Antifungal Agents: Drugs Used to Treat Fungal Infections

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Foye's2019

CHAPTER 31

Drugs Used to Treat Fungal Infections

Robert K. Griffith

Drugs covered in this chapter[a]:

POLYENES
- Amphotericin B
- Natamycin
- Nystatin

AZOLES
- Butoconazole
- Clotrimazole
- Econazole
- Efinaconazole
- Fluconazole
- Flutrimazole
- Isavuconazole
- Itraconazole
- Ketoconazole
- Luliconazole
- Miconazole
- Oxiconazole
- Posaconazole
- Sertaconazole
- Sulconazole
- Terconazole
- Tioconazole
- Voriconazole

ALLYL AMINES
- Butenafine
- Naftifine
- Terbinafine

ECHINOCANDINS
- Anidulafungin
- Caspofungin
- Micafungin

MISCELLANEOUS
- *Amorolfine*[a]
- Ciclopirox
- Flucytosine
- Griseofulvin
- Tavaborole
- Tolnaftate
- Undecylenic acid

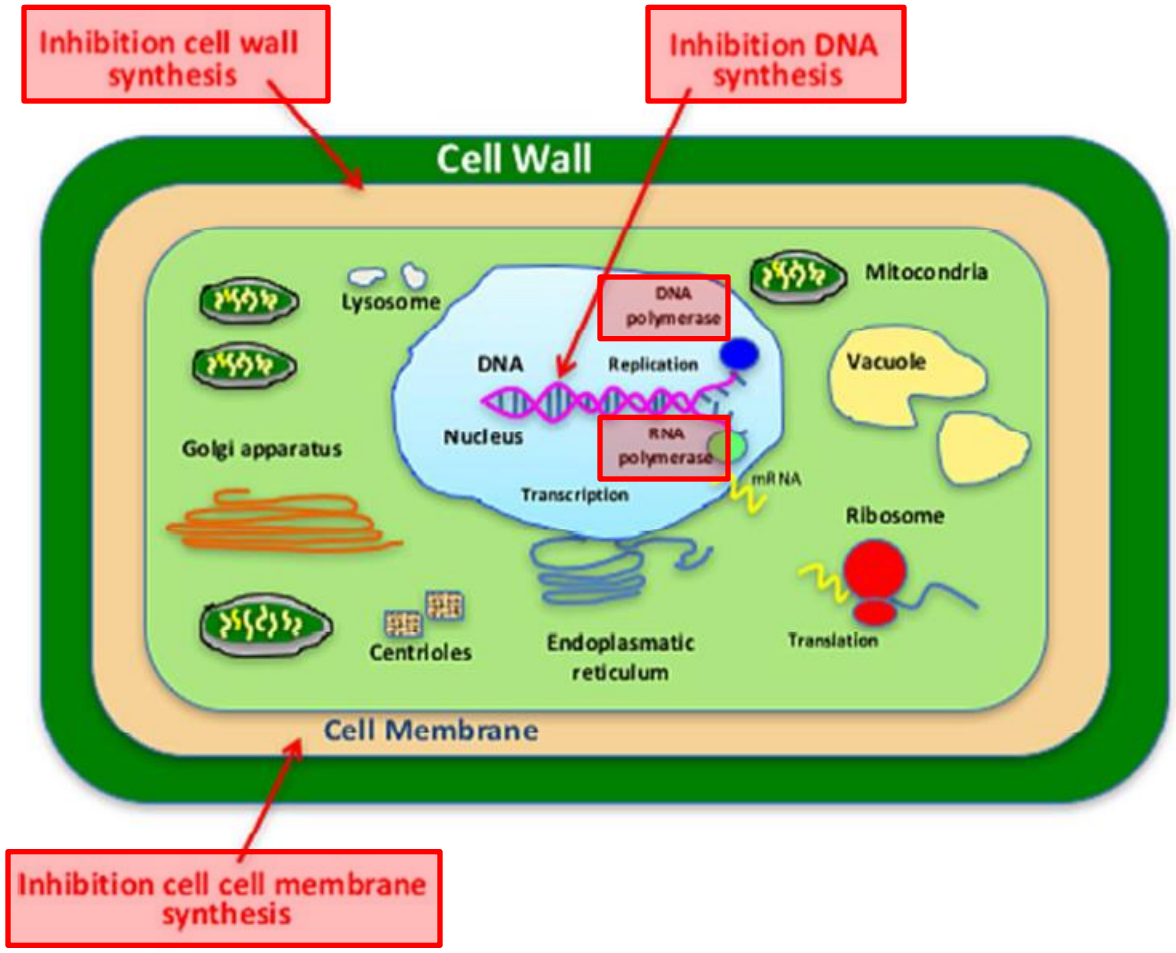
[a]Not approved for market in the United States, but is approved in Australia and the UK and can readily be purchased online.

Types of Fungus

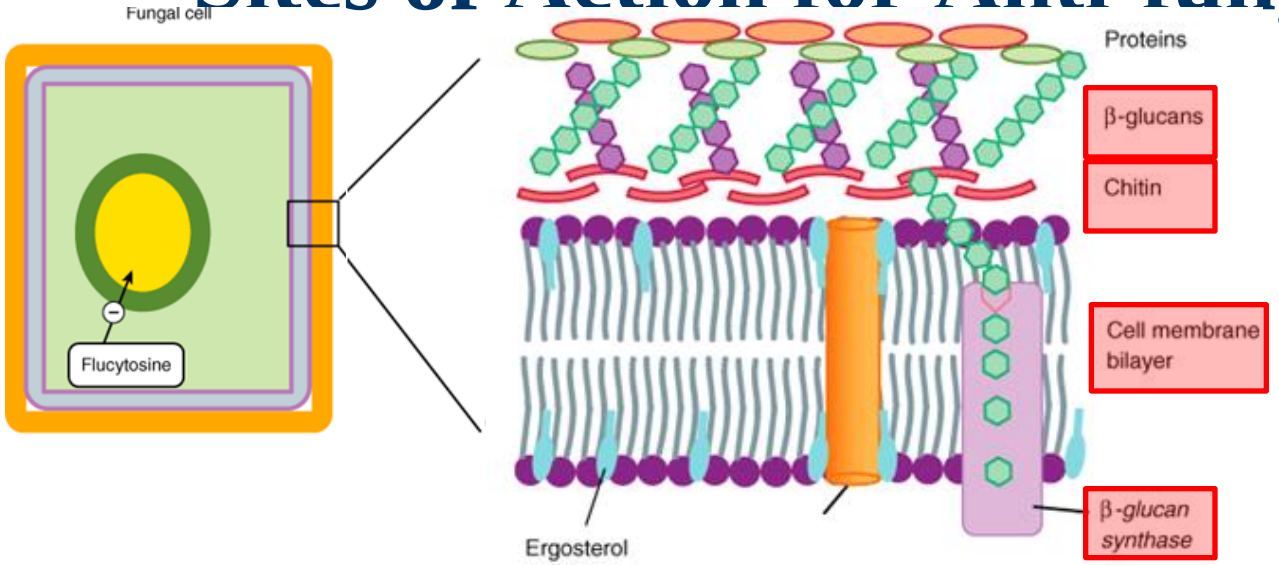
- Eukaryotes:
- Yeast: candida; cryptococcus
- Mold: Aspergillus
- Rusts
- Mushrooms

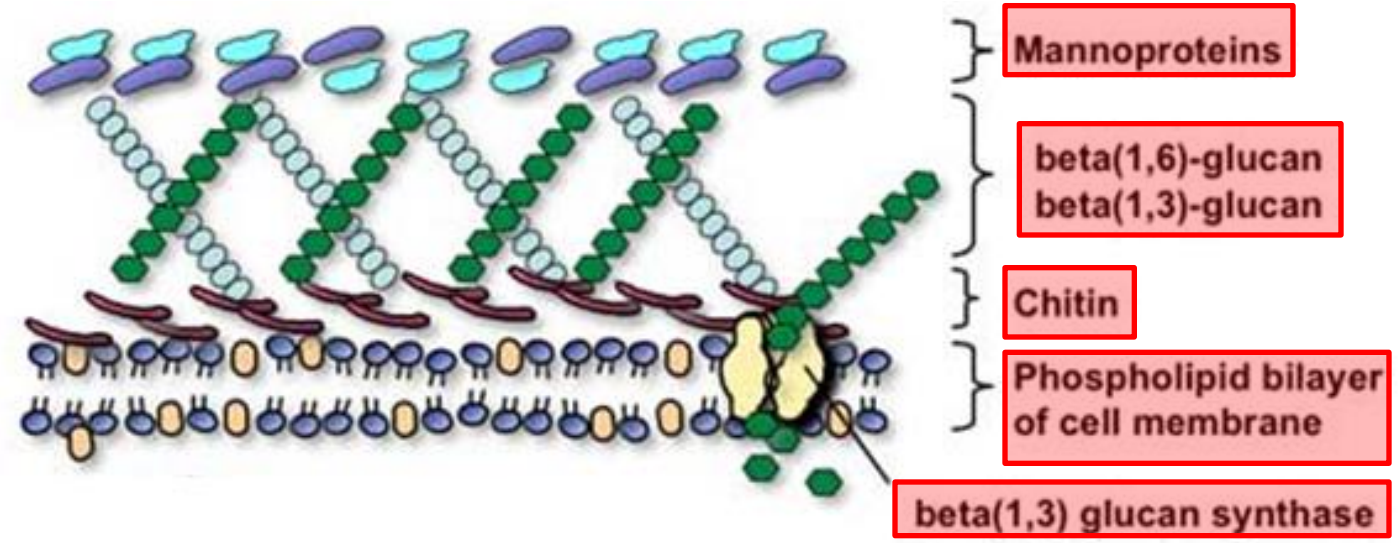
…

Fungus Cell (Cell Membrane & Cell wall) & Sites of Action for Anti-fungal Agents



Fungus Cell (Cell Membrane & Cell wall) & Sites of Action for Anti-fungal Agents





Pharmacologic Classification of Antifungal Agents

1. Cell membrane non-selective interacting agents: undecylenic acid, phenols

2. Cell membrane disruptors: polyenes: amphotericin B; nystatin and …

3. DNA interfering: pyrimidine based: nucleoside providers: flucytosine

4. Microtubule inhibitor: griseofulvin

5. Ergosterol biosynthesis inhibitors:

a. Epoxidase inhibitor (Allyl amines): naftifine, tolnaftate, …

b. Demethylase inhibitor (Azoles): miconazole, ketoconazole, …

c. Reductase & isomerase inhibitor (Morpholines): fen-propi-morpholine

Pharmacologic Classification of Antifungal Agents – Contd.

6. Cell wall biosynthesis inhibitors:1,3-glucan synthase inhibitors:

- ✓ echino-candins: caspofungin
- ✓ pneumo-candins

7. Inositol Phosphoryl Ceramide (IPC) synthase inhibitors:

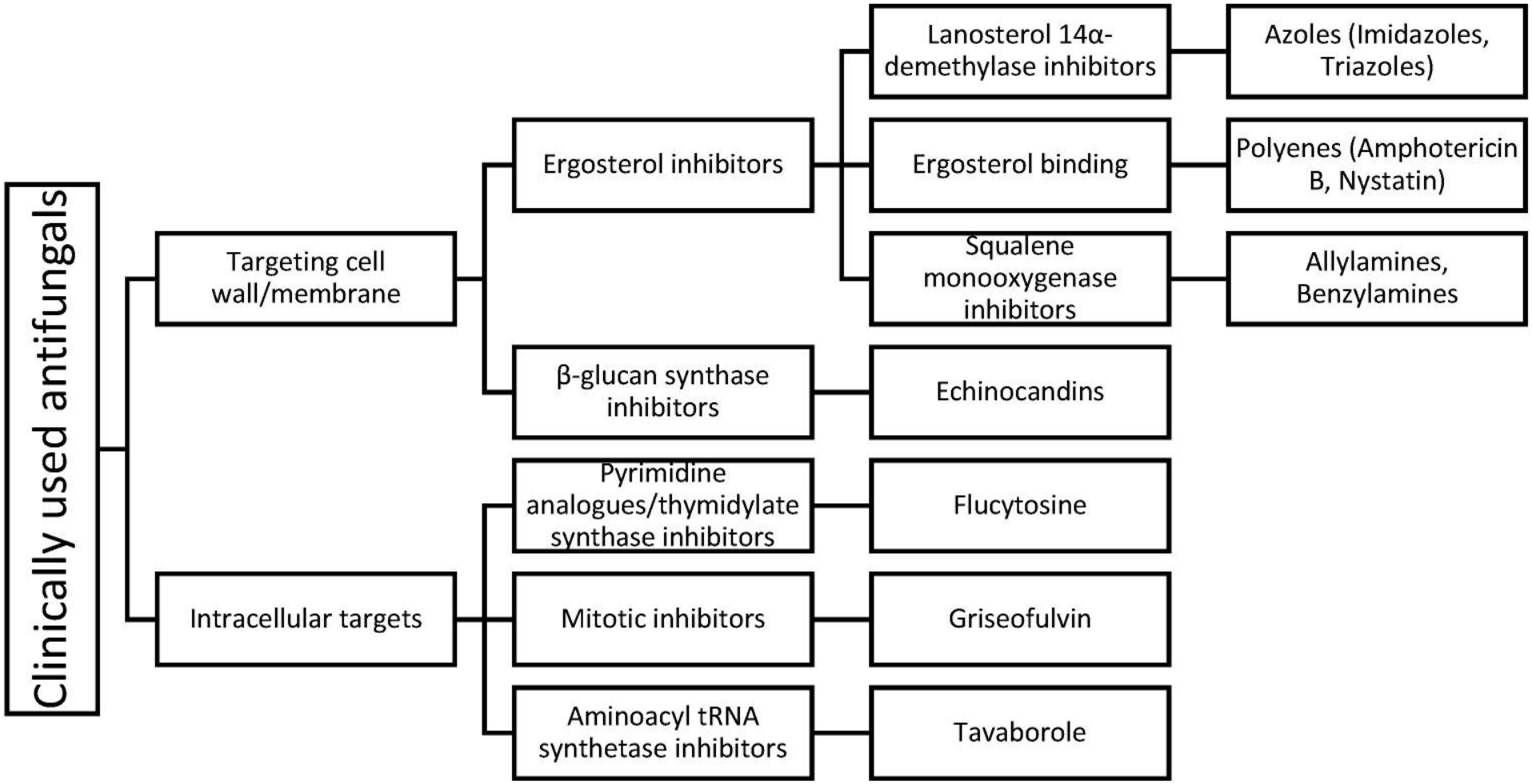
- ✓ cyclic peptides: pradimycin, benanomycin

8. Pentacyclic chelators: benanomycin A

9. Miscellaneous:

- ✓ unclear: might interfere with DNA biosynthesis or …: haloprogin
- ✓ cell metal dependent enzyme inhibitor through cation chelation: ciclopirox
- ✓ terminal A (adenosine) Leu tRNA binder: tavaborole
- ✓ DHODH inhibitor: orotomide (investigational)
- ✓ Gwt1 inhibitor: BIQ, … , fosmanogepix

Clinically Used Antifungals

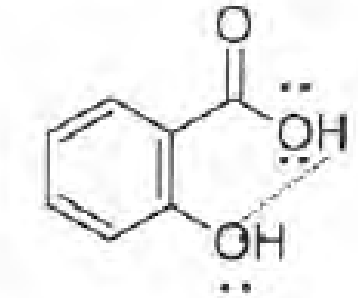


1. Cell Membrane Non-Selective Interacting Agents: Antifungal Agents: Acids/ Phenols

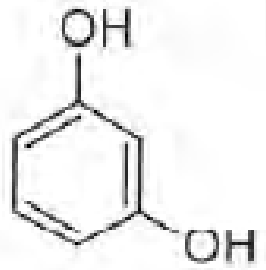
- Fatty acids (acids, salts): undecylenic acid: keratolytic

$$H_2C{=}{=}CH(CH_2)_8COOH$$

- Salicylic acid: antiseptic & keratolytic



- Phenols:
- ✓ resorcinol: antiseptic & keratolytic



1. Cell Membrane Non-Selective Interacting Agents: Topical Antifungal Acid

- Undecylenic acid 
- ✓ derived from castor oil
- ✓ as Zn salt

- MOA: non-specific interaction with components in cell membrane
- ✓ as fungistatic

- OTC for topical usage in dermatophytic infections

1. Cell Membrane Non-Selective Interacting Agents: Whitfield Ointment

- Introduced by a dermatologist called Arthur Whitfield (1868-1947)

