Antiviral Agents-Section2

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

Drugs covered in this chapter:

INHIBITORS OF VIRAL ATTACHMENT, PENETRATION OR EARLY REPLICATION
- Amantadine
- Amphotericin B methyl
- Ester
- Interferon/PEG-IFN
- Rimantadine
- Tecovirimat

NEURAMINIDASE INHIBITORS
- Oseltamivir
- Peramivir
- Zanamivir
- Baloxavir marboxil

FUSION INHIBITORS
- Enfuvirtide
- Maraviroc

ACYCLIC NUCLEOLSIDE ANALOGUES
- Acyclovir
- Adefovir dipivoxil
- Cidofovir
- Famciclovir
- Ganciclovir
- Penciclovir
- Valacyclovir

CONVENTIONAL NUCLEOSIDE ANALOGUES
- Ribavirin

NONNUCLEOSIDE ANALOGUES
- Foscarnet
- Letermovir

ANTIRETROVIRAL AGENTS—NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir disoproxil
- Zidovudine

ANTIRETROVIRAL AGENTS—NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
- Delavirdine
- Doravirine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

HIV PROTEASE INHIBITORS
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

INHIBITORS OF HCV PROTEASE NS3/NS4A
- Glecaprevir
- Grazoprevir
- Paritaprevir
- Voxilaprevir

INHIBITORS OF HCV PROTEASE NS5A AND NS5B
- Daclatasvir
- Dasabuvir
- Elbasvir
- Ledipasvir
- Ombitasvir
- Pibrentasvir
- Sofosbuvir
- Velpatasvir

DRUG COMBINATIONS FOR HCV INFECTION
- Epclusa
- Harvoni
- Mavyret
- Technivie
- Viekira Pak/Viekira XR
- Zepatier

HIV INTEGRASE INHIBITORS
- Dolutegravir
- Elvitegravir
- Raltegravir
- Bictegravir

Steps Involved in Viral Life Cycle: A DNA Virus

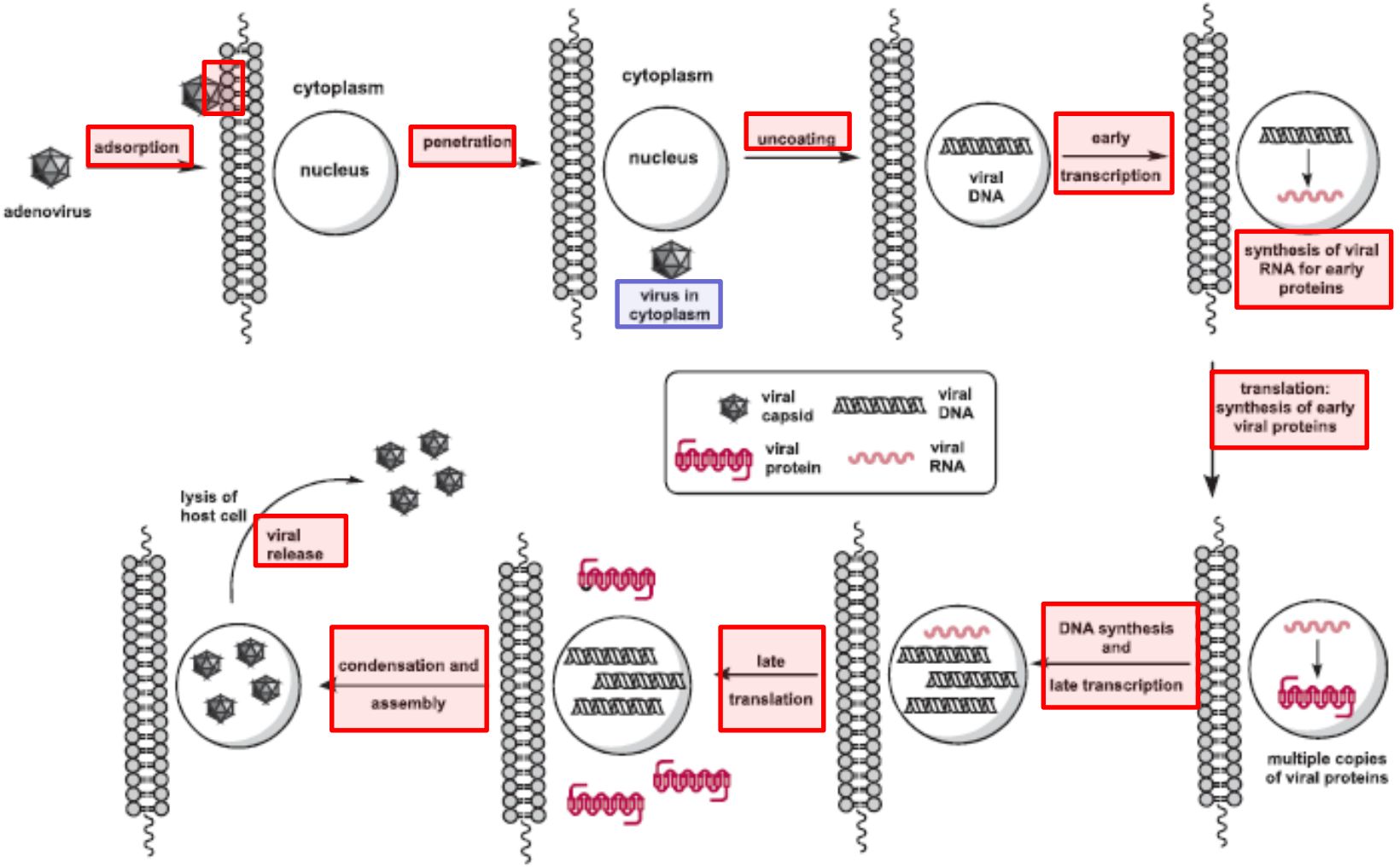


Figure 30.1 Steps involved in the viral life cycle.

Classes of Antiviral Agents

1- Penetration interfering agents; chemokine binders:

1a- Early step antiviral agents

1b- NeurAminidase Inhibitors (NAIs): anti Influenza virus

1c- HIV fusion inhibitors against gp41/ gp120 & CCR5 as antagonist: anti HIV

2- DNA interfering agents; DNA polymerase inhibitors:

2a- Acyclic nucleoside analogues (antimetabolite)

2b- Conventional nucleoside analogues (antimetabolite)

2c- Non-nucleoside analogues

2d- agents affecting translation by the ribosome

2e- Endonuclease inhibitor: anti Influenza virus

3- INtegrase (Strand Transfer) Inhibitors (IN(ST)Is): anti-retrovirus: anti HIV

4- Reverse Transcriptase Inhibitors (RTIs): anti HIV

4a- Nucleoside RTI (NRTI)

4b- Non- Nucleoside RTI (NNRTI): anti HIV

5- PRotease Inhibitors (PRIs): anti HIV & anti HCV

6- RNA dependent RNA polymerase (RdRp) Inhibitors

7- siRNA

8-Vaccines

3- INtegrase Strand Transfer Inhibitors (INSTIs; INIs): Anti HIV

Chapter 38

Antiviral Agents and Protease Inhibitors

Patrick M. Woster

Drugs Covered in This Chapter*

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

HIV INTEGRASE INHIBITORS

HIV INTEGRASE INHIBITORS

- Dolutegravir
- Elvitegravir
- Raltegravir
- Bictegravir

3- HIV INtegrase & INIs

- HIV Integrase: 32KD & three domains including:
- ✓ Amino domain: Zn binding site
- ✓ Catalytic domain: CCD: Mg binding site
- ✓ Carboxy domain

- MOA: retroviral integrase (IN): beneficial in HIV
- ✓ essential for replication of the HIV virus

- Each HIV contains 40-100 integrase molecules:
- ✓ to facilitate the insertion of viral cDNA into the host cell genome

- Integrase inhibitor: inhibit insertion of viral genome to the host DNA
- ✓ Raltegravir
- ✓ Elvitegravir: phase III clinical trial

3-Integrase Inhibitors (INIs): Anti HIV: SAR

- Chemistry:

✓ di-keto/acid or amide: 1,2 or 1,3-dicarbonyl: to provide chelate

✓ acts near acid catalytic residues in enzyme (integrase)

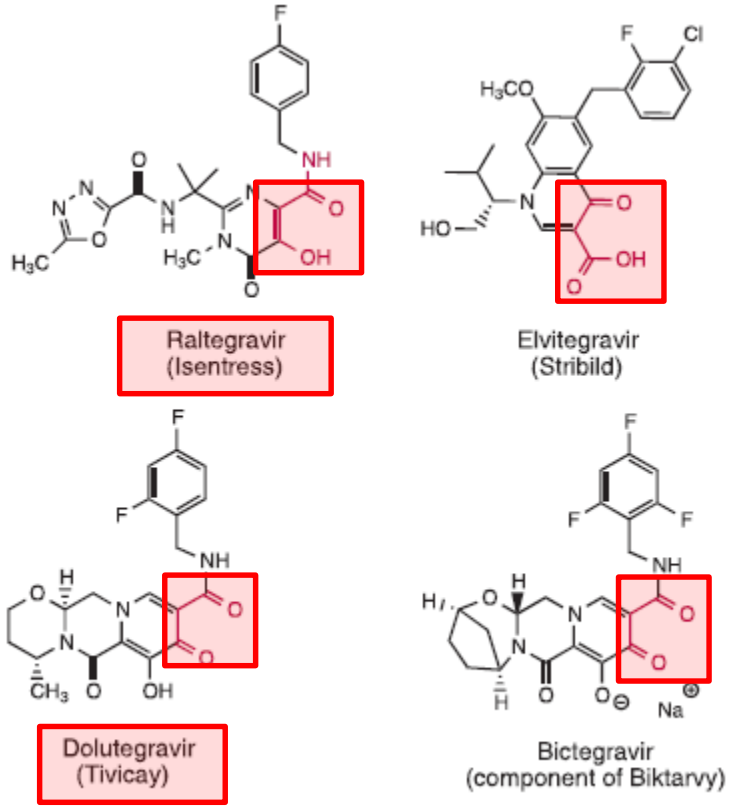
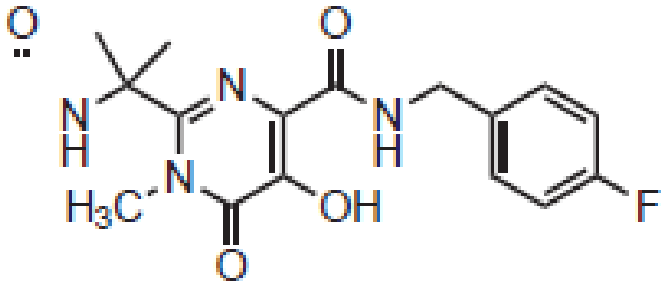


