**PHARMACOLOGICAL CHARACTERIZATION OF PWT2-UFP-101**

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A novel chemical strategy for the facile synthesis of tetrabranched peptides named peptide welding technology (PWT) has been developed and validated in our laboratories (Guerrini et al., 2014). In the present study the PWT approach has been applied to UFP-101 a nociceptin/orphanin FQ (N/OFQ) related peptide acting as N/OFQ receptor (NOP) antagonist (Calo et al., 2002). PWT2-UFP-101 was characterized in vitro in a BRET based assay for studying receptor interaction with G protein and in the electrically stimulated mouse vas deferens bioassay, and in vivo in the forced swimming and locomotor activity assays in mice. In vitro PWT2-UFP-101 maintains the antagonist activity, competitive behavior, and potency (pA2 8.58 in the BRET assay and 7.59 in the mouse vas deferens bioassay) of the linear peptide. In vivo, the tetrabranched derivative (1 nmol, i.c.v.) was able to elicit similar antidepressant like effects as UFP-101, being 10 fold more potent. However, the antidepressant like effect of PWT2-UFP-101, but not UFP-101, was associated with inhibition of spontaneous locomotor activity. These findings suggest that the PWT strategy can be applied to peptide antagonists to increase their in vivo potency, however this is associated with a reduction of their selectivity of action.

Calo et al. (2002). British journal of pharmacology 136: 303-311.

Guerrini et al. (2014). Bioorganic & medicinal chemistry 22: 3703-3712.