Pharmaceutical Chemistry

Mohammad Jafarzadeh

Faculty of Chemistry, Razi University

Synthesis of Essential Drugs

By *R.S. Vardanyan* and *V.J. Hruby*, Elsevier, 2006

36. Antiviral Drugs

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics, specific antivirals are used for specific viruses.

Viruses cause more diseases than any other group of parasites. They can cause blindness, deafness, paralysis, mental retardation, various birth defects, and in at least a few plants and animals, cancer.

Viruses causes of well-known viral diseases: mumps, smallpox, chicken pox, influenza, poliomyelitis, and yellow fever.

There is suspicion that viruses are the cause of multiple sclerosis, Hodgkin's disease, Down's syndrome, and possibly even schizophrenia.

Along with the significant progress made in the area of treating bacterial infections, the development of chemotherapy of viral diseases has been relatively modest.

There is only a small selection of attainable drugs for treating a very limited number of viral infections.

Viruses are one of the great mysteries of biology. It is very hard to differentiate it as a living or nonliving entity. Viruses occupy a place somewhere in between a molecule and a live organism.

At the same time, they also can be considered the most minute organism and the largest molecule. No signs of life are observed in viruses for a long time, and they can remain in this state for years. However, at any moment they can be “resurrected”—the only thing they need is a receptive cell.

Each virus is only able to attack a limited assortment of cells. This allows them to be divided into three main groups: viruses that attack plants, viruses that attack animals (including humans), and viruses that attack single-cell organisms (microbes and bacteria).

Viruses are much simpler organisms than bacteria, and they are made from protein substances and nucleic acid. A single nucleoprotein molecule formed from molecules of nucleic acid that are chemically bound to a bulky protein molecule can be considered a simple viral particle.

The protein molecule plays the role of a protective membrane. Thus the virus can be schematically described as a nucleic acid insert that is protected by a protein covering.

A virus can contain either ribonucleic acid or deoxyribonucleic acid, but it never contains both of them together. The type of nucleic acid is the basis of one of the classifications of viruses.

Viruses are obligatory intracellular parasites, which, upon entering a cell (i.e. after being infected) use many biochemical systems of the host cell.

Entering a live cell with relative ease and being involved in its complex mechanisms as if it were a part of its chromosomal apparatus creates a huge problem for finding selective toxicity of drugs against viruses. It makes the virus a powerful instrument for research.

In the viral process of multiplying, it generally uses the host cells' apparatus of biosynthesis by modifying it in some way. Therefore, it is very hard to select compounds for clinical use that have beneficial antiviral activity that do not damage the normal cell metabolism of uninfected host cells (not having a toxic effect on them).

There are certain antiviral drugs that have a certain selective action against cells infected by viruses, and which suppress the replicating cycle of the virus.

Despite the fact that the exact **mechanism of infection** is extremely specific to each type of virus, the general scheme of infection can be represented in the following manner.

A virus is absorbed at the surface of a host cell, most likely by an electrostatic or hydrophilic interaction. It is possible that many viruses bind to certain virus-specific receptors. Then the virus permeates through the membrane of the host cell, where it releases nucleic acid from its protein protection, thus losing its individuality as a virus.

Then the viral nucleic acid begins to act as if it was a functional part of the “host” cell. It begins to replicate, and transcription of the viral genome takes place either in the cytoplasm, or in the nucleus of the host cell.

As a result of these events, a large amount of viral nucleic acid and protein are made to make new generations of virions. During this process, the replication mechanism of the host cell is turned off, and thus the described cycle is repeated over and over again.

Chemotherapy of viral infections is achieved by three different approaches:

1. preventative immunization; use of endogenic antiviral substances, for example an interferon that is believed to bind with specific receptors on the surface of the cellular membrane

2. activate RNA and protein synthesis inside the cell, which exhibits an antiviral effect;

3. use of antiviral drugs.

One approach for creation of antiviral drugs is to interfere with the ability of a virus to get into a target cell. A number of “entry-inhibiting” or “entry-blocking” drugs are being developed.

Two entry-blockers, amantadine and rimantidine, have been introduced into medicinal practice.

