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SYNTHESIS OF 1-[(2-HYDROXY-1-(HYDROXYMETHYL)ETHOXY)METHYL]-1,2,4-TRIAZOLE-3- AND 5-CARBOXAMIDES

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Coupling of trimethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate with 2-O-(chloromethyl)-1,3-di-O-benzyl glycerol, followed by amination and removal of the protecting groups afforded 1-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]-1,2,4-triazole 3- and 5-carboxamides, 1a and 1b, respectively.

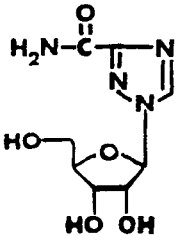
1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (I) was reported to have broad spectrum of antiviral and anticancer activities[2,3]. Recently, a novel guanine acyclic nucleoside analog, 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]guanine (II) was reported independently by several laboratories[4-7] to possess potent antiviral activity against herpes simplex virus type 1 and type 2 with significant favorable therapeutic index. Based on these findings, we would like to report the synthesis of 1-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]-1,2,4-triazole-3- and 5-carboxamide (1a and 1b) as potential antiviral agents. Compounds 1a and 1b were structurally related to I and II.

Trimethylsilyl derivative of methyl 1,2,4-triazole-3-carboxylate 2, which was prepared from the respective ester[2], was reacted with 1 molar equivalent of 2-O-(chloromethyl)-1,3-di-O-benzyl glycerol (3)[6] in anhydrous MeCN at room temperature for 2 days to give a mixture of 1-[(2-benzoxy-1-(benzoxymethyl)ethoxy)methyl]-1,2,4-triazole-3-carboxylic acid methyl ester 4a and 5-carboxylic acid methyl ester 4b. The two isomers were separated by silica gel chromatography ($CHCl_3$-AcOEt, 2=1): 4a (syrup, 31% yield, R_f = 0.39), NMR ($CDCl_3$) δ 3.51 (m, 4H, H-3', H-5'), 3.96 (s, 3H, CH_3OCO), 4.12 (m, 1H, H-4'), 4.50 (s, 1OH, C_6H_5), 5.75 (s, 2H, H-1'), 7.30 (m, 1OH, C_6H_5), 8.32 (s, 1H, H-5); 4b (syrup, 27% yield, R_f = 0.61), NMR ($CDCl_3$) δ 3.50 (m, 4H, H-3', H-5'), 3.96 (s, 3H, CH_3OCO), 4.10 (m, 1H, H-4'), 4.48 (s, 4H, $ArCH_2$), 6.08 (s, 2H, H-1'), 7.32 (m, 1OH, C_6H_5), 7.96 (s, 1H, H-3).

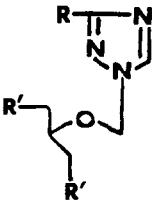
A solution of 4a (2.1 g, 5.90 mmol) in MeOH (30 mL) saturated with NH_3 was stirred in a pressure bottle at room temperature for 24 hr. The solvent was spin-evaporated in vacuo and the residue was crystallized from EtOH to give 5a (1.7 g, 84% yield): mp 94-95°C; NMR (DMSO-d_6) δ 3.50 (m, 4H, H-3', H-4'), 4.05 (m, 1H, H-3'), 4.41 (s, 4H, $ArCH_2$), 5.76 (s, 2H, H-1'), 7.30 (m, 1OH, C_6H_5), 7.70 (d, 2H, $CONH_2$, D_2O exchangeable), 8.71 (s, 1H, H-5). Compound 5b (syrup, 2.0 g, 89% yield) was prepared from 4b (2.35 g, 5.71 mmol) by the same procedure as for 5a: NMR (DMSO-d_6) δ 3.52 (m, 4H, H-3', H-5'), 4.18 (m, 1H, H-4'), 4.42 (s, 4H, $ArCH_2$), 6.09 (s, 2H, H-1'), 7.30 (m, 1OH, C_6H_5), 7.82 (s, 1H, H-3), 7.90 (d, 2H, $CONH_2$ D_2O exchangeable).

Acyclic nucleoside 5a (0.8 g, 2.02 mmol) in 150 mL of CH_3OH was shaken with 0.2 g of 10% Pd-C at 50 psi of hydrogen pressure at room temperature for 20 hr. After work-up, the product was recrystallized from water to give 1a (0.32 g, 73% yield), mp 136-137°C; NMR (DMSO-d_6) δ 3.48 (m, 4H, H-3', H-5'), 3.60 (m, 1H, H-4'), 4.61 (t, 2H, OH, D_2O exchangeable), 5.71 (s, 2H, H-1'), 7.68 (d, 2H, $CONH_2$), 8.90 (s, 1H, H-5). Compound 5b (0.8 g, 2.02 mmol) was also debenzylated by catalytic hydrogenation (60 hr) to give 1b (0.35 g, 80% yield): mp 142-143°C; NMR (DMSO-d_6) δ 3.44 (m, 4H, H-3', H-5'), 3.62 (m, 1H, H-4'), 4.59 (t, 2H, OH, D_2O exchangeable), 8.10 (s, 1H, H-3).

All new compounds gave satisfactory elemental analyses for carbon, hydrogen and nitrogen. The biological activity of 1a and 1b are under investigation.



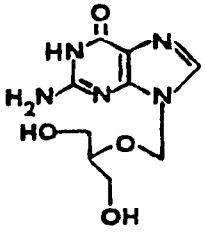
I



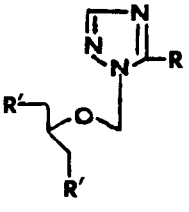
4a R= $COOCH_3$, R'= $OCH_2C_6H_5$

5a R= $CONH_2$, R'= $OCH_2C_6H_5$

1a R= $CONH_2$, R'= OH



II



4b R= $COOCH_3$, R'= $OCH_2C_6H_5$

5b R= $CONH_2$, R'= $OCH_2C_6H_5$

1b R= $CONH_2$, R'= OH

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