Antiviral Agents:
Drugs Used to Treat Viral Infections

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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 in Viral Life Cycle: A DNA Virus

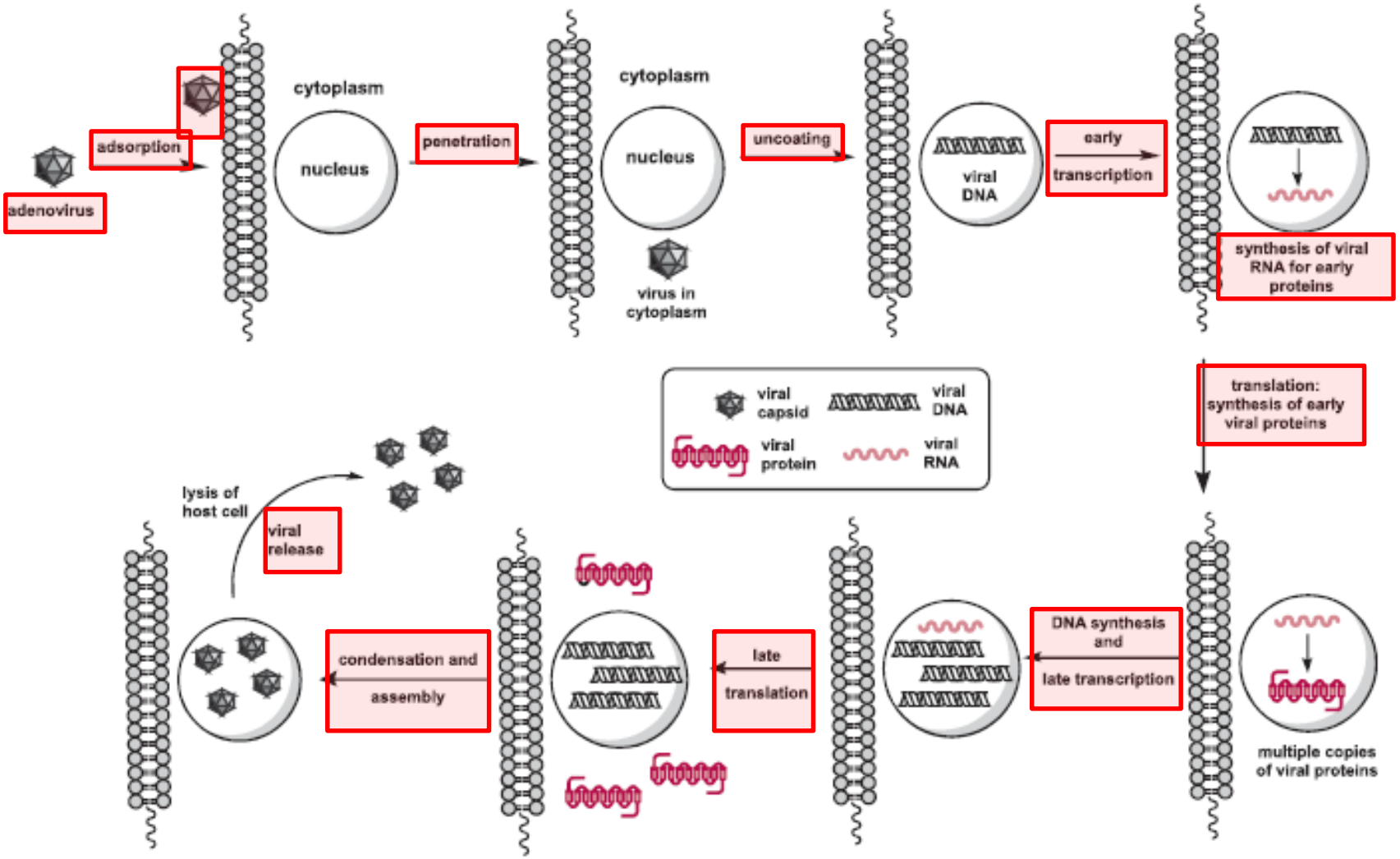


Figure 30.1 Steps involved in the viral life cycle.

Steps in Viral Life Cycle: A RNA Virus: HIV (RNA Virus) Replicative Cycle

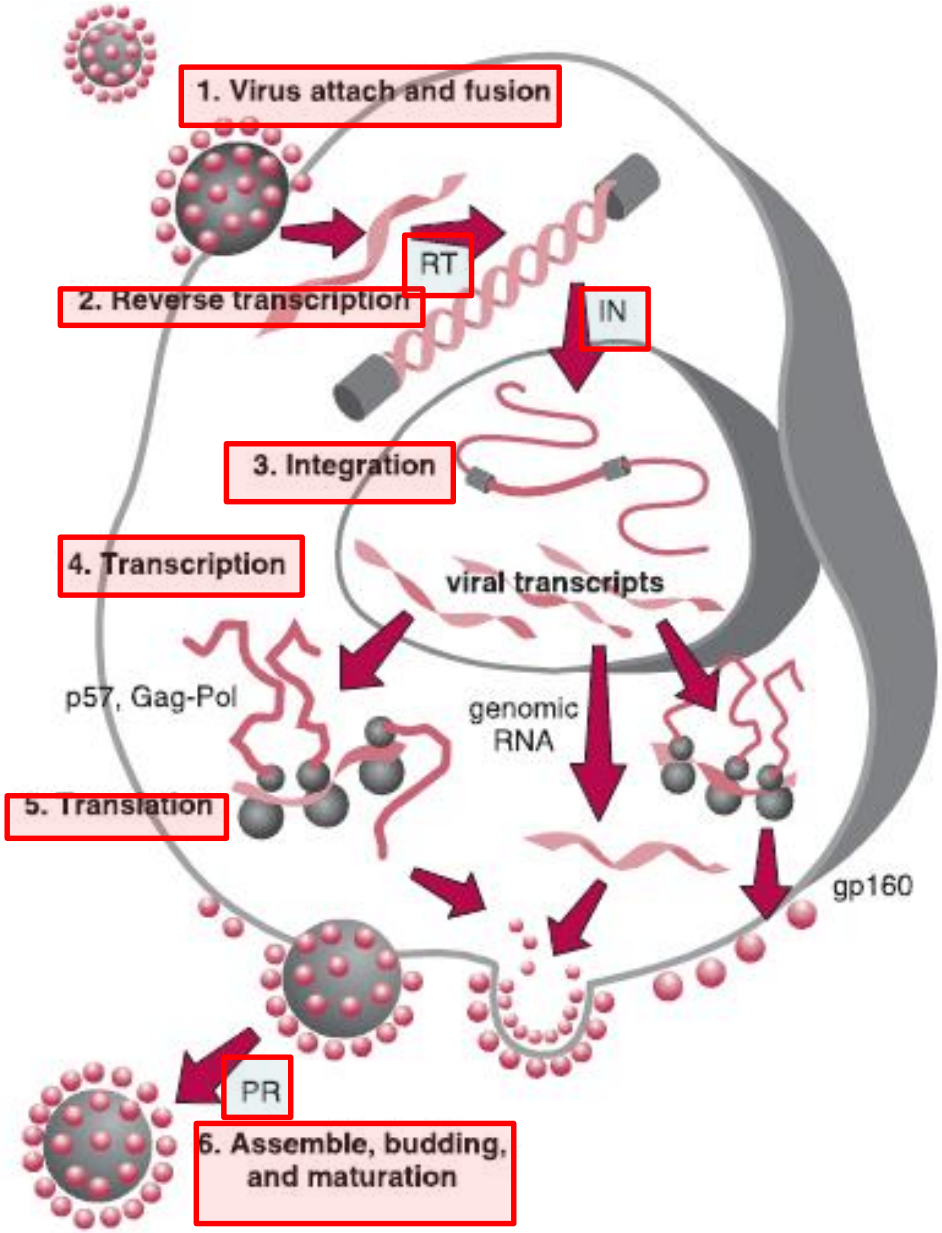


Figure 30.2 Replicative cycle of human immunodeficiency virus (HIV). (1) The virus gp120 protein binds to CD4 resulting in fusion of the viral envelope and the cellular membrane and the release of viral nucleocapsid into the cytoplasm. (2) The nucleocapsid is uncoated and viral RNA is reverse transcribed by reverse transcriptase (RT). (3) The resulting double-stranded proviral DNA migrates into the cell nucleus and is integrated into the cellular DNA by integrase (IN). (4) Proviral DNA is transcribed by the cellular RNA polymerase II. (5) The mRNAs are translated by the cellular polysomes. (6) Viral proteins and genomic RNA are transported to the cellular membrane and assemble. Immature virions are released. Polypeptide precursors are processed by the viral protease (PR) to produce mature viral particles. Used with permission from Tyler KL, Fields BN. *Fields Virology*. 2nd ed. New York: Raven Press; 1990:191-239.

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 & anti HBV & anti HCV

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: against coronavirus including COVID19

7- siRNA

8-Vaccines

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

- Chemistry:

✓ di-keto/acid or amide: 1,2 or 1,3-dicarbonyl: to provide chelate pyridine or pyrimidine scaffold possessing carbonylic substitute

✓ acts near acid catalytic residues in enzyme (integrase) at N-terminal

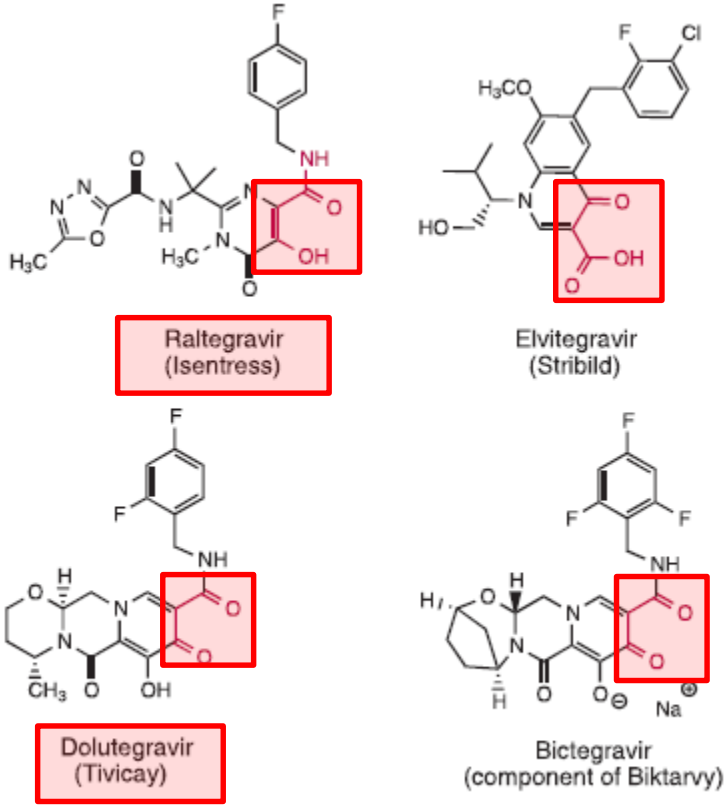
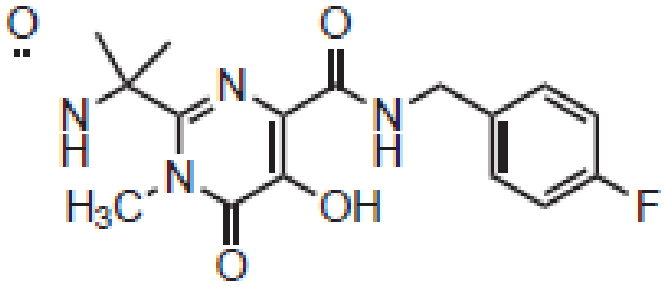


