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Molecular properties of N-benzoyl-2-hydroxybenzamide derivatives related to *Plasmodium falciparum* inhibition

Verlucia A. M. Freitas, Karen C. Weber

Departamento de Química - Universidade Federal da Paraíba

Abstract: The current treatment of choice for malaria, caused by *Plasmodium falciparum*, are artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with a second antimalarial drug. Unfortunately, artemisinin resistance has been reported in 2014 and is now widespread in southeast Asia. This poses a challenge for the development of new drugs able to tackle the three stages of Plasmodium infection in humans [1]. Molecular modeling tools play an important role in this problem, being a research field of strong potential, as demonstrated by the continuous interest of pharmaceutical industry in computational methods applied to lead optimization [2,3]. In the search for new compounds, Stec and coworkers [4] reported the synthesis and biological evaluation for a set of N-benzoyl-2-hydroxybenzamides and related compounds as potent agents against *P. falciparum*. In the present work, we performed a quantitative structure-activity relationship (QSAR) study on these compounds in order to determine the most relevant molecular properties responsible for antimalarial activity. Molecular structures were modelled in Gaussview 5.0 and optimized with the DFT method using M06-2X functional and 6-311+g(d,p) basis set in Gaussian 09 [5]. At this level of calculation, we have also obtained several electronic descriptors such as frontier orbital energies, dipole moment, polarizability and NBO charges. Thousands of topological, physicochemical and molecular descriptors were obtained with the E-Dragon platform [6]. The whole data set was divided into training and test sets, containing 30 and 7 compounds, respectively. Variable selection was undertaken with Ordered Predictor Selection (OPS) and Genetic Algorithm (GA) techniques, in combination with the use of Partial Least Squares (PLS) and Multiple Linear Regression (MLR) methods for QSAR model building. These analyses were performed with the aid of QSAR-modeling [7], Pirouette 3.11 [8] and Matlab 6.5 [9] software. The best model was achieved with the OPS-PLS combination, with statistical parameters of q^2 = 0,69 and r^2 = 0,76, and r^2_{pred} = 0,94 for the test set. This model was submitted to the additional *y*-scrambling and leave-N-out validation tests, which indicated that a robust and statistically stable model was achieved. The results obtained reveal that the antimalarial activity of the hydroxybenzamides under study depend on the following descriptors: dipole moment and polarizability, derived from DFT calculations; Mor30v, Mor32p and Mor32p, which reflect the three-dimensional distribution of molecular branching; RDF115e, RDF105e and RDF105u, which are based on radial distribution function of substituents; MATS6p, MATS6m and MATS6e, which are 2D-autocorrelation descriptors calculated from Euclidean distances between atoms or points in the molecular surface; and BIC5, an

information index descriptor calculated from graph theory [6]. These findings are of considerable relevance since the methodology applied was able to provide a QSAR model of good predictive power, which can be used to predict the biological activity against *P. falciparum* for similar molecules, helping so in the decision-making step of new active compound synthesis.

Key-words: QSAR, hydroxybenzamides, DFT.
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