

## When Macrocyclic Peptides Meet the Crystal Structure of a Melanocortin Receptor

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**ABSTRACT:** This work reveals some key factors for the design of a novel generation of selective melanocortin ligands at the MC4 receptor.

### INTRODUCTION

G-protein-coupled receptors (GPCRs) activated by endogenous peptide ligands are considered to be next-generation targets for the development of novel drugs in medicine and for agricultural applications. The resolution of crystal structures for several peptide GPCRs has advanced our understanding of peptide–receptor interactions and fueled interest in correlating peptide heterogeneity with receptor-binding properties.<sup>1</sup>

Understanding of peptide–GPCR recognition has important implications for the design of peptides and peptide-like molecules as new pharmacological tools and crystal structures provide considerable assistance in validating binding hypotheses.

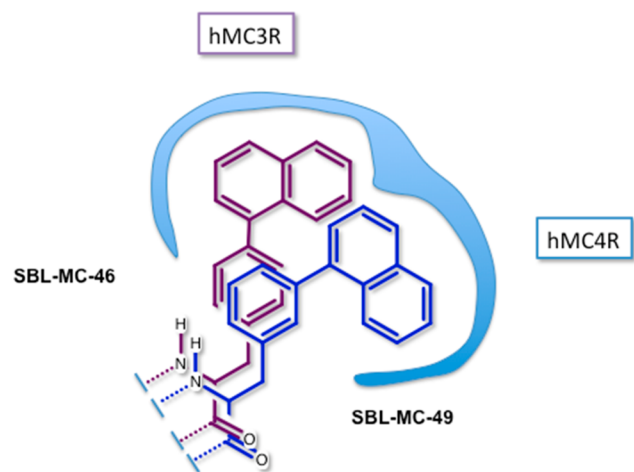
The melanocortin-4 receptor (MC4R) plays a central role in the control of energy homeostasis and is structurally distinct from any other reported GPCRs. MC4R has drawn much attention as a therapeutic target for treating obesity and related forms of obesity.<sup>2</sup> The recent report of the crystal structure of the MC4R in complex with the MC3R/MC4R nonselective antagonist SHU-9119 (Ac-Nle-c[Asp-His-DNal(2′)-Arg-Trp-Lys]-NH<sub>2</sub>) allowed for the first time the identification of structural features of the peptide binding with this receptor and provides a structural basis for the design of novel MC4R ligands.<sup>3</sup>

In this issue of the *Journal of Medicinal Chemistry*, Martin et al. reports the first results on how to design novel MC ligands by exploring the binding pockets for critical residues in the SHU-9119 structure.<sup>4</sup>

In this work, the authors performed a systematic modification of all SHU-9119 residues with a limited number of coded and uncoded amino acids. This rational way to perform modifications of the SHU9119 sequence not only allowed the discovery of ligands with improved affinity for hMC4R but also revealed several structural features leading to enhanced selectivity for hMC4R over hMC3R.

The authors reported the discovery of SBL-MC-37 (Ac-DOrn-c[Asp-His-DNal(2′)-Arg-Trp-Lys]-NH<sub>2</sub>) as a potent antagonist at hMC4R, which is only 1.3-fold lower than SHU-9119. Impressively, SBL-MC-37 displays 103-fold selectivity for hMC4R over hMC3R. The authors further showed that modifications in position 7 are critical in steering the selectivity

between hMC4 and hMC3 receptors (Figure 1). The variation of the amide bond in the cyclization motif of the cyclic peptide