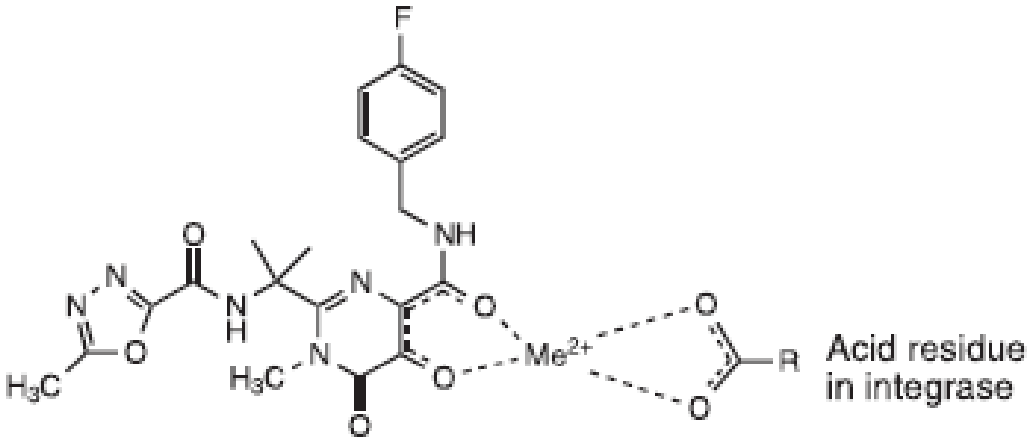
Figure 30.18 Integrase strand transfer inhibitors (INSTIs). Red highlight indicates the pharmacophore in INSTIs.

3-INtegrase Inhibitors (INIs): Anti HIV: MOA

- Mechanism of action for retroviral integrase (IN): beneficial in HIV
- ✓ INIs: Inhibit insertion of viral genome to the host DNA
- ✓ Inhibit cDNA integration via chelation to the divalent cations
- ✓ Raltegravir
- ✓ Elvitegravir

RALTEGRAVIR





Raltegravir

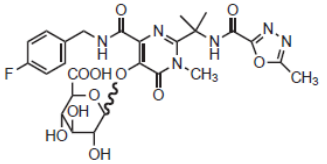


Figure 30.19 Chelation complex between raltegravir and integrase.

Antiretroviral (Anti-HIV) Agents:
4- Reverse Transcriptase Inhibitors (RTIs):

4a- Nucleoside RTIs (NRTIs)
4b- Non-Nucleoside RTIs (NNRTIs)

4-Reverse Transcriptase Inhibitors (RTIs)

- MOA:

✓ interfere with replication of HIV

✓ stop synthesis of infective viral particles

4a- Nucleoside RTIs (NRTIs)

4b- Non-Nucleoside RTIs (NNRTIs)

- HIV protease inhibitors: inactivate RT & block release of viral particles from the infected cells

Chapter 38

Antiviral Agents and Protease Inhibitors

Patrick M. Woster

Drugs Covered in This Chapter*

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

4a

ANTIRETROVIRAL AGENTS—NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir disoproxil
- Zidovudine

4b

ANTIRETROVIRAL AGENTS—NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

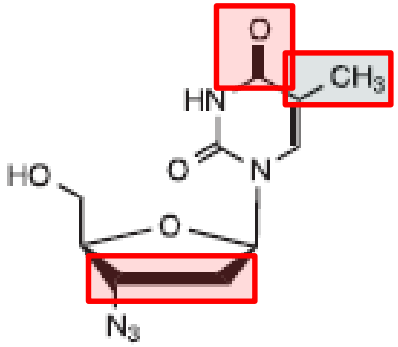
- Delavirdine
- Doravirine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

4a- NRTI

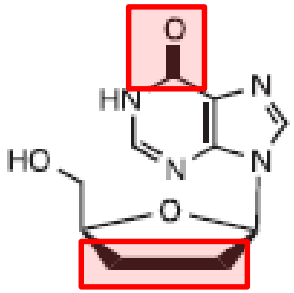
- In combination with PrI & NNRTI gives synergistic effects:

- Zidovudine (AZT)
- Didansine (ddI): DDI
- Zalcitabine (ddc)
- Stavudine
- Lamivudine
- Abacavir
- Emtricitabine

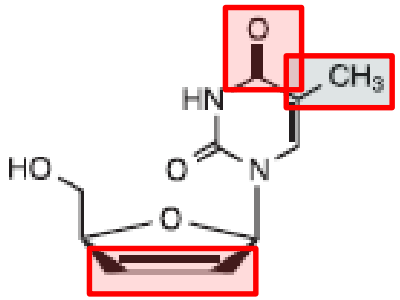
4a- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)



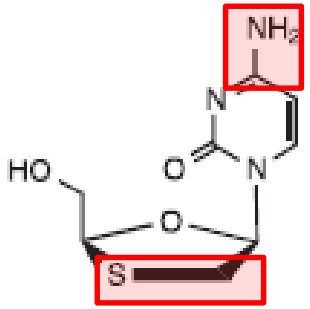
Zidovudine(AZT, ZDV)
(Retrovir)



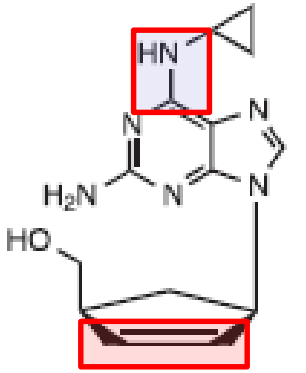
Didanosine(ddI)
(Videx)



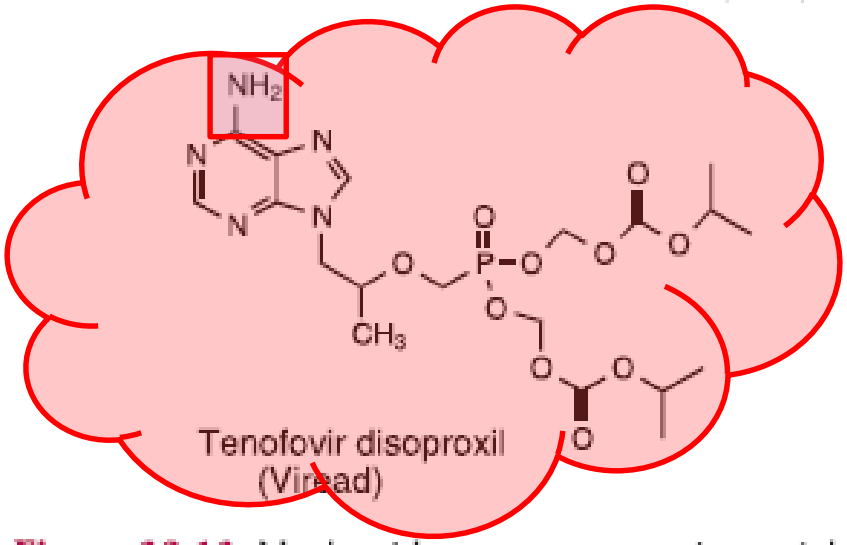
Stavudine
(2',3'-Dideoxy-2',3'-dide-hydrothymidine, D4T)
(Zerit)



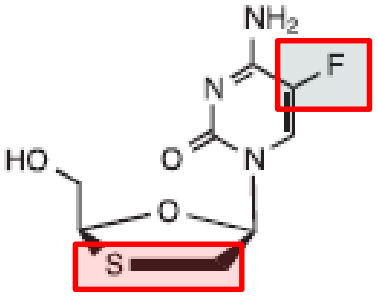
Lamivudine
(2'-Deoxy-3'-thiacytidine, 3TC) (Epivir)



Abacavir (ABC)
(Ziagen)



Tenofovir disoproxil
(Viread)



Emtricitabine
(Emtriva)

Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

4a- Nucleoside Reverse Transcriptase Inhibitors (NRTIs): SAR

- SAR: Chemistry: purine & pyrimidine analogues

+ ribose mimicking portion:

✓ removal of 3'-hydroxy group on ribosyl group

✓ removal of 2'&3'-hydroxy: dideoxy-adenosine; dideoxy-cytidine

✓ removal of 2'&3'-hydroxy & dihydrogen of C2'-C3': didehydro-dideoxy-thymidine

✓ +/-bio-isosterism of C3' at ribosyl: by S (thio)

or substitution of C3' - N_3 (azide)

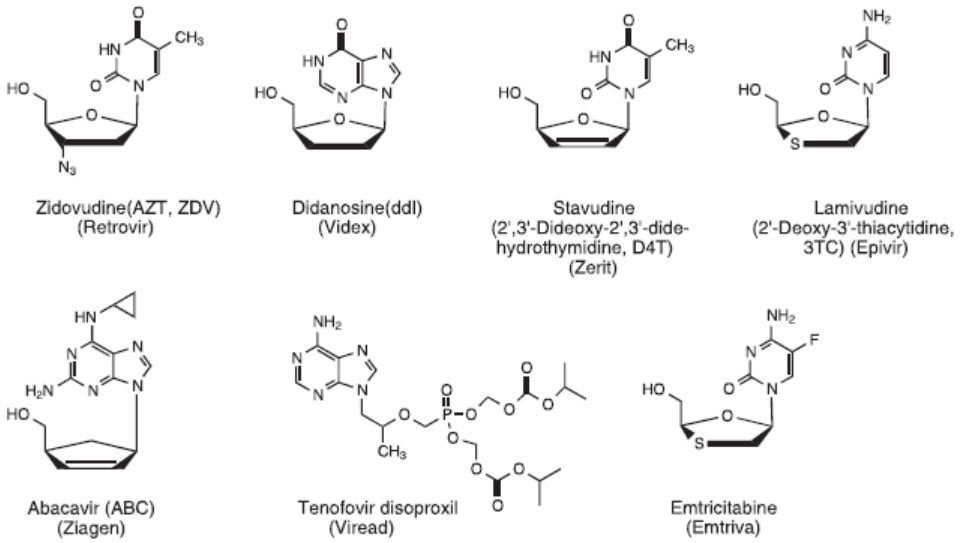


Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

4a- Nucleoside Reverse Transcriptase Inhibitors (NRTIs): MOA

- MOA: incorporation into the viral DNA: chain terminating blockade due to lack of 3'-hydroxy needed for DNA propagation

