The Chemistry of Mycophenolic Acid – Synthesis and Modifications Towards Desired Biological Activity

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Abstract: Mycophenolic acid (MPA) is a basis for the immunosuppressive drugs used in clinic against rejection in solid organs transplantations. Since its physiological activity is very promising, numerous studies have been performed to establish mechanism of action, structure – activity relationship (SAR), synthesis of MPA derivatives to improve or extent its clinical use to anticancer one, especially. The reported methods for preparation of MPA analogues have been achieved by semi-synthetic approaches or total synthesis and accomplished by *in vitro* or / and *in vivo* evaluations. In this review we would like to bring together chemical aspects of these compounds and their implementations within biological activity, their synthesis and structural modifications referred to the structure-activity relationship (SAR).

Keywords: Mycophenolic acid, MPA, MPA analogues.

INTRODUCTION

Mycophenolic acid (4*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoic acid (**1**) Fig. (**1**) is a type of immunosuppressive drug widely used for prophylaxis and treatment of organ rejection in transplantation [1-4].

The mechanism of its action is based on inhibition of inosine-5'-monophosphate dehydrogenaze (IMPDH). The enzymes involved in nucleotides biosynthesis are crucial for supporting cell proliferation. In general, there exist two pathways of nucleotide biosynthesis – *de novo* (when purine or pyrimidine ring has to be assembled) and salvage pathway (when already existed nucleobases are recycled).

IMPDH (inosine-5'-monophosphate dehydrogenaze) is the enzyme which catalyzes the rate determining step in guanine nucleotide biosynthesis *de novo*. This NAD^+ dependent reaction involves conversion of IMP (inosine-5'-monophosphate) to XMP (xanthine-5'-monophosphate) [5]. Mycophenolic acid is active towards two human isoforms of the enzyme: IMPDH I (expressed in normal cells) and IMPDH II (observed at high levels in neoplastic cells) [1, 6].

In commerce are applied: ester - mycophenolate mofetil (**2**) (MMF; CellCept®, Roche AG) and sodium salt – mycophenolate sodium (**3**) (MPS; Myfortic®, Novartis Pharma AG) [7-9] both in combination with corticosteroids and calcineurin inhibitors (cyclosporine A, tacrolimus) [10-13]. The FDA approved MMF as an immunosuppressive agent for organs transplant in 1995 [1]. This compound possesses also interesting antiviral, antibacterial, antifungal and antipsoriatic properties [11, 14-16]. The anticancer activity of MPA has been also examined, however its glucuronide metabolite MPAG (**4**) occurred to be not active [1, 17, 18].

SYNTHESIS OF MPA

The structure of mycophenolic acid (**1**) includes six-substituted benzene ring fused with lactone moiety. Other functional groups are: hydroxyl, methoxyl, methyl and alkyl side chain bearing six carbons, double bond in *trans* conformation and free carboxylic group. This compound was discovered by Gosio in 1896 [1], and its structure was established by Clutterbuck [19] and Raistrick [20]. The first synthesis was published by Birch and Wright [21, 22]. Further modifications and other methods aimed at improving yield, reducing number of stages or using distillation or crystallization instead of chromatography purification to scale-up purpose [23-33]. However, synthesis of MPA (**1**) from commercially available starting materials is still rather time-consuming. Mycophenolic acid (**1**) is also produced from *Penicillium brevicompactum* [1, 32]. The widespread method is a solid-state fermentation, which enables to reach higher fermentation productivity, lower catabolic repression, low water demand, lower sterility demand in comparison with other biotechnological processes [34]. On the other hand, chemical synthesis provides various structure alteration, in some cases difficult to achieve by simple modifications of MPA molecule. Those target molecules are challenging for organic chemists looking for relevant synthetic strategies.

Analogues of MPA were also produced by microbial transformations, however their biological activity examinations were not reported [1, 35, 36].

The key step in the first synthesis of MPA described by Birch and Wright (Scheme **1**) was Alder –Rickert reaction of 1,3-dimetoxy-4,6-dimethyl-1,3-cyklohexadiene (**5**) with dimethyl acetylenedicarboxylate DMAD (**6**). The bicyclic Diels-Alder adduct (**7**) was not isolated, but heated to achieve five-substituted benzene (**8**) *via* propylene elimination. The substituents were modified towards allyl ether (**9**) which underwent Claisen rearrangement to phenol (**10**). Then, transformations of introduced side chain gave mycophenolic acid (**1**) [21].

Patterson described synthetic pathway (Scheme **2**) from commercially available methyl 2-hydroxy-4-metoxybenzoate [23, 24]. The convenience of this laboratory method is a reduction of chromatographic separations and scaled-up to several grams of MPA. The starting material (**11**) holds three substituents in the aromatic ring. *N,N*-Diethyl-4-methoxy-2-(prop-2-enyloxy)benzamide (**12**) gave phenol (**13**) in Claisen rearrangement, which was brominated and methylated at 6 position, after protection of phenol group. Then, *N,N*-

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