

5-Phenylethenylbenzofuroxans with distinct in vivo anti-chagasic activities

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Introduction

Parasitic diseases represent a major health problem in Latin America. Despite this reality, pharmacological responses for this disease are still inadequate. To this objective, our group has investigated and developed new agents derived from the benzofuroxan (benzo[1,2-c]1,2,5-oxadiazole *N*-oxide) heterocycle. The developed compounds have been excellent *in vitro* anti-*T. cruzi* agents, against different strains of epimastigote form of the parasite. Moreover, the new benzofuroxan derivatives were less or as cytotoxic as the reference drugs (Nfx, Bnz, ketoconazole and terbinafine). From these studies lead compounds were identified, specifically 5-(2-phenylethyl)benzofuroxan (isomers *E* and *Z*, **19**) and its phenyl-substituted derivatives (5-[2-(3,4-methylenedioxyphenyl)ethenyl]-benzofuroxan *E* and *Z* isomers, **3** and **4**, and, 5-[2-(4-chlorophenylethenyl)benzofuroxan studied as the mixture of *E* and *Z* isomers, **5** and **6**. These compounds have been the subject of the following preclinical studies: *in vivo* efficacy, *in vitro* toxicity, safety and pharmaceutical feasibility. These studies were performed as part of a research project supported by DNDi (Drugs for Neglected Disease initiative) organization, which have as the primary goal the development of new and more effective drugs for people suffering from neglected diseases in developing countries. Compounds **1-6** were tested *in vivo* on a murine model of *T. cruzi* infection, in order to complete the pre-clinical profile of these potential antichagasic drugs.

Results and Discussion

In the *in vivo* studies with *T. cruzi* Tulahuen 2 strain was employed. The 5-arylethenylbenzofuroxans **1-4** (Figure 1) were studied as pure isomers and as equimolecular mixtures of *E* and *Z* geometric isomers while compounds **5** and **6** were studied only as the equimolecular mixtures of *E* and *Z* geometric isomers. Derivatives **19E**, **19E:19Z** (50:50) or **19Z** were administered orally during 30 days at a dose of 60 mg/Kg/day. The best profiles in the parasitemia curves were observed for derivative **1** and the mixture **1:2**. (Figure 1)

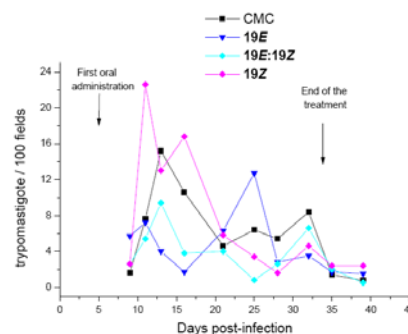


Figure 1. Parasitemia profile for 5-(2-phenylethyl)-benzofuroxan after successively recrystallizations.

These results demonstrate that the compounds are not as active as expected by its *in vitro* activities. These derivatives were prepared by successive recrystallizations (DNDi-rec). The purifications were performed in order to obtain extremely pure compounds. Besides, it was also tested the derivatives obtained after the column chromatography purification (DNDi-col). These two samples were characterized by X-ray powder Diffractometry (Figure 2).

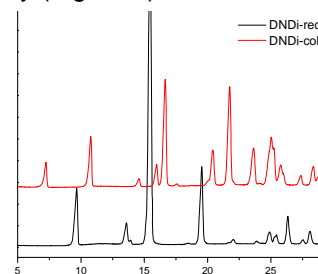


Figure 2. X-rays powder diffractograms of the DNDi-rec and DNDi-col.

The DRX analysis clearly showed that the samples have different crystalline structure, originating possible forms or new polymorphs. Thus, it justifies the difference in its activity in the organism.

Conclusion

The different x-ray diffraction powder patterns suggest that changes in the crystalline structure could be responsible of the differential in vivo antichagasic activities of these 5-phenylethenylbenzofuroxan.

Acknowledgements

DNDi, PROSUL [1] <http://www.who.int/ctd/chagas>.