Anti-Tubercular Agents
Anti-Mycobacterium Agents
Anti-Tuberculosis (TB) Agents

SECTION 7
Drugs Impacting Infectious and Neoplastic Disease Processes

CHAPTER 29

Drugs Used to Treat Bacterial Infections

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Drugs covered in this chapter—Continued

Special purpose antibiotics
- Bacitracin
- Chloramphenicol
- Dalbavancin
- Daptomycin
- Linezolid
- Mupirocin
- Oritavancin
- Polymyxin B
- Quinupristin/dalfopristin
- Retapamulin
- Tedizolid phosphate
- Telavancin
- Vancomycin

Antitubercular drugs
- Capreomycin
- Cycloserine
- Ethambutol
- Ethionamide
- Isoniazid
- Kanamycin
- *Para*-aminobenzoic acid
- Pyrazinamide
- Rifabutin
- Rifampin
- Rifapentine
- Streptomycin

Nontuberculous mycobacteria therapeutics
- Clofazimine
- Dapsone
- Thalidomide

[a]Drugs listed include those available inside and outside of the United States; drugs available outside of the United States are shown in italics.

Chemical Classification for Anti-Mycobacterium Agents

- Amide or hydrazide: isoniazid (INH);ethionamide; pyrazinamide
- Di-amino-alkanol: ethylene di-amine: ethambutol
- Macrocyclic lactam: Rifamycin: rifampin, rifabutin, rifapentine
- Amino-glycoside: streptomycin; kanamycin
- Salicylic acid: PASA
- Cyclic peptide: cycloserine; capreomycin
- Sulfones: dapson; sulfoxone sodium
- Phenazine: clofazimine
- Quinoline: bedaquiline
- Fluoroquinolones: lev/ofloxacin; moxifloxacin

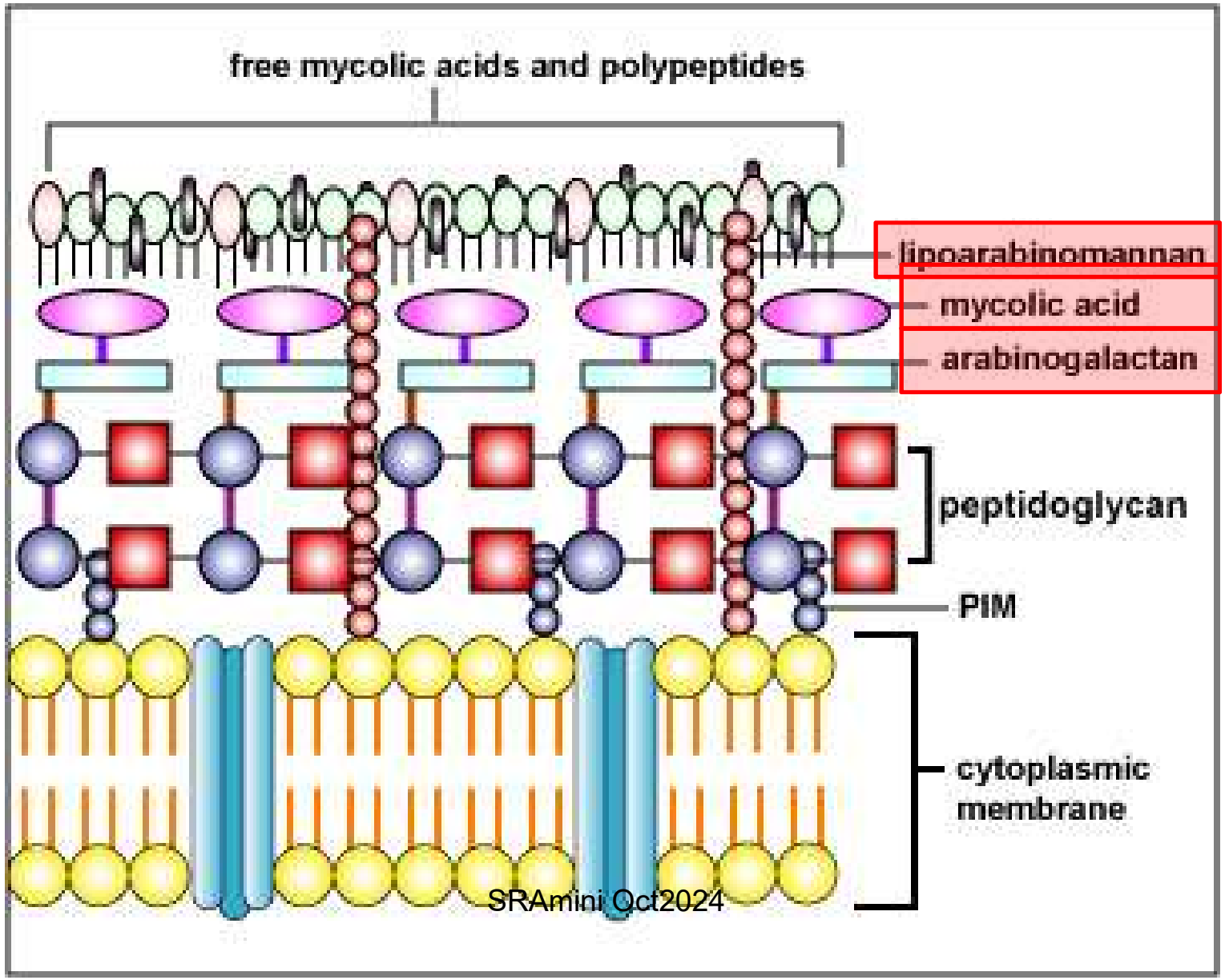
Characteristics of Mycobacteria

- Acid fast bacilli
- Slow growing
- Difficult to stain
- High lipid content in the cell wall
- Unique cell envelope
- Major types of mycobacterium:

✓ *mycobacterium tuberculosis*

✓ *mycobacterium leprae*

Mycobacterium Cell Wall



Mycobacterium Cell Wall

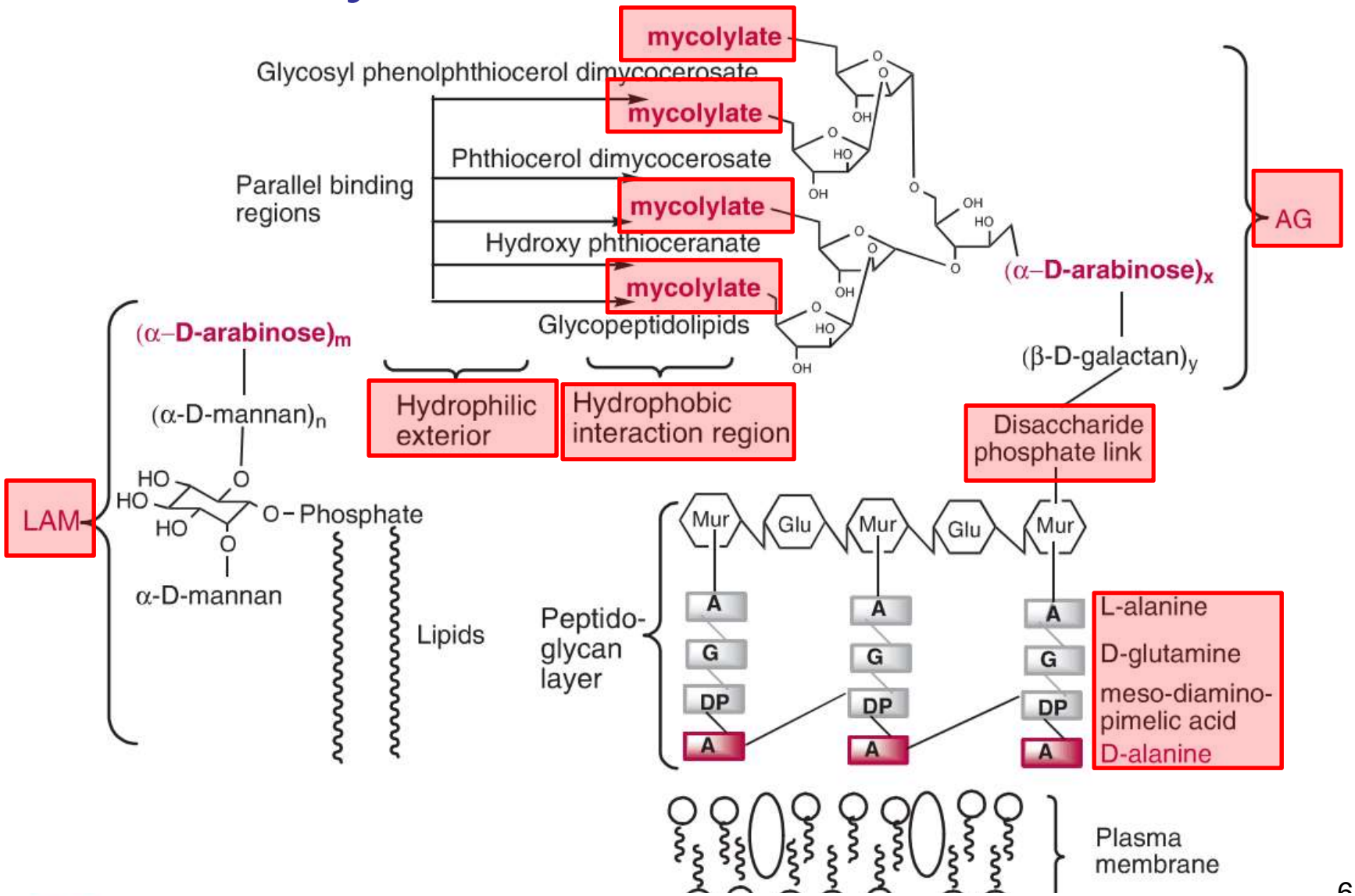
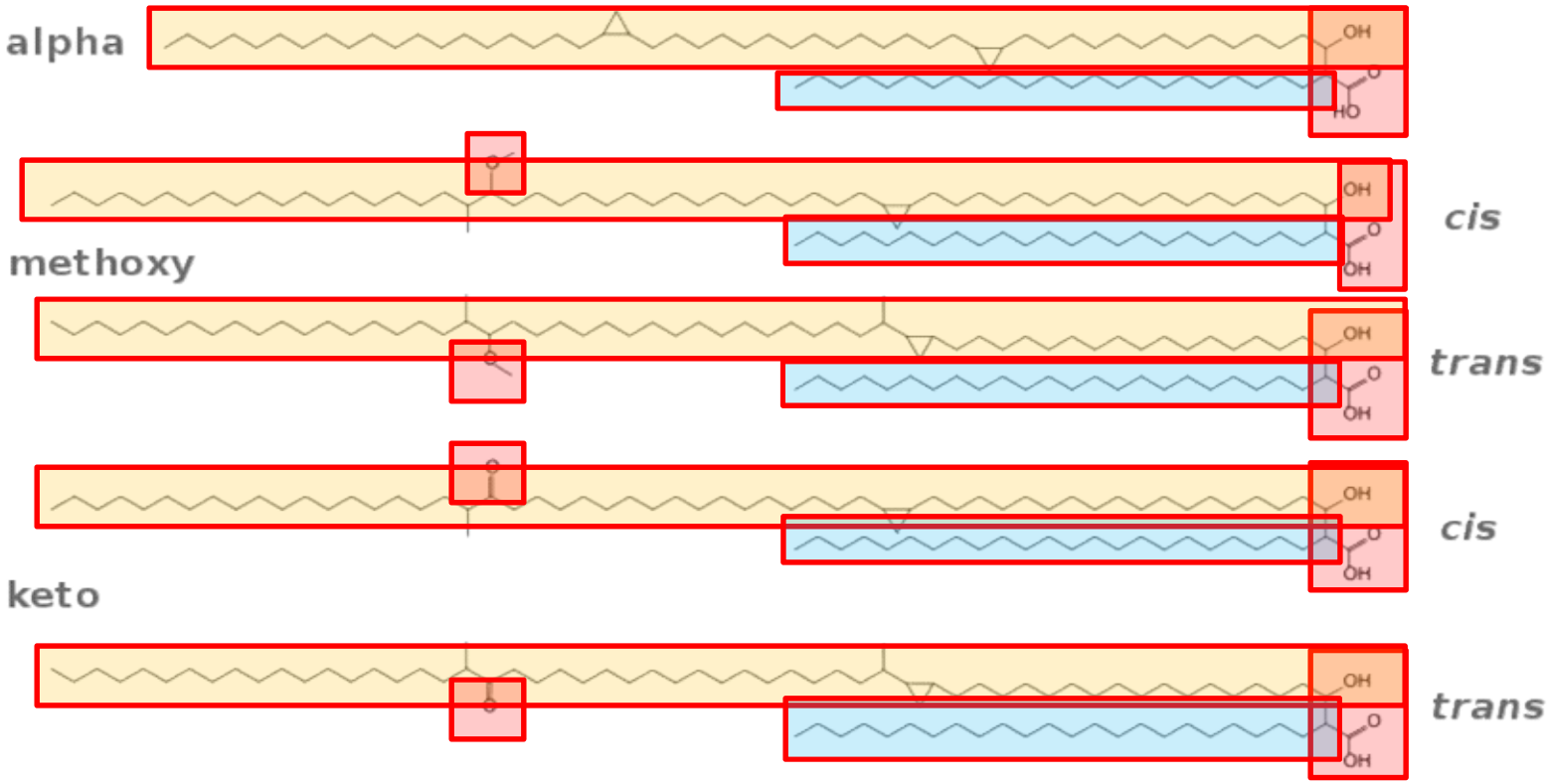


Figure 29.36 Diagrammatic representation of the cell wall/cell envelope of mycobacterium with drug sites of action highlighted in red. AG, arabinogalactan; LAM, lipoarabinomannan

Structures of Mycolic Acids

- β-hydroxy side chain + α-alkyl shorter side chain



Structures of Mycolic Acids in the Cell wall of Mycobacterium

- Alkanoic acid (56 & 58C)

α-alkyl side chain (24C)

+ β-hydroxy

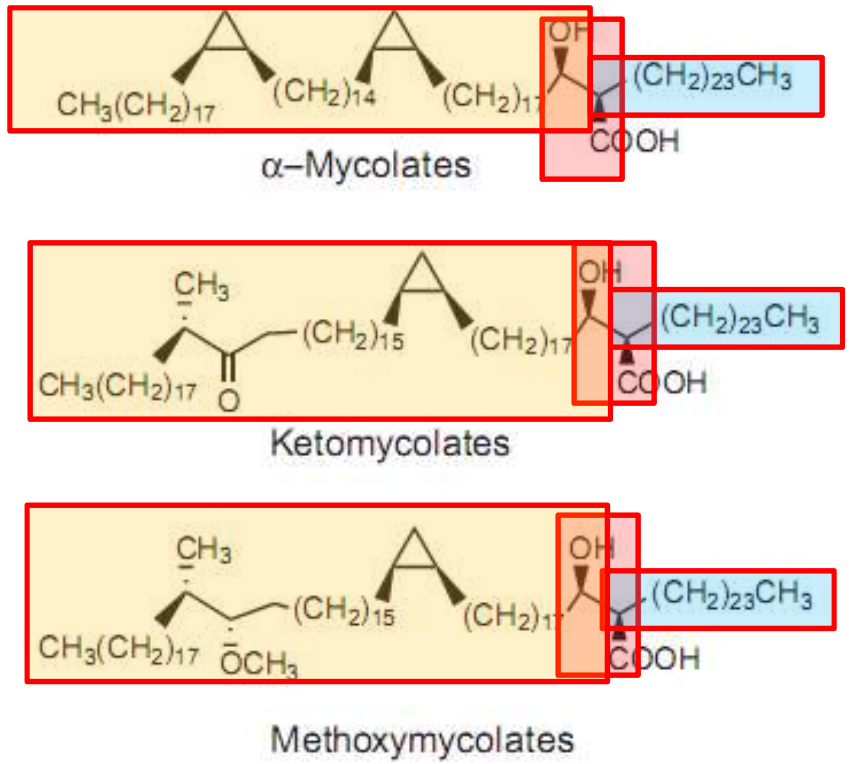
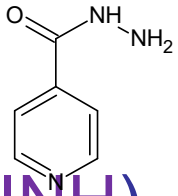


FIGURE 36.3 Mycolic acids.

Amide/Hydrazide: Isoniazid (INH)



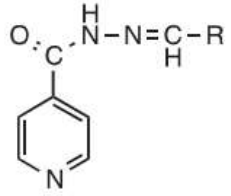
- Iso-Nicotinyl-Hydrazine; Iso-Nicotinic acid Hydrazide (INH)
- First line against M. *tuberculosis*
- MOA: interfere with cell wall mycolic acid biosynthesis

✓ through inhibiting fatty acid elongation via NADH dep. enoyl reductase

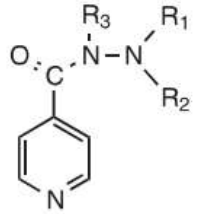
✓ via acylating of NADH

- Prodrug: study bio-activation process & metabolites.
- SAR:

✓ consider INH derivatives.

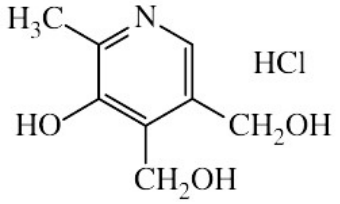


Isoniazid hydrazones



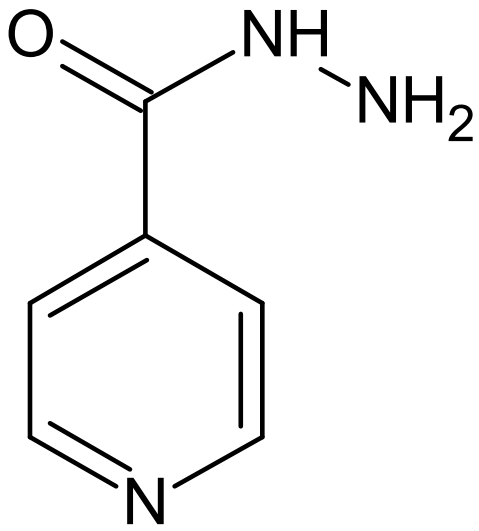
Isonicotinic acid hydrazides

- Side effect: co-administration: vitamin B_6: why?

