Lesson 9

Anti-HIV drugs (part 1)

Characteristics of human immunodeficiency virus

The family *Retroviridae* is a large group of viruses that can infect vertebrates. They are enveloped viruses and have a unique replicative cycle that differs radically from that of other viruses. Virions contain nucleic acid in the form of single-stranded RNA which is transformed into double-stranded DNA in the target cell via a process called reverse transcription. This DNA version of the viral genome is then integrated into the cell's DNA, allowing the virus to persist and produce offspring throughout the life of the cell.

Retroviruses are an ancient group of viruses. There is evidence to suggest that the ancestors of modern retroviruses existed 10 million years ago.

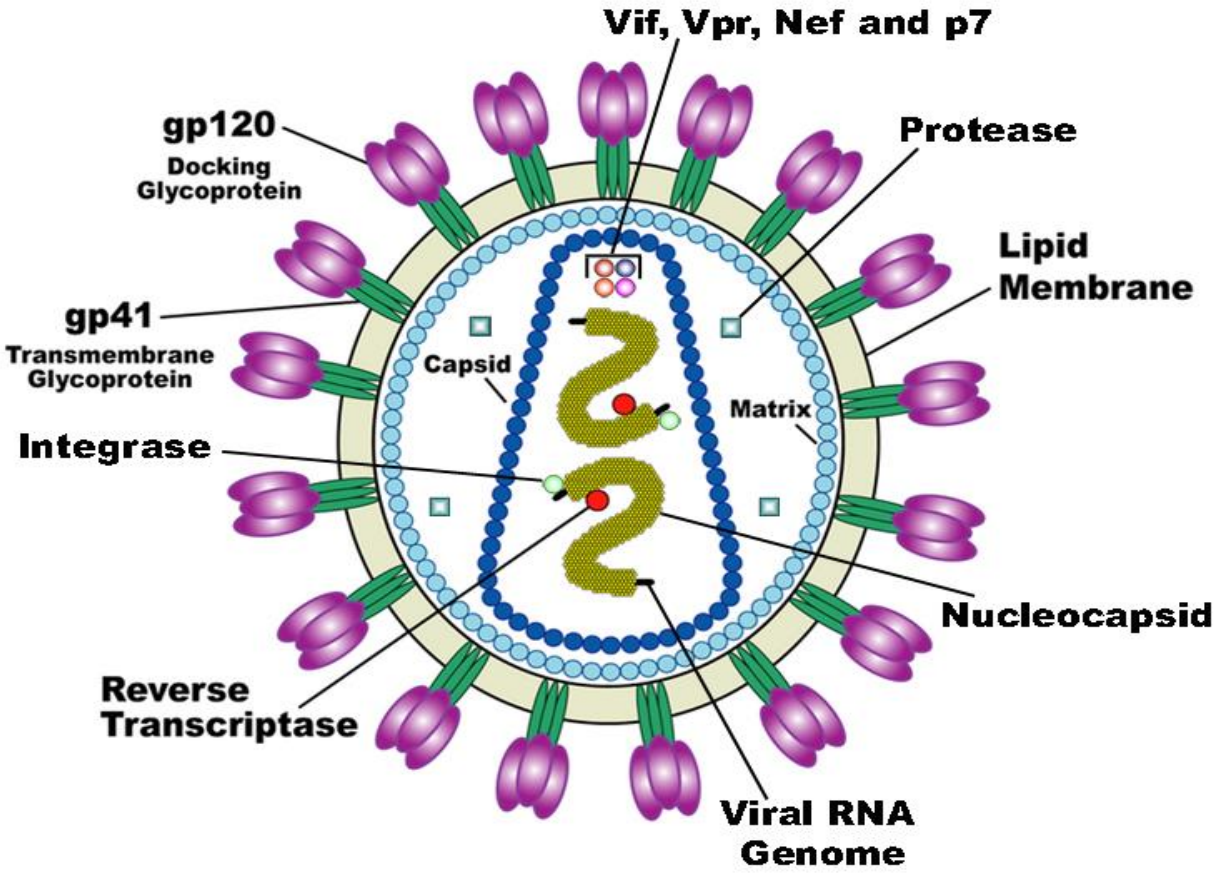
The family *Retroviridae* comprises two subfamilies: the *Orthohertrovirinae* and the *Spumaretrovirinae*. Differentiation between these subfamilies is based on morphological characteristics, differences in genome replication and variations in gene expression and viral protein function.