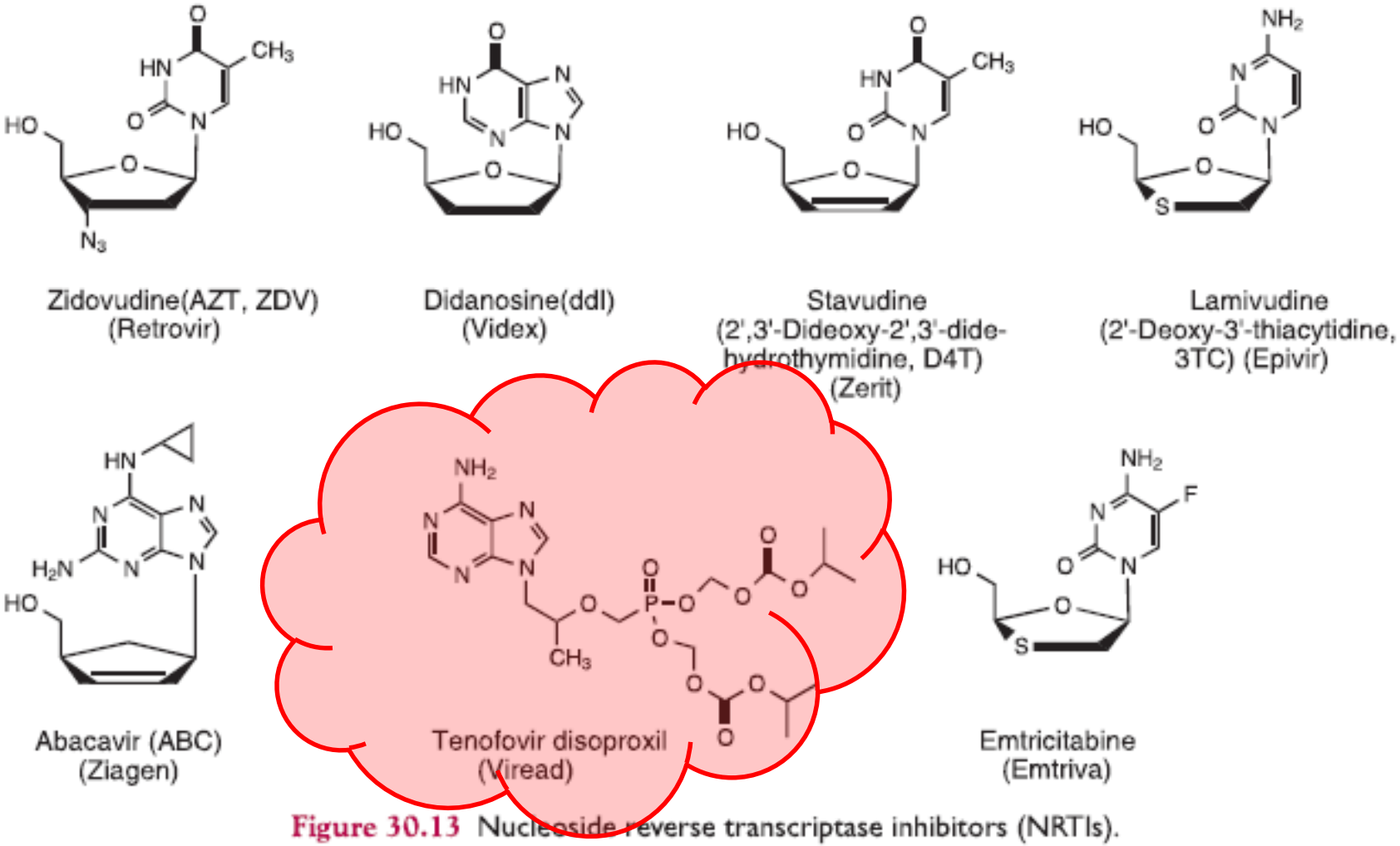


Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

4a-NRTI: Tenofovir

- Adenosine analogue: as disoproxil derivative
- Prodrug: active metabolite: diphosphate form:

✓ Produced initially by plasma esterase then by kinase:

✓ competes with dATP

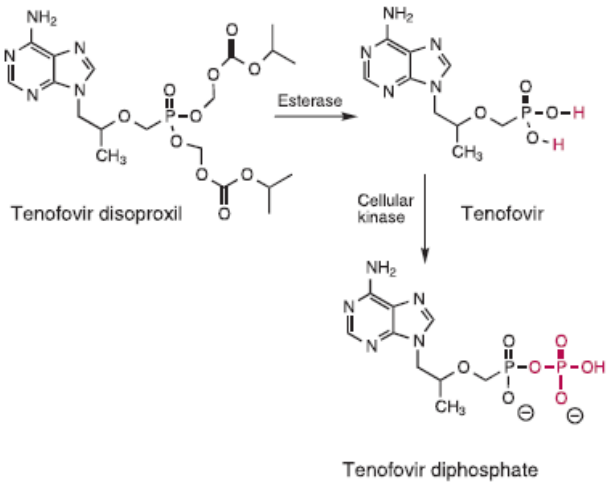


Figure 30.14 Metabolic activation of tenofir disoproxil.

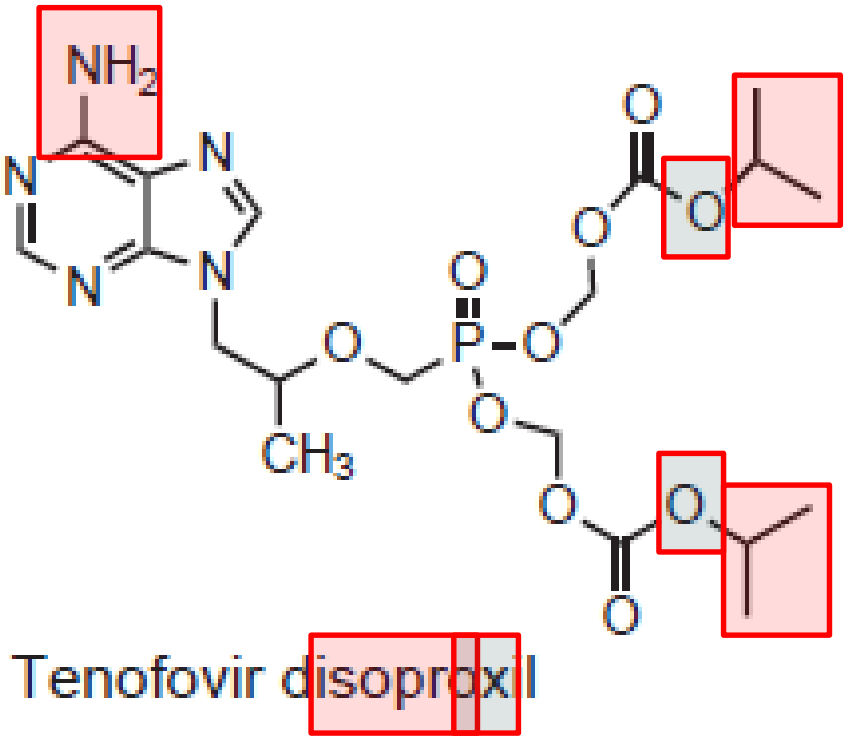
- MOA: reverse transcriptase inhibitor

✓ also might compete with deoxyadenosine triphosphate

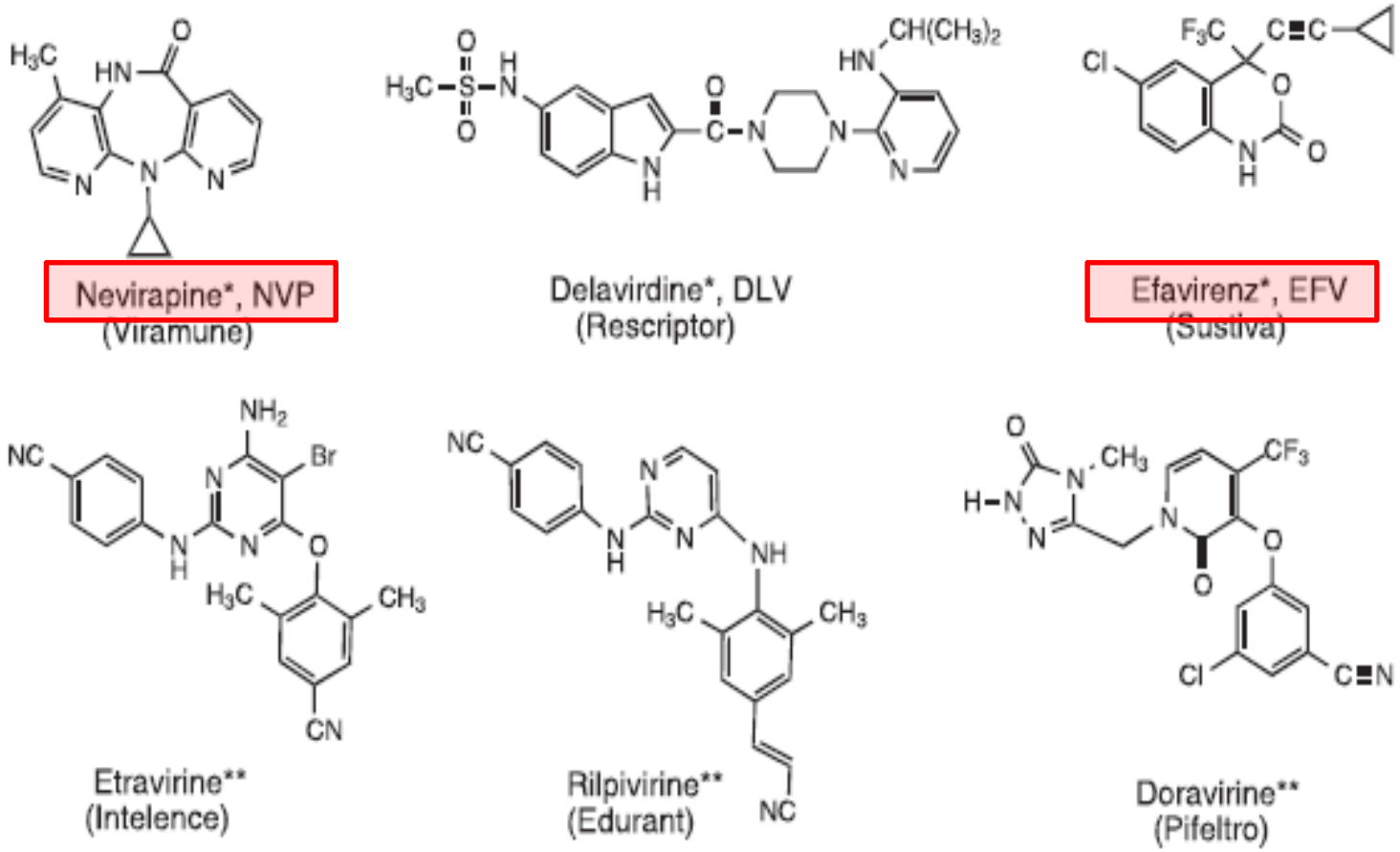
✓ incorporate into viral DNA

✓ & results in premature termination

4a-NRTI: Tenofovir: Dosage Forms



4b- Non-Nucleoside RTI: SAR



*First-generation NNRTIs **Second-generation NNRTIs

Figure 30.15 Nonnucleoside reverse transcriptase inhibitors (NNRTIs).