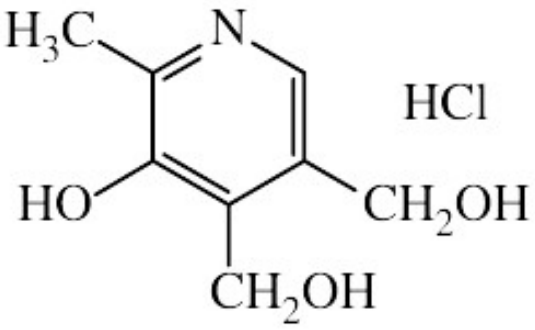


PYRIDOXINE

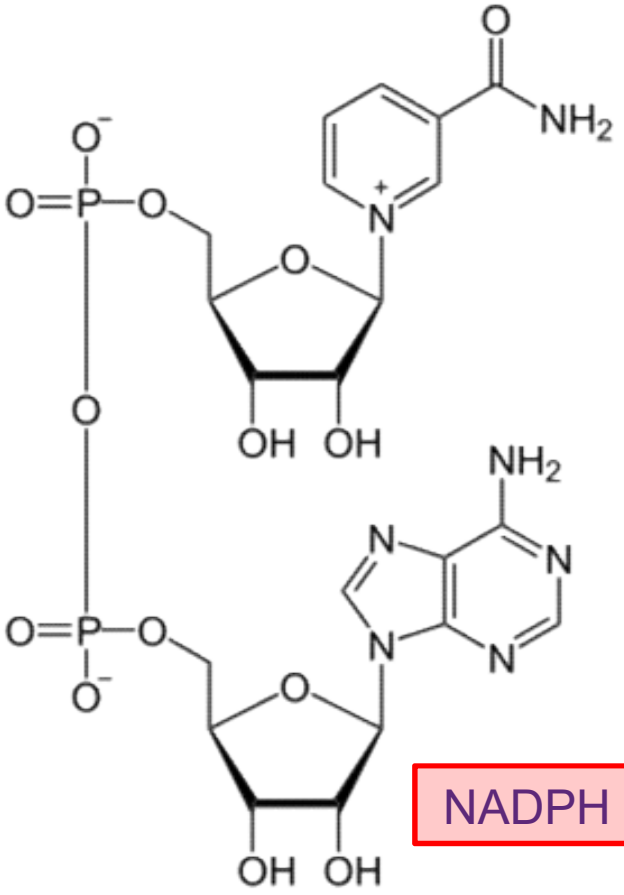
INH & Biologic Correlated Structures



INH



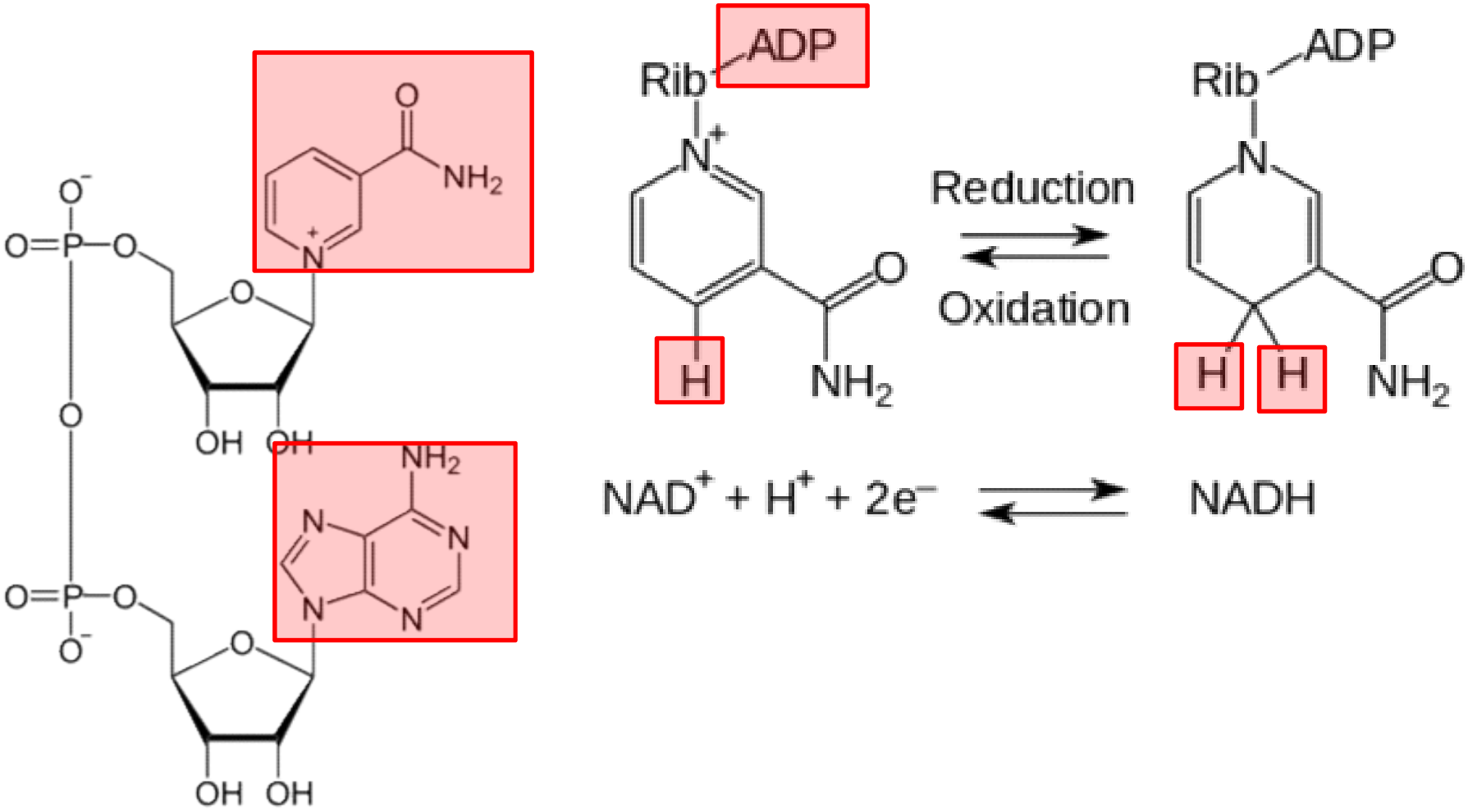
PYRIDOXINE



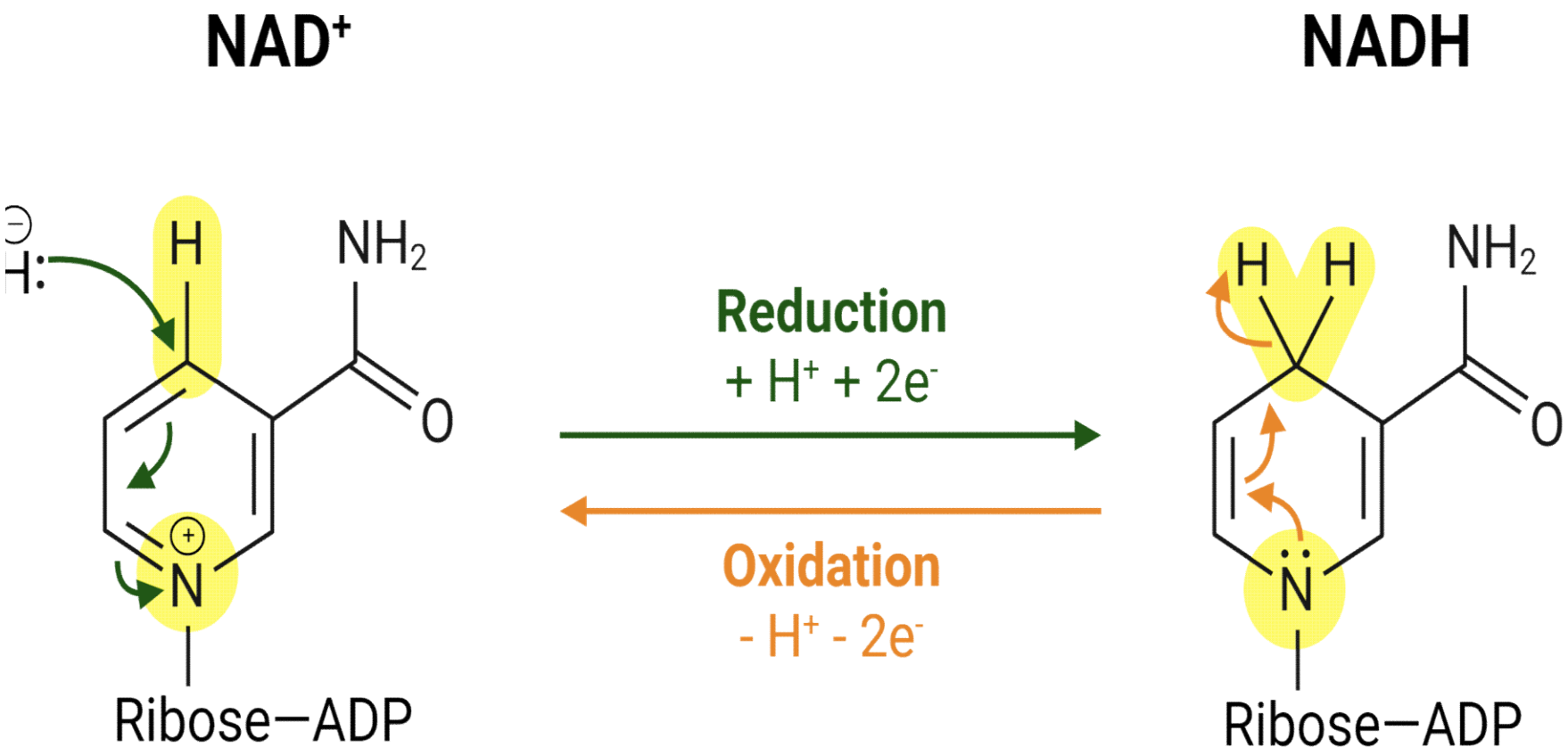
NADPH

NAD^+ & NADH

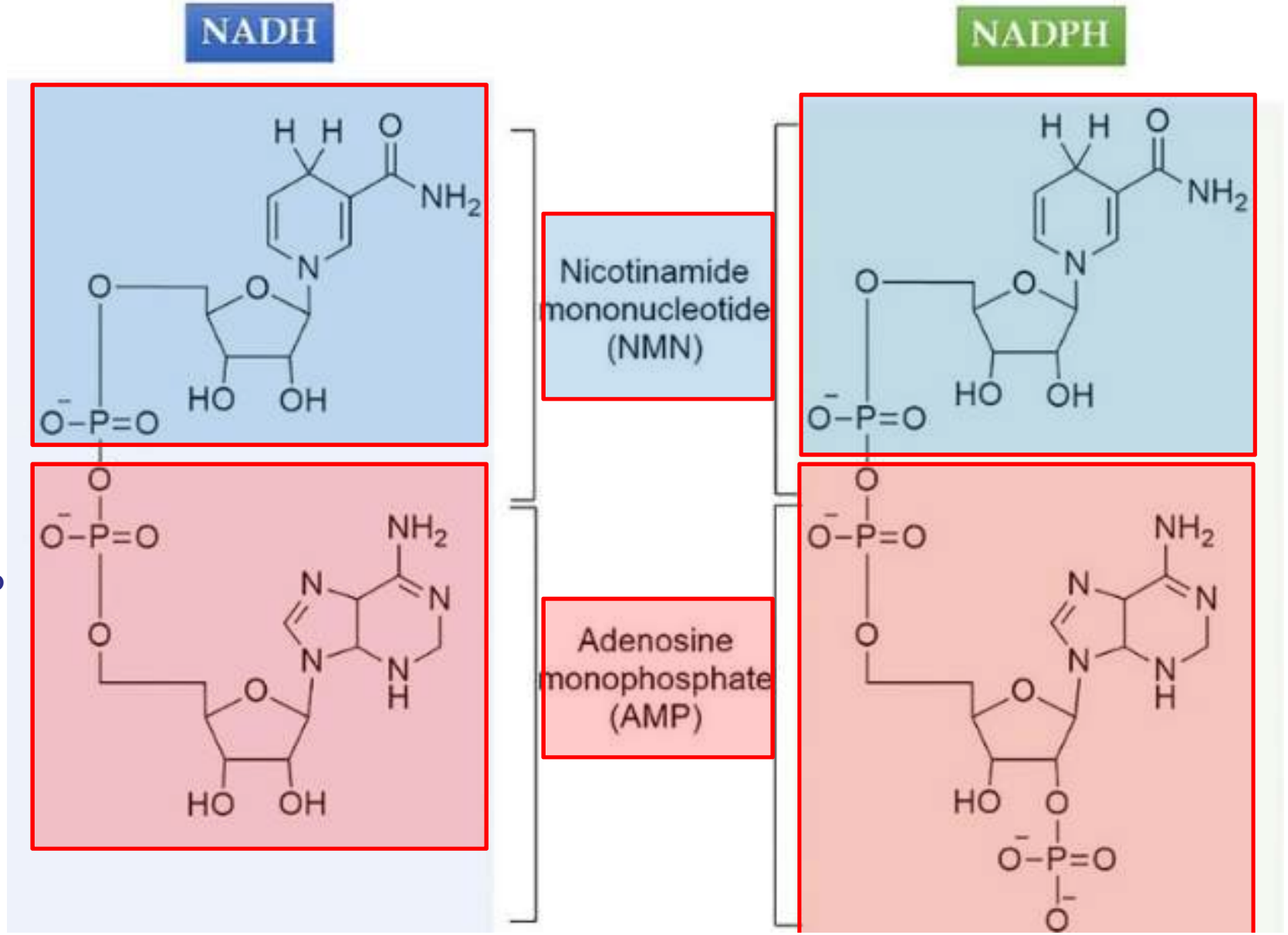
- Nicotinamide Adenine Di-nucleotide: NAD



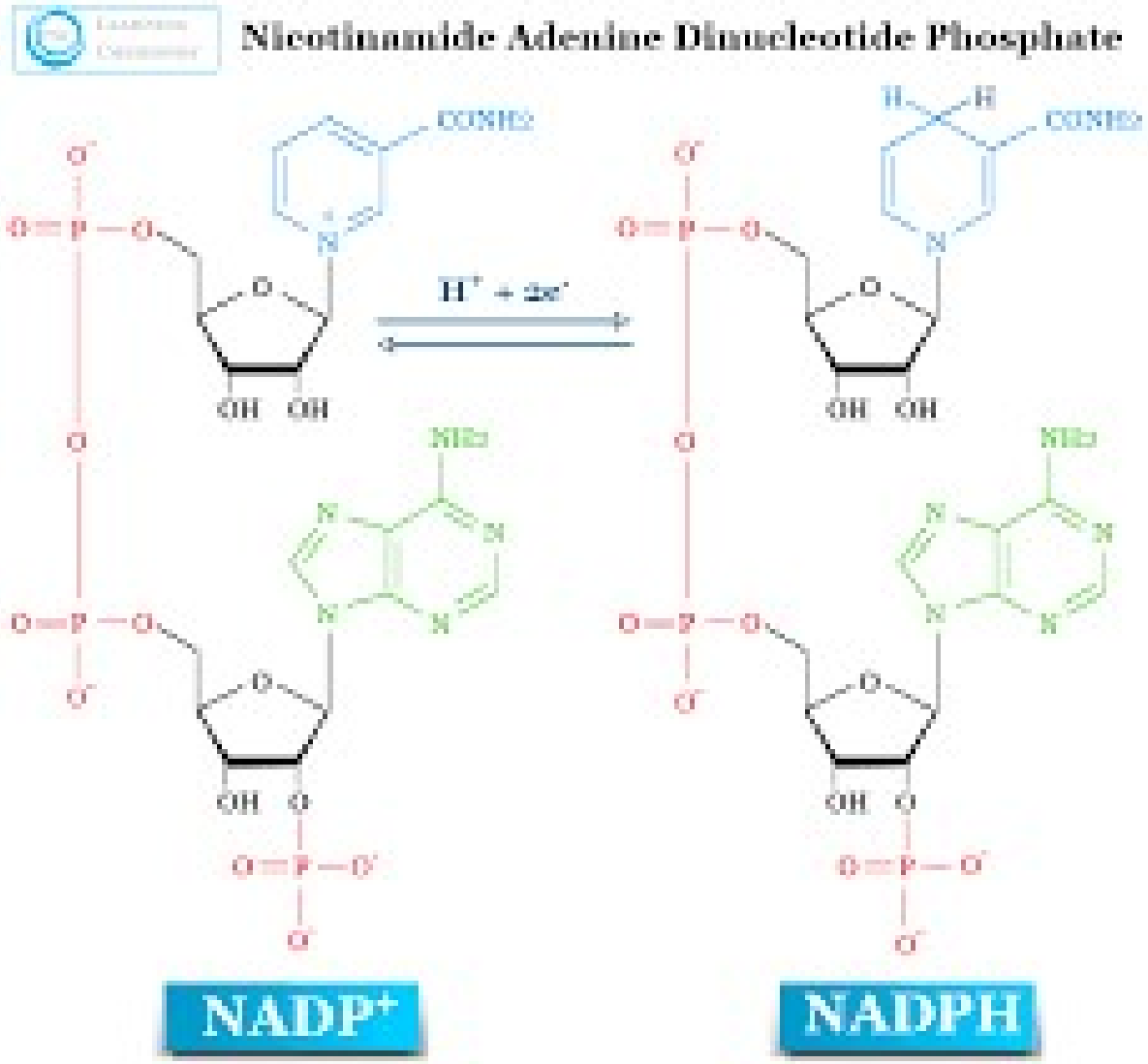
NAD^+ & NADH


NAD+
NADH
H
NH2
O
N
Ribose—ADP
Reduction
+ H+ + 2e-
Oxidation
- H+ - 2e-
H
H
NH2
O
N
Ribose—ADP

