Unusual Dimeric flavonoids anti-tripanossomal *in vitro* and *in vivo* from *Arrabidaea brachypoda*

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Introduction

Chagas disease is a parasitic disease caused by the flagellate protozoan *Trypanossoma cruzi*. This disease is transmitted to humans mainly in rural endemic areas through the infected feces of triatomine insects. The World Health Organization (WHO) reports that globally approximately 10 million people are infected by *T. cruzi*, and more than 25 million people are at risk of infection in endemic countries[1]. The aqueous ethanol extract of the roots from *Arrabidaea brachypoda* and your three new compounds a Brazilian medicinal plant[2], exhibited significant *in vitro* and *in vivo* activity against *T. cruzi*, the parasite responsible for Chagas disease.

Results and Discussion

Targeted isolation of the active constituents led to the isolation of three unusual dimeric flavonoids. The structures were elucidated using UV, ECD, NMR and HRMS analysis, as well as by chemical derivatization (fig 1). The anti-T.cruzi activity and cytotoxicity toward mammalian cells were determined for these substances. Two compounds exhibited selective activity against the trypomastigotes and also inhibited the parasite invasion process and its intracellular development in host cells with similar potencies to benznidazole. In addition one compound reduced the blood parasitemia of T. cruzi-infected mice (Tale 1).

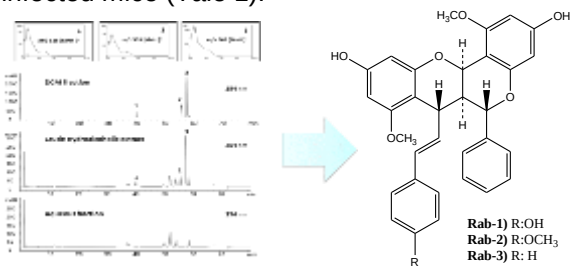

Figure 1. HPLC-PDA and structure of Rab-1, Rab-2 and Rab-3.

Table 1. Cruzain activity, macrophage cytotoxicity and anti-*T. cruzi* activity of dimeric flavonoids.

Substâncias	% cruzaina inibição a 25 µM	Células hospedeiras LC_{50} (µM)	Y strain *T. cruzi*, IC_{50} (µM)	
			tripomastigostas	Amastigotas
Rab-1	0	>20	>20	>20
Rab-2	0	15.65 (± 0.02)	5.31 (±1.15)	5.90 (± 0.33)
Rab-3	0	17.32 (± 0.84)	6.63 (± 0.39)	6.84 (± 0.41)
Benzonidazol	-	>20	11.30 (± 1.84)	13.99 (±0.39)
Violeta Genciana	-	0.48±0.05	-	-
E-64c	100	-	-	-

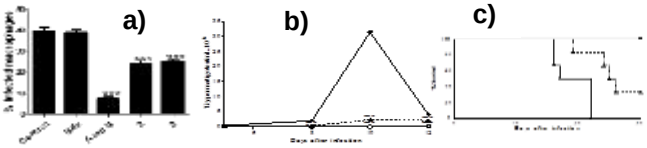

Figure 2: Evaluation anti *T.crzy* of compounds.

The compounds Rab-**2** and Rab-**3** inhibited cell invasion. Mouse macrophages were infected with Y strain trypomastigotes and treated with compounds Rab-**2** or Rab-**3** (Fig 2a). The treatment with compound Rab-**2** substantially reduced the parasitemia in infected mice. (Fig 2b and 2C).

Conclusion

This study has revealed that these two dimeric flavonoids represent potential anti-T. cruzi lead compounds for further drug development. This project resulted in a patent filing (BR10201319279) and a pharmaceutical formulation for topical use.

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