Characterizing the Binding Affinity of Second-Generation HIV Maturation Inhibitors to Viral Protein Targets Using Solution NMR Spectroscopy

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Around 40.8 million people are living with HIV at the end of 2024 (World Health Organization, 2024). Around 630,000 deaths were due to HIV-related causes. These numbers highlight the need for modern and effective HIV maturation inhibitors. Based on this information the researchers established: How can the dissociation constant between maturation inhibitor derivatives and HIV proteins be measured while establishing a correlation between protein-drug affinities and inhibitor effectiveness in biophysical assays? The researcher suggests that while realizing protein- drug aliquots in solution NMR Spectroscopy, it will be observed that different chemical structures will lead to different interactions with the protein and thus different binding constants. Also, inhibitors that bind tightly will be more effective at stabilizing HIV protein assemblies, making them resistant to disassembly. During HIV-1 maturation, the Gag polyprotein is cleaved by HIV protease into numerous proteins that assemble into infectious viral particles (Chen et al., 2020). This study investigates how different HIV-1 maturation inhibitors affect the structure and stability of the CTD-SP1 junction using Nuclear Magnetic Resonance (NMR) spectroscopy, UV-Vis thermal disassembly assays, and dissociation constant (Kd) analysis (Chen et al., 2020). The compounds Dioxo, PPG, and ED-BVM showed strong binding affinities (low Kd values) and increased resistance to thermal disassembly, suggesting improved stabilization of the CTD-SP1 junction. In contrast, MA-BVM and the original compound BVM showed weaker binding and minimal stabilizing effects. These results provide new insights into how specific compounds regulate CTD-SP1 dynamics and contribute to the design of future maturation inhibitors targeting HIV-1.

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