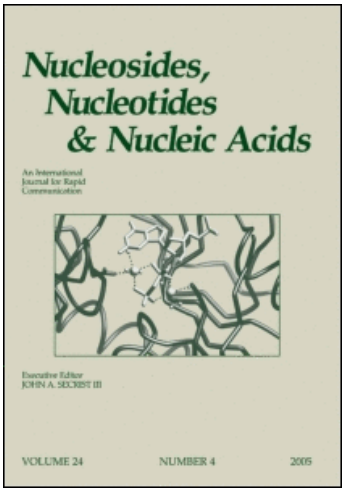

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Synthesis and Antiviral Activity of 3-(β-D-Ribofuranosyl)-1,2,4-oxadiazole-5-carboxamide

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(5&6), 845–849 (2000)

SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3-(β-D-RIBOFURANOSYL)-1,2,4-OXADIAZOLE-5-CARBOXAMIDE+

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Abstract: 3-(β-D-Ribofuranosyl)-1,2,4-oxadiazole-5-carboxamide (5) was prepared by condensation reaction of amidoxime **6** with monoethyl oxaloyl chloride followed by reaction with ammonia. The compound **5**, however, did not exhibit any significant activity against herpes simplex virus type-I (HSV-I) and semliki forest virus (SFV).

In search of potential antiviral and anticancer drugs, *seco*-analogs of purine nucleosides have been extensively explored. The better conformational mobility and supposedly similar uptake mechanism to natural substrates have generated interest in such compounds. *seco*-Analogs of guanosine such as acyclovir (**1**)[2], ribavirin (**3**)[3] and tiazofurin (**4**)[4] have shown significant antiviral and anticancer activities. The glycone component has been reduced in acyclovir to hydroxyethoxymethylene, which adapts a conformation similar to the natural substrate guanosine[2b]. This results in the selective recognition of the glycone component of acyclovir by viral enzymes and its conversion first to give the monophosphate and then by cellular enzymes to a triphosphate derivative, which inhibits viral growth. Acyclovir is, therefore a very selective and minimally toxic antiviral drug. Truncated heterocyclic analogs, including ribavirin, tiazofurin and others are also effective antimetabolites. These analogs on the other hand also resemble 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICAR, 2), a precursor in nucleic acid biosynthesis[5].

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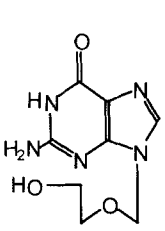

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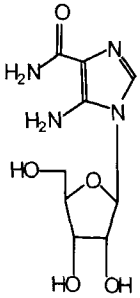

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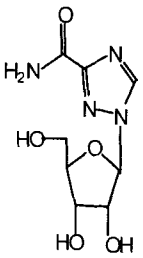

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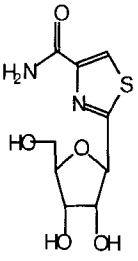

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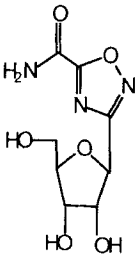

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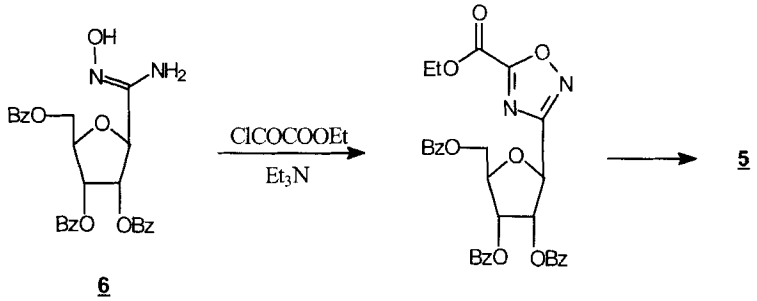
Thus the essential features necessary for biological activity in nucleoside analogs appear to be the presence of a ring nitrogen atom adjacent to the carboxamide function and the β-D-ribofuranosyl moiety as glycosyl component. In view of the potential activity of the azole carboxamide nucleosides, we undertook the synthesis of the hitherto unknown 3-(β-D-ribofuranosyl)-1,2,4-oxadiazole-5-carboxamide and evaluation of its antiviral activity. Repke *et. al*[6] have earlier synthesized 3-(β-D-ribofuranosyl)-1,2,4-oxadiazole-5-alkanes. Recently a simple synthesis of 1,2,4-oxadiazole by the reaction of an amidoxime and a nitrile in the presence of a Lewis acid was reported by Yarovenko et al[7]. By adopting a similar strategy, we synthesized the product by the reaction of an amidoxime with a suitable acid chloride.