4b-NNRTI: MOA

- In combination with PrI & NRTI gives synergistic effects:
- MOA: Binding site; selectivity

- Nevirapine;
- Delavirdine;
- Efavirenz

Metabolism of Nevirapine

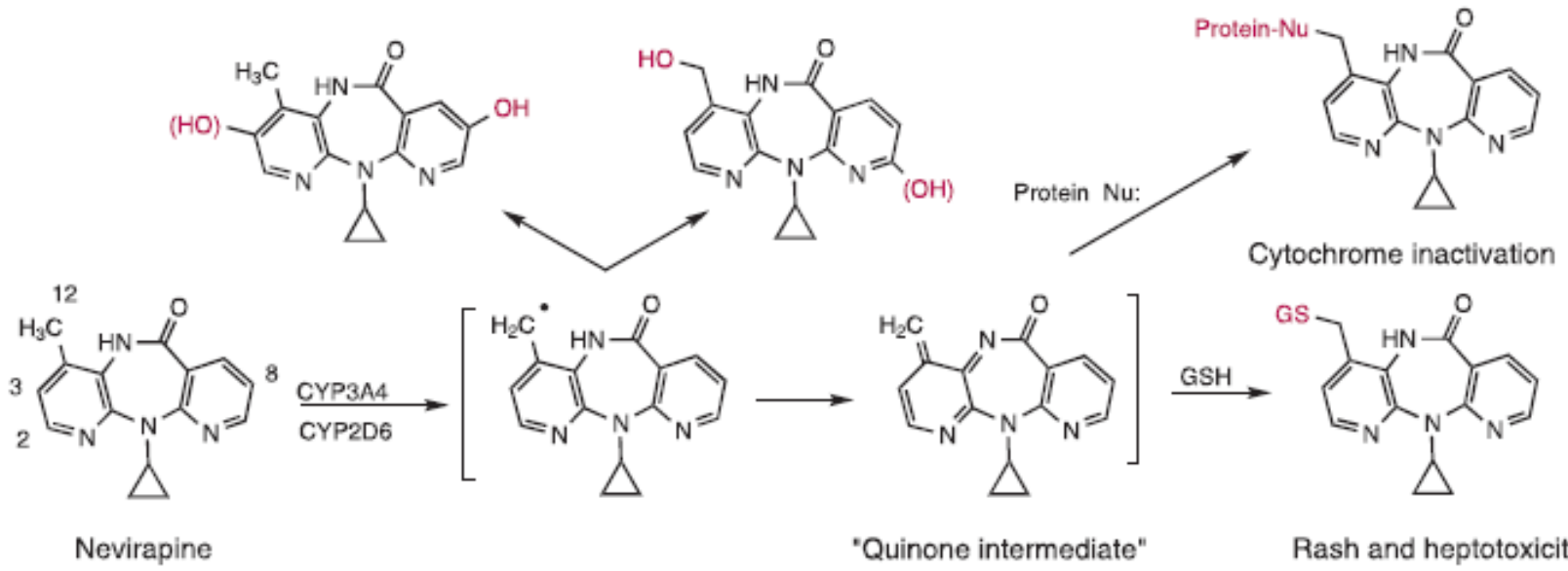


Figure 30.16 Metabolic oxidation of nevirapine by CYP3A4 leading to C2 or C12 hydroxylation or by CYP2D6 leading to C3 or C8 hydroxylation and an explanation for side effects associated with a quinone intermediate.

5- Protease Inhibitors (PIs):

- ✓anti-HIV
- ✓anti HCV

CHAPTER 30

Drugs Used to Treat Viral Infections

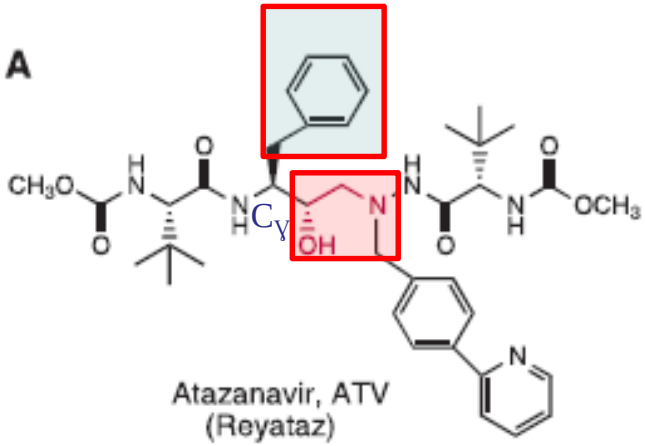
Patrick M. Woster

HIV PROTEASE INHIBITORS

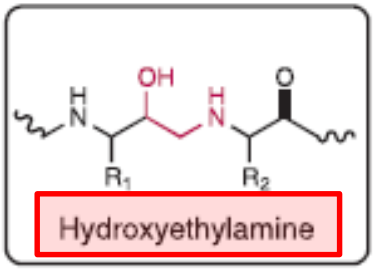
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

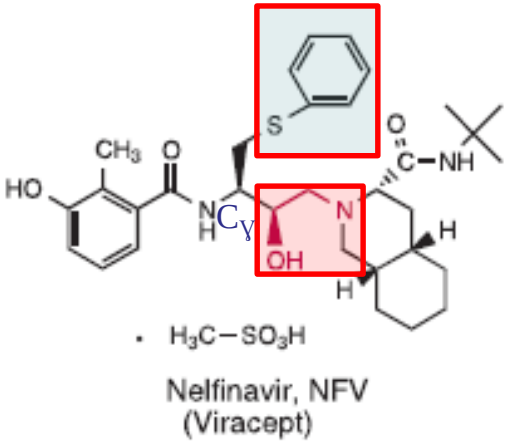
✓Saquinavir: the first FDA approved PrI
✓Ritonavir
✓Indinavir
✓Nelfinavir
✓Lopinavir
✓Amprenavir/Fosamprenavir
✓Tipranavir

5- HIV PrIs: SAR



ß-Hydroxy ethyl





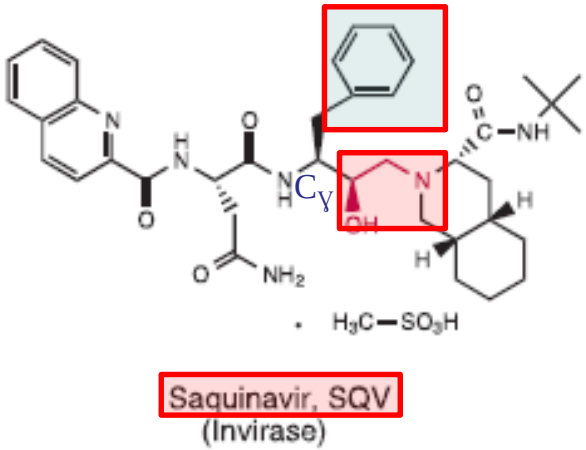


Figure 30.23 Structures of HIV protease inhibitors that are used clinically.

5- HIV PrIs- Continued

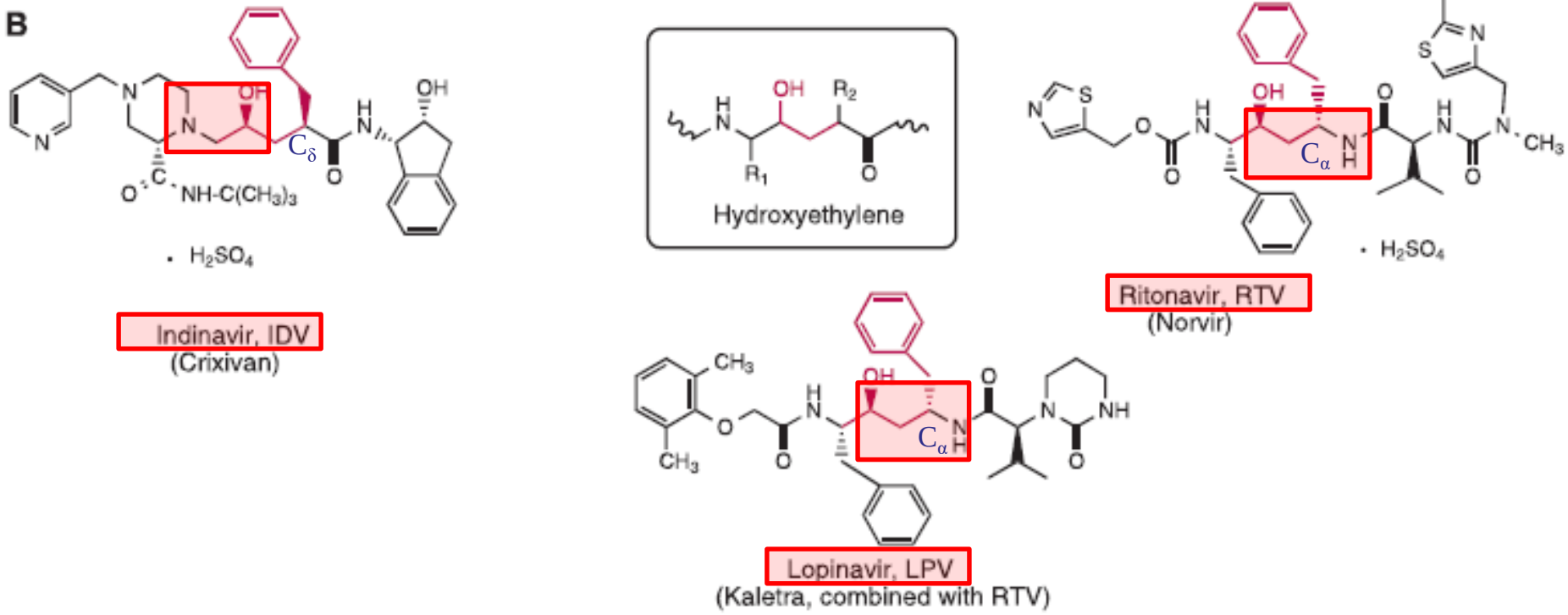
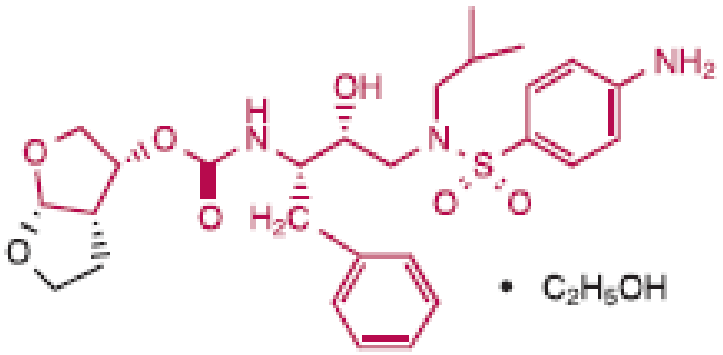


