Anti-HIV drugs

HIV-1 reverse transcriptase inhibitors

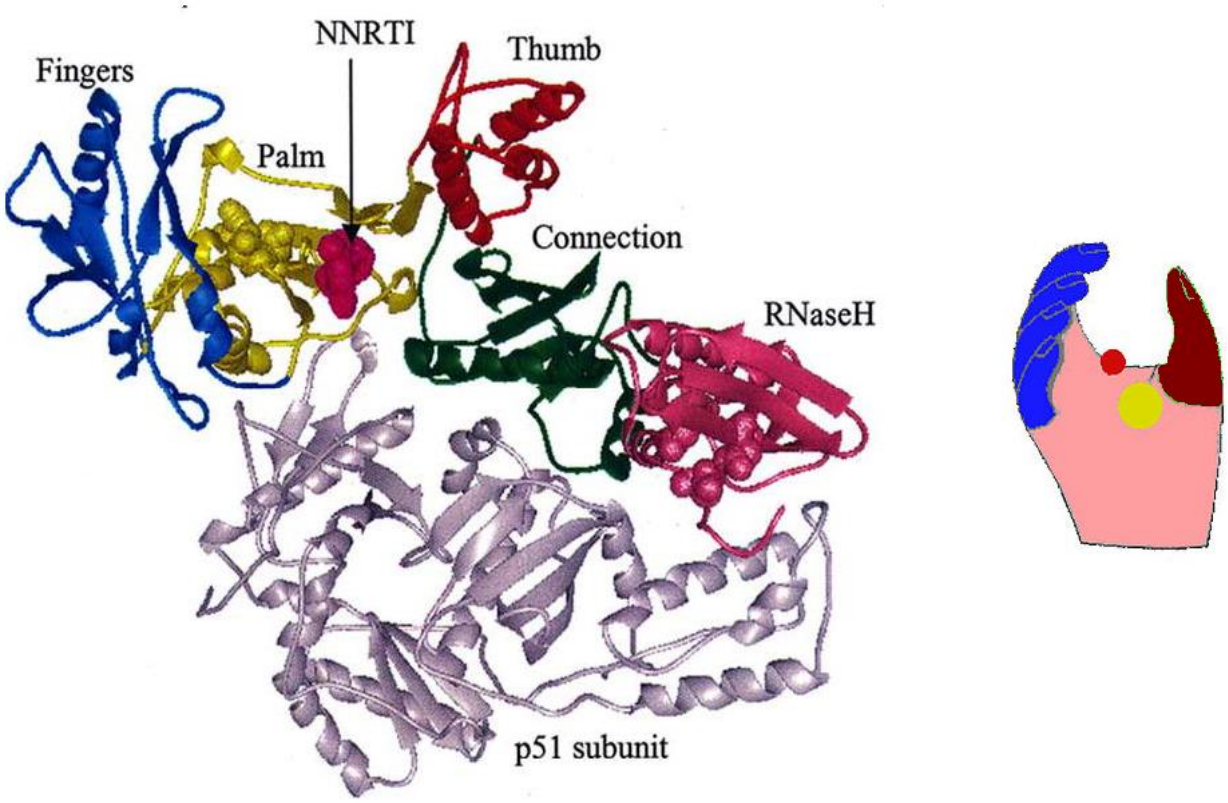
HIV-1 reverse transcriptase is an excellent target for chemotherapeutic action on the virus.

HIV is a retrovirus and its genome in the virion is represented as single-stranded RNA. The viral RNA is transformed into double-stranded proviral DNA in the infected cell by reverse transcription. Reverse transcription is carried out by a viral enzyme, reverse transcriptase.

Functions of reverse transcriptase:

- ✓ RNA-dependent DNA polymerisation leading to the formation of an RNA:DNA hybrid;
- ✓ RNA chain degradation in RNA:DNA-hybrid;
- ✓ DNA-dependent DNA polymerization leading to the formation of proviral DNA.

HIV-1 reverse transcriptase is a heterodimer consisting of two subunits, p66 and p51. The crystal structure of the HIV-1 reverse transcriptase showed that the p66 subunit has a resemblance to the right hand and consists of the following regions: 'fingers', 'palm' and 'thumb'. The p51 subunit is not directly involved in catalytic processes, but it provides a structural aid that allows the p66 subunit to carry out its functions.



