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SYNTHESIS AND CYTOTOXICITY PROFILING OF PYRIDINE-BASED MELANOSTATIN PEPTIDOMIMETICS TARGETING PARKINSON'S DISEASE

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INTRODUCTION & AIM

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder of central nervous system (CNS), characterized by the progressive loss of mesencephalic dopaminergic neurons.[1] Current therapies provide symptomatic relief but do not halt disease progression, highlighting the urgent need for novel and innovative therapeutic strategies.[2] Melanostatin (MIF-1), a hypothalamic neuropeptide and positive allosteric modulator (PAM) of dopamine D_2 receptors, has emerged a promising candidate for PD treatment.[2] However, its peptide nature restricts clinical use due to its poor oral bioavailability and limited metabolic stability.[2]

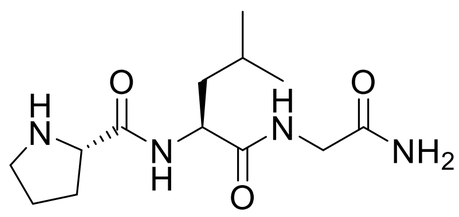


Figure 1. *Structure of* MIF-1

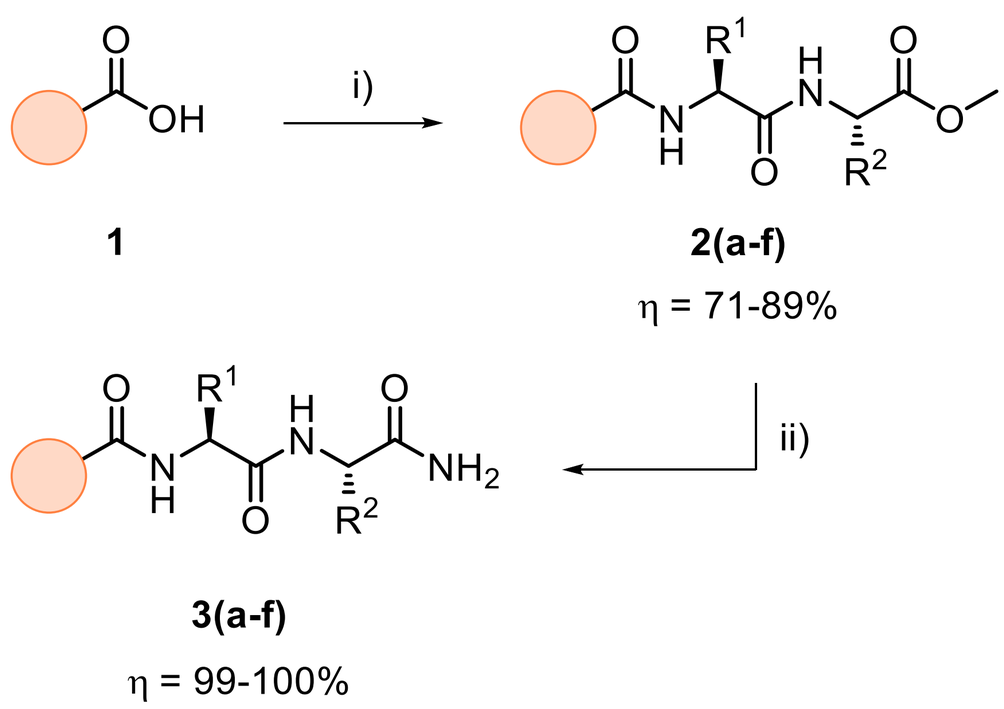
In this work, we designed and synthesized twelve novel analogs using pyridine-based carboxylic acids as prolyl surrogates to address the pharmacokinetic limitations of MIF-1. Pyridine-based scaffolds are known for their structural versatility and CNS drug-like properties, including neuroprotective and neurotransmitter-modulating effects.[3-4]

METHOD

The synthesis route is depicted in **Scheme 1**. Starting with the selected pyridine scaffold (**1**), tripeptides **2(a-f)** were synthesized by peptide coupling with *C*-terminal dipeptides (**a-f**), in good yields (71-89%). Subsequently, methyl ester groups of **2(a-f)** were converted into the corresponding primary amides **3(a-f)** via ammonolysis with NH_3 7 M in MeOH in quantitative yields.

Toxicological assays were carried out for both esters and amides in differentiated human SH-SY5Y neuroblastoma cells using the MTT reduction assay. The results are depicted in **Figure 2**.

RESULTS & DISCUSSION



Scheme 1. Synthesis of MIF-1 peptidomimetics. *Reagents and conditions*: (i) Et_3N, TBTU, dipeptides **a-f**, anhydrous CH_2Cl_2; (ii) NH_3 7 M in MeOH.

Structure-cytotoxicity relationship studies in differentiated SH-SY5Y cells identified that, in this group of analogs, the methyl ester group acts as a toxicophore, whereas the corresponding amide counterparts exhibited improved toxicological profiles.

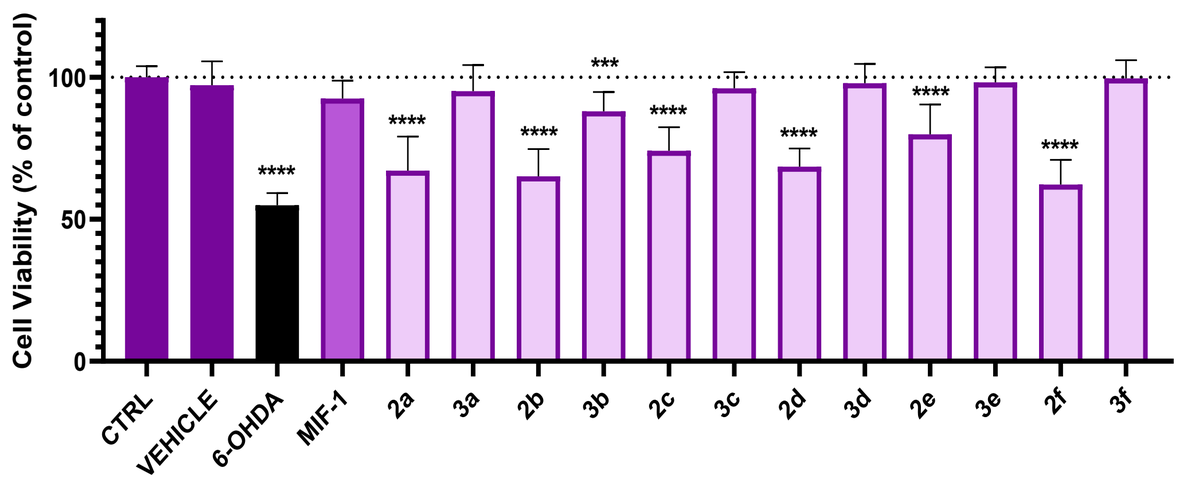


Figure 2. MTT reduction assay. Data are expressed as a percentage of control and are presented as mean ± standard deviation from at least three independent experiments, each performed in triplicate. Statistical analyses were performed using the analysis of variance (ANOVA) test followed by the uncorrected Fisher's LSD (*p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 vs. control).

CONCLUSION

These findings offer valuable insights for the development of novel pyridine-based MIF-1 analogs with adequate toxicological profiles, contributing to the development of safer and more effective anti-Parkinson agents.

FUTURE WORK / REFERENCES

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