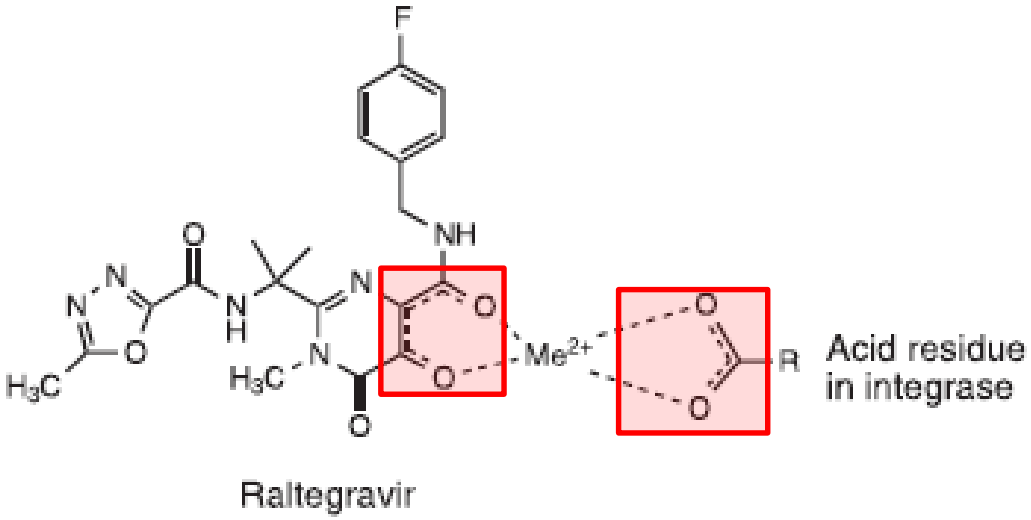
Figure 30.18 Integrase strand transfer inhibitors (INSTIs). Red highlight indicates the pharmacophore in INSTIs.

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

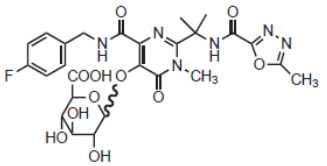


Figure 30.19 Chelation complex between raltegravir and integrase.

Antiretroviral (Anti-HIV) Agents:

4. Reverse Transcriptase (RT) Inhibitors
5. HIV Protease Inhibitors

Antiretroviral (Anti-HIV & Anti-HBV & Anti-HCV) 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

4a

ANTIRETROVIRAL AGENTS—NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

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

Adefovir

4b

ANTIRETROVIRAL AGENTS—NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

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

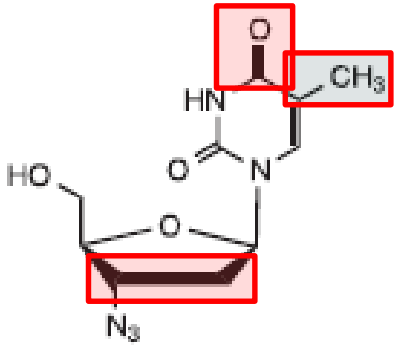
Antiretroviral (Anti-HIV & Anti-HBV & Anti-HCV) Agents:

4- Reverse Transcriptase Inhibitors (RTIs):

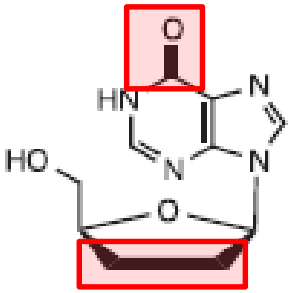
4a- Nucleoside RTIs (NRTIs)

4b- Non-Nucleoside RTIs (NNRTIs)

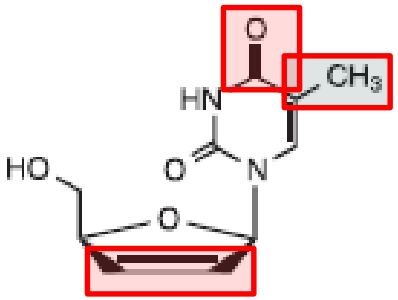
4a- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)



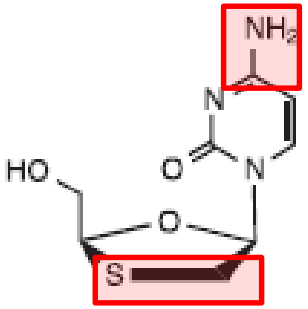
Zidovudine(AZT, ZDV)
(Retrovir)



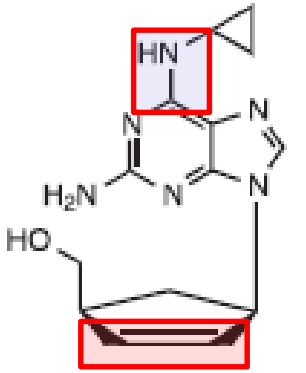
Didanosine(ddI)
(Videx)



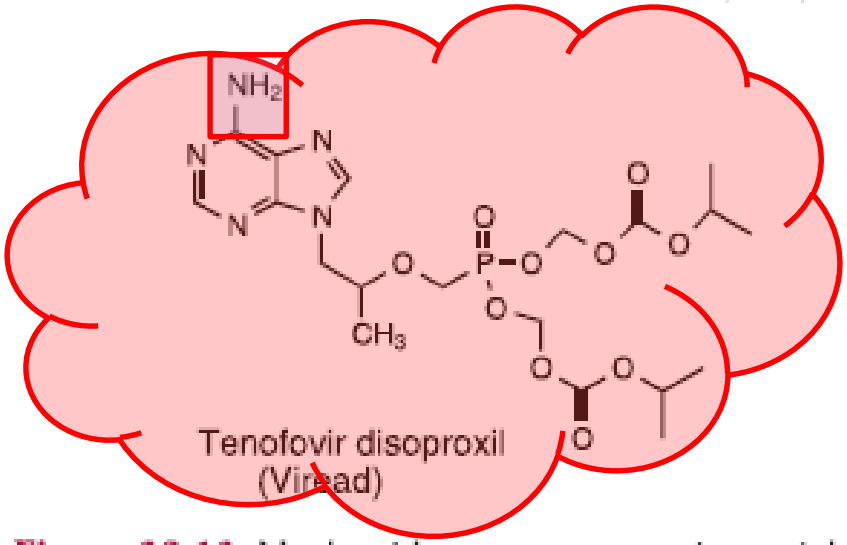
Stavudine
(2',3'-Dideoxy-2',3'-dide-hydrothymidine, D4T)
(Zerit)



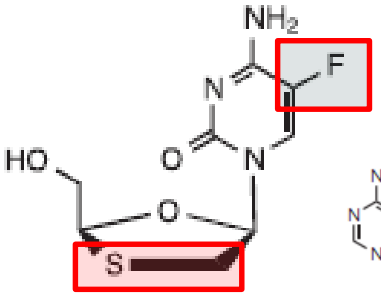
Lamivudine
(2'-Deoxy-3'-thiacytidine, 3TC) (Epivir)



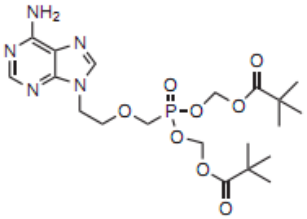
Abacavir (ABC)
(Ziagen)



Tenofovir disoproxil
(Viread)



Emtricitabine
(Emtriva)



Adefovir dipivoxil

Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

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

- SAR: Chemistry: purine & pyrimidine analogues

+ ribose mimicking portion:

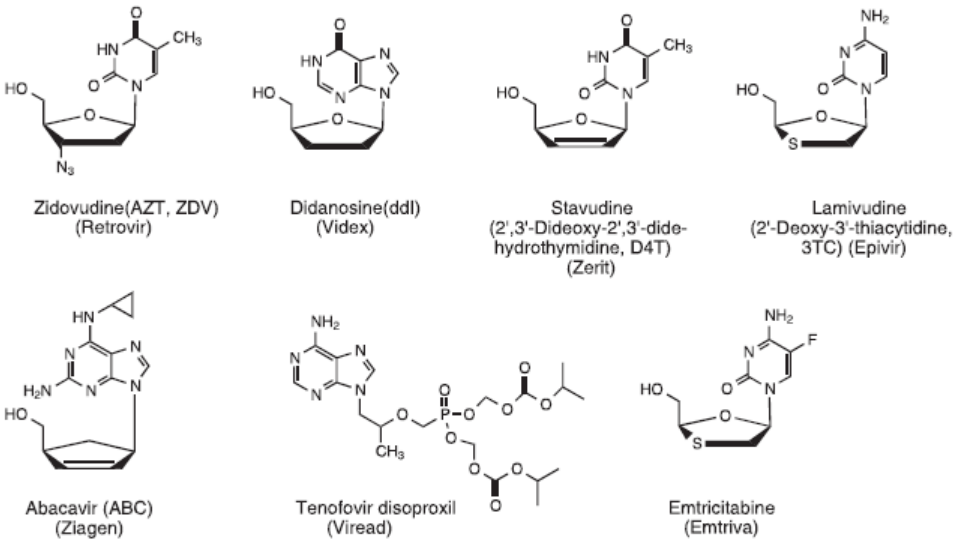
✓ removal of 2’ & 3’-hydroxy groups on ribosyl group:

dideoxy-adenosine; dideoxy-cytidine

✓ removal of 2’&3’-hydroxy & di-hydrogen of C2’-C3’: didehydro-dideoxy-thymidine

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

or substitution at C3’: by azide (-N_3)



