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**Structural-based Antiflaviviruses Drug Discovery and Delivery System Optimization**

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Flaviviruses are life-treathening, positive-sense RNA viruses, including West Nile, Dengue and Zika. There is an urgent need for new therapeutic approaches, as current antiviral therapies are often ineffective and vaccines available are losing efficacy due to vector resurgence and resistance. We have identified pyridobenzothiazole (PBTZ) as a promising class of flaviviruses inhibitors. However, cell-based assays have revealed limited efficacy due to poor bioavailability. To overcome this challenge, enhance drug stability, improve targeting and minimize side effects, we are exploring nanoparticle-based delivery systems. Specifically, we employ microalgosomes, obtained via tangential flow filtration, loaded with PBTZ using saponin treatment, electroporation and sonication, as well as PLGA nanoparticles. We are performing confocal microscopy experiments to assess cellular uptake, localization, and delivery efficiency of PBTZ-loaded nanoparticles. Additionally, NS4A a flavivirus non-structural protein involved in viral replication, stability and membrane remodeling, represents a promising but poorly characterized target. To elucidate its structure we have expressed NS4A using Rosetta, followed by purification, circular dichroism (CD), crystallography and AFM.Our findings suggest that NS4A is composed of alpha-helices and plays a critical role in membrane interactions and remodeling