A second approach is to target the processes that synthesize virus components after a virus invades a cell. Develop “nucleotide or nucleoside analogs” that look like the building blocks of RNA or DNA, but jam the enzymes that synthesize the RNA or DNA once the analog is incorporated.

The first successful antiviral, acyclovir, is a nucleoside analog, and is effective against herpesvirus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analog.

The first drugs on pharmaceutical market proposed as antiviral agents were idoxuridine and citarabine, and a while later, vidarabine, which is a first-generation antiviral drug. They have **limited clinical use** because of their **narrow therapeutic index** (ratio of effective and lethal doses). These drugs have a direct effect on viral replication; however, they also inhibit certain host cell functions.

Later, amantadine, acyclovir, ribavirin, and zidovudine were suggested. Currently, a number of new drugs have been suggested for treating acquired immunodeficiency syndrome (AIDS)—ribavirin, ampligen, dideoxycytidine, and foscarnet.

Research in the area of antiviral drug synthesis has only recently allowed a significant step to be made in the area of treating diseases caused by herpes simplex virus, and just recently for treating AIDS. These drugs act by inhibiting the process of virus cell multiplication.

Currently, amantadine, vidarabine, trifluridine, idoxuridine, sciclovir, ribavirin, and zidovudine are used as antiviral drugs.

An analysis of the **mechanisms of action** of existing and used viral drugs permits the conclusion to be made that they can **increase resistance of the cell** to a virus (interferons), **suppress adsorption of the virus** in the cell or its **diffusion into** the cell, and the process of its "**deproteinization**" in the cell (amantadine); as well as **antimetabolites** that inhibit the synthesis of nucleic acids.

The clinical "usefulness" of these pyrimidine and purine drugs depends directly on their ability to selectively block synthesis of viral nucleic acids while not stopping the synthesis of "host" cell nucleic acid.

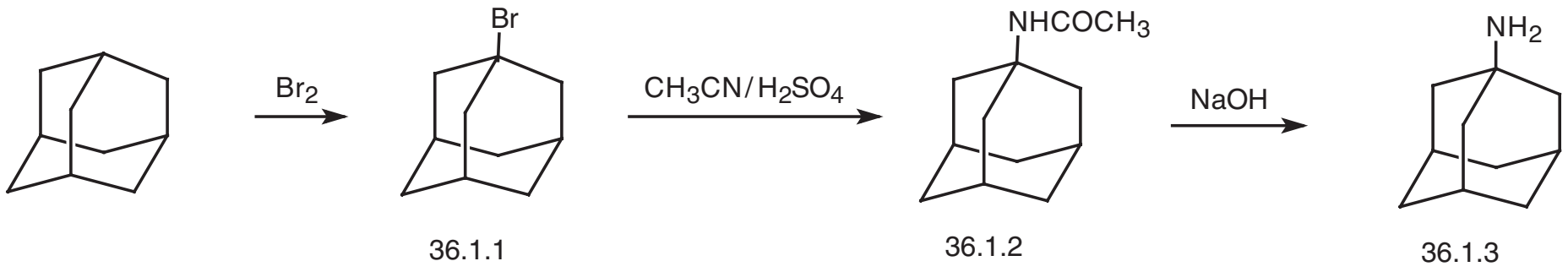
Amantadine

It is a primary amine derivative of adamantane. It has an effect on mycoviruses, which are RNA-containing viruses. It has a **very narrow spectrum of action** and is used only for treating and preventing influenza A. It is also used for treating Parkinsonism.

The mechanism is believed that it is an ion channel blocker. It has also been suggested that amantadine inhibits absorption of viral particles into the host cell, which is expressed in the breakdown of diffusion of the virus into the cell, or inhibition of the “stripping process” of the virus.

The main use is for the prevention of type A2 influenza.