The reaction of 2,3,5-tri-0-benzoyl-β-D-ribofuranosyl amidoxime (**6**)[6] with monoethyl oxaloyl chloride yielded 3,5-disubstituted oxadiazoleriboside **7** which on treatment with ammonia gave 3-β-D-ribofuranosyl-1,2,4-oxadiazole-5-carboxamide (**5**) after deprotection and amidation[8].



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The chemical ionization (CI) mass spectrum for the amide **5**, which was recorded on a `Kratos MS-30' with methane as reagent gas, gave peaks of protonated molecular ion $[M+H]^+$, m/z=246 as well as of cluster ions $[M+C_2H_5]^+$, m/z=274 and $[M+C_3H_5]^+$, m/z=286. The observed chemical shift for the C-1' proton, coupling constant and optical rotation are in favor of the β-configuration for the nucleoside.

Compound **5** was assayed for its antiviral efficacy against herpes simplex virus type-I and semliki forest virus proliferation. It exhibited 40% inhibition of HSV-1 at 0.24 μM/ml in *in vitro* assay while the standard phosphonoacetate at 0.07 μM/ml showed 98% inhibition. In an *in vivo* assay against semliki forest virus (SFV) infection in mice, a 30% survival was observed with **5** at 40.8 μM/kg dose against 90% survival with an interferon inducer (0.6 mg/kg) under similar condition. The interferon inducer, a mycoviral ds RNA preparation, was earlier discovered in our laboratory from the fungus *Aspergillus ochraceus* ATCC 28706, which served the purpose of a standard antiviral substance[10].

Such a marginal antiviral activity has also been observed with the isomeric N-nucleoside structure 5-(β-D-ribofuranosyl)-1,2,4-oxadiazole-3-carboxamide synthesized by Hennen and Robins[11].

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8. 3-β-D-Ribofuranosyl-1,2,4-oxadiazole-5-carboxamide : To a mixture of amidoxime (1.0 g, 2 mmole) and monoethyl oxaloyl chloride (0.6 g, 4.4 mmole) in n-butyl acetate (15 ml), triethylamine (0.5 g, 4.4 mmole) was added gradually. The resulting reaction mixture was refluxed for 2 hr. It was cooled, washed with water and dried (Na_2SO_4). The solvent removed *in vacuo* and the product passed through silica gel column. Elution with chloroform gave the product as an oil (1.0 g, 86% yield). This product was then treated with methanolic ammonia at room temperature for 24 hr. The solvent removed and crude product so obtained was chromatographed over silica gel column. Elution of the column with $CHCl_3$: MeOH (1 : 1, v/v) gave the product **5** (0.2 g, 50% yield) ; m.p. 112-14°C, $[\alpha]_D$-31.0 (1%, DMSO), ^{1}H-NMR (DMSO-d_6) ; 8.5 and 8.2 (2brs, 1H each for NH_2), 4.9 (d, J=4.0 Hz, 1H, H-1') and other sugar protons, ^{13}C-NMR (DMSO-d_6), 169.52, 169.26, 154.39, 85.78, 75.67, 74.27, 71.37 and 62.01 ; Anal. Calcd. for $C_8H_{11}N_3O_6$: C, 39.18; H, 4.52; N, 17.13; Found : C, 39.45; H, 4.69; N, 16.91.

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