ENGINEERING OXYTOCIN ANALOGS BY TARGETED PRO^7 EXCHANGE WITH A CHIRAL 2-AZABICYCLIC RESIDUE: CONFORMATIONAL CONTROL AT THE BACKBONE LEVEL

Bartosz Łagan[1], Volodymyr Lyakh[1], Radosław Tymoszewicz-Gaida[1], Elżbieta Wojaczyńska[1]

[1]Wrocław University of Science and Technology, Faculty of Chemistry, Department of Quantum and Physical Chemistry, Wrocław, Poland
bartoszlagan@gmail.com

Oxytocin is a clinically established cyclic nonapeptide whose therapeutic utility is fundamentally constrained by its very short in vivo half-life, resulting from rapid enzymatic degradation and conformational flexibility of the peptide backbone.[1] Despite decades of effort and the development of multiple oxytocin analogues, including sequence and side-chain modifications, improvements in metabolic stability remain limited and often accompanied by altered biological profiles.

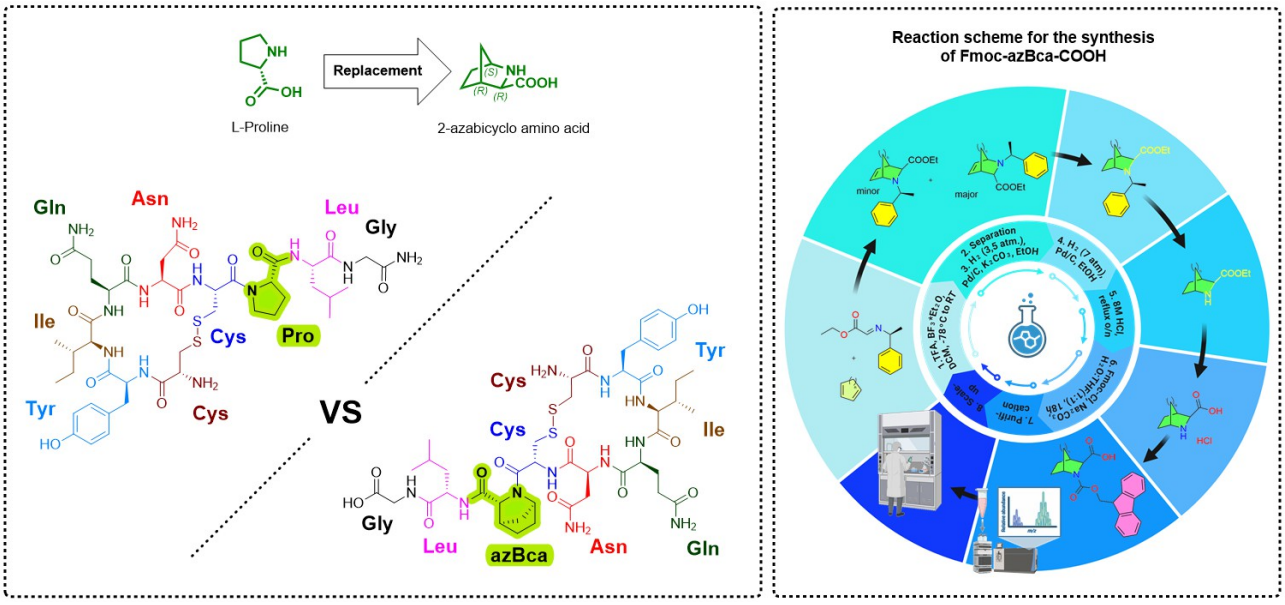

Fig. 1. Oxytocin (Pro^7) and the Pro^7→azBca analogue, alongside the synthetic route to the protected chiral azBca amino-acid building block.

An important yet underexploited factor contributing to oxytocin instability is the conformational heterogeneity associated with proline-containing motifs, which can modulate both receptor interaction and enzymatic recognition. In this context, replacement of native proline with conformationally constrained, non-natural amino acids represents a promising strategy to subtly control backbone geometry and evade proteolytic pathways.[2] Precedents from oxytocin and vasopressin-related systems indicate that minimal backbone rigidification can enhance peptide lifetime without compromising activity.[3] A conformational engineering approach is explored here as a route toward next-generation oxytocin analogues with improved stability.

[1] M. Manning et al., "Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics," Journal of Neuroendocrinology, vol. 24, no. 4, pp. 609–628, Feb. 2012, doi: 10.1111/j.1365-2826.2012.02303.x.
[2] C. L. Jenkins et al., "Substituted 2-Azabicyclo[2.1.1]hexanes as Constrained Proline Analogues: Implications for Collagen Stability," The Journal of Organic Chemistry, vol. 69, no. 25, pp. 8565–8573, Aug. 2004, doi: 10.1021/jo049242y.
[3] V. J. Hruby, F. Al-Obeidi, and W. Kazmierski, "Emerging approaches in the molecular design of receptor-selective peptide ligands: conformational, topographical and dynamic considerations," Biochemical Journal, vol. 268, no. 2, pp. 249–262, Jun. 1990, doi: 10.1042/bj2680249.