The subfamily Orpharetrovirinae contains six genera:

- ✓ Alpharetrovirus (birds' leukaemia and sarcoma viruses);
- ✓ Betaretrovirus (mouse tumour virus and monkey Mason-Pfizer virus);
- ✓ Gammaretrovirus (endogenous human retrovirus-W, viruses inducing leukaemia and sarcomas in rodents and monkeys and reticuloendotheliosis in birds);
- ✓ Deltaretrovirus (bovine leukaemia virus and human HTLV-I and -II);
- ✓ Epsilonretrovirus (fish retroviruses);
- ✓ Lentiretrovirus (HIV-1 and HIV-2 and horse infectious anaemia virus).

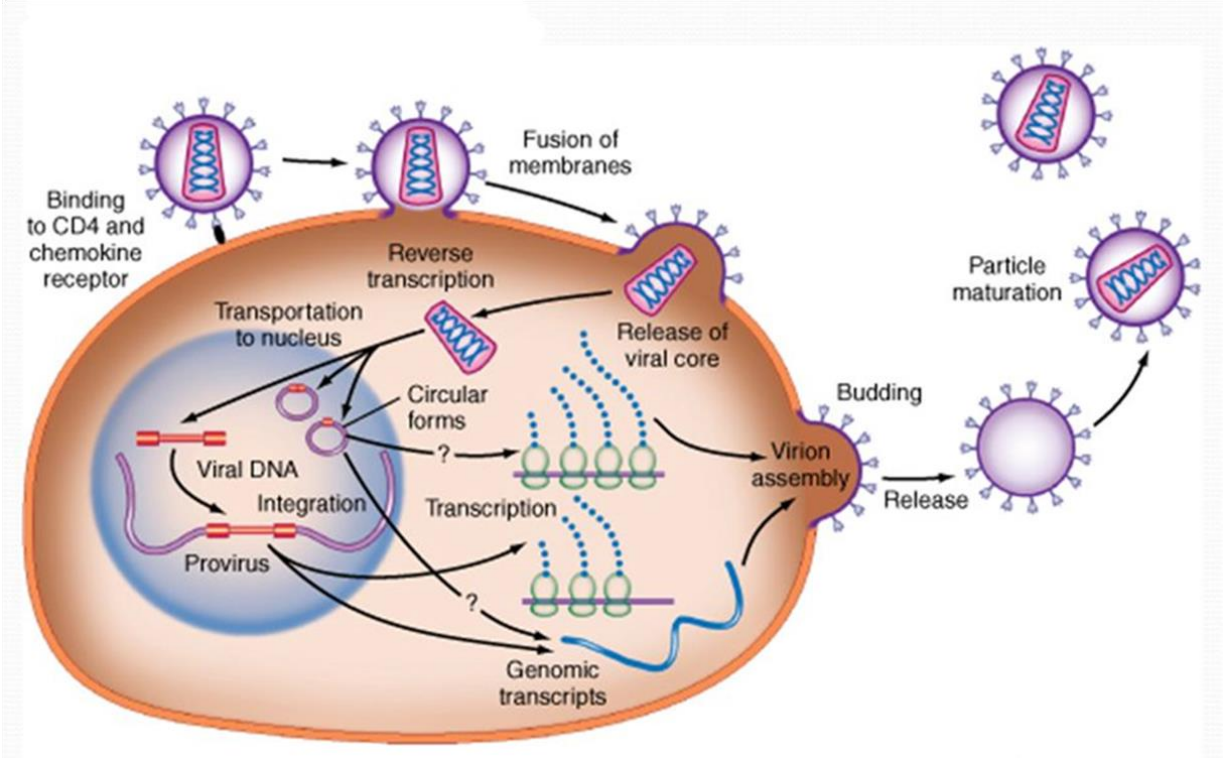
Of the human pathogens, only two belong to the retrovirus family: HIV, which is the etiological agent of AIDS, and the human T-lymphotropic virus, which induces human T-cell lymphoma (HTLV-I) and degenerative diseases of the nervous system, such as spastic parapareses (HTLV-II).

