**Allosteric HIV-1 Integrase Inhibitors: Indole Derivatives Designed to Promote IN Multimerization**

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Numerous drugs have successfully been developed and approved to combat HIV infection over the past 40 years. Mutations of the viral target proteins, however, make these drugs less effective over time and continue to spur on the discovery and design of novel compounds with unique mechanisms of action. For this reason, compounds targeting a unique allosteric site on HIV-1 Integrase (IN), the enzyme responsible for integrating viral RNA into the host’s DNA, are being developed. This allosteric site is the binding site for the cofactor LEDGF/p75, a host cell protein that promotes the activity of integrase, and is located at the IN CCD dimer interface. The binding of small molecule drugs at this allosteric binding site results in the inactivation of the protein due to the formation of aberrant integrase multimers, occurring as a result of interaction of the CTD subunit of another integrase protein with the CCD dimer interface. Initial lead compounds targeting this site were built upon a quinoline core scaffold, but using a scaffold hopping approach, the required pharmacophore was subsequently transferred to an indole core. The indole core scaffold was specifically selected due to the flexibility of known synthetic routes to indoles, existence of commercially available starting materials, and the ease of functionality of the indole core. Extension of early indole inhibitors through substitution at the C5- and C6-positions on the benzene ring of the indole system has facilitated the preparation of more potent compounds, presumably through the promotion of additional interactions with the incoming CTD unit of IN. The highly efficient and modular construction of these compounds has taken advantage of bromoisatin substitution for the introduction of unique groups through late-stage Suzuki coupling reactions. Variation of the Suzuki coupling partners has allowed exploration of the steric and electronic properties necessary for efficient IN inhibition.