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Calculation of Quantitative Structure-Activity Relationship Descriptors of Artemisinin Derivatives

Jambalsuren Bayarmaa[1] and Vladimir Frecer[2]

[1]Department of Biochemistry and Bioorganic Chemistry, Faculty of Biology, National University of Mongolia E-mail: bayarmaa_j@biology.num.edu.mn
[2]Area of Pure and Applied Chemistry, International Center for Sciense and High Technology-UNIDO, Trieste, Italy E-mail: vladimir.frecer@ics.trieste.it

Abstract

Quantitative structure-activity relationships are based on the construction of predictive models using a set of known molecules and associated activity value. This accurate methodology, developed with adequate mathematical and computational tools, leads to a faster, cheaper and more comprehensive design of new products, reducing the experimental synthesis and testing on animals. Preparation of the QSAR models of artemisinin derivatives was carried out by the genetic function algorithm (GFA) method for 91 molecules. The results show some relationships to the observed antimalarial activities of the artemisinin derivatives. The most statistically significant regression equation obtained from the final GFA relates to two molecular descriptors.

Key words: molecular model, descriptor, QSAR technique, artemisinin derivatives

Introduction

Malaria is one of the most serious parasitic diseases in the world. There are millions of acute cases of malaria each year globally, resulting in more than one million deaths. The clinical disease caused by *Plasmodium falciparum* is widely distributed and entrenched in areas of the world where climates are suitable for its transmission. The present level of annual global malaria incident consisted of about 500 million, 350 million in the African region and 125 million in the South East Asian region. Deaths due to malaria are occurring in increasing numbers because of frequent failure of the conventional treatments using drugs such as chloroquine, mefloquine and sulfadoxine-pyrimethamine, against *P. falciparum*, the populations of which have developed a high degree of resistance.

Combination therapies with formulations containing an artemisinin compound have emerged as a more reliable treatment option. Artemisinin is naturally formed in *Artemisia annua* L (sweet wormwood). This herb of the Asteraceae family has been used for treatment of fever and malaria in China over many centuries. Additional names found in China for artemisinin are qinghaosu and huanghuahaosu. Artemisinin and its derivatives are only the group of compounds that is still effective against drug-resistant *P. falciparum* strains, and has the ability to quickly reduce parasite level (Krishna, 2004). From the other side, it has short plasma half-life, limited bioavailability, poor solubility in oil and water, and the low yield from natural sources (Woodrow, 2005). These reasons prompted to develop new chemotherapeutic artemisinin derivatives. By the chemical modification of artemisinin at the position of C10 semisynthetic derivatives as artesunate, artemether, artelinic acid and dihydroartemisinin were produced, which have more antimalarial activities *in vitro* than artemisinin itself (Pinheiro, 2003). Many derivatives have been synthesized using dihydroartemisinin by adding different radicals on its rings. But, the development of a new drug is a very long and expensive process. To overcome these difficulties scientists start to use a variety of computational methods to identify novel compounds, design compounds with increased selectivity, efficacy and safety and develop compounds into clinical trial candidates. One of these methods is the Quantitative Structure-Activity Relationship (QSAR) technique. The present work is related to the design of a new antimalarial active artemisinin analog.