Dengue, a mosquito-borne viral infection of humans transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, has become a continuing global threat, since 2.5 billion people living in tropical and subtropical regions of the world (see map above) are at risk of infection.\(^1\,^2\) It is caused by a *flavivirus* with a single positive-stranded RNA genome\(^3\,^4\) and four distinct serotypes.\(^5\)

The dengue virus infection can result in classic dengue fever, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Classic dengue fever mainly occurs in older children and adults, showing symptoms like acute febrile illness, frontal headache, muscle and joint pains, nausea, vomiting and rash. The incubation period takes 4 to 7 days and the febrile, painful period lasts for up to 7 days. DHF primarily affects children under the age of 15 years and is characterized by a sudden appearance of fever, followed by bleeding, thrombocytopenia and plasma leakage. The severe form of DHF which includes circulatory failure, hypotension or shock is defined as DSS.\(^6\,^7\)

The dengue virus genome encodes a serine protease with a classical catalytic triad (His51, Asp75 and Ser135, see image on the right)\(^8\,^9\) which is responsible for the post-translational proteolytic processing of the polyprotein precursor and essential for the viral replication,\(^10\,^11\) making it an important and attractive therapeutic target.\(^12\)

Our projects include syntheses, characterization and testing of DENV-2 NS2B-NS3pro inhibitors based on the structure of cinnamic acid amides and diaryl thioethers. Possible binding modes are analyzed by docking studies (see image on the right). Since a good specificity for the DENV-2 NS2B-NS3pro should be achieved, other serine proteases of the human organism, such as trypsin, chymotrypsin and thrombin are included in the testing procedures.
Synthesis and characterization of Dengue Virus Type 2 NS2B-NS3 protease inhibitors

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