Synonym: simmetrel, viregit, and mantadan



Acyclovir

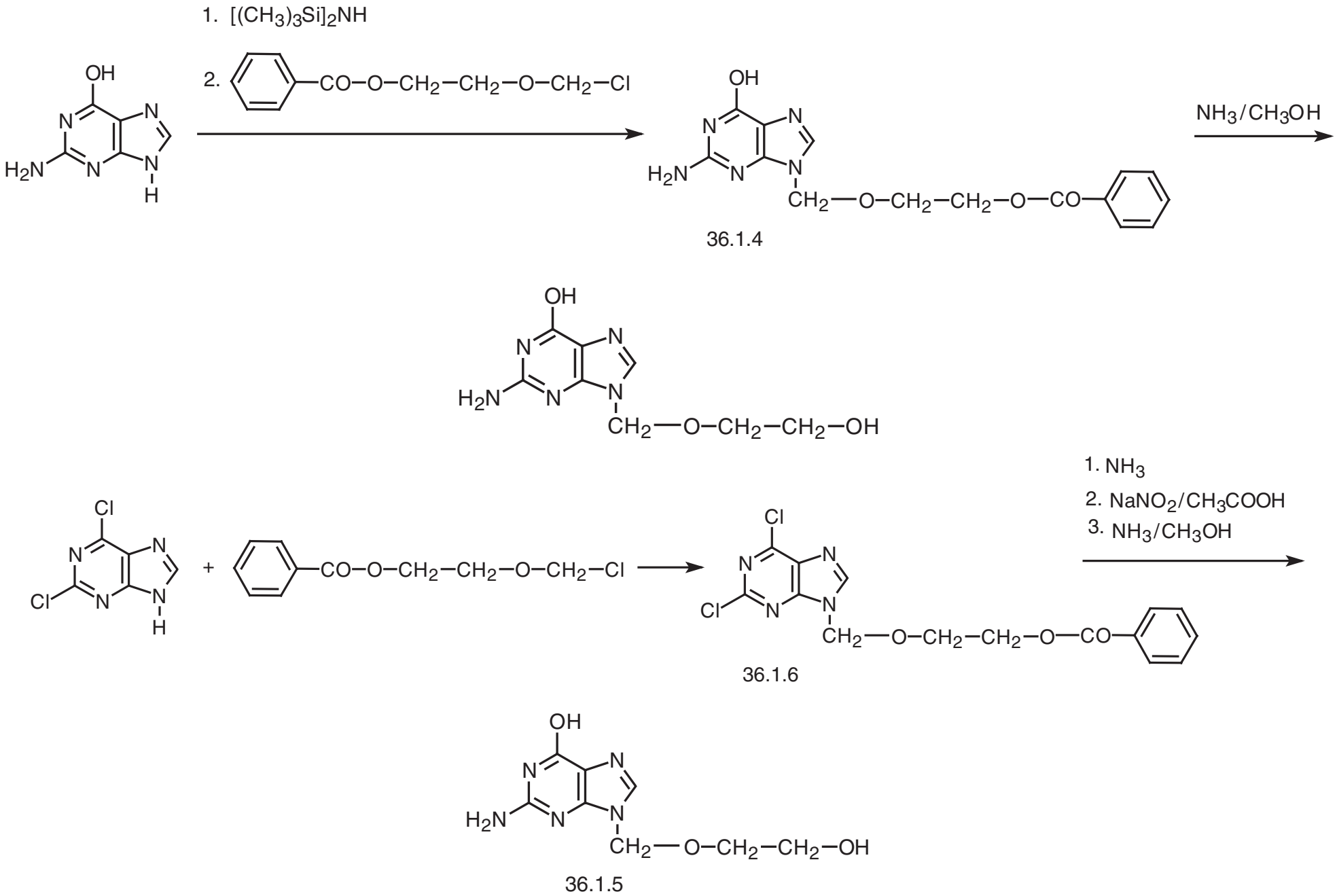
The chemical structure of acyclovir looks like a nucleoside analog of guanosine in side chain of which, instead of the traditional cyclic sugar residue a 2-hydroxyethoxymethyl acyclic side chain is present.

Acyclovir possesses antiviral activity with respect to types 1 and 2 of herpes simplex (attacked the eyes and genetilia), chicken pox, shingles virus, Epstein–Barr virus, and cytomegalovirus.

Mechanism of activity: its transformation to triphosphate and subsequent inhibition of viral DNA synthesis. Its action is highly selective. Acyclovir diffuses into the infected cell and phosphorylates thymidine kinase of herpes simplex to a monophosphate. Uninfected cells do not use acyclovir as a substrate.