- Includes mixture of benzoic acid (3%), salicylic acid (6%) in the base of lanolin or short chain alcohol or fatty alcohol

- Topical ointment applied in athlete's foot

- Not applied in thinner skin areas

2. Cell Membrane Disruptors: Polyenes

- Polyenes: amphotericin B, nystatin & natamycin
- SAR: chemistry:

✓ macrocyclic lactone (26 & 38 membered) + amino-sugar:

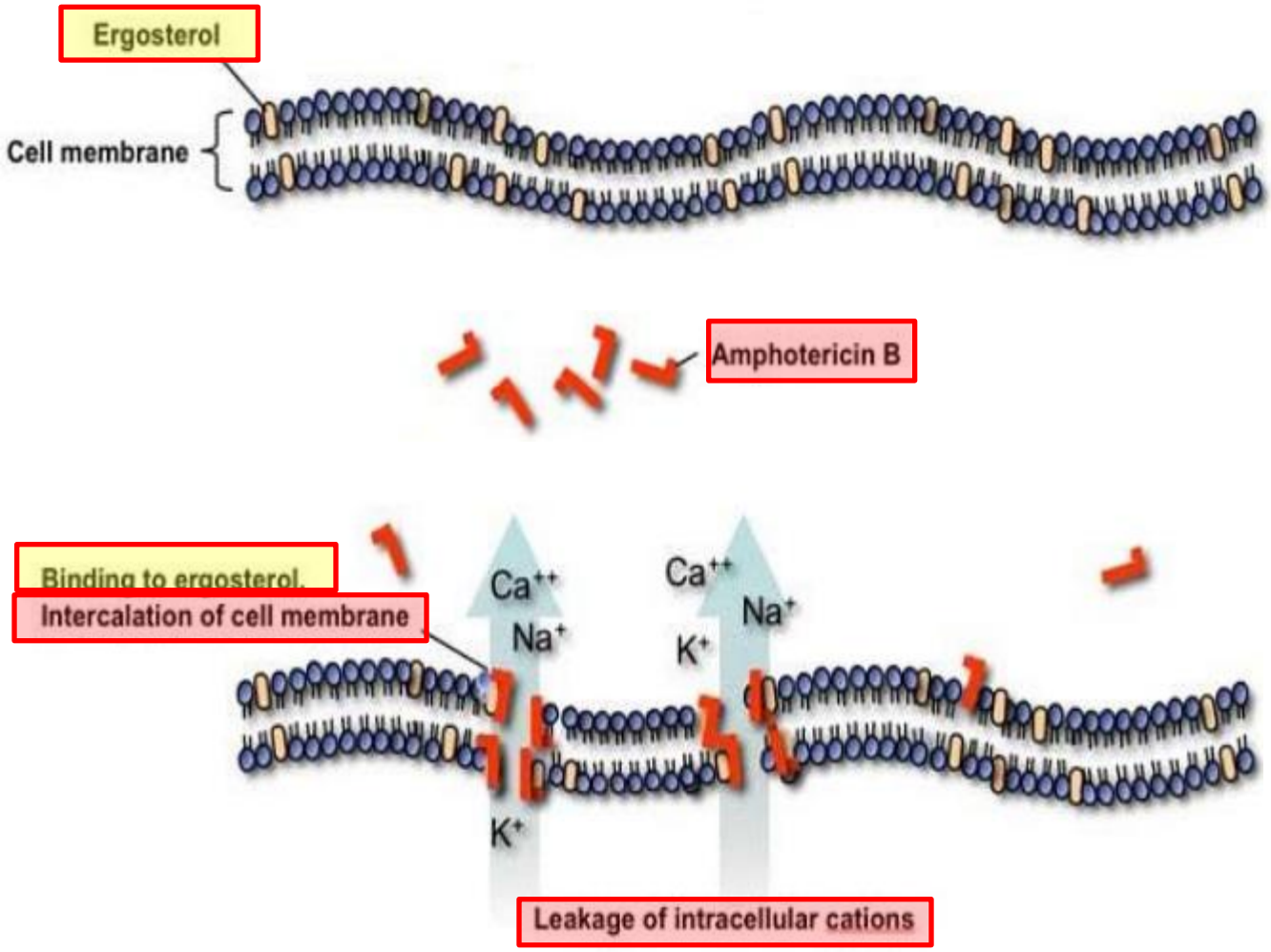
✓ lipophilic aglycone + hydrophilic glycone & hydroxylated portions

- MOA:

✓ affinity to sterols (ergosterol) in cell membrane: form pores

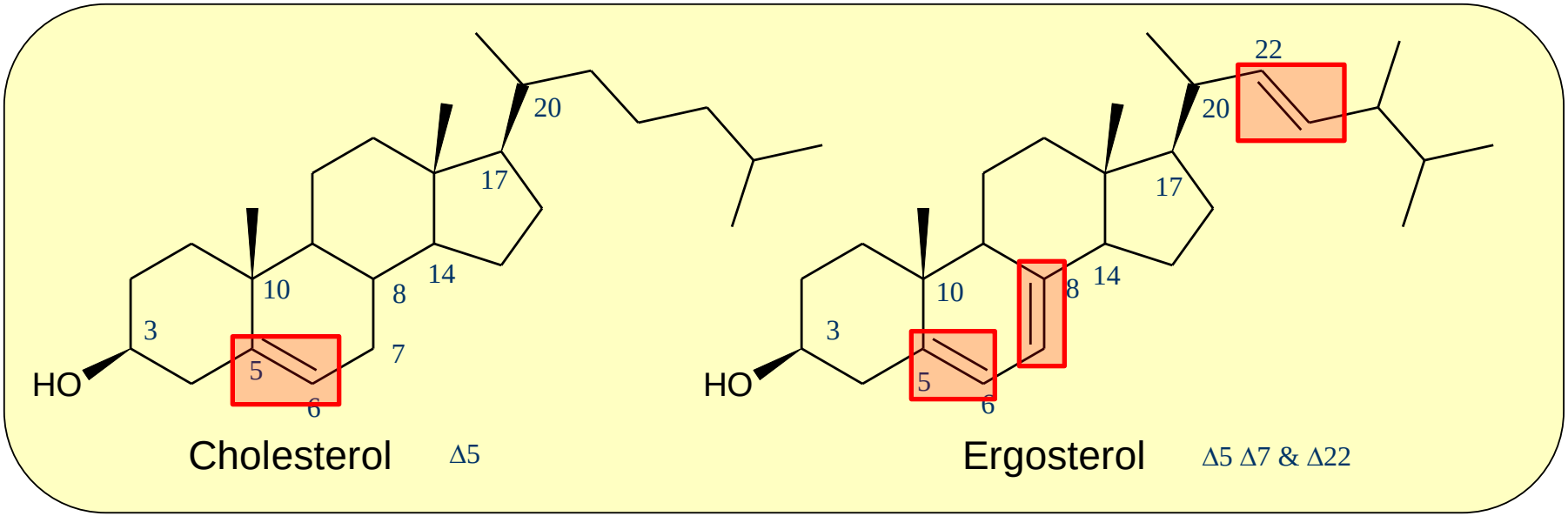
✓ so provide disruption & leakage in membrane

MOA for Polyenes on Cell Membrane of Fungi

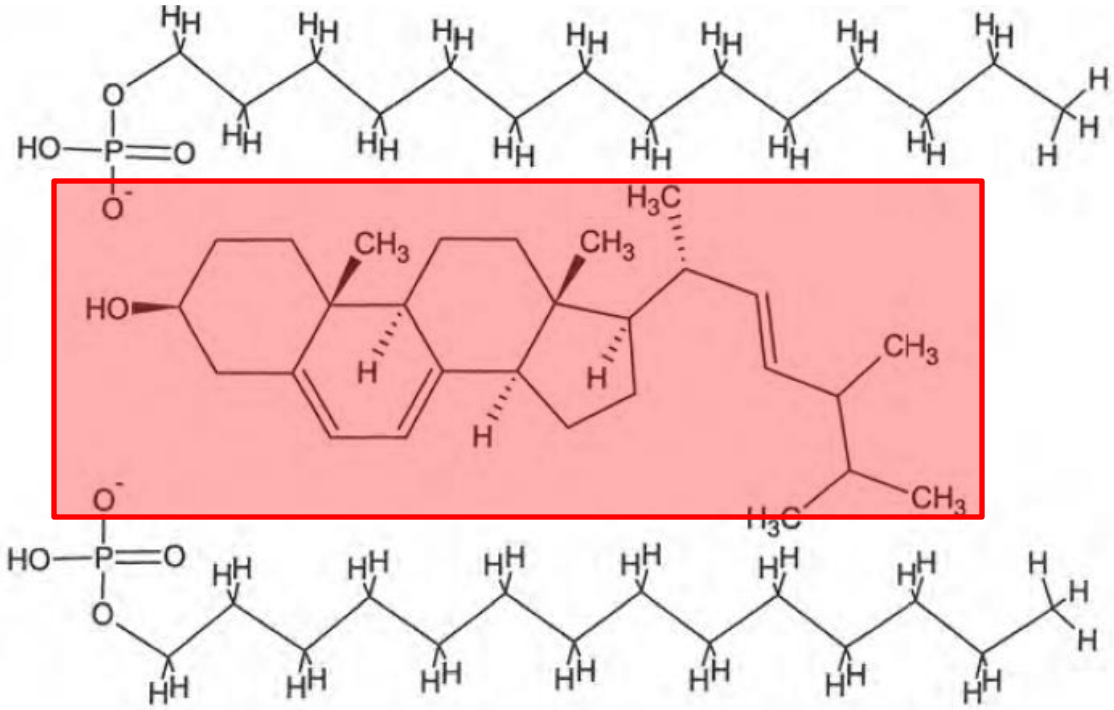


Sterols in Cell Membrane: Cholesterol in Human & Ergosterol in Fungi

- Compare their 27C structures.



Ergosterol in Lipid Bilayer



Ergosterol

Figure 6.1 • Ergosterol embedded in a lipid bilayer.

Cholesterol in Lipid Bilayer

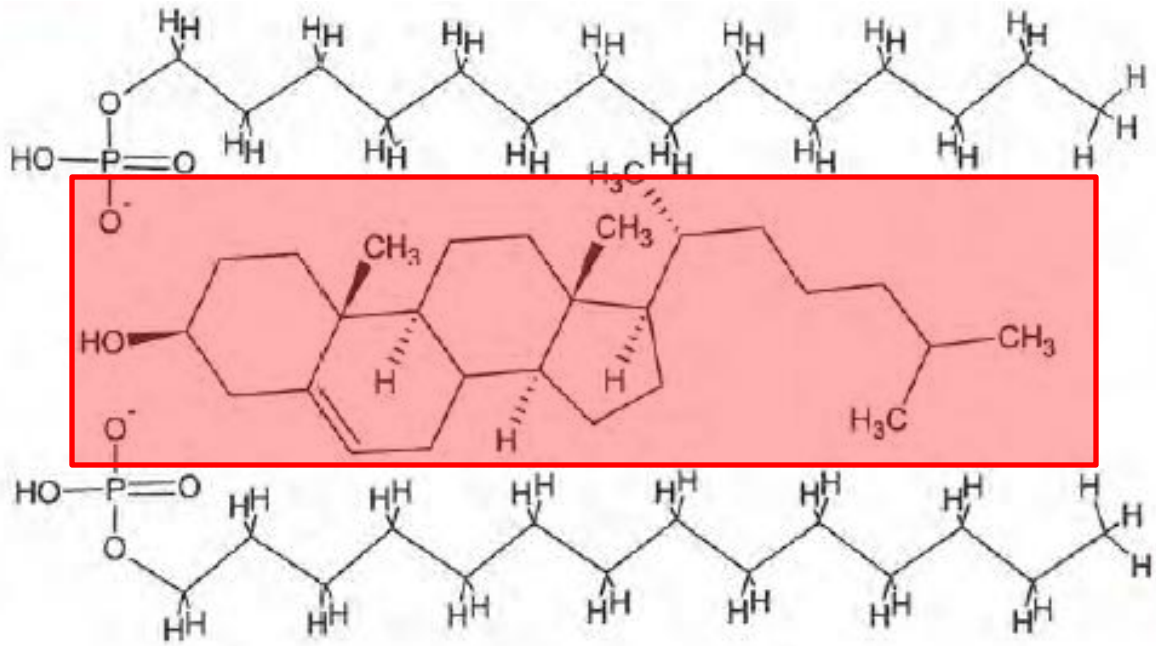
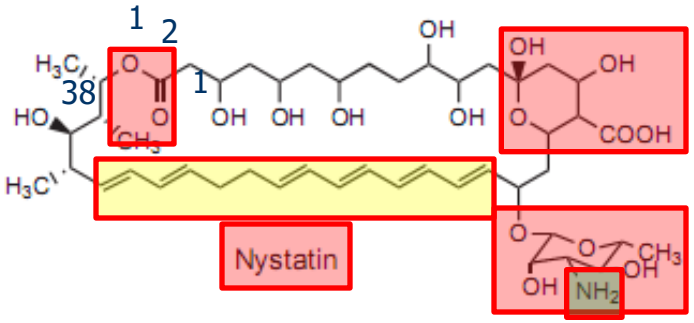


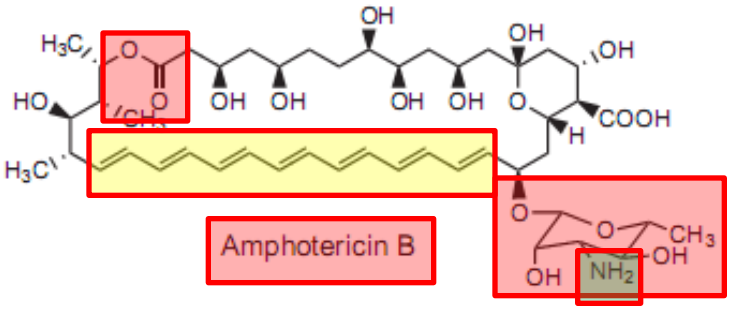
Figure 6.2 • Cholesterol embedded in a lipid bilayer.

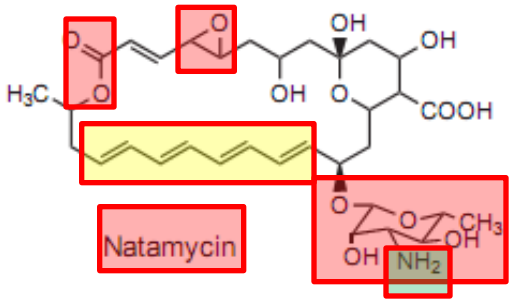
2. Cell Membrane Disruptors: Polyenes: SAR

- 38 membered lactone: nystatin & amphotericin B



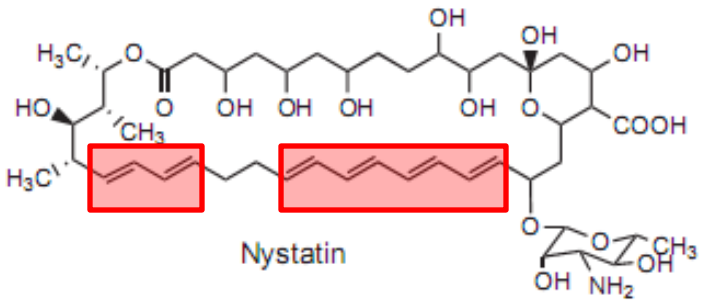
- 26 membered lactone: natamycin





2. Cell Membrane Disruptors: Polyenes: Nystatin

- Isolated from cultures of bacterium *streptomyces*
- Chemistry: 38 membered lactone: hexa-ene: not completely conjugated
  - ✓ aglycone: 38 membered nystatinolide & glycone: mycosamine
- Very little absorption
- Systemic usage is not recommended: too toxic
- Dosage forms:
  - ✓ powder to prepare oral drop: 100,000 IU
  - ✓ vaginal tab: 100,000 IU
  - ✓ oral tab: 500,000 IU
  - ✓ topical ointment: 100,000 IU

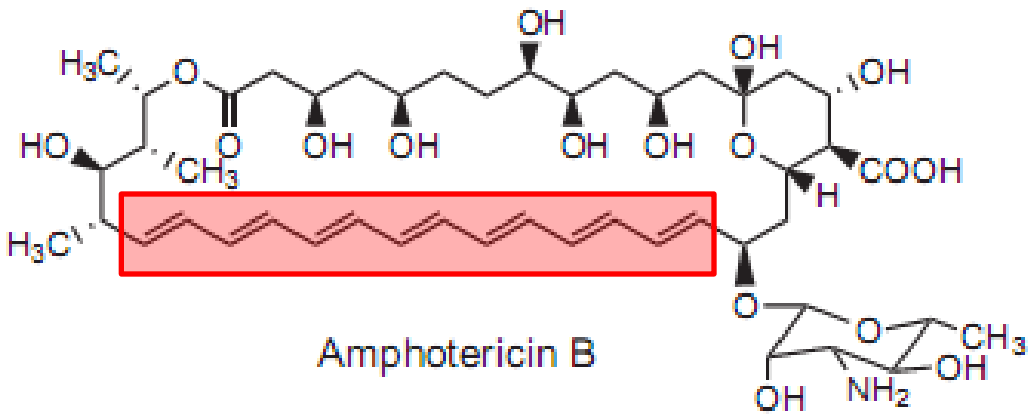


Nystatin

2. Cell Membrane Disruptors: Polyenes: Amphotericin B

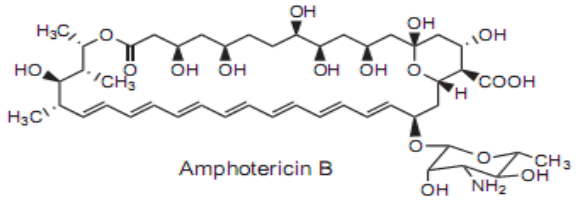
- Amphocin®; fungizone®
- Chemistry: 38 membered lactone: completely conjugated hepta-ene
- ✓ aglycone: 38 membered lactone & glycone: mycosamine
- The drug of choice for many systemic life threatening fungal infection

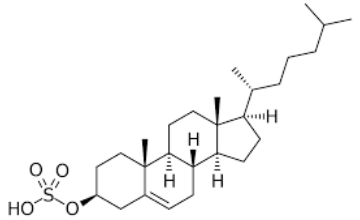
- Nephrotoxic & hepatotoxic: what is the solution?