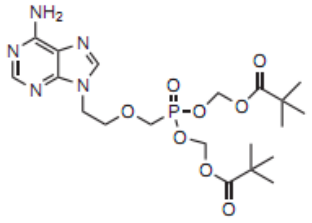


Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

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

- MOA: bio-activation through phosphorylation by kinase:

incorporation into the viral DNA: chain terminating blockade

due to lack of 3'-hydroxy needed for DNA propagation:

preventing 3'-5'-phospho-diester bonding

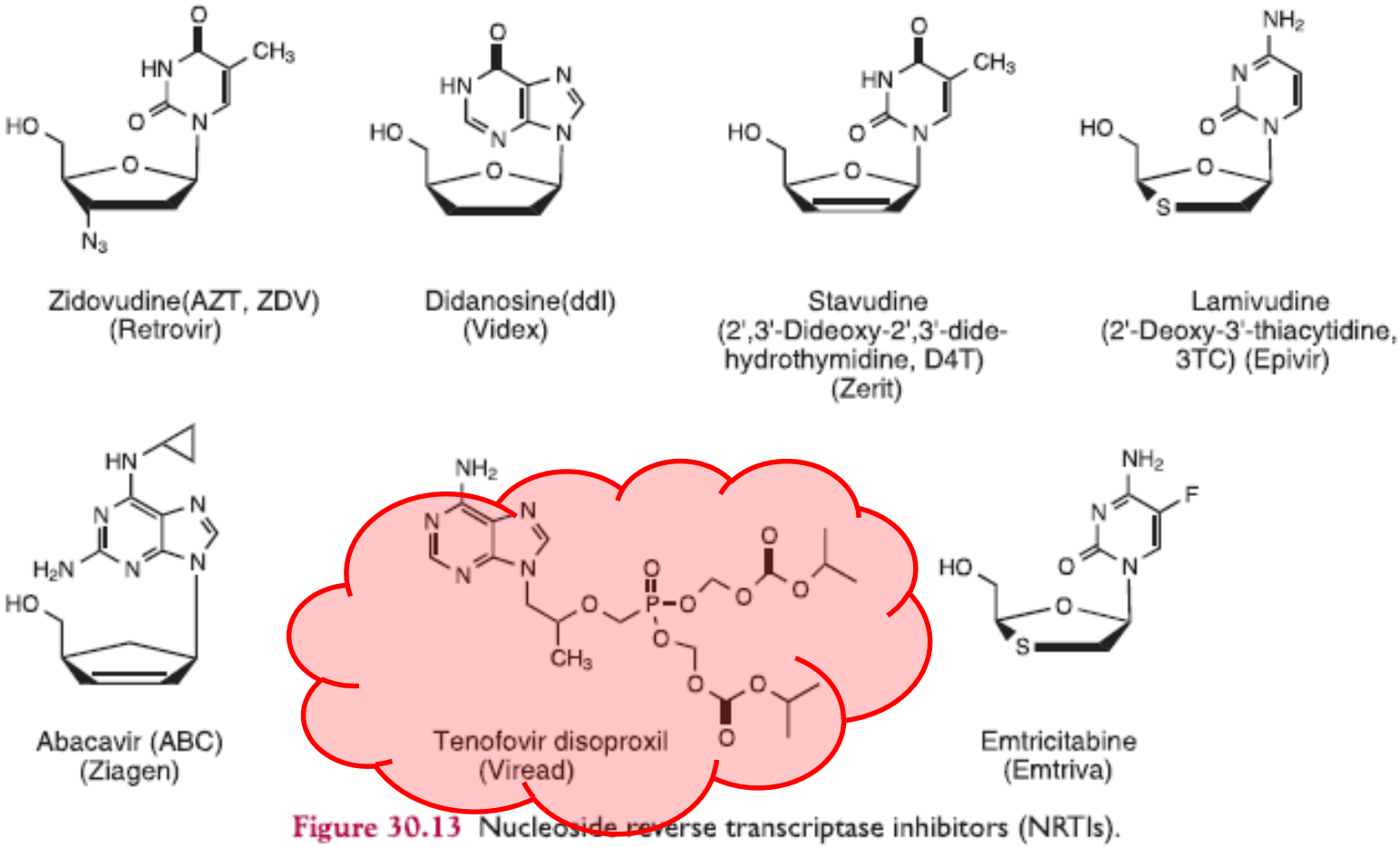


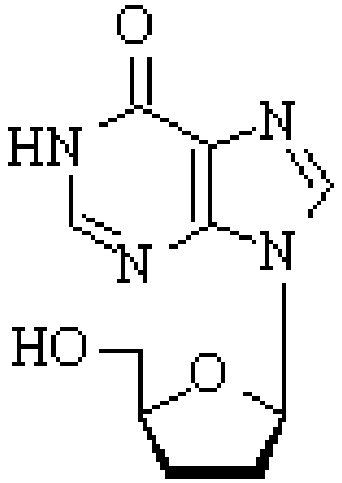
Figure 30.13 Nucleoside reverse transcriptase inhibitors (NRTIs).

4a-NRTI: Didanosine (ddI)

- Purine analogue: dideoxy-inosine analogue
- Prodrug:

✓ active metabolite is dideoxy-adenosine triphosphate: ddATP

✓ Competitive inhibitor



- MOA:

✓ incorporates to developing viral DNA:

✓ prevents 3’-5’-phospho-diester bonding

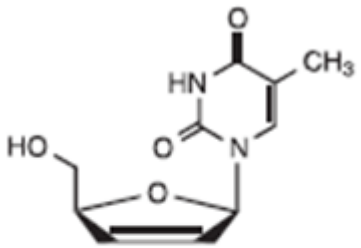
✓ results in termination of chain elongation: due to …

✓ virustatic on retroviruses

4a-NRTI: Stavudine (D4T)

- Pyrimidine analogue
- 2’,3’-didehydro-dideoxyThymidine: D4T

- In monotherapy
- In progress steps of HIV



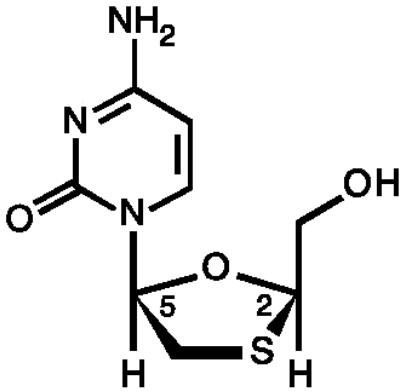
Stavudine
(2',3'-Dideoxy-2',3'-dide-
hydrothymidine, D4T)
(Zerit)

4a-NRTI: Lamivudine (3TC)

- Pyrimidine analogue: ddC analogue
- 2’-deoxy-3’-ThiaCytidine= 3TC
- SAR: …

✓ Bioisoterism

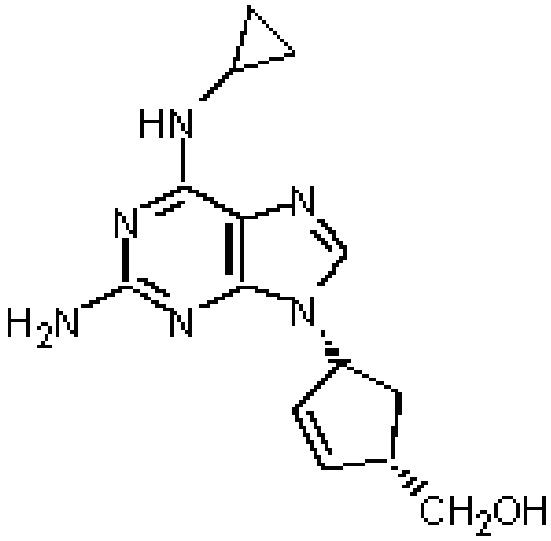
- Active metabolite: 5’-3-TC- triphosphate



- Most in combination therapy
- against HIV & HBV
- Daily single dose
- MOA: competitive inh. of RT: virustatic on retroviruses

4a-NRTI: Abacavir (Ziagen)

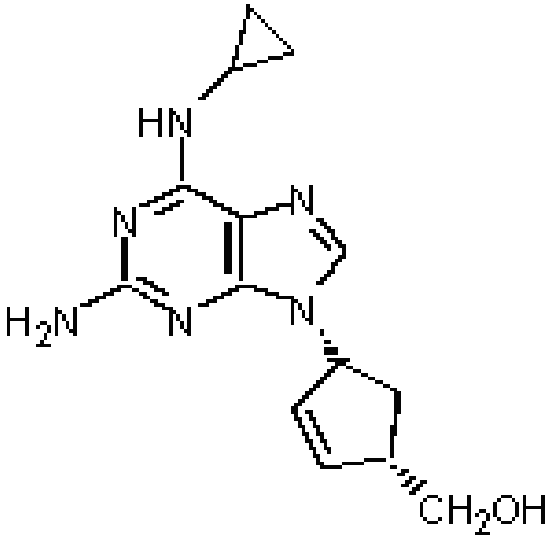
- Purine analogue
- ABaCavir= ABC
- In combination therapy against HIV

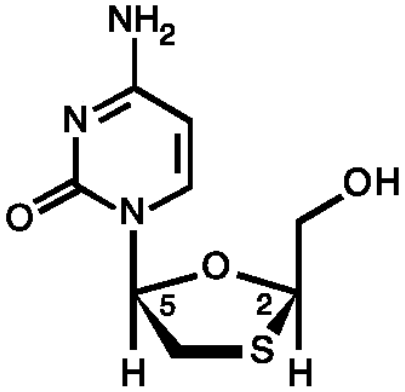


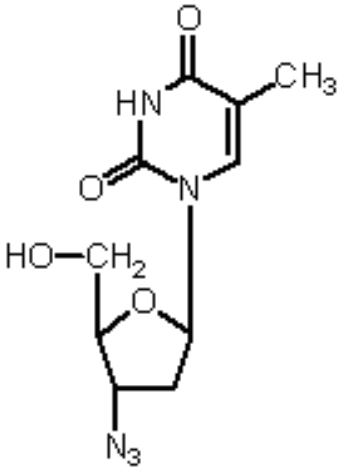
4a- NRTI: TRIZIR

- Novel combined NRTIs:

- 300mg ABC + 150 mg 3TC + 300mg ZDV







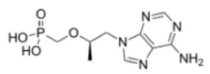
4a-NRTI: Tenofovir

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

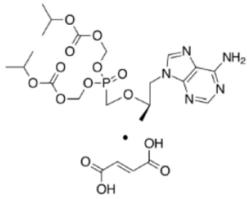
✓ produced initially by plasma esterase then by kinase:

✓ competes with dATP

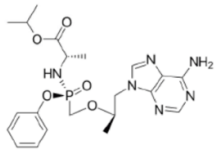
TENOFOVIR



TENOFOVIR DISOPROXIL FUMARATE (TDF)



TENOFOVIR ALAFENAMIDE (TAF)



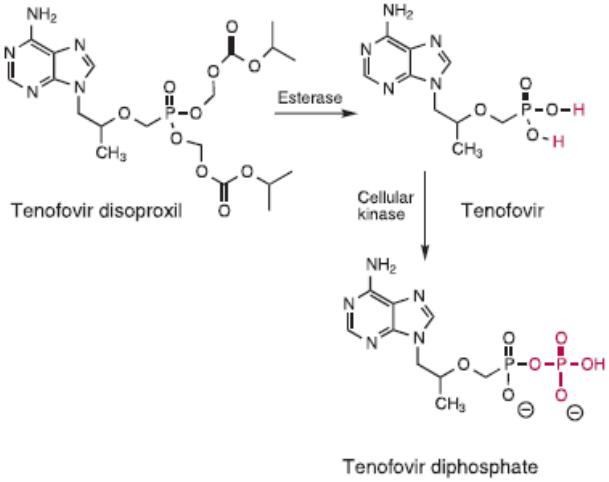


Figure 30.14 Metabolic activation of tenofir disoproxil.