The monophosphate is subsequently transformed to a diphosphate, and then a triphosphate, which inhibits viral DNA polymerase, as well as viral DNA, where it acts in the process of breaking the chain, thus preventing further elongation of the DNA chains and correspondingly, replication of the DNA virus.

Synonym: aovirax, cycloviran, and sifiviral


1. [(CH3)3Si]2NH
2. CO–O–CH2–CH2–O–CH2–Cl
NH3/CH3OH
36.1.4
1. NH3
2. NaNO2/CH3COOH
3. NH3/CH3OH
36.1.6
36.1.5

Vidarabine

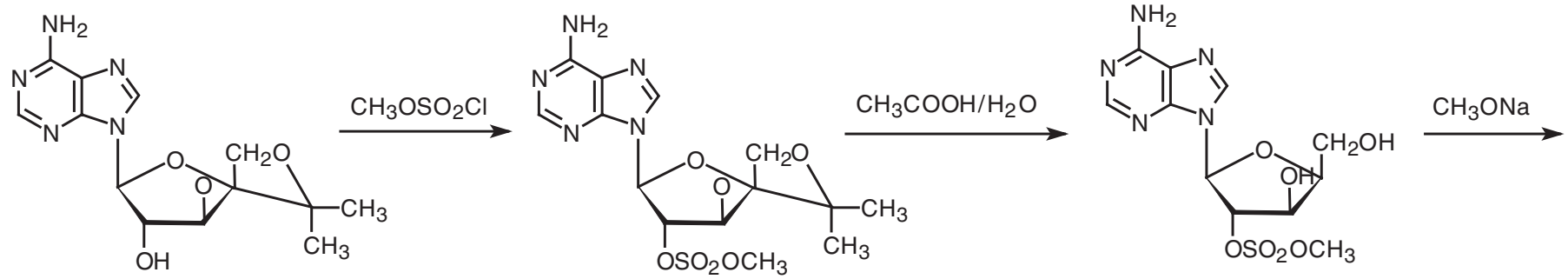
Vidarabine (adenine arabinoside) is the stereoisomer of adenosine. This analog of a purine nucleoside exhibits selective activity against the herpes virus. The ribose residue is replaced with an arabinose residue.

Like acyclovir, it turns into mono-, di-, and triphosphate in cells infected by a virus, thus inhibiting DNA polymerase, and correspondingly preventing DNA synthesis of the virus approximately 20–40 times more than in “host” cells.

It is easily metabolized to a less active, yet nonetheless antiviral compound—arabinosylhypoxanthine. It has been successfully used for herpetic encephalitis, and for complicated shingles.

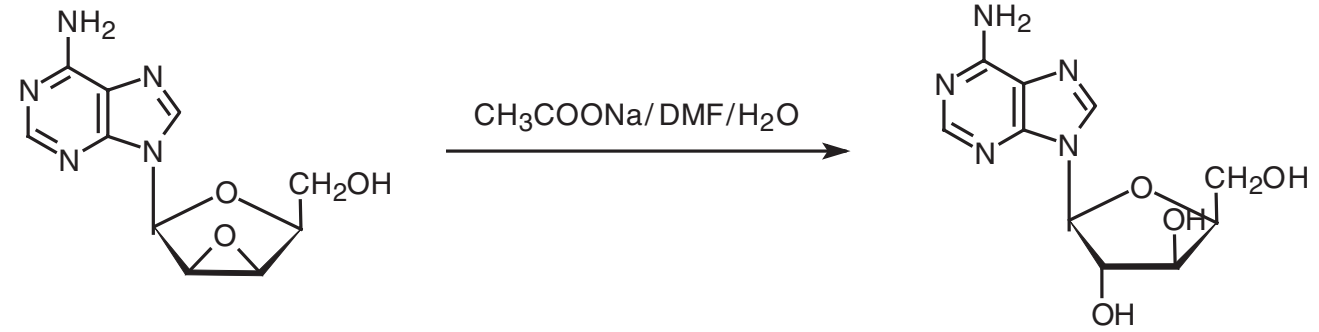
It is used in the form of eye drops for herpetic keratoconjuctivitis.

