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Synthesis and biological activity of mycophenolic acid-amino acid derivatives

Dorota Iwaszkiewicz-Grzes [a], Grzegorz Cholewinski [a, *], Agata Kot-Wasik [b], Piotr Trzonkowski [c], Krystyna Dzierzbicka [a]

[a] Department of Organic Chemistry, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland
[b] Department of Analytical Chemistry, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland
[c] Department of Clinical Immunology and Transplantology, Medical University of Gdansk, ul. Debinki 7, 80-211, Poland

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ABSTRACT

In search of new immunosuppressants we synthesized 11 amino acids derivatives of MPA as methyl esters **10a–k** using EDCI/DMAP and their corresponding amino acid derivatives in free acid form **11a–k** by hydrolysis of ester group with LiOH/MeOH. New analogs were evaluated as growth inhibitors of lymphoid cell line (Jurkat) and human peripheral blood mononuclear cells (PBMC) from healthy donors. According to obtained results recovering of free carboxylic group increased their activity. Additionally, the cytotoxic properties depends on the substituent and configuration at chiral center in amino acid unit. The compounds **10j**, **11e** and **11h** exhibited higher potency than MPA **1** *in vitro*.

1. Introduction

Transplantation is the optimal treatment for selected patients with end-stages organ failure, increasing life expectancy and improving quality of life. Research in the field of immunosuppression has been continuous since 1954, when at Boston performed the first life-sustaining transplant [1,2]. The first successful chemical immunosuppressant was 6-mercaptopurine. Its derivative, azathioprine, is still used today [1]. Thereafter were discovered a number of new compounds including mycophenolic acid (MPA) **1** (Fig. 1) and its derivatives. Mycophenolate mofetil (MMF, CellCept) **2** (Fig. 1) and mycophenolate sodium (MPS, Myfortic) **3** (Fig. 1) are used clinically as immunosuppressants.

In modern transplantology inosine-5′-monophosphate dehydrogenase (IMPDH), is a major therapeutic target [3–9]. This enzyme is responsible for the catalysis of NAD-dependent oxidation of inosine monophosphate (IMP) to xanthosine 5′-monophosphate (XMP), which is used in the *de novo* biosynthesis of guanine.

Mycophenolic acid, (4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid (MPA) **1** (Fig. 1), binds to the N subsite of IMPDH and is one of the most potent inhibitors of *h*IMPDH (human IMPDH) ($K_i = 7$ nM) [5]. MPA **1** reduces the availability of guanine nucleotides, especially GTP. This causes a disturbance in DNA and RNA synthesis, while it induces apoptosis [9]. Reduction of GTP in lymphocytes and monocytes, causing cessation of proliferation, and inhibits glycosylation of membrane proteins [10,11]. MPA was first licensed for transplantation in 1995 and rapidly grew in popularity, becoming the second most widely prescribed immunosuppressant in the United States in 2004 [11]. MPA **1** was firstly isolated in 1896 by Gosio from *Penicillium stoloniferum* and was probably first antibiotic [7,12].

MMF **2** (Fig. 1) is the 2-morpholinoethyl ester prodrug of MPA and has been widely used as an immunosuppressant in kidney, heart, and liver transplantation procedures. The two most frequently observed adverse events with both drugs are leukopenia and gastrointestinal disorders, especially diarrhea [13-15].

There were described many structural modifications of MPA [16–23], however only several ones displayed similar or better immunosuppressive activity. For example, it concerns β-aminophosphonic MPA derivatives **4** [24,25], hydroxamate **5** [26] or (*S*)-α-methylmycophenolic acid **6** [27], RS-97613 **7** [28] (Fig. 2). These results are in good agreement with molecular modeling studies, that polar group at the end of the side chain interacts with Ser 276 of IMPDH [29]. In literature were also reported amide MPA analogs bearing glycine [30–32] and alanine [30] moieties **8** as potential

* Corresponding author.
E-mail address: grzchole@pg.gda.pl (G. Cholewinski).

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