NADH & NADPH: Position of Phosphate Group: 2'-P in NADP Vs 3'-p in DNA Nucleotides



NADP & NADPH



Natural Function of NADH on Reduction of Enoyl Thio-Ester of Acyl Carrier Protein in Active Site of NADH dep. Enoyl Reductase

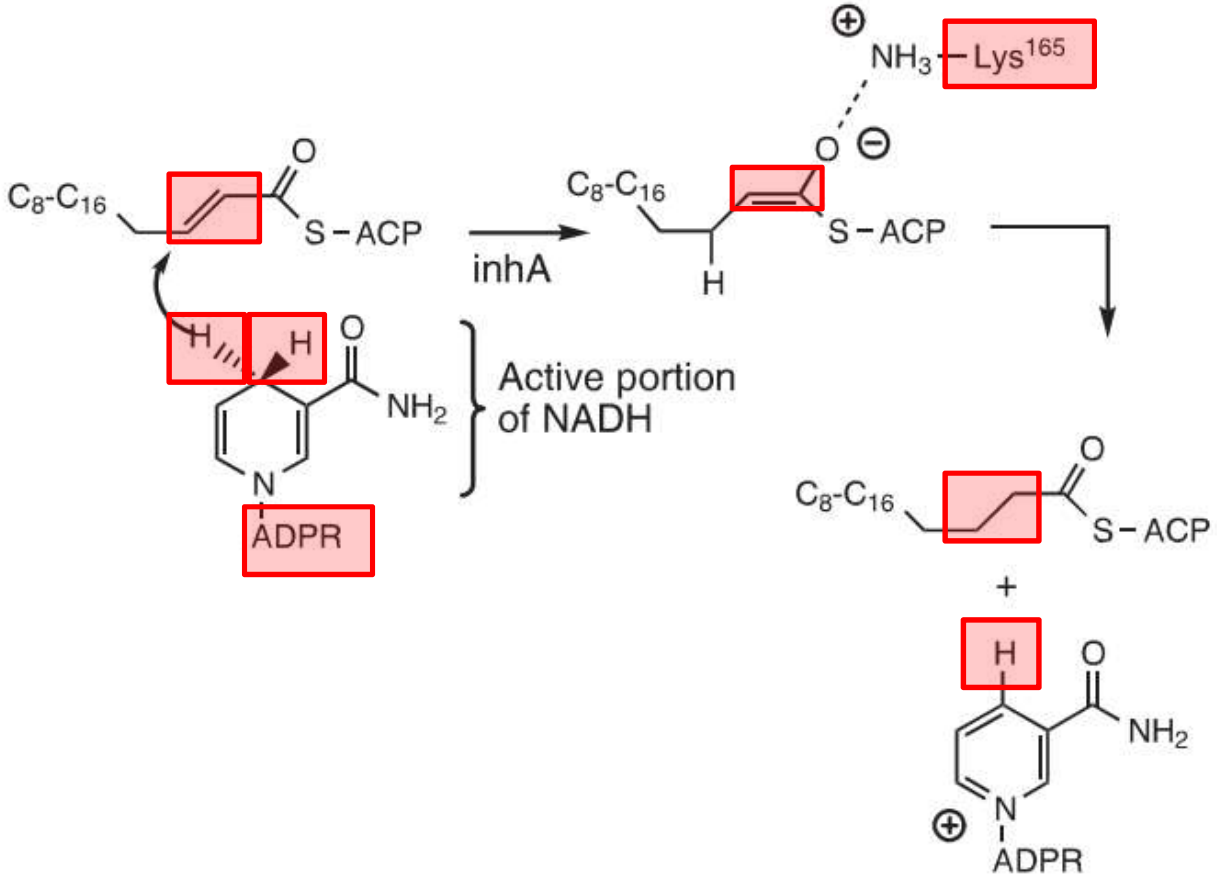


Figure 29.39 Enoylthioester (ACP, acyl carrier protein) reduction catalyzed by NADH (reduced nicotinamide adenine dinucleotide) and InhA (enoyl-acyl carrier protein reductase)

INH Bio-Activation

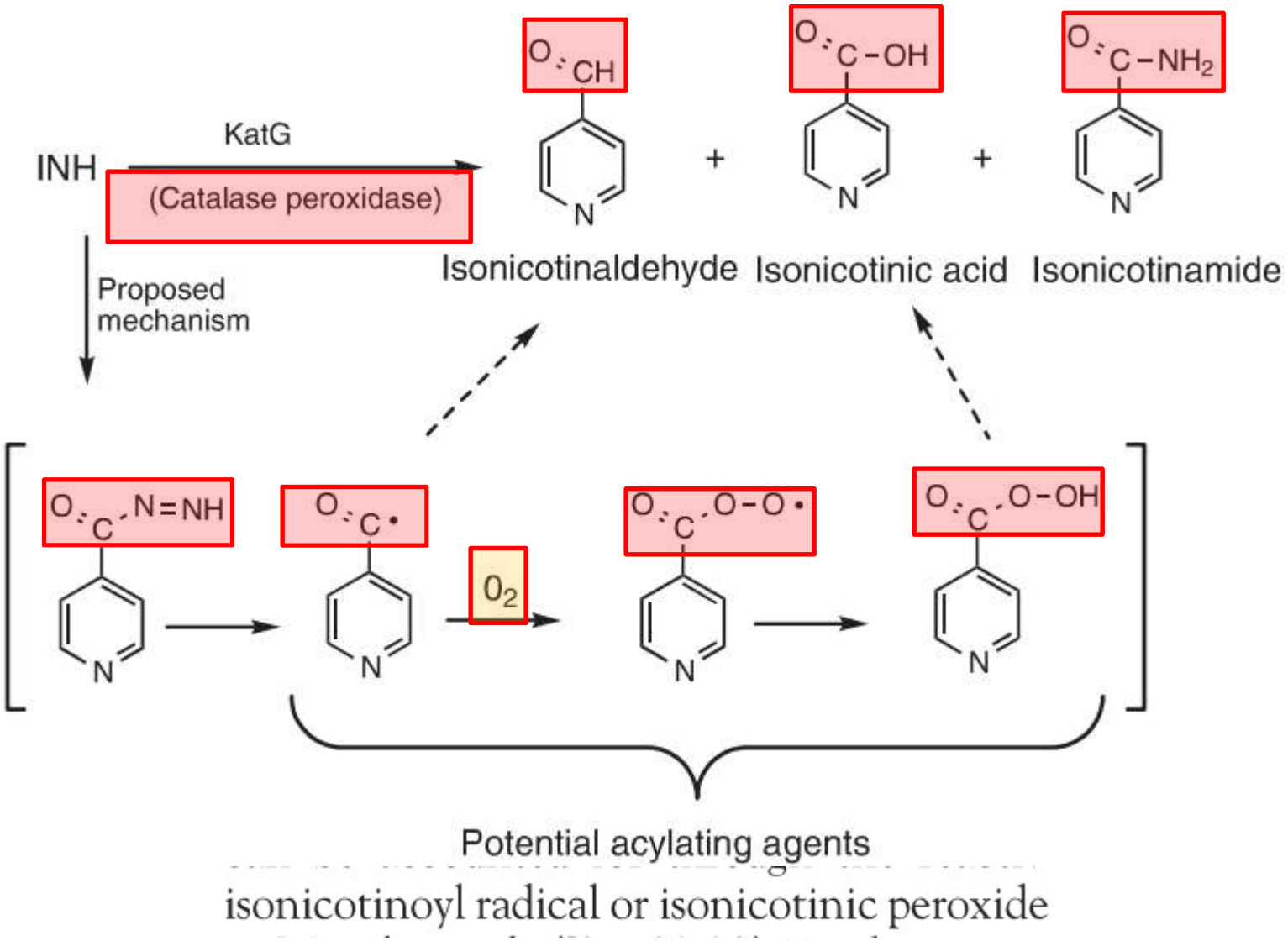


Figure 29.37 Reaction products formed from catalase-peroxidase reaction with isoniazid (INH)

MOA of INH Active Metabolites

- As acylating agent for NAD (cofactor of enoyl reductase)

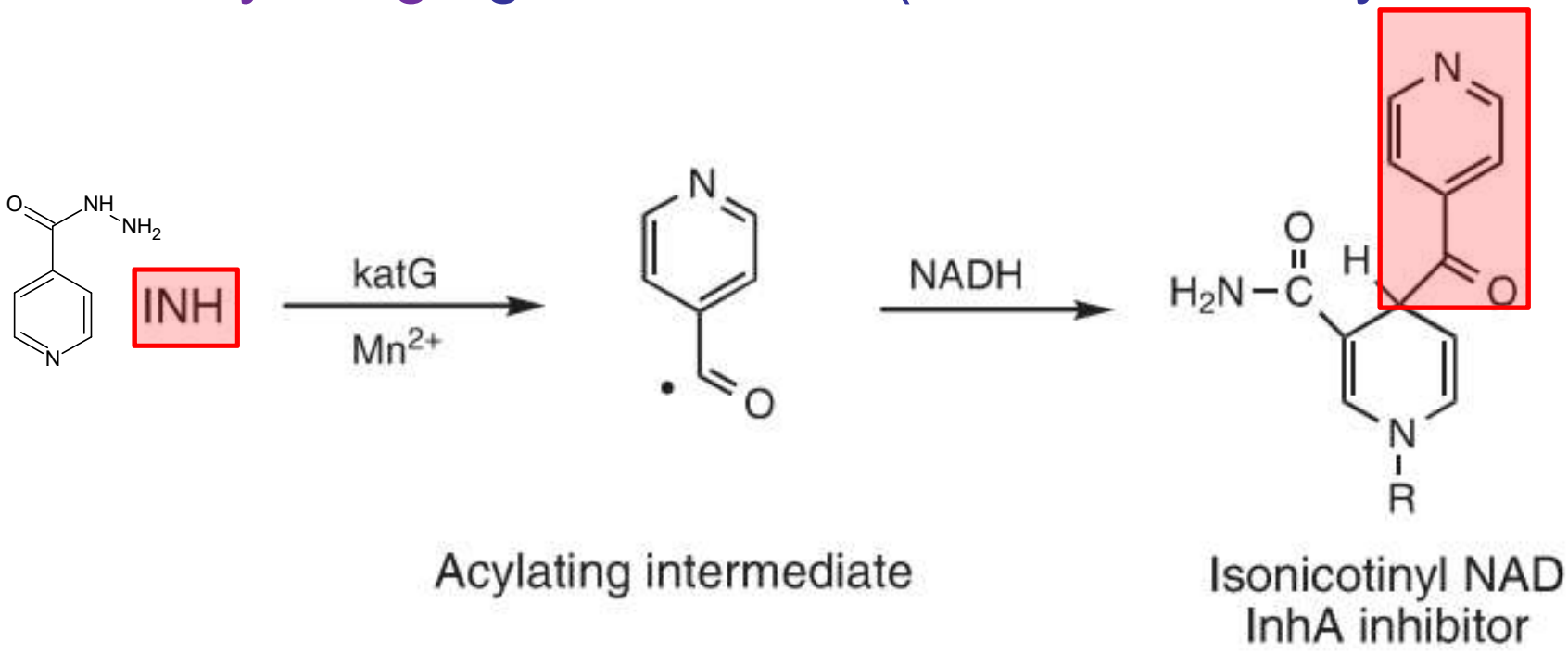


Figure 29.40 Acylation of NADH of NADH-dependent enoylacyl protein (InhA).

Metabolism of INH

- Consider hepatotoxic metabolite: acetylates liver Prs
- Major hepatotoxic metabolite: N-acetyl-hydrazine=N-acetyl-hydrazide

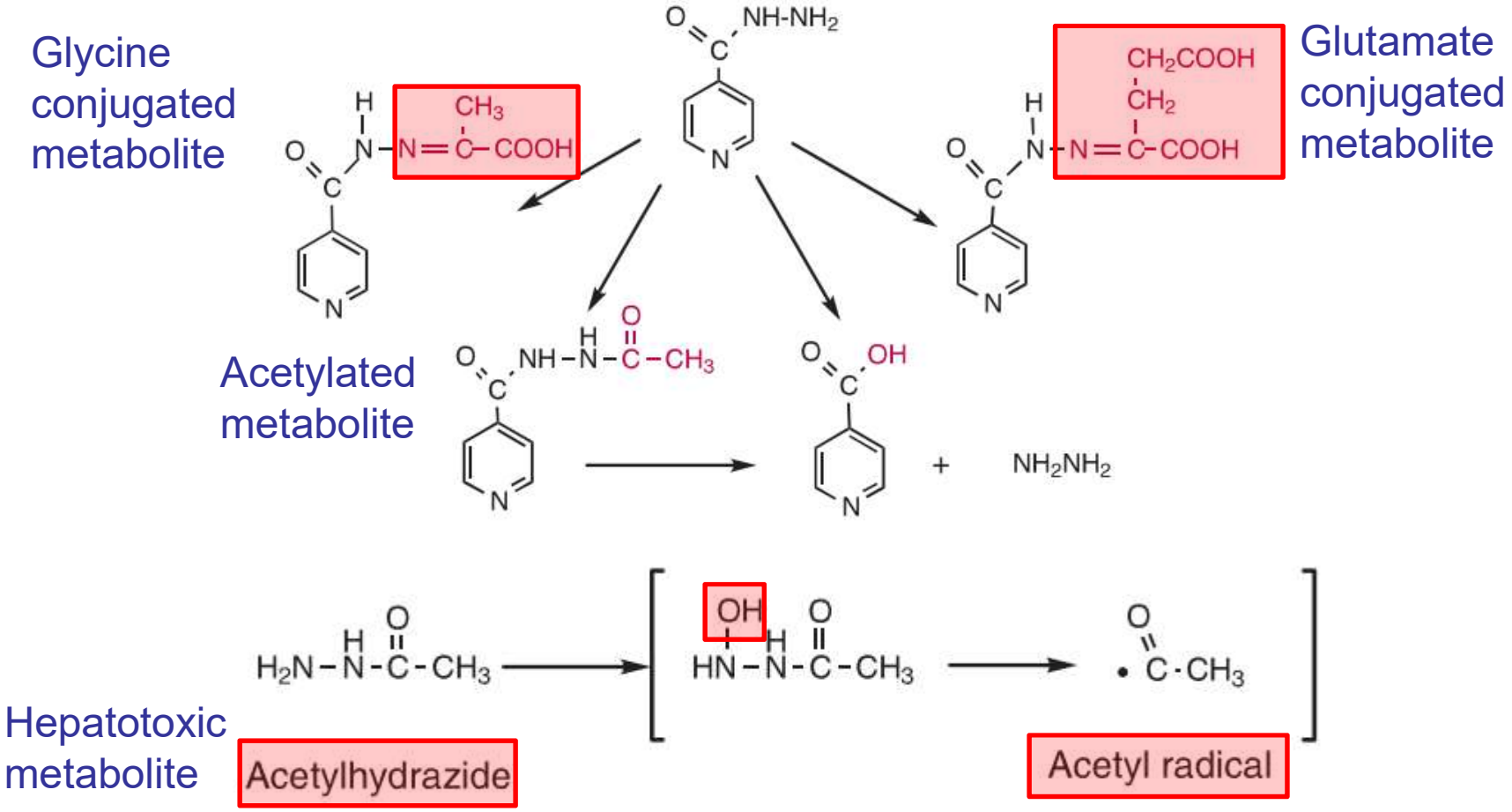
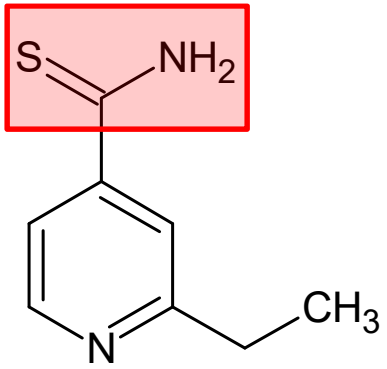


Figure 29.42 Acylating metabolite of isoniazid.

Amide/Hydrazide: Ethionamide



- Second line
- Introduced through INH modification
- MOA: bactericidal against mycobacterium

✓ similar to INH: prodrug:

✓ converted to active acylating agent via oxidation by catalase-peroxidase:

✓ active metabolite: ethionamide sulfoxide: next slide

✓ which inactivates enoyl-reductase: next slide

- SAR

✓ chemistry: Iso-nicotin-amide analogue: thio-amide

- Draw the structure of acetylated NAD by ethionamide.

