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Patent Highlight

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Novel Triterpenone for Treatment of Viral Diseases-HIV Inhibitors

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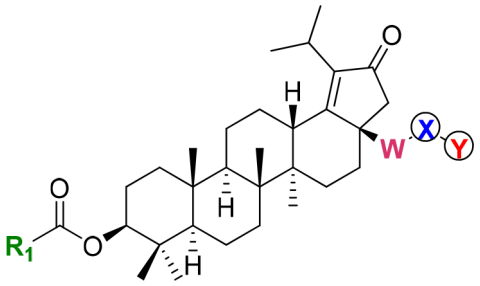

Important Compound Classes. Title. C-3-Novel Triterpenone with C-28 Heterocycle Derivatives as HIV Inhibitors.

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Assignee Company. Hetero Laboratories Limited.

Disease Area. Viral diseases; HIV.

Biological Target. CD4+T cells

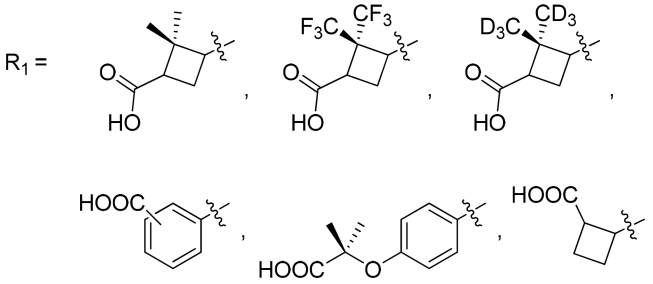
Summary. According to the Joint United Nations Program on HIV and AIDS (UNAIDS, http://www.unaids.org/en/resources/fact-sheet), from the inception of cases of HIV reported, 78 million people have become infected with HIV and 35 million have died from AIDS-related illnesses. There were approximately 36.7 million people worldwide living with HIV/AIDS at the end of 2016. Only about 60% of people with HIV know their HIV/AIDS status. However, in July 2017, 20.9 million people living with HIV were accessing one of the *gold standards* therapies, the highly active antiretroviral therapy (HAART) globally. One of the key features of antiretroviral therapy is that it reduces the amount of virus in the body to a level that is undetectable with current blood tests. A retrovirus is a single-stranded RNA virus with a DNA intermediate, which targets a host cell. Once inside the host cell, the virus uses its own enzyme to produce DNA from its RNA genome, which is a reverse process from regular sequence and is very difficult to detect until it has infected its host. HIV attacks and destroys the body's CD4 cell of the immune system, which makes it difficult to fight off infections and certain HIV-related diseases.

There are naturally occurring antiretrovirals such as betulinic acid with anti-HIV activity, which is found in the bark of several species of plants. Modification of this compound has led to potent anti-HIV agents such as bevirimat, giving rise to novel mechanisms of action. Bevirimat acts by disrupting the genetic material that codes the proteins of a retrovirus (gag processing) and was a first-in-class maturation inhibitor with a potent activity against HIV-1. In addition, other derivatization of betulinic acid have led to their use in other therapeutics such as inhibition of cancer growth, anti-inflammatory activity, antifeedants for plant pests, and so forth.

The staggering statistics of the AIDS epidemic level worldwide has necessitated new and effective drugs for treatment of HIV-infected patients. The global cost of HIV treatment and prevention is estimated to reach $35 billion by 2031 (http://www.aidsmap.com). The present invention relates to C-3 triterpenone with C-28 heterocycle derivatives, which is shown to be useful in the treatment of viral diseases such as HIV-mediated diseases.

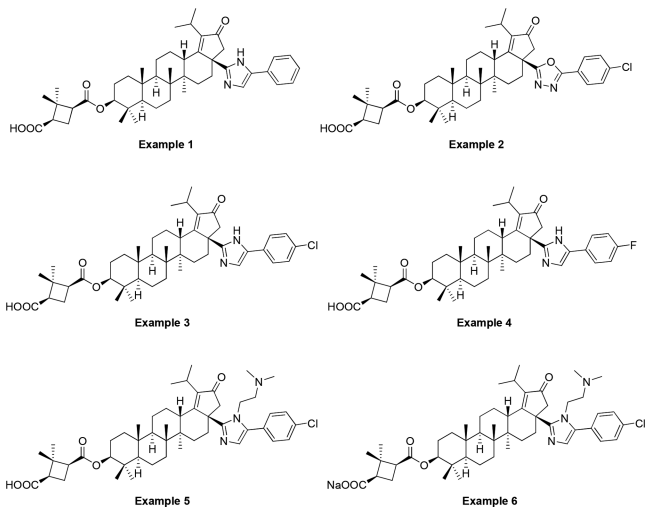
Definitions. Ring X is substituted or unsubstituted heterocycle or heteroaryl, and substituents are alkyl, aminoalkyl or aminocyclyl.

Ring Y is absent or substituted or unsubstituted heterocyclyl, heteroaryl, heteroarylalkyl, halogen, alkoxy, amino, and so forth.



W is absent, NR_2, or CR_3R_4, where R_2 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, or aminoalkyl. R3 and R4 are independently selected from hydrogen, halogen, hydroxyl, and so forth.

Key Structures.



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Biological Assay. Tests for HIV are classified into 1. detection of antibody, 2. identifying of antigen, 3. detection or monitoring viral nucleic acids, and 4. estimation of T-lymphocyte numbers (cell phenotyping). The most effectively and widely used is the antibody detection. Diagnostic test for HIV p24 antigen is based on preantibody or window period (time between exposure to HIV and appearance of detectable HIV antibodies). The detection of p24 antigen by ELISA is a simple and cost-effective technique to demonstrate viral capsid p24 protein in blood during acute infection due to the initial burst of viral replication after infection.

In this invention, membrane-type 2 (MT2) cells were infected with HIV-1 strain 92HT599. After standard protocols, the p24 quantification was carried out using Advance Biosciences kit, which was indicative of the antiviral activity of the test compounds.

Biological Data. In the Table below, for 0% and 40% serum binding assay, A refers to IC_{50} < 10 nM, B refers to IC_{50} = 10.01−50 nM, and C refers to IC_{50} > 50 nM.

Recent Review Articles.

Example no.	Activiral activity IC_{50} (nM)	
	0% serum	40% serum
1	A	B
2	A	A
3	A	B
4	A	C
5	A	C
6	B	-

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Notes

The author declares no competing financial interest.

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