Synthesis of N-heterocyclic Amides of Mycophenolic Acid as Prospective Immunosuppressants

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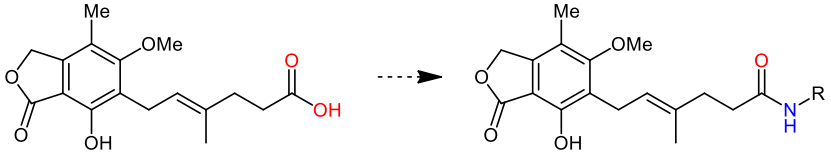
Mycophenolic acid (**MPA**) is a wide-spread immunosuppressant used in the prophylaxis of graft rejection and some autoimmune diseases. Its bioactivity results from anticompetitive and reversible inhibition of inosine-5'-monophosphate dehydrogenase (**IMPDH**), the enzyme which is essential for glycosylation processes, responsible for guanyl nucleotides biosynthesis and lymphocyte T proliferation, thus spawning immunosuppressive properties of **MPA**-based drugs [1].

Despite ubiquitous application in clinics, both prodrugs sodium mycophenolate (**MMS**) and mycophenolate mofetil (**MMF**) bring severe side effects such as opportunistic microbial infections, lymphomas and other malignancies [1]. Therefore newer immunosuppressants are desired, especially those presenting less cytotoxic properties than referential **MPA**. Even with limited possible structural modifications, one may switch its carboxylic acid moiety into an amide counterpart with slight decline in antiproliferative activity however manifesting lowered cytotoxicity than the reference [2].

In the present work one may become acquainted with computational studies, organic synthesis and biological evaluation of novel amides of **MPA** derived from selected heteroaromatic structural cores. The molecular docking assay serves as an *in silico* rationale prompting one to deepen this subject in the context of foraging new antiproliferative agents characterized with high affinity towards the enzyme. Highly effective and simple synthesis of designed multifunctional compounds was optimized without the need of protective groups implementation. Eventually, biological analyses were performed in the form of *in vitro* tests carried out in the T-Jurkat and peripheral mononuclear blood cells (PBMCs) medium, both widely used in the antiproliferative activity determination. In the end, one may familiarise with the actual correlation between computational studies and biological assays in a sense of antiproliferative activity ascertainment.



MPA

NOVEL AMIDES OF MPA
R = heterocyclic structrual core

[1] R. Bentley, Mycophenolic Acid: A one hundred year odyssey from antibiotic to immunosuppressant, *Chem. Rev.* 100 (**2000**) 3801–3826.
[2] J. Walczak et al. Novel amides of mycophenolic acid and some heterocyclic derivatives as immunosuppressive agents, *J. Enzyme Inhib. Med. Chem.* 37 (**2022**) 2725-2741.