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Citation for final published version:

Tselios, T. V., Yannakakis, M. P., Matsoukas, M. T., Mantzourani, Efthymia D. and Platts, J. A. 2014. Structure-based design and synthesis of non-peptide mimetics based on the immunodominant epitopes of myelin proteins. *Journal of Peptide Science* 20 , S191-S192. 10.1002/psc.2688

Publishers page: <https://doi.org/10.1002/psc.2688>

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Structure-Based Design and Synthesis of Non-Peptide Mimetics Based on the Immunodominant Epitopes of Myelin Proteins

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Introduction

Multiple Sclerosis (MS) is an immunologically controlled, inflammatory, demyelinating disease, characterized by destruction of the white matter (myelin) of the Central Nervous System (CNS), leading to serious medical conditions and paralysis [1]. It is believed that MS is an autoimmune disease in which T-cell response is directed to the immunodominant epitopes of the myelin proteins. T-cell response is triggered by the formation of the trimolecular complex between the Major Histocompatibility Complex (MHC), known as Human Leukocyte Antigen (HLA) in humans, the immunodominant epitopes of myelin proteins and the T-cell receptor (TCR) [2]. In this study, the interactions that occur during the creation of the trimolecular complex (pdb file: 1YMM) have been identified. The conformational characteristics that are essential for the disease induction and the rational design of non-peptide inhibitors were proposed. The MBP₈₃₋₉₆ epitope (Glu⁸³AsnProValValHisPhePheLysAsnIleValThrPro⁹⁶) was specifically chosen for the rational design because it is identified as one of the main immunodominant epitope in MS patients [3, 4]. The aim of this study was the rational design and synthesis of non-peptide mimetics with the ability to mimic the immunodominant 83-96 epitope of MBP, to block the formation of the trimolecular complex and therefore the T cell activation. The designed non-peptide mimetics aim to bind to the TCR, prevent and stop the formation of the trimolecular complex and the further stimulation and proliferation of the encephalitogenic T-cells [5, 6].

Results and Discussion

The design of non peptide molecules was achieved by using “structure based” in combination with “ligand based” drug design. The MOE software in a Linux environment was used for the simulation studies while the pharmacophore search was carried out in the zinc-drug alike database. The main steps of the rational design are: i) crystal structure of the HLA/peptide/TCR complex (1YMM), ii) recognition of the key pharmacophore groups, iii) development of pharmacophore model, iv) hit visualization, optimization, v) final molecules and vi) synthesis

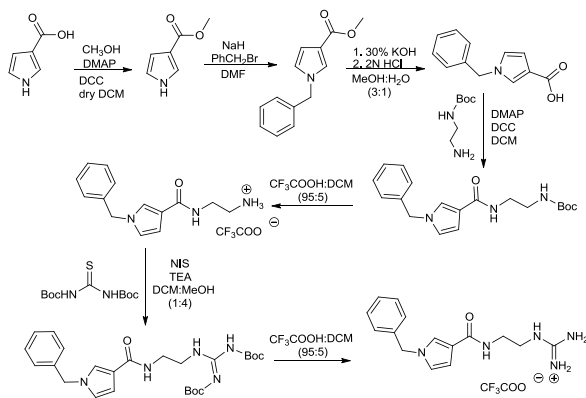


Fig. 1. Synthetic procedure of the pyrrole analogue using the pyrrole-3-carboxylic acid starting material.

Table 1. The MBP₈₃₋₉₆ key residues for interaction with HLA and TCR that are used for the development of the pharmacophore model.

Pharmacophore Groups	Features
F1 (1,4 Å) Aro	Aromatic Ring (His ⁸⁸)
F2 (1,5 Å) Hyd	Hydrophobic isopropyl- group (Val ⁸⁶)
F3 (1,4 Å) Aro	Aromatic ring (Phe ⁸⁹)
F4 (1,6 Å) Cat	Cation and donor (the N terminal of Pro ⁸⁵ interacts with Tyr ⁵⁸ of the TCR β-chain)
V1 (1,8 Å)	Volume exclusion (interaction of Val ⁸⁷ with the HLA receptor)
V2 (1,5 Å)	Volume exclusion (interaction of Phe ⁹⁰ with the HLA receptor)

and biological evaluation. The amino acids Val⁸⁷ and Phe⁹⁰ of the MBP₈₃₋₉₆ are the main anchors in the hydrophobic pockets P1 and P4 of the HLA while secondary anchors have been recognized the amino acid Asn⁹², Ile⁹³ and Thr⁹⁵ that interact with the P6, P7 and P9 pockets. The binding of the TCR to the peptide-HLA complex was mainly determined by the arrangement of the side chain of the Val⁸⁶, His⁸⁸, Phe⁸⁹ and Lys⁹¹ that interact with the P-1, P2, P3 and P5 pockets of the TCR [2,4,5]. The pockets P2 and P3 were selected for the creation of the pharmacophore model (Table 1) because they are hydrophobic and aromatic and the binding of TCR on the HLA-Peptide occurs diagonally from the N terminal of the peptide antigen. 330 hits of zinc database, satisfied the conformational characteristics of model and after the visualization and docking studies of the 330 hits on the TCR, one of them was selected (lead molecule) for further optimization. The optimization includes the next steps: i) extension: addition of functional groups to increase the interaction, ii) simplification: removal of groups that are not a part of the pharmacophore groups and iii) rigidification: for flexible molecules, the number of available conformations is reduced while the bioactive conformation is conserved. The optimization was performed using the LigX of the MOE software following by docking studies. The final molecules have the pyrrole moiety as the main template, are N substituted with the benzyl group (alone or substituted with a negative charged group) and are substituted at position 2 or 3 of the pyrrole with guanidine. The proposed non-peptide mimetic molecules have the following characteristics: i) they are placed deeply on the TCR pockets, ii) they seem to interact strongly with the TCR increasing the binding sites with the TCR, iii) they reveal pi-stacking interactions, iii) they are according to Lipinski's "Rule of Five" for pharmaceutical molecules, iv) they could be absorbed *in vivo*, v) they could be potential bioactive molecules, vi) they could be synthesized simply based on retro-synthetic analysis (Figure 1).

Acknowledgments

This study was financially supported by the "Cooperation" program 09SYN-609-21, (O. P. Competitiveness & Entrepreneurship (EPAN II), ROP Macedonia - Thrace, ROP Crete and Aegean Islands, ROP Thessaly – Mainland Greece – Epirus, ROP Attica).

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