3D QSAR Studies on a Series of Antichagasic Fenarimol Derivatives

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Abstract

Chagas disease is an important neglected tropical disease. In this study, 3D quantitative structure-activity relationship (QSAR) models were developed for a series of fenarimol derivatives featuring potent trypanocidal activity.

Introduction

Chagas disease is considered by the World Health Organization (WHO) one of the most serious neglected tropical diseases. Endemic in Latin America, the disorder is a global public health problem, affecting several countries in North America, Europe, Asia and Oceania.[1] The infection, caused by the protozoan parasite *Trypanosoma cruzi,* affects around 10 million people worldwide, and the available treatments present low efficacy and severe side effects, highlighting the urgent need for new therapeutic options. In this investigation, 3D quantitative structure-activity relationship (QSAR) models were established for a series of fenarimol derivatives (**Figure 1**) with sturdy anti-*T. cruzi* activity. The models were constructed using Comparative Molecular Field Analysis (CoMFA) to characterize the structure-activity relationships for the investigated data set.

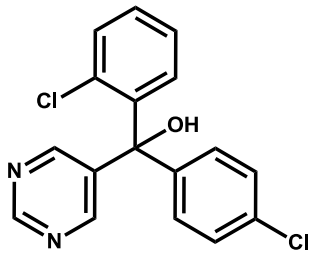

Figure 1. Fenarimol structure (IC_{50}= 350 nM).

Results and Discussion

The data used to develop the QSAR models was retrieved from the literature and consists of 77 compounds derived from the fungicide fenarimol.[2] The biological activity of this series was measured under the same experimental conditions and expressed as the compound concentration required to inhibit by 50% the *in vitro* reproduction of *T. cruzi* (IC_{50}). The IC_{50} values range from 1 nM to 27 µM. A principal component analysis was applied to select training and tests, using 2D digital fingerprints as molecular descriptors. The structural alignment was based on the maximum common substructure (MCS) method. CoMFA steric and electrostatic fields were used to generate the independent variables. The best model was built by applying the region focusing technique, weighted by a *standard deviation*coefficient* (Stdev*Coeff) value of 0.3. Contour maps for a potent dataset compound (IC_{50} = 2 nM) are shown in **Figure 2**.

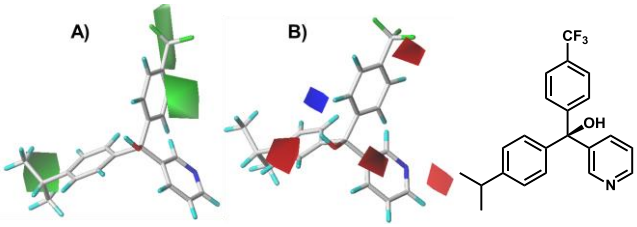

Figure 2. CoMFA steric (A) and electrostatic (B) contour maps for a highly active dataset compound (IC_{50} = 2 nM, pIC_{50} = 8.70).

This model produced a q^2 of 0.71 and r^2 of 0.99 (correlation coefficients with and without cross-validation, respectively). The external predictive ability was demonstrated by a predictive correlation coefficient value (r^2_{pred}) of 0.82. The model displayed a good agreement between experimental and predicted pIC_{50} values and the resulting contour maps were able to identify key structural features that support the biological activity of the investigated series.

Conclusions

The best CoMFA model demonstrated high internal and external consistency as indicated by the applied validation methods, as well as a suitable ability to predict the trypanocidal activity of novel fenarimol derivatives. Furthermore, the 3D contour maps identified structural features that are strongly correlated with the biological activity of the data set. The highlighted aspects are useful guidelines to explore the chemical space in the design of novel anti-*T. cruzi* compounds.

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[1] Goupil, L. S.; McKerrow, J. H. *Chem. Rev*. **2014**, *114*, 11131.
[2] Keenan, M. *et al. J. Med. Chem*. **2012**, *55*, 4189.