

Chapter 37

2D and 3D QSAR Studies on a Series of Antichagasic Fenarimol Derivatives

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ABSTRACT

*Chagas disease is one of the most important neglected tropical diseases. Endemic in Latin America, the disease is a global public health problem, affecting several countries in North America, Europe, Asia and Oceania. The disease affects around 8-10 million people worldwide and the limited treatments available present low efficacy and severe side effects, highlighting the urgent need for new therapeutic options. In this work, the authors developed QSAR models for a series of fenarimol derivatives exhibiting anti-*T. cruzi* activity. The models were constructed using the Hologram QSAR (HQSAR), Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) methods. The QSAR models presented substantial predictive ability for a series of test set compounds (HQSAR, $r^2_{pred} = 0.66$; CoMFA, $r^2_{pred} = 0.82$; and CoMSIA, $r^2_{pred} = 0.76$), and were valuable to identify key structural features related to the observed trypanocidal activity. The results reported herein are useful for the design of novel derivatives having improved antichagasic properties.*

INTRODUCTION

Neglected tropical diseases (NTDs) represent a group of 18 serious conditions prevalent in low-income countries with tropical and subtropical climate (Feasey, Wansbrough-Jones, Mabey, & Solomon, 2010), according to the World Health Organization (WHO). Chagas disease, one of the most important NTDs, is

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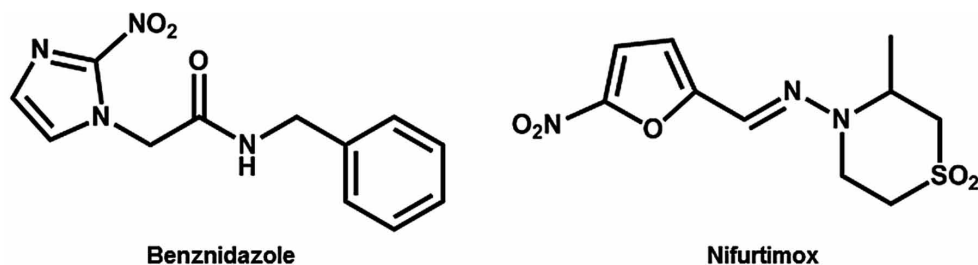
a chronic infection caused by the protozoan parasite *Trypanosoma cruzi* and affects around 8-10 million people, predominantly in Latin American countries such as Brazil, Argentina and Mexico (Viotti et al., 2014). As a result of the international population migration, the disease has reached new boundaries, primarily in North America, Europe, Asia and Oceania, thus becoming an increasing worldwide concern (Hotez et al., 2012). Chagas disease is transmitted to humans while the parasites are eliminated with the feces of triatomine hematophagous bugs during their blood meal (Rassi Jr, Rassi, & de Rezende, 2012).

The limited therapy for the disease is based only on two old drugs – benznidazole (Rochagan®, Roche) and nifurtimox (Lampit®, Bayer) (Figure 1) – which possess low efficacy and severe side effects (Castro, Montalto deMecca, & Bartel, 2006). This exceptionally unfavorable scenario supports the urgent need for the development of novel, safe and effective drugs for Chagas disease (Clayton, 2010).

The repositioning of drugs targeted to different conditions has been one of the most important strategies in NTDs, including Chagas disease (Chatelain & Ioset, 2011). Compounds possessing well-established pharmacodynamics, pharmacokinetics and toxicity profile are attractive alternatives, especially in a field that is not a priority in pharmaceutical research and development (R&D). Eflornithine, for instance, which was initially developed as an anticancer therapy, is used in human African trypanosomiasis (Brun, Blum, Chappuis, & Burri, 2010). Another example is the use of antimycotic agents, such as ketoconazole and fluconazole, in the treatment of leishmaniasis (Sundar & Chakravarty, 2013). Drug repositioning provides an excellent trade-off between risk and reward over traditional R&D strategies, and various studies on the subject have been carried out in Chagas disease drug discovery (Planer et al., 2014).

Antifungals have been investigated as trypanocidal agents since the 1980s, when the *in vitro* inhibitory activity of miconazole and econazole against *T. cruzi* was first determined (Maertens, 2004; Docampo et al., 1981). The strong interest in this class of compounds resulted in the recent approval of the fungicides posaconazole and the prodrug of ravuconazole (E1224) to undergo clinical trials for Chagas disease (de Figueiredo Diniz et al., 2013). These results have stimulated valuable repositioning studies approaching the trypanocidal activity of antifungal agents used as agrochemicals (Nosten et al., 2006). Since the approval of a given compound for use as an agrochemical requires evaluation of its toxicity profile, such molecules are a useful source for repositioning studies in the field of NTDs (Witschel, Rottmann, Kaiser, & Brun, 2012). Among these investigations, the fungicide fenarimol, broadly used as an agrochemical, was identified as a pyrimidine derivative with potent *in vitro* activity against *T. cruzi* ($IC_{50} = 350$ nM) (Figure 2) (Keenan et al., 2012). Recent studies have demonstrated that fenarimol analogs act by inhibiting the *T. cruzi* 14- α -sterol demethylase (CYP51), a key enzyme in the sterol biosynthesis pathway of the parasite (Keenan et al., 2013).

Figure 1. Currently available drugs for the treatment of Chagas disease



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