Amphotericin B

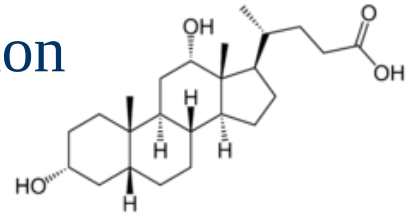
2. Cell Membrane Disruptors: Polyenes: Various Amphotericin B Derivatives & Formulations





- Amphotericin B cholesteryl sulfate: Amphotec®

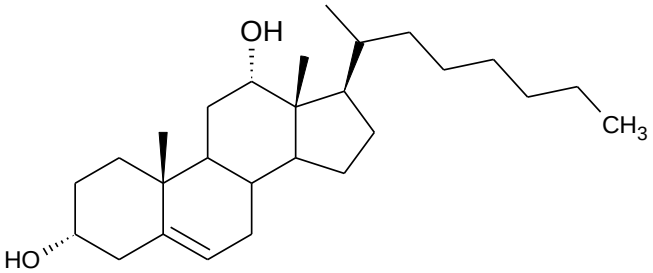
- Amphotericin B deoxy-cholate (C7-deoxy cholate): Amphocen®; Fungizone®
- ✓ a complex with C7-deoxy-cholic acid: IV administration



- Amphotericin B liposomal encapsulation: Amphonex®; AmBisome®
- Amphotericin B nano-liposomal encapsulation: topical gel
- Amphotericin B lipid (phospholipid) complex: Abelcet®
- Find the concentration in the current formulations in clinic.

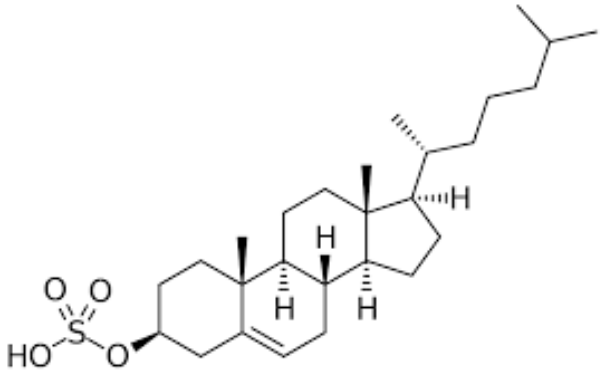
Structure of Cholesterol & Cholic Acid

- Cholesterol: 27C:



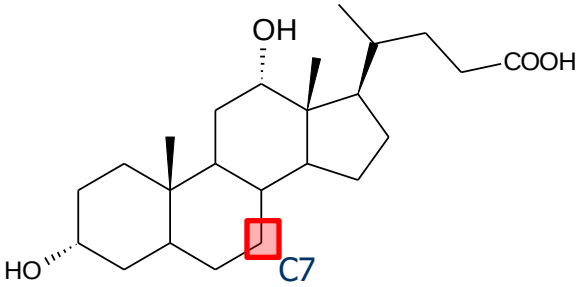
- Cholesteryl sulfate:

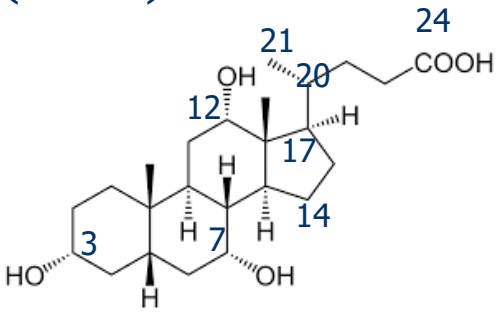
✓ C3-sulfate ester of cholesterol



- Deoxycholic acid: C7-deoxy cholic acid (24C)

✓ deoxycholate: C7-deoxy cholate



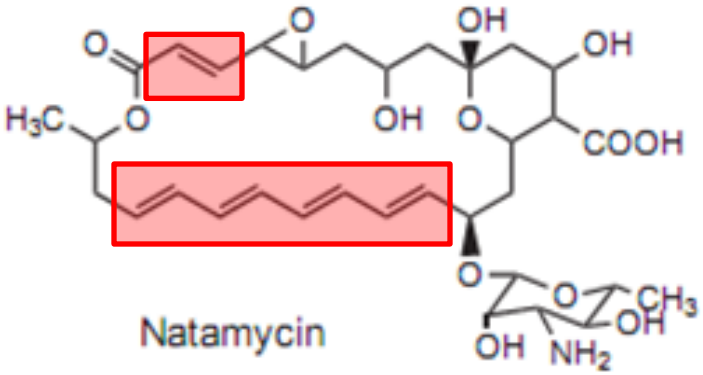


cholic acid

2. Cell Membrane Disruptors: Polyenes: Natamycin

- Chemistry: 38 membered lactone: tetraene to penta-ene
  - ✓ aglycone: 38 membered & glycone: mycosamine

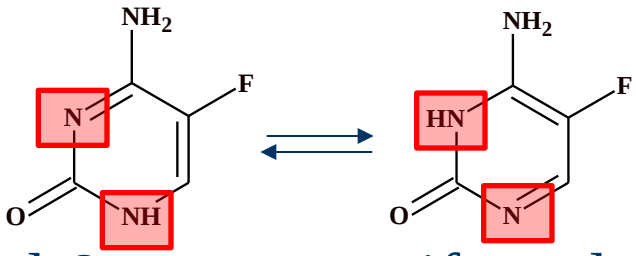
- Dosage form: eye drop: 5%



Natamycin

3. DNA Interfering Pyrimidine: Nucleoside Provider

- Flucytosine: 5-Fluoro-Cytosine; 5-FC



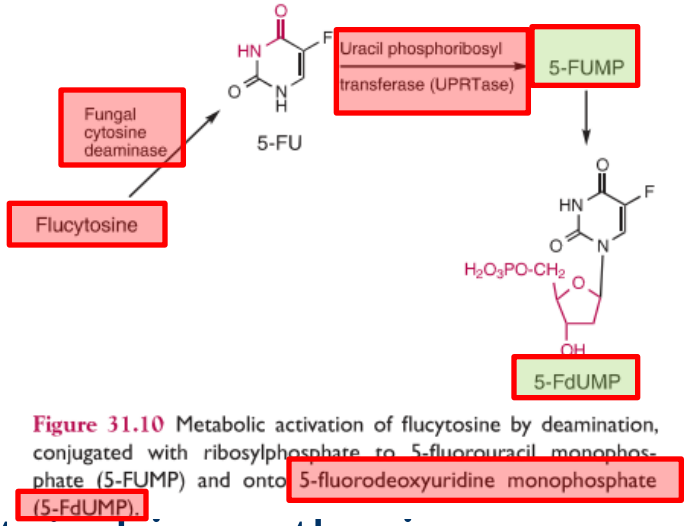


Figure 31.10 Metabolic activation of flucytosine by deamination, conjugated with ribosylphosphate to 5-fluorouracil monophosphate (5-FUMP) and onto 5-fluorodeoxyuridine monophosphate (5-FdUMP).

- Powerful & narrow antifungal
- MOA: interfere with thymine, RNA & protein biosynthesis

✓ a prodrug: is activated by fungal cytosine deaminase & also by intestinal flora:

✓ intermediate metabolite: 5-FU: also toxic to human

- Active metabolites:

✓ 5-FUMP: interfere with RNA & protein biosynthesis

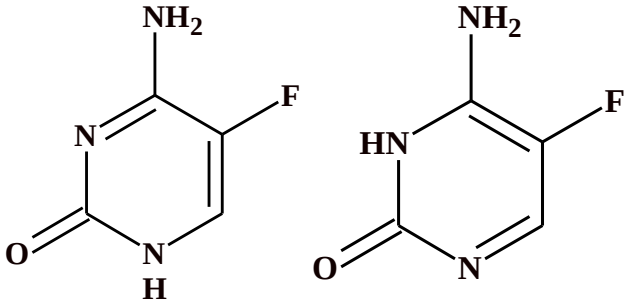
✓ 5-FdUMP through 5-FdUDP: thymidylate synthase inhibitor: Thymineless in DNA synthesis

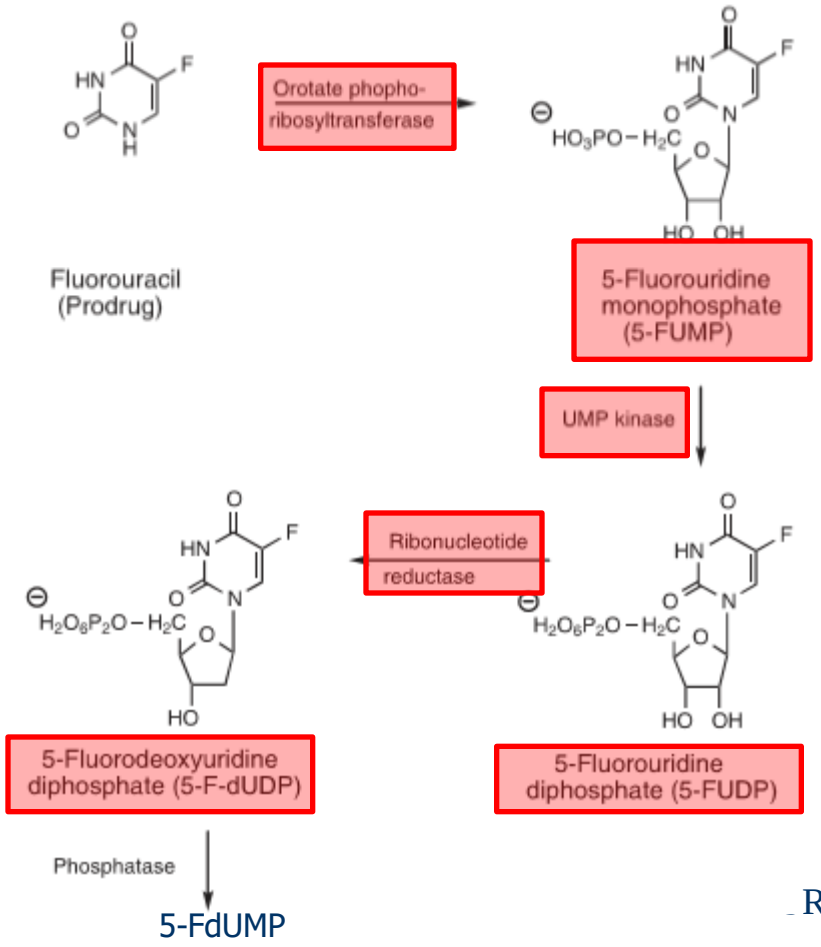
✓ 5-FdUTP: interfere with RNA biosynthesis

- SAR: …

3. DNA Interfering Pyrimidine: 5-FC Bio-Activation

- Systemic infection: *Cryptococcus* & *Candida*
- Resistant mechanisms: what is solution?





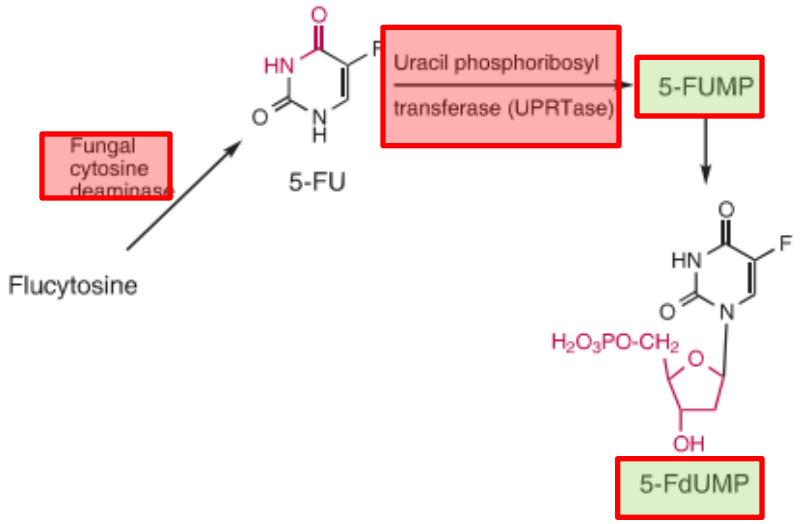


Figure 31.10 Metabolic activation of flucytosine by deamination, conjugated with ribosylphosphate to 5-fluorouracil monophosphate (5-FUMP) and onto 5-fluorodeoxyuridine monophosphate (5-FdUMP).

Thymidylate Synthase & 5-FdUMP

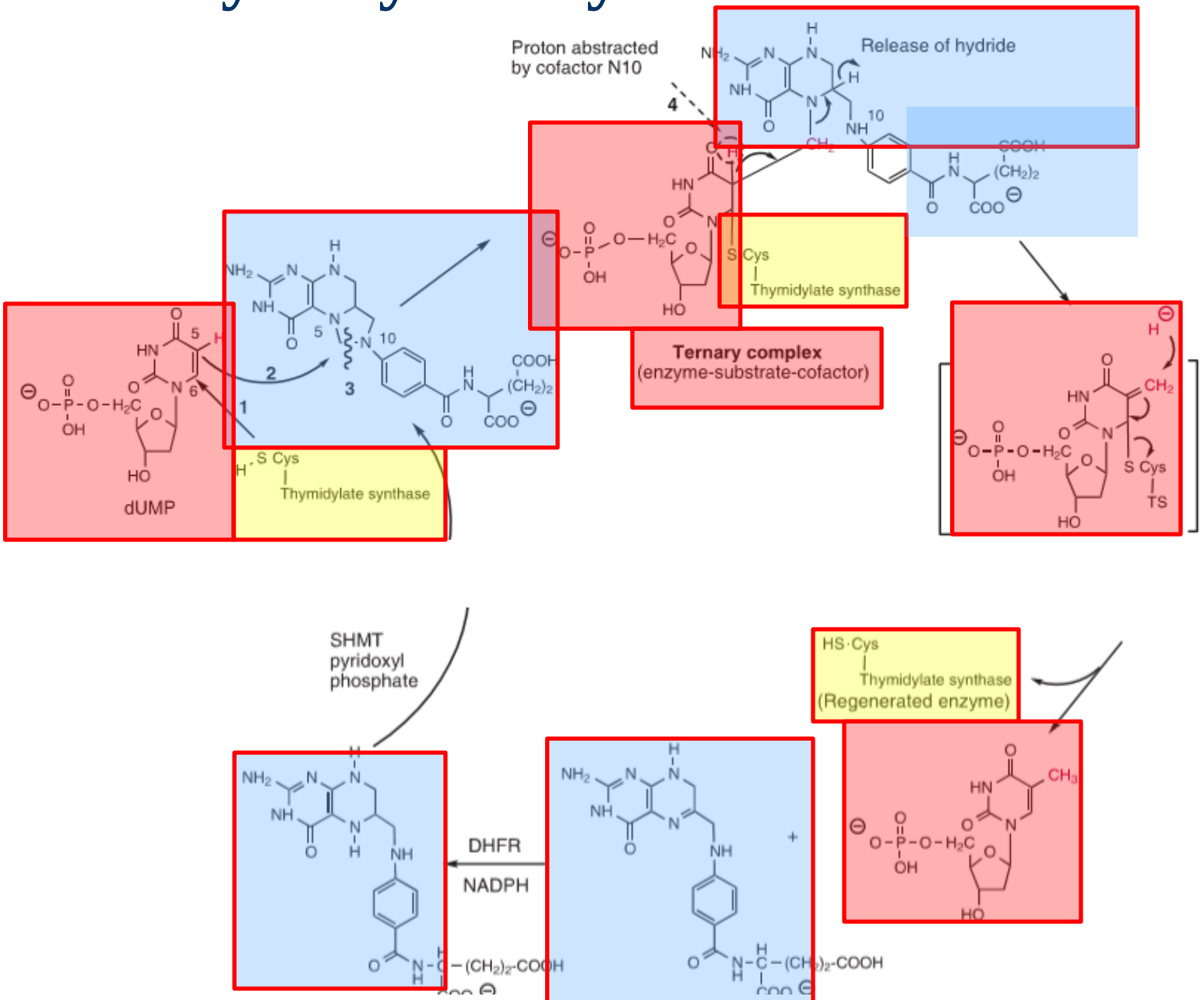
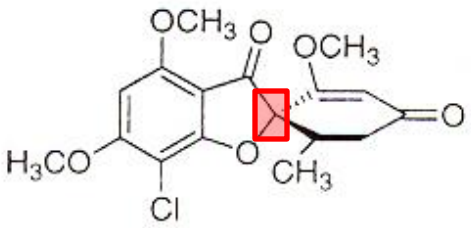


Figure 33.45 Synthesis of deoxythmidine monophosphate (dTMP). DHFR, dihydrofolate reductase; SHMT, serine hydroxymethyltransferase; TS, thymidylate synthase.

