THE UNIVERSITY OF TOLEDO
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Department of Chemistry and Biochemistry

Colloquium Speaker

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Université des Sciences et Technologies de Lille 1

"Novel Inhibitors of HIV Integrase with a High Barrier to Resistance"

Abstract: HIV-1 integrase (IN) is a 32 kDa protein that plays a crucial role in HIV infection by incorporating the retrotranscribed viral DNA into the host chromosomal DNA. IN has been extensively studied as a therapeutic target in the field of AIDS antiretroviral therapy since it establishes irreversible infection and has no cellular equivalent, which limits toxicity.

The first FDA-approved drug acting as a strong selective ST inhibitor is raltegravir (Isentress). Elvitegravir, also recently approved, can be given once daily when combined with a booster (as part of the fixed-dose combination tablet Stribild), but cross-resistance rules out treatment of patients failing on raltegravir therapy. Dolutegravir is considered to be a second-generation HIV-1 integrase inhibitor.

Here, I will present the process from the hit identification to the hit-to-lead optimization of a series of 2-hydroxyisoquinoline-1,3(2H,4H)-dione (HID) derivatives leading to novel candidate IN inhibitors.
MB-76 is issued from the hit identification and displays low nanomolar IC_{50} values (enzymatic inhibition) comparable to that of the first clinically used raltegravir. A marked effect of this compound on both primary IN-catalyzed reactions, strand transfer (ST), and 3′ processing (3′-P), emphasizes a novel IN inhibition mechanism establishing it as a potential new generation IN inhibitor.

In a second round optimization, we further investigated the influence of substitution at position 7 on biological activity. Introduction of electron-withdrawing functional groups such as the nitro moiety at position 7 (VS39) has led to a noticeable improvement of antiviral activity, down to low nanomolar anti-HIV potencies, with advantageous therapeutic indexes going close to those of the clinically used raltegravir and retained potencies against a panel of IN mutants.

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