Pyrophosphate Mimetics: a Mechanism Based Approach to Antiviral Drug Discovery

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Despite little or no sequence homology, enzymes that catalyze phosphoryl transfer reactions share a common active site architecture involving two divalent metal ions with a conserved inter-metal ion distance. Viruses encode a variety of essential phosphoryl transferases including polymerases, ribonucleases and integrases. We have identified highly potent and specific inhibitors of integrase from the human immunodeficiency virus (HIV-1). These compounds are the first inhibitors of integrase to demonstrate activity against HIV-1 both in vitro and in vivo. Extensive characterization of these inhibitors has elaborated the mechanism of action as direct sequestration of the active site divalent metals in integrase. Elements of the inhibitors which interact with the divalent metal ion have been identified and the structure of the minimal pharmacophore is consistent with the observed spatial orientation of the metal ions in the active site of integrase as well as other enzymes in this class. These inhibitors of HIV-1 integrase therefore present an entirely new approach to develop novel agents to treat HIV-1 infection and provide an important proof of concept for a general pharmacophore that can be exploited to inhibit phosphoryl transferases through this conserved mechanism. Consistent with this hypothesis, extensive screening of related compounds has led to the identification of specific inhibitors for a wide variety of viral targets, including RNA and DNA polymerases for a diverse number of human pathogenic viruses.