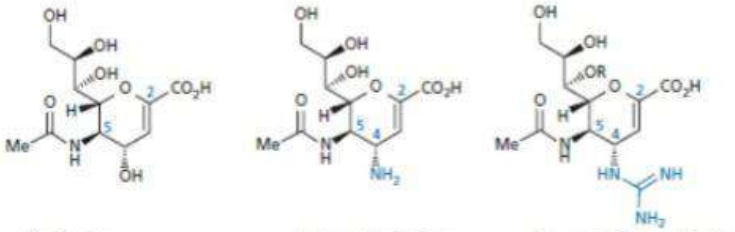
Neuroaminidase inhibitor (NAI): Transition state inhibitors



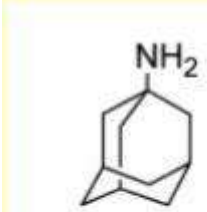
Neu5Ac2en
K_i (M) 4×10^{-6}; IC_{50} 5–10 μM

4-Amino-Neu5Ac2en
K_i (M) 4×10^{-8}

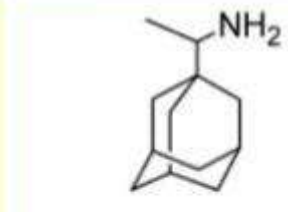
Zanamivir (Relenza); R=H
K_i (M) 3×10^{-11}
Laninamivir (Inavir); R=Me

FIGURE 20.44 Transition-state inhibitors for the enzyme neuraminidase.

Neu5Ac2en (DANA): 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid, is a highly active neuraminidase inhibitor (not specific for the viral enzyme).

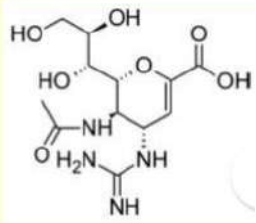


Amantadine

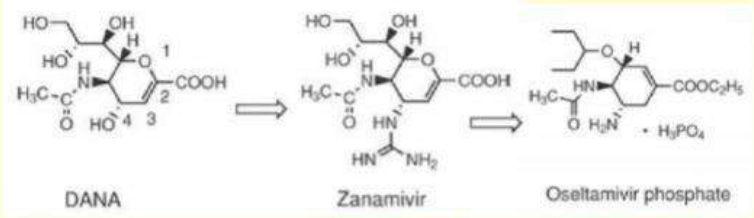


Rimantadine

Zanamivir



Neuroaminidase inhibitor (NAI): Transition state inhibitors



DANA

Zanamivir

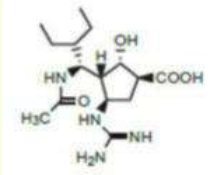
Oseltamivir phosphate

(Not selective for the viral NA). Inactive in vivo

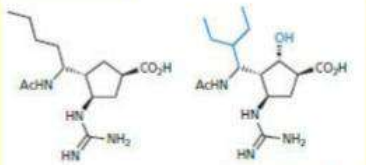
First selective drug Powder Inhalation

Carbocyclic drug Oral Tablet

Acyclovir
DNA terminator



Peramivir



Peramivir (BCX 1812)

FIGURE 20.52 Development of peramivir (BCX 1812).

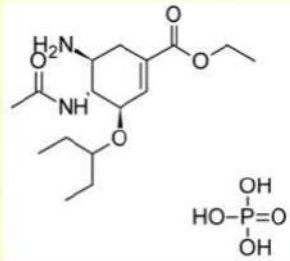
Oseltamivir phosphate

It is given orally

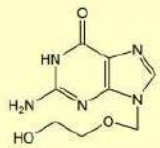
Oseltamivir is actually a **prodrug** in its ethyl ester form.

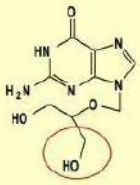
Ester hydrolysis releases the active oseltamivir molecules.

If administered within 2 days after



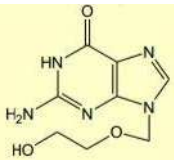
Gancyclovir:





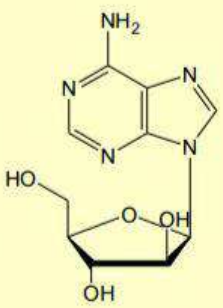
Valacyclovir

Esterase

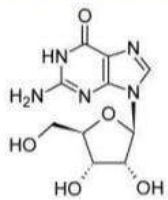


Acyclovir
Oral bioavailability 15-30%

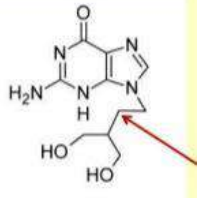
2'-deoxyguanosine
DNA component



Vidarabine (ara-A)