Synonym: Vira-A



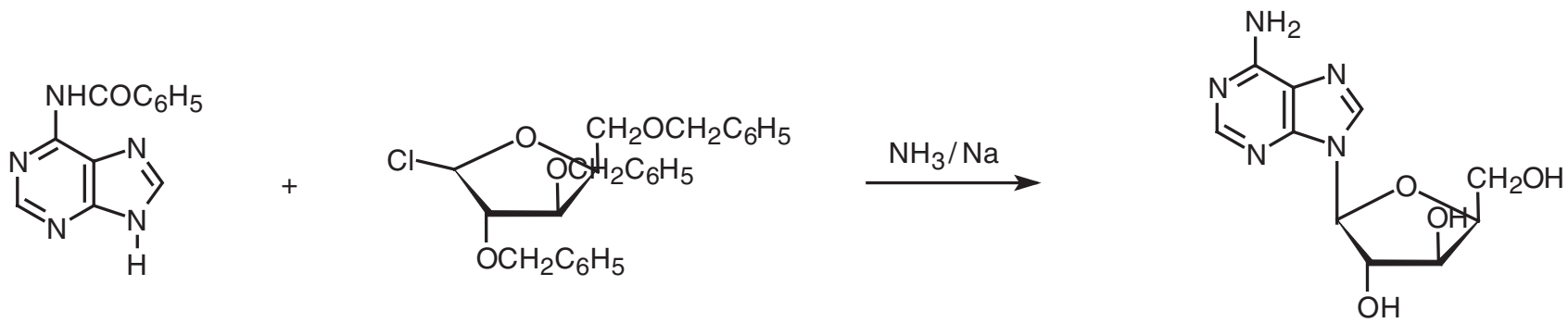
36.1.7

36.1.8



36.1.9

36.1.10



36.1.10

Idoxuridine

It is an analog of timidin—and iodinated derivative of deoxyuridin.

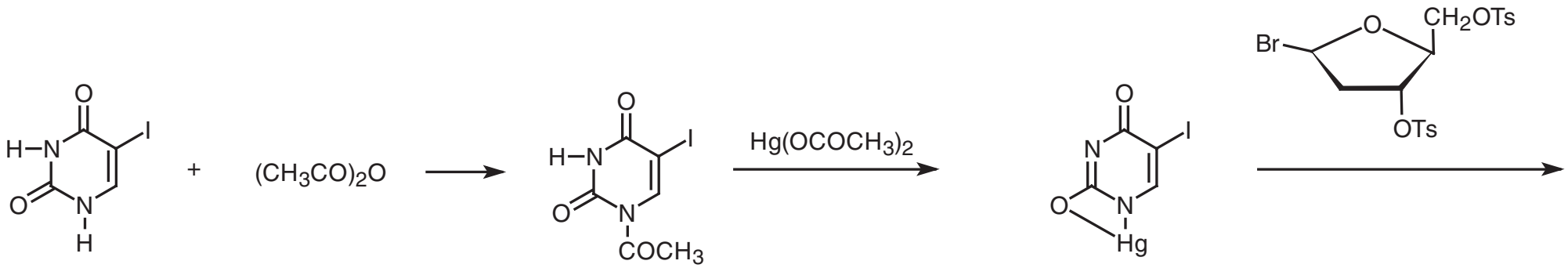
Idoxuridine has an **effect on viral DNA**, and does **not have an effect on viral RNA**.

The primary action of idoxuridine consists of inhibiting viral DNA replication by incorporating right in the DNA itself. Upon systemic introduction, this nucleoside is phosphorylated by both viral, as well as cellular thymidine kinase to an active triphosphorylated compound, which inhibits synthesis of both viral and cellular DNA.

Since this drug also affects mammalian cells and also possess theratogenic, mutagenic, and immunosuppressive action, its use is **limited to external use**.

