Using aza-Proline for the Assembly of a Melanostatin aza-Peptide Derivative

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Introduction

Due to their biochemical nature, bioactive peptides possess a short biological half-life and thus are generally not suitable to be used as pharmaceuticals. By incorporating aza-amino acid residues in biologically active peptides, the stability and bioavailability of peptide drugs are increased as a result of resistance towards peptidases.[1,2] The replacement of α-carbons with nitrogen atoms is known to increase the acidity of the amino group, which allows the establishment of stronger hydrogen bonds than the ones formed by proteinogenic amino acids.[2] This may also result in improved activity and selectivity of aza-peptides.[3] Moreover, the α-nitrogen atom can interchange between planar and pyramidal geometries in a dynamic manner,[4] making aza-amino acids very useful for the design of secondary structures in peptides and proteins.[2,4]

Melanostatin is an endogenous hypothalamic neuropeptide with the potential to be used as a treatment for Parkinson’s disease.[5] Pharmacologically, this peptide binds to dopamine D2 receptors (D2R) and acts as a positive allosteric modulator (PAM), decreasing the amount of dopamine needed to activate them.[5] Since the D2R are involved in the aetiology of Parkinson’s disease, the development of potent PAM for these receptors is considered to be a good alternative to reduce the dependence on levodopa therapy, which has major side effects.

In this work, it is reported the preparation of aza-proline and its incorporation in Melanostatin neuropeptide for the assembly of the correspondent aza-peptide derivative. The main goal of this project is to study the influence of the aza-amino acid residue on the biological half-life and PAM activity of Melanostatin.

Objective

To assemble the Melanostatin aza-peptide derivative (scheme 1), we started with the synthesis of activated aza-proline from hydrazine, which has similar properties to ammonia. Next, we proceeded with the coupling of aza-proline with methyl L-Leucylglycinate dipeptide, followed by the conversion of the C-terminal ester into a primary amide.

Synthesis

This work focused on the synthesis of a Melanostatin aza-derivative using aza-proline as a proline surrogate. A reliable and synthetic route was developed for the preparation of activated aza-proline from hydrazine in 5 reaction steps, with 68% global yield. Then, the aza-peptide was successfully assembled by peptide coupling with a global yield of 28%. The critical step of this synthetic route was the coupling of activated aza-proline with the dipeptide L-Leucyl-Gly-OMe, which requires further optimization.

This aza-peptide will be evaluated through pharmacological and biological assays to study, respectively, its potency and efficacy as PAM of D2R and to assess its cytotoxicity. As such, this project is expected to further appraise the application of aza-peptides in the development of novel peptide pharmaceuticals, while studying an alternative treatment for Parkinson’s disease.

Conclusion

References


Thanks are due to Fundação para a Ciência e Tecnologia (FCT, Portugal) for funding our Research Unit (ref. UIDB/50006/2020). IES-D and SCS-R thank FCT for funding through the Individual Call to Scientific Employment Stimulus (Ref. 2020.0231.0200.0006/C/CP1596/C/70000) and doctoral grant SFRH/BD/147463/2019, respectively. XG-M thanks Xunta de Galicia for financial funding with references GPC2017/GI-1557 and RED/122017-REDIG.