Efficacy of new synthetic alpha-pyrones against *Trypanosoma cruzi* using marine compounds as scaffolds

Daiane D. Ferreira[1], Marta L. Lima, Mariana K. Galuppo, Juliana Q. Reimão[2], Juliana M. Guerra[1], Angela Russell[3], Graham Wynne[3], Roy Y. L. Lai[4], Melissa M. Cadelis[4], Brent R. Copp[4], Andre G. Tempone[1]

1- Centre for Parasitology and Mycology, Instituto Adolfo Lutz, SP, Brazil.
2- Faculty of Medicine of Jundiai, SP, Brazil.
3- Department of Chemistry, University of Oxford, UK.
4- School of Chemical Sciences, The University of Auckland, New Zealand

Chagas disease affects more than 8 million people living mainly in developing countries. The mainstay of treatment is chemotherapy, however, benznidazole has several limitations. Safe and effective therapies are urgently needed. Marine alpha-pyrones have been previously identified as scaffolds with potential antiprotozoan activities. In this work, twenty-seven examples of 3-substituted 4-hydroxy-6-methyl alpha-pyrones were synthesized and their antiparasitic efficacy evaluated against *Trypanosoma cruzi*. The mechanism of action and the *in vivo* efficacy of the most selective compound against *T. cruzi* was evaluated using different techniques. *In vitro* data indicated that fifteen of the alpha-pyrones were effective against *Trypanosoma cruzi* trypomastigotes, with 3-undecanoyl (**10**) and 3-tetradecanoyl (**11**) substituted pyrones being the most potent, with IC_{50} values of 1 and 2 µM, respectively, and selectivity index >70. Using flow cytometry analysis and fluorescent-based assays, pyrone **11** was found to induce a rapid hyperpolarization of the mitochondrial membrane potential of *T. cruzi*, without affecting plasma membrane permeability. An experimental acute phase-murine model, demonstrated that **11** (30 mg/kg/day; 5 days), had no efficacy at the first parasitemia onset of *T. cruzi*, but reduced the second onset by 55% ($p<0.05$), suggesting a delayed action in mice. Additionally, a histopathology study demonstrated no toxic effects to the treated mice. Future drug design studies using these marine derivatives could represent new possibilities for the treatment of Chagas disease.