Structure of the HIV-1 virion:

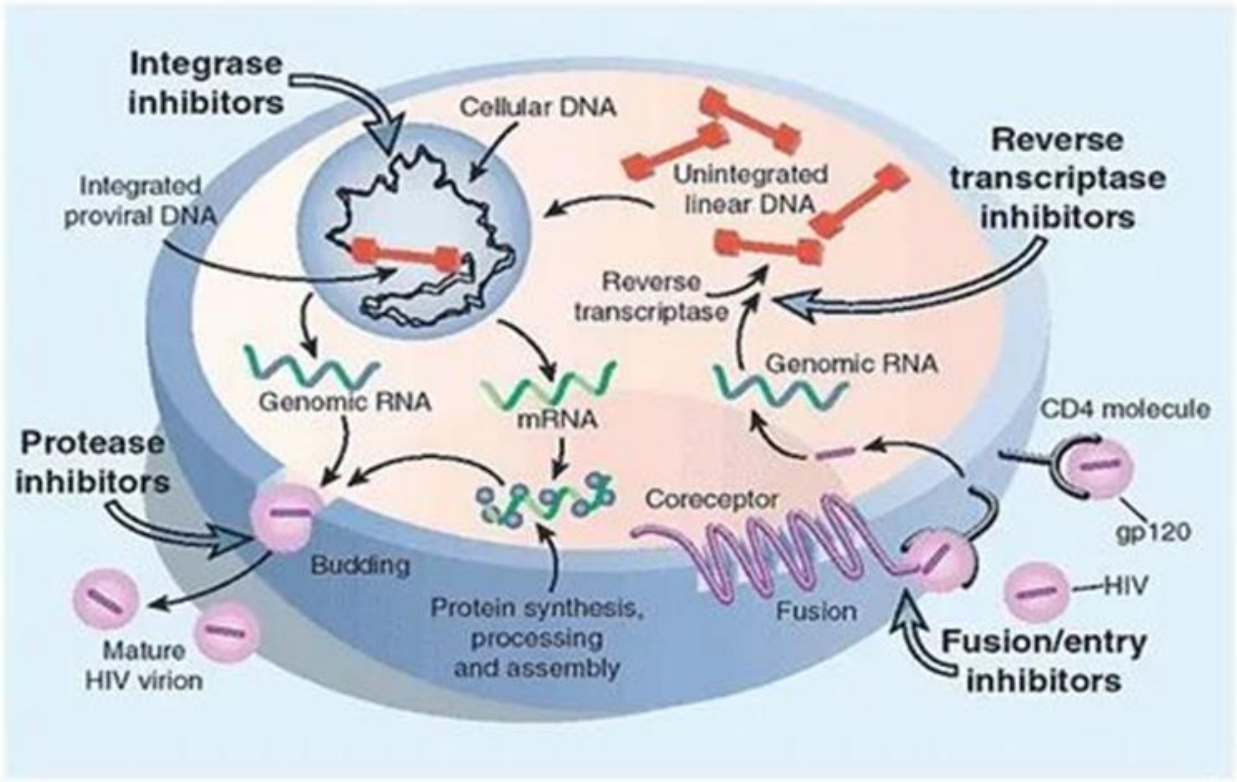


The life cycle of HIV-1 includes:

- Target cell recognition, binding, fusion;
- deprotection, release of genetic material;
- replication of viral genome (Genomic RNA reverse transcription);
- Transport of proviral DNA into the nucleus and integration with cellular DNA;
- translation and synthesis of viral polypeptides; slicing of proteins by viral protease;
- protein maturation in the endoplasmic reticulum and Golgi apparatus;
- Virion self-assembly and budding.



Each of the stages in the life cycle of HIV can be treated with chemotherapeutic drugs to suppress the development of the infection in humans. Particular importance is attached to the early stages, as it is thought that lifelong HIV infection can be prevented before proviral DNA is incorporated into cellular DNA.



Drug targets of anti-HIV therapy

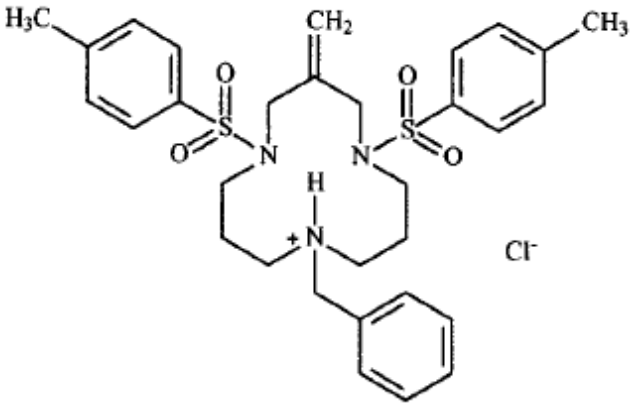
Inhibitors of HIV-1 entry into the cell

Thus, three main groups of inhibitors of HIV-1 entry into the cell can be distinguished:

- inhibitors of virus attachment and binding to the CD4 cellular antigen;
- inhibitors of virus binding to CCR5 and CXCR4 co-receptors;
- fusion inhibitors.

