Synthesis and Pharmacological Evaluation of Melanostatin Analogues Containing 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.

Melanostatin **(MIF-1**, Figure 1) is a neuropeptide that acts as a positive allosteric modulator (PAM) of the Dopamine D_2 Receptors (D_2R), 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.

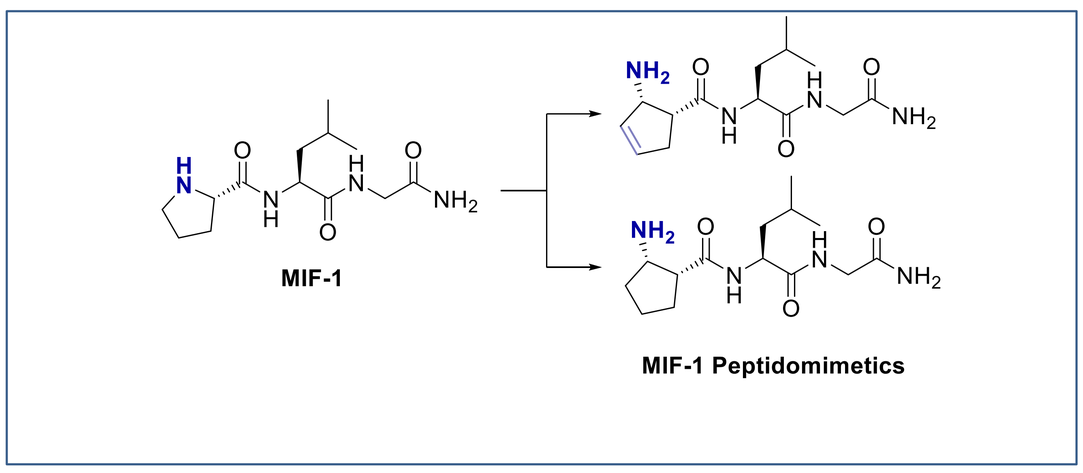


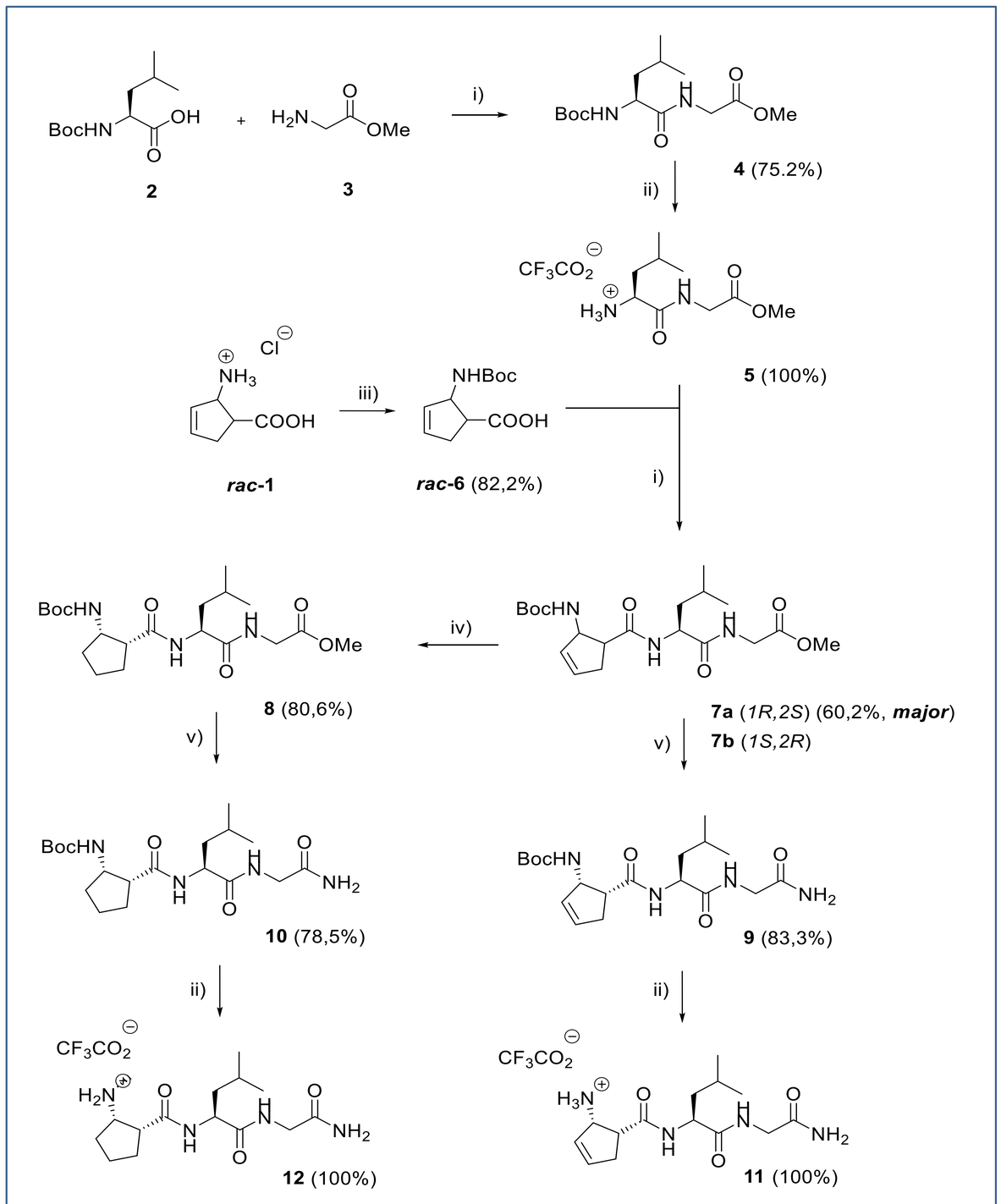
Figure 1. Structures of MIF-1 and MIF-1 peptidomimetics.