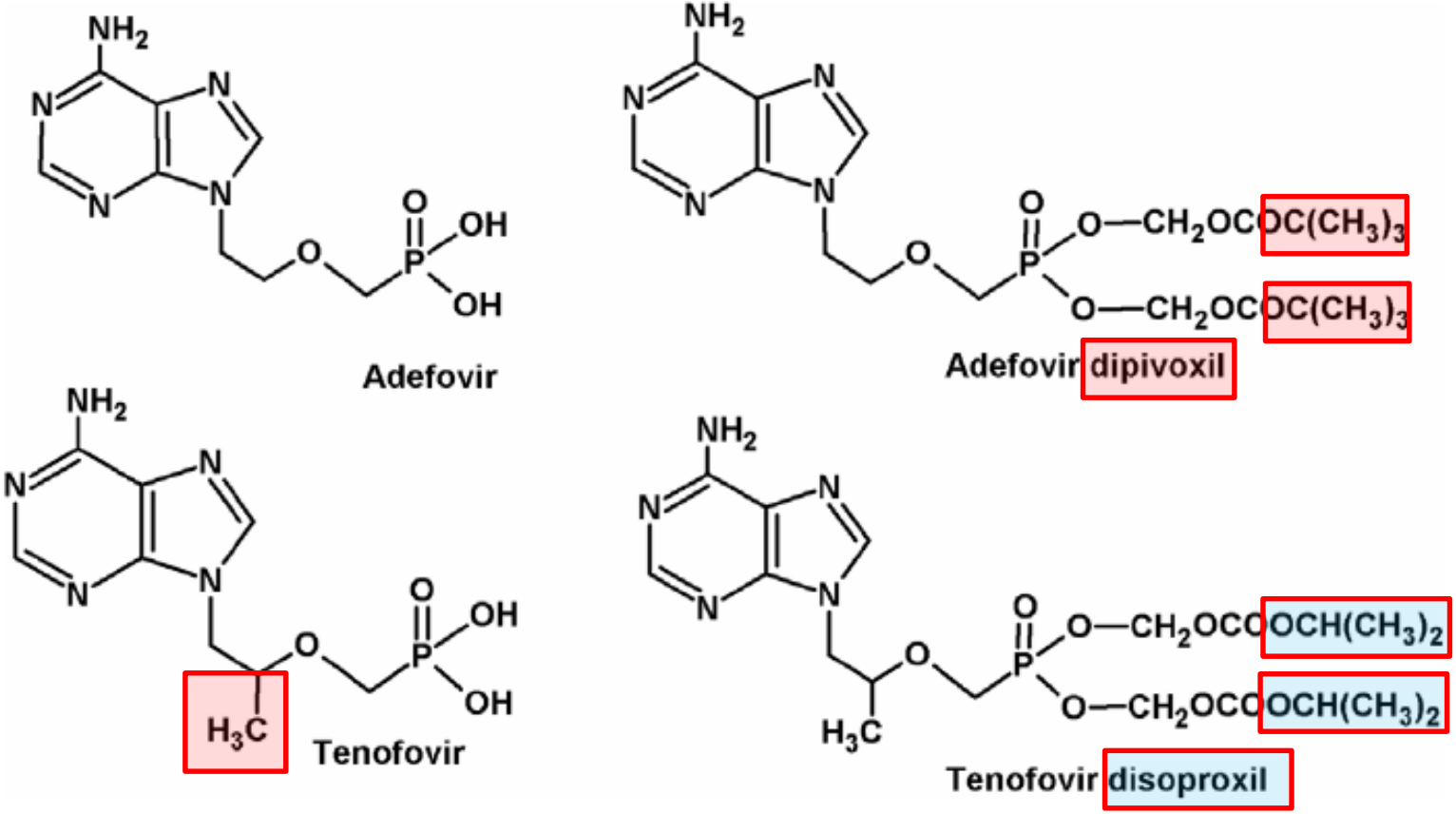
- MOA: reverse transcriptase inhibitor: anti-HIV

✓ also might compete with deoxy-adenosine triphosphate (dATP)