Figure 30.23 Structures of HIV protease inhibitors that are used clinically.

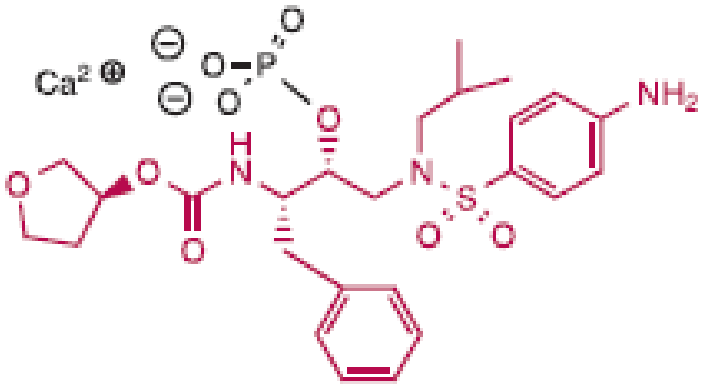
5- HIV PrIs- Continued

ß-Hydroxy ethyl

C

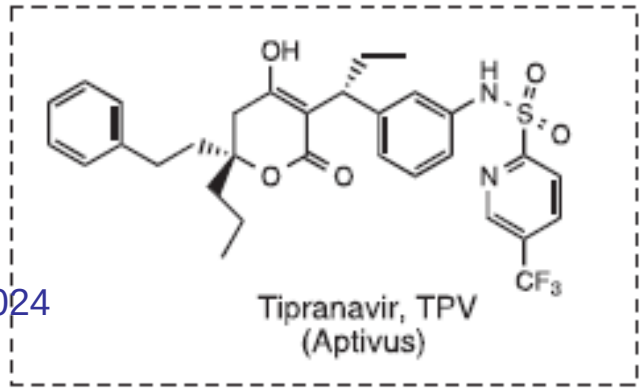


Darunavir ethanolate
(Prezista)



Fosamprenavir calcium, FOS-APV
(Lexiva)

D

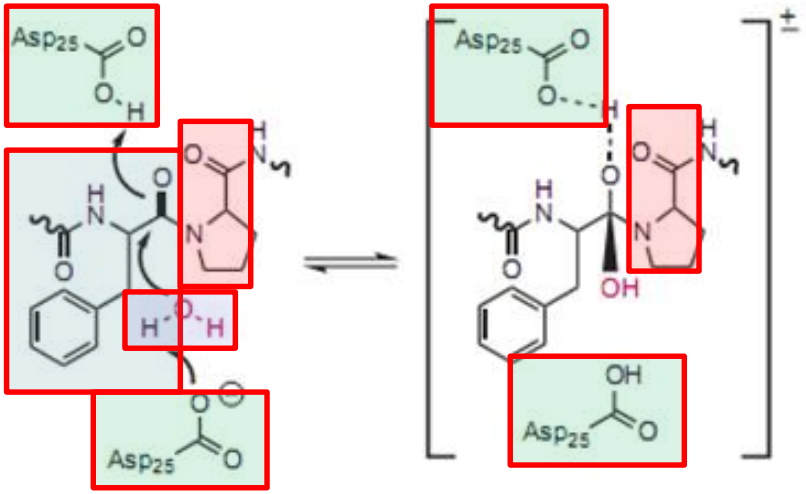


Tipranavir, TPV
(Aptivus)

Figure 30.23 Structures of HIV protease inhibitors that are used clinically.

5- HIV Protease

- Protease: essential for growth of HIV (RNA virus)
  mediate post-translational modification of proteins
  similar to CYP450 related metabolizing enzymes
  dimer structure with Asp residues: two conserved Asp_{25} residues
  = aspartic protease
- Activates RT
- Plays an important role in the release of infectious viral particles
- Several HIV protease cleavage sites:
- but enzyme prefers amino terminal side of a Pro in adjacency to Phe



B. Role pf twp Asp_{25} residues in formation of the hydrolytic transition state.

HIV Protease Inhibitor Design

- Pepstatin: Statin:
- Asp-protease Inhibitors:

✓ possessing un-natural amino acid:

✓ mimic tetrahedral transition state

✓ possessing hydroxyl group

- Pharmacophores for PrIs:

✓ $HO\text{-}CH_2CH_2\text{-}$

✓ $HO\text{-}CH_2CH_2\text{-}NH_2$

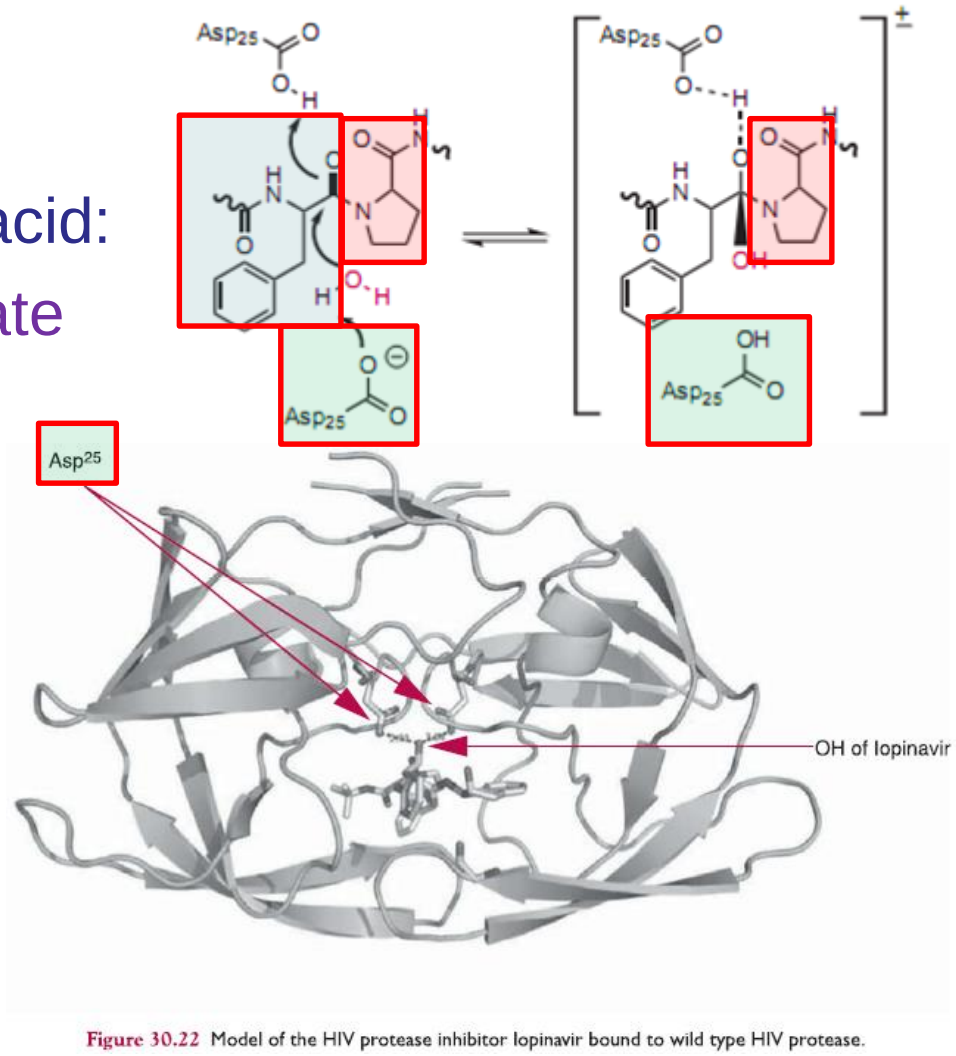


Figure 30.22 Model of the HIV protease inhibitor lopinavir bound to wild type HIV protease.

