Exploring the Bioisosterism of Proline residue in Melanostatin neuropeptide using heteroaromatic scaffolds

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Introduction

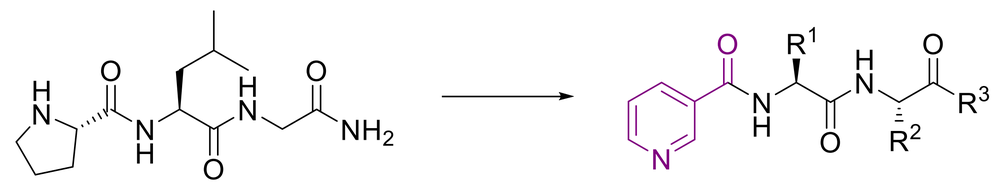
Parkinson's disease (PD) is the most common motor neurodegenerative disorder of the central nervous system, affecting 20 million people worldwide.[1] Common symptoms include tremors, bradykinesia, gait alterations, sleeping disorders, fainting, and dementia. Currently, PD treatments are focused on dopamine (DA) potentiation through the administration of a DA precursor - levodopa (L-DOPA) - and coadministration of inhibitors of the catechol-O-methyl transferase and monoamine oxidase B enzymes.[2] Even though L-DOPA regimen is able to control the progression of PD motor symptoms, long-term therapy causes serious health concerns. In this sense, pharmacological alternatives are mandatory.

Melanostatin

Melanostatin (MIF-1, **Figure 1**), is an endogenous hypothalamic neuropeptide derived from the oxytocin hormone that acts as a positive allosteric modulator (PAM) of the D2 Receptors (D_2R).[3-5] By increasing the D_2R affinity for DA, these receptors are activated at lower DA concentration, being thus clinically relevant. Previous studies developed by our research group reveal that the replacement of L-Proline (Pro) residue by heteroaromatic scaffolds are well tolerated, rendering analogues with PAM activity comparable to the parent neuropeptide.[3-5]

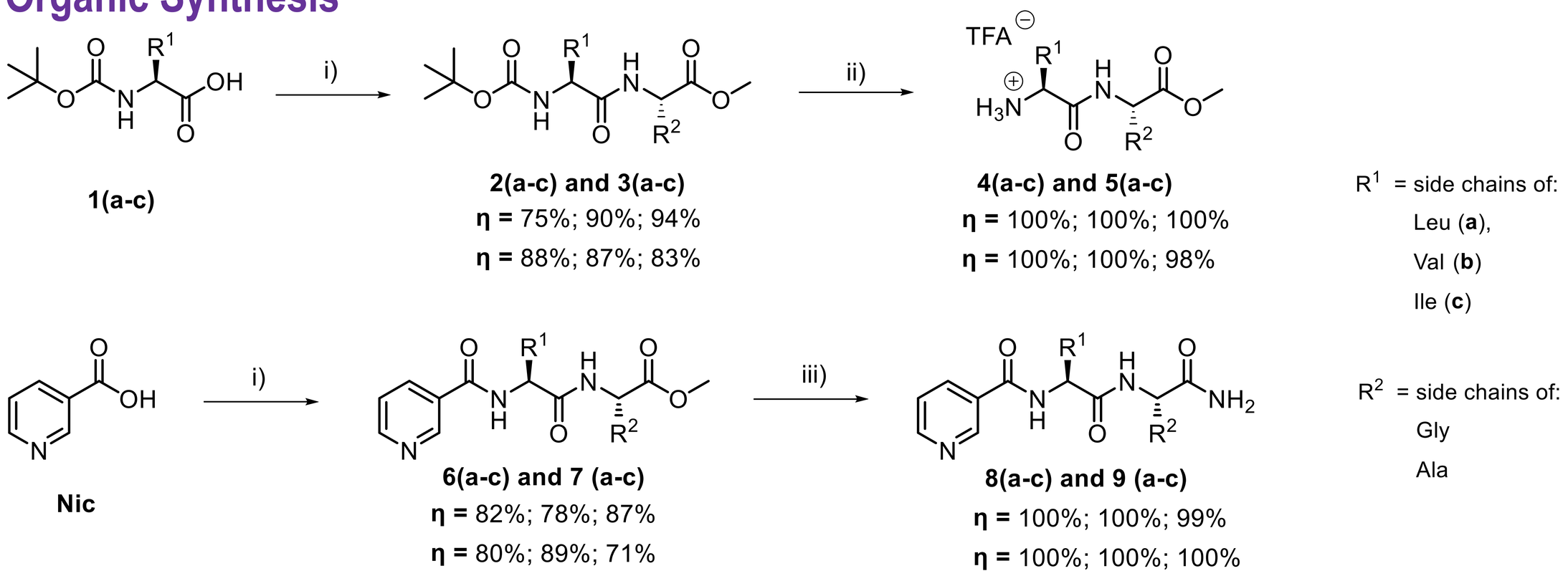
Aim

In this work, twelve novel MIF-1 analogues (Figure 1) were synthesized and chemically characterized by incorporation of Niacin, also known as Vitamin B_3, as a Pro surrogate.



MIF-1 **MIF-1 Peptidomimetics**

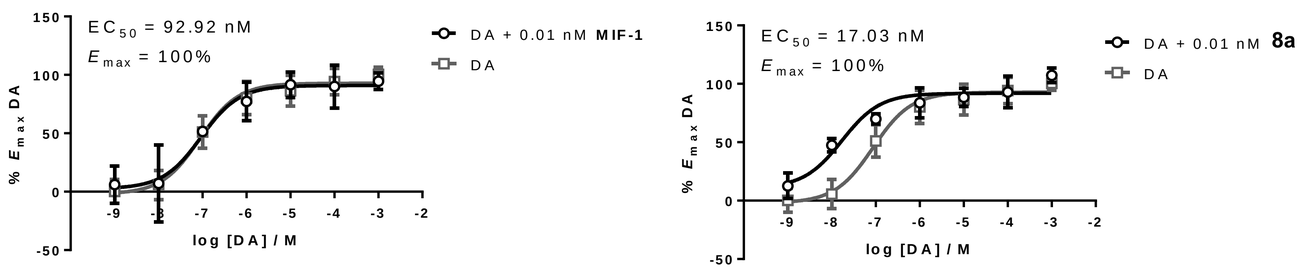
Organic Synthesis



Scheme 1. Synthesis of MIF-1 peptidomimetics. Reagents and conditions: (i) Et_3N, TBTU, CH_2Cl_2; (ii) TFA, CH_2Cl_2; (iii) NH_3 7 M in MeOH.

Preliminar Pharmacological Assays

Preliminar pharmacological assays reveal that peptidomimetic **8a** enhanced DA pontency more than 3 times at subnanomolar concentration when compared with MIF-1.



Undergoing Work

Currently, the peptidomimetic **8a** is undergoing toxicity and other biological assays. This work is expected to provide useful structure-activity relationship information for the rational design of potent PAMs of D_2R, paving the way for the development of new anti-Parkinson hits.

References:

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