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Original article

Synthesis and biological activity of novel mycophenolic acid conjugates containing nitro-acridine/acridone derivatives

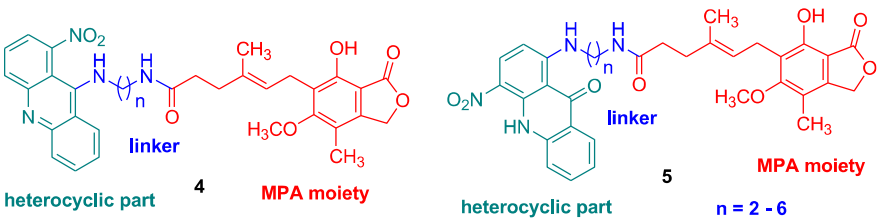
Magdalena Malachowska-Ugarte [a], Grzegorz Cholewinski [a,*], Krystyna Dzierzbicka [a], Piotr Trzonkowski [b]

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

HIGHLIGHTS

- Acridines **4** were more active *in vitro* if compared with acridone analogs **5**.
- Derivatives **4** exhibited higher activity than MPA **1** itself.
- Conjugates **4**, **5** act as IMPDH inhibitors.

GRAPHICAL ABSTRACT



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ABSTRACT

Hybrid pharmacophore anti-proliferative compounds, comprised of mycophenolic acid (MPA) and 1-nitroacridine/4-nitroacridone derivative have been synthesized and evaluated as inhibitors of five different leukemia cell lines (Jurkat, Molt-4, HL-60, CCRF-CEM, L1210) and human peripheral blood mononuclear cells from healthy donors. These conjugates possess different length of the linker between MPA and heterocyclic units. The type of heterocyclic part influenced their cytotoxic and anti-proliferative properties. Coupling of MPA **1** with 9-(ω-aminoalkyl)amino-1-nitroacridines **2** and 1-[(ω-aminoalkyl)-4-nitro-9(10*H*)]-acridones **3** was tested. Although all tested conjugates were active, compounds **4a–e** exhibited the highest potency. Preliminary experiments with GMP suggested that the tested compounds acted as IMPDH inhibitors.

1. Introduction

Mycophenolic acid **1** (Fig. 1) is an antibiotic possessing wide spectrum of biological activity. Its antifungal, antibacterial, antiviral, as well as immunosuppressive properties are well known [1,2]. MPA is uncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), the crucial enzyme in *de novo* biosynthesis of purine nucleotides. There are two isoforms of IMPDH- type I and II. Type I is expressed constitutively, while the level of type II is increased radically in activated lymphocytes and tumor cells [3]. Mycophenolic acid is used (as mycophenolate mofetil MMF or mycophenolate sodium MPS) as immunosuppressive drug in solid organ transplant patients.

Although it has proved beneficial biological activity, MPA exhibits severe metabolic drawbacks. Its C-4 hydroxyl group is highly susceptible to glucuronidation *in vivo*. Moreover, MPA metabolites undergo subsequent cleavage, which causes many adverse effect in immunosuppressive therapy [1]. For this reason numerous MPA derivatives were obtained and for most of them biological activity has been tested [4]. For instance, Pankiewicz and co-workers developed MPA conjugates with adenosine as promising compounds in human leukemia [5]. Anderson and colleagues designed indole analogs of MPA which exhibited interesting properties in prostate cancer [6,7].

Natural and synthetic acridine derivatives possess fungicidal, antimicrobial, anti-parasitic, anti-inflammatory, anticancer and antiviral activity, widely described in the literature [8–15]. Their

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

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