5- Protease Inhibitors (PrIs)

- PrI rational design: as transition state mimetic
- mimic tetrahedral transition state of hydrolysis in active site of protease

- Chemistry: oligopeptide like structures:

✓ peptidomimetic:

possessing HO-CH_2CH_2-; HO-CH_2CH_2-NH_2 as pharmacophore & non-peptide structures

- PrI in RNA virus such as HIV: inactivate RT & also block release of viral particles from the infected cells

Metabolism for Saquinavir

- Inactive metabolites

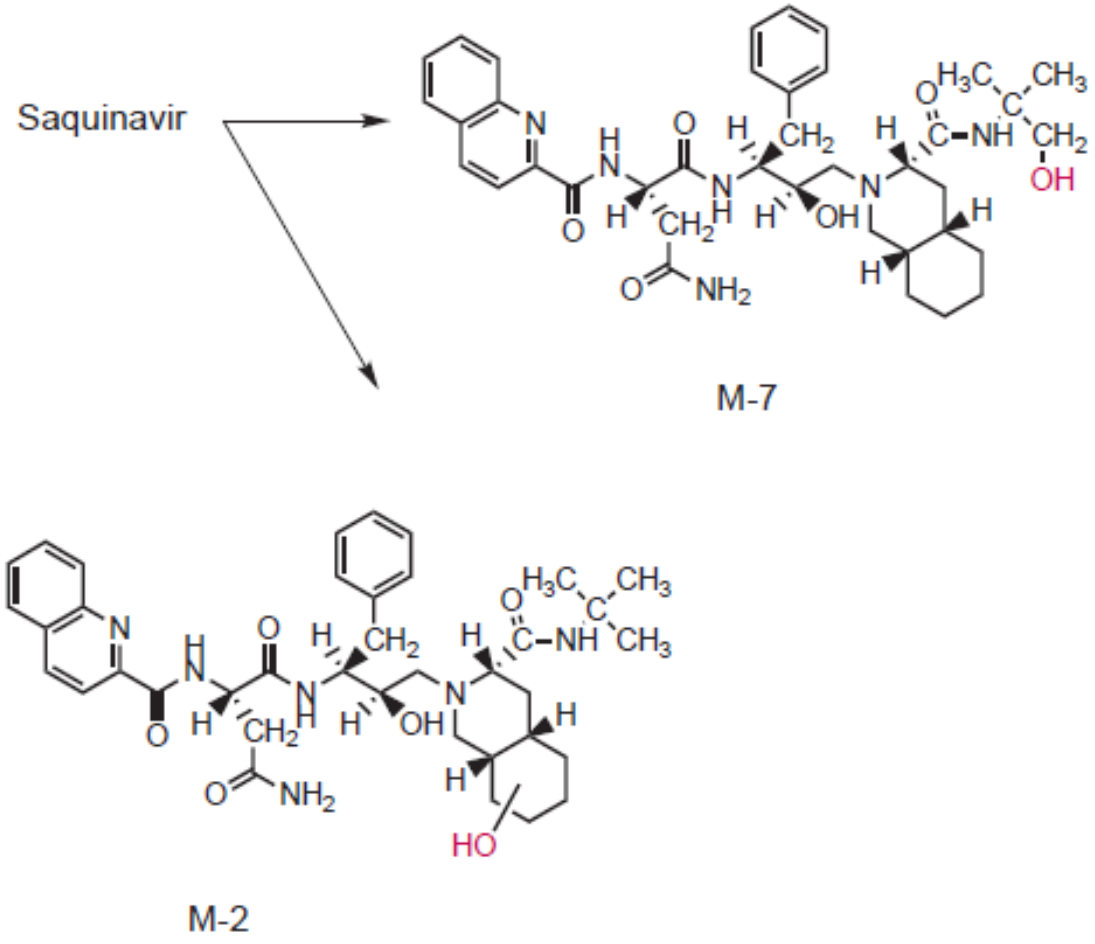
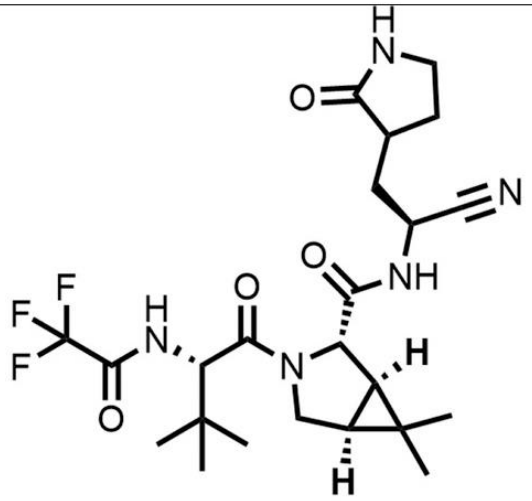


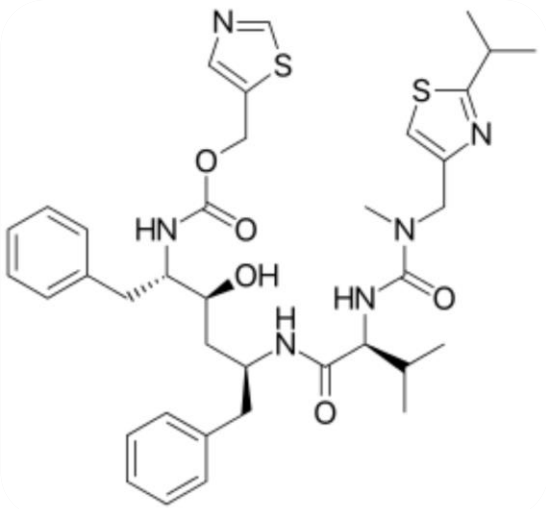
FIGURE 38.21 Major metabolic products from saquinavir.

Paxlovid® against Covvid19

- Includes two PrIs: nirmatrelavir + ritonavir



Nirmatrelvir



Novel Targets in Hepatitis Viral Infections (HCV): NS3/4A; NS5A & NS5B Inhibitors

- NS Pr_s: Non-Structure proteins

✓ located in endoplasmic reticulum

✓ phosphoproteins responsible in RNA replication

✓ acts via RNA polymerase

✓ Essential NS3/4A enzyme: cleaves HCV polyprotein:

✓ generate NS4A, NS4B, NS5A, NS5B

✓ critical in HCV virus: hepatitis

- Current drugs:

✓ sobiovir®; sofosbuvir

✓ daklibiox®; daclatasvir

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

INHIBITORS OF HCV PROTEASE NS3/NS4A

- Glecaprevir
- Grazoprevir
- Paritaprevir
- Voxilaprevir

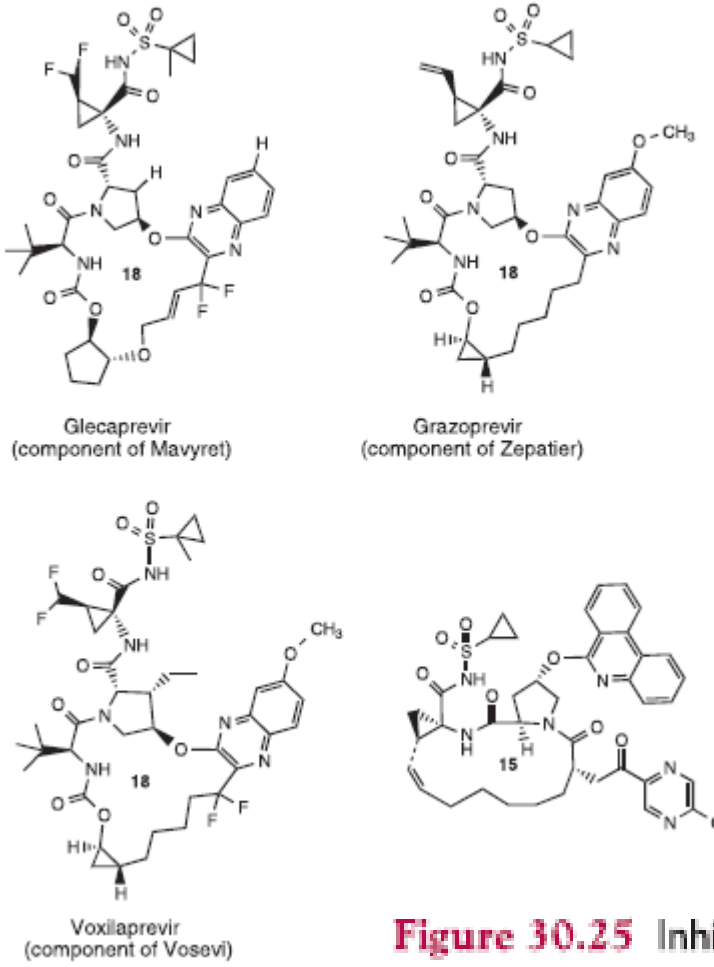
DRUG COMBINATIONS FOR HCV INFECTION

- Epclusa
- Harvoni
- Mavyret
- Technivie
- Viekira Pak/Viekira XR
- Zepatier

INHIBITORS OF HCV PROTEASE NS5A AND NS5B

- Daclatasvir
- Dasabuvir
- Elbasvir
- Ledipasvir
- Ombitasvir
- Pibrentasvir
- Sofosbuvir
- Velpatasvir

5- HCV Protease NS3/4A Inhibitors



Glecaprevir
(component of Mavyret)

Grazoprevir
(component of Zepatier)

Voxilaprevir
(component of Vosevi)

Figure 30.25 Inhibitors of HCV protease NS3/4A.

