



XI International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications

Seville, Spain, 2–5 July 2002

AZIDE GROUP CONTAINING 3-ARYL-1, 3-DIKETO ACID DERIVATIVES ARE POTENT INHIBITORS OF HIV-1 REPLICATION

Antivir Ther. 2002;7(Suppl 1):S13 (abstract no. 15)

ES Svarovskaia¹, R Barr¹, X Zhang², GCG Pais², C Marchand³, Y Pommier³, TR Burke Jr² and VK Pathak¹

¹HIV Drug Resistance Program, NCI at Frederick, Frederick, Md., USA; ²Laboratory of Medicinal Chemistry, NCI at Frederick, Frederick, Md., USA; and ³Laboratory of Molecular Pharmacology, NCI, NIH, Bethesda, Md., USA

BACKGROUND: Previous studies have shown that diketo acid derivatives are potent inhibitors of HIV-1 integrase and HIV-1 replication (Hazuda et al., [Science. 2000 Jan 28;287\(5453\):646-50](#)). The goal of the project was to identify novel diketo acid derivatives that inhibit HIV-1 replication and to characterize their *in vitro* and *in vivo* antiviral activity.

METHODS: A series of derivatives were synthesized and tested for their ability to inhibit the 3' processing and strand transfer reactions *in vitro* and viral replication *in vivo*. The ability of the compounds to inhibit 3' processing and strand transfer activities was determined in *in vitro* assays. Their ability to inhibit HIV-1 replication was measured in a single cycle as well as a multi-round assay. The structure of viral DNA 2-LTR circle junctions was determined in the presence and absence of the compounds by quantitative real-time PCR and DNA sequencing.

RESULTS: Among the compounds tested, two compounds containing azide groups significantly inhibited HIV-1 replication in both single round and multiple round assays. The therapeutic indices of the compounds (IC₅₀ 7–13 μM; CC₅₀ 60–600 μM) were similar to L708,906. We also constructed integrase mutants T66I and T66I/S153Y that were previously shown to be resistant to L708,906 compound (Hazuda et al., [Science. 2000 Jan 28;287\(5453\):646-50](#)). These mutants were resistant to the azide group containing diketo acid derivatives, indicating that these derivatives inhibit HIV-1 replication at the level of integration. In addition, amounts of 2-LTR circles in the presence of azide group containing diketo acid derivatives were shown to be elevated in comparison to untreated control during HIV-1 infection. The 2-LTR circle junctions

present in cells infected in the absence and presence of the compounds were characterized by DNA sequencing.

CONCLUSION: These results indicate that diketo acid derivatives containing azide groups are potent inhibitors of HIV-1 integrase and viral replication.

PRESENTING AUTHOR: VK Pathak

2002-07-02
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