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New conjugates of mycophenolic acid and their antiproliferative activity

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ABSTRACT

The new conjugates of mycophenolic acid (MPA) were obtained in the reaction of N^6-(ω-aminoalkyl)adenosines with MPA in the presence of EDCI as a coupling reagent. New compounds **4a–h** were evaluated on leukemia cell line (Jurkat) and PBMC from healthy donors. Length of the linker influenced observed activity. The compound **4b** possessing 1,3-diamine spacer exhibited the most promising results and can be considered to further investigations.

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Mycophenolic acid; MPA; adenosine; synthesis; antiproliferative activity

1. Introduction

Mycophenolic acid (MPA) **1** (Scheme 1) is widely reported as an uncompetitive inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH) and its derivatives, mycophenolate mofetil (MMF, CellCept) and mycophenolate sodium (MPS, Myfortic), are used in prevention of organ rejection transplant and autoimmune disorders treatment [1–4]. However, numerous side effects such as myelosuppression, vomiting, diarrhea, nausea limit usage of these prodrugs, and various structural modifications were reported [5–14]. One of the alterations is a conjugate forming, where MPA is connected to other bioactive molecules [15–17]. Pankiewicz and coworkers rationalized series of inhibitors of IMPDH as a nicotinamide adenine dinucleotide-dependent enzyme. Mycophenolic adenine dinucleotides include derivatives revealing higher potency toward both isoforms of IMPDH than reference tiazofurin adenine dinucleotide and in some cases comparable to MPA, which is one of the most potent *h*IMPDH1 and 2 inhibitor [18–22].

In this paper, we report synthesis of the new conjugates **4a–h** (Scheme 1) possessing adenosine attached with a simple diamine linker and MPA, followed by their preliminary antiproliferative activity investigations.

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