AMIDOXIME PRODRUGS CONVERT TO POTENT CELL-ACTIVE MULTIMODAL INHIBITORS OF THE DENGUE VIRUS PROTEASE

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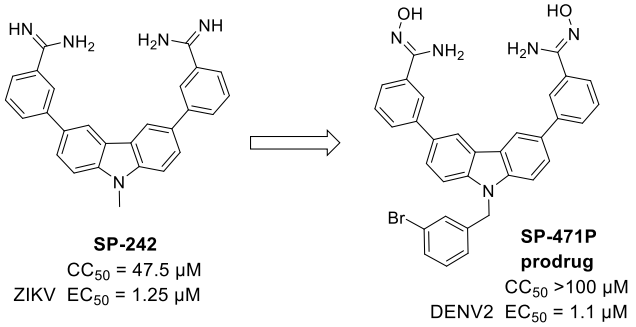
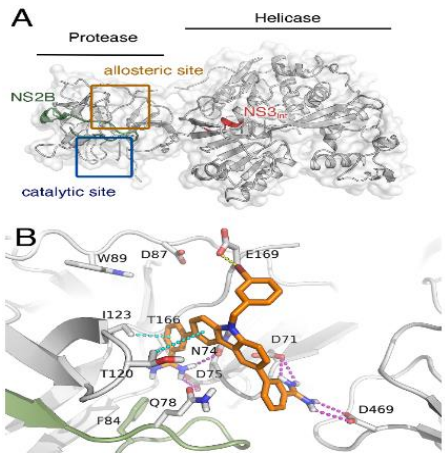
The flavivirus genus of the *Flaviviridae* family comprises Dengue, Zika and West-Nile viruses which constitute unmet medical needs as neither appropriate antivirals nor safe vaccines are available. The dengue NS2BNS3 protease is one of the most promising validated targets for developing a dengue treatment, however reported protease inhibitors suffer from toxicity and cellular inefficacy. Here we report SAR on our Zika-active carbazole scaffold SP-242, culminating prodrug compound **SP-471P** (EC_{50}= 1.10 μM, CC_{50} > 100 μM) that generates SP-471; one of the most potent, non-cytotoxic and cell-active protease inhibitors described in the dengue literature. In cell-based assays, **SP-471P** leads to inhibition of viral RNA replication and complete abolishment of infective virus particle production even when administered 6 h post-infection. Mechanistically, **SP-471P** appears to inhibit both normal intermolecular protease processes and intramolecular cleavage events at the NS2BNS3 junction, as well as at the NS3 internal sites, all critical for virus replication. These render SP-471 a unique to date multimodal inhibitor of the dengue protease.





References

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