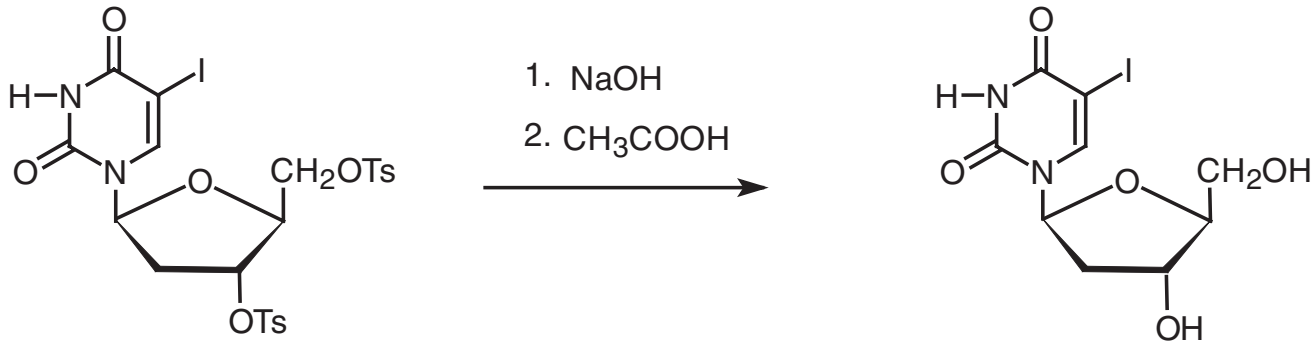
It is used primarily for ophthalmology for herpetic infections of the eye (keratitis).

