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

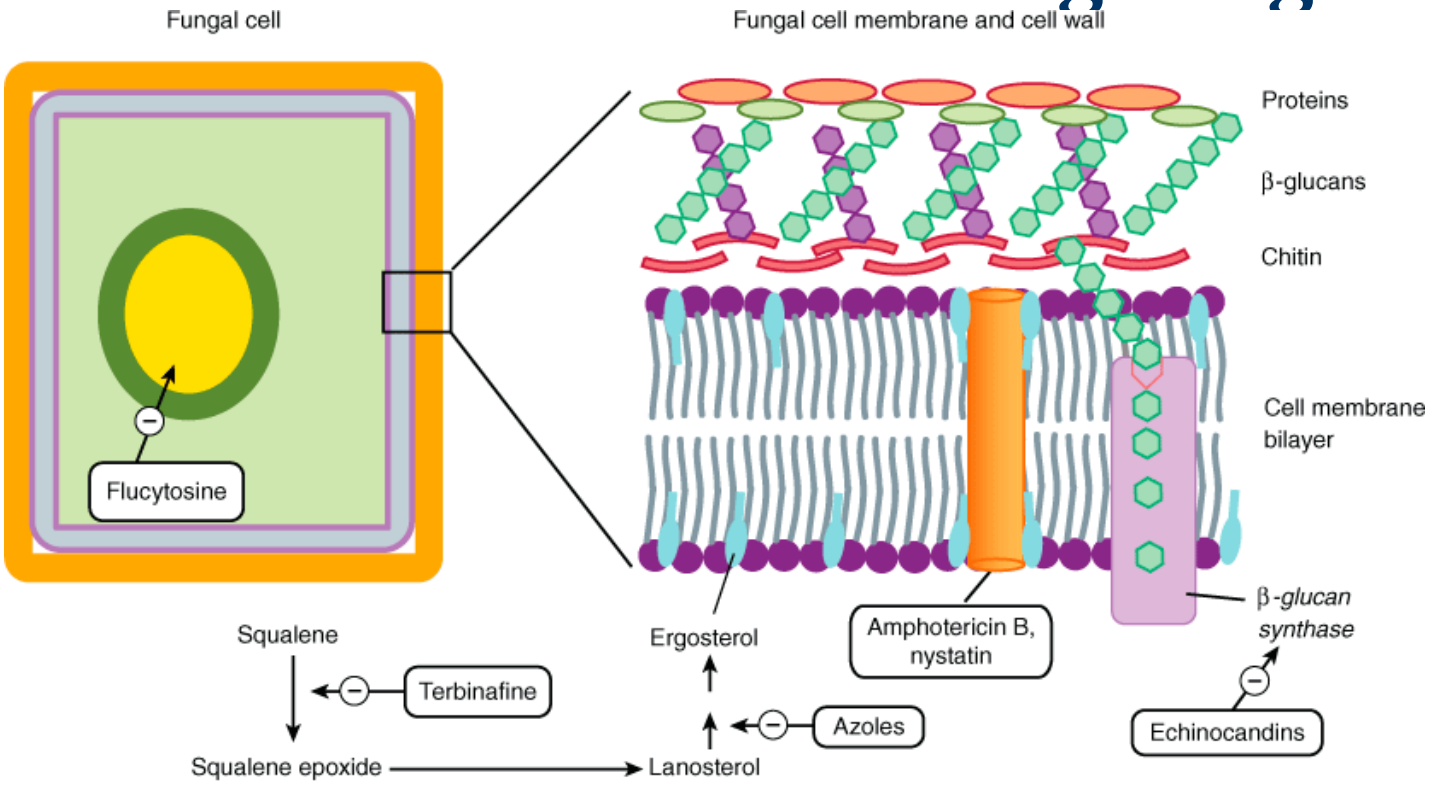
ALLYL AMINES
- Butenafine
- Naftifine
- Terbinafine

ECHINOCANDINS
- Anidulafungin
- Caspofungin
- Micafungin

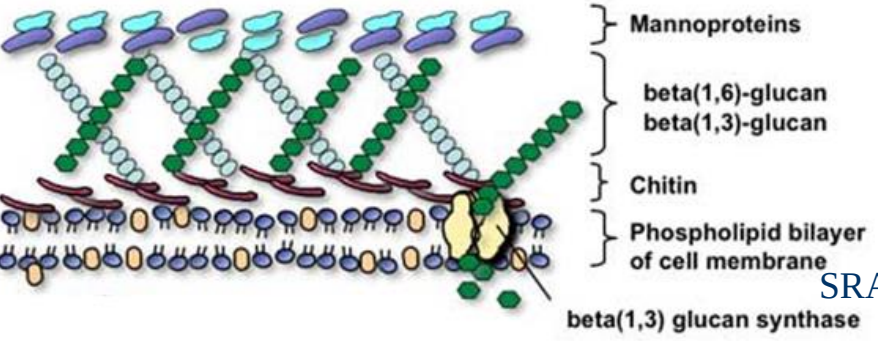
MISCELLANEOUS
- *Amorolfine*[a]
- Ciclopirox
- Flucytosine
- Griseofulvin
- Tavaborole
- Tolnaftate
- Undecylenic acid

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

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



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com



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:

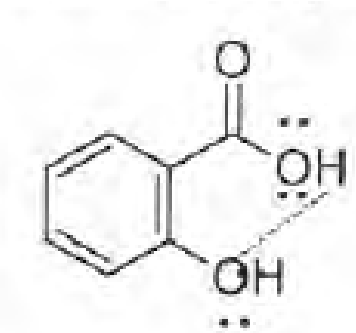
- ✓ unclear: might interfere with DNA biosynthesis or …: haloprogin
- ✓ cell metal dependent enzyme inhibitor through cation chelation: ciclopirox
- ✓ terminal A (adenosine) Leu tRNA binder: tavaborole
- ✓ DHODH inhibitor: orotomide (investigational)
- ✓ Gwt1 inhibitor: BIQ, … , fosmanogepix

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

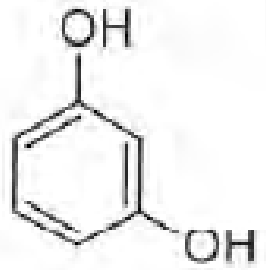
- Fatty acids (acids, salts): undecylenic acid: keratolytic

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

- Salicylic acid: antiseptic & keratolytic



- Phenols:
- ✓ resorcinol: antiseptic & keratolytic



2. Cell Membrane Disruptors: Polyenes

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

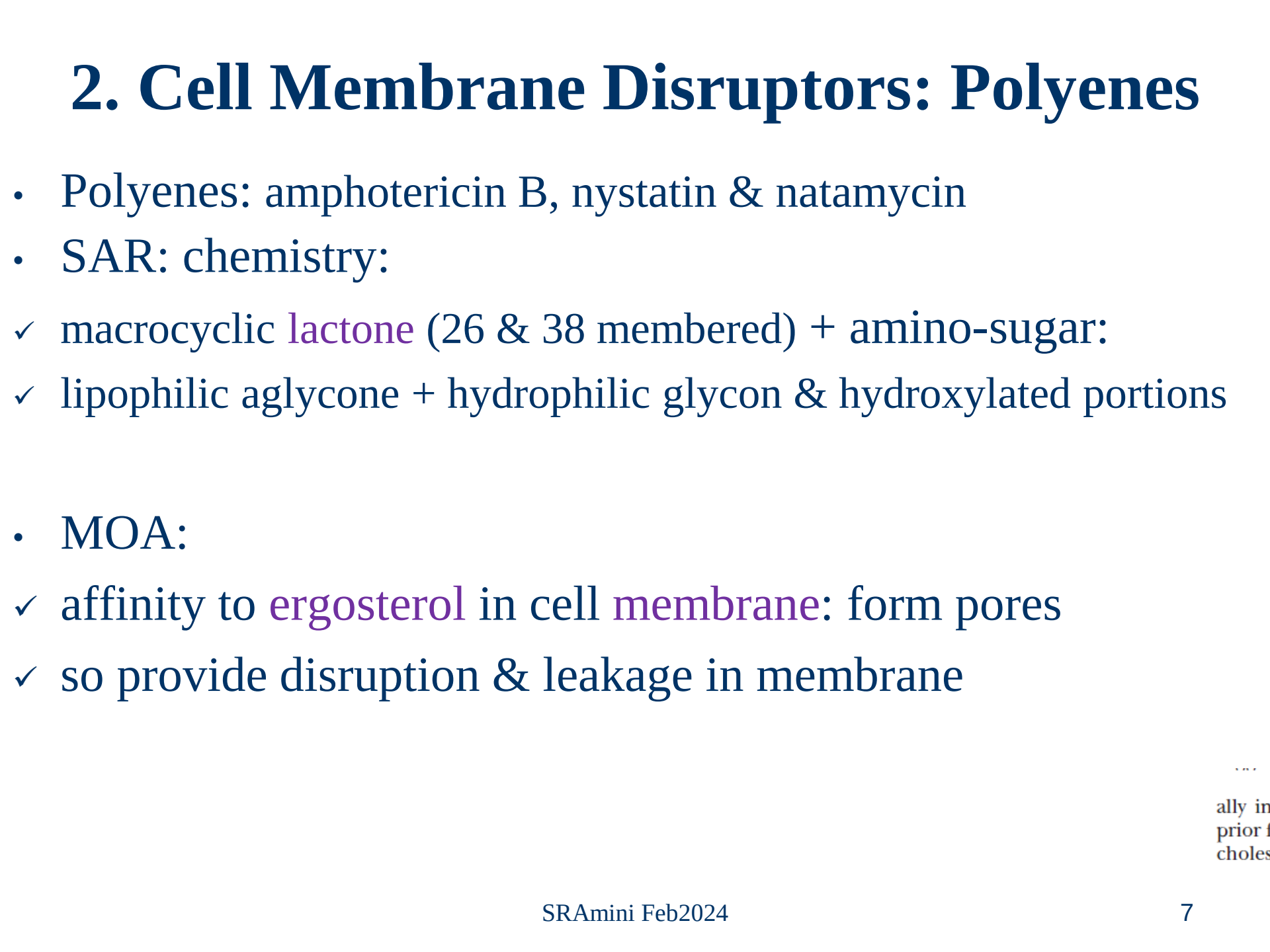
✓ macrocyclic lactone (26 & 38 membered) + amino-sugar:

