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Synthesis of C-Nucleoside Analogues: 2-[2-(Hydroxymethyl)-1, 3-dioxolan-5-yl]1, 3-thiazole-4-carboxamide and 2-[2-(Mercaptometh- yl)-1, 3-dioxolan-5-yl] 1, 3-thiazole-4-carboxamide

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Abstract: Novel C-nucleosides of tiazofurin analogue (2-[2-(hydroxymethyl)-1, 3-dioxolan-5-yl]1, 3-thiazole-4-carboxamide) and its thiol-substituted derivative (2-[2-(mercaptomethyl)-1,3-dioxolan -5-yl]1, 3-thiazole-4-carboxamide) were synthesized from methyl acrylate through a multistep procedure. Their structures were confirmed by IR, ^{1}HNMR, ^{13}CNMR and elemental analysis.

Keywords: C-Nucleosides, tiazofurin, selenazofurin, 1, 3-dioxolane, thiol-substituted.

C-Nucleosides are an unique class of nucleosides in which the glycosidic chain is connected to the pendant heterocyclic base by a C-C bond instead of the C-N bond of the natural nucleosides. As a result, they are resistant to the chemical and the enzymatic hydrolytic cleavage of the glycosidic bond. Among the synthetic C-nucleosides, tiazofurin(2-β-D-ribofuranosylthizole-4-carboxamide NSC-286193)[1] and selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide NSC-340847)[2], which exhibit distinguished antitumor and antiviral activities, have been gained significant attention. Consequently, various analogues of tiazofurin have been synthesized to improve its chemotherapeutic index, including modification of the sugar ring[3] as well as modification of the thiazole ring[4]. However, most of the modified sugar moieties are still monoheteroatom ring, and researches on 1, 3-dioxolane sugar moieties is limited[5]. 1, 3-Dioxolane nucleosides are another interesting class of sugar-modified nucleosides, in which the 3'-carbon is replaced by an oxygen atom. The first example of this class of compounds, (±)-dioxolanyl thymine[6], was found to exhibit potent anti-HIV activity *in vitro* moderately. Other dioxolane nucleosides such as DAPD[7]and OddC[8] are also very promising anti-HIV and anti-HBV agents. On the basis of these interesting biological activities of 1, 3-dioxolane nucleosides as well as C-nucleosides, it was of interest to synthesize hybrid 1, 3- dioxolane C-nucleosides. Here, we synthesized a series of 1, 3-dioxolane tiazofurin analogues (2-[2-(hydroxymethyl)-1, 3-dioxolan-5-yl]1, 3–thiazole–4-carboxamide) and its thiol-substituted derivative (2-[2-(mercaptomethyl)-1,3-dioxolan-5-yl]1,3-thiazole-4-carboxamide). The synthetic route is outlined in **Scheme 1** and

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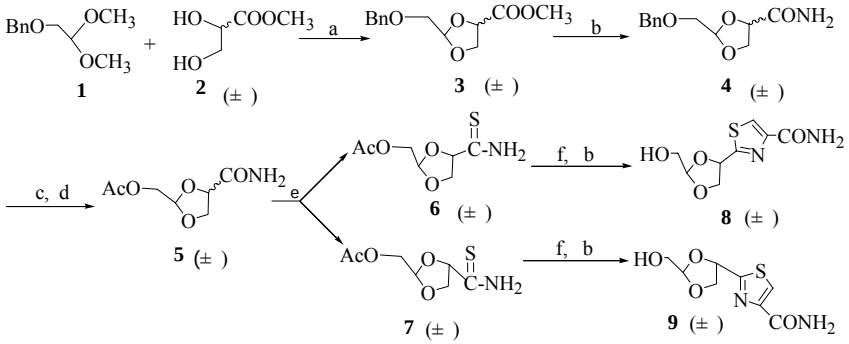
Scheme 2.