5- HCV Protease NS3/4A Inhibitors

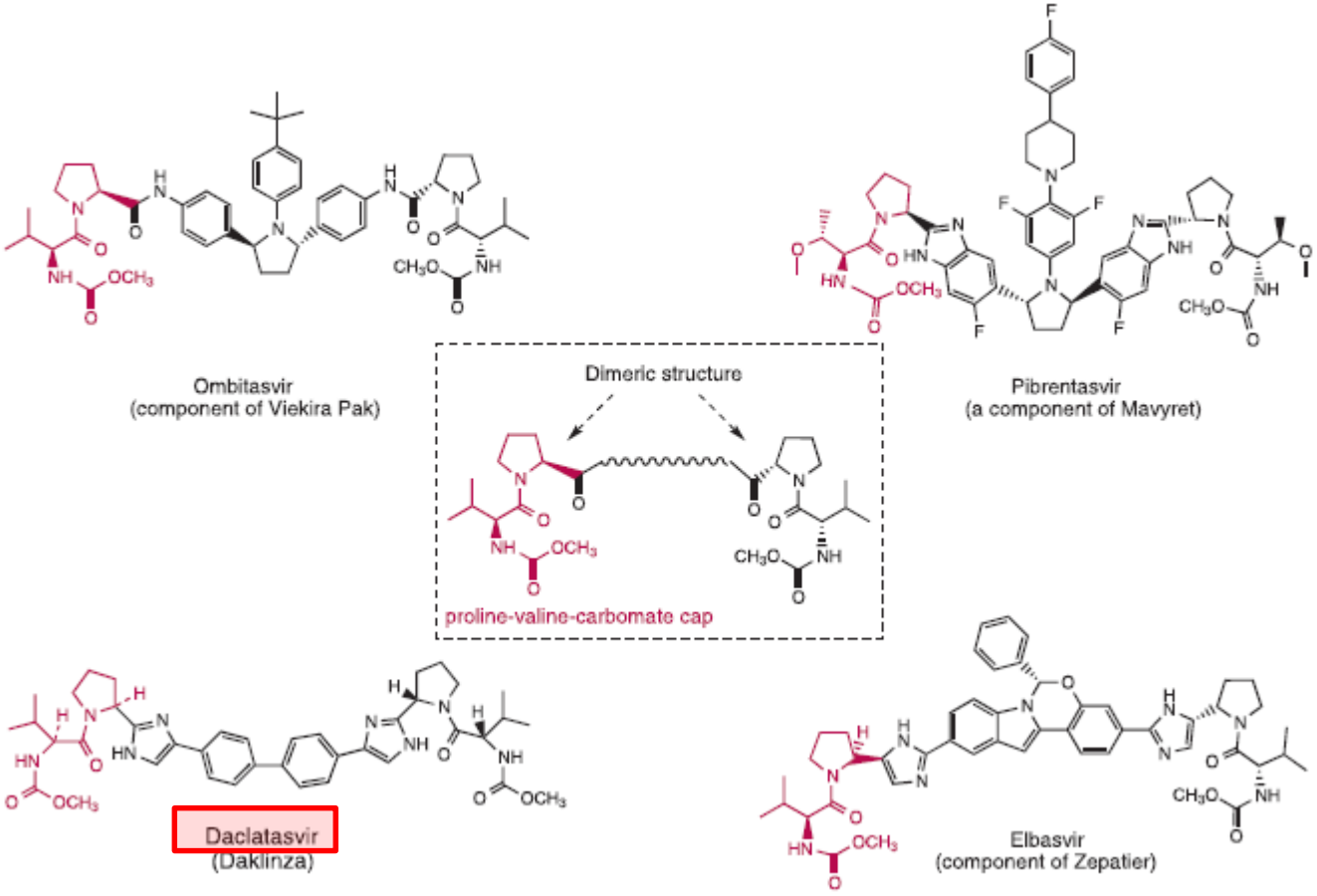
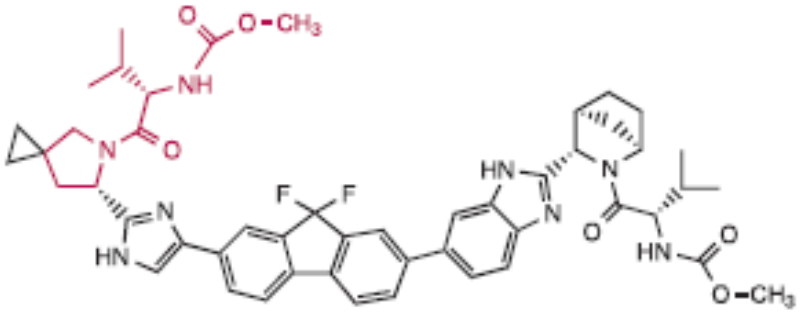
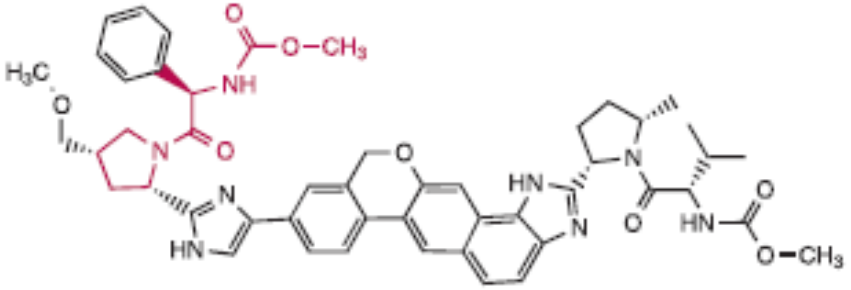


Figure 30.25 Inhibitors of HCV protease NS3/4A.

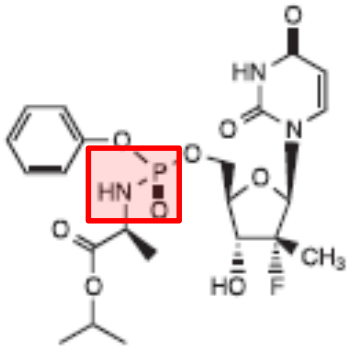
5- HCV Protease NS5A & NS5B Inhibitors



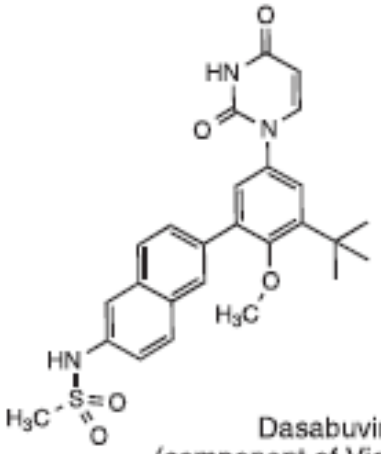
Ledipasvir
(a component of Harvoni)



Velpatasvir
(a component of Epclusa and Vosevi)

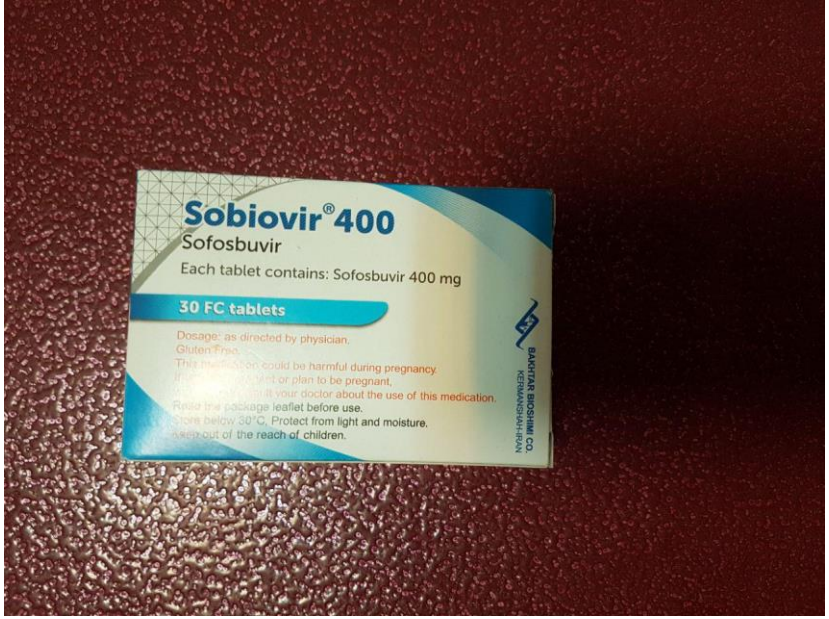


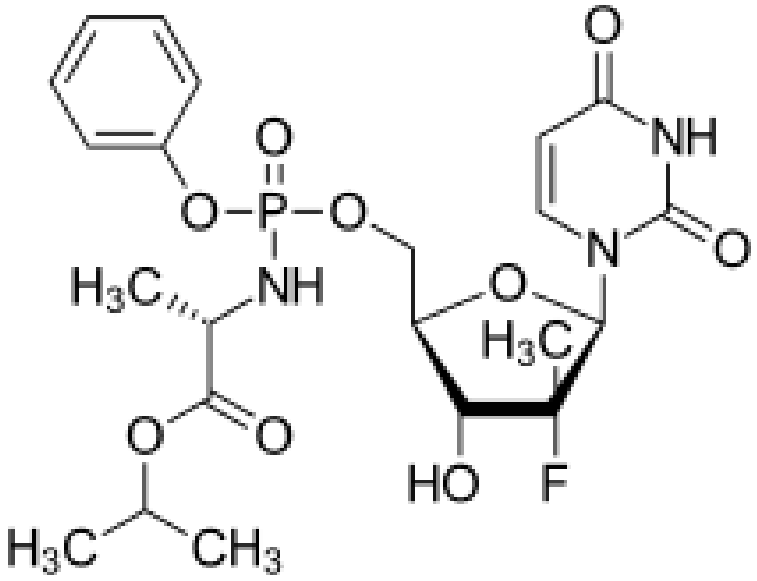
Sofosbuvir (Sovaldi)
(component of Epclusa,
Harvoni, Vosevi)

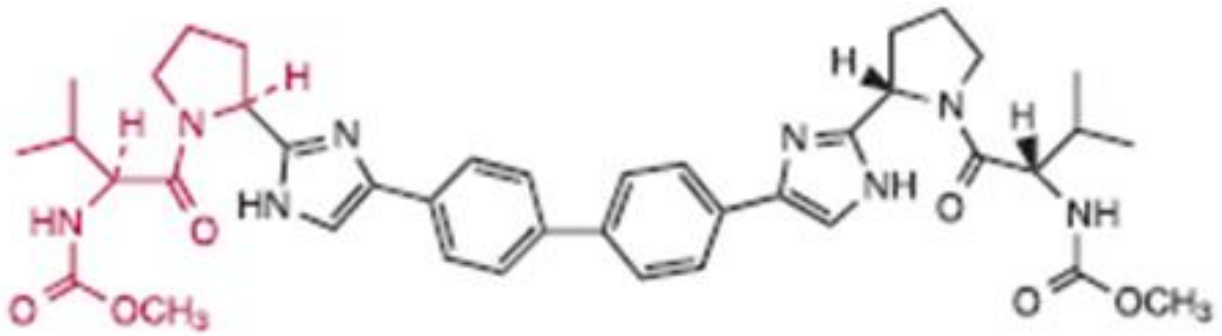


Dasabuvir
(component of Viekira Pak)

Figure 30.26 Inhibitors of HCV protease NS5A and NS5B.