Inhibitors of virus attachment to the cell.

A prospective class of inhibitors that inhibit virus binding to CD4 are ***cyclotriazasulfonamides***, whose antiviral properties were discovered in 2006:



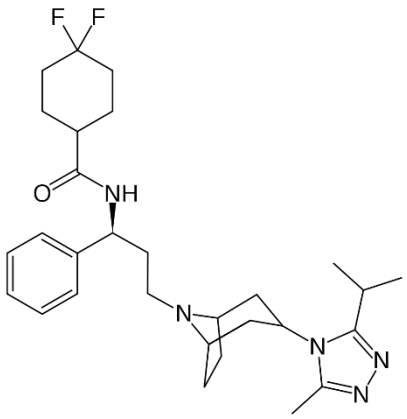
These compounds downregulate CD4 expression by an unknown mechanism. In-depth biochemical studies of this group of compounds are currently underway.

Inhibitors of virus binding to CCR5 and CXCR4 co-receptors.

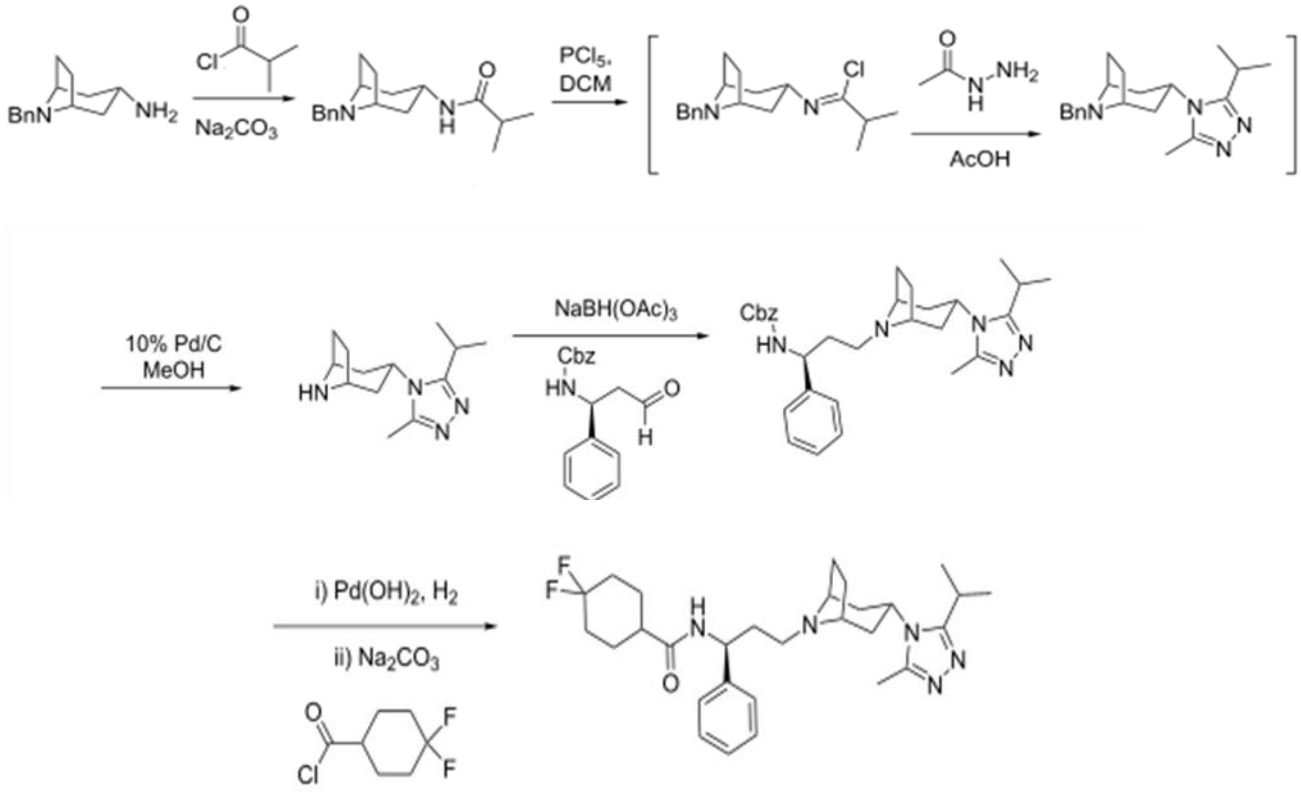
The existence in the human population of individuals resistant to HIV-1 infection was found to exist. Examination of their genome revealed the absence of the cellular receptor CCR5. Consequently, its absence does not significantly affect the growth and development of individuals. For this reason, the use of small molecules targeting the inhibition of this receptor should be safe.

