

A NEW SMALL MOLECULE CLASS OF EARLY STAGE HIV-1 INHIBITOR THAT TARGETS THE CAPSID PROTEIN

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Using a high throughput, full replication HIV-1 antiviral screen, we have identified a new small molecule inhibitor class that targets the capsid protein (CA). The compounds exhibit antiviral activity against HIV-1 laboratory strains and clinical isolates in T-cell lines and peripheral blood mononuclear cells (PBMCs). The collective results of stage identification assays, quantitative PCR, and time of addition experiments show that the compounds act early in the replication cycle, specifically at a point subsequent to viral entry, but prior to reverse transcription. HIV-1 variants selected for resistance to this class contain up to five amino acid substitutions in HIV-1 CA, which we demonstrate are able to confer significant resistance to several members of this class of compound. We show, through calorimetric and crystallographic methods, that the compounds bind specifically to the N-terminal domain of HIV-1 CA *in vitro*. Our results demonstrate that this novel class of inhibitors acts through a mechanism unique to any previously reported, possibly by affecting the viral uncoating process.