Four classes of HIV-1 reverse transcriptase inhibitors are currently known:

- nucleoside reverse transcriptase inhibitors (NRTIs) - bind to the active centre of reverse transcriptase;

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) - bind to the allosteric centre of the enzyme;

- Non-nucleoside inhibitors, but bind to the active site of reverse transcriptase;

- RNAase inhibitors - bind to the joint domain and inhibit dissociation of the RNA-DNA complex.

However, only the first two classes of reverse transcriptase inhibitors, NRTIs and NNRTIs, are of therapeutic value.

Nucleoside reverse transcriptase inhibitors (NRTIs) of HIV-1.

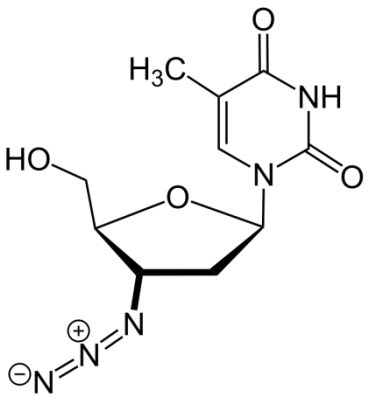
All nucleoside reverse transcriptase inhibitors can be classified into derivatives of their corresponding nucleotide bases:

- ✓ Thymidine analogues - zidovudine, phosphazid, stavudine, telbivudine, clevudine

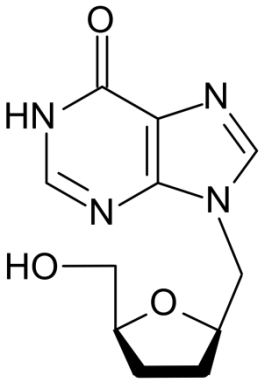
- ✓ Adenine analogues - didanosine, adefovir
- ✓ Cytidine analogues - zalcitabine, lamivudine, emtricitabine
- ✓ Guanine analogues - abacavir
- ✓ Adenosine analogues - tenofovir
- ✓ Guanosine analogues - entecavir

NRTIs were the first drugs approved by the FDA for the treatment of HIV infection and AIDS. Their structure is similar to that of naturally occurring nucleosides. After incorporation of NRTI into the growing DNA strand, further elongation is blocked, resulting in an end to DNA synthesis and therefore stopping the reproduction of the virus.

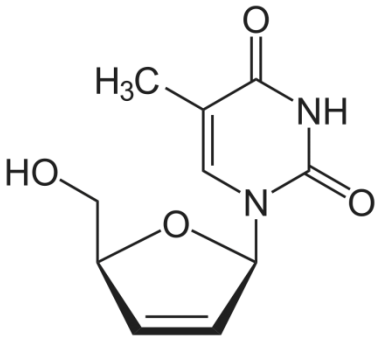
Examples



Azidothymidine
(Zidovudine, AZT)



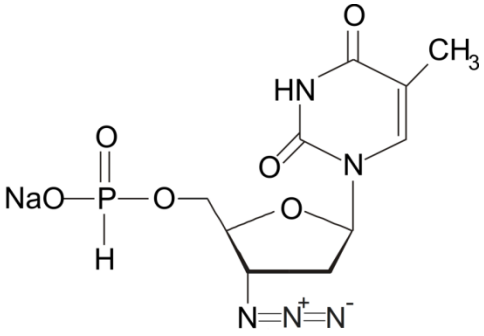
Didanosine



Stavudine

Nicavir

Nicavir (sodium salt of 5'-H-phosphonate AZT, phosphazide) is the first success in the creation of depot-formulations of AZT. Nicavir was licensed in the Russian Federation in 1999 as a drug for the treatment and prevention of HIV infection.