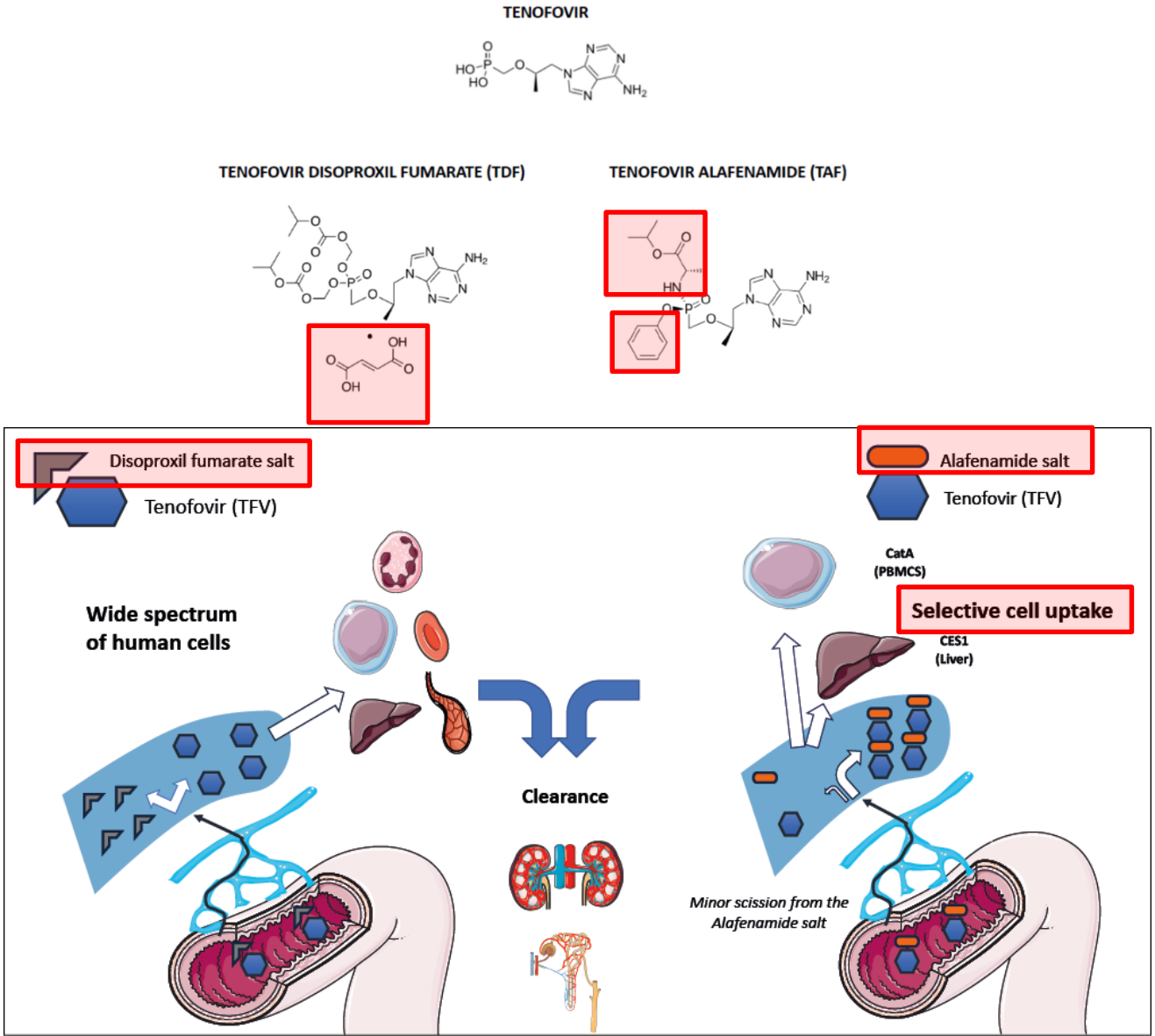
✓ incorporate into viral DNA

✓ & results in premature termination

Compare Adefovir to Tenofovir



Tenofovir as Two Types of Prodrugs: TDF & TAF



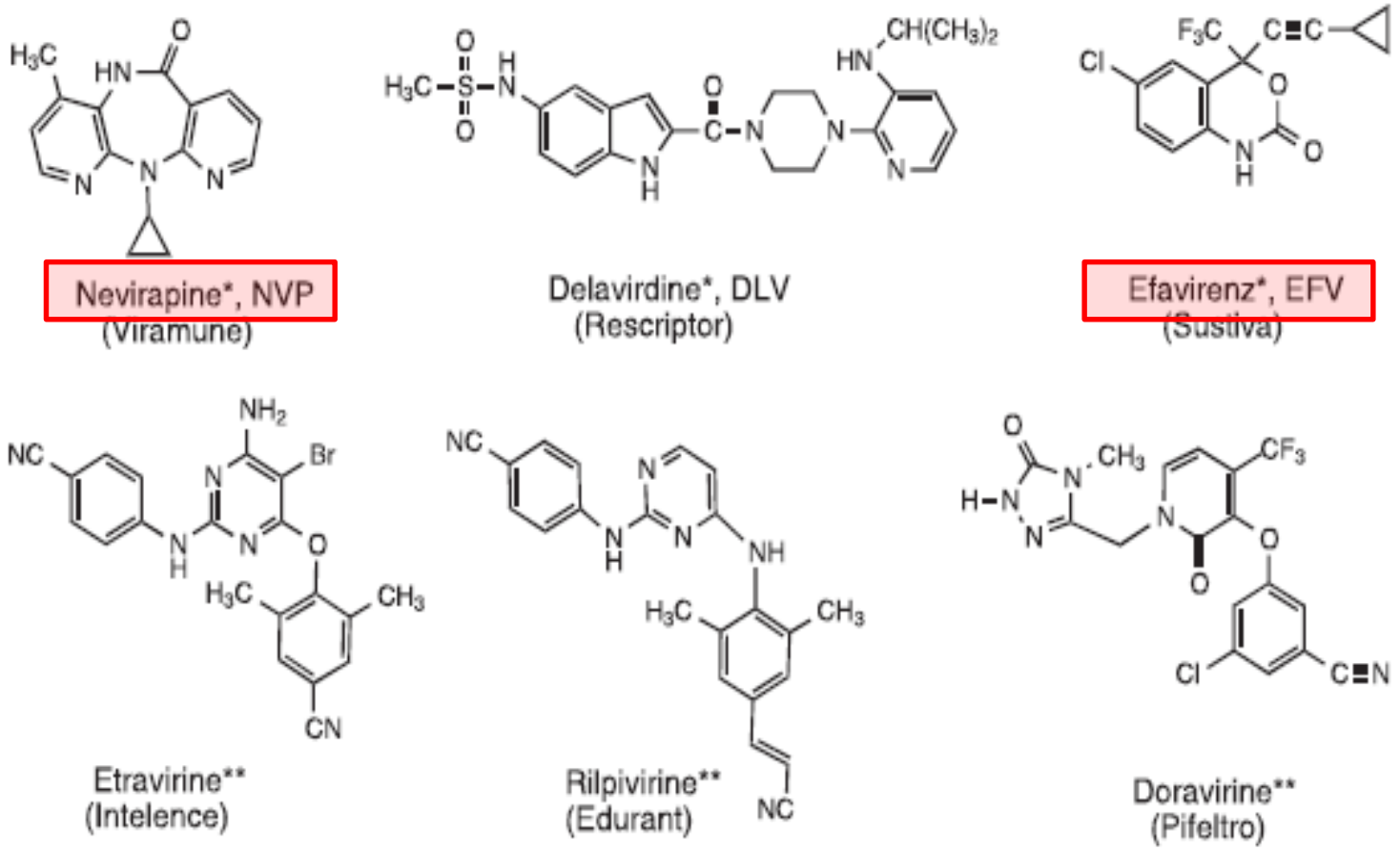
Antiretroviral (Anti-HIV & Anti-HBV & Anti-HCV) Agents:

4- Reverse Transcriptase Inhibitors (RTIs):

4a- Nucleoside RTIs (NRTIs)

4b- Non-Nucleoside RTIs (NNRTIs)

4b- Non-Nucleoside RTI: SAR



*First-generation NNRTIs **Second-generation NNRTIs

Figure 30.15 Nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Metabolism of Nevirapine

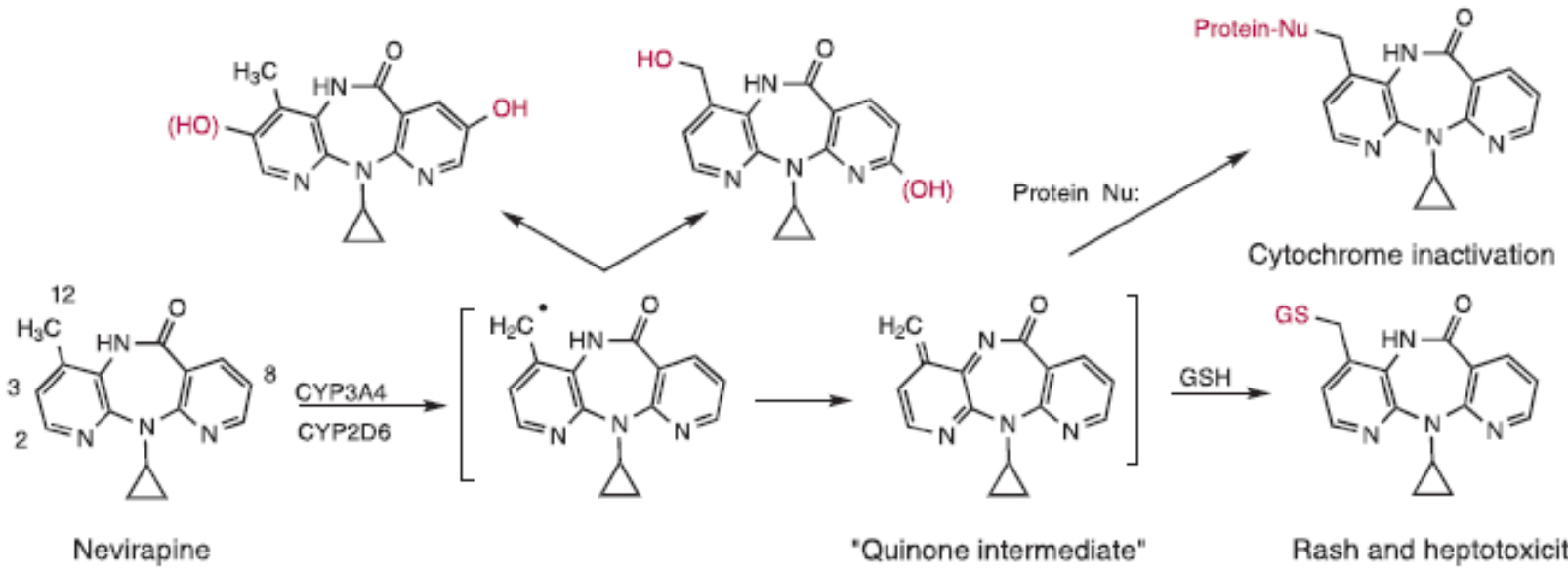


Figure 30.16 Metabolic oxidation of nevirapine by CYP3A4 leading to C2 or C12 hydroxylation or by CYP2D6 leading to C3 or C8 hydroxylation and an explanation for side effects associated with a quinone intermediate.

5- Protease Inhibitors (PIs):

- ✓anti-HIV
- ✓anti HBV & anti-HCV

CHAPTER 30

Drugs Used to Treat Viral Infections

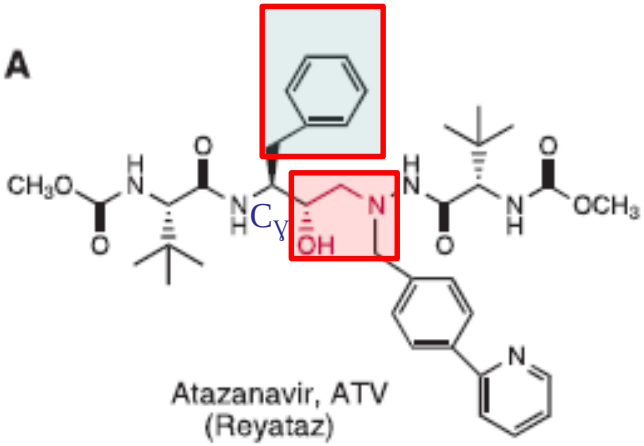
Patrick M. Woster

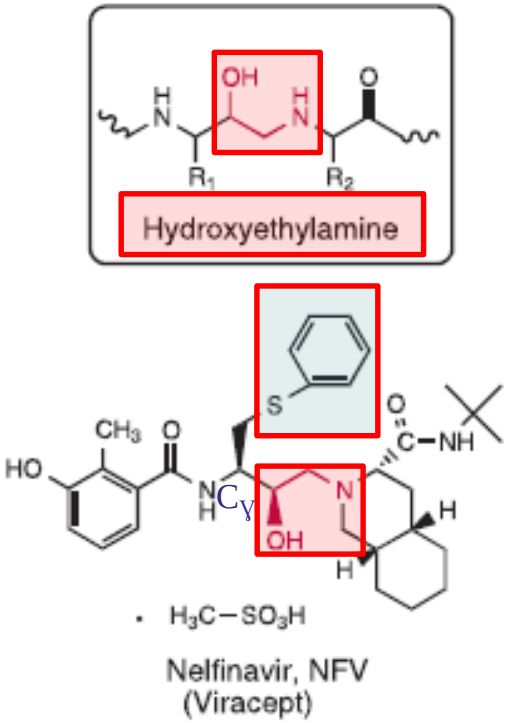
HIV PROTEASE INHIBITORS

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

5- HIV PrIs: SAR

ß-Hydroxy ethyl
ß-Hydroxy ethyl amine





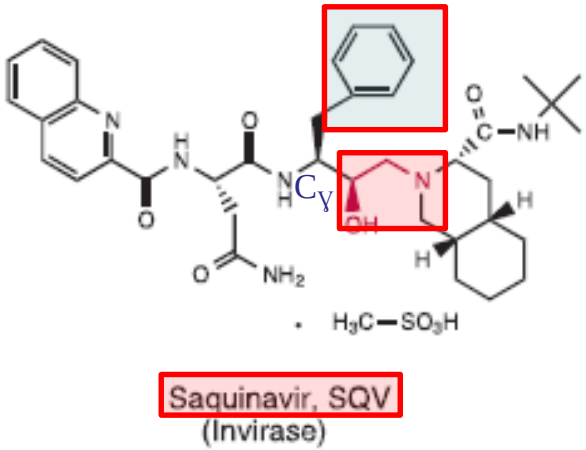


Figure 30.23 Structures of HIV protease inhibitors that are used clinically.

