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MAPPICINE INHIBITORS OF HIV-1 REVERSE TRANSCRIPTASE-ASSOCIATED RIBONUCLEASE H

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INTRODUCTION: Current therapeutics for treatment of HIV infection are directed at two viral targets, protease and the DNA polymerase activity of reverse transcriptase (RT). Viral resistance to these therapeutics is an increasingly serious problem, thus identification of drugs directed at new HIV targets is essential. The ribonuclease H (RNase H) activity of RT resides in a subdomain that is spatially distinct from the RT DNA polymerase active site. The viral RNase is absolutely essential for retroviral replication and thus presents a logical target for antiviral intervention. However, while numerous inhibitors of HIV-1 RT DNA polymerase activity have been identified (including 10 drugs in current clinical use), very few inhibitors of RNase H have been identified, and none are in preclinical development. We have developed a fluorescence-based assay for HIV RT RNase H that enables high-throughput screening for inhibitors of this potential target. Using this screening assay, we have discovered that certain analogues of mappicine are potent inhibitors of HIV-1 RT-associated RNase H.

OBJECTIVES: To characterize the antiviral properties of mappicine analogue inhibitors of HIV-1 RT-associated RNase H.

RESULTS: Initial screening of a small library of 110 mappicine analogues using a novel fluorescence-based high-throughput screening assay for HIV RT RNase H resulted in the identification of two compounds with reasonable antiviral potency, but unfortunately with significant cytotoxicity. A larger library of 560 mappicine analogues was prepared by fluorour-tagged combinatorial synthesis and screened, leading to the identification of 55 additional inhibitors. Of these, mappicine 756 was among the most potent ($IC_{50} \approx 2 \mu M$ against RT-associated RNase H *in vitro*). Mappicine 756 showed very good antiviral activity against the wild-type HIV-1 IIIB strain ($EC_{90} \approx 2.5 \mu M$) and had virtually no cytotoxicity ($CI_{50} > 100 \mu M$) as assessed in several cell lines. Importantly, mappicine 756 retained full antiviral potency against several drug-resistant HIV-1 strains, including

virus with high-level resistance to nevirapine, delavirdine and efavirenz, the three clinically approved non-nucleoside RT inhibitors. HIV strains resistant to mappicine 756 developed upon serial passage of the virus in the presence of increasing concentrations of the drug, leading to virus with 80-fold resistance to the drug. Several mutations were found in the virus resistant to mappicine 756; these mutations localized only in the segment of the RT gene corresponding to the RNase H subdomain.

CONCLUSIONS: The good antiviral activity in the absence of significant cytotoxicity suggest that mappicine analogues may represent an interesting new class of antiretroviral agents, those targeting RT-associated RNase H. Structural variants of mappicines are readily prepared by combinatorial methods, and it is therefore expected that improvements in antiviral potency may be attained.

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