QSAR Modeling Using Quantum Chemical Descriptors of Benzimidazole Analogues With Antiparasitic Properties

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ABSTRACT

This article describes how benzimidazole is a privileged scaffold that has been used as a basis to develop antiparasitic compounds. Herein, the relationship between the chemical structure and biological activity against *Trichomonas vaginalis* of sixty nine benzimidazole analogues was studied using Density Functional Theory and multiple linear regression analysis. The best QSAR model obtained highlights the correlation between the $pIC_{50}$ with frontier orbital energy gap, Van der Waals volume, number of hydrophobic atoms, Harmonic Oscillator Model of Aromaticity Index, partition coefficient, and number of total second C(sp$^3$). The model has values of $R^2 = 0.784$, $Q^2 = 0.720$ with the validation parameters: $F$-test = 37.51, SPRESS = 0.274, and SDEP = 0.262. The average values of $R^2_{adj}$ (Obs) and (Calc) are very close (0.763 and 0.760 respectively), which suggests a relatively stable predictivity of the model for these data. The QSAR model developed can be employed to estimate the biological activity of new compounds based on a benzimidazole core scaffold.

KEYWORDS
Aromaticity Index, Biological Activity, DFT, Gap, Linear Regression, PCA, Protozoan, *Trichomonas Vaginalis*

INTRODUCTION

The protozoan of *Trichomonas vaginalis* (*T. vaginalis*) causes a sexually transmitted disease known as trichomonosis. Each year the World Health Organization reports more than 160 million new cases of this disease (“Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections: Overview and Estimate,” 2001). In order to treat this disease, some benzimidazoles are currently used as drugs. Benzimidazoles have a large impact in clinical medicine because of their therapeutic properties as antiparasitic agents (Kleeman, Engel, Kutscher, & Reichert, 1999). In fact, the benzimidazole ring shows an important heterocyclic system having different biological activities against various pathogens such as *Kiehiella pneumoniae* (Yalçin & Şener, 1993), *T. vaginalis* (Navarrete-Vázquez et al., 2003), *Candida albicans* (Şener, Yalçın, & Sungur, 1991; *Turker, Sener, Yalcin, Akbulut, & Kayalidere, 1990*), among others. In the search for new drugs that act against the protozoan *T. vaginalis*, Pérez-Villanueva et al. reported a series of synthetic benzimidazoles as promising antiparasitic agents (Pérez-Villanueva, Medina-Franco, et al., 2011). The authors of that work emphasized that that set of benzimidazoles was obtained through an extensive investigation of several years. The authors determined the biological activity of the benzimidazoles against a series of parasites including *T. vaginalis* (Andrzejewska et al., 2002; Andrzejewska et al., 2004; Hernández-Luis et al., 2010; Navarrete-Vázquez et al., 2006; Navarrete-Vázquez et al., 2003; Pérez-Villanueva, 2011).
Romo-Mancillas, et al., 2011; Valdez-Padilla et al., 2009). The changes of the antiparasitic activity against \textit{T. vaginalis} of that set of compounds is due to substitutions in positions 1, 2, 5 and 6 of the benzimidazole ring (see below). Of note, the molecular target associated with the antiparasitic activity vs. \textit{T. vaginalis} remains unknown.

Computational chemistry allows exploring and predicting the biological activities of untested compounds reducing time and resources of experimental studies (Navarrete-Vázquez et al., 2006; Zhang, Golbraikh, Oloff, Kohn, & Tropsha, 2006; Zheng et al., 2013). In fact, some drugs available in the clinic were designed with the aid of quantitative structure-activity relationship studies (QSAR). QSAR models have been useful for understanding the relationship of molecular properties against the biological activity of different compounds. These models help in the development of new molecules with desirable biological properties (Nargotra et al., 2009).

Studies applying the Density Functional Theory (DFT) have been used to explore the structure-activity relationships of large data sets (Carvalho, Borges, & Bernardes, 2005; Golbraikh & Tropsha, 2003; Hillebrecht & Klebe, 2008; Horvath & Jeandennans, 2003). Indeed, some authors, state that DFT provides a solid basis for the development of computational strategies. This is because quantum chemical methods allow to define the molecular quantities that characterize the energy, structure, and chemical reactivity of a molecule (Chekroun, Jarid, Benharref, & Boutilib, 2002; Geerlings, De Proft, & Langenaeker, 2003; Hansch, Hoekman, Leo, Weininger, & Selassie, 2002; Hansch, Kurup, Garg, & Gao, 2001; Hansch, Li, Blaney, & Langridge, 1982; Karelson, Lobanov, & Katritzky, 1996; Koch, 2000; Leach, 2003; McDonagh, Nath, De Ferrari, van Mourik, & Mitchell, 2014; Solie, Johnson, & Barrett, 1994). These computational tools provide physical information on the nature of intramolecular activity and pharmacological effects which include relevant electronic properties to satisfy the design needs of QSAR models with quantum data (Chaudry & Popelier, 2003; Harding, Wedge, & Popelier, 2009; Karelson et al., 1996). Based on these principles, the use and implementation of quantum descriptors has been increasing since the last decades (Kubiny, 1994; McCoy & Sykes, 2003; O’Brie & Popelier, 2001; Parthasarathi, Padmanabhan, Subramanian, Maiti, & Chattaraj, 2003; Parthasarathi, Padmanabhan, Subramanian, Sarkar, et al., 2003; Puzyn, Suzuki, Haranczyk, & Rak, 2008).

A large number of QSAR analysis and models have been reported to help understanding the SAR of benzimidazoles as active compounds. However, most of these models do not include electronic parameters or electron density methods (Kim, Ryu, & Hah, 2013; Sharma, Sharma, Sahu, & Kohli, 2013). The goal of this work was to develop a robust QSAR model for a series of synthetic benzimidazoles reported in the literature with activity against \textit{T. vaginalis}. The model included descriptors calculated with DFT methods that characterize accurately electronic effects. The predictive ability of the model was assessed my means of an external set. The QSAR model presented here can be used to guide the design new benzimidazole derivatives as antiparasitic compounds with activity against \textit{T. vaginalis}.

**METHODS AND COMPUTATIONAL PROCEDURE**

**Data Set and Experimental Data**

Sixty nine benzimidazoles derivatives with activity against \textit{T. vaginalis (Tv)}, whose biological activities have been reported (Aguayo-Ortiz et al., 2014) were considered in the present study. Figure 1 shows the benzimidazole scaffold and Table S1 summarizes the substituents in the chemical structures and their corresponding biological activity. The biological activity was expressed as pIC$_{50}$ (-log \text{IC$_{50}$}) values (Table 1). Quantum chemistry studies were performed in order to find a relationship between the biological activity and the molecular properties. A total of forty-five molecular descriptors were calculated for each compound using \textit{DFT}, \textit{MOE} and \textit{Dragon’07} software.
2D and 3D QSAR Studies on a Series of Antichagasic Fenarimol Derivatives
www.igi-global.com/article/2d-and-3d-qsar-studies-on-a-series-of-antichagasic-fenarimol-derivatives/171145?camid=4v1a

Fraction Lipophilicity Index (FLI): A Metric for Assessing Oral Drug-Likeness of Ionizable Chemical Entities
Anna Tsantili-Kakoulidou, Maria Chatzopoulou and Vassilis J. Demopoulos (2019).
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