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PATENT HIGHLIGHT

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HIV Integrase Inhibitors for Treatment of HIV Infections and AIDS

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Title:	Macrocyclic Compounds as HIV Integrase Inhibitors		
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Priority Application:	PCT/CN2012/078465	**Priority date:**	11 July 2012
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Disease Area:	HIV infection and AIDS	**Biological Target:**	HIV integrase inhibition

Summary:

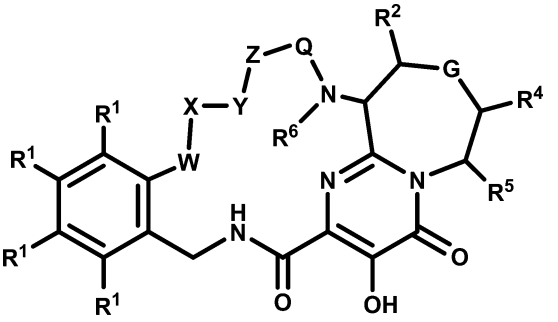
The invention in this patent application relates to macrocyclic compounds, represented generally by formula (I) that are inhibitors of HIV integrase. These compounds may potentially be useful for treatment of HIV infections and AIDS.

Acquired immune deficiency syndrome (AIDS) is a disease that causes progressive destruction of the human immune system and degeneration of the central and peripheral nervous system. The etiological agent of this disease is the retrovirus known as human immunodeficiency virus (HIV), particularly two of its stains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus.

An essential and a common step in the replication process of the HIV retrovirus is the integration of the proviral DNA into the host DNA in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by the retroviral integrase, an enzyme produced by the retrovirus that enables its genetic material to be integrated into the DNA of the infected host cell. Evidence obtained from nucleotide sequencing and amino acid sequence homology of HIV has shown that three enzymes, reverse transcriptase, integrase, and an HIV protease, are essential for the replication of HIV. Thus, inhibition of any of these three enzymes is a clinical target to treat HIV infections.

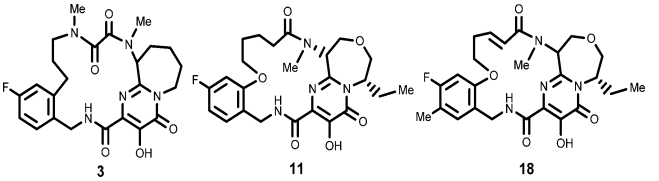
Known antiviral drugs that are inhibitors of HIV replication are also effective in the treatment of AIDS. For example, azidothymidine (AZT) and efavirenz are reverse transcriptase inhibitors, while indinavir and nelfinavir are protease inhibitors. The compounds disclosed in this patent application that show activity as inhibitors of HIV replication through inhibition of HIV integrase may also be effective in the treatment of AIDS.

Important Compound Classes:



Formula (I)

Key Structures: The inventors described the synthesis and structures of 28 examples of formula (I) including compounds **3**, **11**, and **18**.



3 **11** **18**

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Biological Assay: In vitro inhibition of HIV replication

Biological Data: IC_{95} data from the above assay were obtained in the presence of 10% NHS (normal human serum). The reported IC_{95} values ranged from 6 to 2262 nM; the data for three representative compounds (**3**, **11**, and **18**; structures above) are listed in the following table:

Compound	IC_{95} (nM)
3	2262
11	9
18	6

Claims: Claims 1−12: Composition of matter, variations of formula (I)
Claim 13: Composition of matter, 25 specific examples listed by structure
Claims 14 and 19: Pharmaceutical composition
Claims 15−16 and 20: Method for the inhibition of HIV integrase
Claims 17−18: Use of compounds in therapy

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Wainberg, M. A.; Mesplede, T.; Quashie, P. K. *Curr. Opin. Virol.* **2012**, *2* (5), 656−662.
Hazuda, D. J. *Curr. Opin. HIV AIDS* **2012**, *7* (5), 383−389.
Blanco, J.-L.; Martinez-Picado, J. *Curr. Opin. HIV AIDS* **2012**, *7* (5), 415−421.

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Notes

The authors declare no competing financial interest.