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DISCOVERY OF A POTENT ANTIVIRAL HIV INTEGRASE INHIBITOR WITH POTENTIAL CLINICAL UTILITY

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Current therapies available for treatment of HIV infection target only two of the three constitutive viral enzymes required for replication, namely the retroviral reverse transcriptase and protease. While drugs targeting these enzymes are often effective in managing the disease, the emergence of multidrug-resistant variants along with toxicities associated with chronic administration, point to a need for new therapies. The third enzyme, HIV-1 integrase, is an attractive target for chemotherapeutic intervention in the treatment of AIDS in large part due to the absence of viruses harbouring resistance to yet unknown integrase inhibitors. Unlike the reverse transcriptase and protease enzymes, successful drug candidates based on inhibition of integrase have yet to emerge despite a number of laboratories working on the problem. Previously, we disclosed a series of HIV-1 integrase inhibitors discovered through screening that have anti-replicative activity in cell culture. This antiviral activity is directly linked to the compound's integrase inhibitory activity. In cells infected with HIV-1, treatment with these inhibitors results in formation of circular forms of unintegrated proviral DNA, recapitulating the phenotype of integrase deficient viruses. These screening leads come from a single class of molecules broadly described as 4-aryl-2,4-diketobutanoic acids (DKAs). While optimization of these leads produced DKA compounds with promising antiviral activity, concerns about their metabolic reactivity caused us to seek alternatives for the DKA pharmacophore. Stepwise replacement of three critical elements of the pharmacophore led to a completely novel, metabolically stable series of condensed heterocyclic compounds. These compounds are exceptionally potent inhibitors of HIV-1 integrase strand transfer functionality. In cell culture the antiviral activity of these agents against wild-type virus is similar to that of the more potent approved antiretroviral drugs. Further, the antiviral activity of these compounds is undiminished against a variety of diverse clades and viral variants expressing significant resistance to all of the currently available licensed HIV-1 inhibitors, including protease inhibitors, nucleoside reverse transcriptase

inhibitors and non-nucleoside reverse transcriptase inhibitors. The leading compound from this new series has good pharmacokinetics in rats, dogs and rhesus macaques. Its absolute oral bioavailability and half-life in these species, along with its stability in isolated human hepatocytes, suggests a high potential for good pharmacokinetics in humans. Following preliminary safety assessment studies, this compound has moved into Phase I clinical trials for evaluation in healthy volunteers.

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