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Synthesis and antiproliferative activity of conjugates of adenosine with muramyl dipeptide and nor-muramyl dipeptide derivatives

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ABSTRACT

We synthesized a series of MDP(D,D) and nor-MDP(D,D) derivatives conjugated with adenosine through a spacer as potential immunosuppressants. New conjugates **8a–k** were evaluated on two leukemia cell lines (Jurkat and L1210) and PBMC from healthy donors. The conjugates **8a–k** and MDP(D,D)/nor-MDP(D,D) derivatives **7e**, **f**, **i**, **j** were active against L1210 cell line. Unconjugated nor-MDP(D,D) had better antiproliferative properties, but the conjugates **8b**, **f**, **g** had the highest values of selectivity index. Both cell lines as well as PBMC were resistant to analogs **11a**, **b** with the 6-aminohexanoic linker.

Immunosuppression is well-established strategy of treatment in medicine. Depression of immune activities with pharmacological compounds is able to cure or alleviate symptoms of autoimmune and allergic diseases as well as maintain transplanted organs.

Many naturally derived substances have an impact on the human immune system. They can either promote or suppress the immune response. Compounds with recognized immunosuppressive action are, that is, cyclosporine[1] isolated from the soil fungus *Tolypocladium inflatum*, mycophenolic acid produced by *Penicillium* spp.[2,3] or tacrolimus that was first isolated from the fermentation broth of *Streptomyces tsukubaensis*.[4] The bacterial cell wall peptidoglycan (PGN) is a component that has an opposite effect – it activates the immune system. In 1974 it was demonstrated that muramyl dipeptide (*N*-acetylmuramyl-L-alanyl-D-isoglutamine, MDP **1**) (Fig. 1) is the minimal structure of bacterial PGN required for immunoadjuvant activity.[5] MDP acts through intracellular NOD2 receptor expressed in immune cells, including monocytes, macrophages, T lymphocytes, granulocytes, dendritic cells and also in intestinal epithelial cells.[6] Injection of MDP is pyrogenic[7] and can induce uveitis,[8] arthritis[9] or meningitis.[10] Therefore, many derivatives of MDP have been synthesized in order to gain less toxic agents with better pharmacological properties.[11,12] Structure modifications have led to construction of compounds not only with nonpyrogenic adjuvants[13] but also derivatives and conjugates with antitumor,[14] antiviral,[15] antibacterial or hepatoprotective actions.[16] However, in 1976 it was observed that a change of Ala to D-Ala in a peptide part of MDP entirely alternates its properties. The data showed depression of the humoral response by *N*-AcMur-D-Ala-D-Glu-NH_2.[17] Later, researchers revealed that the replacement of L-alanine for D-alanine causes the loss of activity towards NOD2 receptor.[18]

In this Letter we would like to report the synthesis of new series of MDP(D,D) and nor-MDP(D,D) derivatives linked through an 2-aminoethyl (as reported previously)[19] or 6-aminohexanoic acid spacer to the adenosine, whose cytotoxic and antiproliferative activities were evaluated. In order to achieve compounds that decrease the humoral immune response we modified the peptide part of MDP by replacing L-alanine with D-amino acids. To amplify the immunosuppressive action an adenosine fragment was attached. Adenosine **2** (Fig. 1) is a purine nucleoside that is constitutively present at low levels outside cells.[20,21] In case of hypoxia or ischemia its concentration raises and protects cells and tissues mediating its effects via four types of adenosine receptors: A_1, A_{2A}, A_{2B} and A_3, belonging to the G-protein-coupled receptor family.[21] A_{2A} receptors are expressed ubiquitously in the body, but they can be found mainly in the immune system on monocytes/macrophages,[22] T cells,[23] dendritic cells,[24] neutrophils.[21] One of the effects of adenosine acting through A2A receptors is

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