MOA of Ethionamide

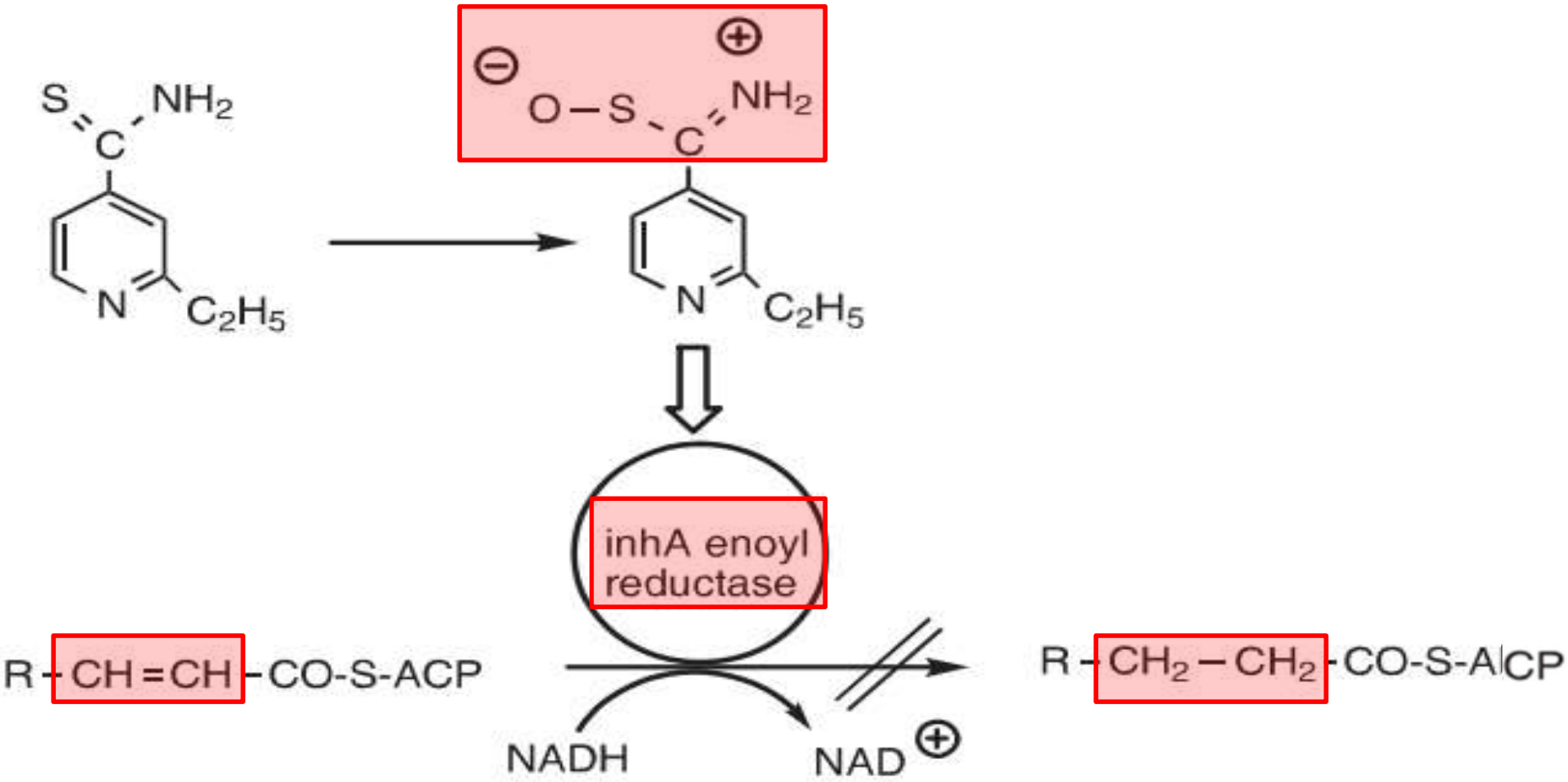


Figure 29.49 Mechanism of action of ethionamide.

Metabolism of Ethionamide

- Follow metabolites.

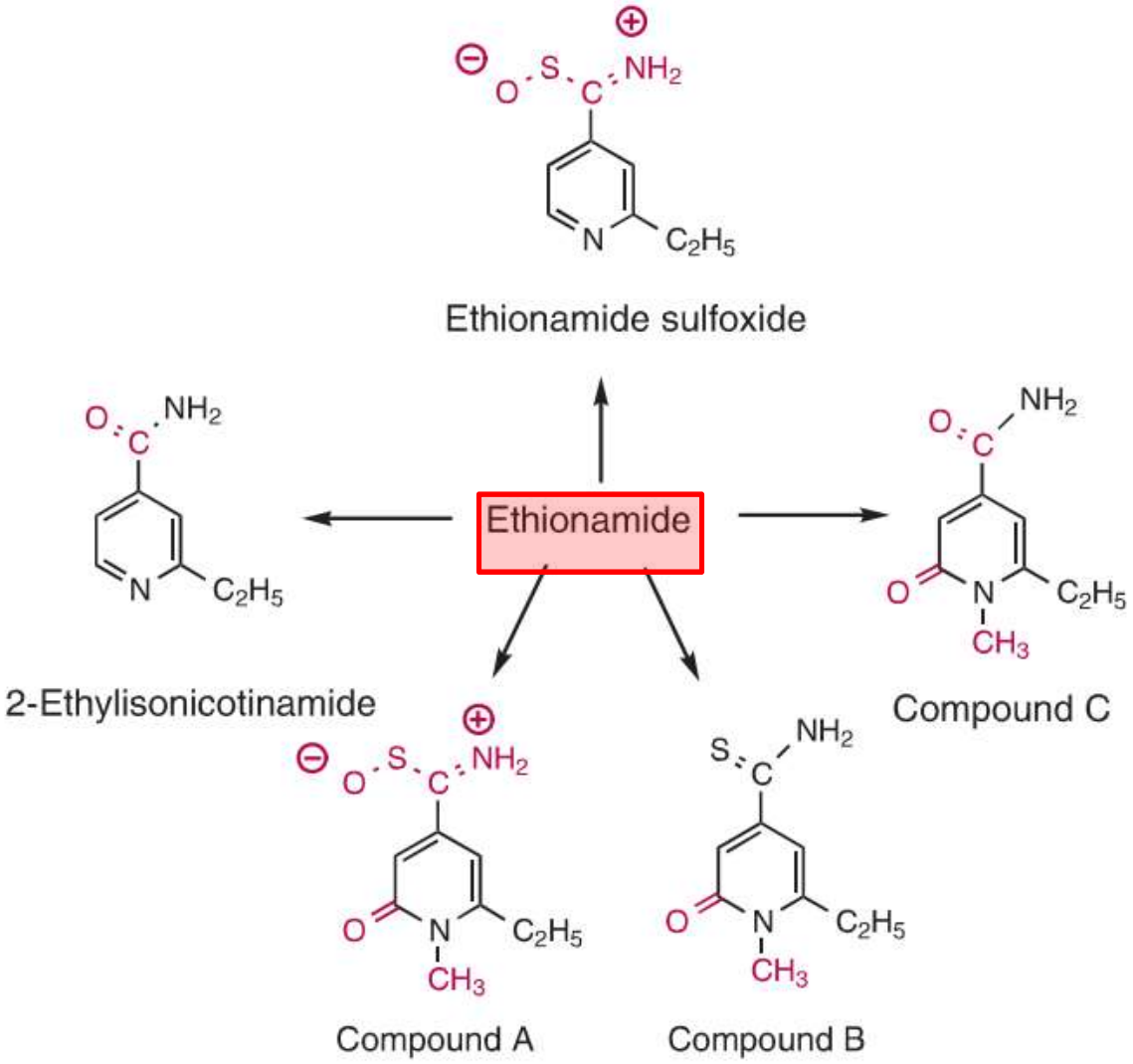
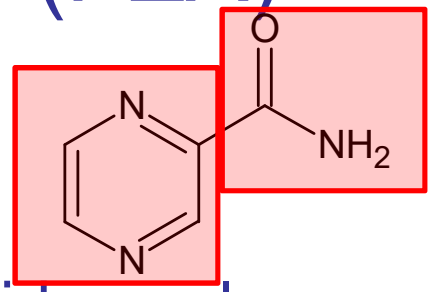


Figure 29.50 Metabolism of ethionamide.

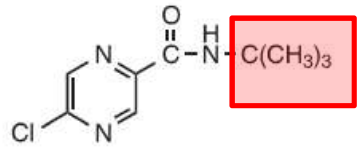
Amide/Hydrazide: PyraZinAmide (PZA)



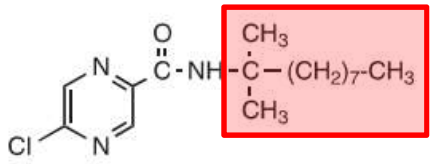
- First line
- Chemistry: pyrazine-2-carboxamide: Nicotinamide analogue
- Bactericidal against M. tuberculosis
- MOA: unknown: pyrazinoic acid at pH = 5.4

✓ through pyrazinamidase: lowers pH

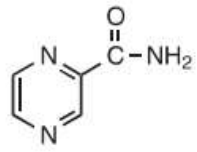
- PDG: decrease pH: interferes with energetic of the membrane
- SAR: bio-isosterism of pyrazine.



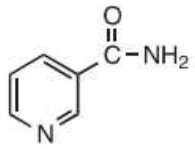
tert-Butyl 5-chloropyrazinoate



2'-(2'-Methyldecyl) 5-chloropyrazinoate

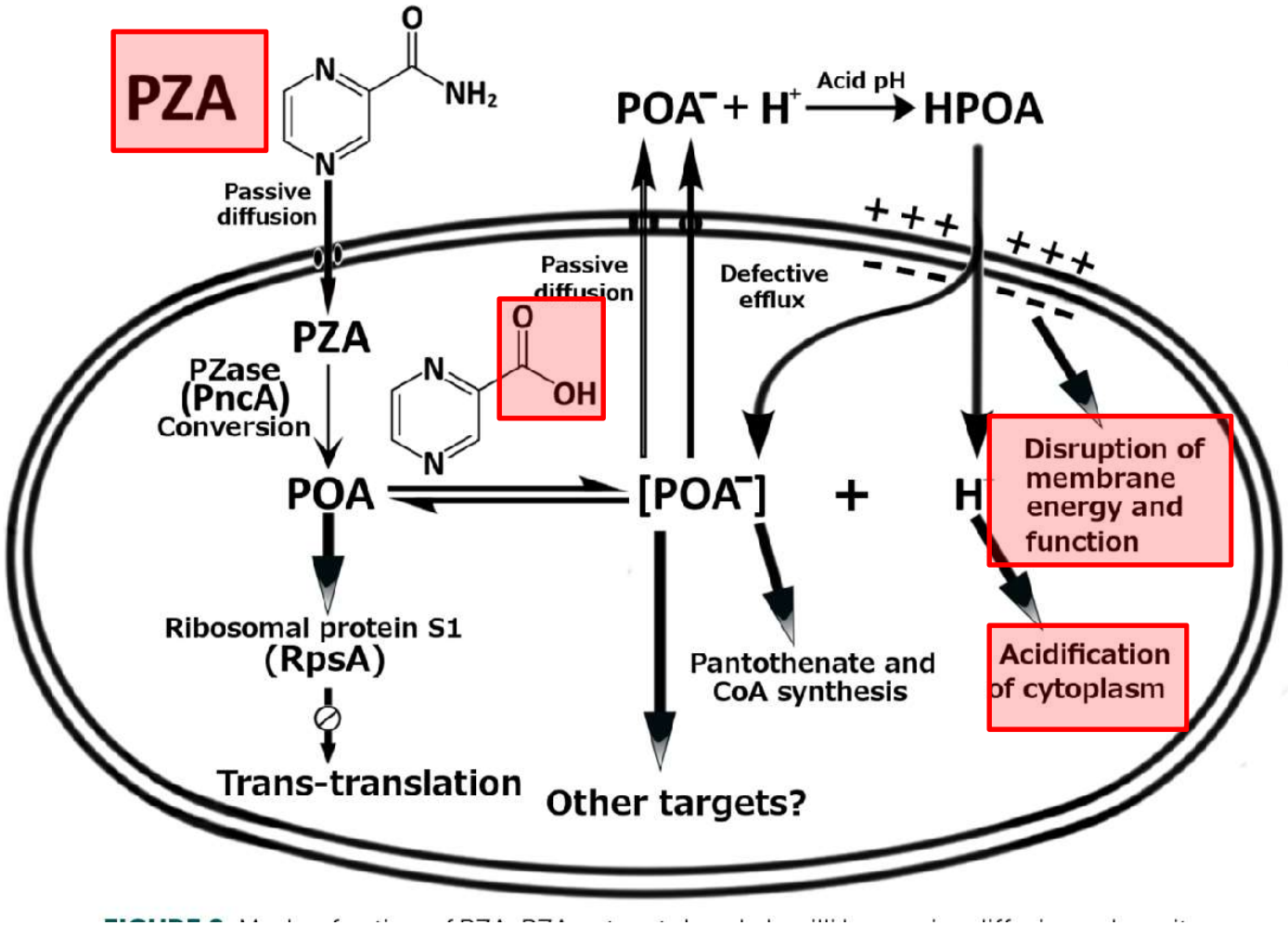


Pyrazinamide



Nicotinamide

Suggested Individual MOA for PZA



Metabolism of Pyrazinamide

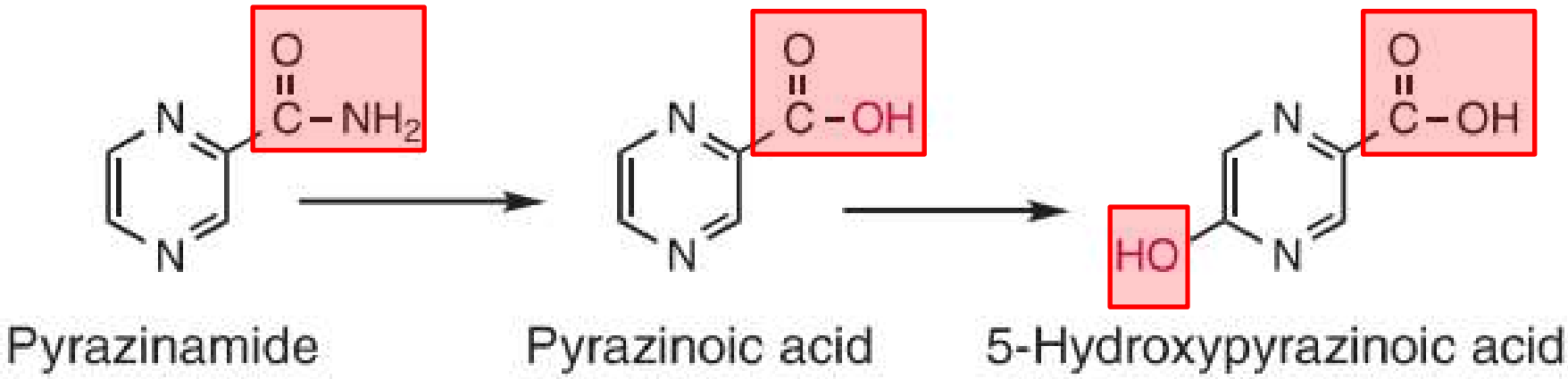
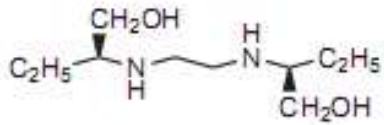


Figure 29.45 Metabolism of pyrazinamide.

Di-Amino-Alkanol: Ethambutol (EMB)



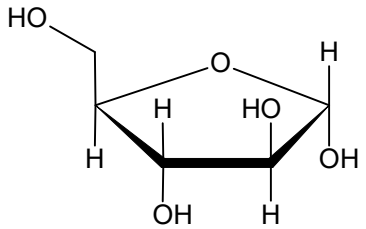
Ethambutol

- First line
- Mostly against G^+; bacteriostatic
- MOA: bacterial cell wall inhibitor: inhibition of AG synthesis;

✓ mimic arabinan by inhibiting arabino-furanosyl-transferase:

✓ hence increase cell wall permeability

✓ provides synergism with intra-cellular drugs



- SAR:

✓ N,N-butanol ethylene-di-amino to mimic arabino-furanose

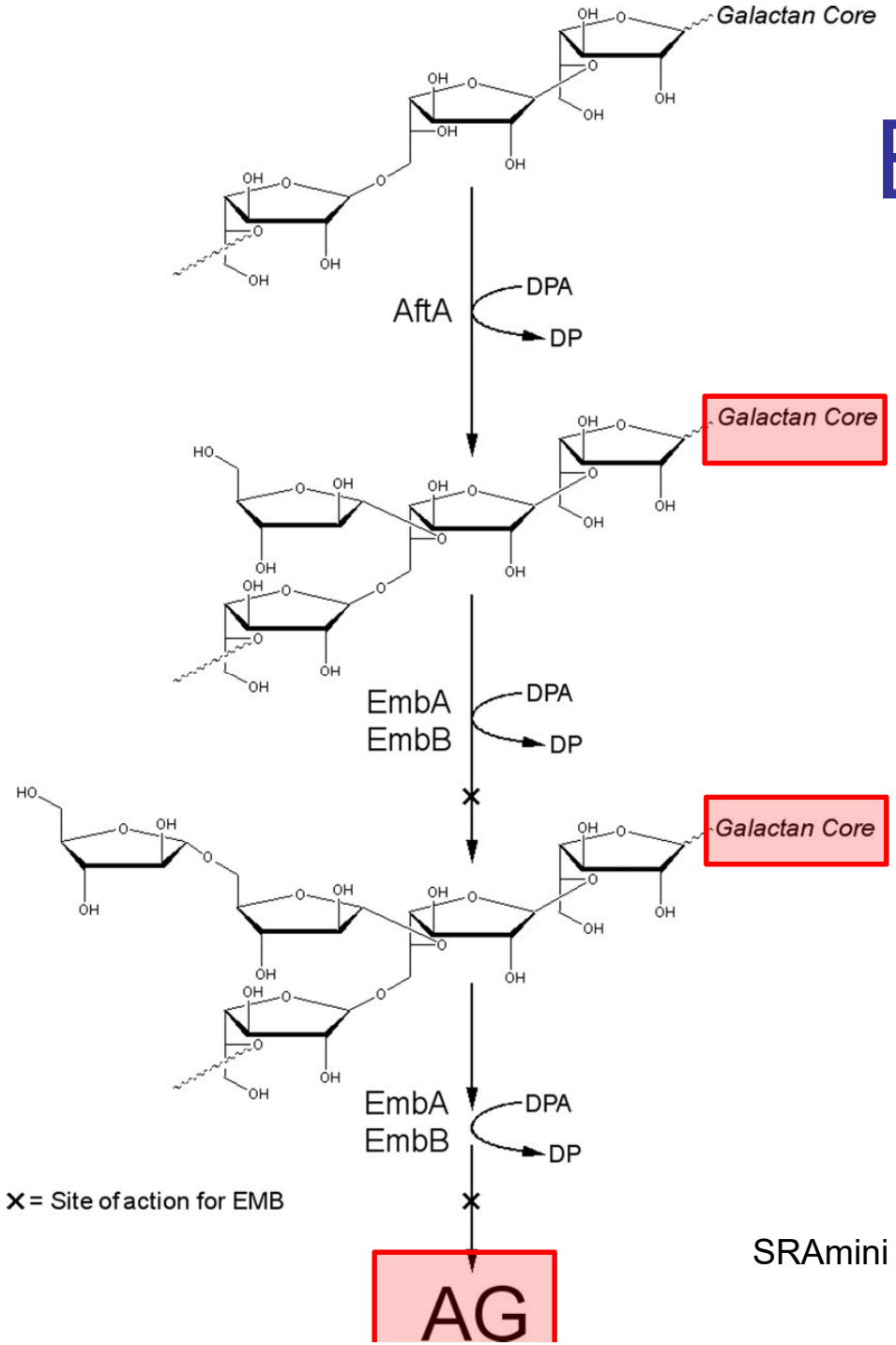
✓ (+) enantiomer is 200-500 more active than (-) enantiomer