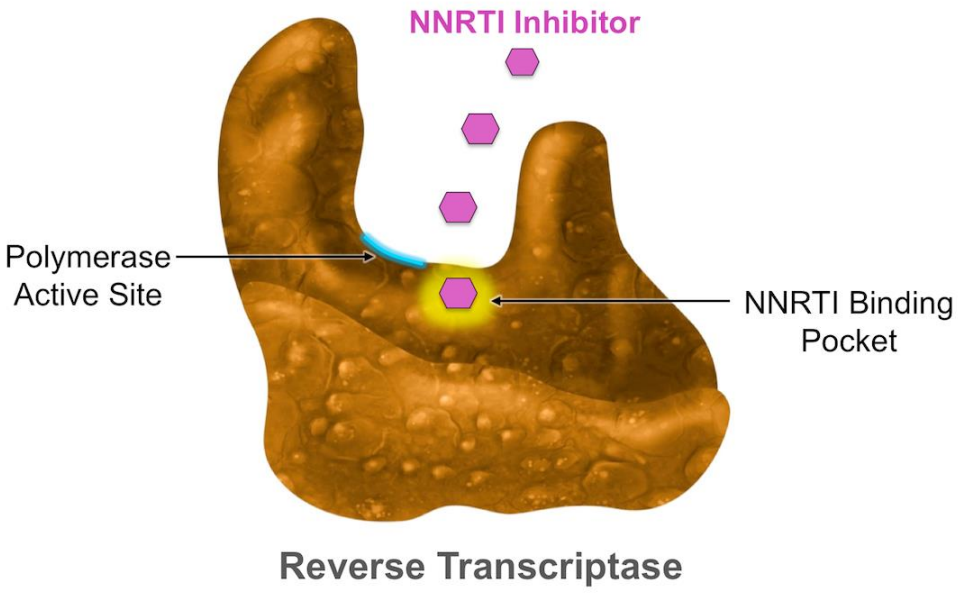


Nicavir is well tolerated in adults and children. During treatment with nicavir, no side effects commonly observed for AZT, such as vomiting, nausea, headache, diarrhoea, myalgia, anaemia, thrombocytopenia and neutrocytopenia were observed.

Non-nucleoside reverse transcriptase inhibitors (NNOTIs) of HIV-1.

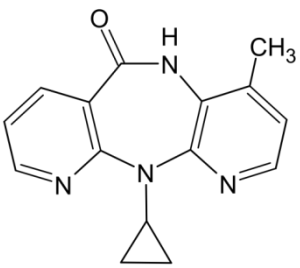
Unlike NRTIs, they do not participate in metabolic processes, have much lower toxicity and their use is accompanied by minimal side effects. HIV-1 NNRTIs are highly specific for viral RT enzyme. They bind to the hydrophobic "pocket" of the RT of HIV-1, located 10 Å from the active centre of the enzyme and block its activity.

The hydrophobic pocket is located in the "palm" region of the p66 subunit. Once in the hydrophobic pocket, NNRTIs block the polymerisation process or reverse transcriptase conformational changes required for the catalytic process.

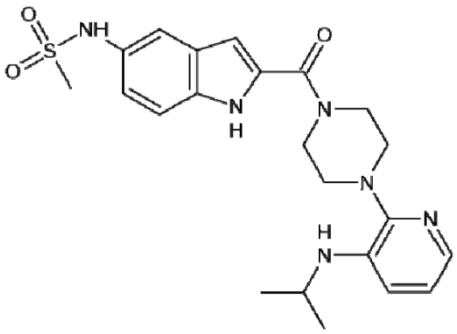


Five drugs belonging to the class of NNRTIs are currently approved for clinical use.

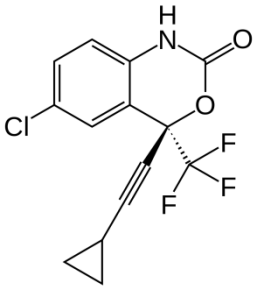
First-generation NNRTIs: *nevirapine, delavirdine* and *efavirenz* are sensitive to the development of drug resistance, even with a single amino acid mutation in the hydrophobic reverse transcriptase pocket.



Nevirapine

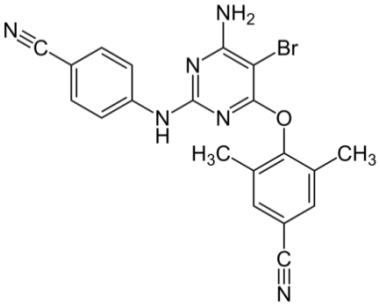


delavirdine

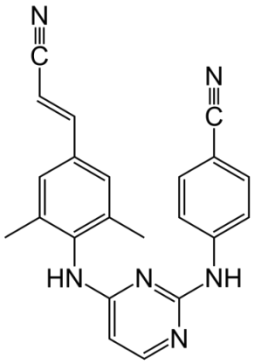


efavirenz

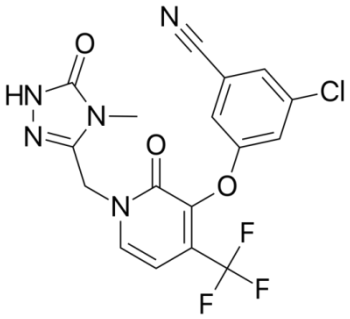
Second-generation NNRTIs: *etravirine*, *rilpivirine* and *doravirine* retain antiviral activity against most clinically important HIV mutants.