Maroviroc

And thanks to screening, follow-up design, preclinical and clinical trials, in 2007 the FDA approved maroviroc for the treatment of HIV-infected patients. Maraviroc, marketed under the brand names Selzentry (USA) and Celsentri (EU).



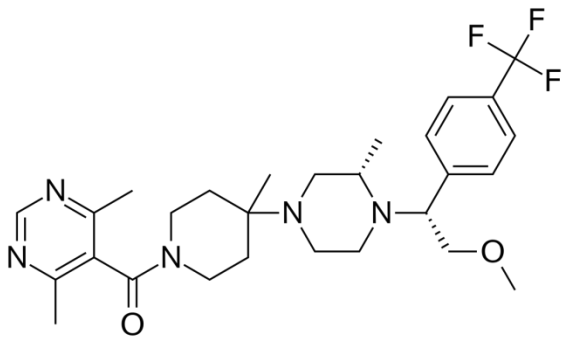
Maraviroc synthesis



Vicriviroc

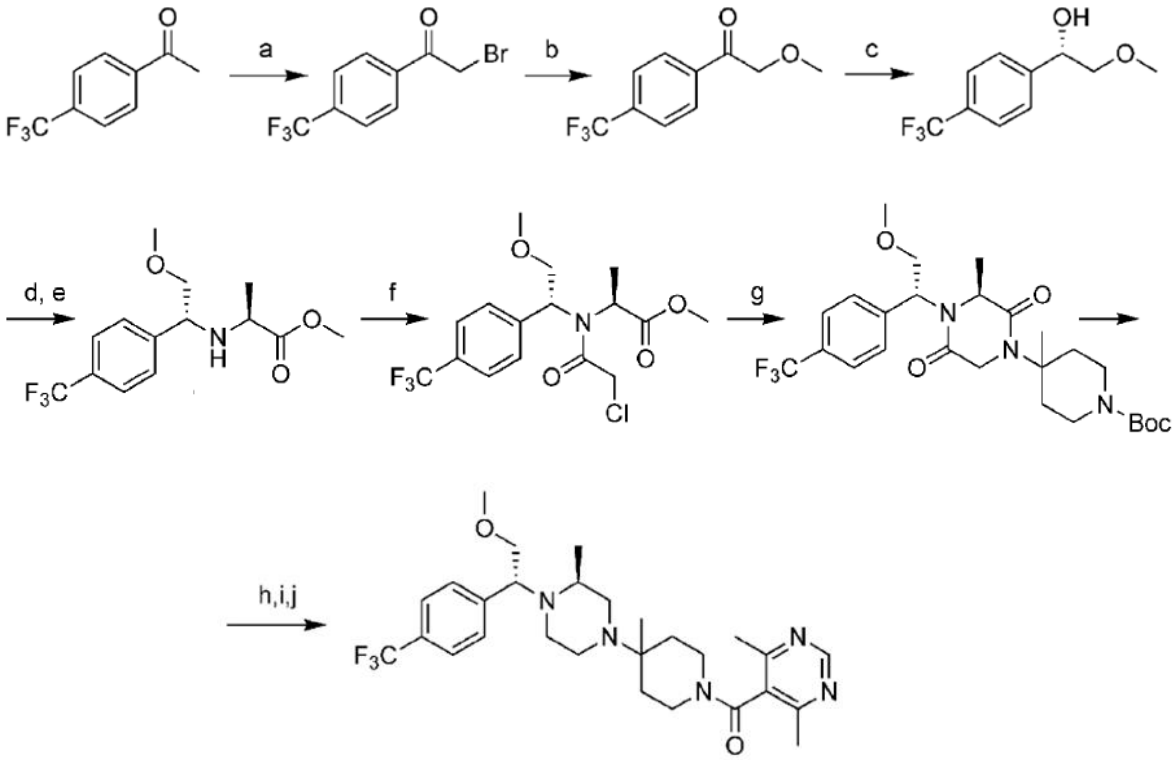
Vicriviroc is another CCR5 inhibitor, which has shown an inhibitory effect at nanomolar concentrations. This drug is currently in clinical trials.