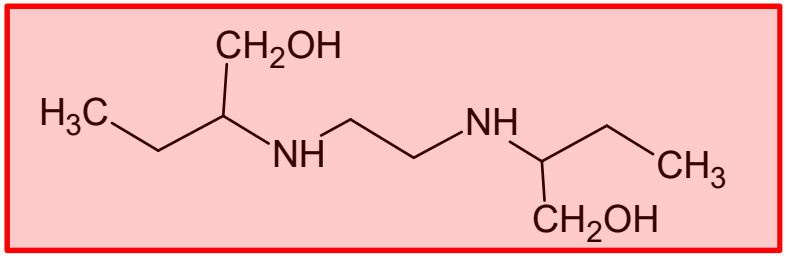
✓ water soluble

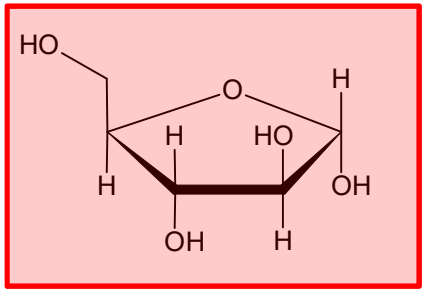
✓ Metabolism: inactive metabolites

✓ resistance: ?

Ethambutol (EMB)







MOA:

inhibit arabino-furanosyl transferase

Site of Action for EMB

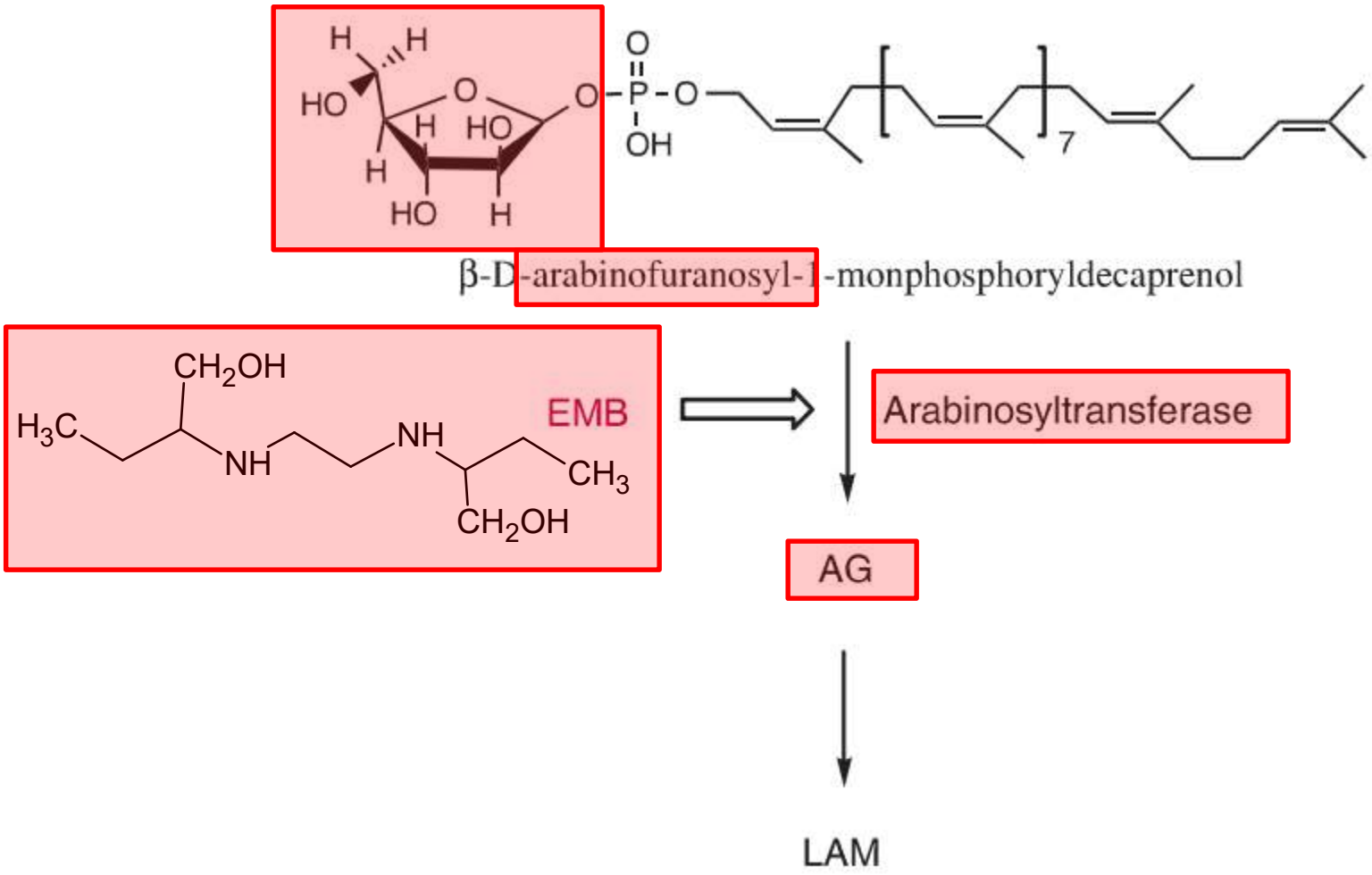


Figure 29.46 Site of action of ethambutol (EMB) in cell wall synthesis. AG, arabinogalactan; LAM, lipoarabinomannan.

Metabolism of EMB

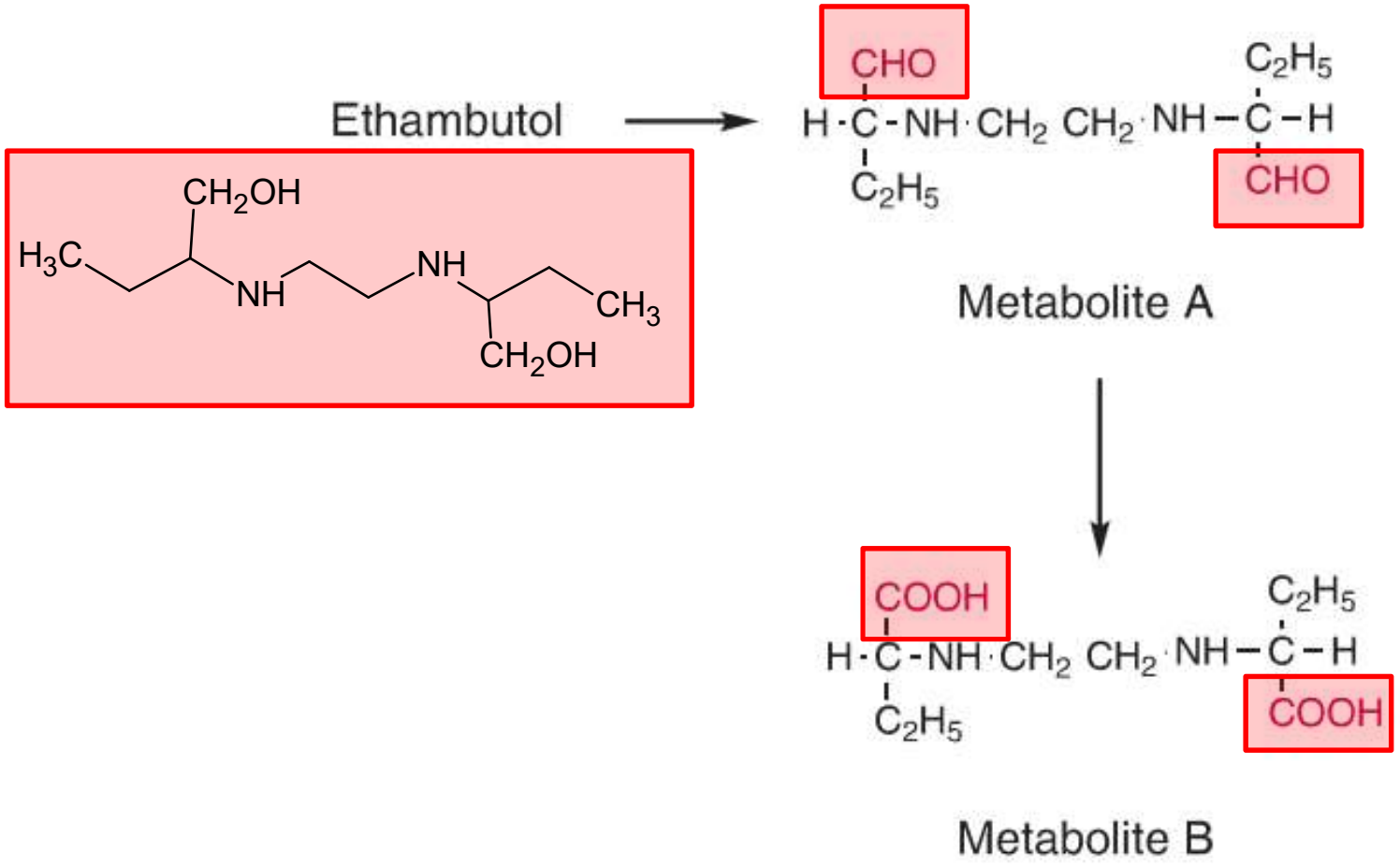
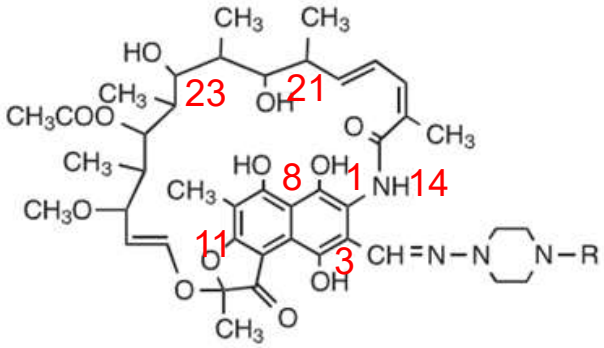


Figure 29.47 Metabolism of ethambutol.

Macrocyclic Lactam: Rifamycins

- First line:
- Produced by *Streptomyces Mediterranean*
- Semi-synthetic derivatives
- Against G^+
- MOA: DNA Dep. RNA Polymerase Inh. (DDRP) (metallo-enzyme)

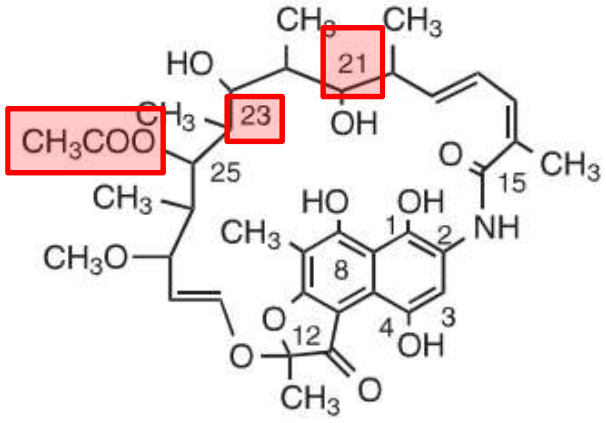


- ✓ block initiation of chain formation in RNA synthesis
- ✓ through π–π interaction of naphthalene & aromatic amino-acid
- SAR: macrocyclic lactam: 30 membered: zwitterionic:
- ✓ C1, C4 & C8: OH;
- ✓ C1 & C8: chelates to Zn^{2+}
- ✓ C21 & C23: hydrogen bond to active site of DDRP
- Side effects & drug interactions: hepatotoxic:
- ✓ powerful CYP450 oxygenase inducer

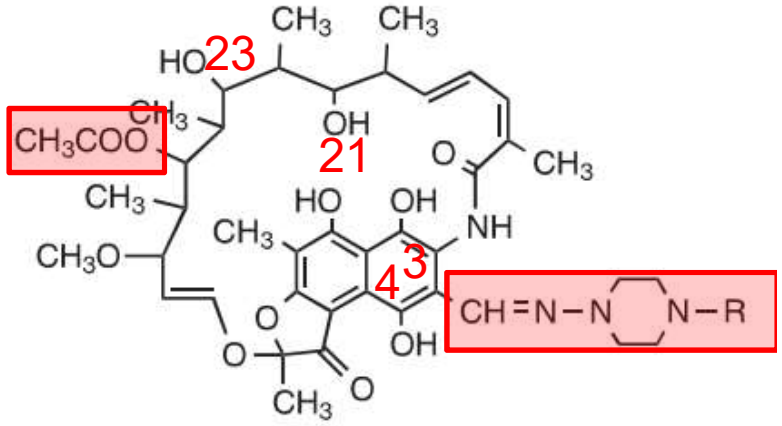
Rifamycins

- Intermediate: 3-formyl trifamycin: derivatized to:

✓ rifampin (RIF)
✓ Rifapentine
✓ Rifabutin



Rifamycin SV

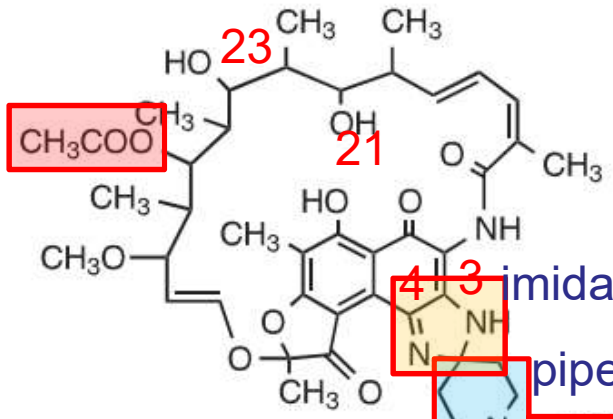


Rifampin

Rifapentine

$R = CH_3$

R =



imidazoline

piperidine

isobutyl

Rifabutin

Rifamycin Binding to DDRP

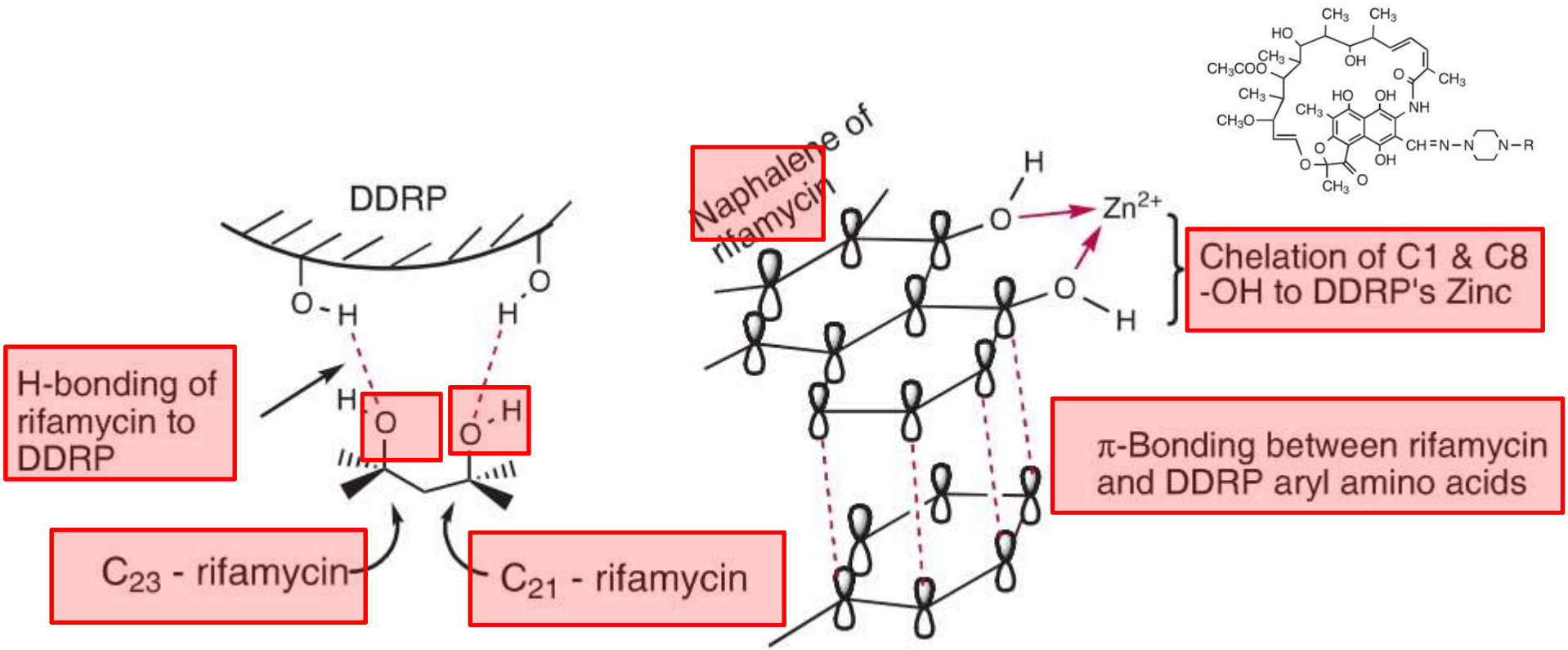
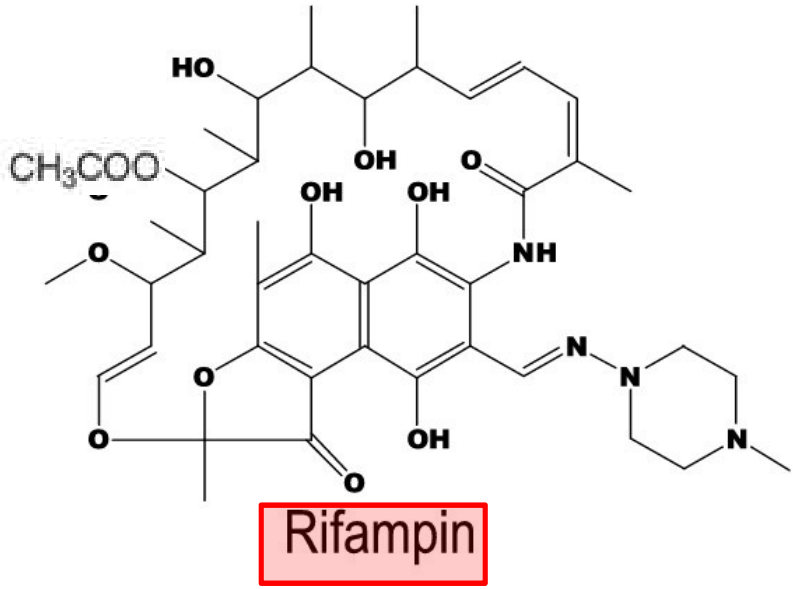
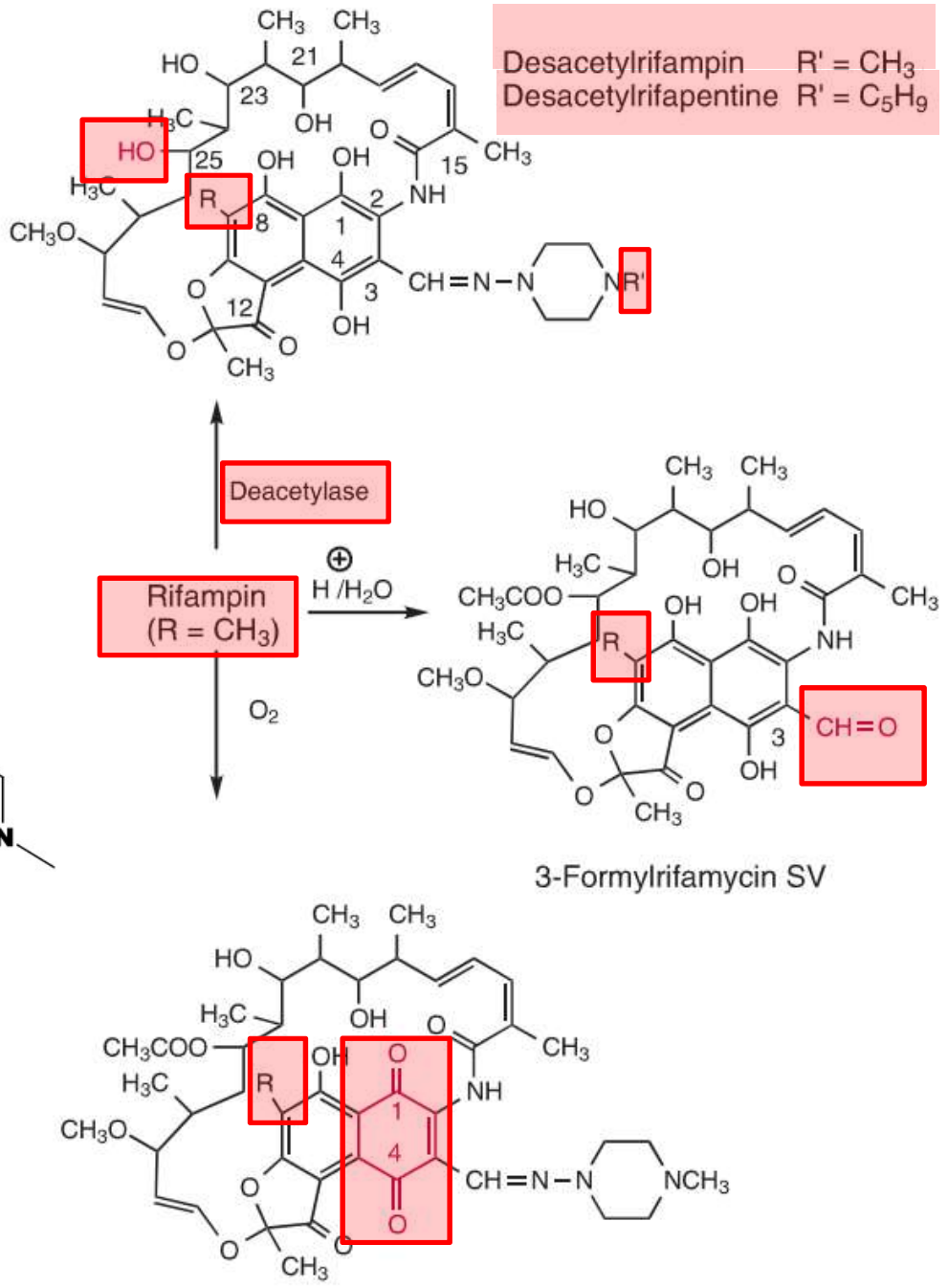


Figure 29.43 Binding of rifamycin to DNA-dependent RNA polymerase (DDRP).

Metabolism of Rifampin





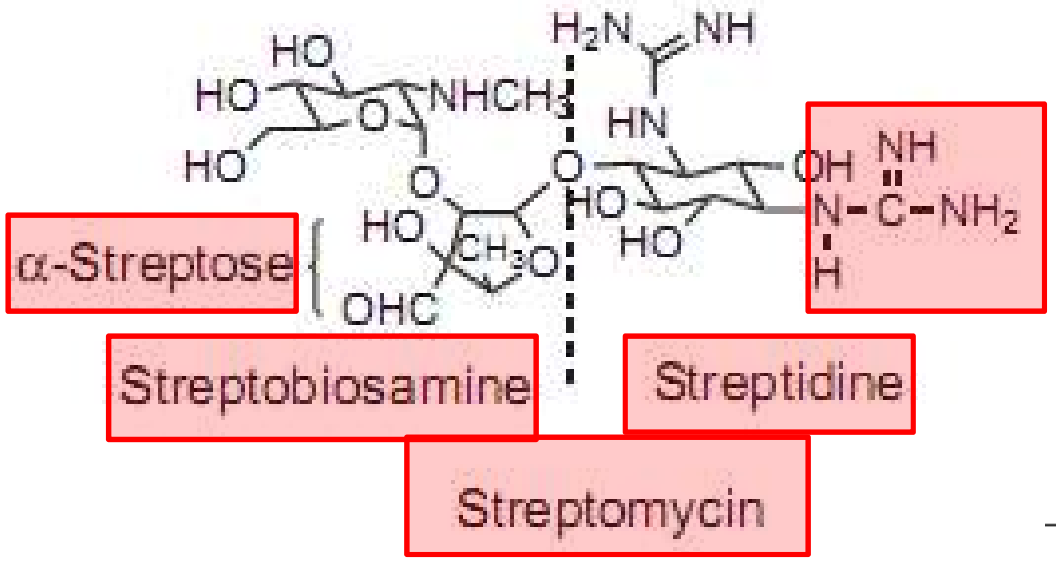
COO

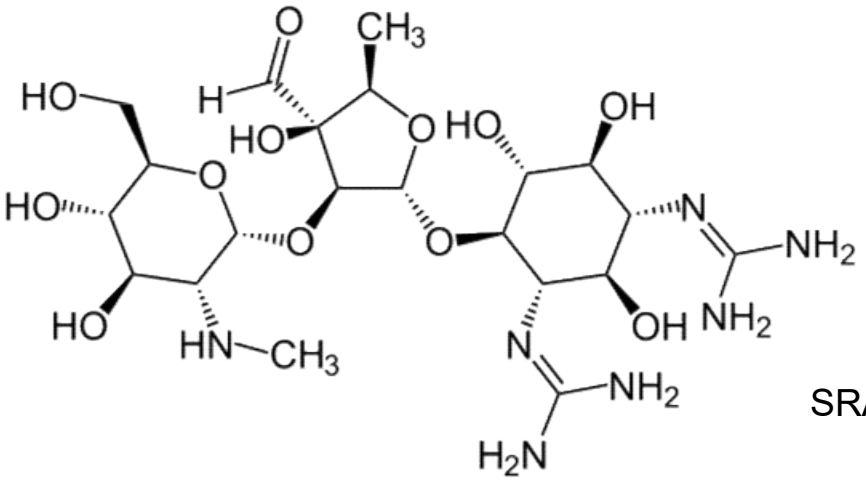
SRA

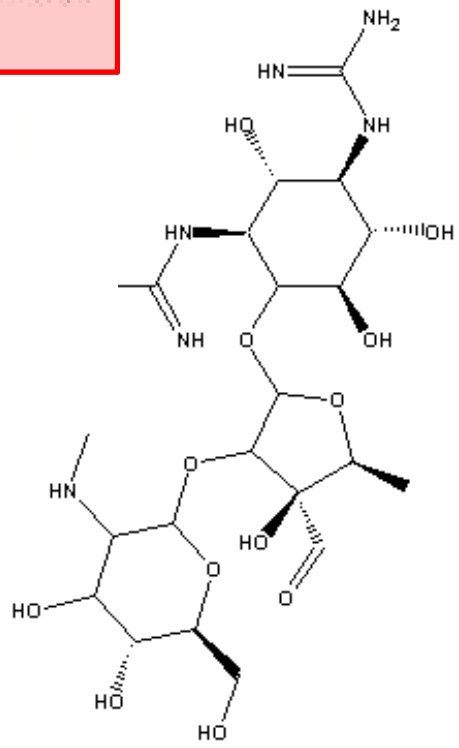
Figure 29.44 Metabolism and in vitro reactions of rifampin.

AminoGlycoside: Streptomycin (STM)

- First line: in some texts is introduced as second line







AminoGlycoside: Streptomycin (STM)

- First line: in some texts is introduced as second line
- Isolated from manure containing soil: by *S. griseus*
- MOA: Pr synthesis inhibitor

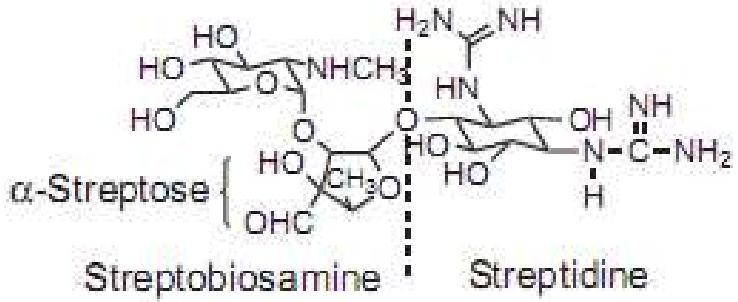
✓ penetration to cytoplasm membrane through El-dep. process

✓ Induce misreading of genetic code

✓ inhibit translational initiation

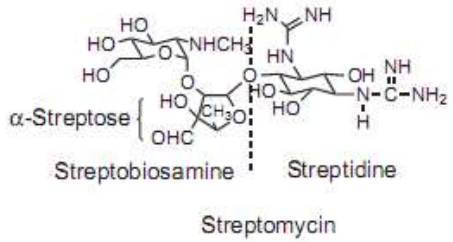
- SAR:

✓ salts: tri-hydrochloride or sesqui-sulfate



Streptomycin

Streptomycin (STM): SAR



- Basic properties
- Water soluble: poor GI absorption
- Modifications on α-streptose: change in aldehyde:

✓ reduction to alcohol: potent with high SE

✓ oxidation to carboxyl

✓ Schiff base: oxime; semi-carbazone; phenyl-hydrazone

✓ oxidation of methyl to methylene hydroxy: active

- Modifications on glucosamine:

✓ demethylation or large alkylation: reduces activity

- Modifications on streptidine:

✓ removal or change of guanidine: decreases activity

Metabolism of STM

- Inactivation & resistance through metabolic enzymes:

✓adenyl-transferase & phospho-trasnferase

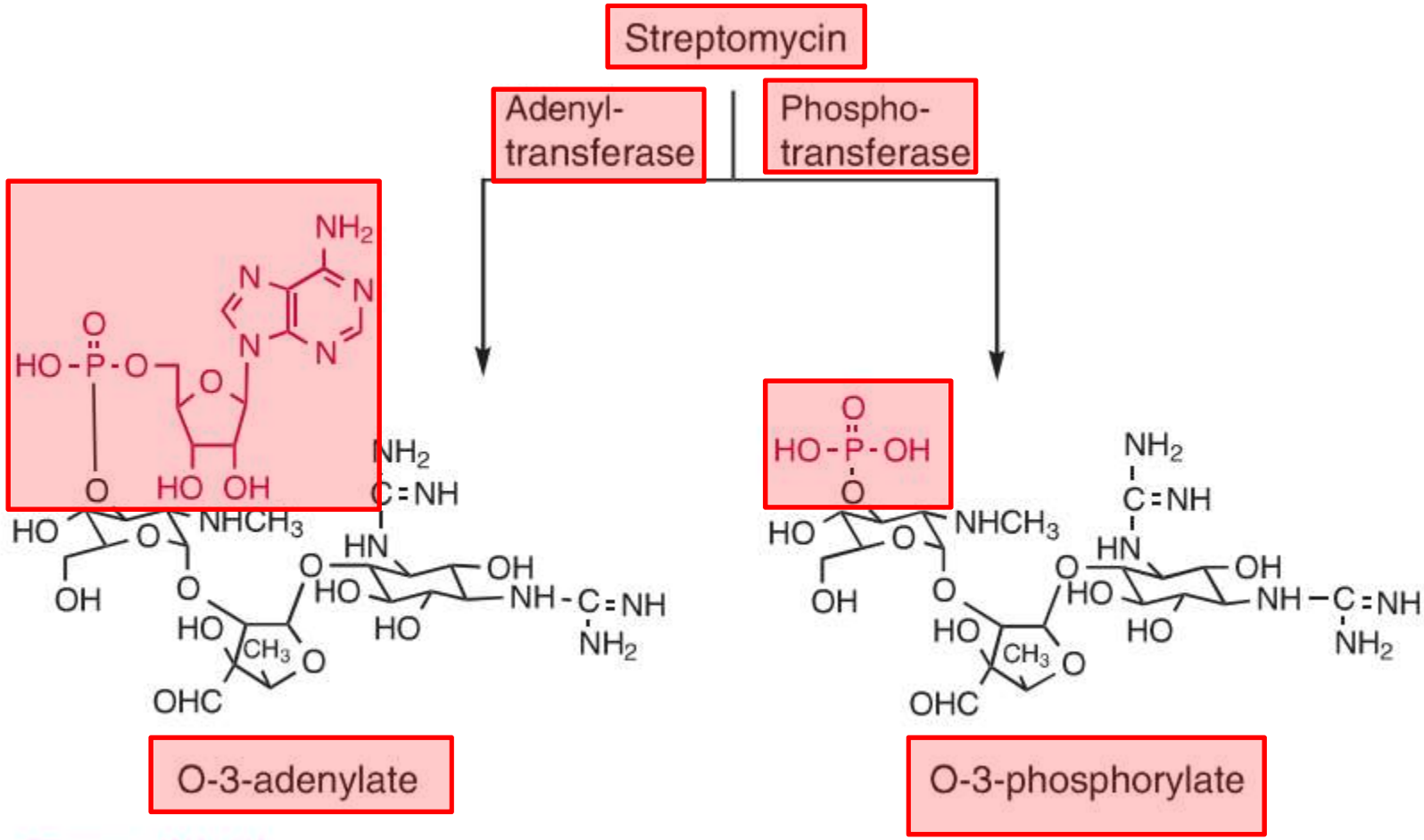
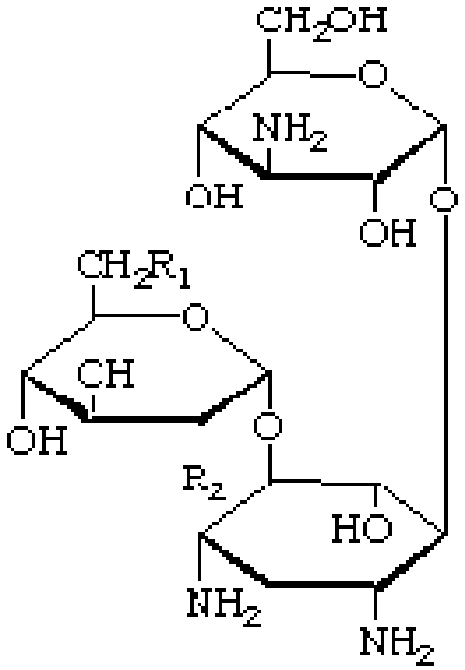


Figure 29.48 Metabolism of streptomycin (STM) as a mechanism of resistance.