✓ lipophilic aglycone + hydrophilic glycon & hydroxylated portions

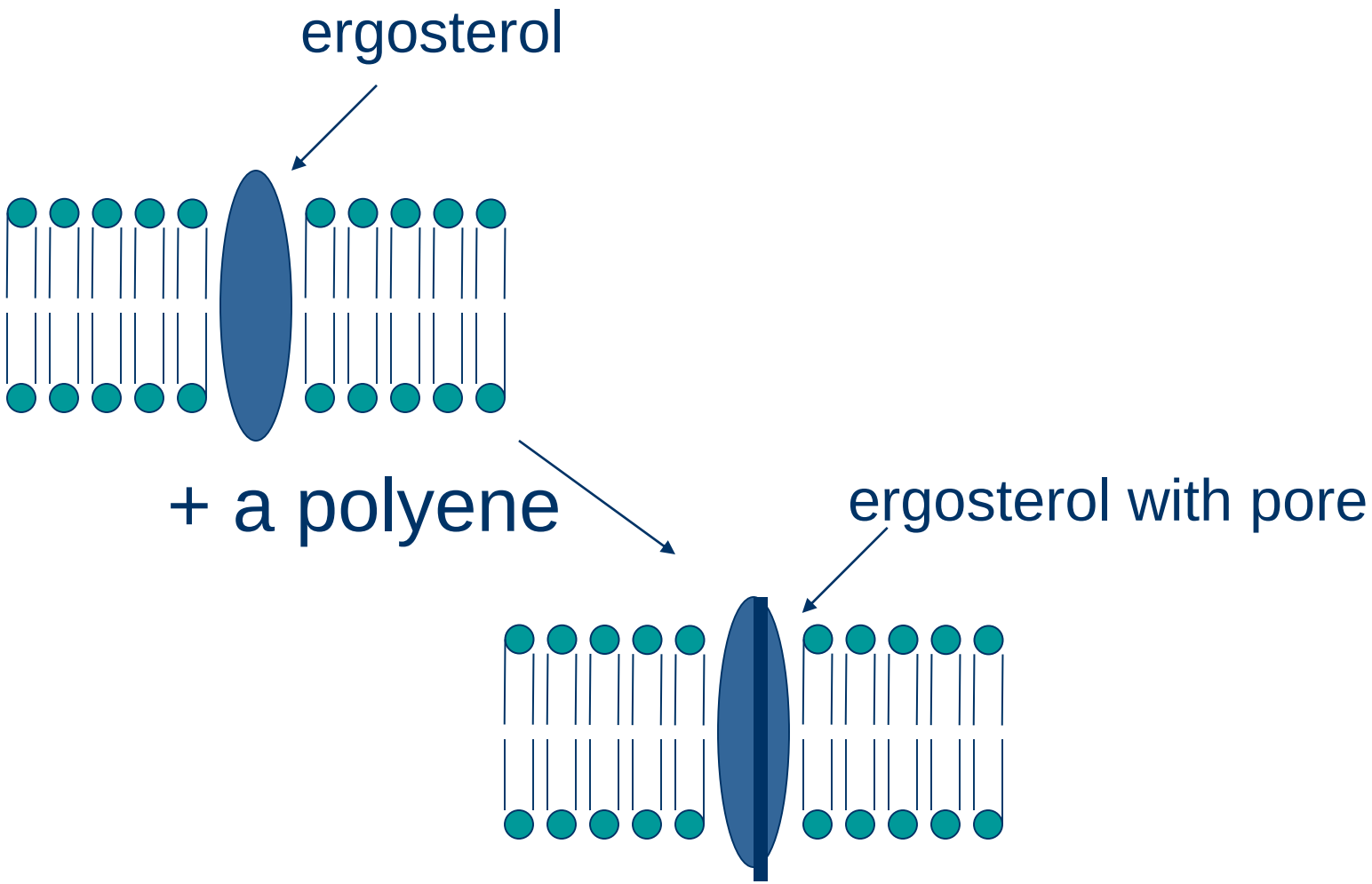
- MOA:

✓ affinity to ergosterol in cell membrane: form pores

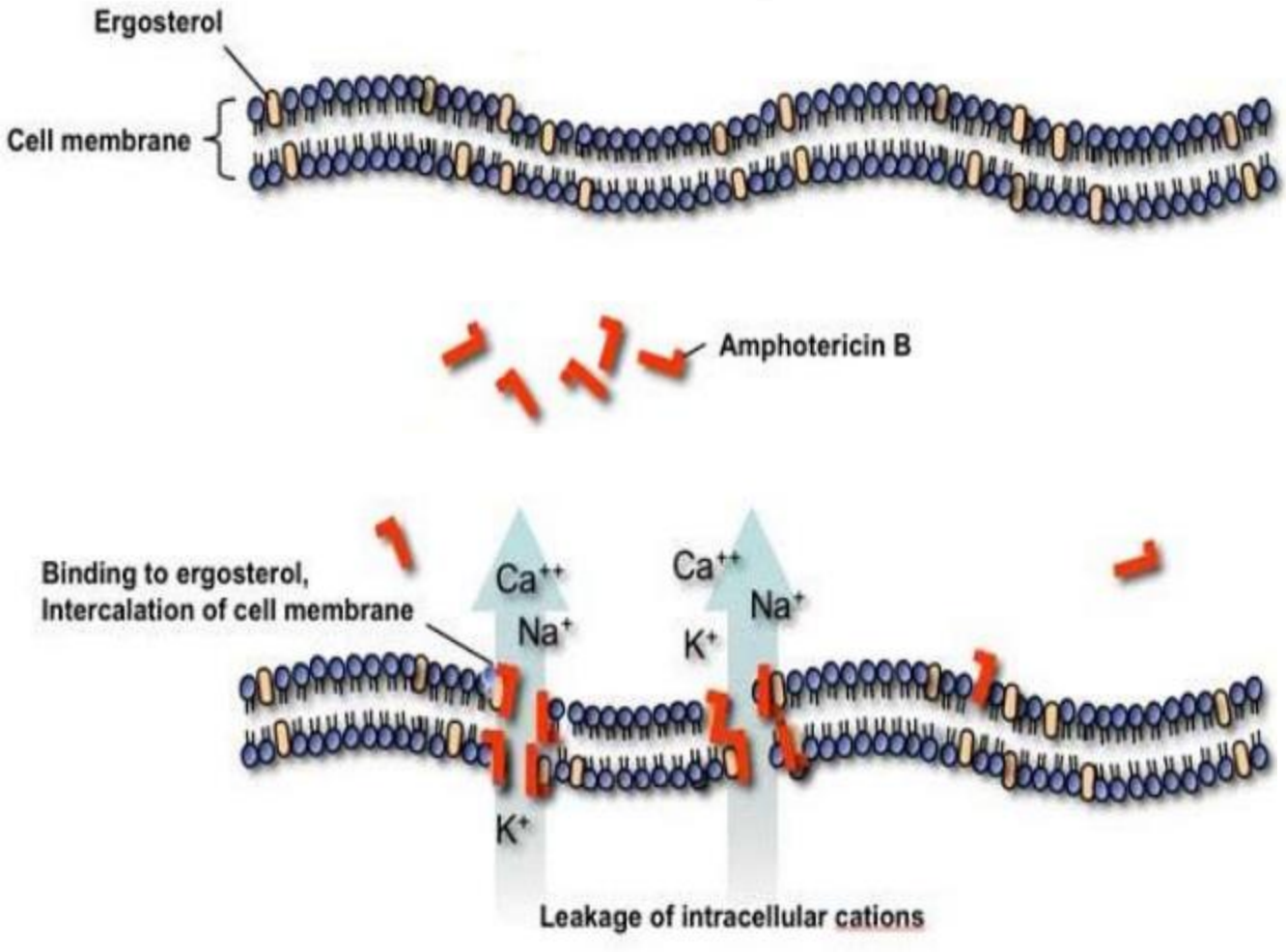
✓ so provide disruption & leakage in membrane



MOA for Polyenes on Cell Membrane of Fungi

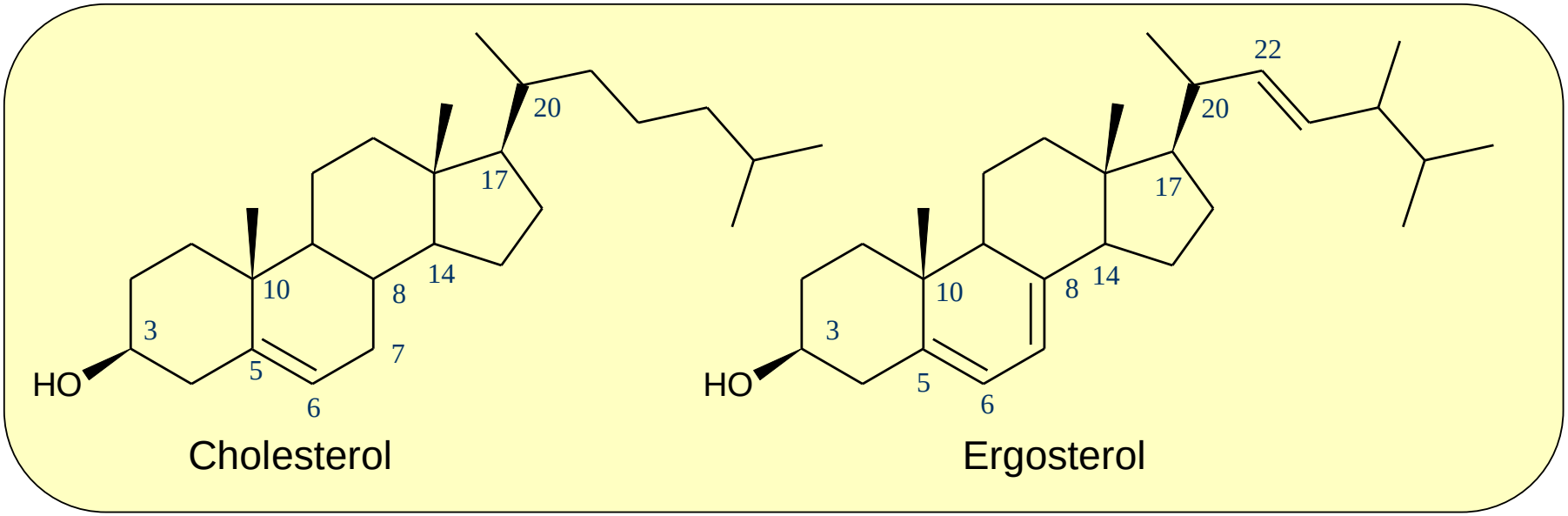


MOA for Polyenes on Cell Membrane of Fungi



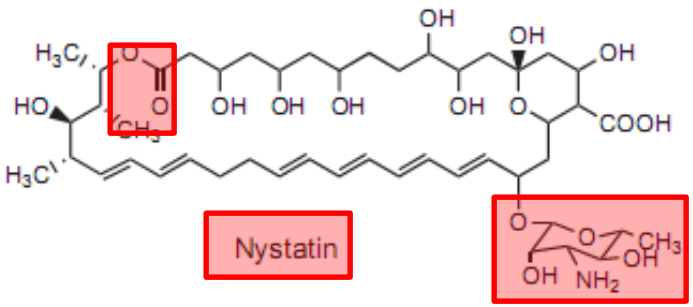
Sterols in Cell Membrane: Cholesterol & Ergosterol

- Compare their 27C structures.

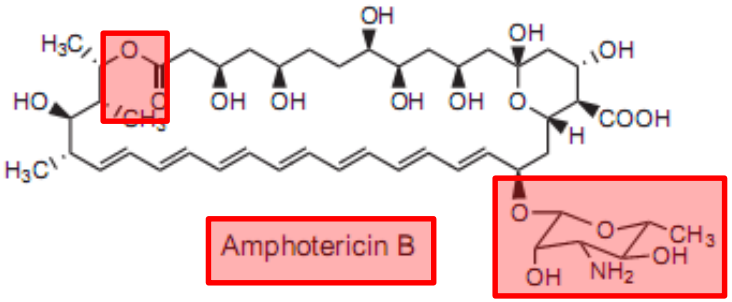


2. Cell Membrane Disruptors: Polyenes: SAR

- 38 membered lactone: nystatin & amphotericin B



- 26 membered lactone: natamycin



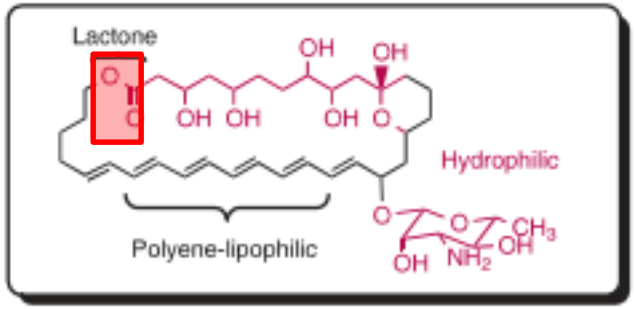
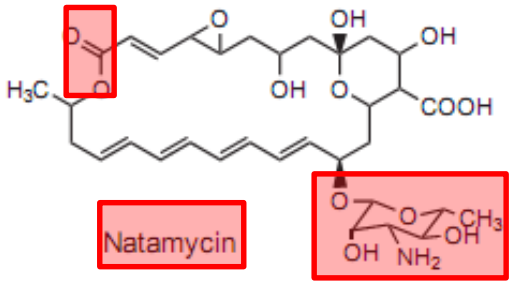


Figure 31.1 Commercially available polyenes. Insert indicates chemical features of this class of antifungal agents.



