

DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW HYBRID DRUGS USEFUL TO TREAT HEMATOLOGICAL DISORDERS

Sickle Cell Disease (SCD) is characterized by a punctual mutation (GTG to GAG) at the sixth codon of the β -globin gene what leads to the substitution of glutamic acid to valine residue in the gene for β -globin chain. Nowadays, hydroxyurea (HU) is the only drug approved to treat the disease. However, the drug has several adverse effects such as mielosuppression and genotoxicity in long term therapy. AH these factors together justify the discovery of new drugs to treat SCD symptoms. Resveratrol, a stilbenoid, is a phytoalexin produced naturally by several plants and it is present in large quantity in red wine. It has been reported that this compound demonstrated potent antioxidant, antiinflammatory and analgesic effect useful to treat SCD symptoms. In addition, some studies have shown that resveratrol is able to induce gamma-globin gene expression. Nitric oxide has an important role in SCD. The beneficial effects of NO include: vasodilation, inhibition of platelet aggregation and induction of gamma globin gene expression. We have previously reported that nitric oxide donor compounds are also able to induce gamma-globin gene expression and fetal hemoglobin. In a continuing effort to develop new candidate drugs to treat hemoglobinopathies symptoms (such as SCD) with improved pharmacodynamic profile, we propose here the design, synthesis, and pharmacological evaluation of new resveratrol derivatives (compounds 1-12), obtained by molecular hybridization of the prototypes resveratrol (1) and NO donors subunits represented by furoxan and organic nitrate esters.

PRINCIPAL INVESTIGATOR

JEAN LEANDRO DOS SANTOS
School of Pharmaceutical Sciences
Paulista State University (Unesp)

ABOUT THE PROJECT

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CONTACT

✉ santosjl@fcar.unesp.br