Etravirine



rilpivirine

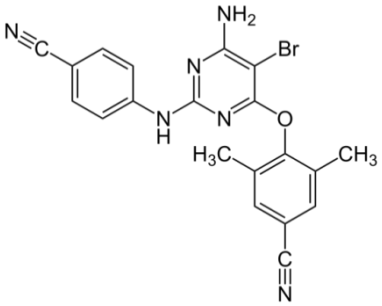


doravirine

The main disadvantage of NNRTIs is the rapid emergence of HIV resistance to them.

Etravirine

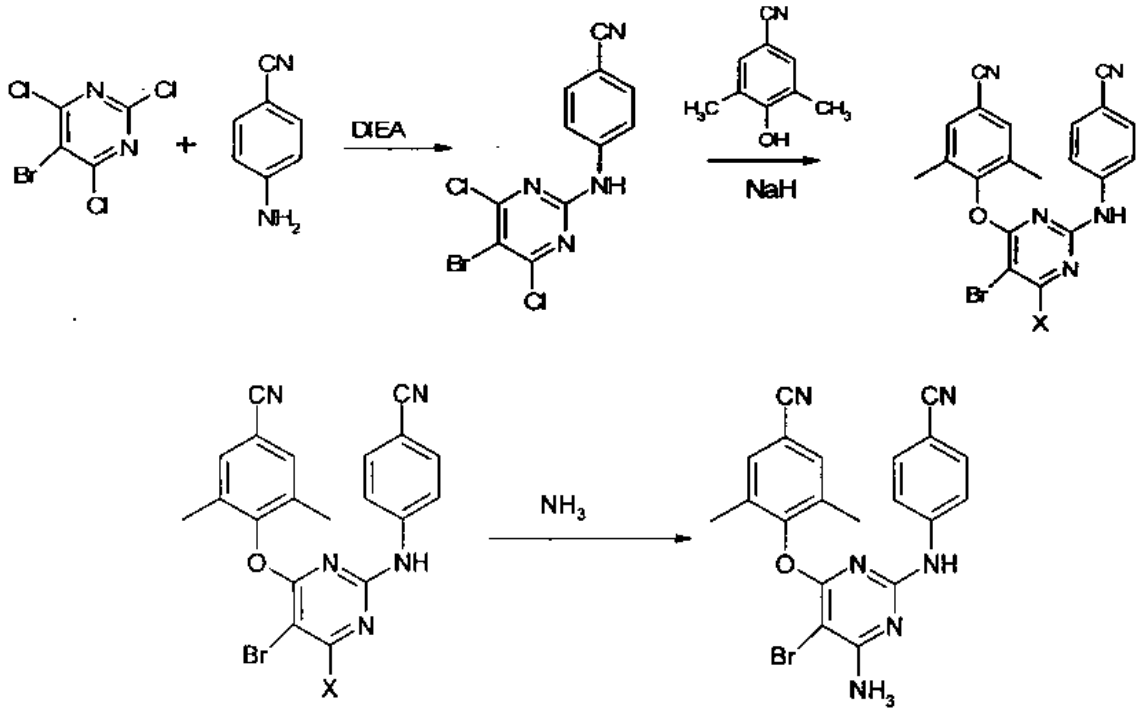
Etravirine (brand name Intelence, formerly known as TMC125) is a medicine used to treat HIV. Unlike currently available drugs in this class, resistance to other NNRTIs does not appear to lead to resistance to etravirine.