4. Microtubule Inhibitor: Griseofulvin

- Chemistry: spiro structure
- Produced by an unusual *Penicillium*
- MOA:



Griseofulvin

- ✓ bind to the tubulin protein
- ✓ interfere with the function of mitotic spindle: inhibit cell division
- ✓ may interfere directly with DNA replication
- ✓ incorporates into keratin & protects newly formed skin
- ✓ SAR: …
- Clinical application: superficial fungal infection: fingernail & toenail
- Dosage form: oral form
- Not penetrates skin & nail in topical form
- SEs: toxicity including hepatic, renal & photosensitivity

5. Ergosterol Biosynthesis Inhibitors: Within Three Sites of Action

- 5-a. Squalene epoxidase inhibitor (allyl amines):

✓ naftifine; tolnaftate, terbinafine, butenafine

- 5-b. Lanosterol demethylase inhibitor (azoles):

✓ miconazole; ketoconazole, fluconazole, …

- 5-c. Reductase & isomerase inhibitor (morpholines):

✓ fenpropimorph

5. Key Steps in Ergosterol Biosynthesis & Sites of Action for Inhibitors

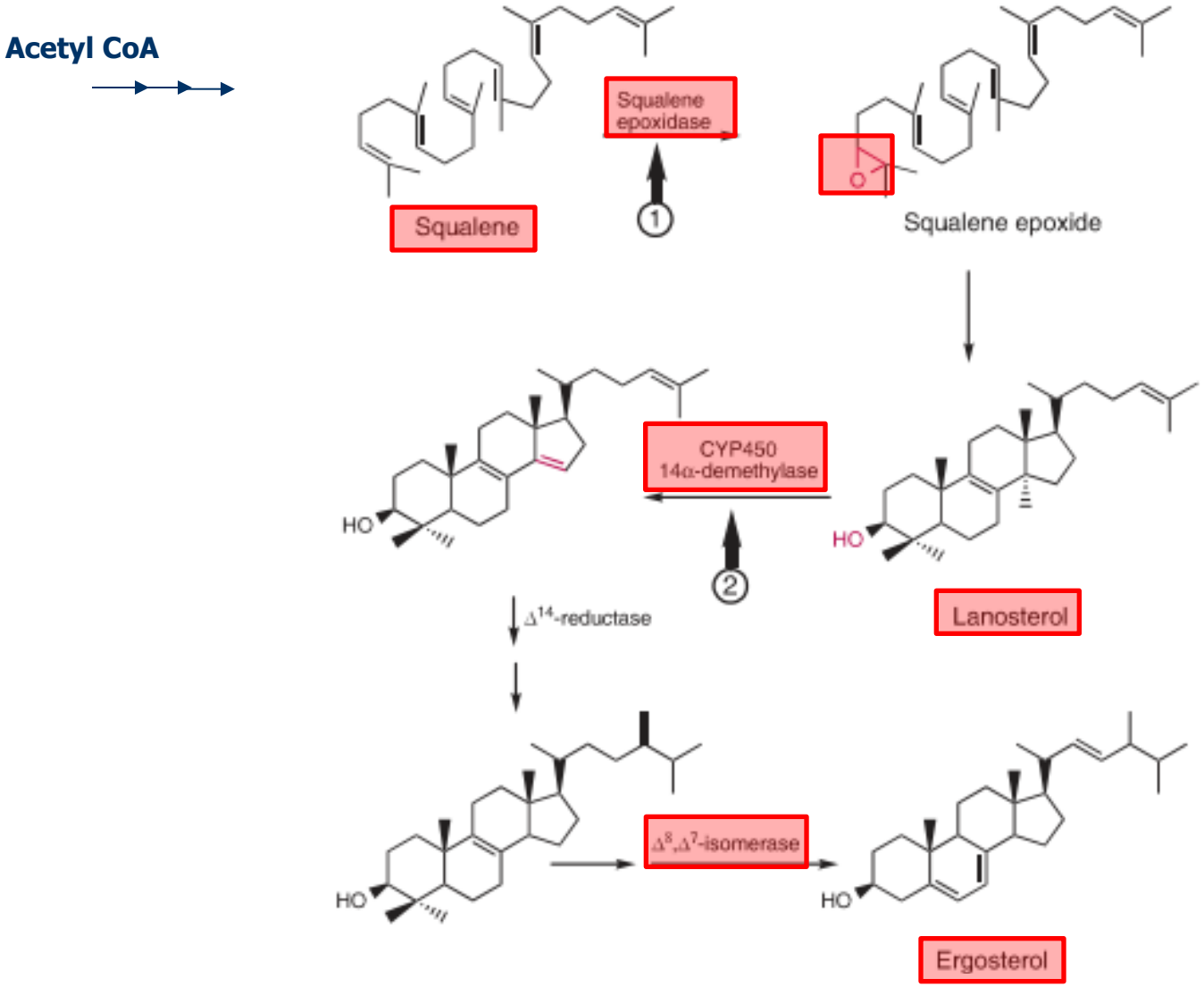


Figure 31.2 Key steps in the biosynthesis of ergosterol by fungi. Enzymatic steps known to be the site of action of currently employed antifungal agents are indicated by a heavy black arrow and a number.

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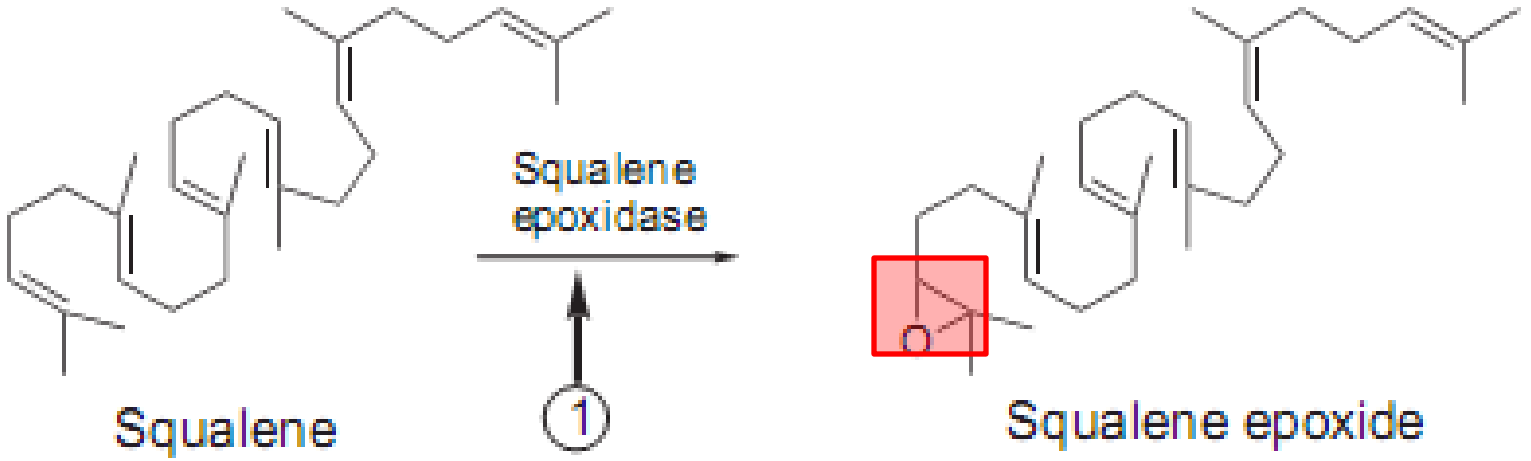
5. a. Squalene Epoxidase Inhibitor: Allylamines

- MOA: squalene epoxidase inhibition:

✓ decrease production of sterol in cell membrane: ergosterol depletion

✓ increase unchanged squalene in cell membrane



5. a. Allyamines & the Related Structures: SAR

- Chemistry: …
- SAR: …
- ✓ pharmacophore:

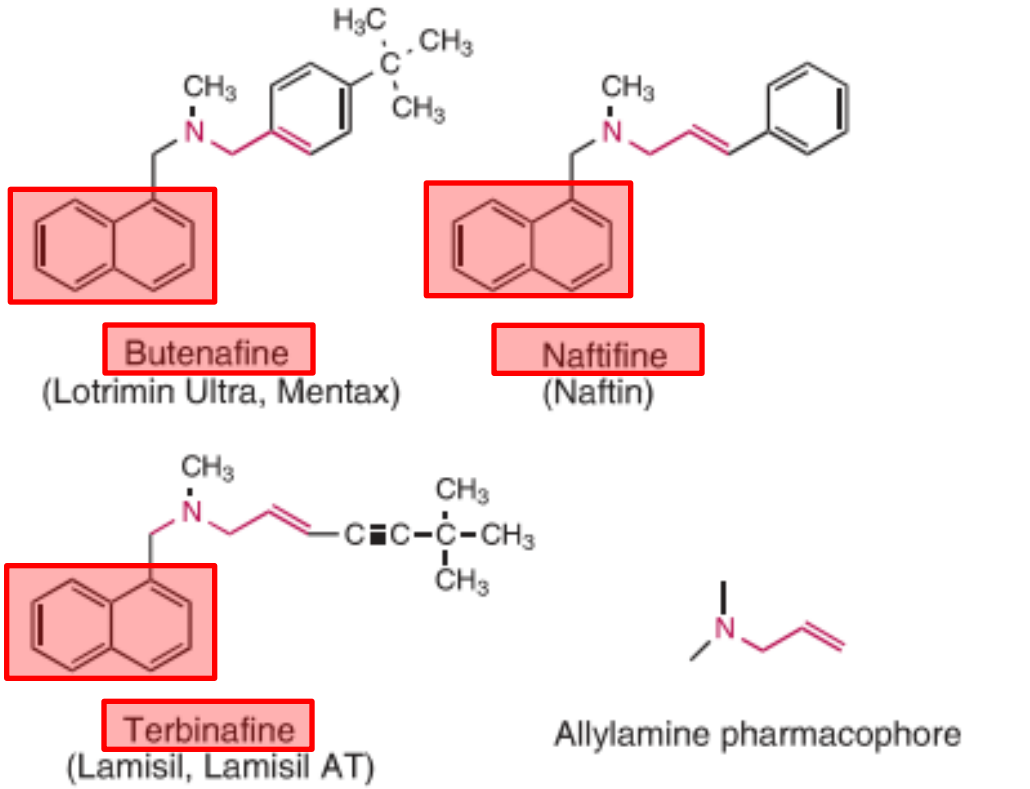


Figure 31.7 Allyl amine squalene epoxidase inhibitors. Butenafine and nafttifine are topical only. Terbinafine may be used topically or systemically.

5. a. Squalene Epoxidase Inhibitor: Allylamines

- Butenafine: topical: wider spectrum than tolnaftate
- Naftifine: topical; against *tinea*
- Terbinafine: topical & oral
- Tolnaftate: topical

5. b. Demethylase Inhibitors: Azoles

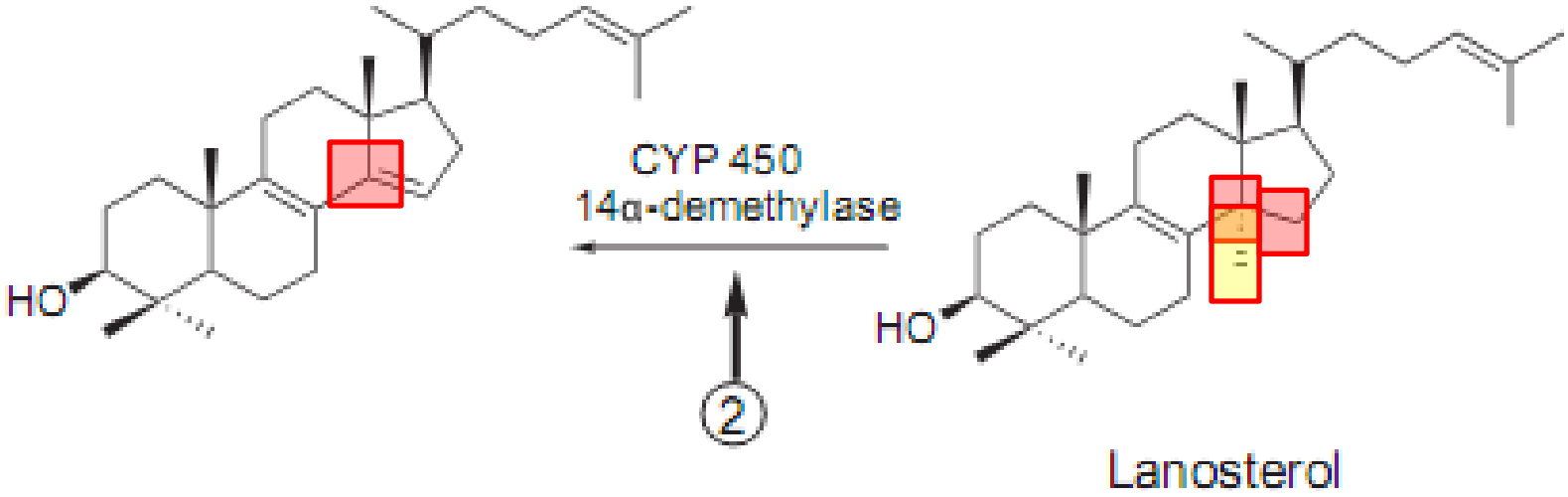
- MOA:

✓ ergosterol biosynthesis inhibitor by inhibiting lanosterol 14α-demethylase

- Lanosterol 14α-demethylase:

