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ANTIVIRAL ACTIVITY OF SPI-256 AGAINST WT AND MDR STRAINS

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BACKGROUND: SPI-256 is an HIV protease (HIV PR) inhibitor designed using structure-based approaches to be potent against wild-type (WT) and multi-drug-resistant (MDR) HIV PR. We report here the evaluation of SPI-256's *in vitro* activity using enzymatic and different cell-based antiviral assays.

METHODS: The enzyme inhibition was characterized using recombinant WT and MDR HIV PRs and fluorogenic substrate. Antiviral activity was evaluated in cell-based assays in PBMC and MT4 cells. The PhenoSense HIV assay (Monogram Biosciences) was used to evaluate the antiviral activity of SPI-256 against a panel of highly PI-resistant MDR HIV strains.

RESULTS: SPI-256 is highly active against purified WT and MDR-HIV proteases with K_i in the picomolar range; it is superior in activity to all approved HIV PIs, including LPV and ATV. In cell-based assays, SPI-256 demonstrated potent antiviral activity against subtype B and non-B HIV primary isolates, and against viruses with different co-receptor tropism, with IC_{50} values ≤ 2 nM. SPI-256 retained low nanomolar potency (<30 nM) against a selected panel of 7 highly PI resistant MDR strains derived from clinical isolates in MT4 cells. In the PhenoSense assay, SPI-256 exhibited an average IC_{50} value of 0.3 nM (range: 0.2-0.4 nM) against viruses lacking known PI resistance mutations, and was 4-50 fold more potent than FDA-approved PIs (IC_{50} 1.2-16.3 nM). Among isolates with > 50-fold resistance to reference PIs (IC_{50} range: >252 to >2,925 nM) and/or 6 primary PI mutations ($n=12$), the average SPI-256 IC_{50} was 12.9 nM (range: 1.8-34 nM). SPI-256 exhibited an IC_{50} of 85 nM in PBMC against a dual-tropic, primary MDR-HIV strain that was recently isolated from a patient with rapid progression to AIDS, which contained 12 mutations in PR accompanied by p7/p1 gag cleavage site mutations.

CONCLUSIONS: SPI-256 is more potent than currently approved PIs against WT HIV-1 in different *in vitro* assays. It maintains nanomolar potency against worst-case scenario MDR HIV isolates and is equipotent against viruses of different clades and co-receptor tropism. SPI-256 has the potential to be used as part of first line as well as salvage therapy in treatment regimens world-wide.

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