A Quantitative Structure-Activity Relationship Study on the Antimalarial Activities of 4-Aminoquinoline, Febrifugine and Artemisinin Compounds

Yu Heng Ou, Department of Soil and Environmental Sciences, National Chung Hsing University, Taichung, Taiwan
Chia Ming Chang, Department of Soil and Environmental Sciences, National Chung Hsing University, Taichung, Taiwan

ABSTRACT

Quantum chemical molecular descriptors representing different types of chemical reactivity were employed to investigate the antimalarial activities of 4-aminoquinoline, febrifugine, artemisinin and their derivatives. The quantitative structure-activity relationship results reveal that: (i) the antimalarial activities of 4-aminoquinoline compounds against the chloroquine-sensitive Plasmodium falciparum 3D7 strain are mainly affected by the electron flow and polarization interactions; (ii) The reactivity descriptors for the activities of febrifugine compounds against the chloroquine-resistant Plasmodium falciparum FCR-3 strain are the electron-acceptance chemical potential, the maximum nucleophilic and electrophilic local softness, the maximum positive charge of the hydrogen atom, etc.; (iii) The electron-donation chemical potential, the maximum negative charge, the inverse of the apolar surface area and the molar volume of artemisinin compounds are the most important descriptors for evaluating the activity against the chloroquine-resistant Plasmodium falciparum W-2 strain.

KEYWORDS
4-Aminoquinoline, Antimalarial Activity, Artemisinin, Febrifugine, Quantitative Structure-Activity Relationship

1. INTRODUCTION

Malaria is a life-threatening disease caused by protozoa of the genus Plasmodium and remains one of the world’s greatest public health problems. Half of population in the world is at the risk of malaria, especially in tropical and subtropical areas. The widely-spread disease is transmitted through the bite of infected female Anopheles mosquitoes (José C Pinheiro, Kiralj, Ferreira, & Romero, 2003), leading to over one million deaths from malaria every year. Most of the deaths are attributed to the parasite species Plasmodium falciparum, which can kill patients in hours. When it gets into the human body, P. falciparum can be able to modify the surface of infected red blood cells by interposing parasite proteins (Bowman et al., 1999). The enzymes (cysteine and aspartic proteinases) break

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down hemoglobin into amino-acids and heme (Pandey, Tekwani, Singh, & Chauhan, 1999). All the amino-acid contents are used to build parasite proteins, while only a small portion of heme is merged into parasite hemoproteins, and the rest of heme is detoxified (polymerized) catalyzed by parasite enzymes (Kamchonwongpaisan, Samoff, & Meshnick, 1997). Many drugs such as chloroquine and other traditional antimalarials have been investigated for their efficacy in the treatment of malaria, but strains of *P. falciparum* that are resistant to some of these drugs have appeared (O’Neill & Posner, 2004; Posner & O’Neill, 2004). Hence, it is important to discover new medicines for malaria, and many drugs especially isolated from medical plants have been investigated for their efficacy in the treatment of malaria (Muthaura et al., 2015).

In order to develop new drugs or explain how molecular properties of the drugs can be related to biological activity, the quantitative structure-activity relationship (QSAR) approach is usually used to describe how a given biological activity varies as a function of the molecular descriptors based on molecular structures (Hadaru et al., 2007; Liang, Ren, & Li, 2013; Liu et al., 2008; Najafi, Sobhanardakani, & Marjani, 2013; Paliwal, Sharma, & Paliwal, 2012; J. C. Pinheiro, Ferreira, & Romero, 2001; Rajkhowa, Hussain, Hazarika, Sarmah, & Deka, 2013; Saha & Gupta, 2009; Santos et al., 2013; Sen & Chatterjee, 2013; Sharma & Patil, 2013; Shrivastava, Mundada, & Pathak, 2011). Ojha & Roy reviewed the QSAR reports published in previous literatures and some pharmacophore models and docking studies of antimalarial drugs, and tried to address the physical and chemical properties and structural characteristics required for antimalarial activity in different chemical classes (Ojha & Roy, 2015). In addition, docking studies of antimalarial compounds against different targets were reviewed to explore patterns of interaction at the molecular level, with a focus on the existing knowledge of QSAR and pharmacophore models for different classes of antimalarial drugs (Roy & Ojha, 2010).

There is an urgent need to modify existing antimalarial drugs through structural changes and to find new pharmacophores to prevent induced resistance. In the work of Ojha & Roy, different quantitative structure-activity relationship (QSAR) models were developed to study the significant antimalarial activity of 1,2,3,4-tetrahydroacridin-9(10H)-one (THA) analogs against W2 (Ojha & Roy, 2013). In this regard, Aher & Roy developed a two-dimensional quantitative structure-activity relationship (2D-QSAR) and a 3D-pharmacophore models using aminothiazole and aminopyridine compounds for the activity against multidrug-resistant strain (k1) of *P. falciparum* (Aher & Roy, 2014). Moreover, a series of 53 endotoxin analogs with antimalarial activity were selected for the development of robust QSAR models using different chemometric tools for clinically relevant multidrug resistant malaria strain TM-90-C2B (Ojha & Roy, 2011). Najafi et al. studied twenty-one 4-aminoquinoline derivatives with activity against *P. falciparum* various clones (3D7, W2) by using QSAR models through genetic algorithms with multiple linear regression (GA-MLR) method (Najafi et al., 2013). The results showed two different models against chloroquine-sensitive (3D7) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* with good adjustment levels.

Many compounds originally extracted from traditional Chinese medicines have been also investigated for their antimalarial activity. Febrifugine, a quinazoline alkaloid isolated from *Dichroa febrifuga* roots, and their analogues exhibit powerful antimalarial activities against *Plasmodium falciparum* (Hirai et al., 2003; Kikuchi et al., 2014; Kikuchi et al., 2002; Takaya et al., 1999). Sen and Chatterjee have developed a 3D-QSAR for febrifugine analogues against *P. falciparum* (Sen & Chatterjee, 2013). They showed that the effect of a H-bond acceptor at positions C-6, N-1”, and C-3”, a positive ionizable group at N-1’ position, addition of an electron-withdrawing group at C-6 and N-3’ were important factors and vital structural modifications for febrifugine-based antimalarial compounds.

Artemisinin, the drug extracted from the plant *Artemisia annua L.* by Youyou Tu, the Chinese researcher who was awarded for the Nobel Prize in 2015, is still recognized as the most potent antimalarial drug against the resistant strains of *P. falciparum* (Klayman, 1985). Santos et al. investigated QSAR of artemisinin and their 20 derivatives with different antimalarial activities against
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