POTENTIAL ANTITRIPANOSOMAL DERIVED FROM NITRO-HETEROCYCLIC COMPOUNDS

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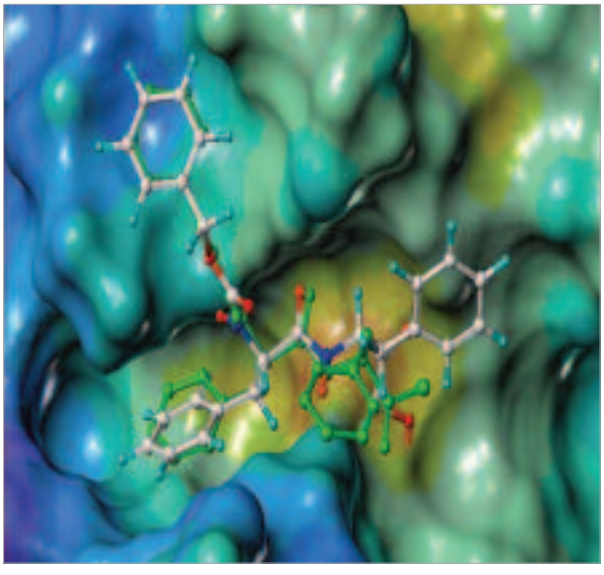

Cruzain inhibitor identification by virtual screening

Chagas' disease is endemic for most of Latin America, serioulsy affectinq the health of infected people and shortening their lives. Around 16 to 18 million people are estimated to be infected and about 50 thousands of deaths are registered each year in the 21 endemic countries. The therapeutic armamentarium against he parasitosis is scarce, s only two drugs have been used, none of them sufficiently effective at the chronic stage of this disease. Considering that only people from underdeveloped countries are inffected or under the risk of contracting the parasitosis, the interest is relatively low to the countries responsible for developing most of the therapeutic drugs in use to date. Thus, searching for new drugs against the disease is mainly a task for those underdeveloped countries, among the above. Taking into account the high activity showed by the nitro-heterocyclic derivatives that have been already synthesized by our group, and/or others using diverse approaches, our main goal is to find new and effective drug candidates among this class of compounds. This objective will necessarily be supported by *in vitro* and *in vivo* assays, as well as by mutagenicity tests. The study of the mechanism of action of those candidates through electrochemical methodologies, by using biosensors with immobilized nucleic acids and enzymes, and the elucidation of the chemical structure-biological activity (QSAR), especially by molecular modeling – assisted 3D-QSAR, are the rational bases for the design of new and more effective nitro-heterocyclic derivatives. We hope to contribute in an integrated way to the search for better antitripanosomal agents.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The results obtained by using computational and electrochemical methods indicate the advances not only in the synthesis of prodrugs, but also in the understanding of their mechanisms of action at the molecular level. Such synthesized prodrugs, polymeric or not, comprise bioisosteric analogues of the nitro-heterocyclic derivatives originally proposed – nitrofural and hydroxymethylnitrofural – and of structures of congenerous compounds, such as benzhydrazides, and others selected by virtual screening. Application has been made for the invention patent "Dendrimeric prodrug, process for its preparation and compositions containing it", P.I. 0.705.122-0, published on February 6th, 2008, in Revista da Propriedade Industrial Nº 1935, p. 87, item 2.1. Similarly, we applied modern methodologies antichagasic compounds planning to a series of semicarbazone analogues taken from the literature, and as results we generated QSAR models with a high prediction, and a restricted series of synthesized and substituted phenylhydrazones, all of which demonstrated a "promiscuous" mechanism of cruzain inhibition. Also, we proposed models of virtual screening, applied them to a library of 3,294,714 compounds, and one of them permitted the discovery of a compound with a promising inhibitory activity (K_i= 21 ÌM). In addition, we demonstrated the importance of the experimental validation of the models obtained by calculation. The application of electrochemical methodologies allowed for the stabilization study in aqueous medium of the anionic nitro-radicals derived from nitrofural, as well as the study of their interaction with natural biological electron acceptors, oxygen, cysteine and glutathione. In addition, the electrochemical characterization of the prodrug hydroxymethylnitrofural was also conducted. Molecular modeling data were then consolidated with the voltametric results obtained from the oxidation of primaquine and prodrugs (both their succinyl and maleyl derivatives), which thus allowed for determining their respective molar volumes based on their estimated coefficients of diffusion and electrophoretic mobility in aqueous medium. We also characterized in aqueous medium the redox properties of 5-nitro-2-thiofilidene-4- and 5-nitro-2-furfurilidene-4-R-benzhydrazides, barely soluble in water, by using modified carbon paste electrodes, in which the modifying agent was the same as the compound being studied.

MAIN PUBLICATIONS

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