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Neurotensin analogue design: stability and affinity improvement for in vivo analgesic activity.

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Neurotensin (NT) is a tridecapeptide, which was first isolated from bovine hypothalamus.[1] This molecule exerts a variety of physiological effects as hypothermia, analgesia or antipsychotic properties. Structure-activity relationship studies showed the minimal active sequence was the C-terminal fragment called NT(8-13). As many peptides, neurotensin has a short half-life time due to enzyme degradation. Indeed, electrophoresis analysis and plasmatic stability studies highlighted that specific enzymes affect three out of the five peptide bonds.
To overcome neurotensin instability, we developed several NT analogues using different approaches including unnatural amino acid incorporations,[2] peptide bond modifications and cyclisation.[3] One of our objectives was to target the NT-induced analgesic effect. Among the three receptor subtypes, Sarret *et al.*[4] showed that selectivity toward NTS2 receptor is a parameter that has to be considered in the analogue design strategy. Molecular modelling calculations have been instigated to assist the understanding of NTS2 selectivity and help the design of new analogues.
A strategical approach was initiated to study structure-activity relationship of the active NT(8-13) fragment and offered an access to bioactive and resistant NT-analogues. Synthesis, binding affinity as well as *in vivo* analgesic activity on acute and neuropathic pain in rats will be presented.

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