PENN CENTER FOR INNOVATION

CD4 mimetic small molecule inhibitors of HIV-1 entry

Therapeutic development for HIV-1 infection and prevention of transmission

Inventors

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STATE OF DEVELOPMENT

In vitro proof-of-concept

INTELLECTUAL PROPERTY

USSN 9,403,763

REFERENCE MEDIA

LaLonde J.M. et al. J. Med. Chem., 2012, 55, p. 4382-4396.
C&EN News highlight.

APPLICATIONS

- Therapeutic for HIV-1 infected individuals
- Microbicide to prevent acquisition of HIV-1 infection

DESIRED PARTNERSHIP

License
Co-development

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Docket # Y6120

Problem

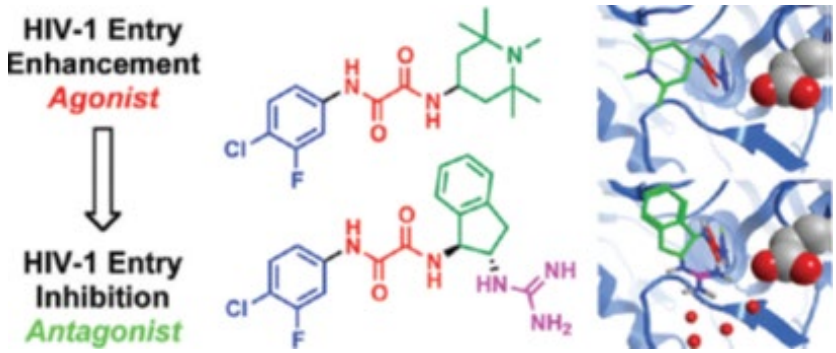
A global pandemic of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) persists, with about 34 million people worldwide currently infected and 2.5 million people newly infected with the virus annually. Inhibition of the initial HIV entry into the host cell has proven elusive to develop therapeutics for HIV-1 infection. Cellular infection by HIV-1 begins when the viral envelope glycoprotein gp120 binds to the T-cell receptor protein CD4 anchored to the cell membrane. This binding event induces a conformational change that exposes the binding site for the transmembrane chemokine co-receptor (CCR5 or CXCRC4), and the rearranged protein helix bundle inserts into the host cell membrane for viral entry.

Solution

In a cross-university collaboration, researchers have utilized structure-based drug design and synthesized dual hotspot small molecule HIV-1 entry inhibitors in a novel structural paradigm for inhibiting the CD4-gp120 protein-protein interaction. More specifically, these inhibitors interact with the Phe43 cavity and aspartic acid D368 within the glycoprotein gp120. The D368 residue makes important contacts with CD4, and compounds that interact with this residue block the interaction with CD4 with higher potency and across a range of HIV-1 strains than previously characterized CD4-mimetic compounds. Furthermore, these new compounds do not activate HIV-1 infection of CD4-negative, CCR5-expressing cells.

Advantages

- Improved antiviral potency
- Antagonists of entry into CD4-negative cells
- Greater breadth of activity against multiple HIV-1 strains that previously described CD4-mimetic compounds
- Small molecule antagonists of viral attachment and entry process
- Minimize undesirable side effects



From LaLonde et al, 2012.