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# The synthesis and structure of a potential immunosuppressant: N-mycophenoyl malonic acid dimethyl ester

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ABSTRACT

The synthesis of a potential immunosuppressant, i.e. dimethyl ester of N-mycophenoyl malonic acid was optimized in the reaction of mycophenolic acid (MPA) with amino malonic dimethyl ester in the presence of propanephosphonic anhydride (T3P) as a coupling reagent. The structural properties of the obtained MPA derivative were investigated by NMR, MS and single crystal X-ray diffraction methods. Theoretical considerations of conformational flexibility based on DFT calculations are presented.

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## 1. Introduction

Mycophenolic acid **1** (MPA) is a potent inosine 5′-monophosphate dehydrogenase (IMPDH) inhibitor which possesses immunosuppressive properties. Due to their immunosuppressive characteristics, both MPA derivatives, namely, mycophenolate sodium (MPS, Myfortic) and mycophenolate mofetil (MMF, CellCept) are used in medicine to prevent organ transplant rejection and to treat autoimmune disorders [1] [2], [3]. The optimization of the synthesis of MPA molecule-based active substance included the synthesis of numerous MPA derivatives (see Refs. [4] [5], [6] [7], [8]) due to the fact that several structural features are crucial for maintaining the biological properties of final compound. Apart from Van der Waals interactions between the MPA and IMPDH molecules, the hydrogen bonds between the lactone moiety of MPA and Gly 326 and Thr 333 of the IMPDH enzyme as well as between the phenol group of MPA and Thr 333 and Gln 441 of IMPDH also play an important role. Similarly, the *trans* configuration of the double bond in the side chain of MPA enables the interaction between its carboxylic group and Ser 276 [9], [10]. As a result, the modification of this polar carboxylic group contributed to obtaining the promising novel MPA analogs with improved therapeutic characteristics [11], [12]. MPA **1** was bonded to amino acid esters, resulting in respective amides that revealed significant antiproliferative activities [13], [14]. Additionally, the ester group in amino acid moieties might be advantageous due to better penetration through the cell membrane [14]. In our previous studies, MPA **1**was coupled to some proteinogenic amino acid esters by means of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI), resulting in respective amides possessing clear inhibitory activity towards IMPDH [13]. These findings encouraged us to synthesize and characterize *N*-mycophenoyl malonic acid dimethyl ester **3** (Scheme 1), which possesses a polar amide together with two ester groups at the end of the side chain. First, the attempt was made to attach amino malonic acid dimethyl ester **2** to MPA **1**with the use of EDCI, however, this approach turned out to be ineffective due to decreased nucleophilicity of the amino group in **2**. Therefore, we optimized the reaction by using propanephosphonic anhydride ($T_3P$) as a coupling agent, which has been reported to work efficiently in case of difficult amidations [15]. As a result, the desired *N*-mycophenoyl malonic acid dimethyl ester **3** was obtained, while

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