✓ a CYP450 related enzyme

✓ possessing heme as cofactor



Molecular Function for Lanosterol 14-α-Demethylase & Its Inhibition by Azoles

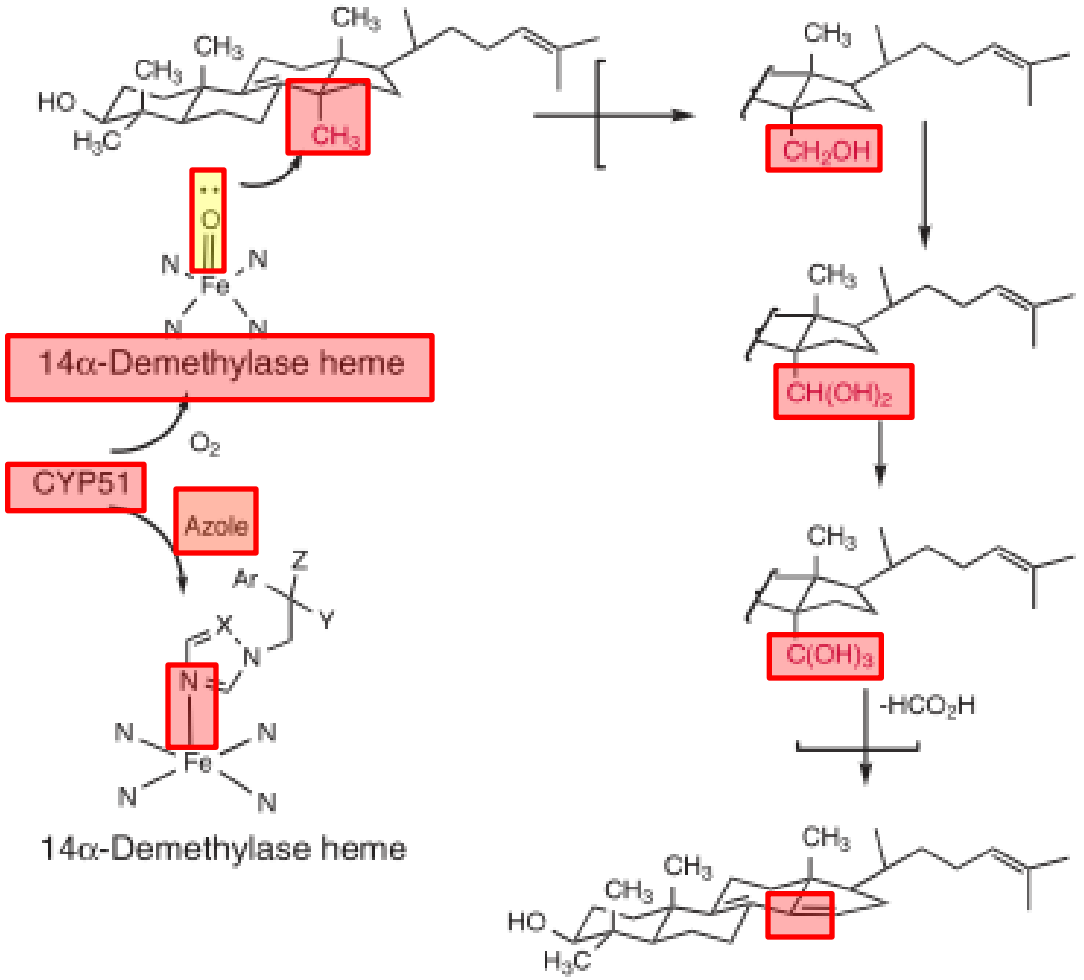
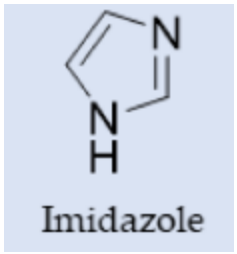


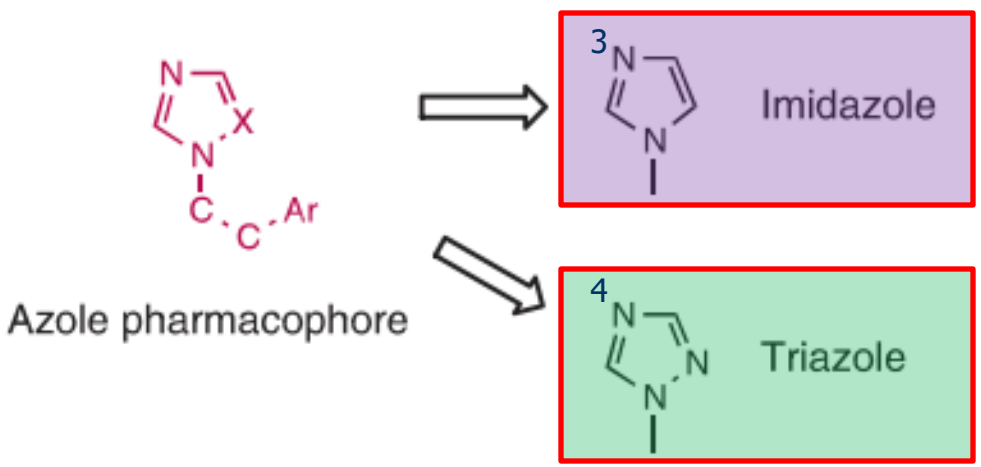
Figure 31.3 Demethylation of the 14α-methyl group from lanosterol via the CYP450 enzyme sterol 14α-demethylase, CYP51. Three successive heme catalyzed insertions of activated oxygen into the three carbon-hydrogen bonds of the 14α-methyl group which raises the oxidation state of the methyl group to a carboxylic acid. The azoles bind to CYP51 through the N3 atom of the azole preventing oxygen transfer.

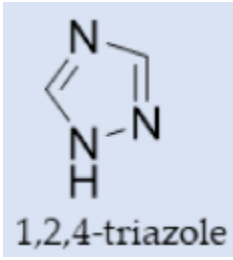
5. b. Demethylase Inhibitors: Azoles: SAR

- Azoles: a large class with broad spectrum
- SAR: …

✓ 1,3-imidazole or 1,2,4-triazole rings: pK_a= 6.5 - 6.8





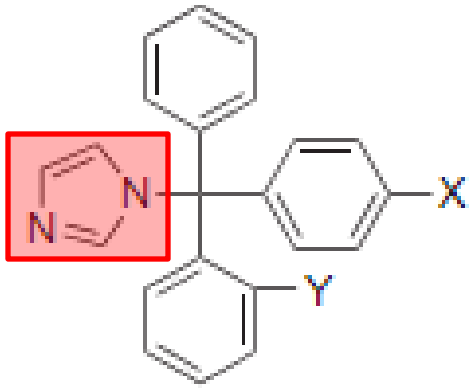


✓ N_1 attached to a side chain containing at least one aromatic ring

✓ what is the role of N_3 in imidazole & N_4 in triazole?

5. b. Demethylase Inhibitors: Azoles: First Imidazole Types

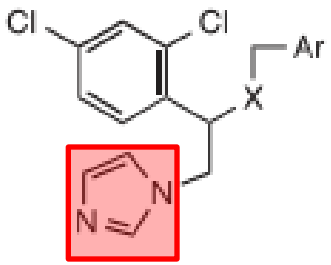
- Clotrimazole
- Flutrimazole
- SAR: …



Clotrimazole (X = H, Y = Cl)
Flutrimazole (X = Y = F)

- Applications: in local infections

5. b. Demethylase Inhibitors: Imidazole Types- Contd.



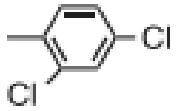
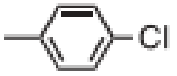
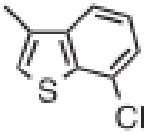
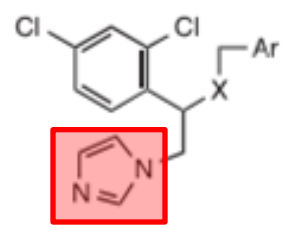
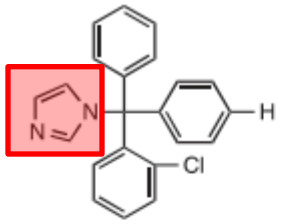
Generic name	Trade Name	X	Ar
Miconazole	Generic, Desenex, Fungoid, Monistat Oravig, Zeasorb	O	
Econazole	Generic	O	
Sulconazole	Exelderm	S	Same
Sertaconazole	Ertaczo	O	
Tioconazole	Vagistat, TZ-3	O	

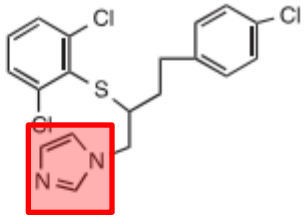
Figure 31.4 Imidazole antifungal agents. All imidazoles are used topically with the exception of ketoconazole which is available in both a topical and systemic dosage form.

5. b. Demethylase Inhibitors: Imidazole Types

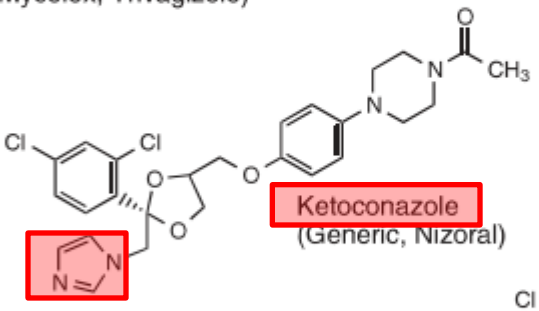




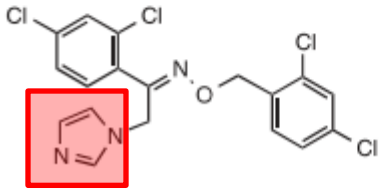
Clotrimazole (Cruex, Lotromin,Desenex, Mycelex, Trivagizole)



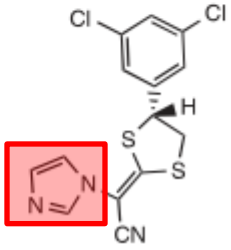
Butoconazole (Femstat,Gynazole)



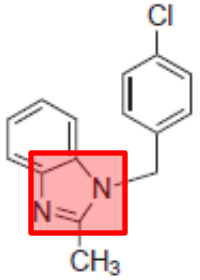
Ketoconazole (Generic, Nizoral)



Oxiconazole (Oxostat)



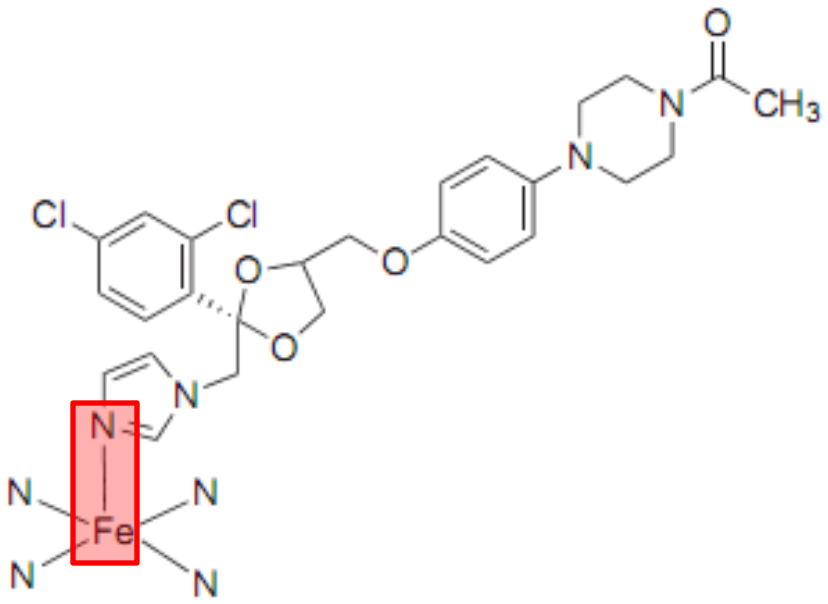
Luliconazole (Luzu)



Chlormidazole

Figure 31.4 Imidazole antifungal agents. All imidazoles are used topically with the exception of ketoconazole which is available in both a topical and systemic dosage form.

Ketoconazole & CYP450 Related Demethylase Interaction

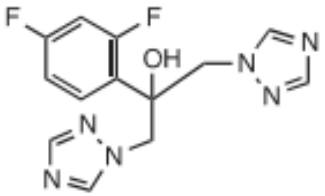


14α-Demethylase heme

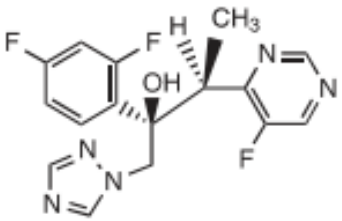
FIGURE 35.4 Mechanism of azole/CYP450 binding. The basic nitrogen of azole antifungal agents forms a bond to the heme iron of CYP450 enzymes, preventing the enzyme from oxidizing its normal substrates. Ketoconazole is representative of the azole antifungals.

5. b. Demethylase Inhibitors:

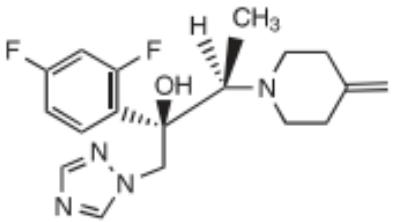
Triazoles Types



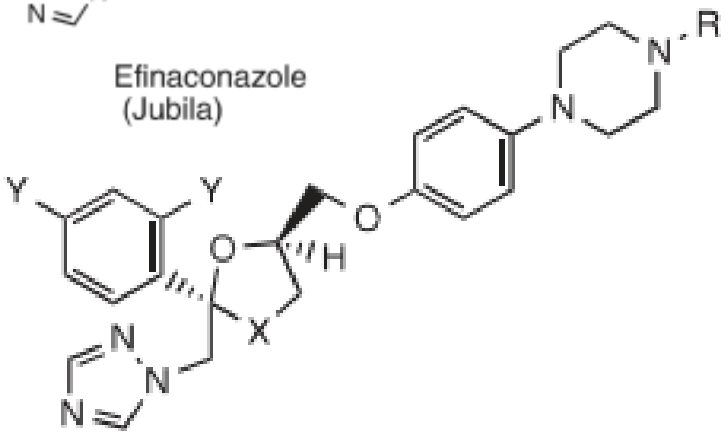
Fluconazole
(Diflucan)



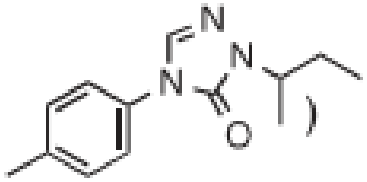
Voriconazole
(Vfend)



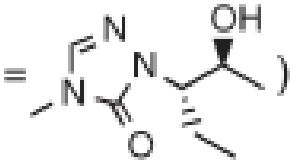
Efinaconazole
(Jubila)



Itraconazole (X=O, Y = Cl, R =
(Generic, Onmel, Sporanox)



Posaconazole (X=CH_2, Y = F, R =
(Noxafil)



Terconazole (X=O, Y = Cl, R =
(Terazol)

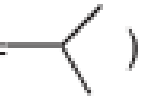


Figure 31.5 Triazole antifungal agents. While efinaconazole, isavuconazole, and terconazole are used topically, the remaining triazoles are used systemically.

