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Antitrypanosomal activity of natural and semi-synthetic chalcones

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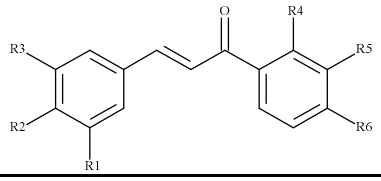
Previous studies performed with *Piper aduncum* (Piperaceae) afforded several compounds, including chalcone with antiparasitic activity [1]. Recently, our group reported the occurrence of a new prenylated dihydrochalcone from leaves of this specie with significant *in vitro* activity against *Leishmania infantum* [1]. In continuation of our studies, the MeOH extracts from inflorescences of *P. aduncum* displayed activity against trypomastigote forms of *Trypanossoma cruzi* (100% of parasite death at 200 μg/mL). Using a bioactivity guided fractionation was isolated 3,4,5-trimethoxychalcone (**1**, EC_{50} = 18.4 μM), which was characterized by analysis of NMR, UV and LRESIMS data. Aiming establish some relationships between structure of chalcones and antitrypanossomal activity, were prepared eleven related derivatives (**2 – 12**) using the Claisen-Schmidt reaction [2]. These compounds were fully characterized by analysis of ^{1}H NMR and LRESIMS data. To evaluation of antitrypanossomal activity, compounds **1 - 12** (Figure 1) were dissolved in DMSO and diluted in RPMI-1640 medium and the viability of the trypomastigotes was verified by the MTT assay [3]. According to the determined IC_{50} values (Figure 1), nine of synthetic derivatives (compounds **2, 3, 5 – 7** and **9 – 12**) killed 100% of trypomastigote forms of *T. cruzi* at the highest tested concentration, resulting in IC_{50} values in the range of 60.1 – 3.3 μM. Despite the expressive potential of compound **1** (EC_{50} = 18.4 μM), the synthetic derivatives **7**, **10** and **11** demonstrated higher antitrypanosomal activity, with EC_{50} values of 3.3, 10.6 and 13.9 μM, respectively. In addition, some synthetic compounds showed a reduced mammalian toxicity, mainly compounds **2, 3, 9 – 11**, with CC_{50} ranging from 77.6 to 127.3 μM. Benznidazole was used as a standard drug and gave an EC_{50} value of 440.7 μM. Considering the relation between the antiparasitic activity and mammalian cytotoxicity, given by the selectivity index (CC_{50}/EC_{50}), compounds **7**, **10** and **11** demonstrated the highest SI, determined as 8.9, 7.3 and 9.2 respectively. Therefore, the obtained data suggested that the 3,4,5-trimethoxy groups in the ring A (compounds **1** and **7**) as well as oxyallyl (compound **10**) or nitro (compound **11**) groups in the ring B play an important role in the antitrypanossomal activity in chalcones derivatives. The finding suggests that natural chalcones and derivatives may be an interesting agent for Chagas disease treatment, indicating that additional studies must be done, including clinical assays (CNPq, FAPESP).



	R1+R2	R1	R2	R3	R4	R5	R6	IC_{50} (μM)	CC_{50} (μM)	SI
1	-	OMe	OMe	OMe	H	H	H	18.4	27.3	1.5
2	-	H	H	H	H	H	H	26.9	89.3	3.3
3	-	H	H	H	OH	H	H	28.9	79.5	2.7
4	-	H	H	H	H	H	OMe	>100	50.4	0.5
5	OCH_2O	-	-	H	H	H	Cl	60.1	>200	3.3
6	OCH_2O	-	-	H	H	OH	H	26.5	24.5	0.9
7	-	OMe	OMe	OMe	H	H	Ph	3.3	29.0	8.9
8	-	H	H	H	H	H	Ph	>100	>200	0.5
9	OCH_2O	-		H	OCH_2CHCH_2	H	H	18.9	82.3	4.3
10	-	H	H	H	OCH_2CHCH_2	H	H	10.6	77.6	7.3
11	-	H	H	H	H	H	NO_2	13.9	127.3	9.2
12	-	H	H	H	H	OH	H	25.9	29.9	1.1

Figure 1 - Structures, IC_{50}, CC_{50} and SI values of compounds **1 – 12**

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