European Journal of Medicinal Chemistry 189 (2020) 112091

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Research paper

Immunosuppressive properties of amino acid and peptide derivatives of mycophenolic acid

Agnieszka Siebert [a], Grzegorz Cholewiński [a, *], Piotr Trzonkowski [b], Janusz Rachon [a]

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

ARTICLE INFO

Article history:
Received 20 December 2019
Received in revised form
20 January 2020
Accepted 21 January 2020
Available online 24 January 2020

Keywords:
Mycophenolic acid
Amino acids
Peptides
Tuftsin
IMPDH inhibitors
Immunosuppressants

ABSTRACT

Mycophenolic acid (MPA) was coupled with amino acids and biologically active peptides including derivatives of tuftsin to modify its immunosuppressive properties. Both amino acid unit in the case of simple MPA amides and modifications within peptide moiety of MPA - tuftsin conjugates influenced the observed activity. Antiproliferative potential of the obtained conjugates was investigated *in vitro* and MPA amides with threonine methyl ester and conjugate of MPA with retro-tuftsin occurred to be more selective against PBMC in comparison to parent MPA. Both amino acid and peptide derivatives of MPA acted as inosine-5′-monophosphate dehydrogenaze (IMPDH) inhibitors.

1. Introduction

Mycophenolic acid (MPA) **1** (Fig. 1) was isolated first time by B. Gosio from *Penicilium brevicompactum*. It possesses antibacterial, antiviral, anticancer and immunosuppressive properties [1,2] .

MPA is an uncompetitive and reversible inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH) and its prodrugs are applied in clinic as immunosuppressants. In 1995 morpholine ester of mycophenolic acid — mycophenolate mofetil (MMF, CellCept ®, Roche AG) was approved by FDA as drug in solid organ transplantation (kidney, liver, heart) for decrease risk of rejection. The second form of the drug is mycophenolic acid sodium salt (MPS, Myfortic ®, Novartis Farma AG). Both forms are used together with other immunosuppressants, like cyclosporine, tacrolimus in transplantation and autoimmune disorders treatment, e.g. psoriasis [1–4].

MPA inhibits IMPDH *via* blocking binding site of NAD^+ cofactor placed near to active center of the enzyme. The structure of IMPDH enzyme in complex with MPA **1** was reported [5] and the role of functional group of **1** in maintenance of activity was explained, like free phenol or carboxylic groups, which are able to hydrogen bond interactions with the enzyme. Biosynthesis of lymphocytes and DNA depends on IMPDH activity, since it involves nucleotides biosynthesis *de novo*. Other cells use both *de novo* and salvage pathway, when nucleobases are recycled. As a result, MPA selectively inhibits proliferation of lymphocytes B and T [1–4]. Furthermore, IMPDH exists in the two isoforms I and II, where IMPDH I is expressed in normal cells, and IMPDH II is up-regulated in activated lymphocytes and neoplastric cells. MPA inhibits both forms with higher activity against IMPDH II [6]. As a result, numerous IMPDH inhibitors revealed not only immunosuppressive, but also anticancer properties [7–11].

Despite of the progress in immunosuppressive treatment, both the risk of rejection and serious side — effects have been not eliminated so far. As a result, numerous studies were performed to increase efficiency and diminish toxicity of novel mycophenolic acid derivatives [12–19].

In our previous work we designed amino acid MPA derivatives possessing potent immunosuppressive activity [20]. These results were in agreement with literature data, that polar group at the end of side chain in MPA is important for maintenance of antiproliferative activity, since enables hydrogen bond interactions with Ser 276 of IMPDH [21].

On the other hand, tuftsin is an endogenous tetra-peptide with the sequence Thr-Lys-Pro-Arg, naturally occurring in human blood,

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

https://doi.org/10.1016/j.ejmech.2020.112091
0223-5234/