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 undercover the role of secondary amine at the N-terminus of this neuropeptide by replacing it with a primary amine.

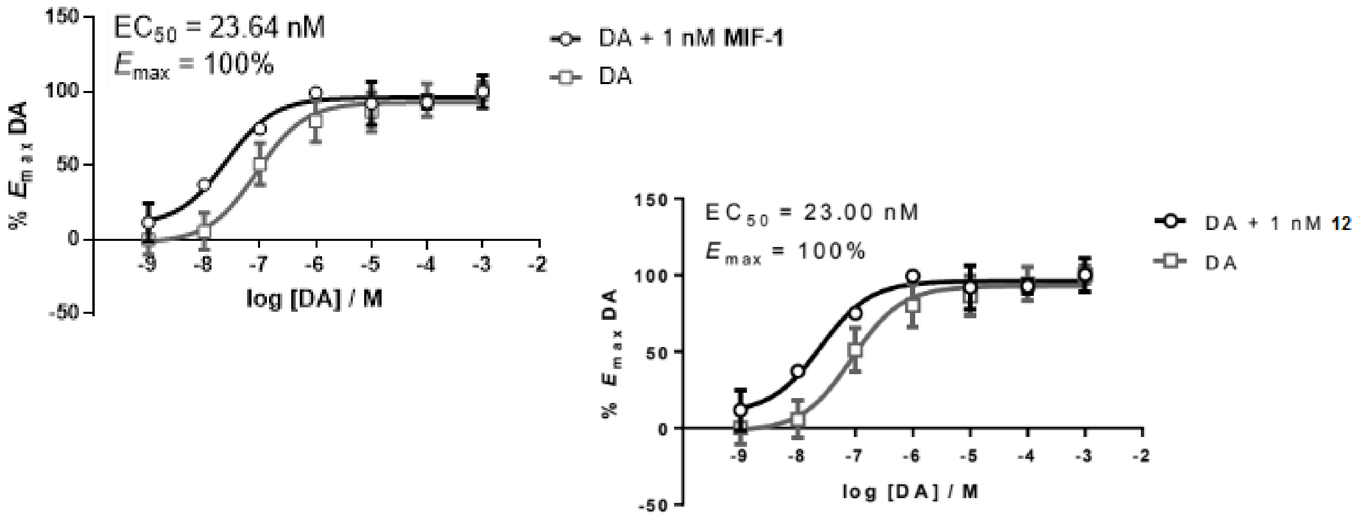
Work Plan: Organic Chemistry



Scheme 2. Synthetic route for the preparation of MIF-1 peptidomimetics **7-12**.

Results and Conclusion

Functional pharmacological assays show that compound **12** has a similar potency to that of MIF-1 at 1 nM (EC_{50} = 23.00 for **12** and 23.64 nM for MIF-1), This result may indicate that lower basicity at the *N*-terminal is well tolerated providing new insights on the rational design of MIF-1 analogues. Currently, compound **12** is undergoing toxicity and other biological evaluations.



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