Sobiovir® 400
Sofosbuvir
Each tablet contains: Sofosbuvir 400 mg
30 FC tablets
Dosage: as directed by physician.
Gluten Free.
Keep out of the reach of children.
BAKHTAR BIOSHIMI CO.
KERMANSHAH-IRAN


O
NH
O
N
O
O
P
O
O
NH
H3C
O
H3C
O
O
HO
F
H3C
CH3



Daclatasvir
(Daklinza)

Metabolism for Sofosbovir

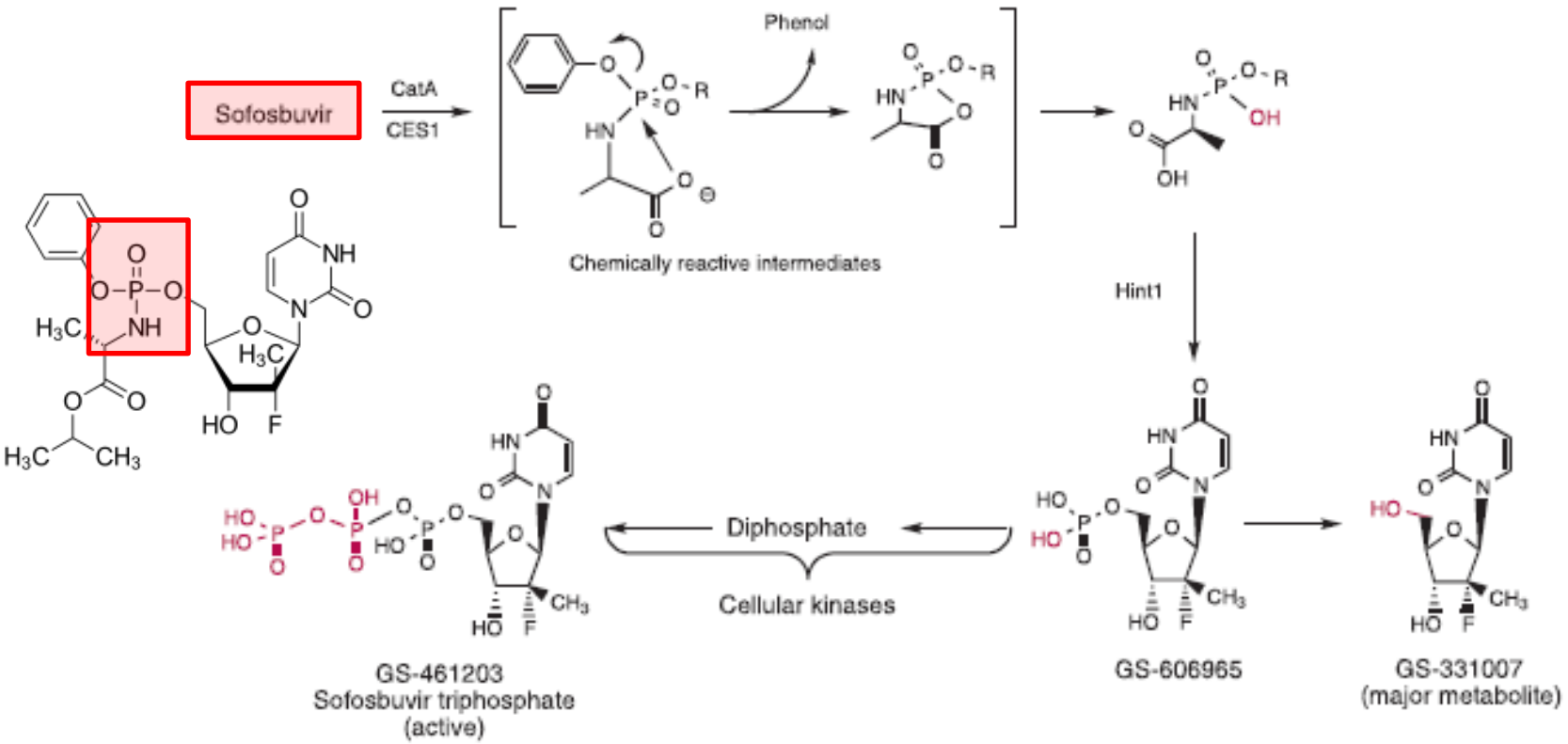


Figure 30.28 Metabolic activation of sofosbuvir to the active triphosphate form. This process is sequentially catalyzed by cathepsin A (CatA), carboxylesterase 1 (CESI) and histidine triad nucleotide-binding protein (Hint1). The intermediate constituent GS-606965 is inactivated by dephosphorylation, or activated to the triphosphate by celluar kinases.

RNA-Dependent RNA Polymerase (RdRp) Inhibitors as Anti-Covvid19

- Remdesivir
- Favipiravir
- Molnupiravir

RNA Dependent RNA Polymerase (RdRp)

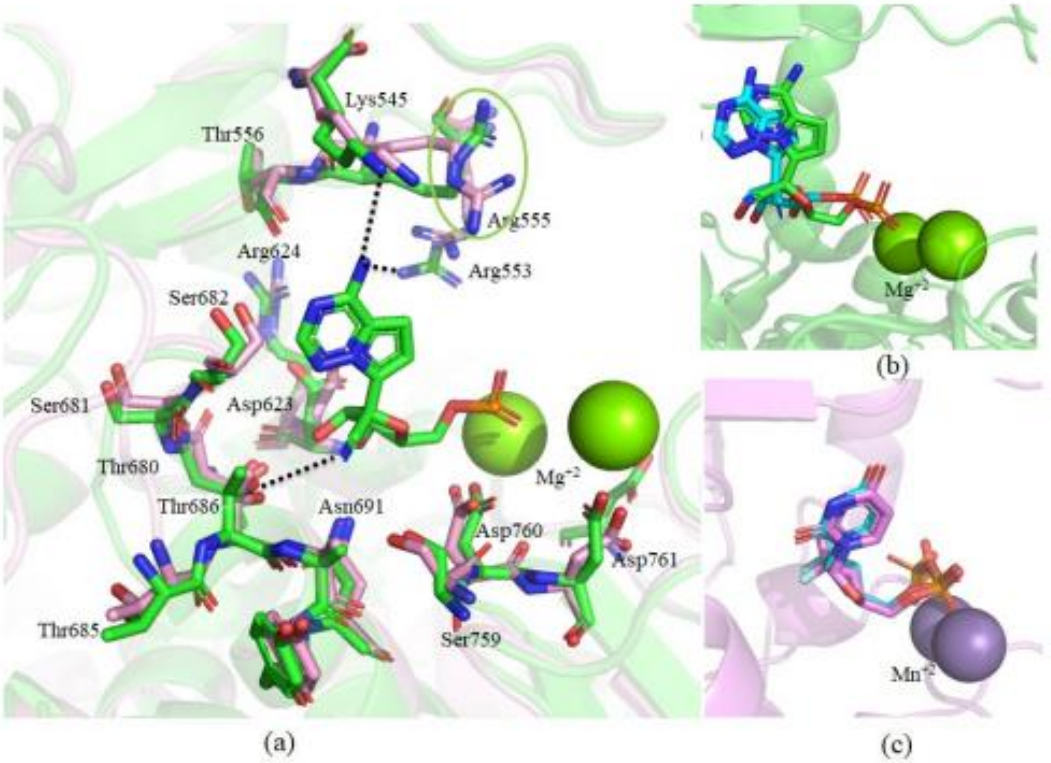
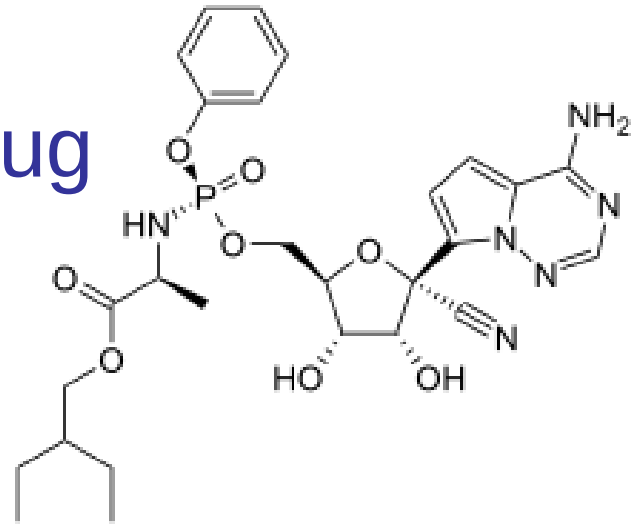


Fig. 1: (a) Superposition of the RdRp without metal ions (in pink, pdb id 6M71) onto the RdRp-Mg^{+2}-RMP complex (in green, pdb id 7BV2). The Arg555 moving away from the active site in the latter structure is marked by a green circle. The hydrogen-bonding interactions (dotted lines) of RMP with different residues of the RdRp protein are also depicted to explain its binding mode. The comparison of docked (in cyan) and experimental binding modes of (b) AMP (in green, pdb id 7BV2), and (c) SMP (in violet, pdb id 4WTG) are also shown.

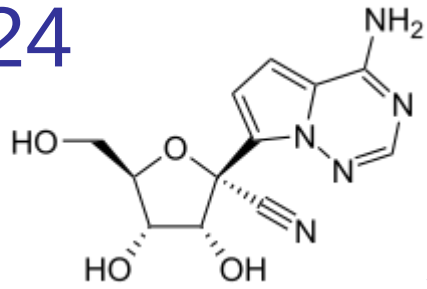
Remdesivir

- Ribonucleotide analogue: prodrug

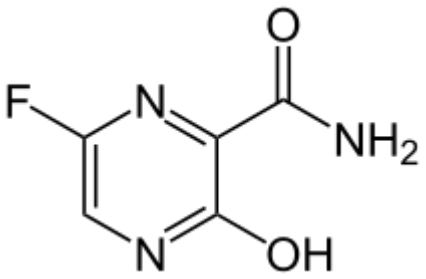


- MOA: interfere with viral RNA dependent RNA polymerase

✓active metabolite: tri-phosphate analogue of GS-441524

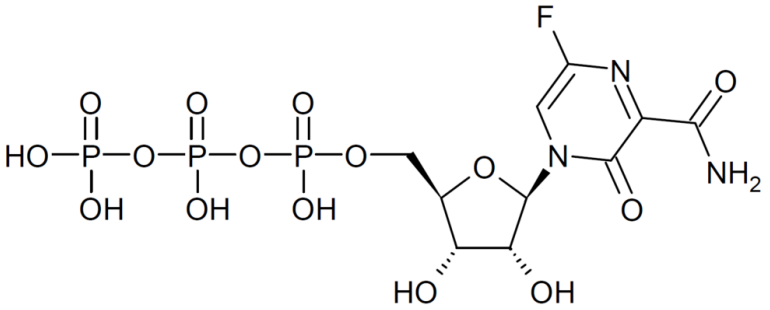


Favipiravir



- Chemistry:
- Since 2014 in Japan

- MOA: selective inhibition of viral RdRp
- Mimics ATP & GTP
- Against influenza



Molnupiravir

- MOA: promotes mutation in the replication of viral RNA
- SAR: prodrug: triphosphate analogue