Vicriviroc was developed by the pharmaceutical company Schering-Plough. Merck has decided not to seek regulatory approval for use in previously treated patients. Clinical trials are continuing in patients who have not previously been treated for HIV.



Vicriviroc has demonstrated a significant reduction in HIV RNA levels in subjects infected with R5. Late-stage clinical trials have not reached their primary efficacy endpoints and Merck has decided not to seek regulatory approval for the drug since January 2010.

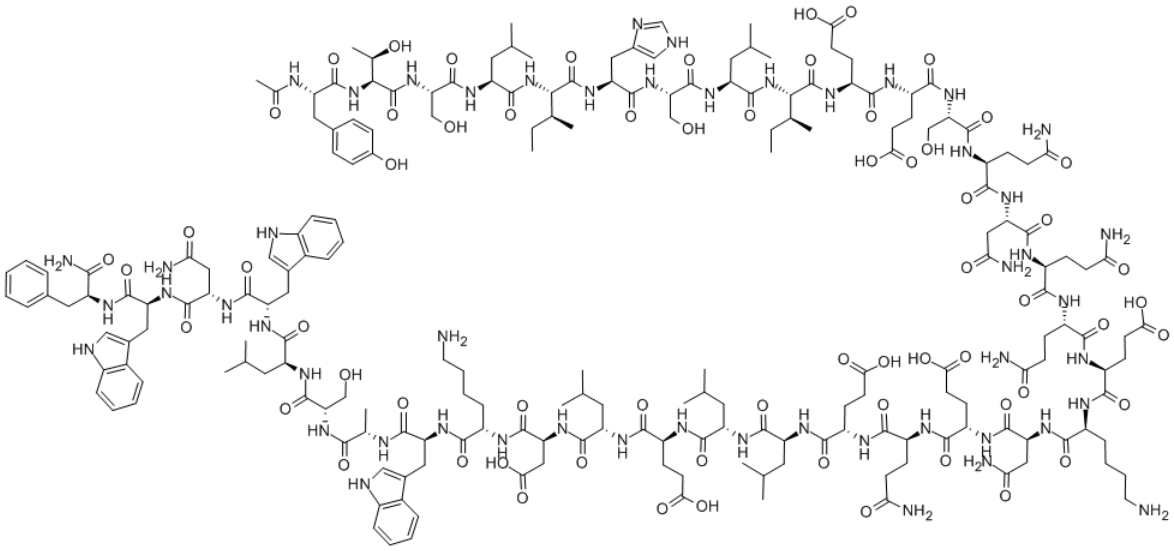
Synthesis



Fusion inhibitors.

Enfuvirtide

The first inhibitor of this stage is enfuvirtide, a peptide consisting of 36 amino acids. Although effective in vivo, the inhibitor quickly develops resistance. In addition, it cannot be used orally.



HIV-1 integrase inhibitors

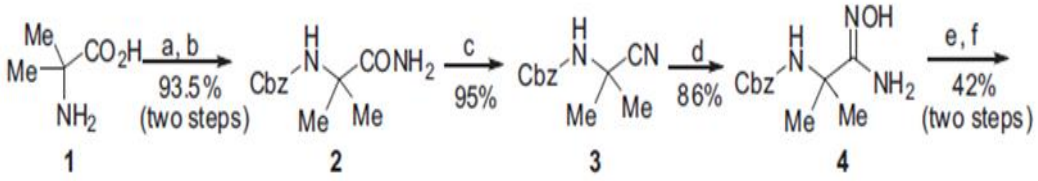
The reverse transcription of genomic RNA is carried out by a viral enzyme, reverse transcriptase, in the cytoplasm. This process results in a DNA copy of the viral RNA. This double-stranded viral DNA is transported to the nucleus. After being transported to the nucleus, the viral DNA is covalently incorporated into the genome of the infected cell through the catalytic activity of the viral enzyme, ***integrase***.

