S38-4 Discovery of Elvitegravir as a Novel Monoketo Acid Class of HIV-1 Integrase Inhibitor

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HIV-1 integrase catalyzes both 3'-processing and strand transfer reactions to integrate viral DNA into host chromosome. Therefore, the enzyme, along with HIV-1 reverse transcriptase and HIV-1 protease, is an essential enzyme for retroviral replication, and represents an important target for interrupting the viral replication cycle. The mainstream diketo acid integrase inhibitors have three functional groups possessing a metal-chelating function to simultaneously coordinate two divalent metal ions, whish have been considered to be essential for the inhibitory activity. Despite this, we found that a monoketo acid compound had an integrase inhibitory activity. The novel monoketo acid integrase inhibitor has only two functional groups, a carboxylic acid and a ß-ketone, which are coplanar. This result shows that the coplanar monoketo acid motif can serve as an alternative to the diketo acid motif, even though the simplified monoketo acid motif is unlikely to fully coordinate with two divalent metal ions. The weaker chelating ability of the monoketo acid motif was disadvantageous for achieving potent activity. However, the highly potent elvitegravir was obtained by structural modification around the monoketo acid moiety of the initial lead compound. The structurally new class of HIV-1 integrase strand transfer inhibitor elvitegravir exhibits an IC_{50} of 7.2 nM in an HIV-1 integrase strand transfer assay and an EC_{50} of 0.9 nM in an acute HIV-1 infection assay, and is in the advanced stage of clinical development.