Perspective

Pharmaceutical BIOPROCESSING

Improved Synthesis of β-D-6-Methylpurine Riboside and Antitumor Effects of the β-D- and α-D-Anomers

Abstract

6-Methylpurine-β-D-riboside (β-D-MPR) has been synthesized by coupling 6-methylpurine and 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribose using conditions that produce the β-D-anomer exclusively. The in vitro antitumor effects of β-D-MPR and 6-methylpurine-α-D-riboside (α-D-MPR) in five human tumor cell lines showed that β-D-MPR was highly active (IC50 values ranging from 6 to 34 nM).

Keywords: 6-Methylpurine-β-D-riboside • 6-methylpurine-α-D-riboside • antitumor activity • synthesis

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Introduction

6-Methylpurine-β-D-riboside (6, β-D-MPR), an antibiotic isolated from culture broths of the basidiomycetes fungi Collybia dryophilia and Collybia maculata, has antifungal, antiviral and antitumor activity. β-D-MPR is an excellent substrate of mammalian adenosine deaminase (ADA) and its mechanism of activation in tumor cells presumably relates to its interaction with this enzyme. Protozoan parasites such as African trypanosomes and Leishmania cannot synthesize purines and must salvage them from their host organisms. Consequently, they are less discriminate than mammalian cells in their enzymatic processing of preformed purines and purine nucleosides. For example, MPdR is cleaved by 5'-(methylthio)adenosine phosphorylase in African trypanosomes but not in human sarcoma 180 cells. Methylpurine (MP) nucleoside analogs are often prepared by fusion of MP to an appropriate O-acylated sugar. This synthetic approach consistently produces product mixtures of α- and β-anomers. For example, MPR, when prepared by fusion of MP with tetra-O-acetyl-β-D-ribofuranose gives a 10:1 mixture of β/α anomers and requires a tedious chromatographic separation of the closely eluting α- and β-anomers to obtain pure the β-anomer.

Description

A variety of nucleoside analogs have been prepared by the fusion of the appropriate nucleic acid with an O-acylated ribose in the presence of an acid catalyst. A drawback of this methodology is the generation of various product mixtures composed of both α- and β-anomers .As stated previously, in the preparation of MPR via a fusion reaction a 10:1 mixture of β/α anomers was consistently produced. Only the N-9 β-anomer of methylpurine was formed under the conditions reported in this paper. Presumably, the difference in electronic contributions to the purine ring system between that of the amino group of adenine and the methyl group of methylpurine led to this discrepancy. Antiparasitic activity of β-D-MPR and α-D-MPR was examined previously in the EATRO 110 strain of Trypanosoma brucei and two clinical isolates of Trypanosoma brucei rhodesiense: β-D-MPR was significantly active, with IC50 values in the range of 0.2- 2.0 μM, whereas α-D-MPR was less than 50% growth inhibitory at concentrations up to 100 μM. Data from our current studies provide further evidence of the highly toxic effects of this

analog in mammalian cells and underscore its lack of selectivity as an antiparasitic agent. Unexpectedly, α-D-MPR exhibited significant antitumor effects in all five human tumor cell lines with IC50 values in the range of 1.47-4.83 μM. The possibility that the activity attributed to α-D-MPR might be due to presence of trace amounts of β-D6MPR was ruled out by determining the purity of α-D-MPR (HPLC and NMR spectroscopy) and by evaluating the antitumor effects of α-D-6MPR in the presence of varying amounts of β-D-MPR using MCF7 breast carcinoma cells. Cellular DNA and RNA are comprised exclusively of β-D-nucleosides and consequently, nucleoside antimetabolites used clinically for cancer treatment are β-anomeric structures. Scant attention has been given to the antitumor effects of α-D-nucleoside structures (α-nucleosides) [5]. The significant antitumor activity of α-D-MPR, an α-nucleoside, is an unusual finding, which warrants further biochemical characterization.Tri-O-benzoyl-6-methylpurine-β-D-riboside (1.882 g, 3.3 mmol) was dissolved in 4:1 methanol/ concentrated ammonium hydroxide (50 mL) and stirred at room temperature for 18 hr. The reaction mixture was concentrated in vacuo and azeotroped 3 times with ethanol. The crude product was dissolved in water (50 mL), extracted with methylene chloride (3 x 50 mL) and the aqueous layer concentrated in vacuo and further dried under vacuum to give 6 (0.82 g, 93%): 1 H-NMR (DMSO-d6) δ 2.75 (s, 3H, CH3), 3.55 (m, 2H, 5′-CH), 3.95 (m, 1H, 4′-CH), 4.0 (m, 1H, 3′-CH), 4.20 (m, 1H, 2′-CH), 5.10-5.50 (br m, 2H, 2′-OH and 3′-OH), 6.00 (m, 1H, 1′-CH), 8.75 (2 overlapping s, 2H, arom H); UV λmax 260.3 nm. The solution was stirred at room temperature for 75 min under nitrogen and then concentrated in vacuo below 35°C. The resulting oil was azeotroped 5 times with toluene and dissolved in acetonitrile (80 ml). 6-Methylpurine (1.632 g, 12 mmol) was added and the reaction mixture was refluxed for 40 hr. After cooling to room temperature, concentrated ammonium hydroxide (1.8 mL) was added and the solution was concentrated in vacuo. The resulting oil was triturated with ether (2 x 200 mL). The ether extracts were combined and concentrated in vacuo. The crude product was dissolved in methylene chloride and applied to a silica gel column (22 X 350 mm) packed in methylene chloride.

Acknowledgement

None

Conflict of interest

No conflict of interest

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