Tripanocidal activity induced by metabolites isolated from the Brazilian plant *Drimys brasiliensis*

Thais Alves da Costa Silva[1], Thiago R. de Morais[2], Giulia E. Guimarães Gonçalves[2], Luciano Caseli[2], Maiara M. Romaneli Silva[3], Marta Lopes Lima[3], Mariana Kolos Galuppo[3], Andre G. Tempone[3] and João Henrique G. Lago[1].

1- Centro de ciências Naturais e Humanas – Universidade Federal do ABC
2- Instituto de Ciências Ambientais, Químicas e Farmacêuticas – Universidade Federal de São Paulo
3- Centro de Parasitologia e Micologia, Instituto Adolfo Lutz, São Paulo, SP

Neglected tropical diseases, including Chagas Disease, affect the poorest population in developing countries, with few therapeutic alternatives, and highly toxic drugs. In the course of selection of new drug candidates, we studied the anti-*T.cruzi* potential of *Drimys brasiliensis* metabolites. Phytochemical analysis from *D. brasiliensis* resulted in the isolation and characterization of three active compounds: polygodial acetal (**1**), *epi*-poligodial (**2**) and polygodial (**3**). The antitrypanosomal activity of compounds was performed against cell-derived trypomastigotes using the colorimetric resazurin assay. To study the plasma membrane integrity of trypomastigotes in the presence of the compounds, a fluorimetric assay was performed using the dye Sytox Green. Finally, the mammalian cytotoxicity was investigated using L929 cells by the colorimetric MTT assay. Our results demonstrated that all compounds induced no mammalian cytotoxicity to the highest tested concentration of 200 µM. Furthermore, the studied compounds were effective against the trypomastigote forms of *T. cruzi*, with IC_{50} values of 2.4 µM (**1**); 5.0 µM (**2**) and 3.4 µM (**3**). The selectivity index (SI), given by ratio between the mammalian toxicity and the activity against the parasites, resulted in values of 83, 40 and 58, respectively. The high selectivity presented by the compounds, prompted us to investigate their ability to disrupt the plasma membrane of *T. cruzi* trypomastigotes. Only compound **1** induced a considerable interference in the plasma membrane permeability (52%) of the parasite after 120 minutes incubation, when compared with the untreated trypomastigotes. The positive control with 0.5% of Triton X-100, indicated maximal permeabilization (100%). This study showed the potential

antrypanosomal activity of three natural compounds isolated from a Brazilian plant. Support: FAPESP 2013/50228-8, 2015/11936-2 and CAPES.