Prelimanary Quantitative Structure-Activity Relationship Study of 9,10-Anthraquinone Analogues Based on their Antiplasmodial Activity

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Anthraquinones isolated from the roots of *Rennellia elliptica* Korth. demonstrated interesting antiplasmodial activity. In addition, a series of 9,10-anthraquinones resembling those isolated from *R. elliptica* were synthesized and preliminary two dimensional quantitative SAR (2D-QSAR) study was performed to examine physico-chemical properties essential for antiplasmodial activity of 9,10-anthraquinones. The analogues of bioactive natural anthraquinones were synthesized through Friedel-Craft reaction between phthalic anhydride and various benzene derivatives in the presence of eutectic mixture of aluminium chloride and sodium chloride. The antiplasmodial activity was determined based on inhibition of the compounds against *Plasmodium falciparum* (3D7) growth *in vitro*. The 2D-QSAR models were developed using 24 anthraquinones as data set using Vlife MDS 3.5 software. Multiple linear regression (MLR) and principal component regression (PCR) methods were used coupled with various feature selection methods i.e. stepwise forward, stepwise forward-backward, genetic algorithm and simulated annealing. The models were accepted considering the term selection criterion such as r^2, q^2, r^2_{se} and pred_r^2. The training and test set were selected using random selection method by selecting randomly 30 % of molecules from data set for test set. Dipole moment and SaaCHE-index descriptors gave negative contribution towards the antiplasmodial activity of 9,10-anthraquinones. The coefficient of regression is moderate with weak internal and external predictive power (40 - 60 %). The descriptors selected did not show clear physical meaning for mechanism of action of anthraquinones. The descriptors selected are mainly structural rather than providing an insight into physico-chemical properties of anthraquinones. The standard errors for all models were relatively high (> 0.9) probably due to human error. This error is probably due the nature of the antiplasmodial assay which requires manual estimation of parasitemia using light microscope. The biological data obtained were not normally distributed which could be due to lack of structural diversity of 9,10-anthraquinones. The presence of outliers in the correlation plots could be due to several factors; the experimental error or the molecules may act as antiplasmodial on a different mechanism of action.

Keywords: Anthraquinones, QSAR, Antiplasmodial, *Rennellia elliptica*, Vlife MDS.