2. Cell Membrane Disruptors: Polyenes: Nystatin

- Isolated from cultures of bacterium *streptomyces*
- Chemistry: 38 membered lactone: hexa-ene

✓ aglycone: 38 membered nystatinolide & glycone: mycosamine

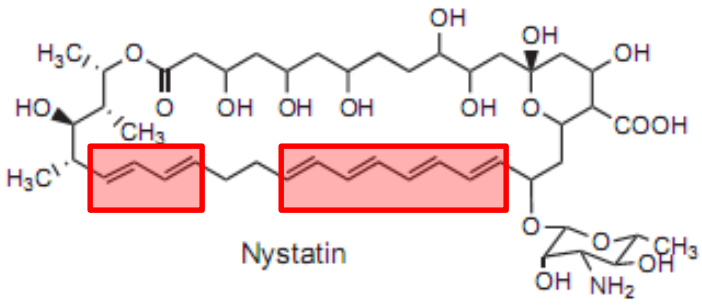
- Very little absorption
- Systemic usage is not recommended: too toxic
- Dosage forms:

✓ powder to prepare oral drop: 100,000 IU

✓ vaginal tab: 100,000 IU

✓ oral tab: 500,000 IU

✓ ointment: 100,000 IU

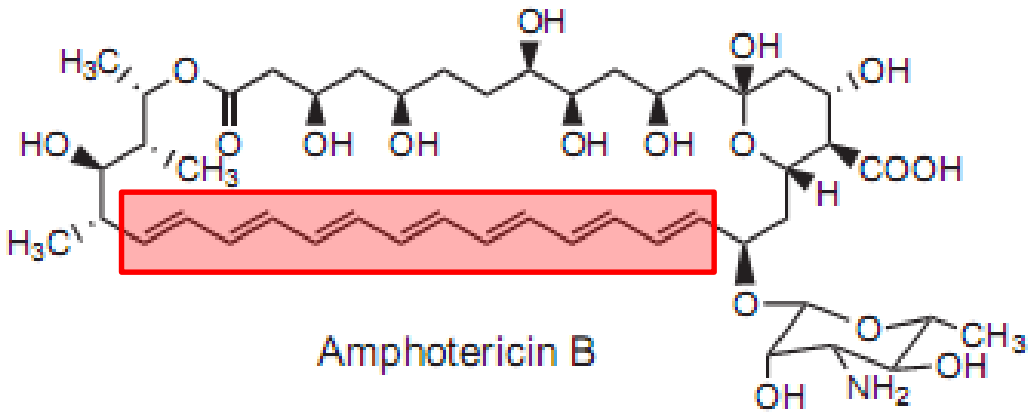


Nystatin

2. Cell Membrane Disruptors: Polyenes: Amphotericin B

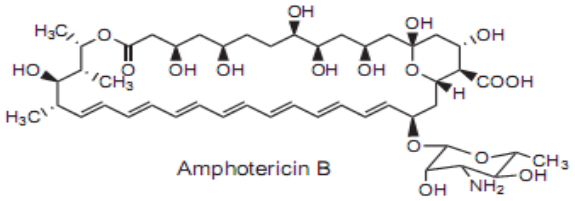
- Amphocin®; fungizone®
- Chemistry: 38 membered lactone: completely conjugated hepta-ene
- ✓ aglycone: 38 membered lactone & glycone: mycosamine
- The drug of choice for many systemic life threatening fungal infection

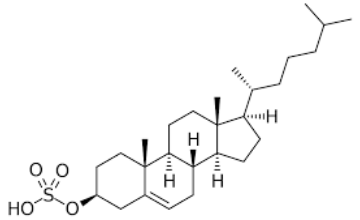
- Nephrotoxic & hepatotoxic: what is the solution?



Amphotericin B

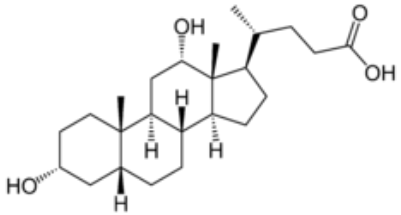
2. Cell Membrane Disruptors: Polyenes: Various Amphotericin B Derivatives & Formulations





- Amphotericin B cholesteryl sulfate: Amphotec®

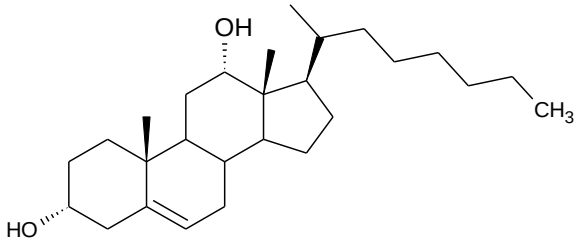
- Amphotericin B deoxy-cholate (C7-deoxy cholate): Amphocen®; Fungizone®
- ✓ a complex with deoxy-cholic acid: IV administration



- 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 formulation in clinic.

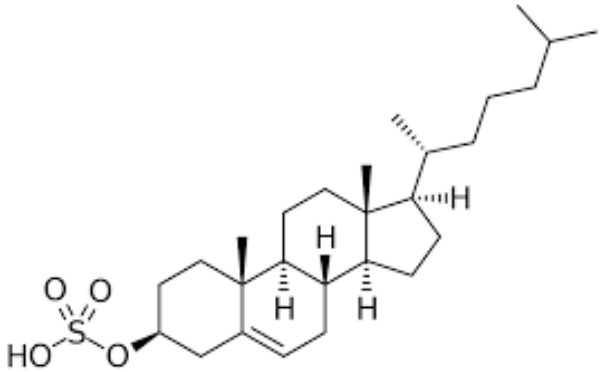
Structure of Cholesterol & Cholic Acid

- Cholesterol: 27C:



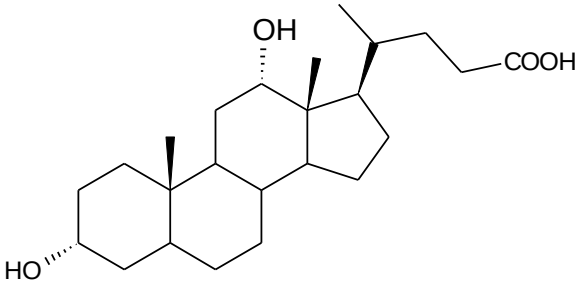
- Cholesteryl sulfate:

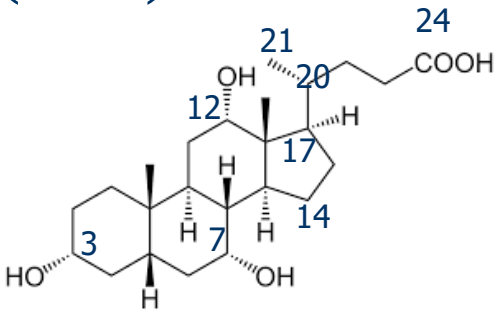
✓ C3-sulfate ester of cholesterol



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

✓ deoxycholate: C7-deoxy cholate

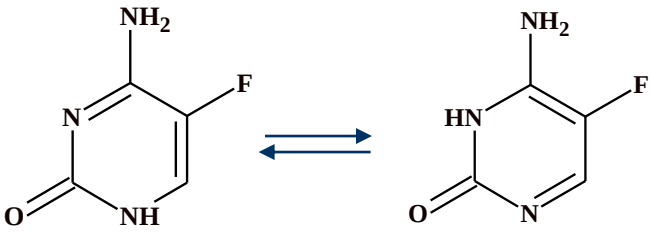




cholic acid

3. DNA Interfering Pyrimidine: Nucleoside Provider

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



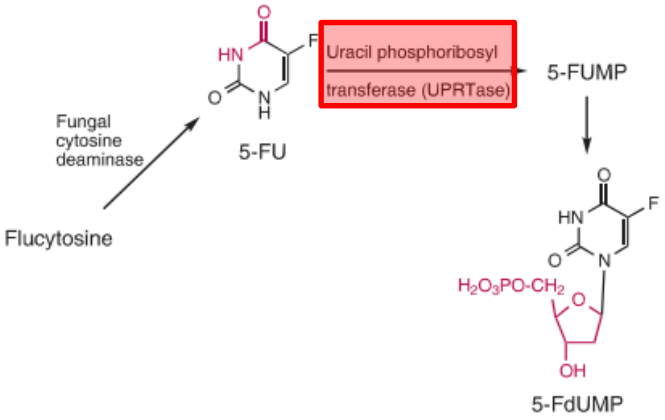


Figure 31.10 Metabolic activation of flucytosine by deamination, conjugated with ribosylphosphate to 5-fluorouracil monophosphate (5-FUMP) and onto 5-fluorodeoxyuridine monophosphate (5-FdUMP).

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

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

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

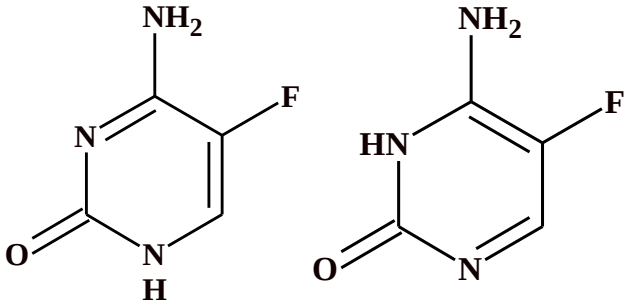
✓ active metabolite: 5-FdUMP: thymidylate synthase inhibitor

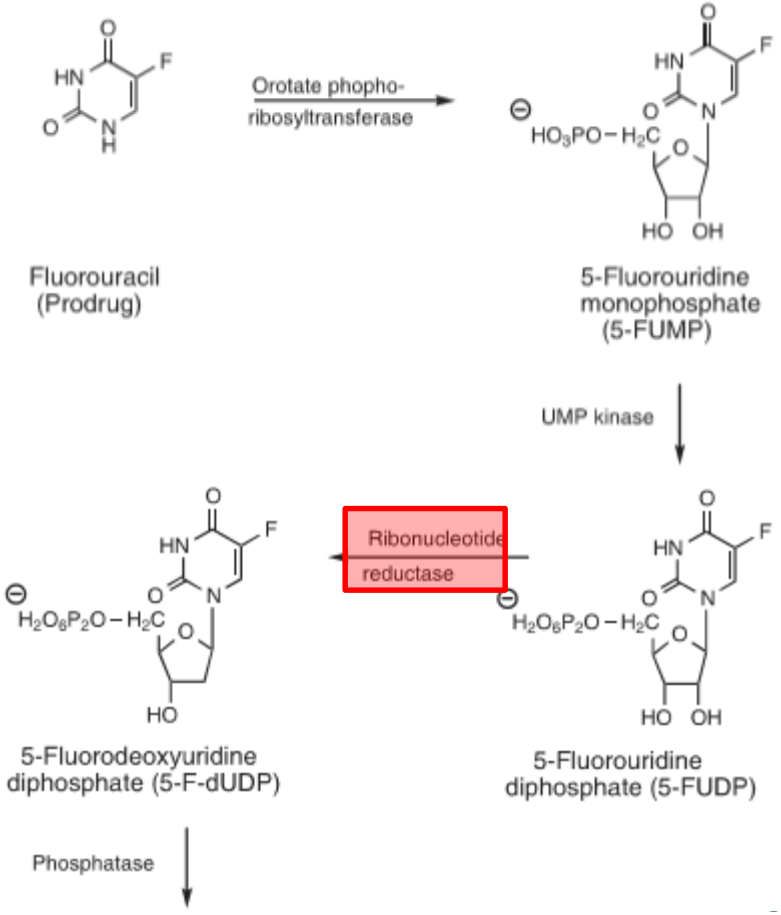
✓ active metabolite: 5-FdUTP: interfere with protein & RNA biosynthesis