5. b. Demethylase Inhibitors: Introduction of Triazole Types

- Modifications on imidazole types to introduce triazole derivatives:

✓ broader spectrum

✓ increased water solubility

- Drugs:

✓ itraconazole

✓ fluconazole

- Agricultural azoles

Metabolic Products of Azoles

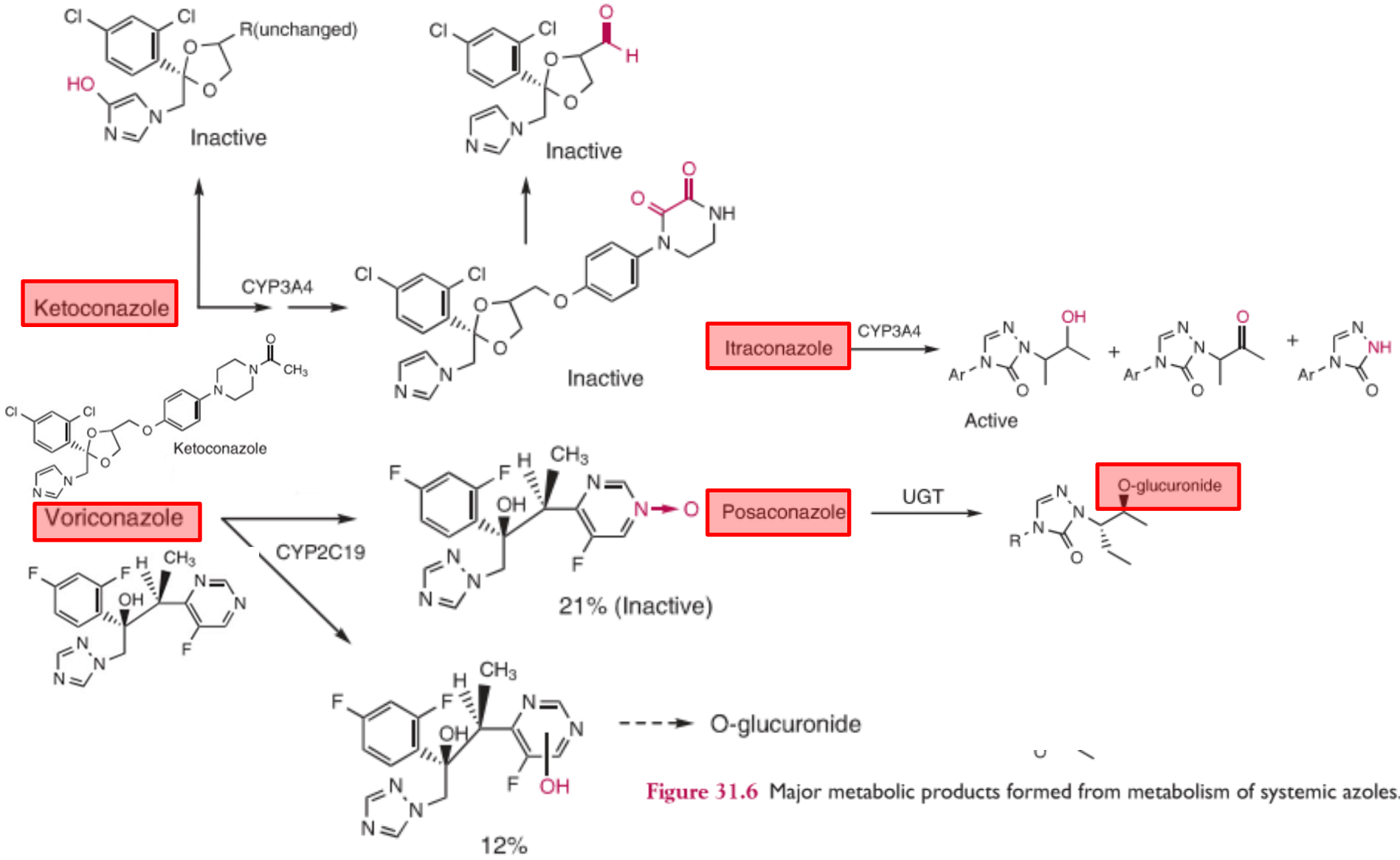
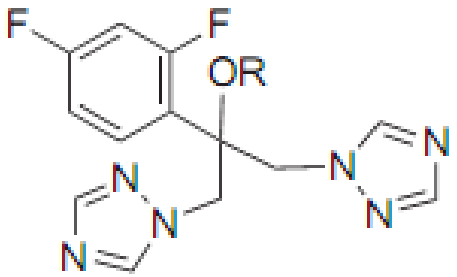


Figure 31.6 Major metabolic products formed from metabolism of systemic azoles.

5. Fluconazole Derivatives

- Fluconazole:

✓ against *Cryptococcus neoformans*



Fluconazole (R = H)
Fosfluconazole (R = —P(=O)(OH)OH)

✓ less water soluble: so needs high volume infusion

✓ Dosage forms: tab & cap:50,100,150,200 mg; inj.: 100,200,400 mg

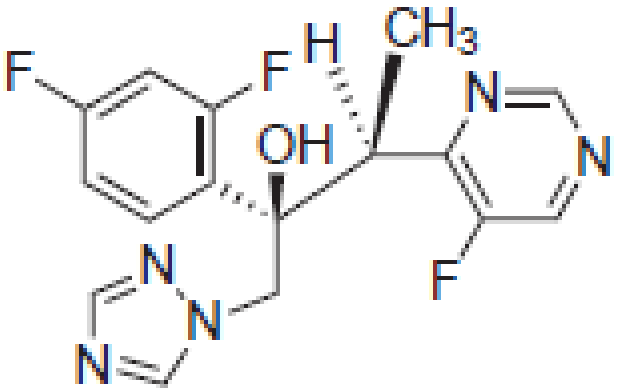
✓ BBB pass

- Fosfluconazole: phosphate ester

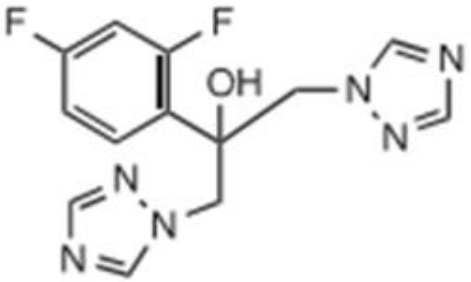
✓ more water soluble: so needs lower volume of injection

5. Azole Analogs: Voriconazole

- Fluconazole analog
- Broader spectrum of activity:
  - ✓ against *Aspergillus* and fluconazole-resistant strains of *Candida* & *Cryptococcus*
- BBB pass
- Dosage forms:
  - ✓ Oral: tab: 50 & 200mg
  - ✓ IV: powder for injection: 200 mg



Voriconazole



Fluconazole

Metabolism of Voriconazole

- Dosage forms: oral & IV

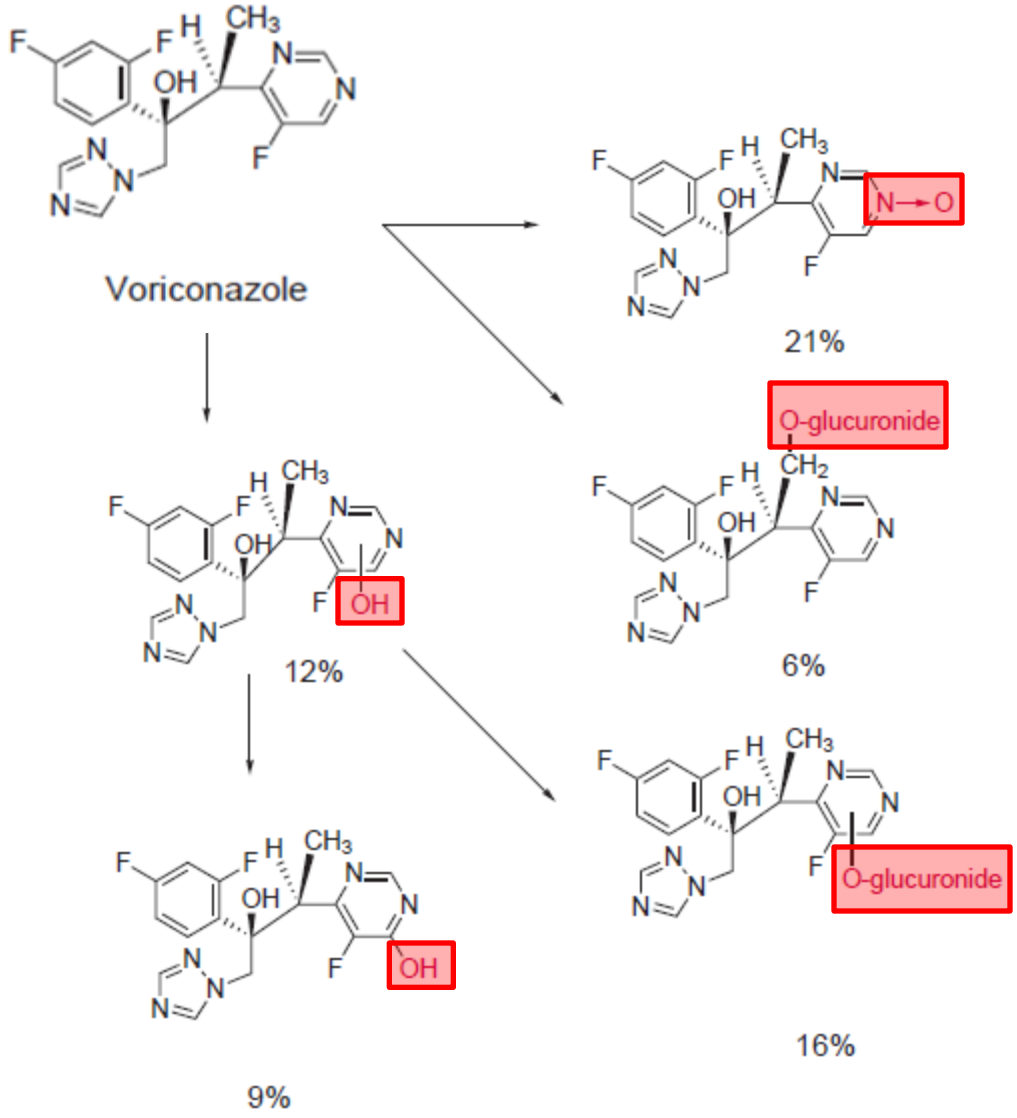
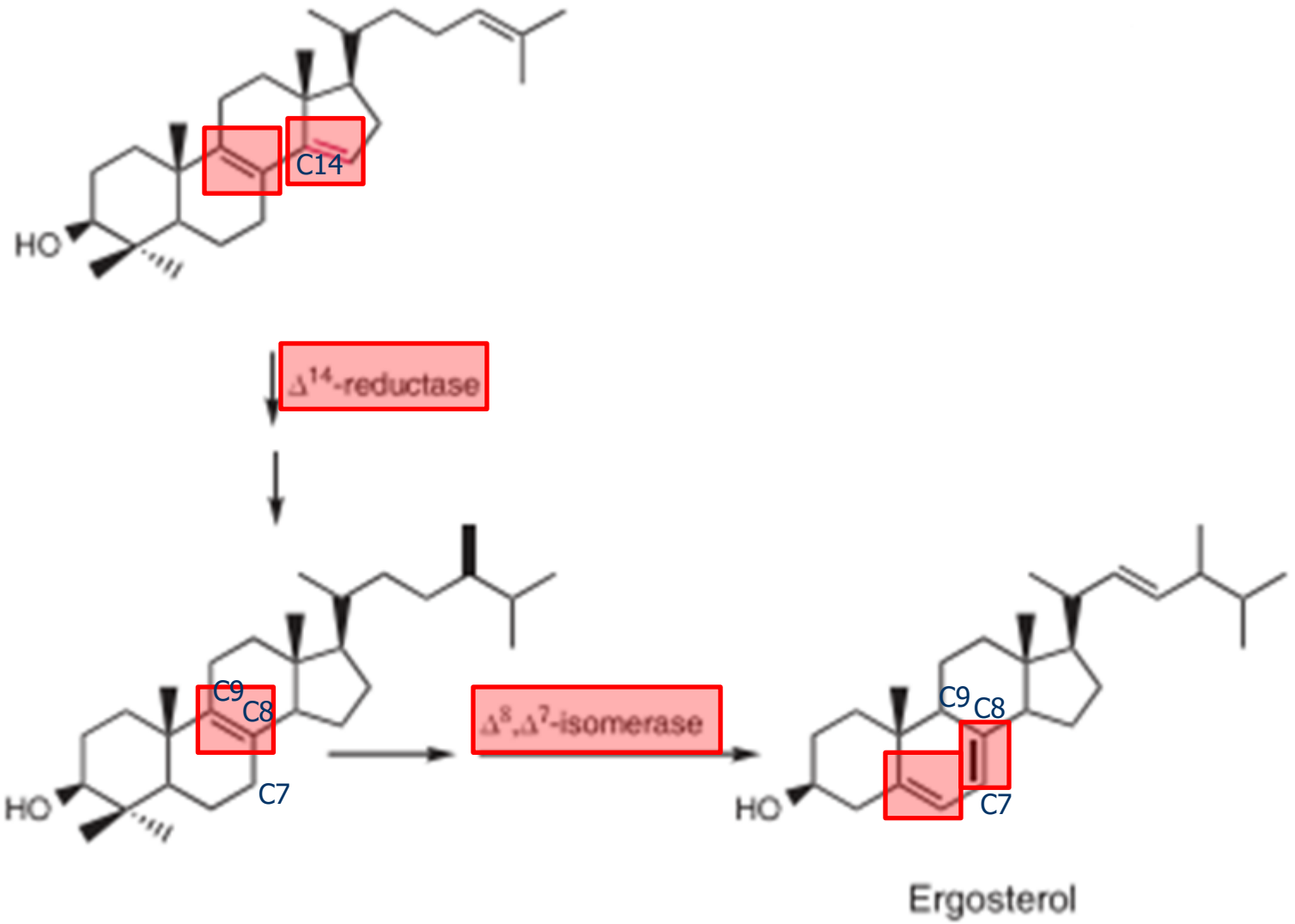


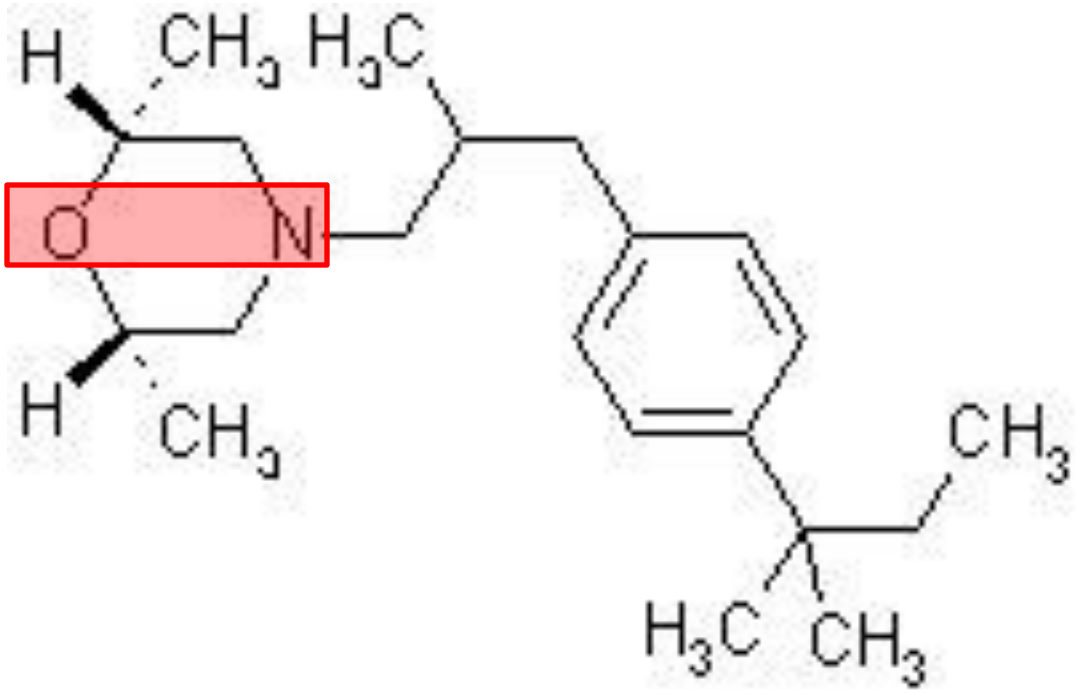
FIGURE 35.7 Major metabolic products resulting from CYP450 metabolism of voriconazole.

5-c. Reductase & isomerase inhibitor: Morpholines



5. c. Reductase Inhibitors: Morpholines

- Amorolfine:
- MOA: Δ14-reductase & Δ8,Δ7-isomerase inhibitor



6. Antifungal Agents: 1,3-Glucan Synthase Inhibitor

- Echinocandins
- Pneumocandins
- Chemistry:

✓ cyclic peptides

✓ + long lipophilic side chains: lipopeptides

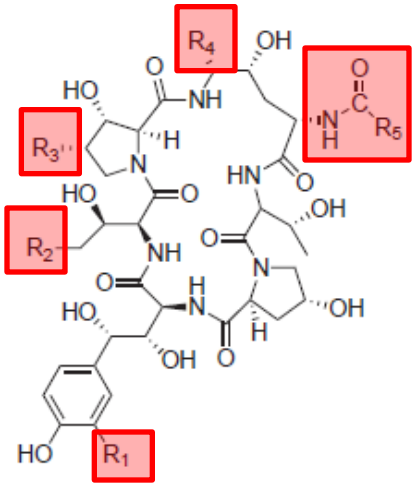


FIGURE 35.9 Echinocandins.