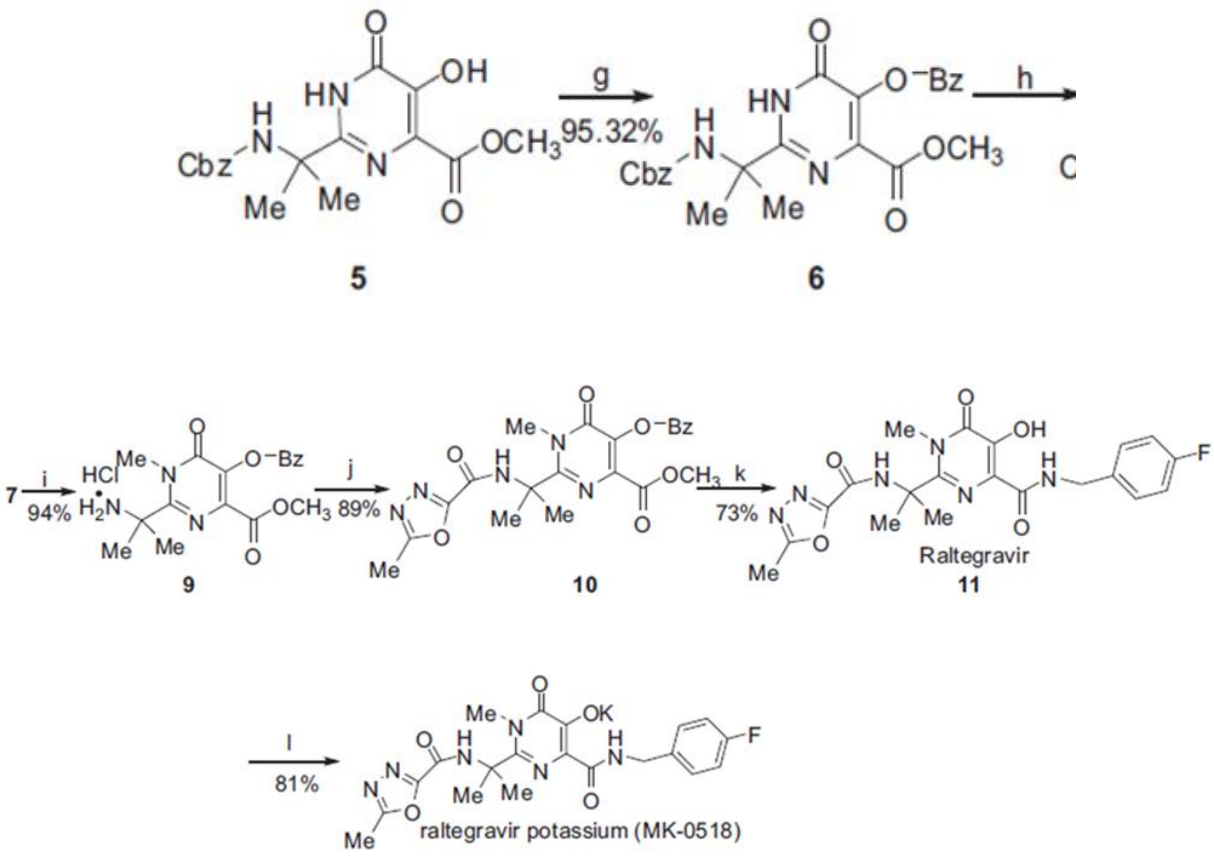
Viral integrase ("VI") has no analogues in the cell, and for this reason it is a very attractive pharmacological target in terms of selectivity and efficacy of antiviral drugs.

Reltegravir

The first integrase inhibitor was *raltegravir*. The drug was approved for the treatment of HIV infection in 2007.