- SAR: …

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

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





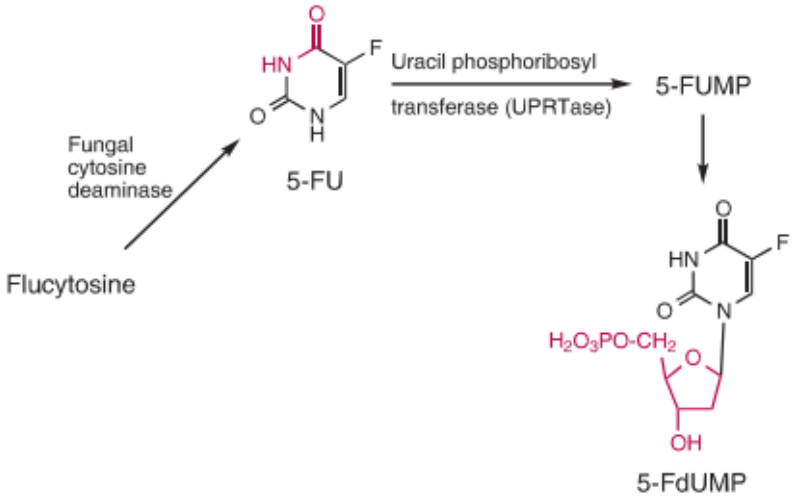


Figure 31.10 Metabolic activation of flucytosine by deamination, conjugated with ribosylphosphate to 5-fluorouracil monophosphate (5-FUMP) and onto 5-fluorodeoxyuridine monophosphate (5-FdUMP).

Thymidylate Synthase & 5-FdUMP

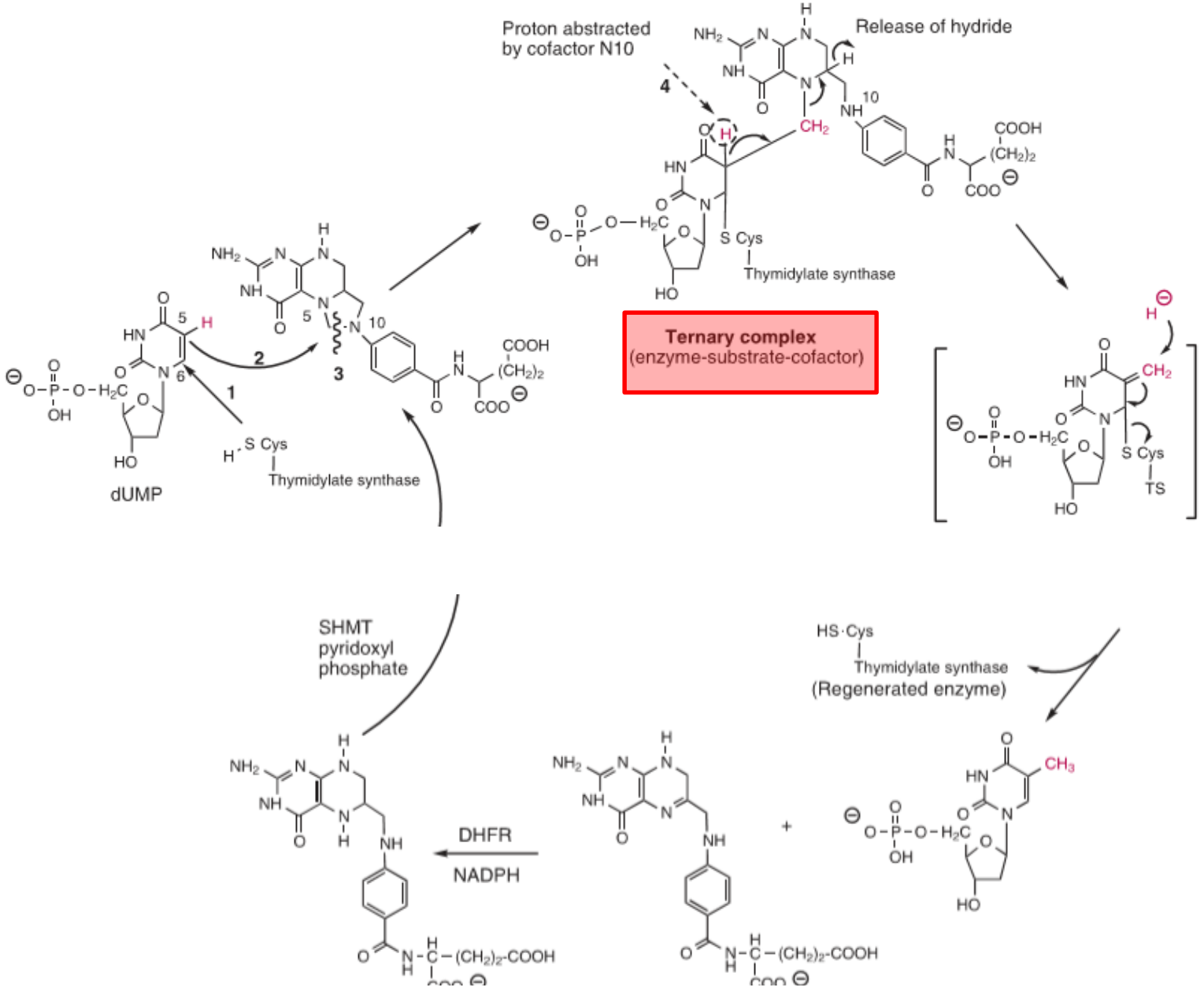
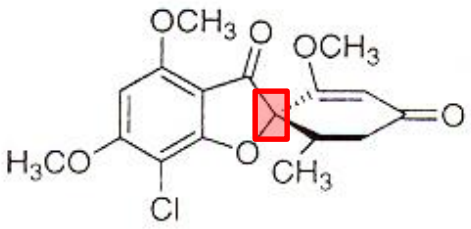


Figure 33.45 Synthesis of deoxythmidine monophosphate (dTMP). DHFR, dihydrofolate reductase; SHMT, serine hydroxymethyltransferase;

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,…

- 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

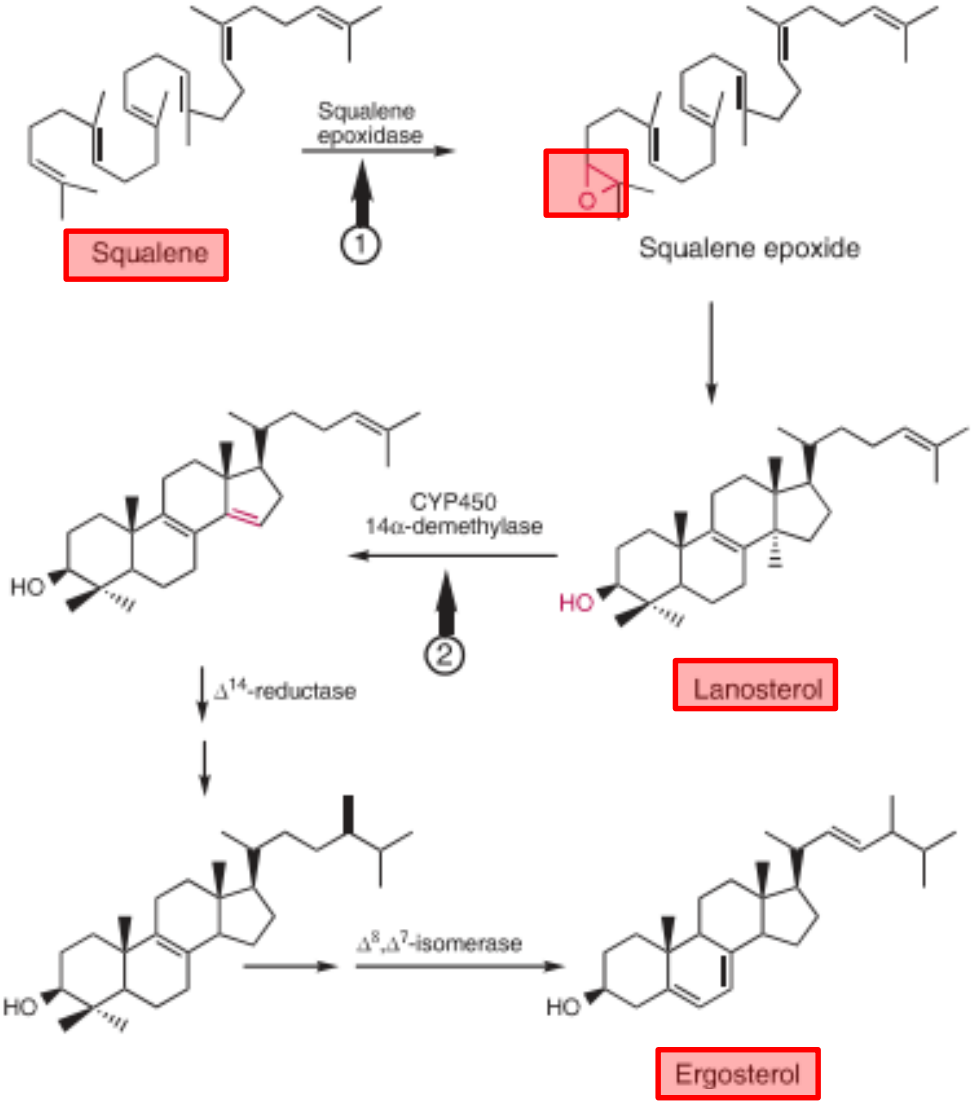
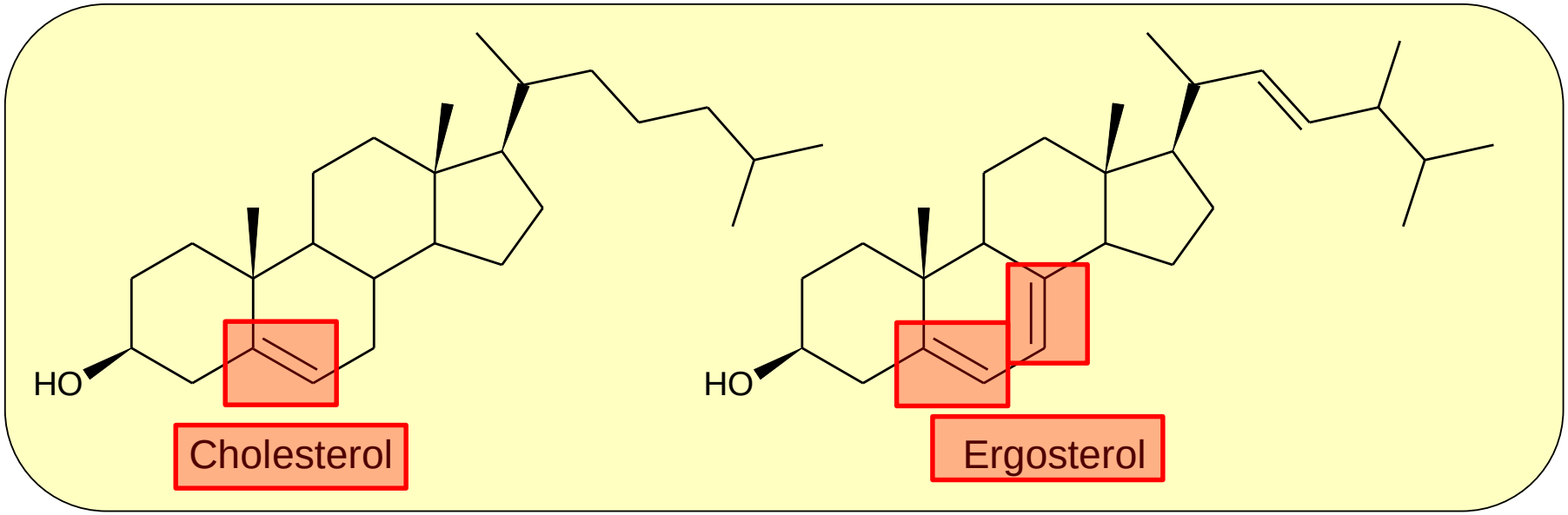


Figure 31.2 Key steps in the biosynthesis of ergosterol by fungi. Enzymatic steps known to be the site of action of currently employed antifungal agents are indicated by a heavy black arrow and a number.