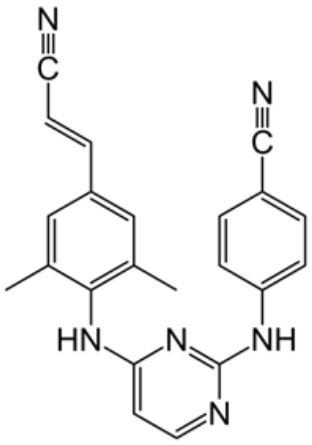
Etravirine is marketed by Janssen, a subsidiary of Johnson & Johnson. In January 2008, the Food and Drug Administration approved its use in patients with

established resistance to other drugs, making it the 30th HIV drug approved in the USA and the first to be approved in 2008. It was also approved for use in Canada on 1 April 2008. Etravirine is licensed in the USA, Canada, Israel, Russia, Australia and the European Union.

Synthesis of etravirine

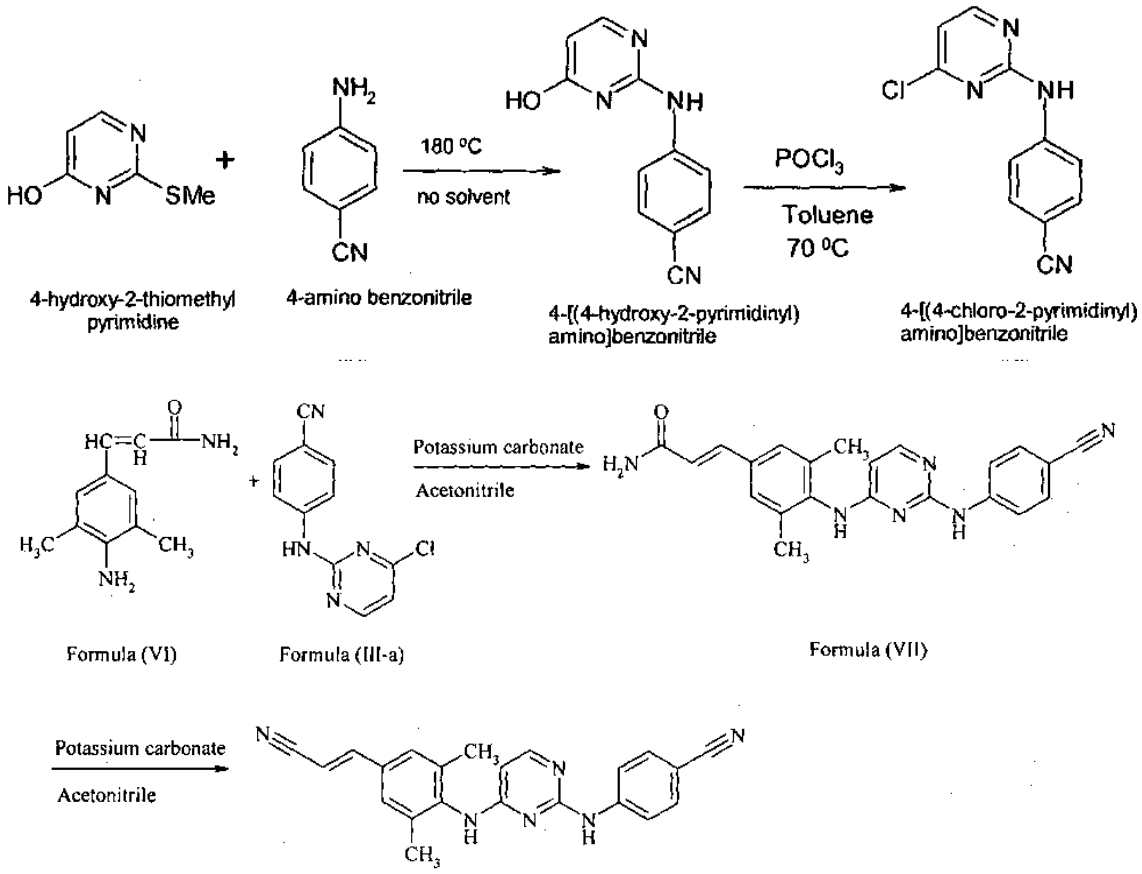


Rilpivirine



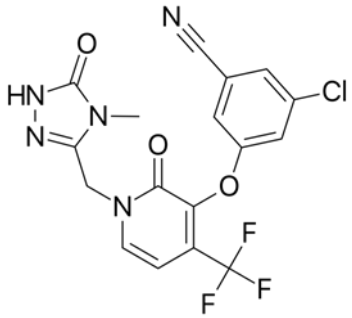
Rilpivirine, marketed under the brand names Edurant and Rekambys, is a medicine developed by Tibotec and used to treat HIV/AIDS. It is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with higher efficacy, a longer half-life and a lower side-effect profile than older NNRTIs such as efavirenz.

