

Novel antiparkinsonian drug hemantane (N-2-adamantyl hexamethylenimine hydrochloride) was shown to reduce motor disturbances in animal models of parkinsonism. Complex mechanism of action, including antioxidant activity, was determined. Efficacy and safety of monotherapy by hemantane 25 mg daily was proved in open-label clinical study in patients with early stages of Parkinson disease. Mexidol (2-ethyl-6-methyl-3-oxypyridine succinate) is an antioxidant widely used in neurological disturbances treatment. The aim of the study was to assess the effects of mexidol and its combination with hemantane in animal models of parkinsonism. Experiments were held in male albino rats and C57BL/6 mice. Tremor was induced by arecoline, catalepsy by haloperidol, parkinsonian syndrome by MPTP. Mexidol reduced rigidity, oligokinesia and tremor, but its effect was lower than of hemantane. It was shown that the effects of combination hemantane (10 mg/kg) and mexidole (200 mg/kg) was higher compared to that of hemantane alone. In mice with MPTP induced parkinsonism the significant increase in the levels of malondialdehyde (MDA) and dienic conjugates in brain were determined. Both drugs administered before MPTP reduced the increase of MDA and dienic conjugates. The combination of hemantane and mexidol was more active for reducing MDA levels. The results obtained proved the antioxidant action of hemantane and the rationale for using of hemantane with mexidol for the treatment of Parkinson disease.

Paper No.: 1909

FOCUSED CONFERENCE GROUP: P13 - MAXIMISING BENEFITS AND MINIMIZING HARMS FROM DRUGS DEVELOPMENT OF NEW CATECHOL-O-METHYLTRANSFERASE INHIBITORS FOR TREATMENT OF PARKINSON'S DISEASE

Nuno Vale(1), N Micaelo(2)

- (1) University of Porto Faculty of Sciences, Department of Chemistry and Biochemistry, Porto, Portugal
- (2) AlcantaraBio, Tecmaia, Portugal

AlcantaraBio is a protein- and drug-design start-up company, specialized in the discovery and improvement of new drugs using computational structure-based design methodologies. We are located in Tecmaia Science Park near Oporto, Portugal. Our mission is to discover new drugs and support the early stages of drug development of academic and industrial partners using structure-based computational tools. We create highly focused, tailor-made libraries of drug candidates towards specific biological targets, and provide a deep structural understanding of the molecular mechanism of drug action. Our recent work has been focused on the development of a new catechol-O-methyl transferase (COMT) inhibitor for Parkinson's disease. A new library of high affinity COMT inhibitors was designed based on the nitrocatechol group. The drug-COMT structural complexes and binding affinities were evaluated with an improved proprietary docking and scoring algorithm. We are proposing a new series of COMT inhibitor candidates with predicted high binding affinity and $\log P < 5$. In-silico studies have demonstrated that our new drug candidates have higher affinity relative to well-known COMT inhibitors, such as: Entacapone, Nebicapone and Tolcapone. These new drug candidates are going to be synthesized and screened for biological activity.

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FOCUSED CONFERENCE GROUP: P01 - CLINICAL PHARMACOLOGY IN THE EMERGING COUNTRIES NEW TIMES, NEW TRENDS FOR ETHIONAMIDE

Nuno Vale(1), HA Santos(2), E Mäkilä(3), J Salonen(3), J Hirvonen(2), P Gomes(1)

- (1) University of Porto Faculty of Sciences, Department of Chemistry and Biochemistry, Porto, Portugal

- (2) University of Helsinki, Faculty of Pharmacy, Division of Pharmaceutical Technology, Helsinki, Finland
- (3) University of Turku, Laboratory of Industrial Physics, Department of Physics, Turku, Finland

Tuberculosis (TB) is a major health problem worldwide, with approximately 1.7 million people dying annually from the disease. The long current drug regimen, the emergence of drug resistant strains and HIV co-infection have resulted in a resurgence in research efforts to address the urgent need for new anti-tuberculosis drugs (Rivers et al, Drug Discov. Today, 2008, 13: 1090-1098). With respect to multi-drug-resistant TB, ethionamide (ETA) is a structural analog of isoniazid that is typically used in case of loss activity of the front-line drugs. However, the activation of ETA has remained obscure and some reports suggest that its metabolites are toxic. Porous silicon (Psi) materials can be used as carriers of drug molecules and have several advantages over the existing materials for drug delivery (Salonen et al, J. Pharm. Sci., 2008, 97: 632-653), overcoming most of the problems related to the oral delivery of poorly soluble drug molecules (Kaukonen et al, Eur. J. Pharm. Biopharm. 2007, 66: 348-356), such as poor dissolution/solubility and/or pharmacokinetic properties in the intestinal lumen, poor permeation properties in the GI tract, as well as high intestinal or hepatic first pass metabolism. With this work, we pretend decrease toxicity associated to ETA and improve biological profile, leading this drug to "first line" agents. For that, we investigated a novel oral formulation technology of Psi microparticles loaded with ETA. The dissolution profiles and the *in vitro* toxicity and permeability tests in Caco-2 cell lines of the drug formulation are evaluated.

Paper No.: 1911

FOCUSED CONFERENCE GROUP: P16 - NATURAL PRODUCTS: PAST AND FUTURE? SCREENING OF PORTUGUESE PROPOLIS AND ITS PLANT SOURCES FOR INHIBITORY ACTIVITY AGAINST PATHOGENIC PROTOZOA

Nuno Vale(1), S Falcão(1,2), V Batista(2), C Freire(1), L Maes(3), M Villas-Boas(2)

- (1) University of Porto Faculty of Sciences, Department of Chemistry and Biochemistry, Porto, Portugal
- (2) CIMO – Escola Superior Agrária, Instituto Politécnico de Bragança, Campus de Sta. Apolónia, Bragança, Portugal
- (3) University of Antwerp, Laboratory of Microbiology, Parasitology and Hygiene Antwerp, Belgium

Propolis is a beehive product with a very complex chemical composition, widely used in folk medicine because of its several therapeutic activities. Its biological properties and chemical composition may vary according to the geographic location and to the different plant sources. Recently, we reported the mechanism for extraction and propolis sample preparation (Falcão et al, Anal. Bioanal. Chem., 2010, 396: 887-897). After that, we developed a new study for Portuguese propolis and plant samples found around the hive, and we present in this study the activity of these samples against pathogenic protozoa. Two different raw propolis samples from the northeast and centre of Portugal, both acquired from local beekeepers, were analysed in the present work. For the plant samples we collect the buds exudates and surface material present on the leaves, stems of *Populus nigra* male and female specimens and *Cistus lanadifer*. These samples were screened for *in vitro* activity against the pathogenic protozoa *Plasmodium falciparum*, *Leishmania infantum*, *Trypanosoma cruzi* and *Trypanosoma brucei*. To assess selectivity of action, cytotoxicity against MRC-5 fibroblast cells was also evaluated. We present in this communication interesting results, according to criteria set up by the WHO Special Programme for Research & Training in Tropical Diseases.