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Structure -based discovery of potential small-molecule inhibitors targeting Zika virus NS3 helicase

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Zika virus (ZIKV) is a mosquito borne pathogen that has been rapidly a rapidly expanding epidemic across Central and South America since 2015. It belongs to flavivirus family and is closely related to Dengue virus and West Nile virus. ZIKV was first isolated in 1947 from a rhesus monkey around the Zika forest of Uganda. ZIKV has been realized as a major health risk, making it a compelling target for viral therapeutics. Its infection causes not only mild symptoms such as fever, headache, arthralgia and conjunctivitis, but frightening neural diseases including Guillain–Barré syndrome, congenital microcephaly, as well as macular atrophy. There's an urgent need to discover and develop direct-acting antiviral agents (DAAs) in view of the current lack of effective medicine for ZIKV. Nonstructural protein 3 (NS3) helicase of ZIKV is considered to be essential for viral replication and have become an attractive target for the development of DAAs. Recent years, in silico virtual screening has been generally accepted as a rapid, efficient, economical approach with low time and labor cost for screening a large set of compounds. Here, an in-silico screening analysis of NCI diversity dataset with ZIKV NS3 protein targets has been carried out using a structure-based molecular docking approach. A total of 1974 compounds with structural simplicity and diversity have been docked. Top-ranked 5% of compounds with drug-like properties were selected for antiviral evaluation by cell-based ZIKV infection assays. Three hits were identified to specifically inhibit the viral infection with EC50 values at a micro-molar level. Different series of potential derivatives with expected better antiviral activities were presented based on similarity search and target-ligand binding modes. Overall, the discovery of these NS3-targeting compounds may serve as novel leads for further optimization and development of clinical ZIKV inhibitors.

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