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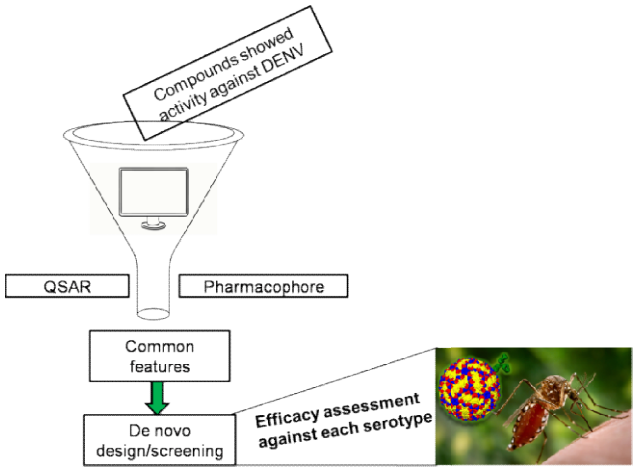
Generating optimal features to find out potent molecules against dengue virus: pharmacophore and QSAR approaches

Kazi Amirul Hossain (kaziamirulhossain@gmail.com)[a]

[a]*Department of molecular modeling, Dr. Reddy's Institute of Life Sciences, Hyderabad- 500046, India*

Graphical Abstract



Abstract.

Dengue is a threat of almost half of the population of most tropical and sub-tropical regions, mainly in Southeast Asia, the Pacific and the Americas, where the mosquito vectors, Aedes aegypti and Aedes albopictusare are profuse. Dengue fever is mainly caused by four major serotype of dengue virus i.e. DENV 1 to 4, but in 2013 a new serotype DENV-5 has been isolated. According to WHO, the first dengue vaccine, Dengvaxia® (CYD-TDV) developed by Sanofi Pasteur was licensed in December 2015 which is active against DENV1-4, but analysis showed that volunteers who were inferred to be seronegative at time of first vaccination had a higher risk of more severe dengue compared to unvaccinated volunteers. So, there are some disadvantages of using vaccine and no other treatments are available till now for dengue fever. The major drawback for dengue drug discovery is the lack of good small animal models, therefore we need computational or in-silico models with speed and accuracy which can facilitate dengue drug discovery. New approaches like Pharmacophore modelling and Quantitative Structure Activity Relationship (QSAR) can produce some valuable data which would be helpful for the designing of new chemical compounds as anti-dengue viral

	drug(s). Few evaluations of natural products as well as synthesised chemicals against different proteins of DENV have been published. In this present study, I have collated the entire molecule tested against DENV, and generating common ligand based pharmacophoric features from them, which could be helpful for the de novo synthesis and screening of compounds from databases against DENV. In addition, I am trying to develop 2D-QSAR models (using both congeneric series like different derivatives of α-ketoamides as well as non-congeneric series of molecules who's biological activities are reported) to get some easily interpretable descriptors responsible for the activity. Finally, the generated hits will be undergoing for ADME analysis to investigate their drug-likeness properties followed by molecular docking and MD simulation to see their affinity against different proteins of DENV.

References

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