Rilpivirine synthesis



Doravirin

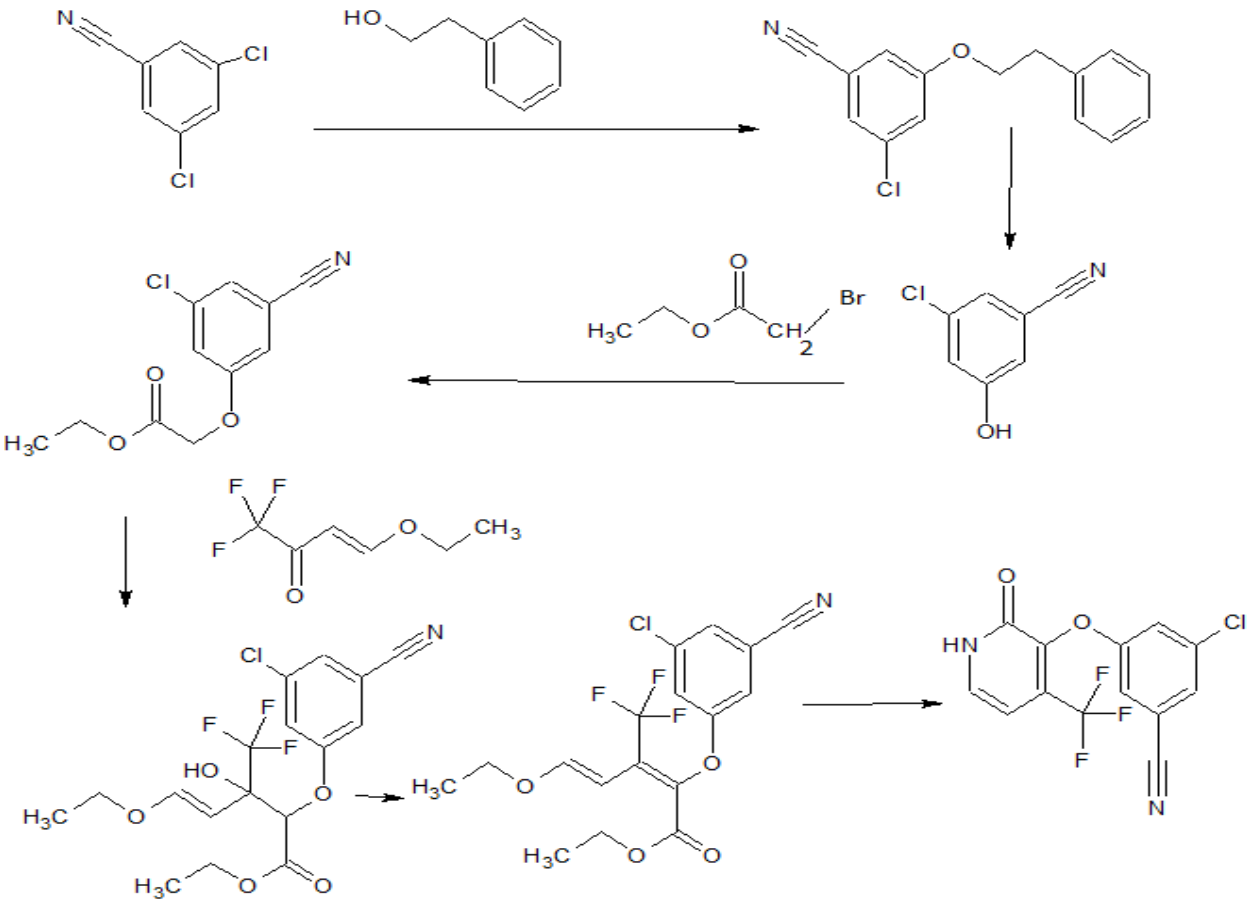
Doravirin, marketed under the brand name Pifeltro, is a non-nucleoside reverse transcriptase inhibitor developed by Merck & Co. for the treatment of HIV/AIDS. Doravirin was approved for medical use in the US in August 2018.



