Pharmacophore Modeling, Quantitative Structure−Activity Relationship Analysis, and Shape-Complemented *in Silico* Screening Allow Access to Novel Influenza Neuraminidase Inhibitors

Areej M. Abu Hammad and Mutasem O. Taha*

Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan, Amman 11942, Jordan

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Neuraminidase (NA) enzyme is one of the valid targets against influenza viruses. With this in mind, the pharmacophoric space of influenza NA was explored using three sets of diverse inhibitors. Subsequently, genetic algorithm and multiple linear regression analysis were employed to select optimal combinations of pharmacophoric models and 2D descriptors capable of yielding self-consistent and predictive quantitative structure−activity relationships (QSARs) against 181 training compounds. The optimal QSAR equations were validated against 43 external test compounds with r^2_{PRESS} values ranging from 0.488 to 0.591. Interestingly, five orthogonal pharmacophores emerged in the optimal QSAR equations suggesting the existence of several distinct ligand/NA binding modes within the NA binding pocket. The resulting pharmacophores were complemented with tight shape constraints and employed as three-dimensional (3D) search queries against the National Cancer Institute (NCI) list of compounds. Several hits exhibited potent inhibitory activities against NA. The highest ranking hit demonstrated an *in vitro* IC_{50} value of 1.8 μM. Docking studies supported the binding modes suggested by our pharmacophore/QSAR analysis.