Amino-Glycoside: Kanamycin

- Second line against TB
- MOA

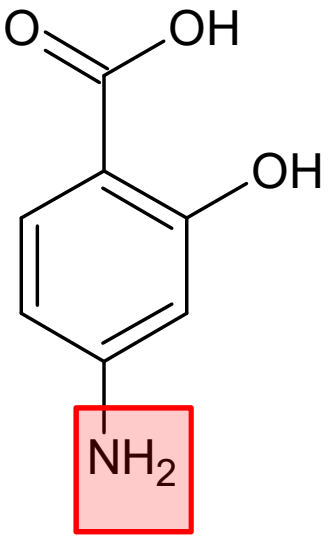


Para Amino Salicylic Acid = PASA

- Second line
- MOA: as anti-metabolite:

✓ interfering with the incorporation of PABA in FA

✓ acts similar to sulfonamides: ?



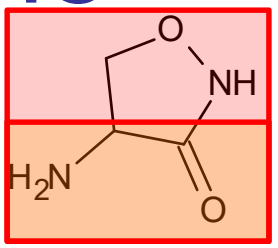
- SAR
- Metabolism:

✓ acetylation

✓ Glu & Gly conjugation

- Discuss about co-administration with INH.

Cyclic Peptide: Cycloserine

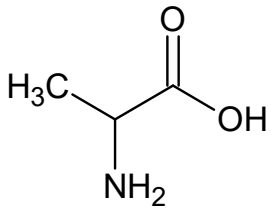


- Second line
- Isolated from *Streptomyces orchidaceous*
- *MOA:* prevent synthesis of peptidoglycan synthesis via interfering Ala-racemase & D-Ala-D-Ala ligase
- SAR:

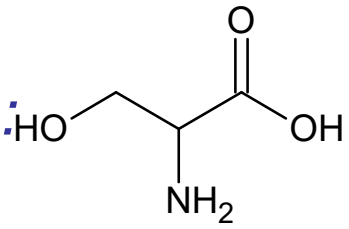
✓ 4-amino-3-isoxazolidinone: *D(+)*

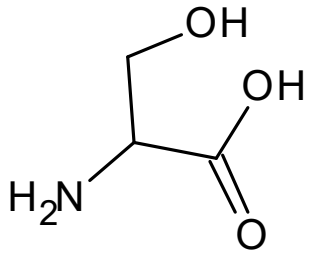
✓ *rigid analogue of D-Alanine & D-Serine: D(+)*

Alanine:



Serine:





Sites of Action for Cycloserine

- D- Ala racemase & D-Ala ligase

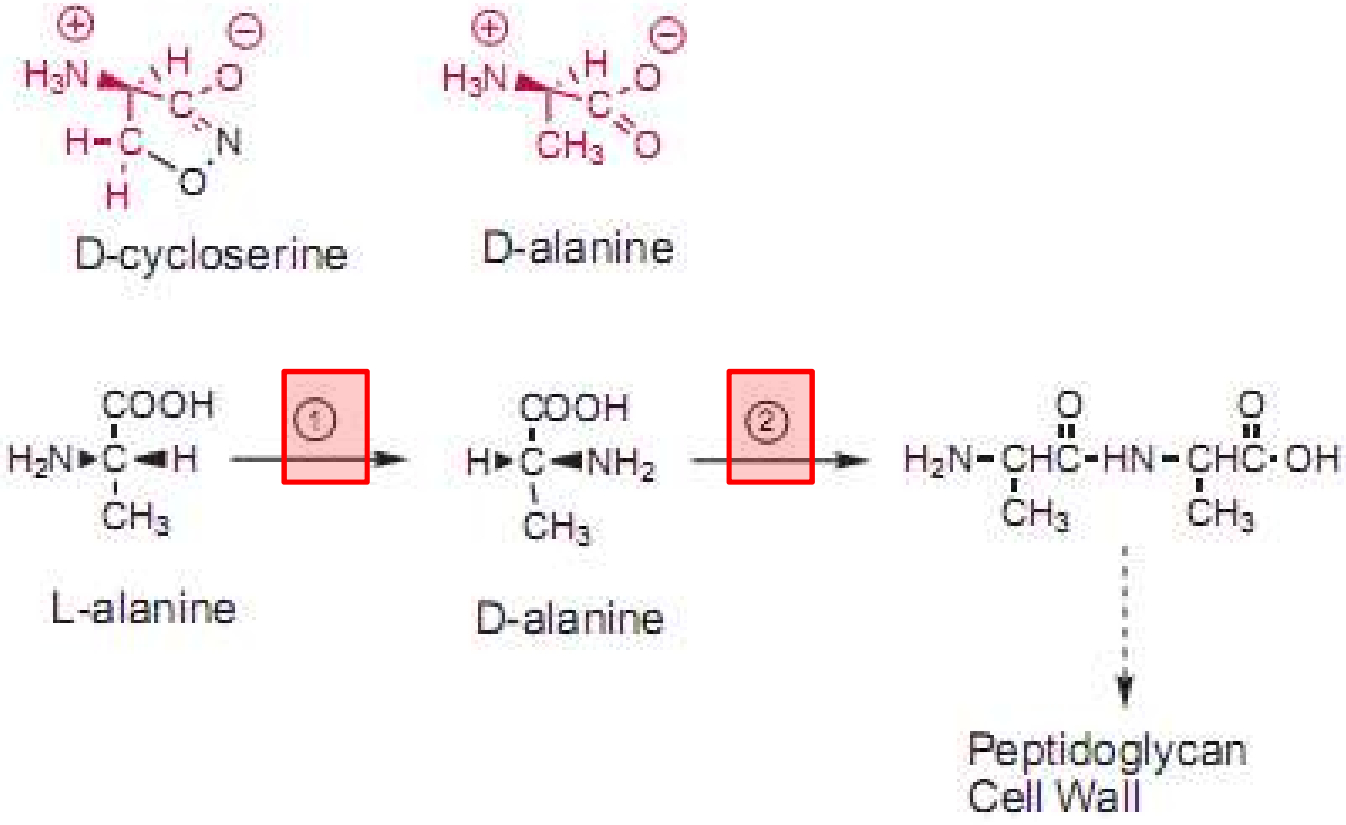
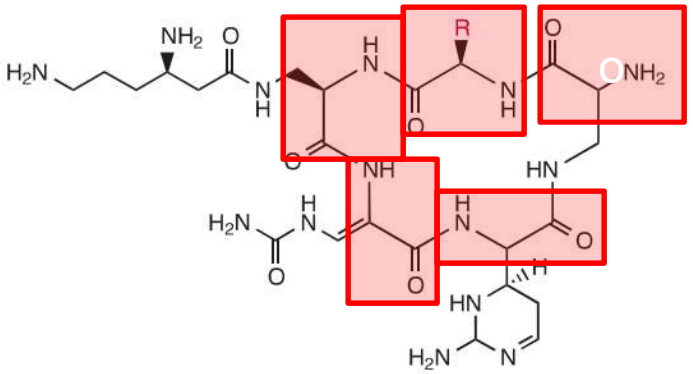


FIGURE 36.15 Sites of action of D-cycloserine: 1, D-alanine racemase; 2, D-alanine ligase.

Cyclic Peptide: Capreomycin

- Second line
- From: Streptomyces *capreolus*
- Similar to viomycin:
- Bacteriostatic
- MOA:



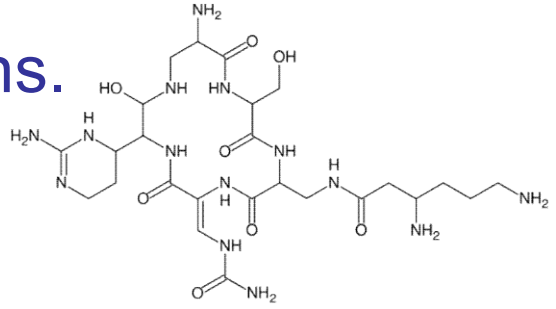
Capreomycin

✓ protein synthesis Inhibitor on mRNA at 70S ribosome

✓ through binding to 30S &/or *50S*

✓ also binds to components in the bacterial cell:

✓ result in the production of abnormal proteins.

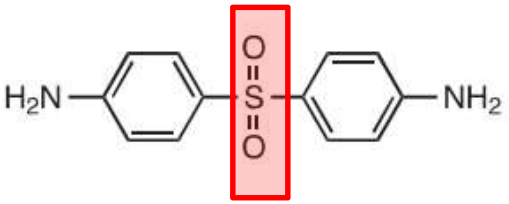


- SAR:

✓ cyclic penta-peptide

Sulfones: Dapsone

- Against T. *leprae*
- MOA: similar to sulfonamide:



4,4'-Diaminodiphenylsulfone (Dapsone)

✓interfering with the incorporation of PABA in FA

✓ anti-inflammatory:

✓ by inh. of myelo-peroxidase catalyzed reactions

- SAR

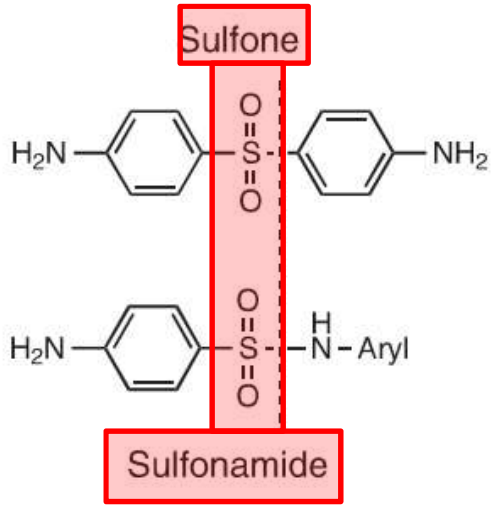
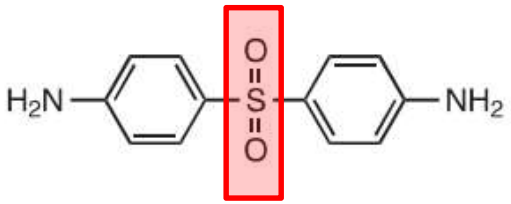


Figure 29.55 Structural comparison of sulfones versus sulfonamide.

Dapsone: SAR

- SAR:

✓ di-amino-di-phenyl-sulfone



4,4'-Diaminodiphenylsulfone (Dapsone)

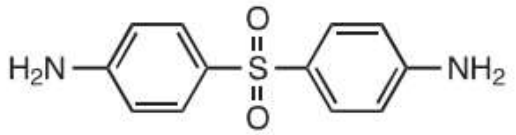
- Water insoluble
- Very weakly basic: pk_a = 1.0
- Modifications:

✓ thiazol-sulfone: similar activity

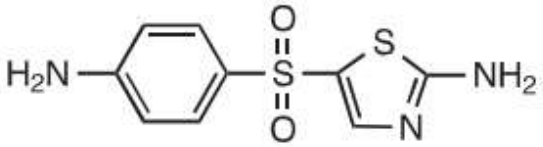
✓ aceto-sulfone: reduce activity; increase water sol.

✓ sulfoxone: adding sulfinate: improves water solubility

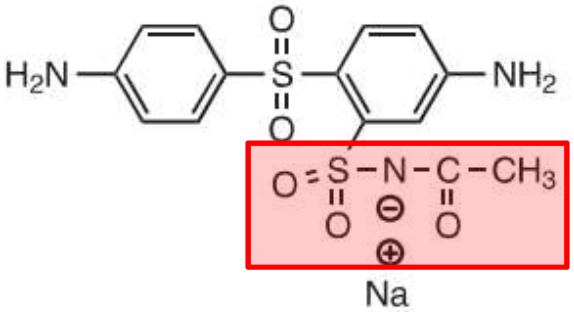
Dapsone Derivatives



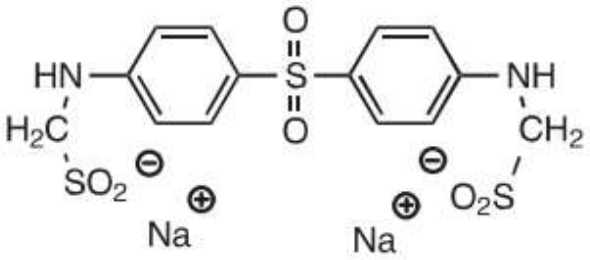
4,4'-Diaminodiphenylsulfone (Dapsone)



Thiazolsulfone



Acetosulfone



Sulfoxone sodium

Metabolism of Dapsone

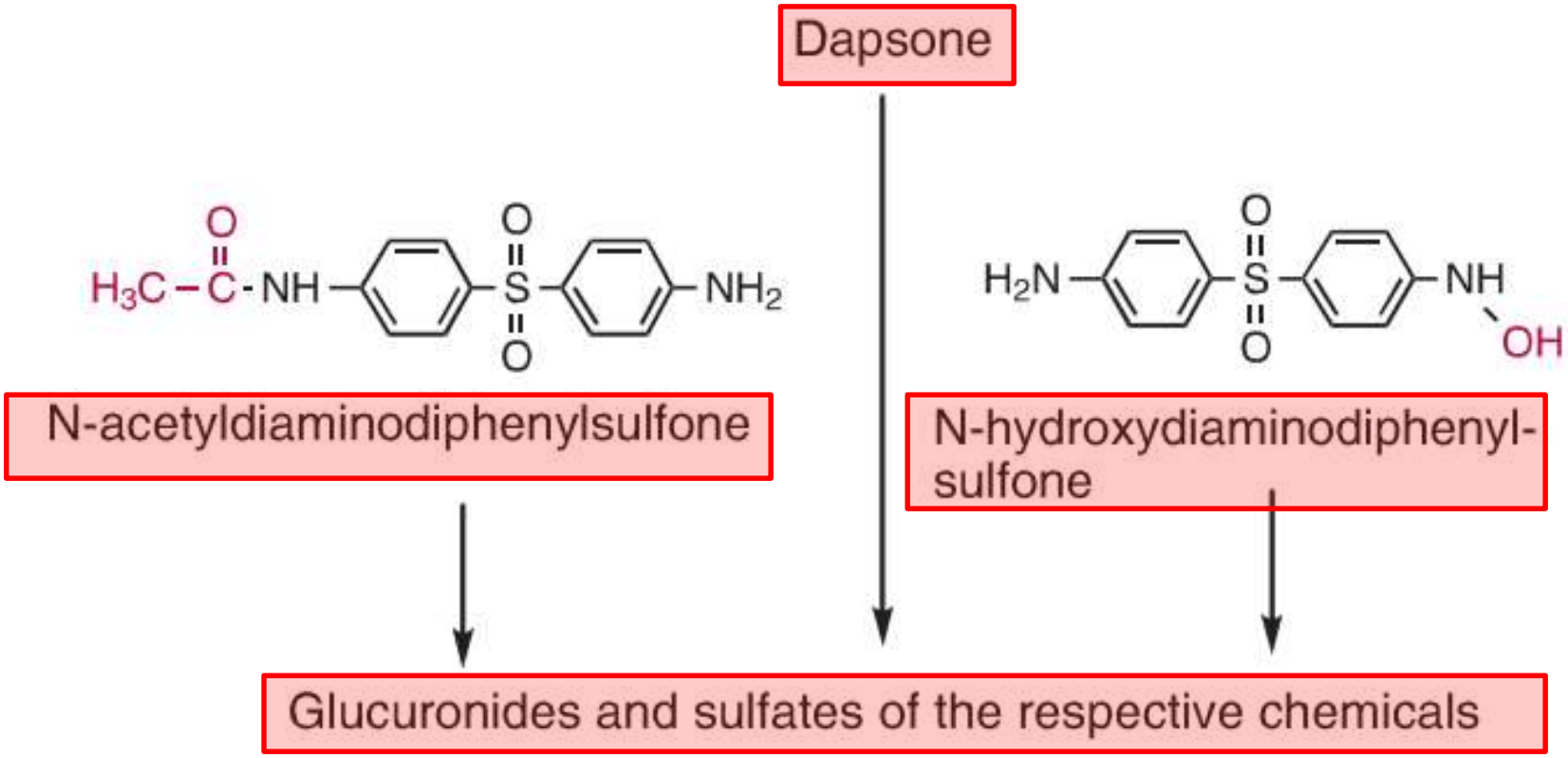


Figure 29.56 Metabolites of dapsone.

