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2D, 3D-QSAR and molecular docking of 4(1*H*)-quinolones analogues with antimalarial activities

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ABSTRACT

Cytochrome bc_1 has become a major focus as a molecular target in malaria parasites, which are the most important vector-borne infectious disease in the world. The inhibition of cytochrome bc_1 blocks the mitochondrial respiratory chain and the consequent arrest of pyrimidine biosynthesis, which is essential for parasite development. The authors developed a theoretical study of two-dimensional, three-dimensional quantitative structure–activity relationships and a docking analysis of a series of 4(1*H*)-quinolones acting as cytochrome bc_1 inhibitors. The predictive ability of the quantitative structure–activity relationship models was assessed using internal (leave-one-out cross-validation) and external (test set with 8 compounds) validation. From the two-dimensional quantitative structure–activity relationship models, the authors emphasized the following descriptors: GCUT_SLOGP_0, SLogP_VSA_5, Kier molecular flexibility index, electrophilicity index, the partition coefficient and the charge of atom 5 of the quinolone ring as the most important to explain the antimalarial activity of the compounds studied. Three-dimensional quantitative structure–activity relationship models showed that the substituents R1 and R4 in 4(1*H*)-quinolones analogues are key modulators to enhance the antimalarial activity. The appropriate binding conformations and orientations of these compounds interacting with cytochrome bc_1 were also revealed by molecular docking. Based on the established models, 8 new compounds with highly predicted antimalarial activity have been theoretically designed and presented as a reference for synthesis and antimalarial evaluation.

1. Introduction

Around the world, malaria is the most significant parasitic disease of humans, and claims the lives of more children worldwide than any other infectious disease. In 2011, approximately 3.3 billion people were at risk of malaria; there were an estimated 219 million cases and an estimated 660.000 deaths [1]. Malaria is caused by protozoa of the genus *Plasmodium* and there are five species that infect humans (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*) among which *P. falciparum* is the most lethal [2]. Although several attempts have been made to produce a vaccine, drugs are the only therapeutic alternative presently; however, the resistance to traditional therapies has increased morbidity and mortality from malaria, making the search for new antimalarial drugs that use novel molecular targets extremely urgent [3]. The mitochondrial electron transport chain has proved to be a valid chemotherapeutic target because of significant differences between plasmodial and analogous mammalian enzymes [4,5]. Atovaquone (**1**, Fig. 1), which is used in combination with proguanil to treat multidrug-resistant *P. falciparum* infections, is a potent inhibitor of the cytochrome bc_1, a protein subunit in the mitochondrial electron tranport chain [6,7]. Atovaquone selectively binds to the Qo site of cytochorome b, close to the site of interaction with the Rieske iron-sulfur protein (ISP). This inhibition of electron transport by atovaquone blocks respiration and produces a collapse of mitochondrial transmembrane potential [8–10].

Endochin (**2**, Fig. 1), a derivative of 4(1*H*)-quinolone, discovered in the 1940s, has prophylactic and therapeutic activity in avian malaria models, yet the lead languished because of inadequate preclinical models and a poor understanding of parasite biochemistry [11]. Currently, research on endochin and its derivatives have been reconsidered using modern biological models and powerful synthesis strategies in order to find new potential drugs containing the quinolone nucleus [12–14]. Mechanistic studies of 4(1*H*)-quinolone analogues have shown that the cytochrome bc_1 is the target for these compounds thus affecting the parasite mitochondrial respiration [15,16].

For many years, studies of quantitative structure–activity relationships (QSAR) have emerged as a powerful technique used in drug discovery [17]. This is a mathematical model of correlation

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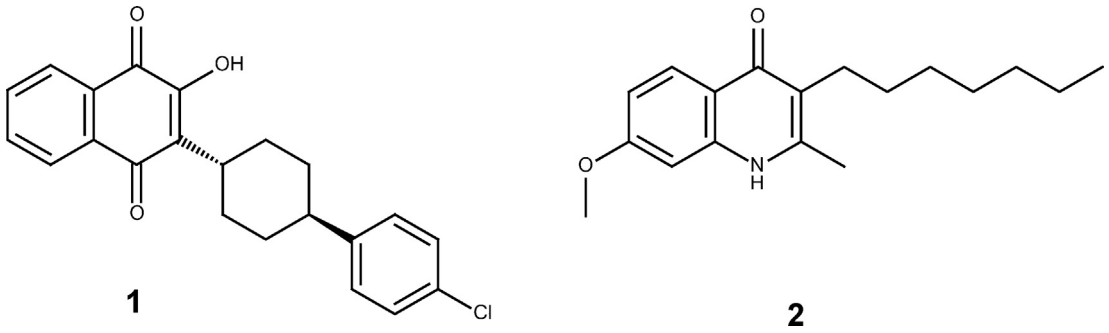

