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QSAR Model for Prediction of some Non-Nucleoside inhibitors of Dengue virus serotype 4 NS5 Using GFA-MLR Approach

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ABSTRACT

B3LYP/631G** basis set of DFT quantum mechanical method was used to optimize the molecular geometry of some non-nucleoside inhibitors of dengue 4 virus. Molecular descriptors were mined from the optimized structure and used along with their experimental inhibitory activity (pIC_{50}) as the database for the study. Genetic function algorithm and multiple linear regressions were used to build a robust quantitative structure-activity relationship model. The statistically satisfactory quality of the model as evidenced by its validation parameters: R^2 = 0.971, R^2_{adj} = 0.961, $cRp^{\wedge 2}$ = 0.809 Q^2 = 0.944 and R^2_{pred} = 0.627. Thus, the model can be used to predict the activity of new chemicals within its applicability domain. The Average Broto-Moreau autocorrelation - lag 1 / weighted by mass, Centered Broto-Moreau autocorrelation - lag 2 / weighted by Sanderson electronegativities, Coefficient sum of the last eigenvector from Barysz matrix / weighted by van der Waals volumes, nhigh lowest polarizability weighted BCUTS and Fraction of sp3 carbons to sp2 carbons are the descriptors that influenced the anti-dengue activity of the studied compounds. The information obtained from the model in this work can be employed to optimize the anti-dengue activity of the compounds.

1.0 Introduction

Dengue infection is a mosquito-borne infection caused by a virus so-called Dengue virus (DNV) a member of the *Flavivirus* mostly found in tropical and sub-tropical regions around the world [1]. The virus is spreads to individuals by infected female Aedes genus, specifically Aedesaegypti or Aedesalbopictus [2-3]. In recent times, dengue infection has been reported in the Caribbean area, South America, and Europe [4].

Annually, at least 40 to 100 million persons are infected by DNV, and over half of the world's population at risk of infecting by this virus [4]. Infections caused by DNV can cause high fever and flu-like symptoms. These infections, in some instances, may also advance into a more acute stage know as dengue hemorrhagic fever and dengue shock syndrome [5-7]. Hence, DNV infections constitute a grave threat globally.

Out of the seven known nonstructural protein (NS) of DNV NS1 to NS5, only NS3 and NS5 have been considered so far as drug targets because they are essential to virus growth and demonstrate enzyme activity, which is desirable in regards to drug screening [8].

With all its fatal consequences, yet there are no effective drugs against dengue viruses [9-11]. This problem is also worsened by the persistent dispersal of these viruses to different geographic expanses as foretold more than a decade ago [12].

The nonexistence of particular medication for the treatment of Dengue fever presages great danger to the global health being of man, particularly in developing countries. The marked anti-dengue potentials of synthetic and medicinal plants have made their in silico structural modification geared towards the design of potent novel drug candidates a sine qua non. This will indeed provide an inroad to the development of the much-expected novel drugs against this virus.

In recent times, Computational methodologies have advanced as an imperative instrument for any drug

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