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In-silico modeling of inhibitory activity and toxicity of some indole derivatives towards designing highly potent dengue virus serotype 2 NS4B inhibitors

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ABSTRACT

The global prevalence of dengue virus (DENV) infection has become a source of great concern to humanity. As such, infection, if left untreated, could progress to a life-threatening stage called dengue hemorrhagic fever or dengue shock syndrome. A large percentage of the world's population could be at risk of being infected by the dengue virus. The DENV NS4B receptor is essential in viral replication and hence could in principle be suitable as a therapeutic target in the treatment of dengue viral infection. The augmentation of existing agents that could inhibit the dengue virus is important. In this research, various classes of molecular descriptors were generated. Quantitative structure-activity relationship studies (QSARs) have been conducted to correlate the molecular properties of some indole derivatives with their anti-dengue activity and toxicity. The inhibitory activity and toxicity prediction models were statistically valid and robust, with acceptable statistical validation factors such as predicted $R^2_{pred.}$, adjusted $R^2_{adj.}$, cross-validated Q^2 and R^2 regression coefficient, etc. ($R^2_{pred.}$ = 0.64448, $R^2_{adj.}$ = 0.59223, cR^2_p = 0.57134, Q^2_{CV} = 0.64448, R^2 = 0.63201) and ($R^2_{pred.}$ = 0.81813, $R^2_{adj.}$ = 0.56015, cR^2_p = 0.5386, Q2CV = 0.50548, R^2 = 0.60645), respectively. The models revealed that the average Broto-Moreau autocorrelation-lag 7/weighted by first ionization potential (AATS7i), number of hydrogen bond acceptors (nHBAcc) for activity and 3D topological distance-based autocorrelation-lag 9/weighted by van der Waals volumes (TDB9v) descriptors were found to strongly influence the anti-dengue biological activity (pEC_{50}) and toxicity (pCC_{50}) of the indole derivatives, respectively. The indole derivatives were predicted to be orally bioavailable with excellent gastrointestinal absorption (94.044–90.219%). The DENV-2 NS4B inhibitory activity, as well as the cytotoxicity of indole derivatives with no experimental data, could be predicted with high precision using the models developed, which could further lead to a cut in experimental cost as well as the design of highly potent and less toxic derivatives.

1. Introduction

Dengue virus (DENV) infection results from diseased mosquito bites, specifically the female *Aedes aegypti or Aedes albopictus,* of the Aedes genus due to a virus called dengue virus [1][2]; an associate of the *Flavivirus*, primarily, found within the tropical and sub-tropical areas around the world [3]. The alarming prevalence of this mosquito-borne viral dengue infection calls for global concern. Every year, about 390 million dengue infections are recorded globally with a large percentage of the incidences taking place in the tropical

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