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Inhibition of dengue virus by curcuminoids

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Abstract

The dengue virus is considered to be a globally important human pathogen prevalent in tropical and subtropical regions of the world. According to a recent estimate, the disease burden due to DENV infections is ~390 million infections per year globally in ~100 countries including the southern US, Puerto Rico and Hawaii, resulting in nearly ~25,000 deaths mostly among children. Despite the significant morbidity and mortality that results from DENV infections, there is currently no effective chemotherapeutic treatment for DENV infections. We identified curcumin as an inhibitor of DENV2 NS2B/NS3protease in a previous high-throughput screening (HTS) campaign. We synthesized four analogues of curcumin (curcuminoids) and tested the in vitro protease inhibition activity and inhibition of replication by cell-based assays. The results revealed that curcumin is a weak inhibitor of the viral protease. However, the analogues exhibited more potent inhibition of DENV infectivity in plaque assays suggesting that the cellular pathway(s) required for viral replication and/or assembly are targeted by these compounds. Further analysis shows that inhibition of genes involved in lipid biosynthesis, and of actin polymerization by curcuminoids, are likely to be involved as their mode of action in DENV2-infected cells. Three of the curcumin derivatives possess good selectivity indices (SI) (>10) when compared to the parent curcumin.