Guanosine

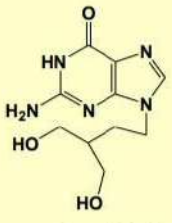


Penciclovir

Famciclovir and penciclovir:

Famciclovir

METABOLIC ACTIVATION



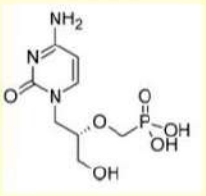
Famciclovir

Penciclovir

Cidofovir (Vistide)
(S)-3-hydroxy-2-phosphonomethoxypropyl cytosine (HPMPC)

An acyclonucleotide analog (dexycytidine-5-monophosphate analogue)

A phosphonic acid derivative.

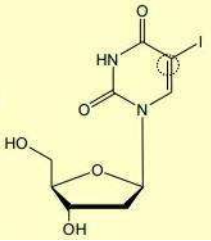


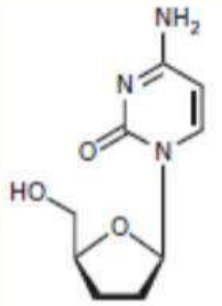
Idoxuridine (Stoxil)
5-iodo-2-deoxyuridine

The drug is an iodinated analog of thymidine

It is converted in cell to mono-, di-, and triphosphate.

Activation is not selective to virally infected





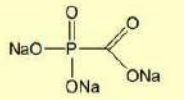
Zalcitabine

Foscarnet

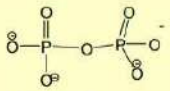
Trisodium phosphonoformate is an inorganic pyrophosphate analog

Not requiring an activation step before attacking the target viral enzyme (Not a prodrug)

It is a reversible, noncompetitive inhibitor with respect to nucleoside triphosphate, that binds to pyrophosphate binding site of viral DNA polymerase and reverse transcriptase (RT).

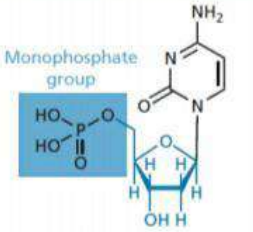


Trisodiumphosphonoformate



Pyrophosphate

Cidofovir



Deoxycytidine monophosphate

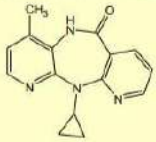
Nevirapine

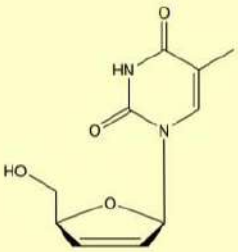
g to RT and direct inhibition at a site different

ZT-resistant strains.

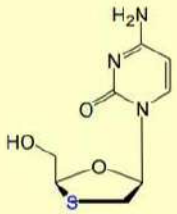
tion.

ash.





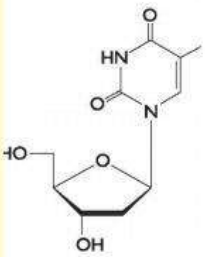
Stavudine
2',3'-Dideoxy-2',3'-didehydrothymidine (D4T)



Lamivudine
2'-Deoxy-3'-thiacytidine, 3TC

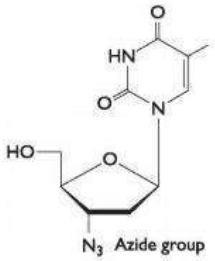
Zidovudine

Nucleoside (DNA component)



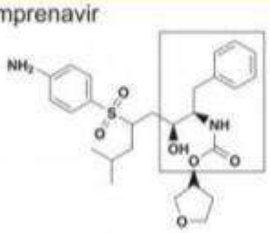
2'-Deoxythimidine

Nucleoside analog (DNA chain terminator)

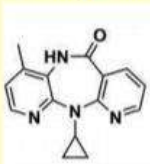


Zidovudine (AZT)
(3'-azido-2'-deoxythymidine)

