

POSTER 28**SYNTHESES AND EVALUATIONS OF MANICOL DERIVATIVES AS INHIBITORS OF HIV-1 RNASE H ACTIVITY**

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RNase H activity of HIV has been recognized as a potential target for antiviral therapy. However, the discovery of potent inhibitors specifically blocking its activity has been slow, and so far no RNase H inhibitor has yet to reach the clinical trial. A high throughput screening of a pure natural product library led us to the identification of a new class of RNase H inhibitor, β -thujaplicinol ($IC_{50} = 0.21 \mu M$) and manicol ($IC_{50} = 0.6 \mu M$), which have an α -hydroxytropolone scaffold. Although the chemical structure of these inhibitors is clearly different from the *N*-hydroxyimides and diketo acids, recent biochemical data shows that these inhibitors might also bind at the active site through metal chelation. However, both inhibitors are cytotoxic, thus preventing evaluation of their antiviral activity. In order to overcome the toxicity issue and increase potency and selectivity, our investigation focused on derivatization of these inhibitors.

SAR studies showed that three oxygen ligands of inhibitors are critical for binding while the substitution on the other part of heptatriene ring was relatively less sensitive. Thus, the terminal alkene moiety on manicol was chosen as a target site for derivatization because of the versatile chemistry of the alkene functional group. Two synthetic schemes were mainly applied, 1) epoxidation followed by a ring opening reaction with a series of amine or mercapto nucleophiles, 2) ozonolysis followed by reductive amination. Fifteen manicol derivatives were initially synthesized and their inhibitory activities were evaluated using a fluorescence based assay. The IC_{50} s of these compounds have a range of sub to low micro molar and the most active compound, JKJ07-37 ($IC_{50} = 0.17 \mu M$) proved slightly more potent than the parent compound. This result was also confirmed by a gel based assay using a substrate containing the HIV-1 polypurine tract (PPT). Although none of these inhibitors displayed antiviral activity in cell cultures, manicol derivatives represent a novel family of HIV-1 reverse transcriptase inhibitor, targeting RNase H activity that may lead to the development of therapeutically relevant compounds to treat AIDS.