A SCAFFOLD HOPPING APPROACH TOWARD INDOLE-BASED ALLOSTERIC HIV-1 INTEGRASE INHIBITORS

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Human immunodeficiency virus (HIV) is a global health issue with an estimated 37.7 million infected individuals and 1.5 million new diagnoses during 2020. The virus attacks CD4 cells, weakening a patient's immune system and potentially leaving them susceptible to life-threatening opportunistic infections. Although there is currently no cure for this disease, there are many treatment options to help manage it. The evolution of resistance to these therapeutics, however, necessitates the development of new drugs, particularly those that target alternative binding sites on key viral proteins. HIV-1 Integrase (IN), for example, has emerged as a viable target for drug development due to its importance within the HIV retroviral life cycle. IN acts to weave viral DNA into the host chromosomal DNA, effectively exploiting the central dogma of biology to produce new HIV-1 assemblies that will travel through the body and advance infection. There are currently five FDA-approved drugs that target IN (Raltegravir, Dolutegravir, Elvitegravir, Bictegravir, and Cabotegravir). These drugs target the IN active-site and impede the HIV-1 life cycle by blocking the HIV-IN strand transfer reaction. An alternative target on IN is the allosteric site to which the important HIV-1 cellular cofactor LEDGF/p75 binds. Compounds binding at this site act at the late-stage, resulting in aberrant multimerization of HIV-IN that inactivates the enzyme and results in the formation of eccentric cores. Our labs have previously developed several different scaffolds that target this site. Here we present the extension of our previous scaffold hopping approach to create new indole-based compounds using a parallel synthetic approach that rapidly incorporates diversity into two key structural motifs found in this class of agent.