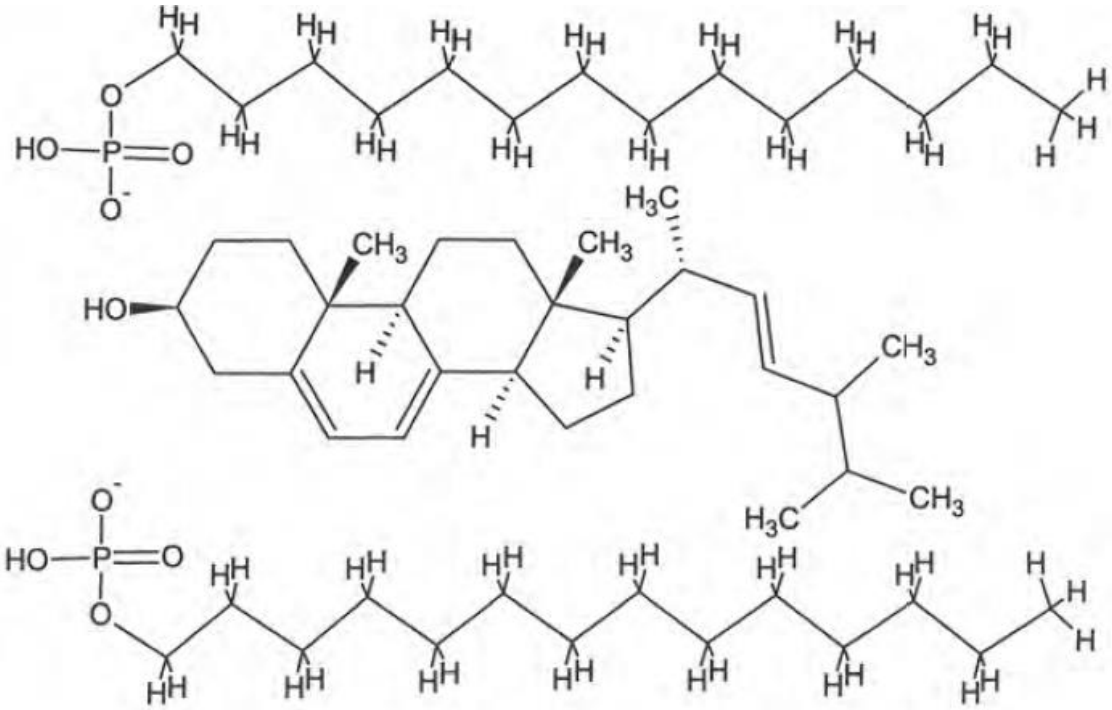
Foye 2013;P1165

Compare Cholesterol & Ergosterol

- What are critical structural differences?



Ergosterol in Lipid Bilayer



Ergosterol

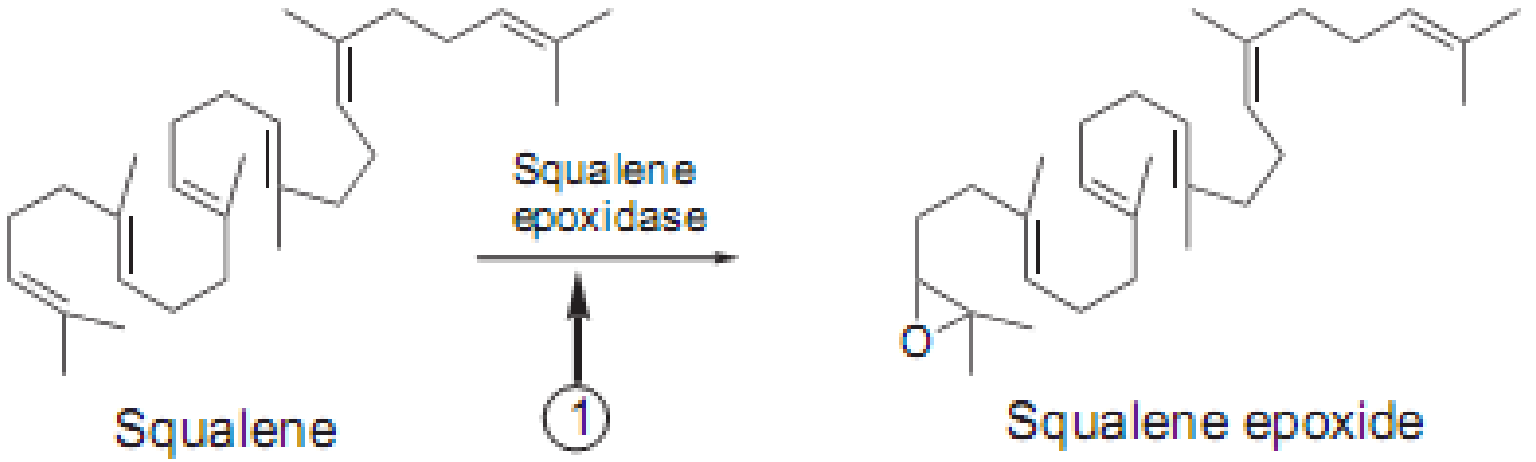
Figure 6.1 • Ergosterol embedded in a lipid bilayer.

5. a. Squalene Epoxidase Inhibitor: Allylamines

- MOA: squalene epoxidase inhibition:

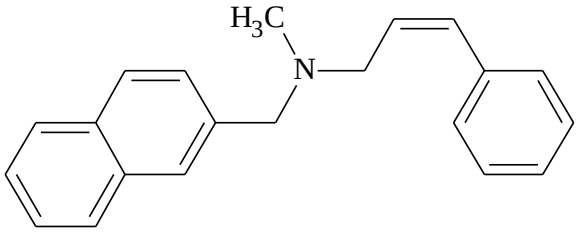
✓ decrease production of sterol in cell membrane: ergosterol depletion

✓ increase unchanged squalene in cell membrane



5. a. Allyamines & the Related Structures: SAR

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



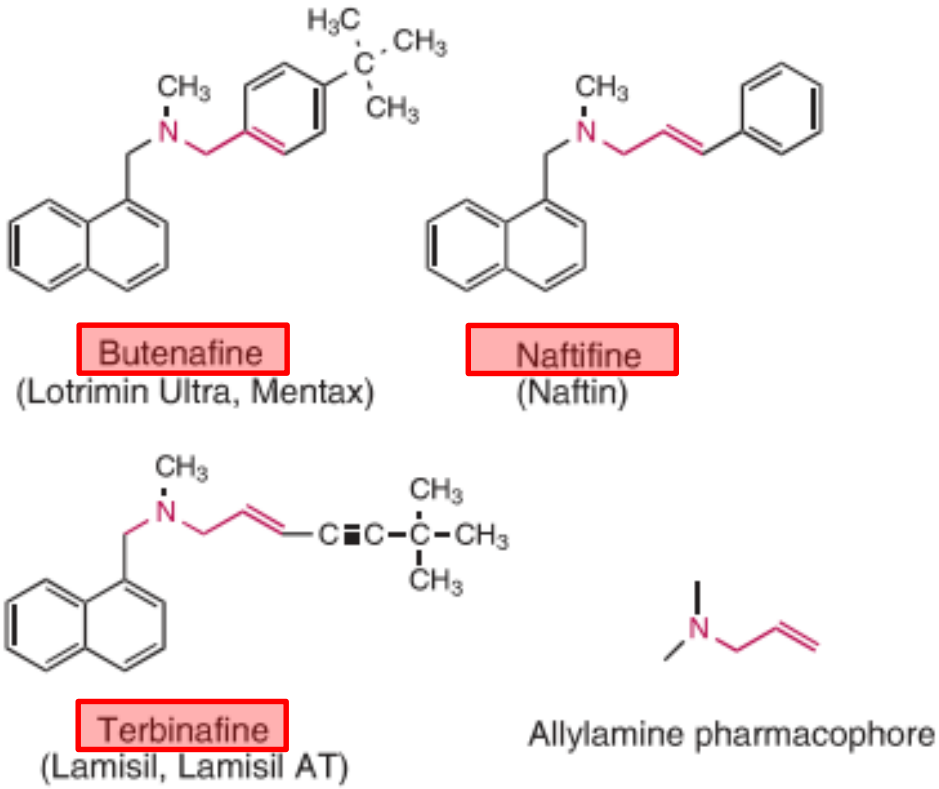


Figure 31.7 Allyl amine squalene epoxidase inhibitors. Butenafine and nafttifine are topical only. Terbinafine may be used topically or systemically.

5. b. Demethylase Inhibitors: Azoles

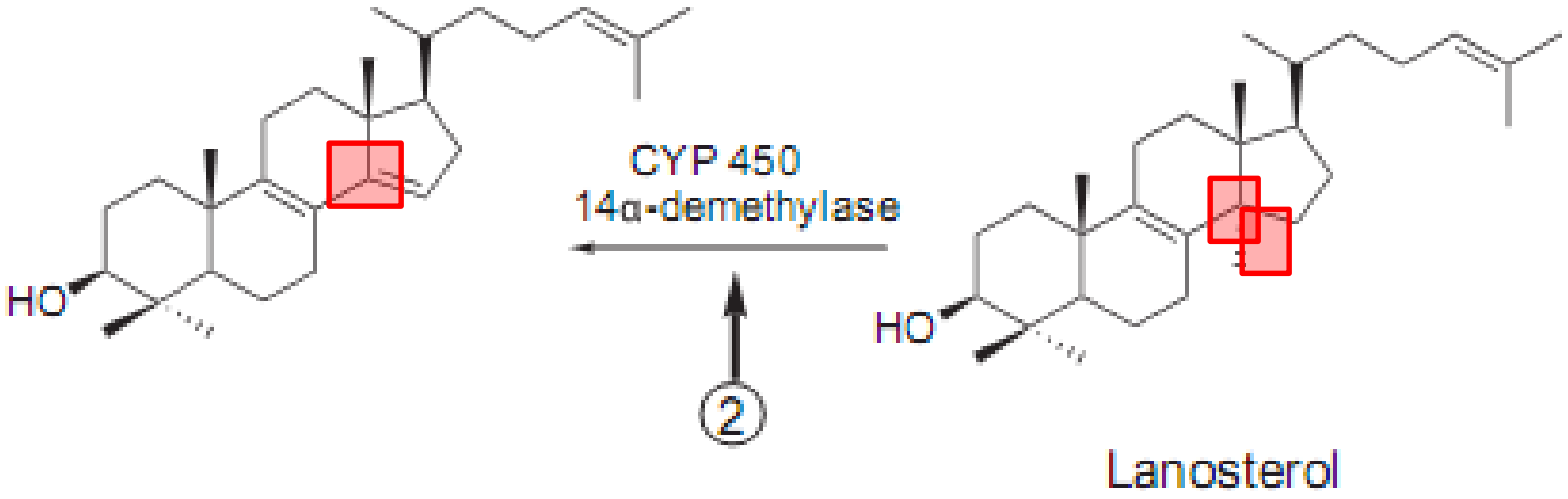
- MOA:

✓ ergosterol biosynthesis inhibitor by inhibiting lanosterol 14α-demethylase

- Lanosterol 14α-demethylase:

✓ a CYP450 related enzyme

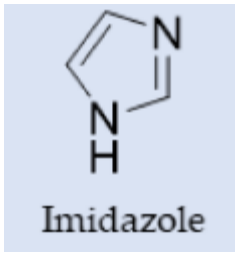
✓ possessing heme as cofactor

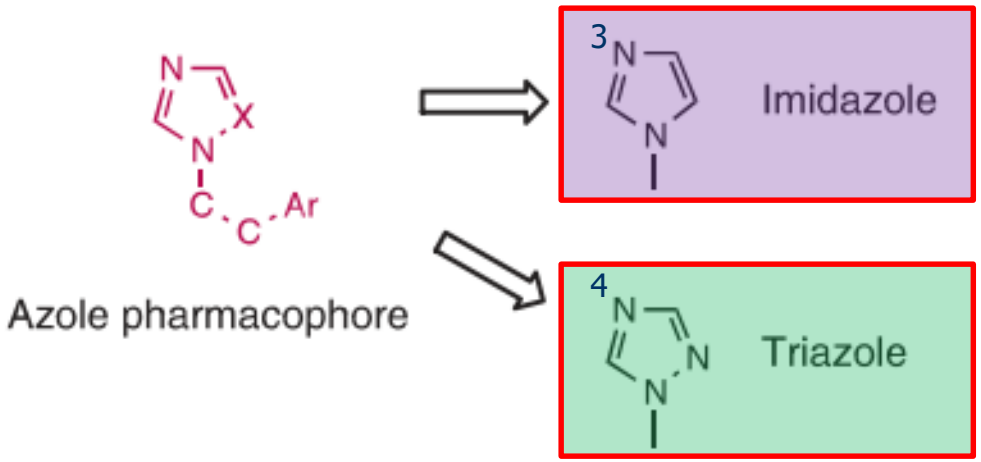


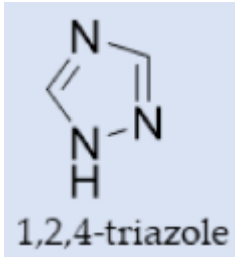
5. b. Demethylase Inhibitors: Azoles: SAR

- 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?

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

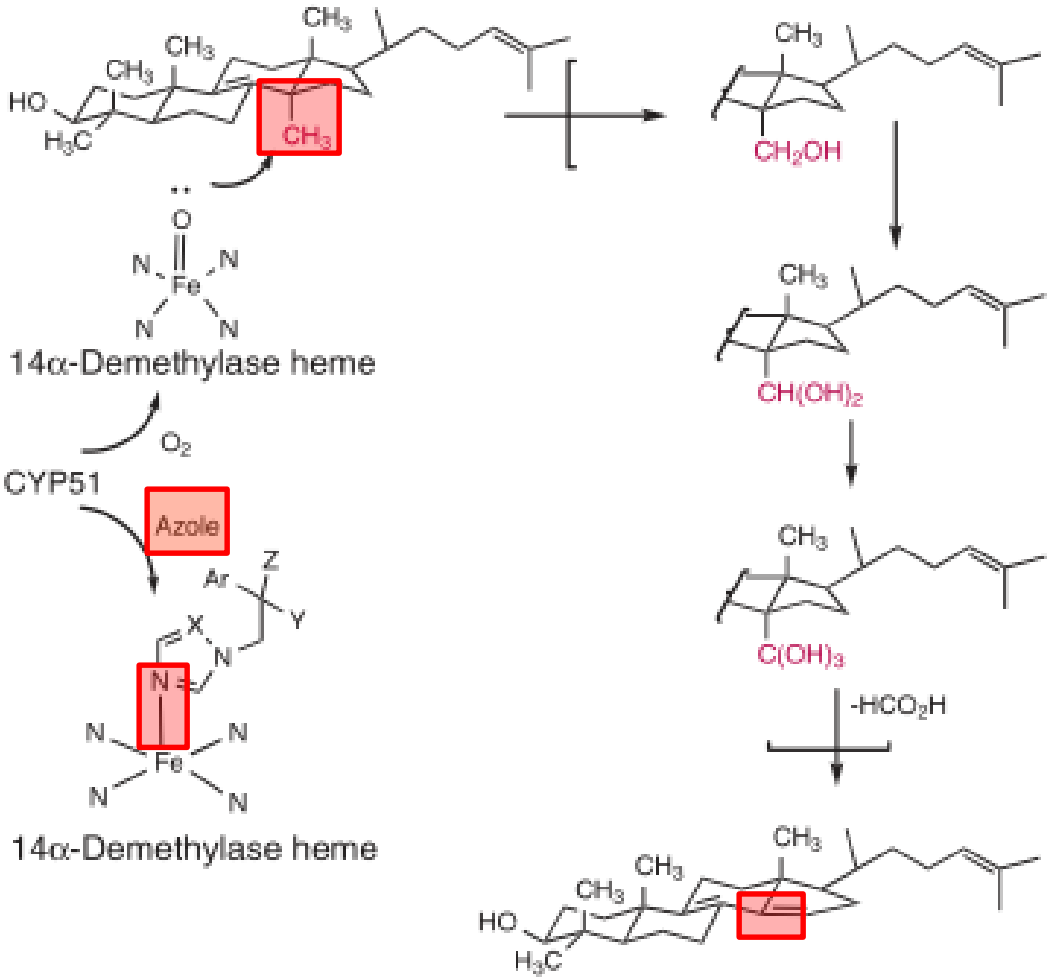
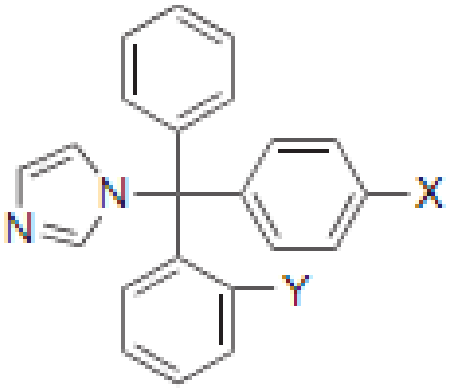


Figure 31.3 Demethylation of the 14α-methyl group from lanosterol via the CYP450 enzyme sterol 14α-demethylase, CYP51. Three successive heme catalyzed insertions of activated oxygen into the three carbon-hydrogen bonds of the 14α-methyl group which raises the oxidation state of the methyl group to a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

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

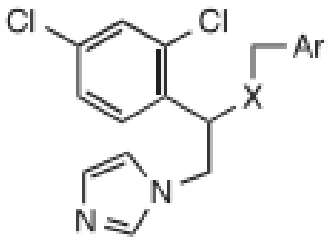
- Clotrimazole
- Flutrimazole
- SAR: …



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

- Applications: in local infections

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



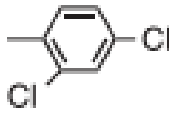
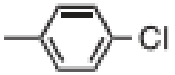
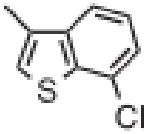
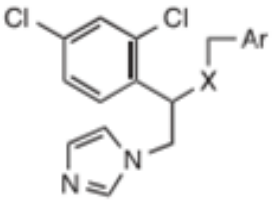
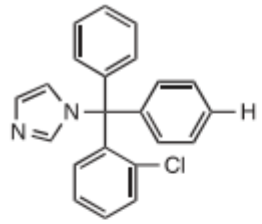
Generic name	Trade Name	X	Ar
Miconazole	Generic, Desenex, Fungoid, Monistat Oravig, Zeasorb	O	
Econazole	Generic	O	
Sulconazole	Exelderm	S	Same
Sertaconazole	Ertaczo	O	
Tioconazole	Vagistat, TZ-3	O	

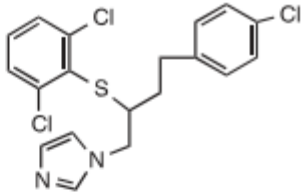
Figure 31.4 Imidazole antifungal agents. All imidazoles are used topically with the exception of ketoconazole which is available in both a topical and systemic dosage form.

5. b. Demethylase Inhibitors: Imidazole Types

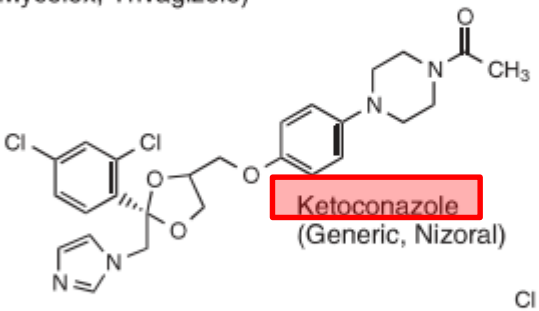




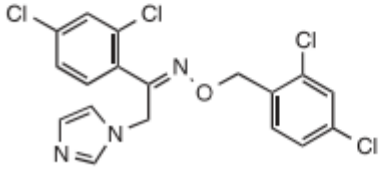
Clotrimazole (Cruex, Lotromin,Desenex, Mycelex, Trivagizole)



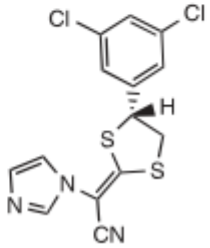
Butoconazole (Femstat,Gynazole)



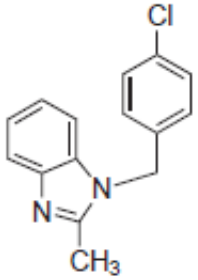
Ketoconazole (Generic, Nizoral)



Oxiconazole (Oxostat)



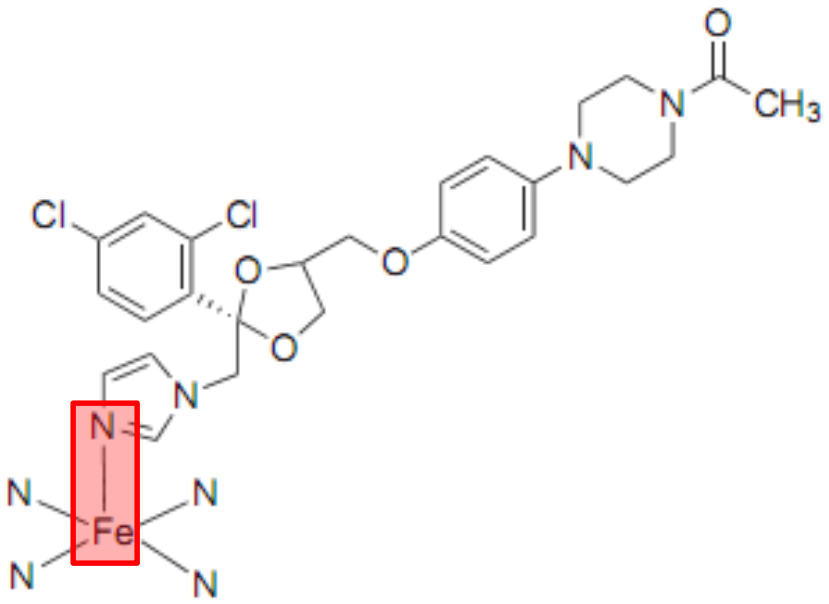
Luliconazole (Luzu)



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.

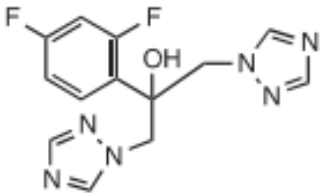
Ketoconazole & CYP450 Related Demethylase Interaction



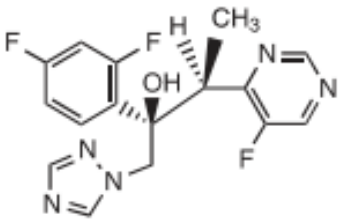
14α-Demethylase heme

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.

