether, rt, 18 h; (i) pTSA, rt, 18 h.

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diverse yields. Cycloaddition of **2**,[4] prepared from **1**, with 2-butyn-1,4-diol in a mixture of toluene/pyridine (9:1) under reflux for 18 h afforded, after chromatography, the crystalline triazole **3**[5] in 38% yield. The carbamoylation[3] of **3** with isopropyl isocyanate was carried out in the presence of $Sn(Bu)_2(OAc)_2$ as a catalyst[2] in CH_2Cl_2 at rt for 4 h to give, after purification, **4**[6] (72%) as crystals, mp 157–160°C. Deblocking of **4** with K_2CO_3 in MeOH at rt for 18 h afforded, after purification, the crystalline **5**[7] in 73% yield. Alternatively, **5** was prepared from **1** via six steps. Thus, acetalation of **1** with a mixture of acetone/dimethoxypropane (3:1) in the presence of *p*-toluenesulphonic acid at rt furnished **6** in 76% yield. The hydroxyl groups of **6** were protected with tetrahydropyran[8] in the presence of *p*-toluenesulphonic acid and gave **7** as a crystalline material in 81% yield. The gluco azide **7** and dimethyl acetylenedicarboxylate were heated in toluene at 80°C for 24 h to give **8** (61%), which was reduced[3] to the alcohol **9** on treatment with LAH in dry ether (48%). Carbamoylation of **9** afforded the crystalline **10** in 67% yield. Acid hydrolysis of **10** furnished **5** in 76% yield (Scheme 1).[9] The anticancer activity of **5** is under evaluation.

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6. Selected spectroscopic data of **4**: ^{1}H NMR ($CDCl_3$): δ 7.35 (br, 1H, NH); 6.13 (d, 1H, $J_{1',2'}=9.3$ Hz, H-1′); 5.95 (t, 1H, $J_{2',3'}=9.3$ Hz, H-2′); 5.41 (t, 1H, $J_{3',4'}=9.4$ Hz, H-3′); 5.34 (s, 4H, $2CH_2$); 5.25 (t, 1H, $J_{4',5'}=9.5$ Hz, H-4′); 4.31 (dd, 1H, $J_{5',6'}=4.8$ Hz, H-6′); 4.12 (dd, 1H, $J_{6',6''}=12.6$ Hz, H-6″); 4.03 (dt, 1H, $J_{5',6''}=2.8$ Hz, H-5′); 3.54 (m, 2H, CH); 2.07, 2.05, 2.03, 1.90 (4s, 12H, 4×OAc); 1.05 (d, 6H, $2CH_3$); 0.92 (d, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): 170.3, 170.1, 169.1, 168.5 (4OAc); 159.7, 158.3 (C=O); 140.1 (C-4); 130.7 (C-5); 85.5 (C-1′); 75.1 (C-5′); 73.1 (C-3′); 69.5 (C-2′); 67.3 (C-4′); 61.3 (C-6′); 58.1, 54.1 ($2CH_2$); 50.1, 49.2 [*C*H(Me)$_2$]; 20.7, 20.6, 20.5, 20.3 (4OAc); 10.8, 10.6, 9.2, 8.5 [CH(*Me*)$_2$].
7. Selected spectroscopic data of **5**: ^{1}H NMR (DMSO-d_6/D_2O): δ 5.97 (d, 1H, $J_{1',2'}=9.5$ Hz, H-1′); 5.19 (s, 4H, $2CH_2$); 4.01 (t, 1H, $J_{2',3'}=9.5$ Hz, H-2′); 3.69 (dd, 1H, $J_{5',6'}=4.6$ Hz, H-6′); 3.65 (m, 2H, 2CH); 3.44 (dd, 1H, $J_{6',6''}=12.0$ Hz, H-6″); 3.34 (dt, 1H, $J_{5',6''}=3.0$ Hz, H-5′); 3.33 (t, 1H, $J_{3',4'}=9.4$ Hz, H-3′); 3.23 (t, 1H, $J_{4',5'}=9.5$ Hz, H-4′); 1.37 (d, 6H, $2CH_3$); 0.89 (d, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6/D_2O): δ 163.2, 158.4 (C=O); 139.3 (C-4); 132.6 (C-5); 86.3 (C-1′); 80.2 (C-5′); 77.1 (C-3′); 71.8 (C-2′); 69.6 (C-4′); 60.6 (C-6′); 57.0, 54.5 ($2CH_2$); 48.8, 47.9 [*C*H(Me)$_2$]; 10.5, 10.2, 9.7, 9.0 [CH(*Me*)$_2$].
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9. All new compounds were purified by column chromatography characterized by ^{1}H NMR (600 MHz, HMQC, COSY, ROESY), ^{13}C NMR and mass spectroscopy and gave correct elemental analysis.