- MOA:

✓ non-competitive inhibitor of β-1,3-glucan synthase

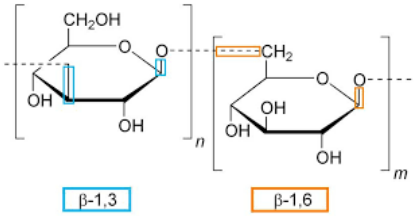
✓ interfere with the cell wall biosynthesis

- Dosage forms: IV infusion; not oral form
- Clinical application: systemic inf.: resistant *candida* & *aspergillus*

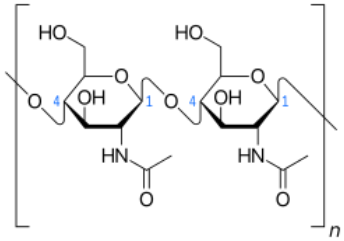
6. Glucans in Cell wall of Fungi & Molecular Mechanism of Glucan Synthase Inhibitors

- Cell wall consists of poly-saccharides: GPI:

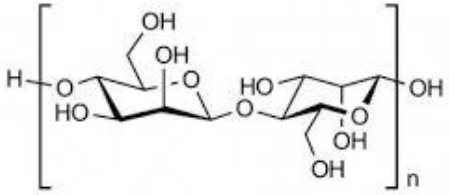
✓ glucans: three types: ß-1,3-glucan & ß-1,6-glucan

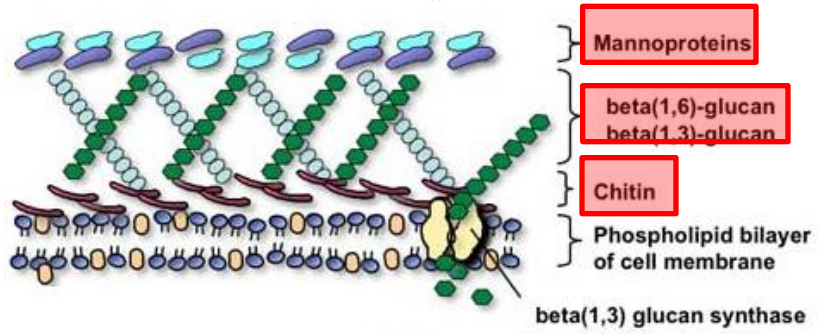


✓ chitin: ß-1,4- linked N-Ac-glucosamine



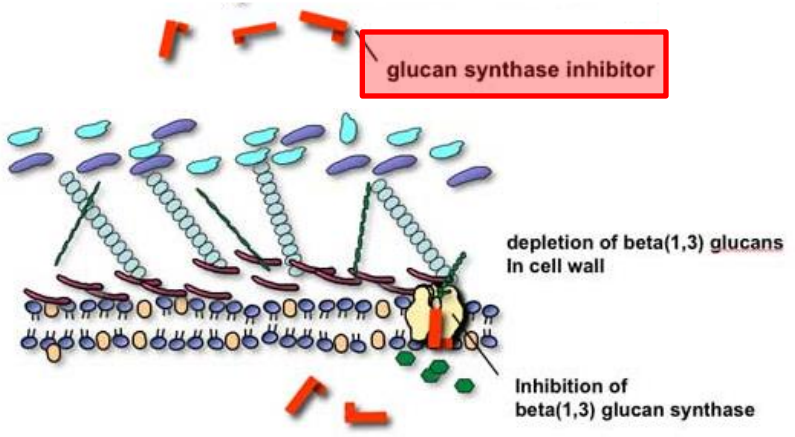
✓ mannans & mannoproteins





- Responsible enzyme:

✓ glucan synthase in CM



6. Antifungal Agents: Echinocandins

- MOA: non-competitive glucan synthase inhibitor
- Semisynthetic lipo-peptides:
- Caspofungin: CPF
- Anidulafungin: ANDF
- Micafungin: MCF

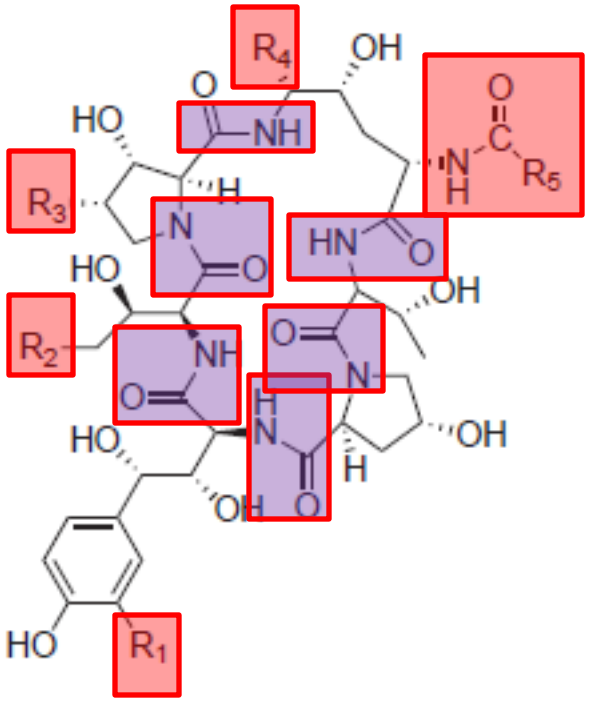
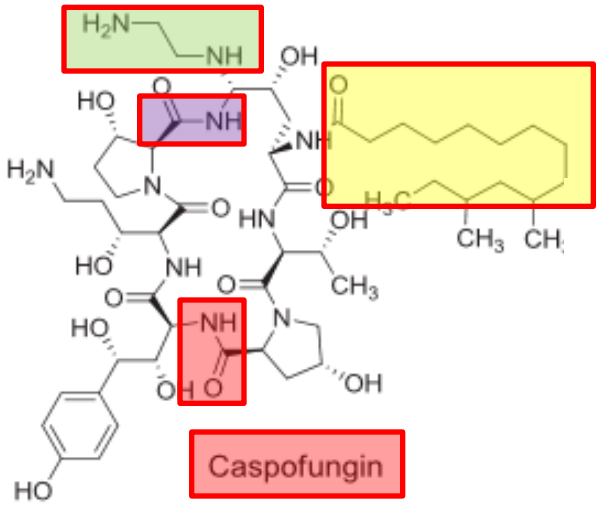
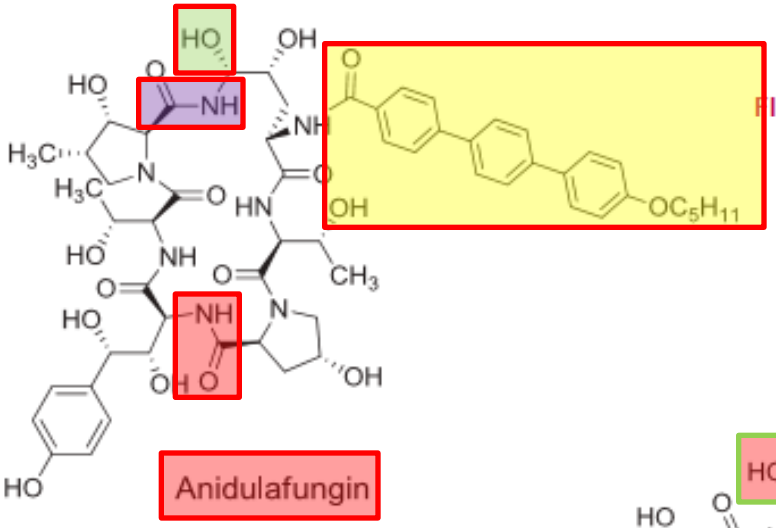


FIGURE 35.9 Echinocandins.

Echinocandins





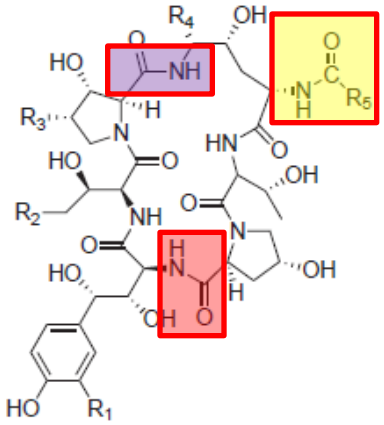


FIGURE 35.9 Echinocandins.

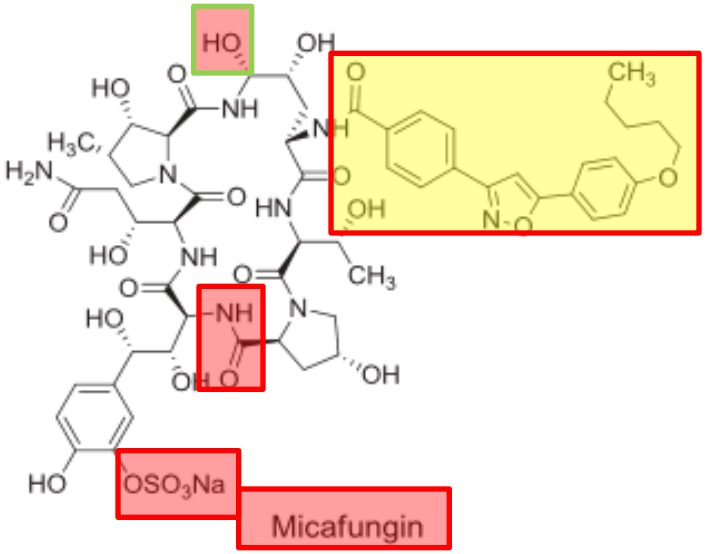


Figure 3. Chemical structures of echinocandins in clinical use.

6. Semisynthetic Echinocandins

- Caspofungin: CPF: R_5: fatty acid (13C): C_{10}-CH_3& C_{13}-CH_3
- Anidulafungin: ANDF: R_5: alkoxy(5C)-tri-phenyl
- Micafungin: MCF: R_5: alkoxy(5C)-tri-aryl (phenyl-iso-oxazole-phenyl)

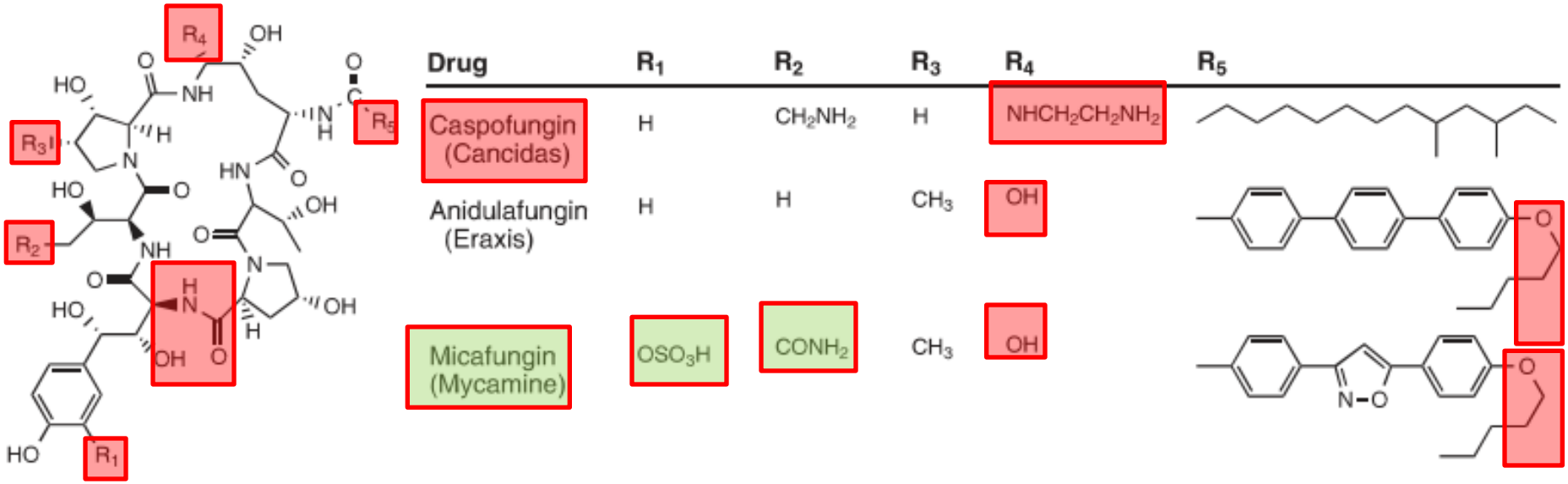


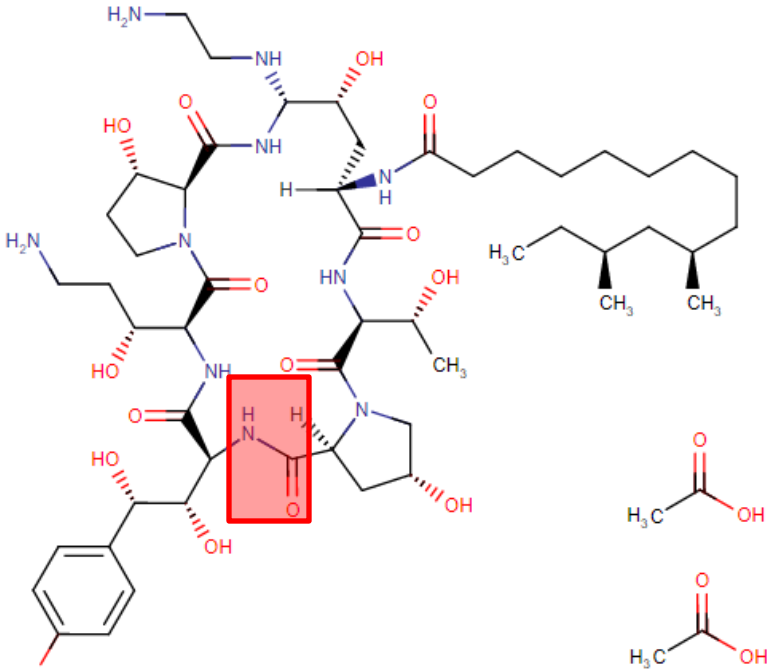
Figure 31.8 Echinocandins.

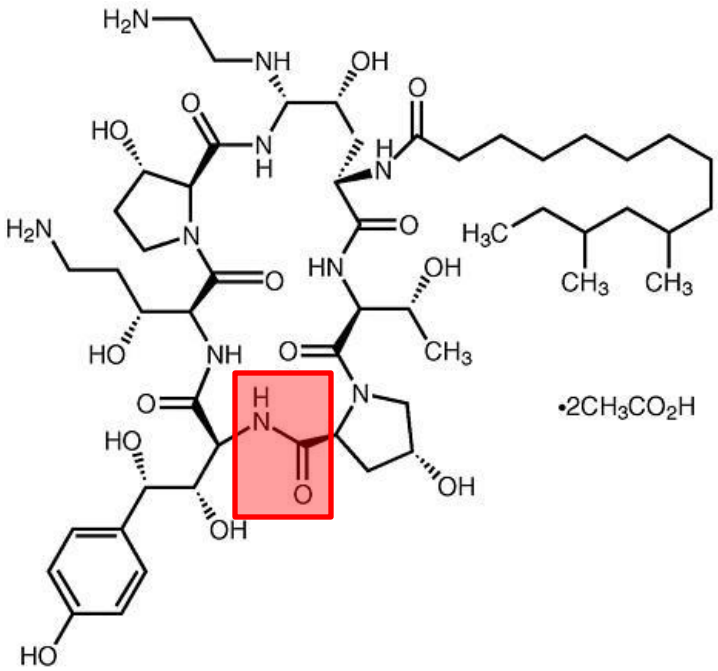
6. Antifungal Agents: Caspofungin

- Chemistry: cyclic (lipo)-peptide: lactam & …
- Cancidas
- MOA: Interfere with ß-1,3-glucan synthase:

✓ cell wall biosynthesis inhibitor

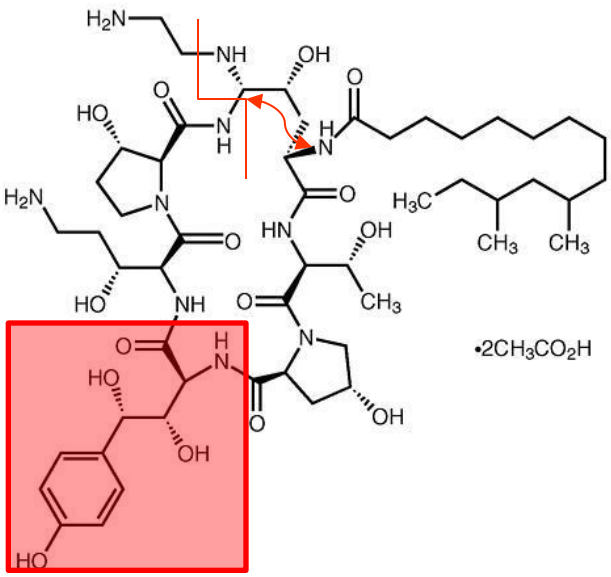
- Dosage forms: inj. 50 & 70 mg





Metabolism of Caspofungin

- Peptide lactam ring opening: via de-amination of ethylene-di-amine
- Sulfotransferase
- Aryl/catechol-O-methyl-transferase