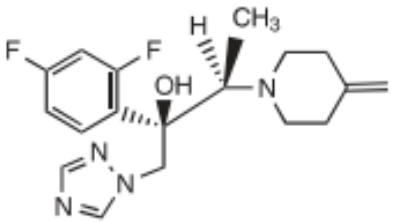
5. b. Demethylase Inhibitors:
Triazoles Types



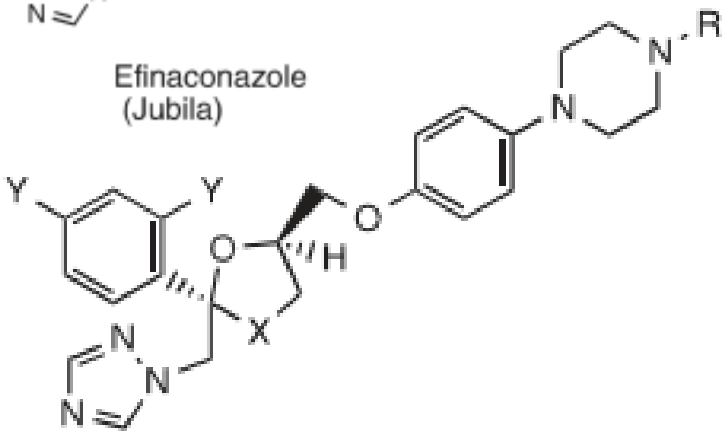
Fluconazole
(Diflucan)



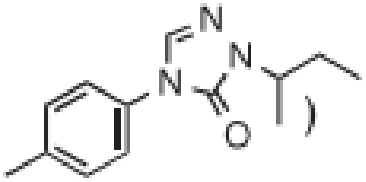
Voriconazole
(Vfend)



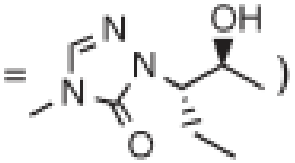
Efinaconazole
(Jubila)



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



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



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

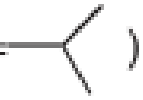


Figure 31.5 Triazole antifungal agents. While efinaconazole, isavuconazole, and terconazole are used topically, the remaining triazoles are used systemically.

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

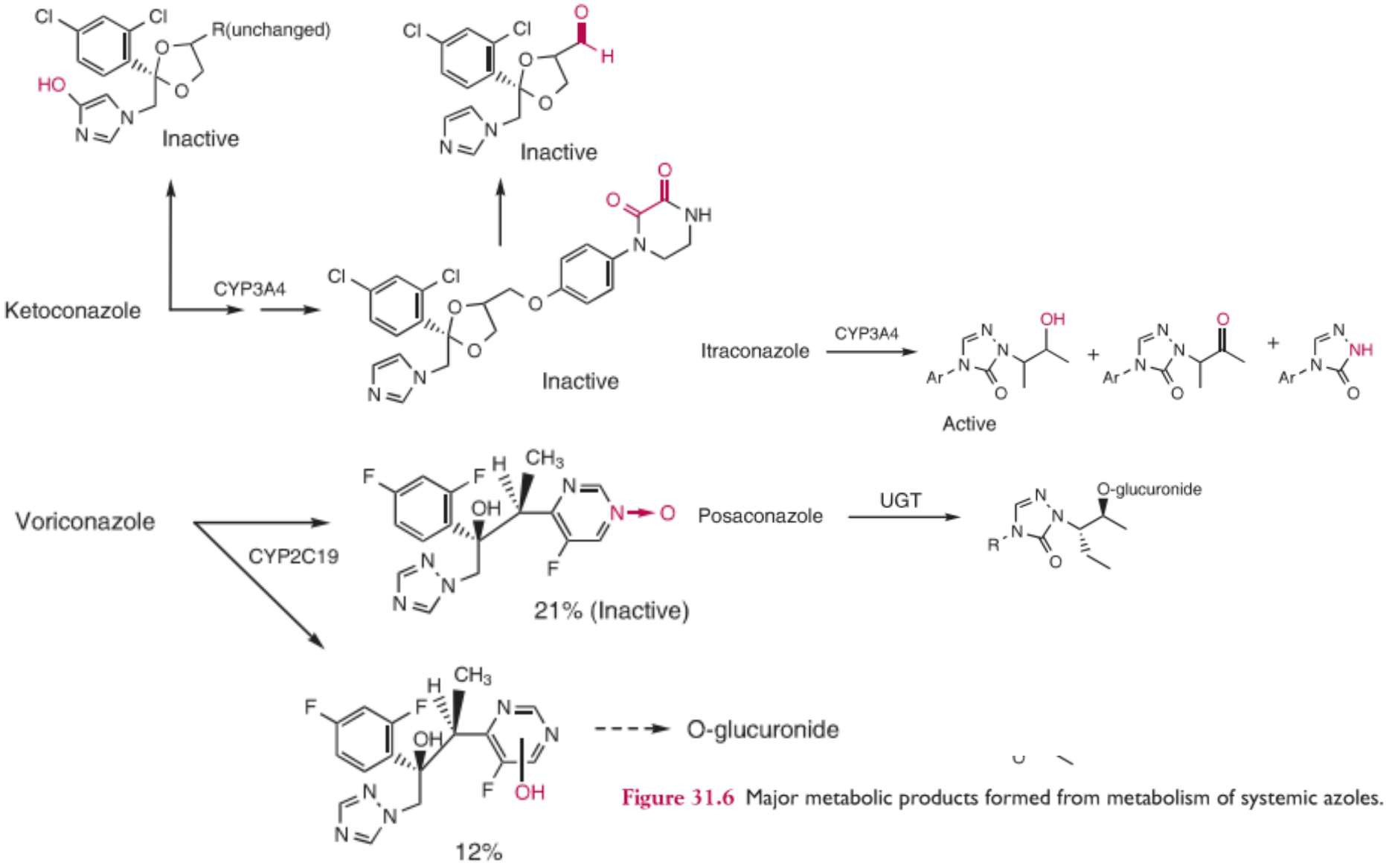
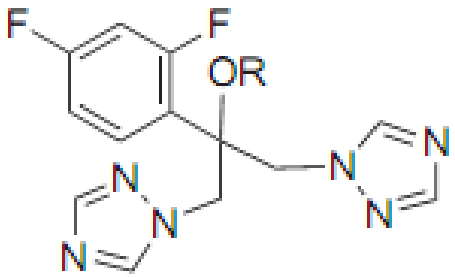


Figure 31.6 Major metabolic products formed from metabolism of systemic azoles.

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:

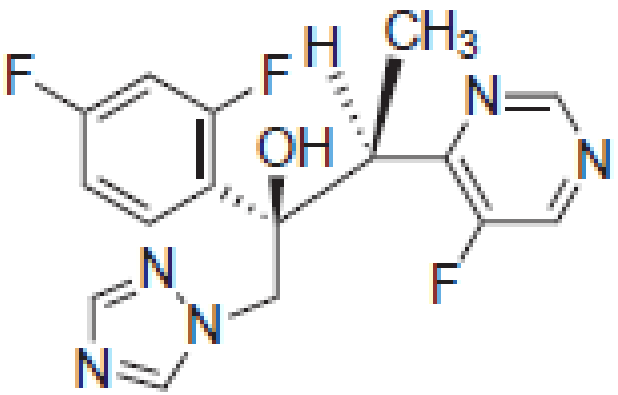
✓ against *Aspergillus* and fluconazole-resistant strains of *Candida* & *Cryptococcus*

- BBB pass

- Dosage forms:

✓ Oral: tab: 50 & 200mg

✓ IV: powder for injection: 200 mg



Voriconazole

Metabolism of Voriconazole

- Dosage forms: oral & IV

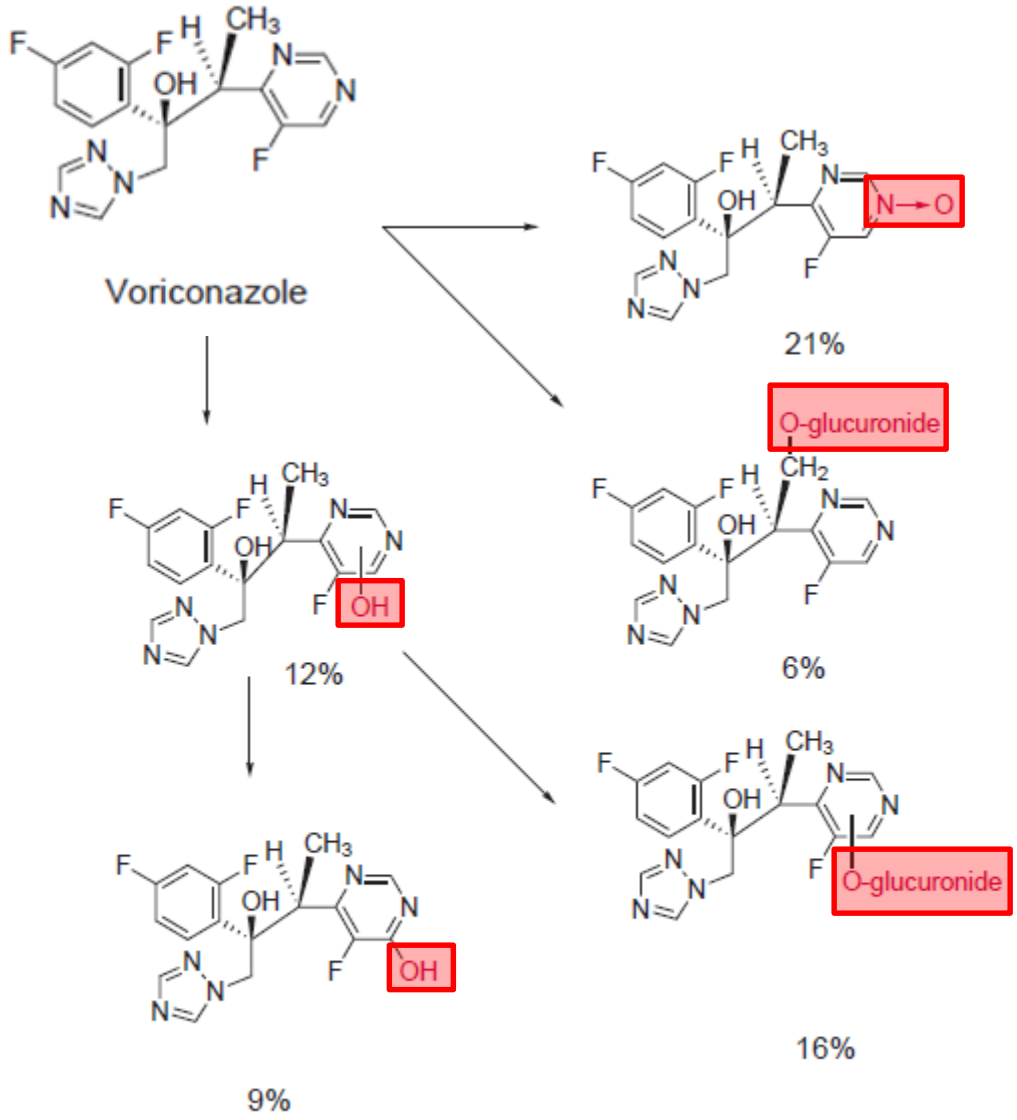
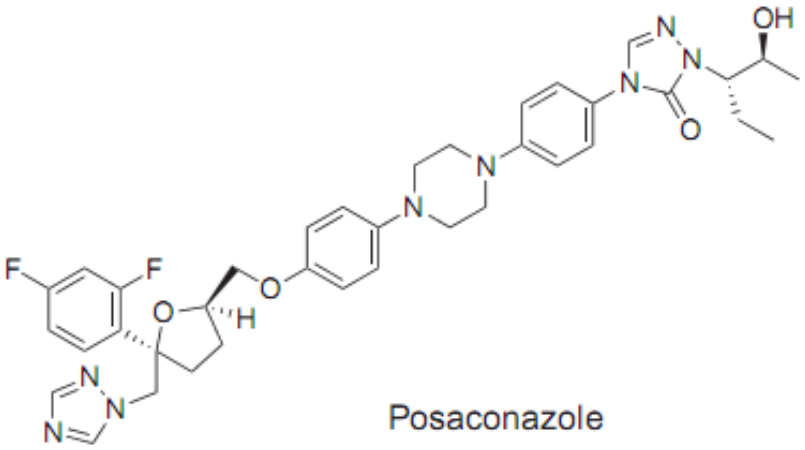


FIGURE 35.7 Major metabolic products resulting from CYP450 metabolism of voriconazole.