Scheme 1



Reagents and conditions: a: *p*-TsOH, benzene, reflux; b: NH_3/MeOH, rt.; c: Pd/C, H_2, ethanol; d: Ac_2O/Pyr., rt.; e: P_4S_{10}, dioxane, reflux; f: $BrCH_2COCOOEt$/EtOH, reflux

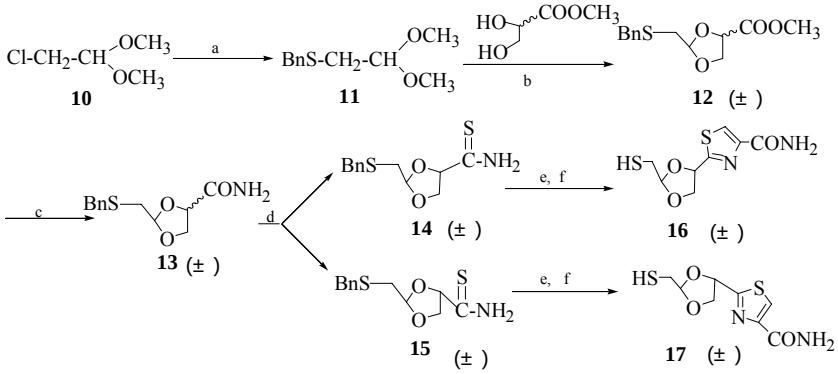
Since 1, 3-dioxolanyl moiety is an acetal, it can be constructed by reacting aldehyde with diol using Lewis acid as catalyst.

Methyl acrylate was chosen as starting material, since it is cheap and convenient to obtain. Oxidation of methyl acrylate with potassium permanganate afforded racemic methyl glycerate **2**. Condensation of benzyloxyacetaldehyde dimethyl acetal **1** with (±) methyl glycerate **2** in the presence of *p*-toluenesulfonic acid provided racemic dioxolane **3** in 67% yield. **3** was smoothly transformed into the corresponding amides **4** with ammonia in methanol. Removal of benzyl group by catalytic hydrogenation would be unsuccessful because sulfur inactivated the palladium catalyst. So the benzyl group was transformed to acetyl group before sulfur was introduced into the reaction system. **4** was deprotected *via* catalytic hydrogenation over Pd/C. The resulting compound was then reacted with acetic anhydride in pyridine to form **5**. **5** was subjected to thiation with tetraphosphorus decasulphide in refluxing dioxane to give **6** and **7.** **6** and **7** have different Rf values on TLC. They could be separated by column chromatography. The structure of the major product was determined to be (±) β-[2-(acetyloxymethyl)-1,3 -dioxolane-5-yl] thioacetamide **6**, whereas the minor product was (±)α-[2-(acetyloxy-methyl)-1,3-dioxolane-5-yl] thioacetamide **7**. These configurations were determined based on ^{1}H-NMR spectral studies of **8**[9] and **9**[10], obtained *via* the treatment of **6** and **7** with ethyl bromopyruvate in refluxing ethanol, followed by ammonolysis. The δ value of the anomeric proton of **8** shifted upfield relative to that of **9.** NOE experiments showed that when H-2 of **8** was irradiated, H-5 peak was enhanced, suggesting in *cis* orientation, while irradiation of H-2 of **9,** no enhancement of H-5 was observed, indicating in *trans* configuration.

Synthesis of 2-[2-(mercaptomethyl)-1,3-dioxolan-5-yl]1, 3-thiazole-4-carboxamide **16**[11] and **17**[12] were accomplished by similar procedures for synthesis of 2-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]1, 3-thiazole-4-carboxamide **8** and **9**, only benzyl-thioacetaldehyde dimethyl acetal **11** was used as starting material instead of benzyl-oxyacetaldehyde dimethyl acetal **1**. Final deprotection of the benzyl groups was done in liquid ammonia with sodium, and ammonolysis was accomplished simultaneously.

^{1}H-NMR spectroscopy confirmed that compound **16** was β-isomer, while compound **17** was α-isomer.