Reltegravir synthesis



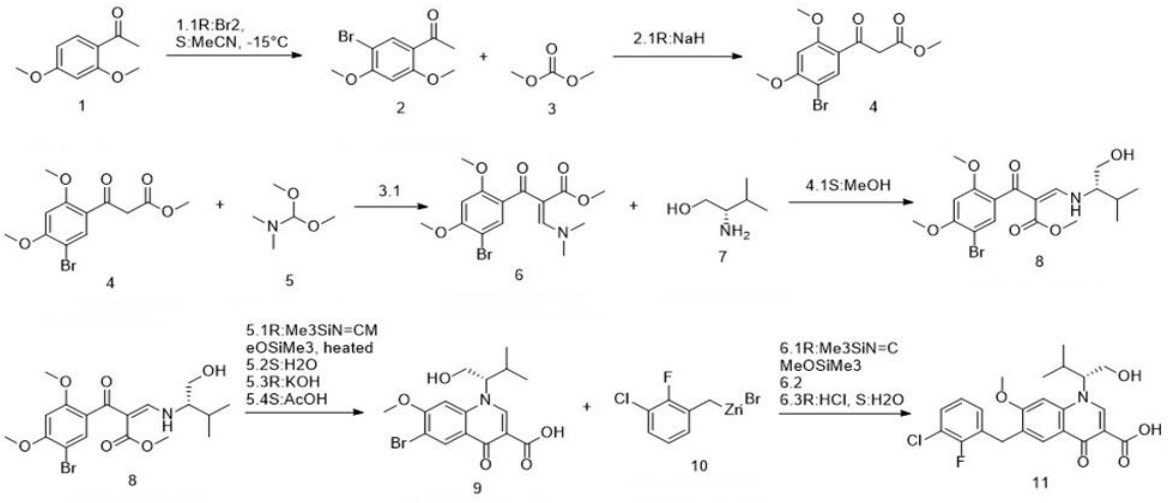


Two other drugs, *elvitegravir* and *dolutegravir*, are in clinical trials. The *compound MK-2048* has successfully completed pre-clinical studies and has entered clinical trials. All of these drugs are second-generation integrase inhibitors. In contrast to the 1st generation, they have a higher barrier to establishing resistance.

Elvitegravir

Elvitegravir was developed by the pharmaceutical company Gilead Sciences. On 27 August 2012, the drug was approved by the US Food and Drug Administration (FDA) as part of a fixed-dose combination known as Stribild. On 24 September 2014, the FDA approved elvitegravir as a single tablet under the trade name Vitekta. On 5 November 2015, the FDA approved the drug for use in patients infected with HIV-1 as part of a second fixed-dose combination tablet known as Genvoya.

Synthesis



HIV-1 protease inhibitors

The main function of HIV-1 protease is to 'cut' the precursor polyproteins (synthesised by mRNA from the viral genome) into small active proteins, from which a new virion is assembled. During the assembly of the virion, the protease carries out 12 such cutting operations in strict sequence. This produces viral enzymes (reverse transcriptase, integrase and protease), structural proteins (capsid and nucleocapsid) and other factors required for the life cycle of the virus.

The first protease inhibitor was approved in 1995. To date, 9 viral protease inhibitor drugs have been approved for the treatment of AIDS and HIV infection.

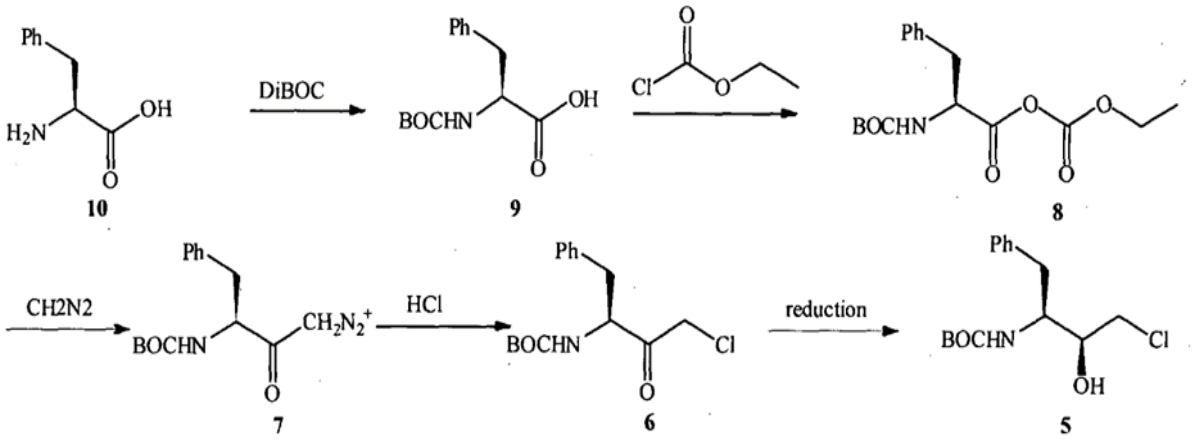
1st generation: Saquinavir (1995, Roche), Ritonavir (1996, Abbott Laboratories), Indinavir (1996, Merck), Nelfinavir (1997, Aguron) - the latter is currently not used.

2nd generation: Amprenavir (1999, Glaxo), Lopinavir (Abbott), Fosamprenavir (prodrug form of Amprenavir, 2003, Glaxo), Atazanavir (2003, Bristol Myers), Tipranavir (2005, Boehringer-Ingelheim), Darunavir (2006, Tibotec).

Darunavir

Darunavir (DRV) is available under the brand name Prezista. Darunavir was approved for medical use in the USA in 2006 and in the European Union in February 2007.

Synthesis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