European Journal of Medicinal Chemistry 143 (2018) 646–655

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis and antimicrobial activity of amino acid and peptide derivatives of mycophenolic acid

Agnieszka Siebert [a], Magdalena Wysocka [b], Beata Krawczyk [b], Grzegorz Cholewiński [a, *], Janusz Rachoń [a]

[a] Department of Organic Chemistry, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland
[b] Department of Molecular Biotechnology and Microbiology, Gdansk University of Technology, ul. G. Narutowicza 11/12, 80-233 Gdansk, Poland

ARTICLE INFO

Article history:
Received 29 June 2017
Received in revised form
10 November 2017
Accepted 28 November 2017
Available online 1 December 2017

Keywords:
Mycophenolic acid
Amino acids
Peptides
Antimicrobial activity
Tuftsin

ABSTRACT

The series of 16 novel amino acid and peptide mycophenolic acid (MPA) derivatives was obtained as potential antibacterial agents. Coupling of MPA with respective amines was optimized with condensing reagents such as EDCI/DMAP and T3P/TEA. Amino acid analogs were received both as methyl esters and also with the free carboxylic group. The biological activity of the products was tested on five references bacterial strains: *Klebsiella pneumoniae* ATCC 700603 (ESBL), *Escherichia* coli ATCC 8739, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* MRSA ATCC 43300, *Staphylococcus aureus* MSSA ATCC 25923. Peptide derivatives proved to be the most versatile ones, their MIC values relative to most strains was lower than MPA alone. It has been noted that the activity of amino acid derivatives depends on the configuration at the chiral center in the amino acid unit and methyl esters indicated better antimicrobial activity than analogs with free carboxylic group.

© 2017 Elsevier Masson SAS. All rights reserved.

1. Introduction

Mycophenolic acid **1** (MPA) possesses interesting scope of biological properties including antimicrobial, antifungal, antiviral, immunosuppressive and antitumor features. MPA **1** (Fig. 1) was discovered in 1896 by Italian physician Bartolomeo Gosio, who collected the fungus from damaged maize and called it *Penicillium glaucum* [1–3]. It was found that the fungus exhibited antimicrobial activity against *anthrax bacterium* [4]. Although MPA **1** occurred to be the first antibiotic isolated in pure and crystalline form, further studies were not continued for a long time [5].

In the 1970s, the biochemical causes of immunodeficiency were investigated in children, and inosine 5′-monophosphate dehydrogenase (IMPDH) was established as an enzyme responsible for the undesired immune response in autoimmune diseases. Studies towards a suitable inhibitor were started, followed by a successful clinical trial with the compound under the trade name Cell Cept **2** (Fig. 2), which was approved for use in kidney transplantation by the US Food and Drug Administration in 1995 [6].

MPA **1** is a competitive and reversible inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH), predominantly isoforms II, which is present in tumor cells and in activated lymphocytes [7,8].

MPA **1** is an active substance of immunosuppressive drugs for the prevention of acute and chronic rejection of allogenic organ transplants. So far, there are clinically applied two derivatives of MPA: mycophenolate mofetil **2** (MMF) known as CellCept produced by Roche and mycophenolate sodium **3** (MPS) (Fig. 2) under the trade name Myfortic manufactured by Novartis [9–11].

MPA **1** possesses significant antimicrobial properties e.g. against *Anthrax bacterium* [4], *Botrytis cinerea* [12]), antifungal like against *Rhizoctonia Solani* [13], antiviral for instance against Dengue virus [14], avian reoviruses (ARV) [15], coronaviruses (MERS_CoV) [16] and rotavirus [17]. Mycophenolic acid **1** exhibits also a wide spectrum of anticancer properties [18–20].

Recent studies in 2015 showed that the combination of rapamycin with MPA significantly improves clinical symptoms (erythema, edema, rash and rash) at atopic dermatitis, also reduced epidermal exfoliation, edema and cellulite [21].

On the other hand, multidrug resistance is also a significant problem in treatment of bacterial infections, and structural modifications of MPA could provide promising antimicrobial agents.

Taking into account such a large number of positive aspects of the MPA, we attempted to modify its structure towards

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

https://doi.org/10.1016/j.ejmech.2017.11.094
0223-5234/© 2017 Elsevier Masson SAS. All rights reserved.