The main objectives of this thematic project are: i) the identification and ii) synthesis of abundant low molecular mass compounds from toxic secretions of spiders and social insects (Hymenoptera) presenting neuroactive actions; iii) pharmacological and physiological assays of these compounds for neurotoxicity/neuroprotection; iv) the screening for polycationic peptides in the venoms of social Hymenoptera, assigning their amino acid sequence and determining their secondary structure; v) peptides synthesis and peptides screening for antibiosis, pain/analgesy and inflammation and vi) the characterization of interactions between antibiotic peptides with natural/synthetic membranes.
**SUMMARY OF RESULTS TO DATE AND PERSPECTIVES**

The use of metabolomic approaches, specially the footprint profile of the defensive secretions from wasps and spiders, has allowed the identification of low molecular compounds with neurotoxic functions. Novel natural products were also detected in the footprint profile, most of them with molecular structures elucidated by spectroscopic techniques (HRMS, LC-MS, MS* and NMR). A large fraction of these compounds had their synthesis route developed, and the synthetic compounds were submitted to a wide range of neurotoxicity and neuroprotective assays (open field behavioral assays, electrophysiology and neuropharmacological tests). More than one-hundred of novel acylpolyaminetoxin structures, from orb-web-spider venoms, were elucidated, as well as twelve alkylindole alkaloid toxins from spider’s web and venoms, and two organ metallic compounds from the oily droplets of Nephilinae spiders’ web. A neurotoxic histaminyl glucoside, presenting blocking activity against different types of ion channel receptors was identified in the venom of some species of social wasps. In addition to this, alkaloid toxins, such as piperidine derivatives were isolated from the species of social wasps. In addition to this, alkaloid toxins from spider’s web and venoms, were elucidated, as well as twelve alkylindole alkaloid toxins from spider’s web and venoms, and two organ metallic compounds from the oily droplets of Nephilinae spiders’ web. A neurotoxic histaminyl glucoside, presenting blocking activity against different types of ion channel receptors was identified in the venom of some species of social wasps. In addition to this, alkaloid toxins, such as piperidine derivatives were isolated from the venom of the banana-spider (*Phoneutria nigriventer*). Several of these compounds proved to be potent neuroprotective agents in experimental assays of epilepsy, with a great potential to become models for the development of new neuropharmaceutical drugs. In parallel to these investigations, a great family of polycationic peptides have been detected in the venom from social wasps through LC-ESI-IT-TOF-MS, and sequenced by using mass spectrometric analysis under CID conditions. These peptides were manually synthesized on solid-phase, purified and its secondary structure analyzed by spectroscopic techniques (circular dichroism, fluorescence, FT-IR, and NMR). The peptides were submitted to a wide range of biological assays, including antibiosis, analgesic effect, anti-hypertensive action, anti-inflammatory action, and anti-proliferative effect and their interactions with membranes (natural and synthetic) were evaluated by the combination of spectrometric and biophysics techniques. Some of these peptides were identified as strong antibiotics against pathogenic bacteria, while other peptides have been identified as selective ligands of some sub-types of G-proteins. Since some of these peptides are involved with the mast cell exocytosis, it was developed an analytical platform combining affinity chromatography with immobilized peptides, as ligands, and membrane proteoliposomes, and proteomic analysis for the bioprospection of G-protein coupled receptors. Five different protein receptors were identified, allowing the expansion of the current knowledge about the mechanisms of mast cell activation induced by the polycationic peptides.

**MAIN PUBLICATIONS**


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