ASSEMBLY OF MELANOSTATIN PEPTIDOMIMETICS USING CHIRAL β-AMINO ACIDS AS PROLINE SURrogATES

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Introduction

Parkinson’s disease is the second most common neurodegenerative disease of the central nervous system (CNS), affecting 20 million people worldwide and causing hundreds of thousands of deaths every year.[1] Melanostatin (MIF-1, Figure 1) is a tripeptide that acts as a positive allosteric modulator (PAM) of the Dopamine D2 Receptors (D2R).[2] increasing the Receptor’s affinity towards dopamine (DA), being thus considered as a possible pharmacological alternative in Parkinson’s therapy, which is focused on DA potentiation within the CNS.

![Figure 1. Structures of MIF-1 and MIF-1 peptidomimetics.](image)

Aim

Considering that proline (Pro) residue of MIF-1 is non-essential to the PAM activity of this neuropeptide and that Pro is not sensitive to chemical derivatizations in comparison with the remaining residues, we aimed to further explore and understand the role of Pro in MIF-1 activity.

To accomplish this goal, several MIF-1 peptidomimetics were designed and synthesized bearing two different β-amino acid as Pro mimetics (Figure 1) in order to uncover the role of secondary amine at the N-terminus of this neuropeptide by replacing it with a primary amine.

Work Plan: Organic Chemistry

The first step in the synthetic route was the preparation of β-amino acid rac-1 (by [2+2] addition of cyclopentadiene (CPD) to chlorosulfonyl isocyanate (CSI), as depicted in Scheme 1.

![Scheme 1. Synthesis of β-amino acid rac-1.](image)

Conclusion

The synthetic plan was successfully completed in 24-31% global yields. The target peptidomimetics (7-12) are currently being pharmacologically evaluated by means of functional assays and results are expected in the upcoming weeks.

References