PLANT-DERIVED PEPTIDES RUBISCOLIN-6, SOYMORPHIN-6 AND THEIR *C*-TERMINAL AMIDE DERIVATIVES: PHARMACOKINETIC PROPERTIES AND BIOLOGICAL ACTIVITY

Azzurra Stefanucci,[*1] Giancarlo Tenore,[2] Stefano Pieretti,[3] Paola Minosi,[3] Gokhan Zengin,[4] Chiara Sturaro,[5] Girolamo Calò,[5] Ettore Novellino,[2] Angelo Cichelli,[6] Adriano Mollica[1]

[1]Dipartimento di Farmacia, Università di Chieti-Pescara "G. d'Annunzio", Via dei Vestini 31, 66100 Chieti, Italy.

[2]Department of Pharmacy, University of Naples "Federico II", Via D. Montesano 49, 80131 Naples, Italy.

[3]Istituto Superiore di Sanità, Centro Nazionale Ricerca e Valutazione Preclinica e Clinica dei Farmaci, Viale Regina Elena 299, 00161, Rome, Italy.

[4]Department of Biology, Science Faculty, Selcuk University, Konya, Turkey.

[5]Department of Medical Sciences, Section of Pharmacology, University of Ferrara.

[6]Department of Medical, Oral and Biotechnological Sciences, "G. d'Annunzio" University Chieti-Pescara, Via dei Vestini 31, 66100 Chieti, Italy

The aim of this work is to investigate the pharmacokinetic properties, antinociceptive and antioxidant activities of rubiscolin-6, soymorphin-6 and their *C*-terminal amides. Rubiscolin-6 and soymorphin-6 are two exhorphins derived from spinach and soybean respectively. The four peptides were synthesized following Fmoc-SPPS strategy to give the final peptides in excellent overall yields and purity following analytical RP-HPLC analysis. None of them shows antioxidant activity and a-tyrosinase inhibition *in vitro*. All compounds are able to activate G-protein coupled receptor at the d-opioid receptor (DOR) at 100 mM concentration however, rubiscolin-6-amide exhibits significative antinociceptive effect after i.c.v. administration in the tail flick test (TF) and s.c. administration in the formalin test (FT). Rubiscolin-6 shows the best *in vitro* intestinal bioavailability in CaCo2 cell monolayer and stability to the brush border exopeptidases in the apical compartment. *In silico* experiments show the interaction of rubiscolin-6 and rubiscolin-6 amide at the binding cavity of DOR compared with the crystallographic ligand TIPP-NH_2.