BIOPROSPECTION OF THE BRAZILIAN ARTHROPODS FAUNA SEARCHING FOR LEADER DRUGS FOR RATIONAL DEVELOPMENT OF NOVEL PHARMACEUTICALS AND PESTICIDES

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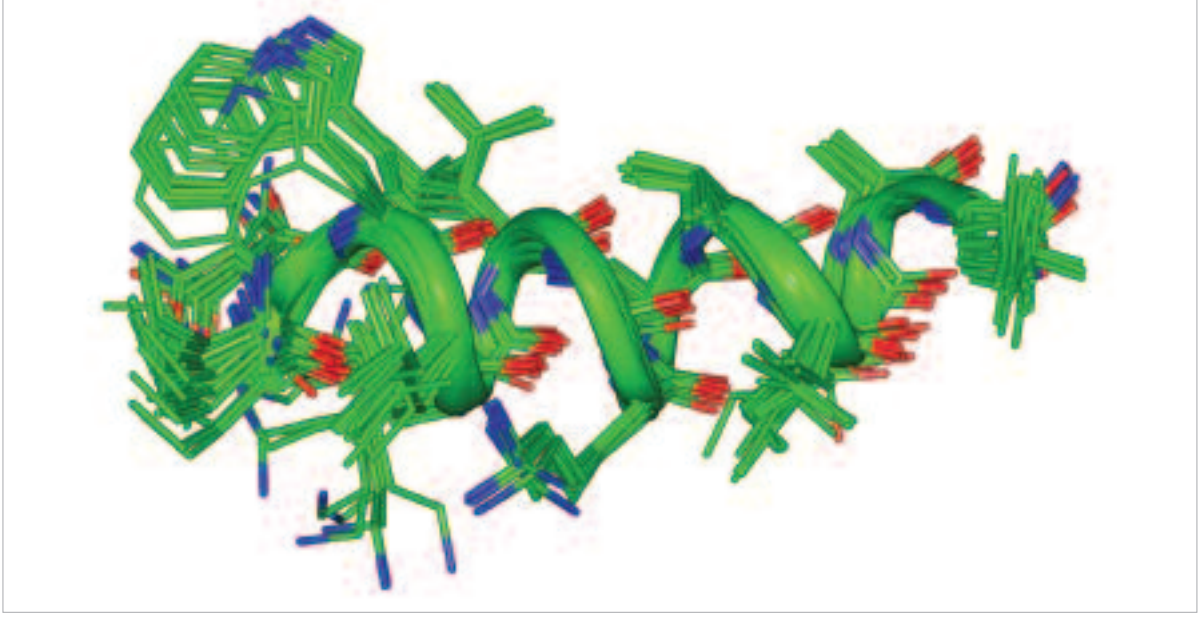

Natural peptides are isolated from different biological sources, purified, sequenced and submitted to investigations of structure and activity. Their secondary structures are studied by using NMR, circular dichroism, molecular modeling and simulations of molecular dynamics. The figure above shows the secondary structure of an antimicrobial peptide determined by NMR analysis. A series of different conformations are overlapped to each other

Recently, the low molecular mass compounds from animal origin have been subject of interest by pharmaceutical and agrichemical companies. The Arthropods are considered a source of potentially important novel molecules, offering notable properties such as: high efficiency, low probability of development of microbial resistance, limited toxicity and low immunogenicity to men. In order to bioprospect these compounds, in the Arthropod fauna from São Paulo State, the main objectives of the present project are: (i) to identify the most abundant low molecular mass compounds from the toxic secretions of spiders and social Hymenoptera presenting neuroactive actions, (ii) to elucidate their molecular structures, (iii) to synthesize and (iv) to submit them to pharmacological and physiological bioassay screenings. Also the polycationic peptides will be investigated, as well as their sequence, structure and for some of these components, their target-receptors will be identified. The elucidation of chemical structures in general will be performed by using a series of spectroscopic techniques. When necessary, the elucidated chemical structures will be synthesized and used for functional characterization. The biological characterization of the neuroactive compounds, will include the classical neuropharmacology approach, immunohistochemistry and electrophysiology methods. The investigation of the action mechanism of the polycationic peptides will focus traditional protocols of pharmacology for pain, analgesy and inflammation and we will also investigate the antibiotic action of these peptides. The promising compounds, presenting some specific potential application at level of therapeutic use, which may be used as models for future drug development, will be submitted to an intensive investigation about structure/ activity relationship for a future rational development of novel drugs.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Several new natural products have been isolated from wasps and spiders secretions, most of them had their molecular structures elucidated by spectroscopic techniques (Nuclear Magnetic Resonance, Mass Spectrometry). A large fraction of these compounds had their synthesis route developed, and the synthetic compounds have been submitted to a wide range of neurotoxicity and neuroprotective assays (with different electrophysiological and neuropharmacological approaches). More than one-hundred of new acylpolyaminetoxin structures from spider venoms have been resolved, twelve alkylindole alkaloid toxins were elucidated from spider webs, and two organometallic compounds had their chemical structure determined from aerial web-spider body secretions. A defensive Spiro glycoside compound, and new analogs of histamine, presenting blocking activity against different types of ion channel receptors, were identified in the venom of some species of social wasps. Several of these natural compounds of animal origin proved to be potent neuroprotective agents, some of them with anti-epileptic activity (even in animal models), with a great potential to become models for the development of new neuropharmaceutical drugs. Some of these compounds showed selective insecticide activity against some arthropods and can become models for the development of new insecticides.

In parallel to these investigations, a great family of polycationic peptides have been isolated and sequenced from the venom of social wasps. The peptides are studied concerning their secondary structures using spectroscopic techniques (circular dichroism, fluorescence, FT-IR, and NMR) and submitted to a wide range of biological assays, including antibiosis, analgesic effect, anti-hypertensive action, anti-inflammatory action, and anti-proliferative effect (against tumor cells strains). The interactions between peptides and membranes (natural and synthetic) are evaluated through 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. Therefore we are currently working on the development of an analytical platform, where it will be possible to combine affinity chromatography and proteomic analysis for the bioprospection of G-protein coupled receptors.

MAIN PUBLICATIONS

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