Synonym: herplex, stoxil, and iduviran



36.1.11

36.1.12



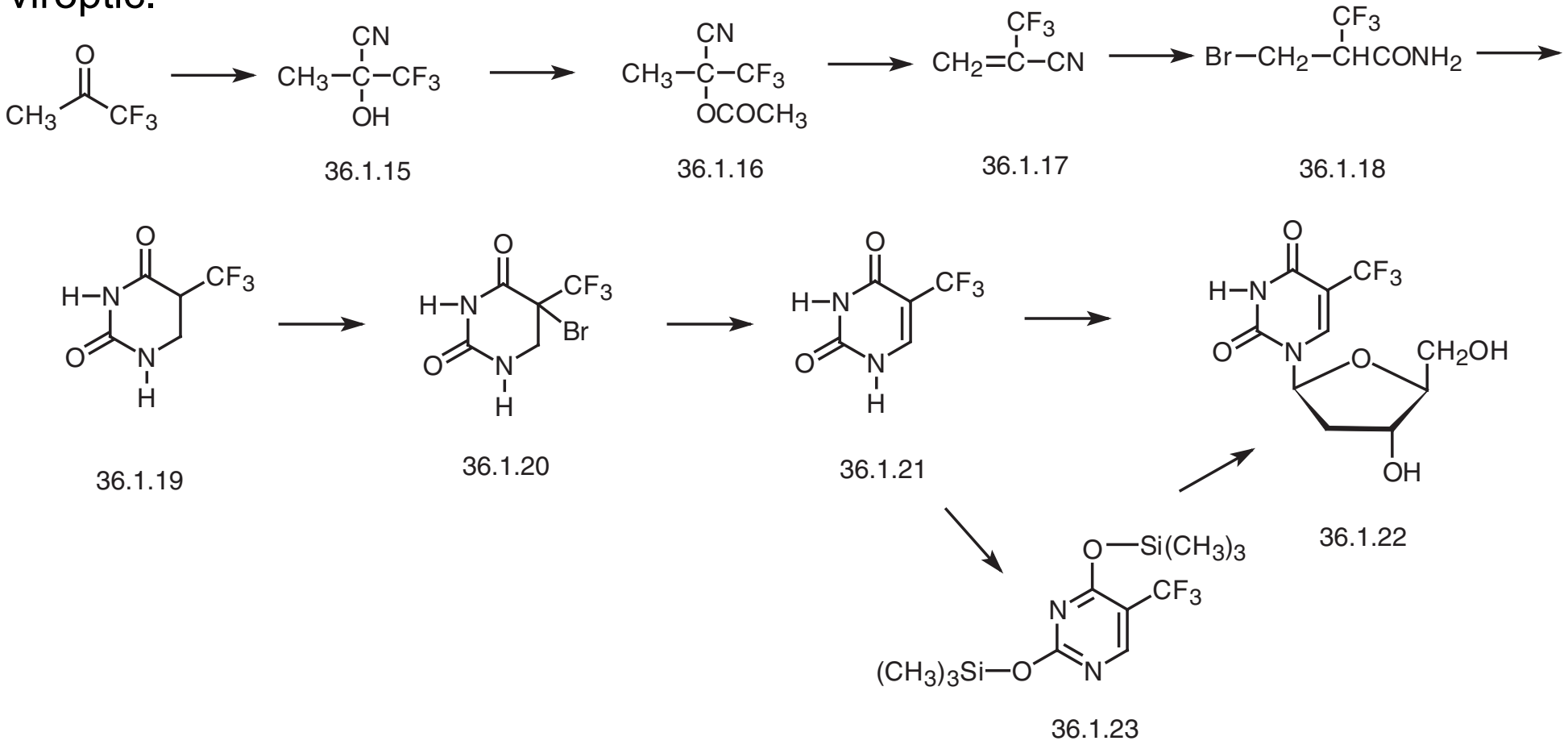
36.1.13

36.1.14

Trifluridine

It is also a halogenated derivative of timidin and is used for keratoconjuctivitis. In terms of action and region of use it is analogous to idoxuridine. It is also (like idoxuridine) turned into triphosphate, which inhibits DNA polymerase.

Synonym: viroptic.



