



Novel 3,28-Disubstituted Betulinic Acid Derivatives as Potent Anti-HIV Agents



Triterpenes, such as betulinic acid (BA) represent a promising class of anti-HIV agents with novel mechanisms. Two types of BA derivatives have exhibited potent anti-HIV profiles. A diverse set of 28,30-disubstituted BA analogues have been synthesized which should serve as leads for the development of a next generation of BA derived 3,28-disubstituted HIV-1 inhibitors.

Benefits

- HIV entry inhibitor
- HIV maturation inhibitor (new class)



For More Information

If you would like more information about this technology or UNC - Chapel Hill's technology transfer program, please contact:

Jackie Quay
Office of Technology
Development
Phone:
Fax:
Email: jlquay@unc.edu

<http://research.unc.edu/otd/>

Office of Technology
Development
UNC - Chapel Hill
308 Bynum Hall
CB 4105
Chapel Hill, NC 27599-4105

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The Technology

Therapy for HIV usually includes 3 or more medications (highly active antiretroviral therapy-HAART), each from a class of drugs with a different mechanism of action. The purpose of combination is to prevent viral replication in more than one mechanism to minimize the potential for viral mutations to escape inhibition. However development of HIV resistance to HAART drugs and the long-term toxicity of such medicines demonstrate that there is still a need for HIV treatments with alternative mechanisms of action.

Triterpenes, such as betulinic acid (BA) represent a promising class of anti-HIV agents with novel mechanisms. Two types of BA derivatives have exhibited potent anti-HIV profiles. C-3 esterification of BA led to the discovery of bevirimat which is a HIV-1 maturation inhibitor (MI) that blocks cleavage of p25 to functional p24, resulting in the production of noninfectious HIV-1 particles. On the other hand, the C-28 side chain was proven to be a necessary pharmacophore for anti-HIV entry activity, as seen with equipotent diastereomers. Mechanism of action studies have revealed that C-28 modified BA derivatives function at a postbinding, envelope-dependent step involved in fusion of the virus to the cell membrane. Recent studies further suggested that they may also function by targeting the V3 loop of gp120, a domain involved in chemokine receptor binding. Although these showed potent antiviral activity in vitro, the clinical development by Rhone-Poulenc (now Sanofi-Aventis) was stopped because of poor "pharmacodynamic properties". However, the high potency and novel mechanism of these compounds suggest that further modification of this compound class as HIV entry inhibitors is warranted. A diverse set of 28,30-disubstituted BA analogues have been synthesized which should serve as leads for the development of a next generation of BA derived 3,28-disubstituted HIV-1 inhibitors.

Opportunity

UNC's Office of Technology Development seeks to stimulate development and commercial use of UNC-developed technologies. UNC is flexible in its agreements, and opportunities exist for joint development, academic or commercial licensing (exclusive, non-exclusive, and field-of-use), publishing, or other mutually beneficial relationships. UNC is pursuing U.S. and international intellectual property protection for this innovation.