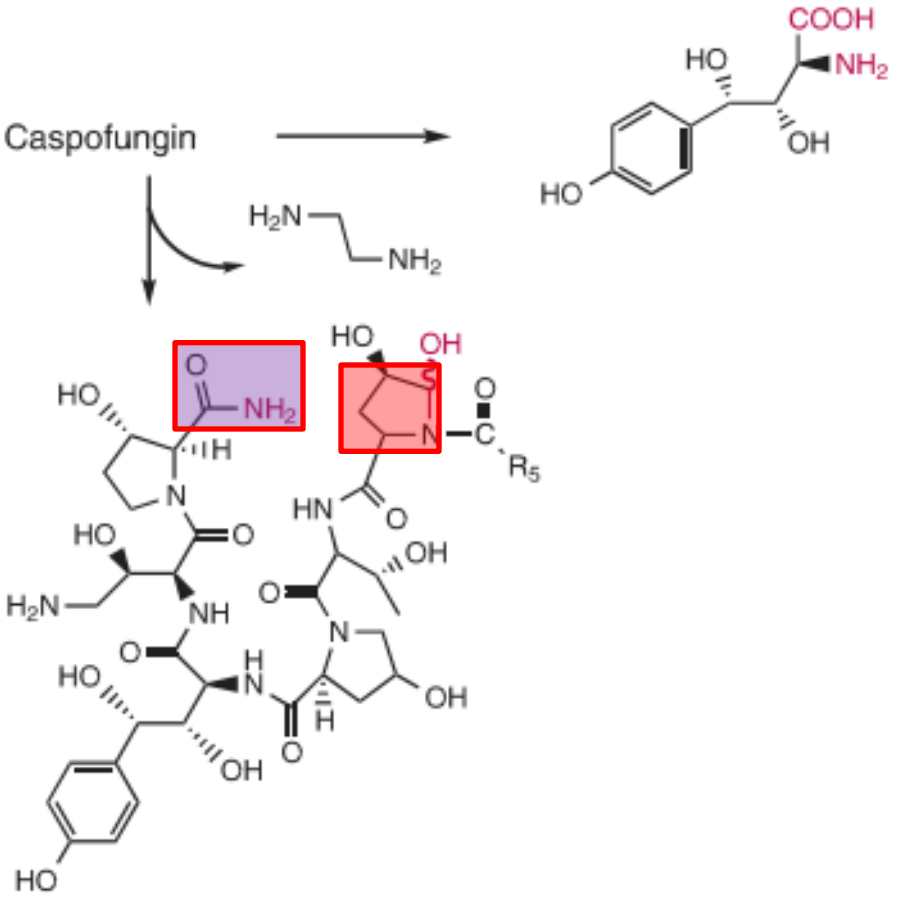


Figure 31.9 Metabolic products formed from caspofungin.

Novel Echinocandins: Rezafungin

- Rezafungin (biafungin): R=O: FDA approved in Mar 2023
- Advantage: prolonged PK: is administered once a week

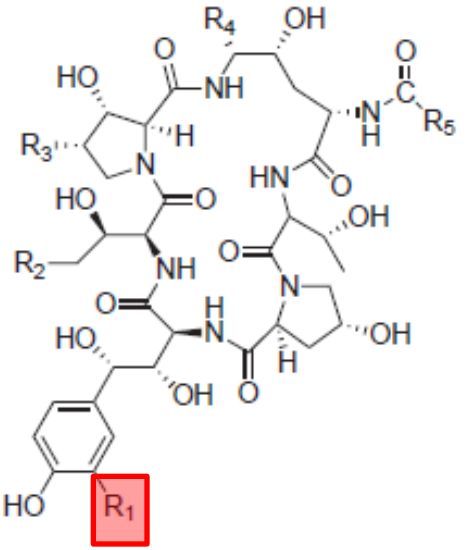


FIGURE 35.9 Echinocandins.

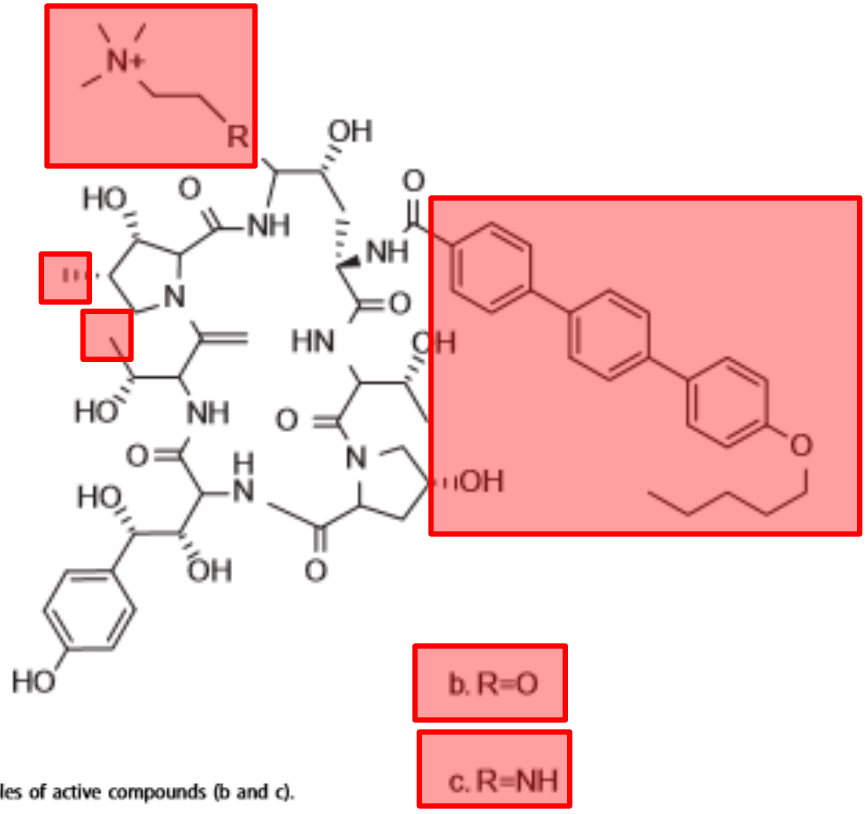
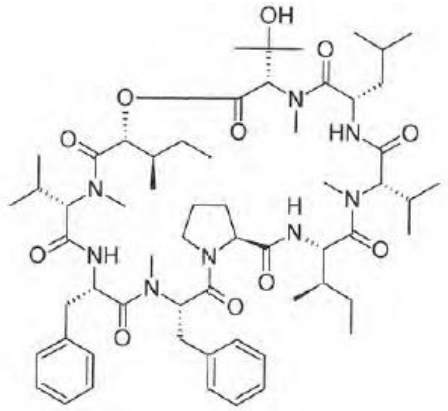


Figure 4. Echinocandin derivatives disclosed by Cidara Therapeutics Inc. General formula (a) and examples of active compounds (b and c).

7. Inositol Phosphoryl Ceramide (IPC) Synthase Inhibitor

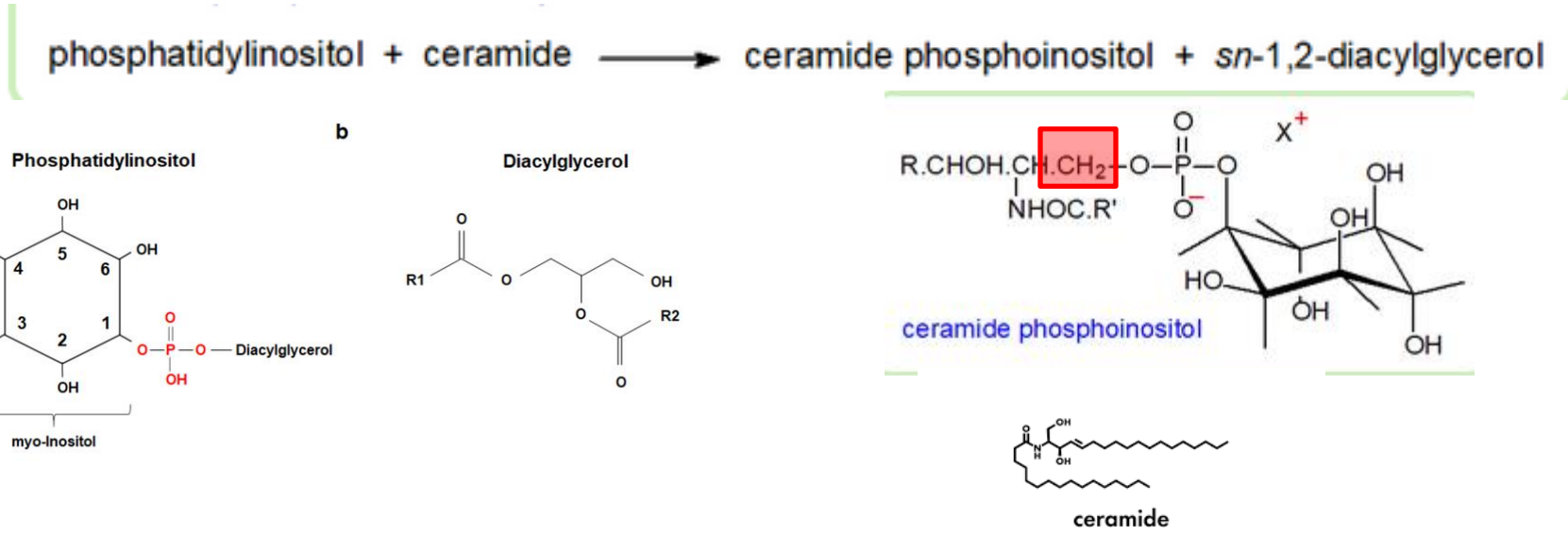
- Aureobasidins: cyclic peptide



Aureobasidin A

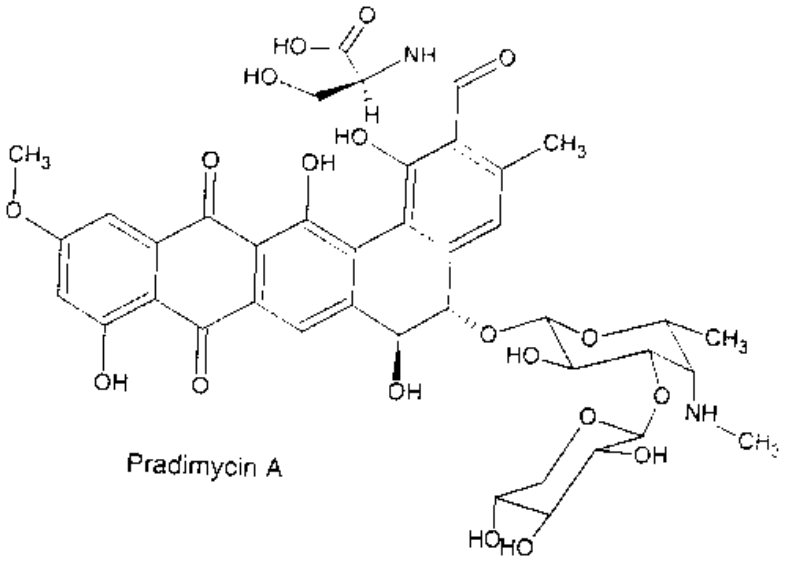
- MOA:

non-competitive inhibitor of Inositol Phosphoryl Ceramide (IPC) synthase

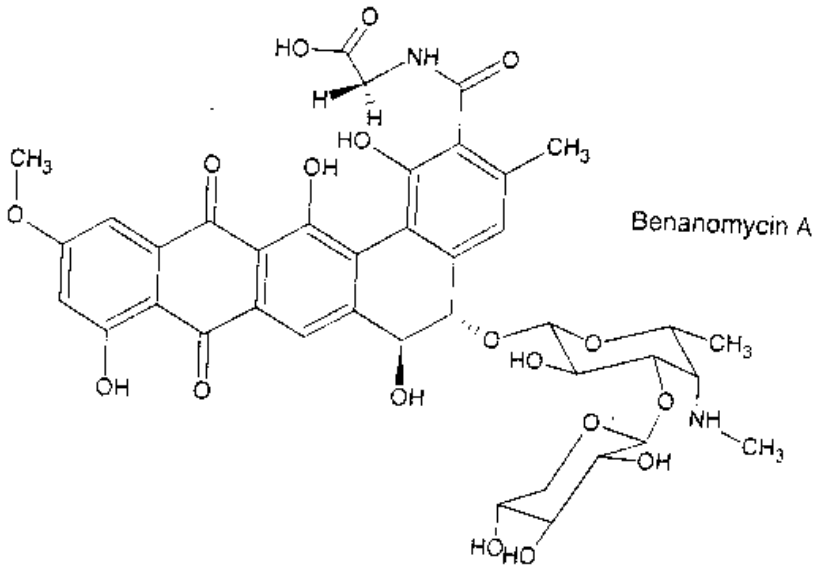


8. Pentacyclic Chelators

- Pradimycin

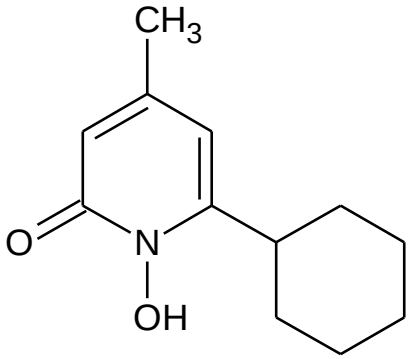


- Benanomycin



9. Miscellaneous: Cicloprox

- Chemistry: hydroxylated pyridin-2-one



- MOA:
- inhibition of metalo-enzymes through chelation of polycations (Fe^{3+}) within fungal cell wall
- SAR: …
- Clinical applications:

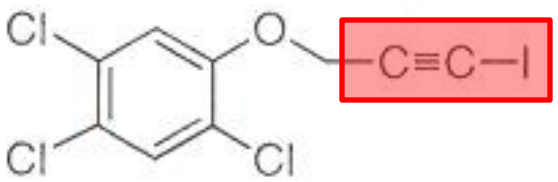
✓ superficial dermatophytes

✓ onychomycosis

✓ nail infections: lacquer formulation

9. Miscellaneous: Haloprogin

- Chemistry: iodinated acetylene
- MOA: unclear
- ✓ non-specific metabolic disruption
- ✓ interfere with DNA biosynthesis
- ✓ interfere with cell respiration



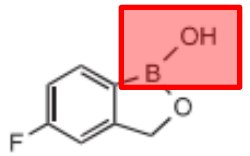
Haloprogin

- Clinical application: dermatophytes: topical

9. Miscellaneous: Tavaborole

- Chemistry: boron derivative
- FDA approved: 2014

Tavaborole



Tavaborole (Kerydin)

- MOA: binds terminal Adenosine Leu tRNA

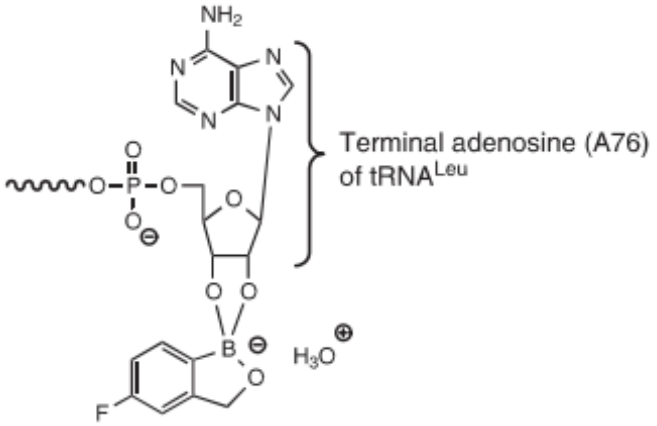
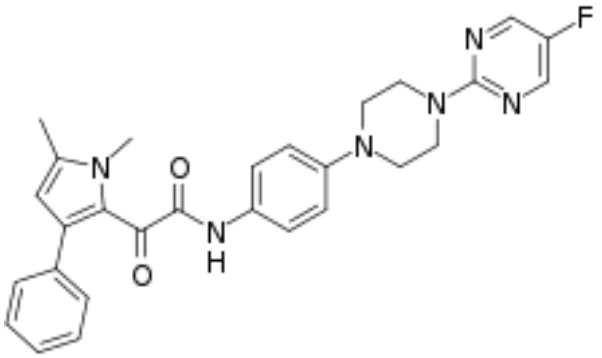


Figure 31.11 Binding between tavaborole and tRNA in the editing active site of leucine-tRNA synthetase (LeuRS).

- Against onychomycosis:
- ✓ nail infections: lacquer formulation
- Dosage form: topical

9. Miscellaneous: Orotomide

- Chemistry: …
- Investigational: discovered in 2015



- MOA: DHODH inhibitor: critical in biosynthesis of UMP
- blocks growth of hyphae
-