Phenazine: Clofazimine (Lamprene®)

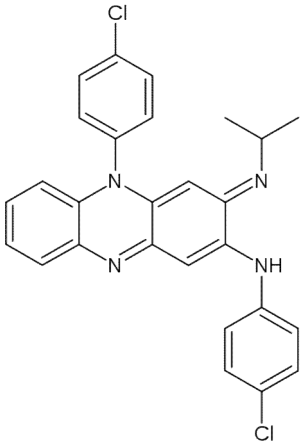
- Second line in leprosy
- Against non-tuberculous mycobacterium infections
- MOA:

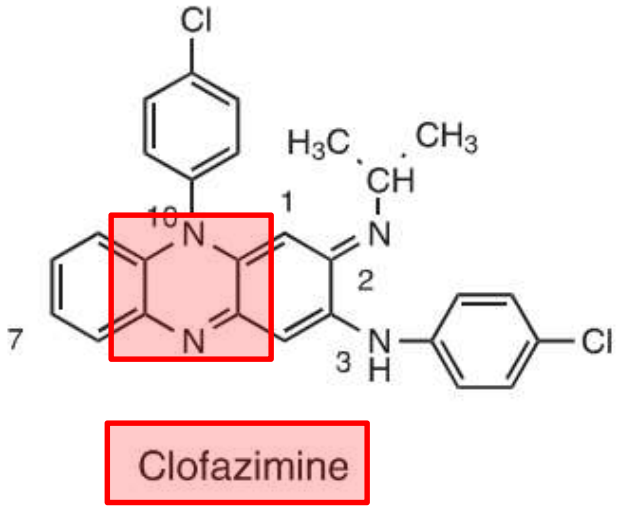
✓ intracellular redox cycling

✓ membrane disruption

✓ increase PG synthesis & generation of oxidants by neutrophils

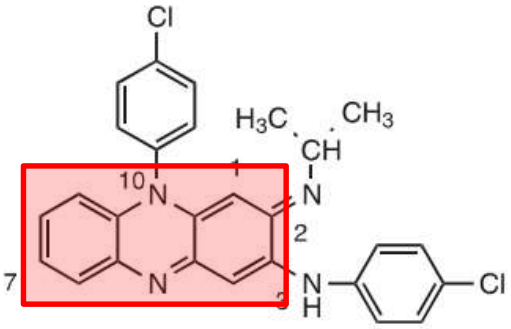
- SAR: …
- Dosage form: Cap 50mg





Clofazimine

Clofazimine: SAR



Clofazimine

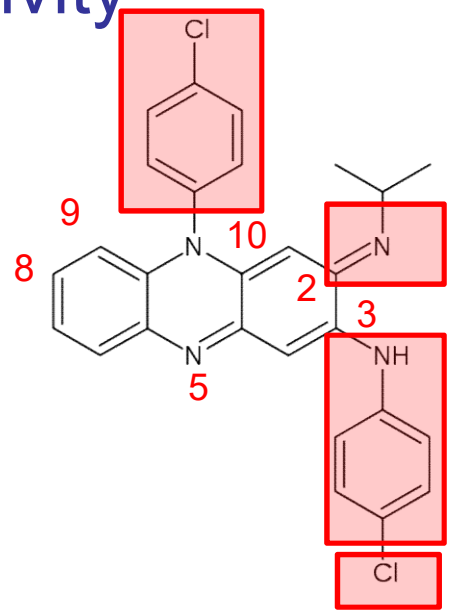
- Phenazine based: di-benzo-pyrazine
- 2-imino:

✓ alkylation or cylco-alkylation: improved activity

- 3- anilino:

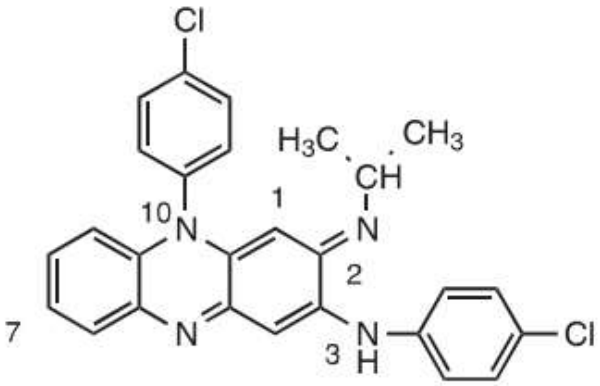
✓ p-chloro: not essential: but increases activity

- N10: p-chloro-phenyl



- Pro-oxidative activity
- water in-soluble dye: dark red
- Lipophilicity: storage in fat tissue

Metabolism of Clofazimine



Clofazimine

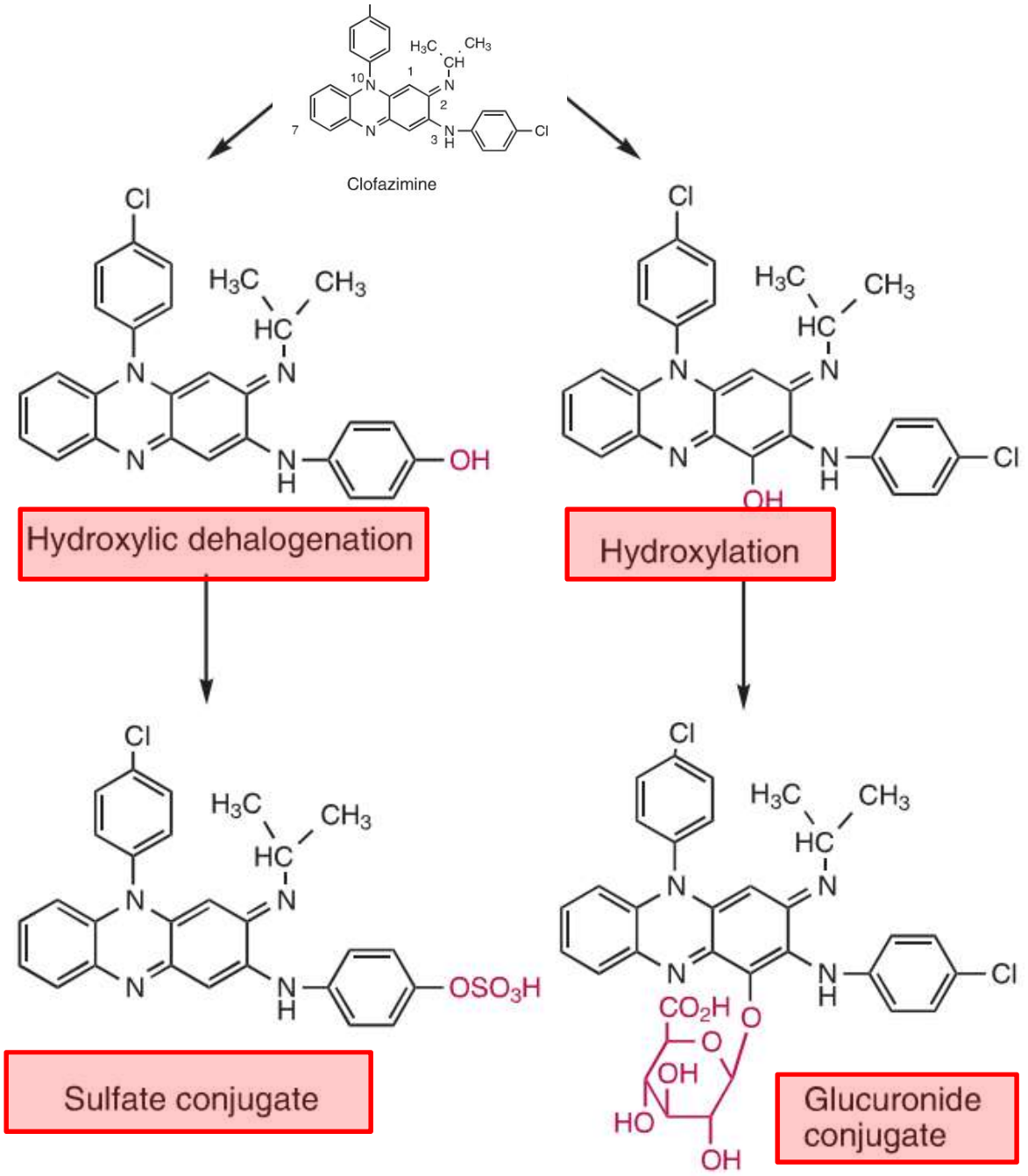
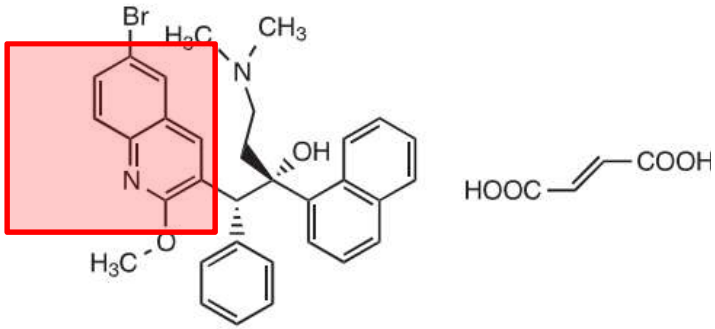


Figure 29.57 Human metabolic products of clofazimine.

Quinoline: Bedaquiline

- Newest against MDR-TB



Bedaquline fumarate

- MOA:

✓time-dep. mycobacterium growth inhibitor

✓through C-ring ATP synthase

✓block electro-chemical gradient energy source

Bedaquiline Binding Sites

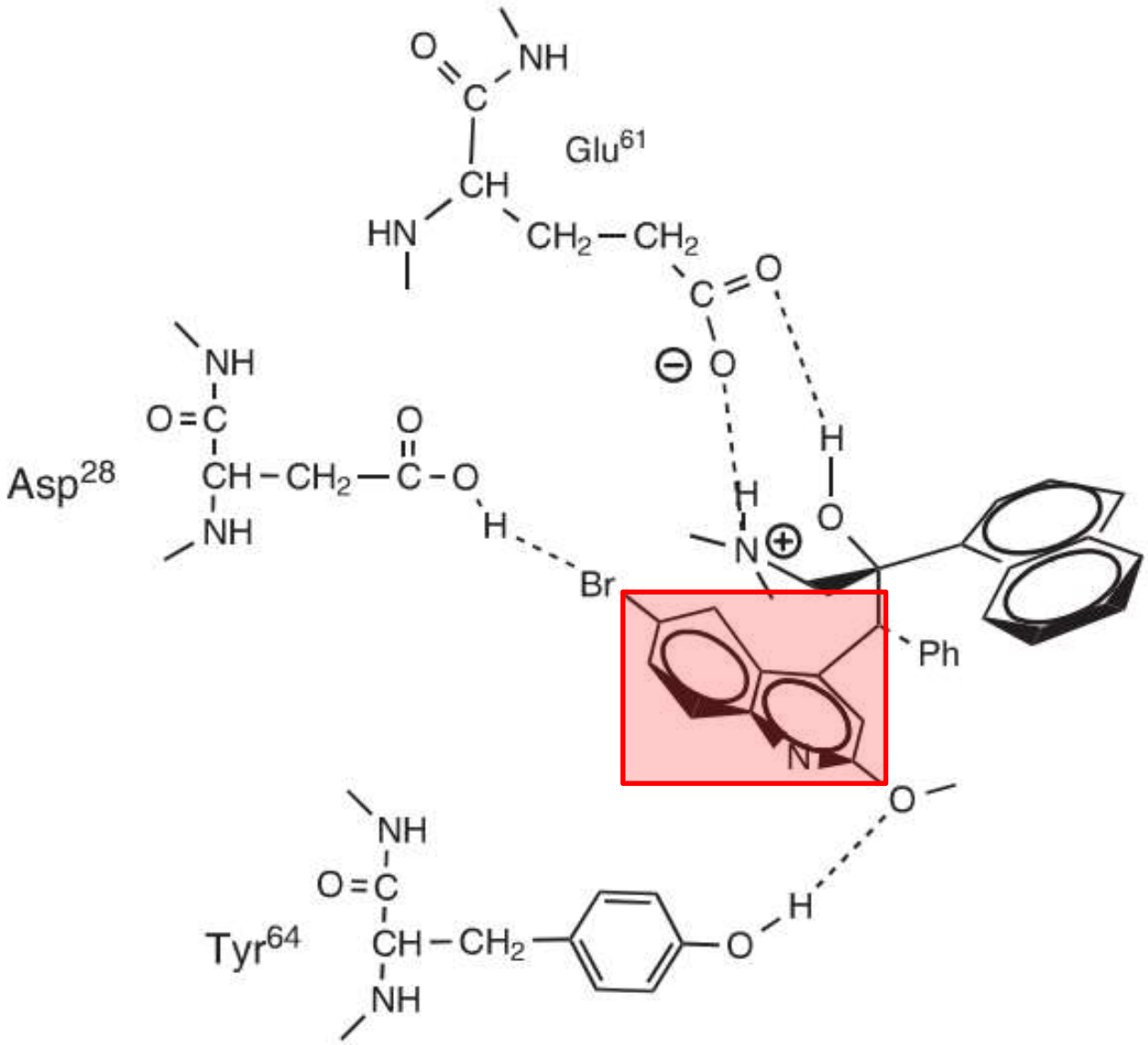


Figure 29.52 Binding of bedaquiline and amino acids in ATP (adenosine triphosphate) synthase C-subunit of *Mycobacterium tuberculosis*.

Fluoroquinolones

- MOA: DNA Gyrase inhibitor

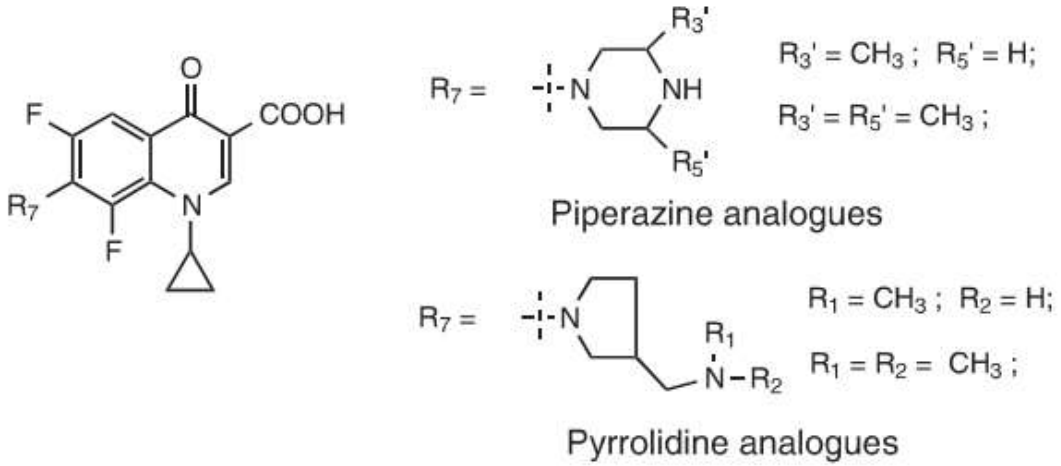
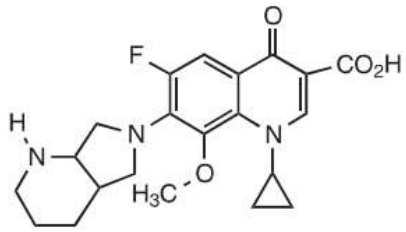


Figure 29.53 4-Quinolones demonstrating high activity against mycobacteria.

Ofloxacin (racemic)(Floxin)
Levofloxacin (1-*S*)(Levaquin)



Moxifloxacin (Avelox)

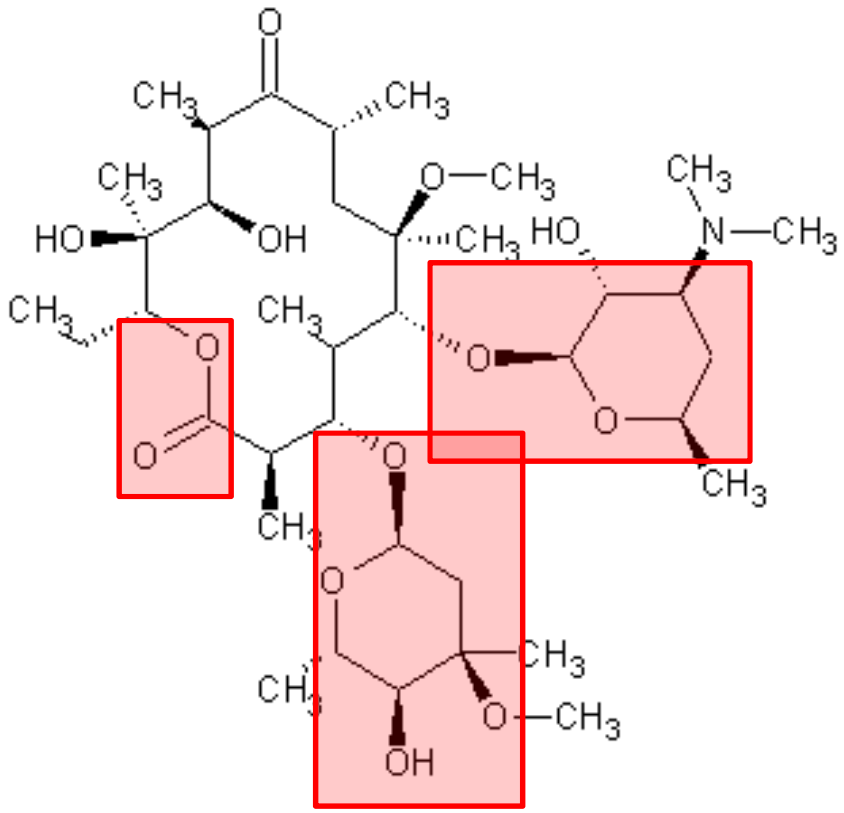
Figure 29.54 Fluoroquinolones active against *Mycobacterium tuberculosis*.

Macrolides: Clarithromycin & Azithromycin

- MOA: Pr synthesis inhibitor
- SAR:

✓ macrocyclic lactone: 14 to 15 membered

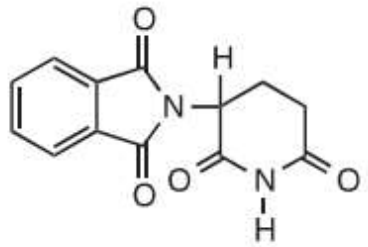
✓ two glycosidic sugars



Immunosuppressive Agent: Thalidomide

- In leprosy:

✓ against ENL (Erythema Nodosum Leprosum)



Thalidomide

- MOA:

✓ through controlling inflammatory cytokines

✓ inhibit synthesis & release of TNF-α by blood mononuclear cells