5- HIV PrIs- Continued

ß-Hydroxy ethyl
ß-Hydroxy ethyl amine

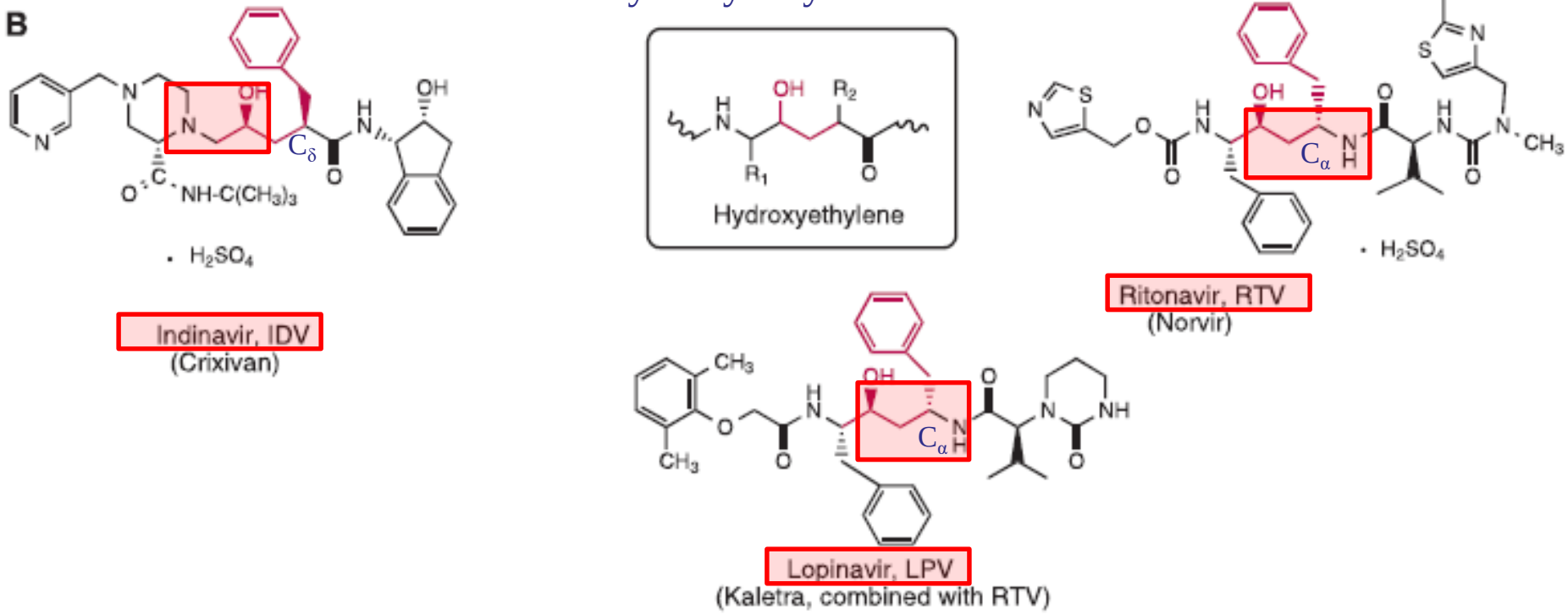
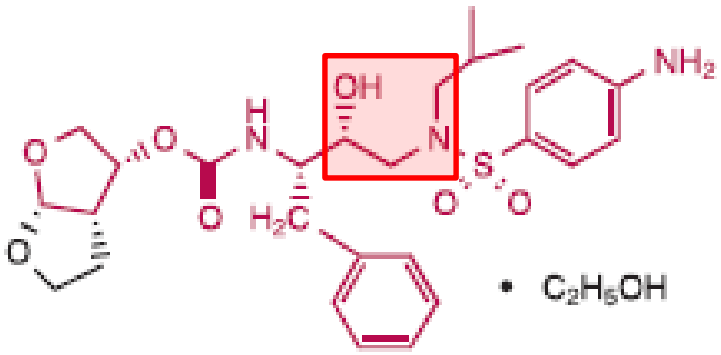


Figure 30.23 Structures of HIV protease inhibitors that are used clinically.

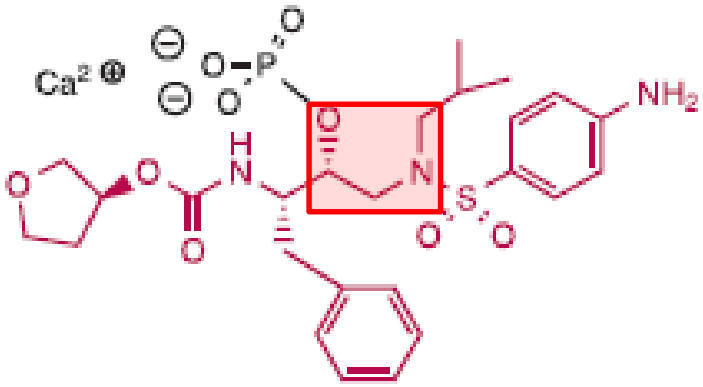
5- HIV PrIs- Continued

ß-Hydroxy ethyl
ß-Hydroxy ethyl amine

C



Darunavir ethanolate
(Prezista)

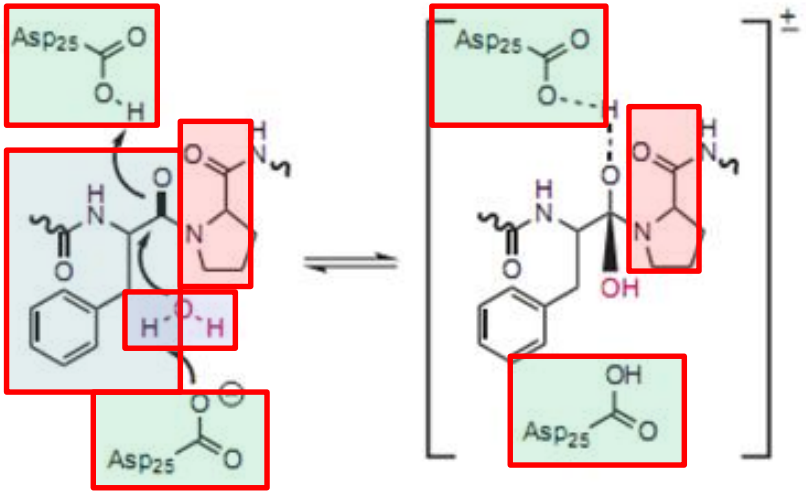


Fosamprenavir calcium, FOS-APV
(Lexiva)

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

HIV Protease as Aspartic 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-CH_2CH_2-

✓ HO-CH_2CH_2-NH_2

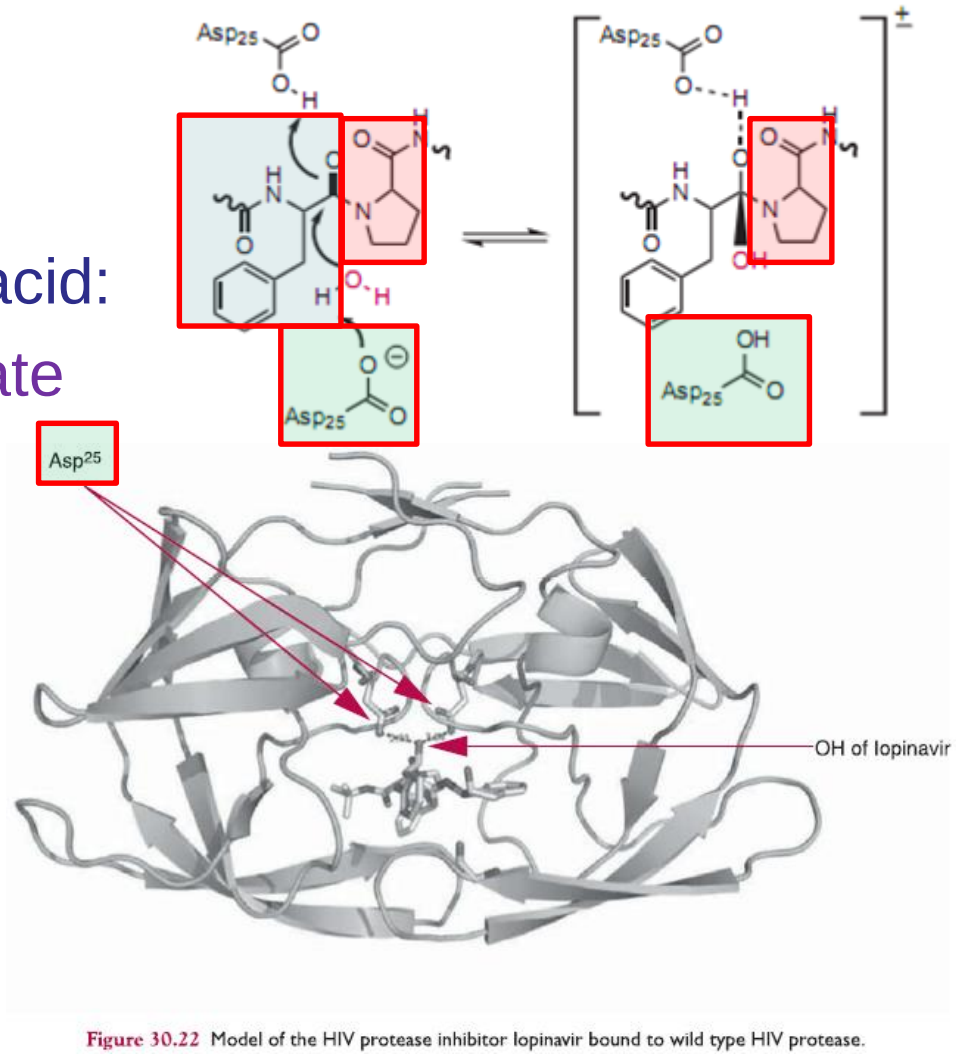


Figure 30.22 Model of the HIV protease inhibitor lopinavir bound to wild type HIV protease.

5- Protease Inhibitors (PrIs): SAR

- 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- or 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

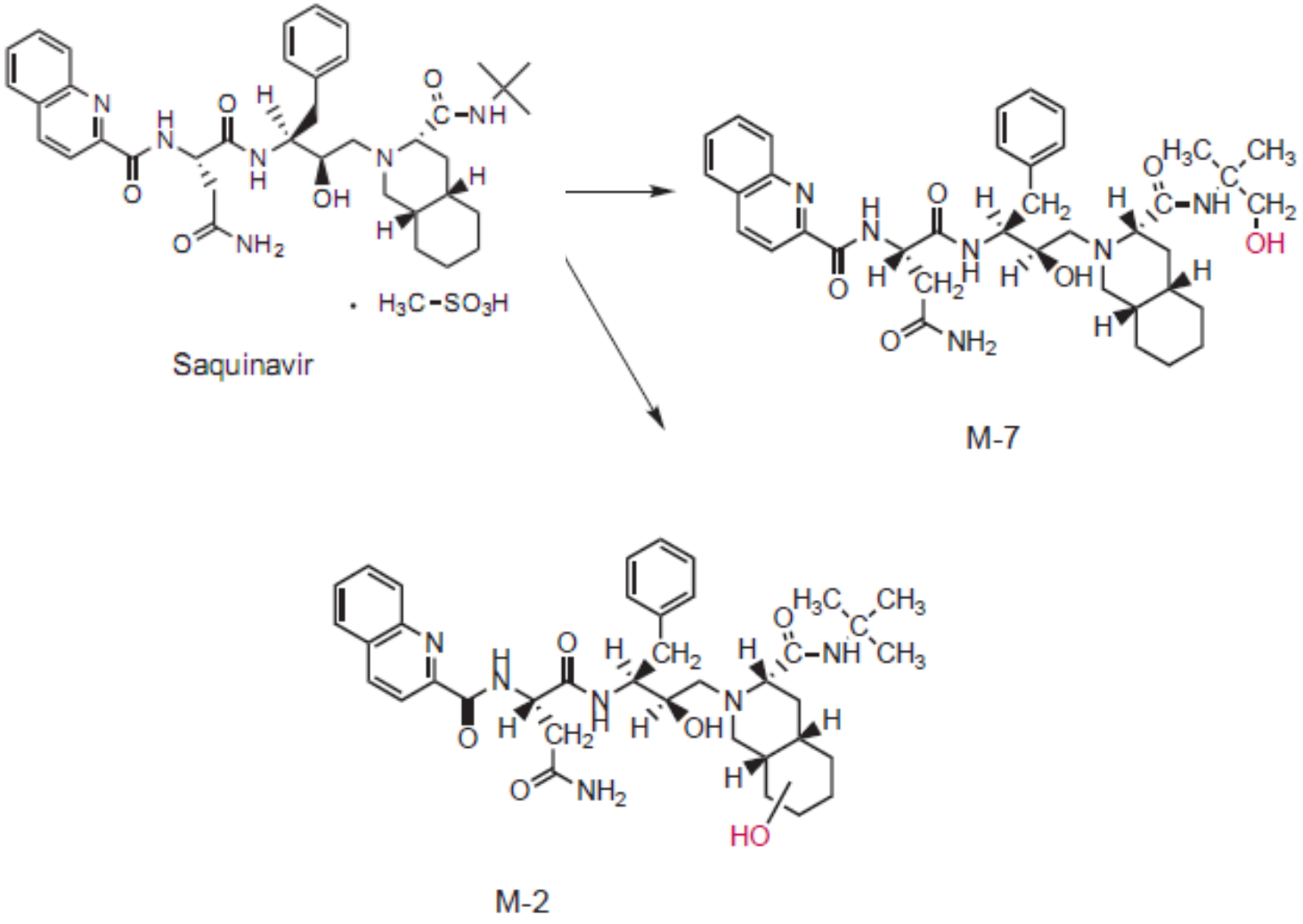


FIGURE 38.21 Major metabolic products from saquinavir.