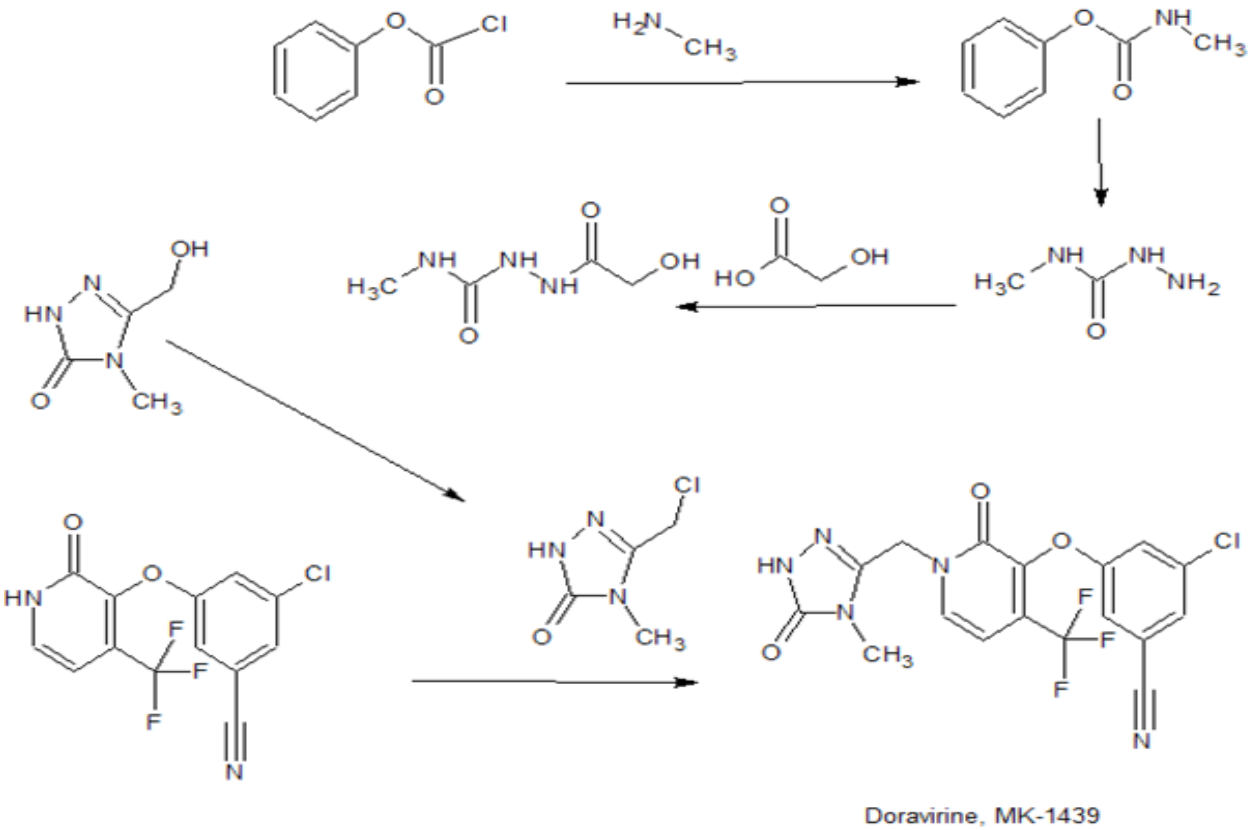
Doravirin is a new antiretroviral drug with once-daily dosing. Doravirin shows improved activity against both wild-type and key resistant strains of HIV.

Synthesis of doravirin:

1.Obtaining phenoxypyridone:



2. Obtaining doravirine



Doravirine, MK-1439

HAART

The availability of a large number of anti-HIV-1 drugs with different mechanisms of action in the clinic has allowed a new principle for the treatment of HIV infection and AIDS, called Highly Active Antiretroviral Therapy (HAART), to be developed as early as the mid-1990s. This method consists of taking three or four drugs, with different mechanisms of action, at the same time.

Disadvantages.

- HAART does not remove the virus from the body, it only prolongs the patient's life.
- The body eventually develops multidrug-resistant strains of HIV-1.
- Has side effects.
- High cost of treatment.

However, the use of HAART delays the onset of AIDS by an average of 15-20 years.