Amprenavir



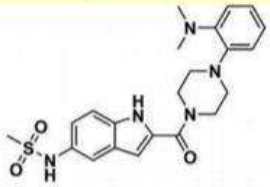
Diazepinone



Nevirapine

Approved in 1996
First generation

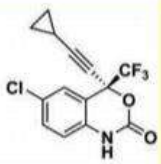
Piperazine



Delavirdine

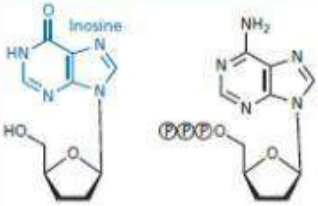
Approved in 1997
First generation

Benzoxazin-2-one



Efavirenz

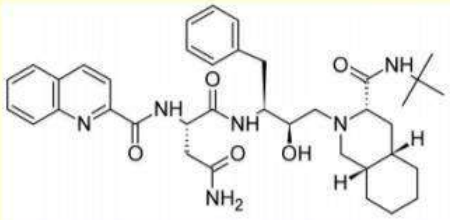
Approved in 1998
Second generation



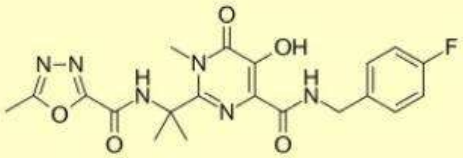
Didanosine

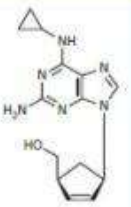
2',3'-Dideoxyadenosine triphosphate

Saquinavir



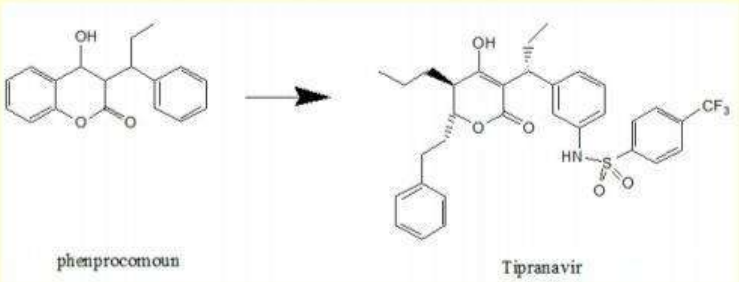
Raltegravir





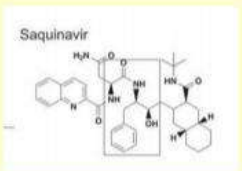
Abacavir

Tipranavir

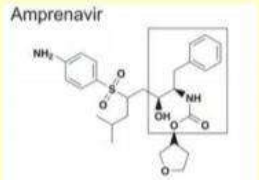


phenprocomoun

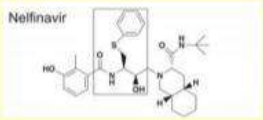
Tipranavir



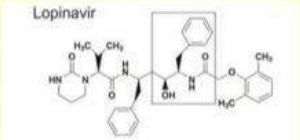
Saquinavir



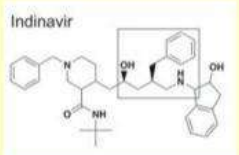
Amprenavir



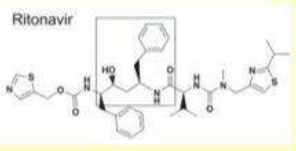
Nelfinavir



Lopinavir



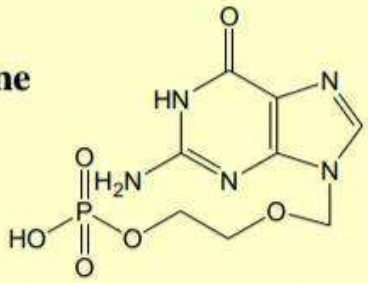
Indinavir



Ritonavir

tion

line



Acycloguanosine monophosphate

(acyclo GMP)

Cellu

2 A

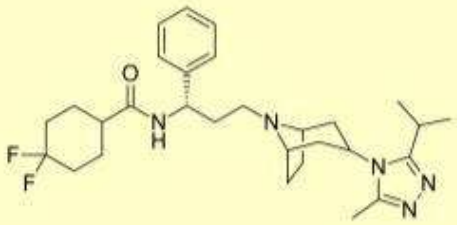
Maraviroc

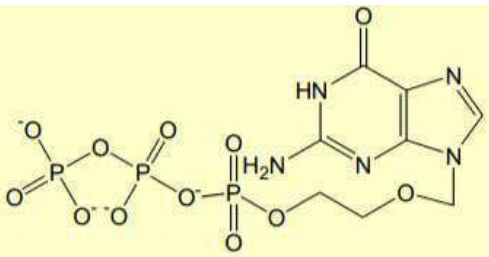
An entry inhibitor

CCR5 receptor antagonist for HIV treatment

FDA approved 2007

Hepatotoxicity





Acycloguanosine triphosphate

(acyclo GTP)