proceedings

Abstract

Kinetic Characterization of Novel HIV-1 Entry Inhibitors: Discovery of a Relationship between Off-Rate and Potency †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 15 August 2019

Abstract: The entry of HIV-1 into permissible cells remains an extremely attractive and underexploited therapeutic intervention point. We have previously demonstrated the ability to extend the chemotypes available for optimization in the entry inhibitor class using computational means. Here, we continue this effort, designing and testing three novel compounds with the ability to inhibit HIV-1 entry. We demonstrate that alteration of the core moiety of these entry inhibitors directly influences the potency of the compounds, despite common proximal and distal groups. Moreover, by establishing for the first time a surface plasmon resonance (SPR)-based interaction assay with soluble recombinant SOSIP Env trimers, we demonstrate that the off-rate (kd) parameter shows the strongest correlation with potency in an antiviral assay. Finally, we establish an underappreciated relationship between the potency of a ligand and its degree of electrostatic complementarity (EC) with its target, the Env complex. These findings not only broaden the chemical space in this inhibitor class, but also establish a rapid and simple assay to evaluate future HIV-1 entry inhibitors.

Keywords: bioisosteres; HIV-1 Env; antiviral; surface plasmon resonance; computer-aided drug design