

## **Structure-based and ligand-based virtual screening of novel methyltransferase inhibitors of the dengue virus.**

### **Abstract**

The dengue virus is the most significant arthropod-borne human pathogen, and an increasing number of cases have been reported over the last few decades. Currently neither vaccines nor drugs against the dengue virus are available. NS5 methyltransferase (MTase), which is located on the surface of the dengue virus and assists in viral attachment to the host cell, is a promising antiviral target. In order to search for novel inhibitors of NS5 MTase, we performed a computer-aided virtual screening of more than 5 million commercially available chemical compounds using two approaches: i) structure-based screening using the crystal structure of NS5 MTase and ii) ligand-based screening using active ligands of NS5 MTase. Structure-based screening was performed using the LIDAEUS (LIgand Discovery At Edinburgh UniverSity) program. The ligand-based screening was carried out using the EDULISS (EDinburgh University LIgand Selection System) program. The selection of potential inhibitors of dengue NS5 MTase was based on two criteria: the compounds must bind to NS5 MTase with a higher affinity than that of active NS5 MTase ligands, such as ribavirin triphosphate (RTP) and S-adenosyl-L-homocysteine (SAH); and the compounds must interact with residues that are catalytically important for the function of NS5 MTase. We found several compounds that bind strongly to the RNA cap site and the S-adenosyl-L-methionine (SAM) binding site of NS5 MTase with better binding affinities than that of RTP and SAH. We analyzed the mode of binding for each compound to its binding site, and our results suggest that all compounds bind to their respective binding sites by interacting with, and thus blocking, residues that are vital for maintaining the catalytic activity of NS5 MTase. We discovered several potential compounds that are active against dengue virus NS5 MTase through virtual screening using structure-based and ligand-based methods. These compounds were predicted to bind into the SAM binding site and the RNA cap site with higher affinities than SAH and RTP. These compounds are commercially available and can be purchased for further biological activity tests.

**Keyword:** Dengue; Virtual screening; Drug discovery.