Fig. 1. Structures of atovaquone, **1**, and endochin, **2**.

statistically validated between the variation in chemical structure and biological activity profile of a series of compounds. QSAR is used primarily to correlate molecular descriptors with biological properties, but it can also be applied to predict activity values of non-synthesized compounds, structurally related to the molecules used to build the model. Molecular descriptors can be two-dimensional (2D, such as electronic and physicochemical properties) as well as three-dimensional (3D) [17,18]. Among the 3D-QSAR methods, the Comparative Molecular Field Analysis (CoMFA) and the Comparative Molecular Similarity Indices Analysis (CoMSIA) are extensively used in the current practice of rational drug design [19]. The 3D-QSAR models help to understand the non-bonding interaction characteristics between the drug molecule and the target because they are vivid and robust [20,21]. On the other hand, molecular docking studies provide the possible binding conformations of the ligands in a receptor. Combined with QSAR, they can offer more insight into understanding the detail of protein-inhibitor interactions and the factors affecting bioactivity, and thus providing information for designing new potential drugs [22–24].

In this study, a series of 4(1*H*)-quinolones with antimalarial activity reported recently in literature were chosen to perform a combined 2D-, 3D-QSAR and docking studies. The aim of this work focuses to establish reliable 2D/3D-QSAR models and determine the probably binding conformations for these compounds and provide a guideline for designing novel antimalarial drugs. Based on these models, new compounds with highly predicted antimalarial activity were theoretically designed and they are waiting for experimental verification.

2. Materials and methods

2.1. Data sets

A series of 48 4(1*H*)-quinolones synthesized by Cross et al. with antimalarial activity against the clinically relevant multidrug resistant malarial strain W2 (chloroquine and pyrimethamine resistant), were taken to perform this study [12]. The general structural formulae of the studied compounds are shown in Table 1. For the development of 2D, 3D-QSAR models the complete set of these molecules (48 compounds) were divided into a training set (40 compounds) to generate the models and a test set (8 compounds) to evaluate the predictive ability of the resulting models. The test compounds were selected manually in order to consider the structural diversity and a wide range of antimalarial activity. The *in vitro* antimalarial activities expressed as the Effective Concentration [EC_{50} (nM)] values were converted to the logarithmic scale pEC_{50} [$pEC_{50} = \text{Log}\,1/EC_{50}$ (M)] and used as dependent variables in the 2D- and 3D-QSAR analyses.

2.2. 2D-QSAR model

2.2.1. Calculations of 2D-QSAR descriptors

The geometry of the compounds were built with Marvin 5.12 software [25], and then optimized by the PM6 semi-empirical method in Mopac2009 [26] to find low-energy conformations for each compound. A set of quantum mechanical descriptors: Energy for highest occupied molecular orbital (E_{HOMO}), energy for lowest unoccupied molecular orbital (E_{LUMO}), dipole moment (μ), polarizability (α) and atomic charges on selected atoms (Q1, Q2, Q3, Q4 and Q5, see Table 1 for index identification) were obtained directly from the semi-empirical PM6 calculation. Another set of electronic descriptors such as chemical hardness (η), electronegativity (χ), electrophilicity index (ω) and chemical softness (S) were obtained based on the Koopmans theorem [27] from previously calculated electronic descriptors. Chemical hardness (η), electronegativity (χ) and electrophilicity index (ω) can be defined as follows:

$$\eta \approx -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \approx \frac{1}{2}(I - A) \quad (1)$$

$$\chi \approx \frac{1}{2}(E_{HOMO} - E_{LUMO}) \approx \frac{1}{2}(I + A) \quad (2)$$

$$I \approx -E_{HOMO} \text{ and } A \approx -E_{LUMO} \quad (3)$$

$$\omega = \frac{\chi^2}{2\eta} \quad (4)$$

Where I and A are the ionization potential and electron affinity of the molecules, respectively. This study has also included the HOMO–LUMO energy gap and the partition coefficient (Log P) as quantum mechanical and thermodynamic descriptors, respectively. There are numerous applications of the HOMO–LUMO energy gap in establishing a correlation between the chemical structure and the biological activity. Log P values were calculated using the XLogP 2.0 software [28].

In addition to quantum mechanical descriptors, 185 2D descriptors for which neither energy minimization nor alignment is required were calculated for the built structures of the 4(1*H*)-quinolones, using QuaSAR module of the software Molecular Operating Environment (MOE version 2009.10) [29].

2.2.2. Statistical analysis

To select the predominant descriptors affecting antimalarial activity of the analogues of 4 (1*H*)-quinolones, a correlation analysis was performed by Minitab 14 statistical software [30], taking each descriptor as independent variables and pEC_{50} as dependent variable.

Initially, the descriptors set (185 2D + 15 QM descriptors) was reduced by eliminating out the descriptors with constant and near-constant values. After, a correlation matrix with the