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REVIEW ARTICLE

New Analogues of Mycophenolic Acid

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ARTICLE HISTORY

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Abstract: ***Background***: Mycophenolic acid (MPA) possesses antibacterial, antifungal, antiviral, immunosuppressive and anticancer properties. It is a non-competitive and reversible inhibitor of dehydrogenase inosine-5'-monophosphate (IMPDH). This compound belongs to the immunosuppressive drugs used for the prevention of both acute and chronic transplant rejection. Until now, two derivatives of MPA have been used clinically: mycophenolate mofetil (MMF, CellCept) and mycophenolate sodium (MPS, Myfortic). They cause, similar to MPA, although at lower degree, the side effects such as vomiting, abdominal pain, diarrhea, nausea, gastrointestinal, urogenital tract, blood or nervous system disorders. These drawbacks and glucuronidation of MPA *in vivo* limit the use of these compounds as pharmaceuticals. Therefore, research is still going on for more effective analogs that are less toxic to the organism and could improve the quality of life of patients.

Conclusion: In this review article, the authors present the synthesis of novel derivatives of mycophenolic acid, together with their initial biological investigations.

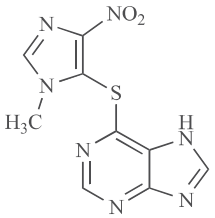
Keywords: Anticancer agents, antiproliferative activity, conjugates, immunosuppressants, IMPDH, Mycophenolic acid.

1. INTRODUCTION

Over the past 40 years, there has been tremendous growth of transplantation. It is a new field of medicine that saves and improves the quality of life of many patients suffering from end-stage heart failure, liver, kidneys and respiratory system failures. The success of organ transplantation is dependent on many factors, including the use of immunosuppressive therapy [1].

Immunosuppressive therapy is aimed at inhibiting of immune response, and as a further consequence, the reduction of graft rejection and prolongation of the survival of the recipient, which determines the success of transplantation. The reported immunosuppressants should be selective in order to reduce the risk of over-immunosuppression, which can lead to bacterial, viral, and fungal infections and an increased risk of malignancy [2]. In the immunosuppressive therapy, drugs with different mechanisms of action, are administered simultaneously. Used regimens of treatment depend on many factors such as the transplanted organ, the degree of risk of the immune response as well as the side effects or other associated disease [3].

Until the mid-90s primary immunosuppressive agent, used in Poland was azathioprine (AZA) **1** (Fig. **1**). AZA **1** found application in the treatment of kidney transplantation. However, now actual participation of AZA **1** in the treatment of transplant is reduced, because it has a lot of adverse effects. AZA possesses mutagenic properties, probably due to the presence of the nitro group which in the organism is metabolised and leads to an abnormal increase of the number of free radicals causing oxidative stress. Moreover, this drug is hepatotoxic, impairs bone marrow, pancreas inflammation, hair loss, fever, cardiac arrhythmias and many others. It is also observed that patients receiving AZA more often suffer from cancer. On the field appeared drugs that act more efficiently - mycophenolate mofetil (MMF) - prodrug of MPA **2** [4, 5] (Fig. **2**). MMF **3** and MPS (mycophenolate sodium) **4** (Fig. **3**) are currently the most widely used antiproliferative immunosuppressants. However, the basic problem of their use are diseases of the digestive, blood, urogenital, nervous system and cancers [6, 7]. Therefore, research is still conducted on better tolerated potential drugs based on the structure of mycophenolic acid.



1

Fig. (1). Structure of azathioprine (AZA).

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