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RESEARCH ARTICLE

Synthesis and biological activity of ester derivatives of mycophenolic acid and acridines/acridones as potential immunosuppressive agents

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Abstract

Improved derivatives of mycophenolic acid (MPA) are necessary to reduce the frequency of adverse effects, this drug exerts in treated patients. In this study, MPA was coupled with *N*-(ω-hydroxyalkyl)-9-acridone-4-carboxamides or *N*-(ω-hydroxyalkyl)acridine-4-carboxamides to give respective ester conjugates upon Yamaguchi protocol. This esterification required protection of phenol group in MPA. Designed conjugates revealed higher potency *in vitro* than parent MPA. Acridine derivatives were more active than acridone analogs and length of the alkyl linker between MPA and heterocyclic units influenced the observed cytotoxicity. Derivatives **2b, 2d, 3a, 3b** displayed the most promising immunosuppressive activity.

Keywords

Acridines, acridones, esterification, IMPDH inhibitors, mycophenolic acid

History

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Introduction

Mycophenolic acid **1** (MPA) (Figure 1) is an uncompetitive inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), the crucial enzyme in *de novo* purine nucleotide biosynthesis. This mechanism allows MPA **1** to decrease proliferation of lymphocytes. Hence, sodium mycophenolate [MPS, Myfortic (Novartis, Basel, Switzerland)] and MPA prodrug: mycophenolate mofetil [2-morpholinoethyl, MMF, CellCept (Roche, Basel, Switzerland)] are widely used in the clinic as immunosuppresants[1–10] in the prevention of allograft rejection and treatment of autoimmune diseases. However, adverse effects related to the treatment with MPA-based drugs, such as diarrhea, leukopenia, sepsis and vomiting, are the barrier to the administration of higher doses and more effective treatment. In order to solve this issue, many structural MPA modifications followed by the assessment of the antiproliferative activity were reported[11–27].

Various types of compounds were considered as potent IMPDH inhibitors[28,29]. Among them acridines possess not only anticancer, antiviral and antibacterial[30–36], but also antiproliferative and immunosuppressive features[28,37]. Additionally, activity can be improved by conjugate forming[38–40]. Recently, we reported potent IMPDH inhibitors bearing MPA covalently bonded to nitroacridine/nitroacridone derivatives via amide bond formation[41]. On the other hand, there are also described promising conjugates possessing ester linkages, i.e. derivatives of muramyldipeptide with acridine/acridone moieties[35] or analogs of MPA with quinic acid[38]. In current work, we elaborated synthesis of the ester conjugates of MPA and acridones/acridines **2a–e**, **3a–e**, in which lack of nitro group may diminish toxicity and can help to optimize the biological activity when applied as a drug.

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Methods

Chemistry

^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$, solutions with Varian Gemini 500 spectrometer (Varian Inc., Palo Alto, CA), with TMS as an internal reference. IR measurements were performed with Bruker IFS66 (Billerica, MA) and UV-VIS with PerkinElmer (Waltham, MA) UV-VIS LAMBDA 18. Mass spectra were recorded with MALDI-TOF spectrometer BRUKER BIFLEX III (DHB or CCA matrix) and HRMS ESI on MaldiSYNAPT G2-S HDMS (monoisotopic masses given). Column chromatography was performed using silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany) and for thin-layer chromatography (TLC) silica gel 60 F254 was used. Solid-phase extraction (SPE) analyses were performed with CHROMABOND Macherey-Nagel columns (Dűren, Germany).

N-(ω-hydroxyalkyl)-9-acridone-4-carboxamides **8a–e**, *N*-(ω-hydroxyalkyl)acridine-4-carboxamides **9a–e** were prepared according to the procedure reported in literature[35].

Synthesis of *tert*-butyldimethylsilyl ether of MPA 6

MPA **1** (2 g, 6.2 mmol), *tert*-butyldimethylsilyl chloride (5.643 g, 37 mmol), imidazole (3.398 g, 50 mmol) were dissolved in dry DMF (10 mL), and the reaction mixture was stirred at room temperature. After 1 h no starting MPA **1** was observed (TLC). Subsequently, water (30 mL), diethyl ether (60 mL) were added and organic phase was separated, washed with five portions of water (20 mL each), and dried over anhydrous $MgSO_4$. Solids were filtered off and solvent evaporated under reduced pressure.

The crude **4** was dissolved in THF (10 mL), water (10 mL), acetic acid (10 mL) and stirred at room temperature. The reaction