Screening of compounds candidate to inhibit the interaction monomer - monomer of the NS1 protein of dengue virus: an approach for docking and molecular dynamics.

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The disease caused by Dengue virus is a major public health problem in Brazil and several other developing tropical countries, affecting populations with low socioeconomic levels, making it a neglected disease. Dengue virus has encoded in its genome three structural proteins and seven nonstructural. The NS1 (nonstructural protein 1) is found in different oligomeric forms glycosylated and its functions are assigned only to the "mature" forms of the protein (dimer and hexameter with sugars). Therefore, inhibition of the maturation of this protein has been appointed as a good investment for the rational drug design. In this study, the partial structure of the monomer protein of NS1 (ID 4o6b) was used to generate the model through the Swiss Model Server. The structure with its 6 disulphide bons and two sugars N-linked was submitted to 5 simulations of Molecular Dynamics (MD) for 30 nanoseconds (different seeds) using Gromacs software. The flexibility and structural stability of their domains were evaluated using all trajectories of simulations in order to select the conformations that best represent the structure around its native state. Compounds experimentally validated for homologous structures were used as positive control to assist in the selection of conformations that could result in high-affinity interaction with it. The conformations of NS1 with better stability had their targets sites defined to be confronted with the ZINC database (89.415 structures of the natural compounds). The compounds were subjected to molecular docking with the program AutoDock Vina to select the best 100 compounds. In the next step, all these selected compounds were simulated again against the target, running 1000 independent simulations for each, to define its energy profile. Finally the best 10 compounds were selected and had evidenced their modes of interaction. The stability of these compounds against NS1 were also checked by MD simulations, where the stability of the interaction showed the best binders / inhibitors against the targets of NS1.

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