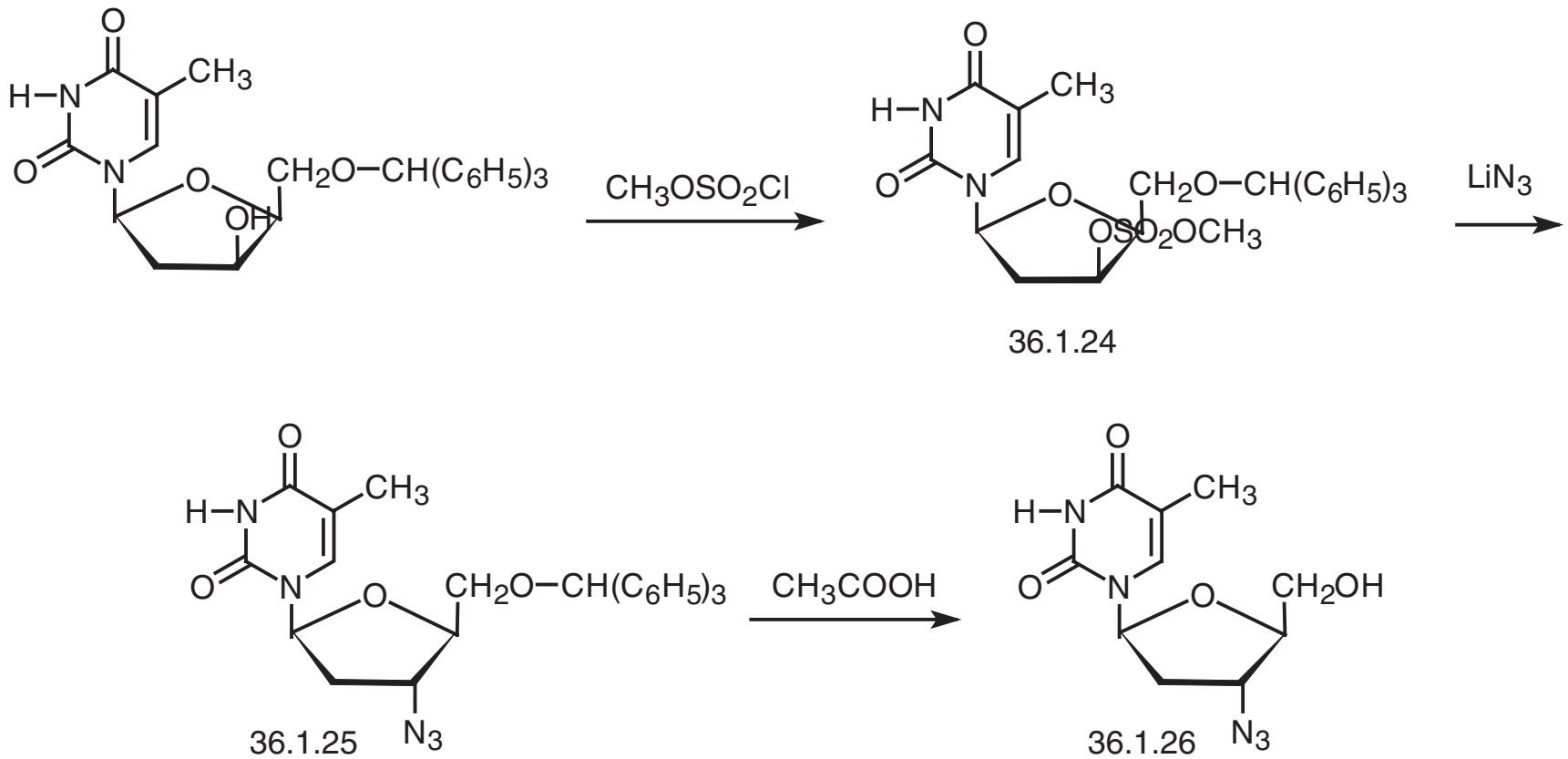
Zidovudine

It is an antiretroviral drug that is clinically active against HIV-1 and is intended to treat HIV-infected patients. Zidovudine is an analog of thymidine that inhibits replication of the AIDS virus.

It also turned into mono-, di-, and triphosphates by the same cellular enzymes that catalyze phosphorylation of thymidine and thymidine nucleosides. Zidovudine-triphosphate is then included in the terminal fragment of the growing chain of viral DNA by viral reverse transcriptase, thus causing the viral DNA chain to break apart in cells infected with the virus.

Zidovudine has been authorized for treating patients with AIDS. It significantly prolongs the life of the patient, although it has a number of toxic effects.

Synonym: azidothymidine and retrovir

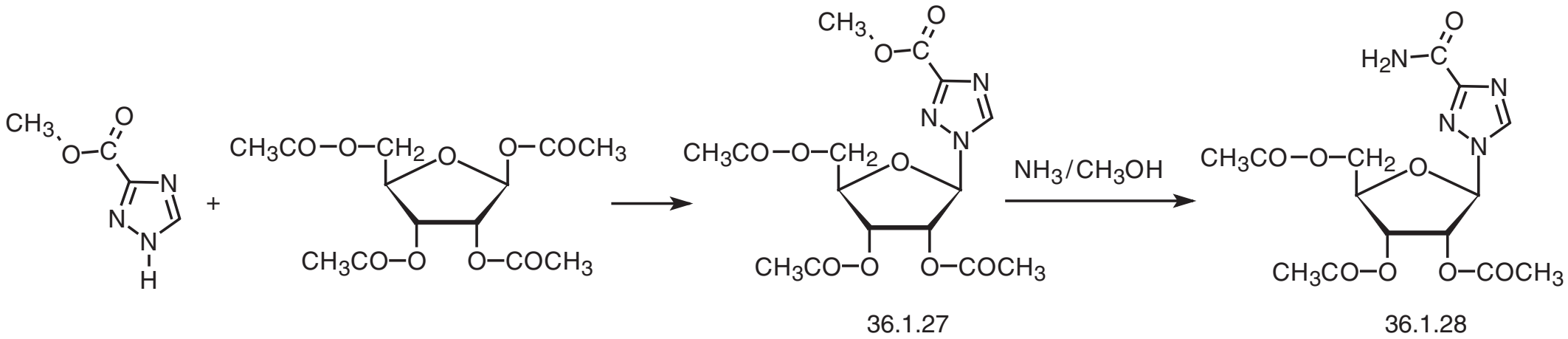

O
H–N
CH3
O
N
O
CH2O–CH(C6H5)3
OH
CH3OSO2Cl
LiN3
OSO2OCH3
36.1.24
36.1.25
N3
CH3COOH
CH2OH
36.1.26
N3

Ribavirin

It is a synthetic analog of nucleosides. It is effective against many DNA and RNA viruses, such as viral influenza and herpes.

The mechanism of its action is not completely known. It has been tried on a number of AIDS patients with various results.

Synonym: virazoll.



36.1.27 36.1.28