□/□-Peptides containing pyrrolidine-based □-residues as useful tools for neuropeptide Y receptor-subtype selectivity

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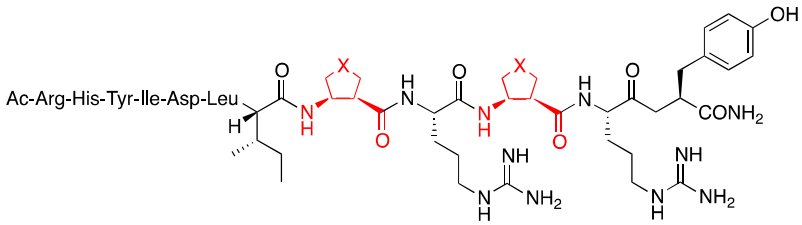
Pyrrolidine-based non-natural amino acids have been shown to be valuable building blocks for the design of pharmaceutically interesting peptides and peptidic foldamers. In this work we show the application of the □-amino acid (3R,4R)-4-amino-pyrrolidine-3-carboxylic acid (*cis*-APC) in the design and synthesis of novel □/□ analogs of neuropeptide Y (NPY). This is a 36-residue long, C-terminally amidated peptide hormone that is expressed in the brain and in the peripheral nervous system, and, upon binding to four NPY Y_n (n=1,2,4,5) receptors, it regulates food intake, the circadian rhythm and cardiorespiratory parameters. Moreover, the NPY/Y_n-receptor system is involved in several pathological disorders like obesity, depression, anxiety-related disorders and epilepsy. To control the Y_n-receptor-mediated function of NPY, it is important to develop NPY analogs with Y_n-receptor-subtype selectivity. For this purpose we have modified the NPY fragment 25-36 by introducing *cis*-APC and other cyclic □-amino acids at positions 32 and 34.[1] The synthesis of these NPY analogs and the ability of the investigated building blocks to modulate receptor-binding selectivity will be presented.



[1] *Leading references*: (a) Berlicki, Ł.; Kaske, M.; Gutiérrez-Abad, R.; Bernhardt, G.; Illa, O.; Ortuño, R. M.; Cabrele, C.; Buschauer, A.; Reiser, O. *J. Med. Chem.* **2013**, *56*, 8422. (b) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, Ł. *J. Med. Chem.* **2014**, *57*, 9718. (c) Berlicki, L.; Pilsl, L.; Weber, E.; Mandity, I. M.; Cabrele, C.; Martinek, T. A.; Fülöp, F.; Reiser, O. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 2208.