Metabolism for Ritonavir

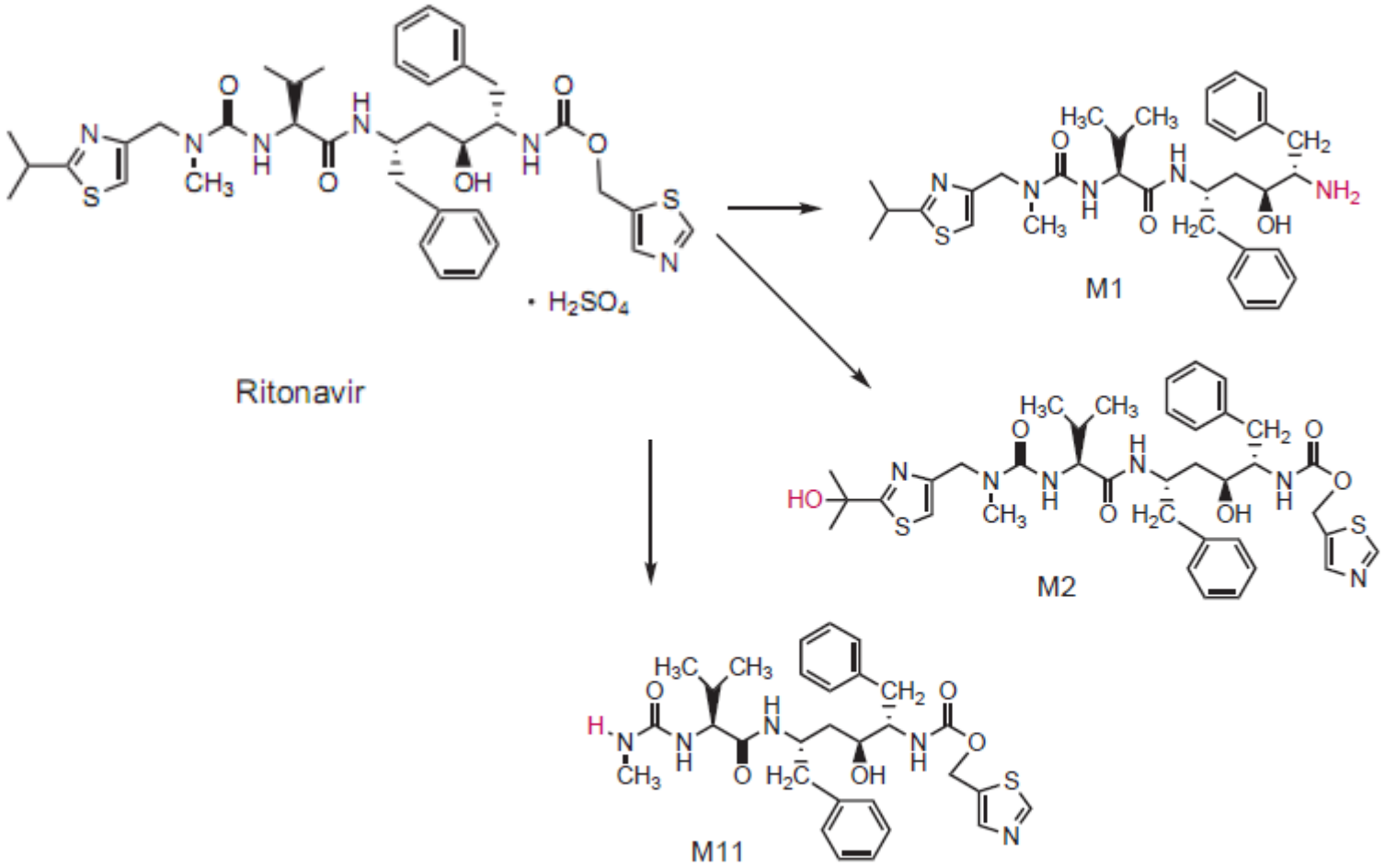
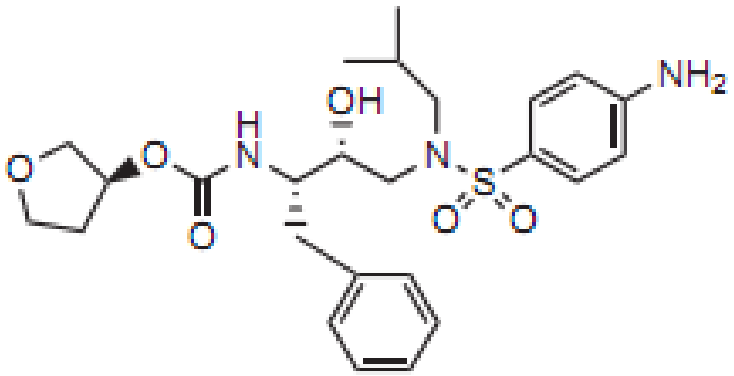
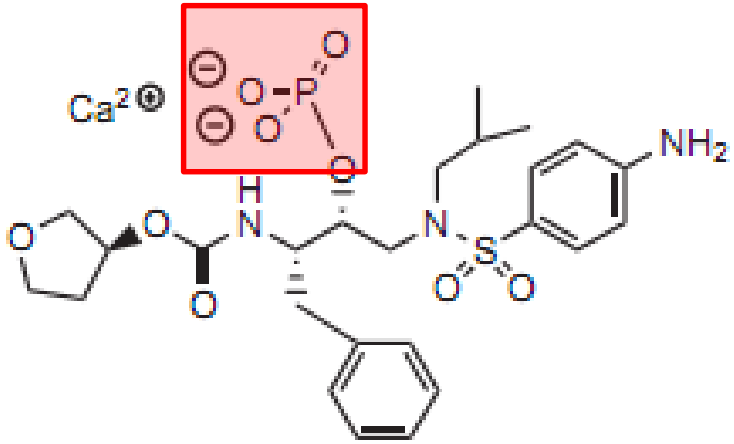


FIGURE 38.22 Major metabolic products from CYP3A4 metabolism of ritonavir.

5- PrI: Amprenavir & Fosamprenavir



Amprenavir



Fosamprenavir calcium

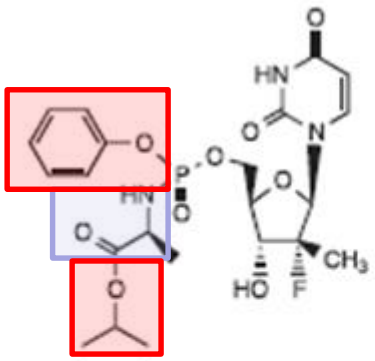
5- HCV Protease (NS5A & NS5B) Inhibitors: Sofosbuvir

- Consider phosphoramide group:

✓ phenyl to oxygen of phosphoramide

✓ Ala conjugated to nitrogen of phosphoramide

✓ isopropyl ester at carboxylate of Ala portion



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

Figure 30.26 Inhibitors of HCV protease NS5A and NS5B.