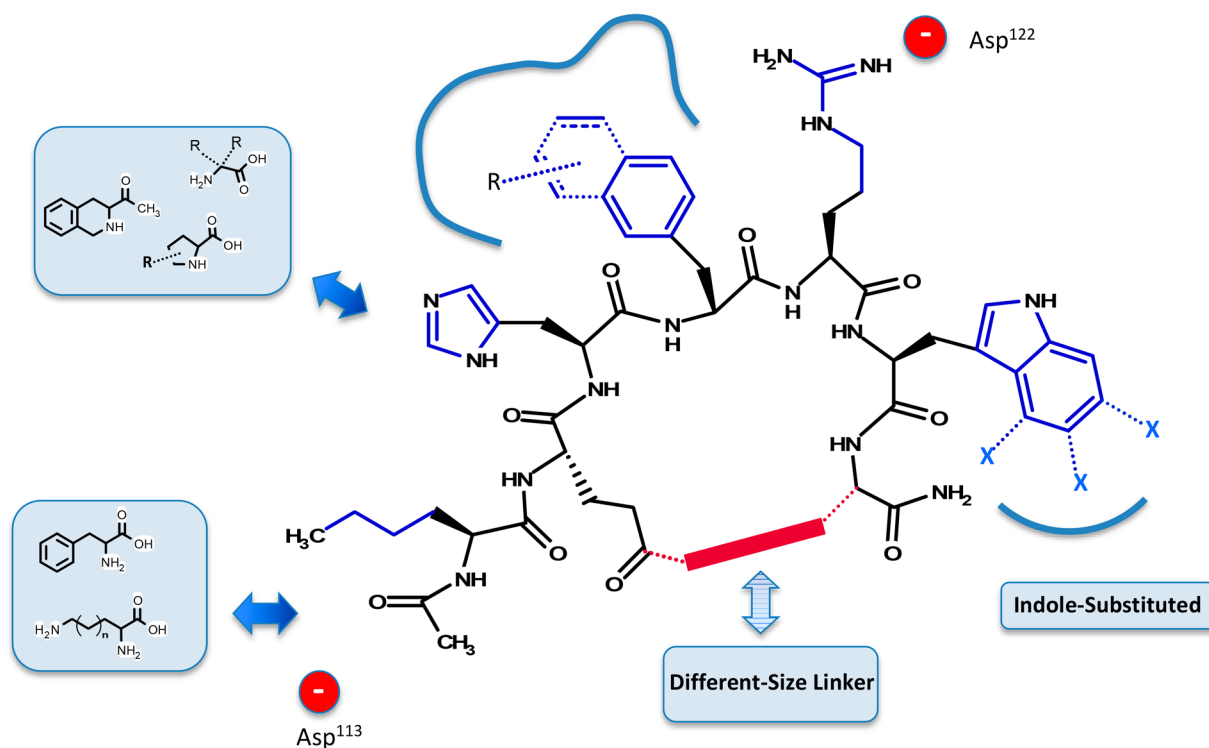
**Figure 1.** Representation of the orthosteric binding pocket of MC3R and MC4R for the binding mode of two of the most important compounds discovered in this study, SBL-MC-46 (Ac-Nle-c[Asp-His-DPhe(*p*Np(1′))-Arg-Trp-Lys]-NH<sub>2</sub>) and SBL-MC-49 (Ac-Nle-c[Asp-His-DPhe(*m*Np(1′))-Arg-Trp-Lys]-NH<sub>2</sub>).

SHU-9119 was also evaluated. Although the lactam-bridge is not directly involved in the interaction with the receptor, the stereochemistry of the amide bond could influence the conformation of the backbone of the peptide macrocycle.

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**Figure 2.** Overview of the structural features that are considered to be important for the design of future melanocortin compounds.

### ■ TOWARD THE NEXT GENERATION OF LIGANDS FOR MC4R

With the results reported in this work, combined with those previously reported in the literature,<sup>5</sup> one can now identify critical structural features used in the structure-guided design toward identification of novel compounds with high potency and selectivity. Figure 2 and sections below provide a brief summary of these critical structural features.

(1) Nle4 residue of MTII/SHU-9119 interacts with a hydrophobic subpocket able to bind other different lipophilic groups, as already demonstrated by previous studies and residues with a positive charge in the side chain. In this case, the stereochemistry of the amino acid residue seems to make some contribution for hMC4R over hMC3R selectivity. The positive charge could interact by a salt bridge with Asp113 close to this pocket.

(2) His6 interacts with an additional hydrophobic pocket that is relatively large and that can tolerate different groups like a Pro residue. In this position, bulkier groups and dialkylglycine derivatives are allowed. A conformational restriction in position 6 can be extremely useful to design selective ligands at the hMCRs. Compounds reported in literature containing a guanidyl group in position 4 of the pyrrolidine ring of proline showed a lack of selectivity at the hMC3R and hMC4R, confirming that an additional positively charged residue in this position is not a determinant for binding.

(3) DPhe7 interacts with a hydrophobic pocket sufficiently wide to accommodate large aromatic groups. This hydrophobic pocket is a determinant for agonist/antagonist activity and selectivity. The structural features and conformational differences of the substituents in this position could be responsible for the selectivity between MC3R and MC4R.

(4) Arg8 is involved in electrostatic interaction. The elongation of the Arg side chain did not result in improved agonist/antagonist potency, indicating, also following previous

studies, that this kind of modification is not able to improve electrostatic interactions with Asp122 and/or Asp126.

(5) Trp9 interacts with a hydrophobic pocket with sufficient space to accommodate the indole group of Trp9 with different substituents. The substituents on the indole moiety could have a clear effect on receptor subtype selectivity.

Lastly, the structural features of the lactam-bridge combined with amino acid substitutions in the core sequence of the peptide could be important to obtain more selective and promising compounds.

### ■ CONCLUSION

The study presented by Martin and colleagues sheds light on critical structural features responsible for MC3 and MC4 receptor selectivity and provides the opportunity to potentially accelerate the development of new therapeutically useful compounds for MC4R-related obesity. The findings of their work will certainly inspire medicinal chemists to design the next generation of melanocortin ligands with improved selectivity and potency.

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#### Notes

The author declares no competing financial interest.

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