Scheme 2



Reagents and conditions: a: NaH, BnSH, THF; b: *p*-TsOH, CH_2Cl_2, reflux; c: NH_3/MeOH, rt.; d: P_4S_{10}, dioxane, reflux; e: $BrCH_2COCOOEt$/EtOH, reflux; f: Na/liquid ammonia

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9. Compound **8**: m.p.: 114-116℃. IR(KBr): 3450, 3164, 2924, 1680, 1595, 1306, 1282 cm^{-1}. ^{1}HNMR($CDCl_3$) δ ppm: 8.22(s, 1H, H-5'), 7.29, 7.06(2s, each 1H, $CONH_2$), 5.38(t, 1H, J=5.1,H-2),5.22(dd, 1H, J_1=5.4, J_2=4.7, H-5), 4.33(dd, 1H, J_1=5.4, J_2=6.0, H-4b), 3.91(dd, 1H, J_1=6.0, J_2=4.7, H-4a), 3.53(m, 2H, H-6), 3.49(brs, 1H, OH). ^{13}CNMR($CDCl_3$) δ ppm: 172.97 (C=O), 163.31(C-2'), 150.87(C-4'), 125.85(C-5'), 104.80(C-2), 75.75(C-5), 71.54(C-6), 63.22(C-4). Anal. Calcd. for $C_8H_{10}N_2O_4S$(230.24): C, 41.73; H, 4.38; N, 12.17; Found: C, 41.95; H,4.48; N, 11.92; MS *m/z* 230.03
10. Compound **9**: m.p.: 111-114℃. IR(KBr): 3443, 3187, 2926, 1691, 1589, 1276 cm^{-1}. ^{1}HNMR($CDCl_3$) δ ppm: 8.22(s, 1H, H-5'), 7.32, 7.16(2s, each 1H, $CONH_2$), 5.44(t, 1H, J=5.7, H-2), 5.37(dd, 1H, J_1=6.8, J_2=6.3, H-5), 4.58(dd, 1H, J_1=6.8, J_2=7.8, H-4b), 4.14(dd, 1H, J_1=7.8, J_2=6.3, H-4a), 3.82(m, 2H, H-6), 3.52(brs, 1H, OH). Anal. Calcd. for $C_8H_{10}N_2O_4S$ (230.24): C, 41.73; H, 4.38; N, 12.17; Found: C, 41.92; H, 4.50; N, 12.28; MS *m/z* 230.11
11. Compound **16**: m.p.: 128-130°C. IR(KBr): 3173, 2931, 2561, 1674, 1601 cm^{-1}. ^{1}HNMR($CDCl_3$)ppm: 8.23(s, 1H, H-5'), 7.37, 7.20(2s, each 1H, $CONH_2$), 5.34(t, 1H, J=6.2, H-2), 5.30(dd, 1H, J_1=5.9, J_2=4.4, H-5), 4.49(dd, 1H, J_1=5.9, J_2=3.8, H-4b), 4.01(dd, 1H, J_1=4.4, J_2=3.8, H-4a),2.65(m, 2H, H-6), 2.21(s, 1H, SH). Anal. Calcd. for

$C_8H_{10}N_2O_3S_2$(246.01): C,39.02; H, 4.10; N,38; Found: C, 39.27; H, 3.93; N, 11.51; MS *m/z* 246.32

12. Compound **17**: m.p.: 127-129°C. IR(KBr): 3189, 2898, 2574, 1683, 1597cm^{-1}. ^{1}HNMR($CDCl_3$) δ ppm: 8.23(s, 1H, H-5'), 7.28, 7.05(2s, each 1H, $CONH_2$), 5.37(t, 1H, J=7.0, H-2), 5.32(dd, 1H, J_1=6.6, J_2=3.7, H-5), 4.52(dd, 1H, J_1=6.6, J_2=4.8, H-4b), 4.08(dd, 1H, J_1=4.8, J_2=3.7, H-4a), 2.72(m, 2H, H-6), 2.20(s, 1H, SH). Anal. Calcd. for $C_8H_{10}N_2O_3S_2$(246.01): C,39.02; H, 4.10; N, 11.38; Found: C, 38.85; H, 4.14; N, 11.26; MS *m/z* 246.09

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