Metabolism for Sofosbovir

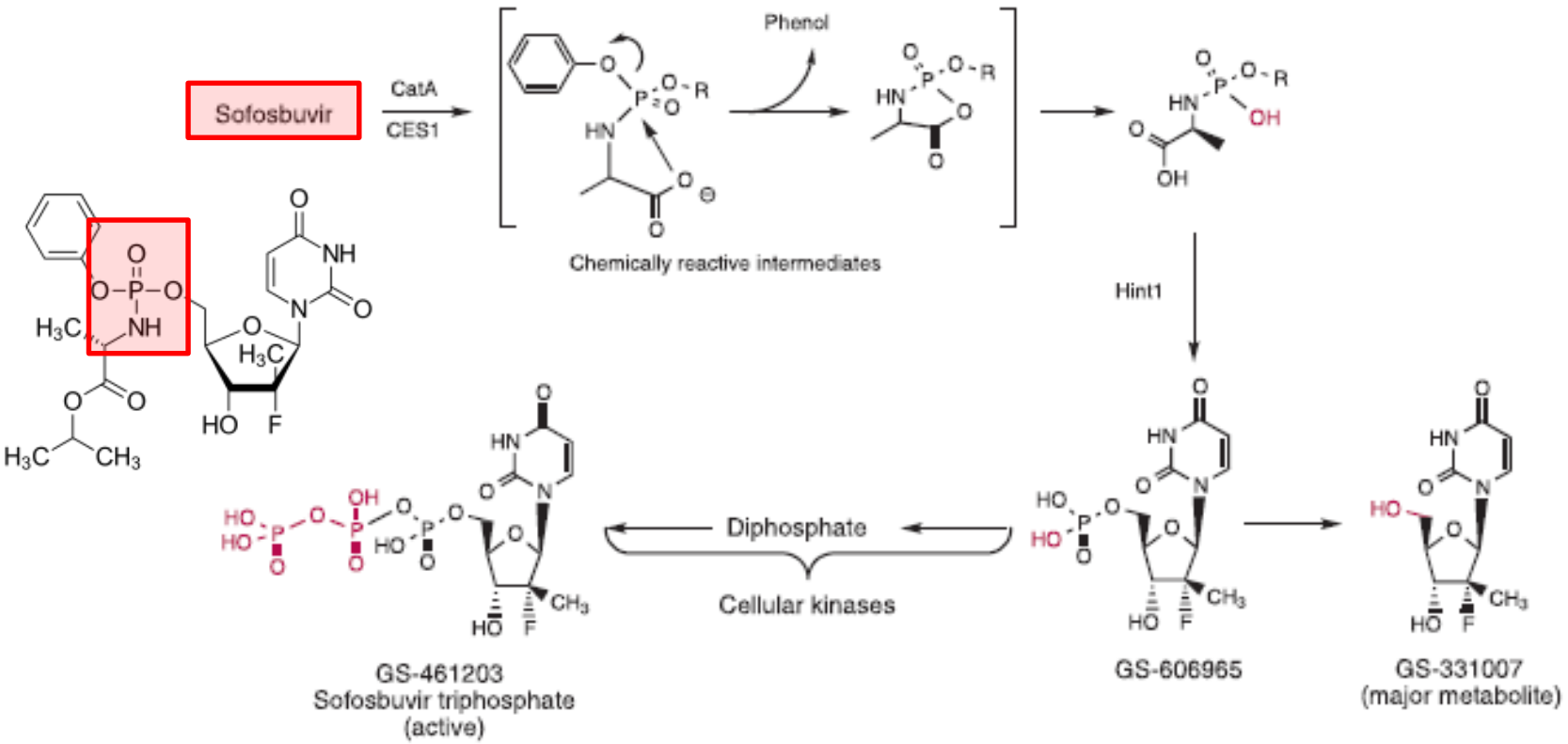
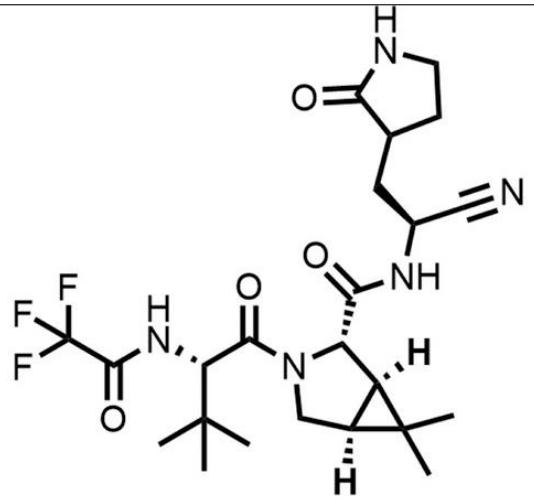


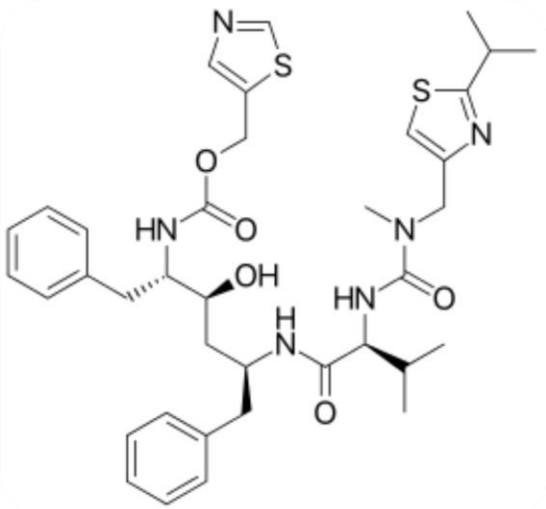
Figure 30.28 Metabolic activation of sofosbuvir to the active triphosphate form. This process is sequentially catalyzed by cathepsin A (CatA), carboxylesterase I (CESI) and histidine triad nucleotide-binding protein (Hint1). The intermediate constituent GS-606965 is inactivated by dephosphorylation,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

Paxlovid® against COVID19

- Includes two PrIs: nirmatrelavir + ritonavir



Nirmatrelvir



RNA-Dependent RNA Polymerase (RdRp) Inhibitors as Anti-COVID19

- ✓ Remdesivir
- ✓ Favipiravir
- ✓ Molnupiravir

RNA Dependent RNA Polymerase (RdRp)

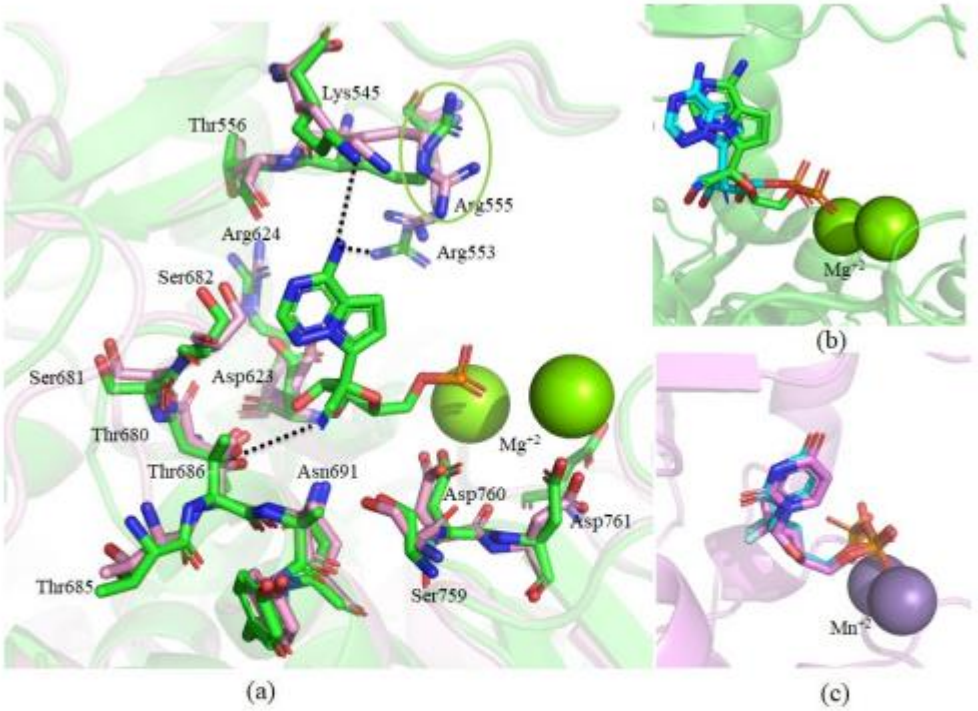
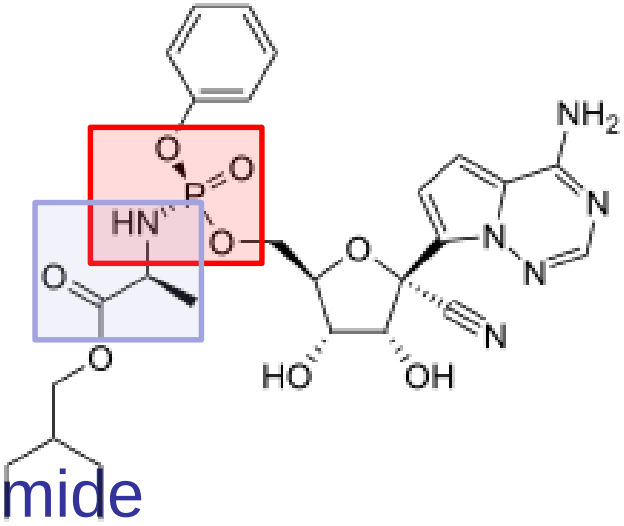


Fig. 1: (a) Superposition of the RdRp without metal ions (in pink, pdb id 6M71) onto the RdRp-Mg^{+2}-RMP complex (in green, pdb id 7BV2). The Arg555 moving away from the active site in the latter structure is marked by a green circle. The hydrogen-bonding interactions (dotted lines) of RMP with different 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.

6- RdRp Inhibitors: Remdesivir

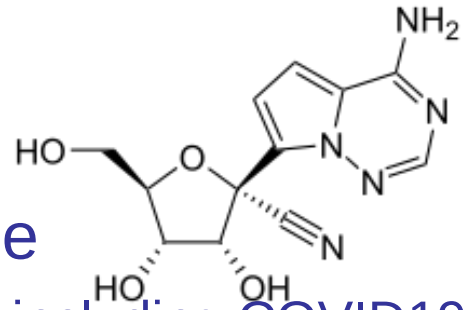


- SAR: chemistry:

✓ ribonucleotide analogue

✓ phosphoramide derivative

✓ Ala conjugation at nitrogen of phosphoramide



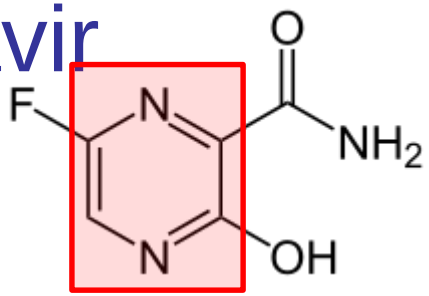
- MOA: interfere with viral RdRp

✓ Prodrug:

✓ final active metabolite: tri-phosphate analogue

- Against RNA viruses: HCV, Ebola virus and coronavirus including COVID19
- Dosage form: injection

6- RdRp Inhibitors: Favipiravir



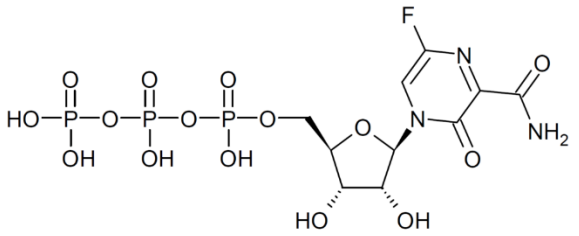
- SAR: chemistry:

✓ pyrazine ring mimicking pyrimidine at NA

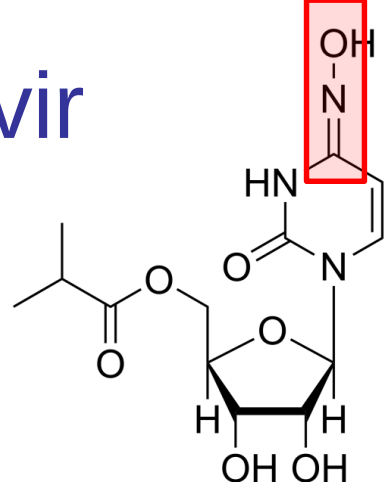
- MOA: selective inhibition of viral RdRp
- Prodrug:

✓ final active metabolite: tri-phosphate analogue: mimics ATP & GTP

- Against influenza and then COVID19



6- RdRp Inhibitors: Molnupiravir



- Chemistry & SAR:

✓ pyrimidine possessing oxime group mimicking pyrimidine at NA

- MOA: inhibition of viral RdRp
- Prodrug:

✓ active metabolite: triphosphate analogue

- Against coronavirus as RNA virus mostly applied against COVID19