5. b. Demethylase Inhibitors: Azoles: Novel Triazole Types

- Posaconazole:
- Broader spectrum
- Less metabolic CYP450 interaction
- Against subtype A of CYP51 in *Aspergillus* which is
- resistant to the older azoles (fluconazole and …)
- Dosage forms:

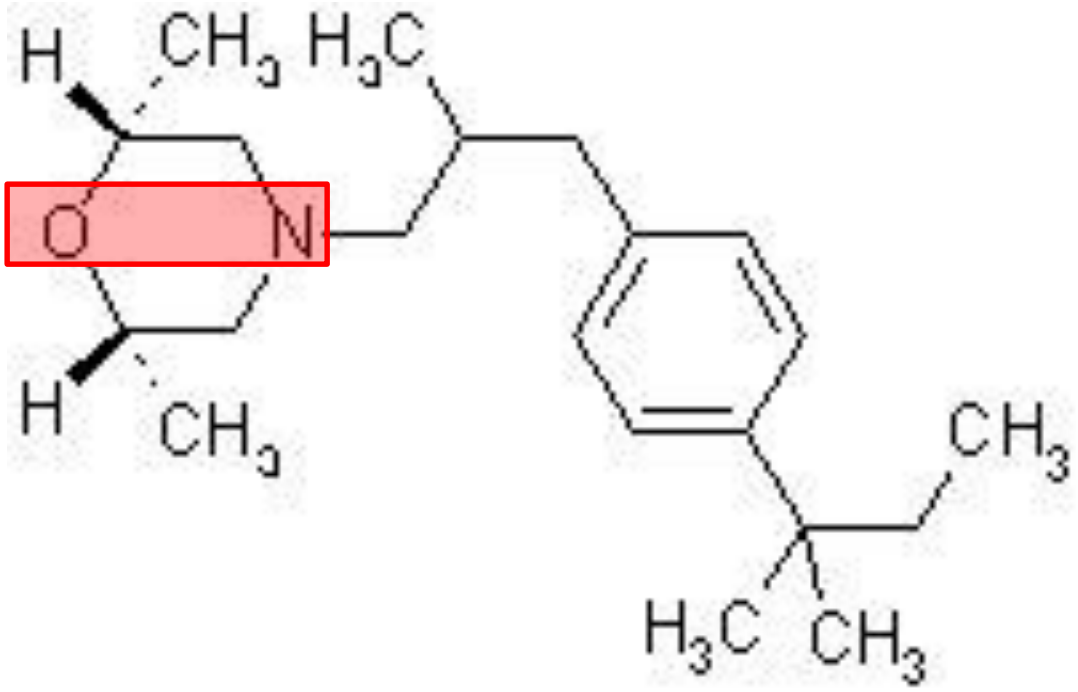
✓ oral (50&200mg)



Posaconazole

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

- 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*

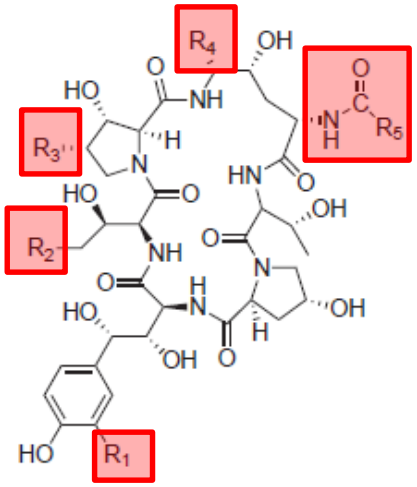
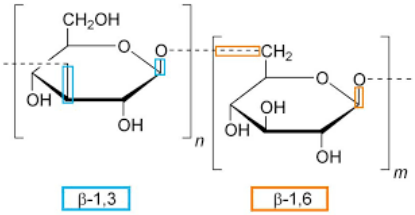


FIGURE 35.9 Echinocandins.

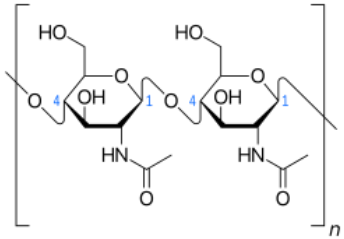
6. Glucans in Cell wall of Fungi & Molecular Mechanism of Glucan Synthase Inhibitors

- Cell wall consists of poly-saccharides: GPI:

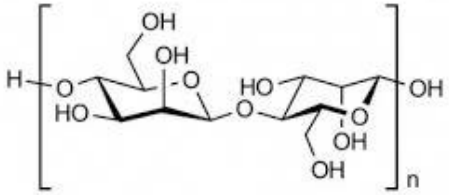
✓ glucans: three types: ß-1,3-glucan & ß-1,6-glucan

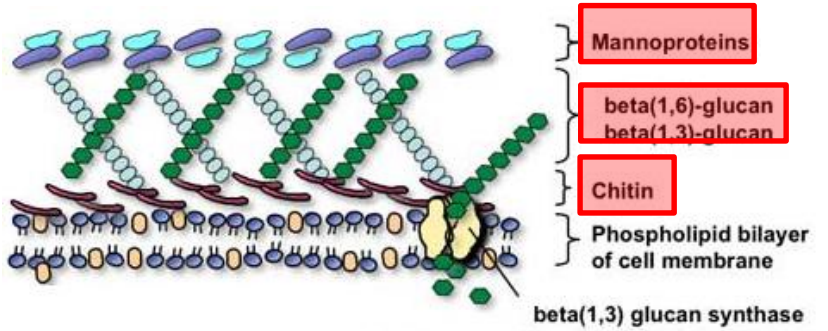


✓ chitin: ß-1,4- linked N-Ac-glucosamine



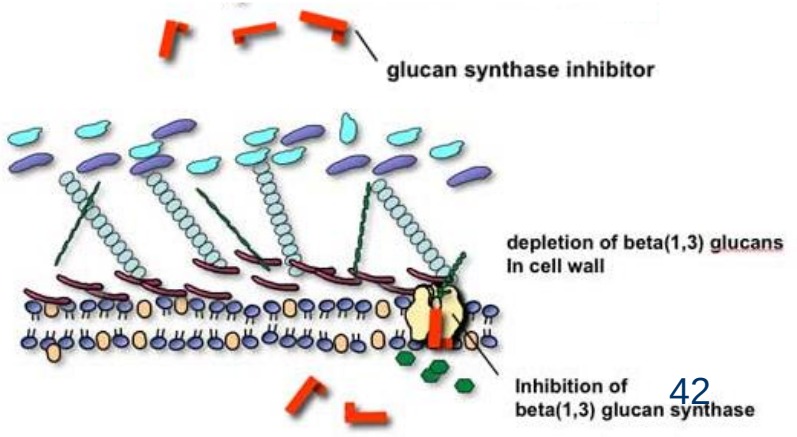
✓ mannans & mannoproteins





- 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

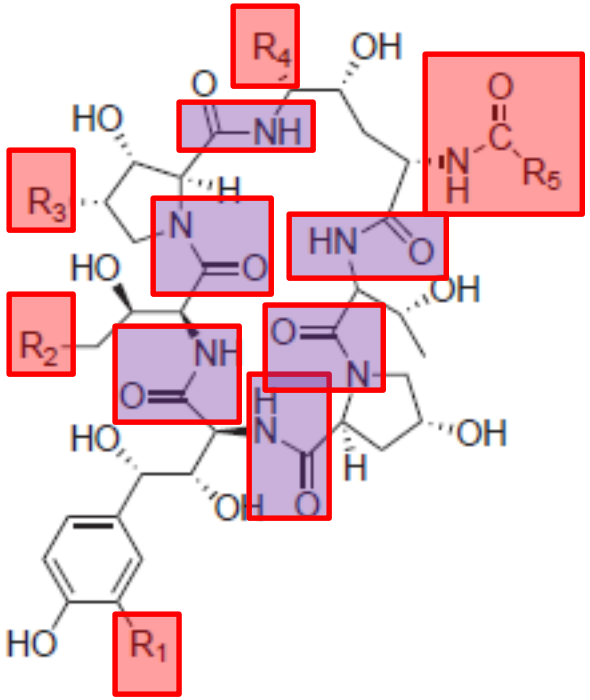
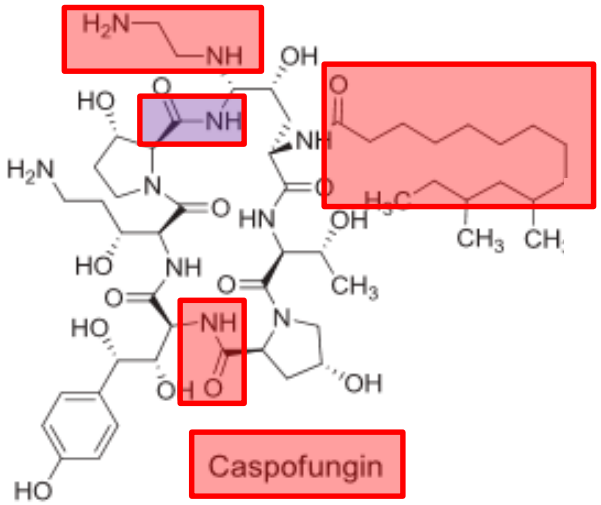
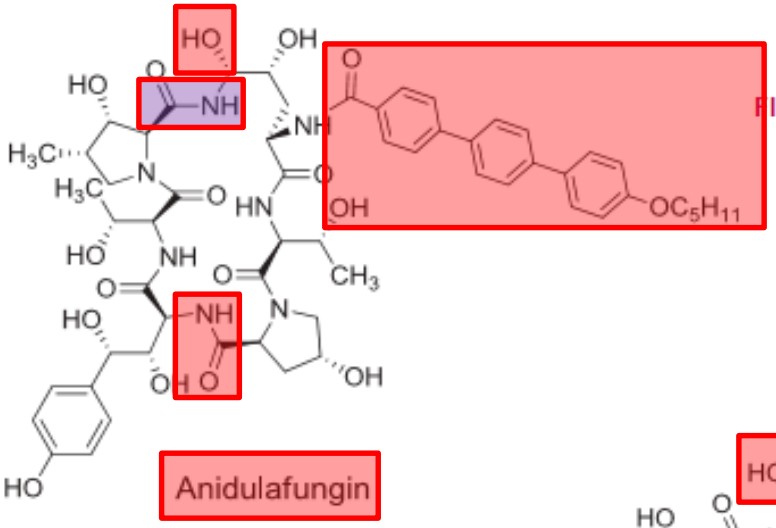


FIGURE 35.9 Echinocandins.

Echinocandins





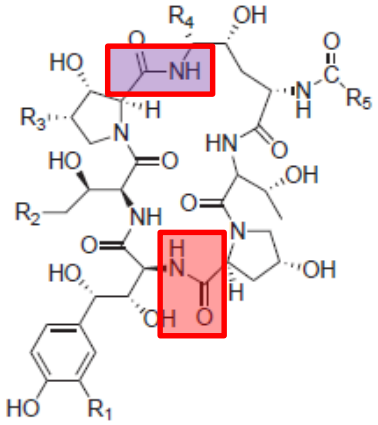


FIGURE 35.9 Echinocandins.

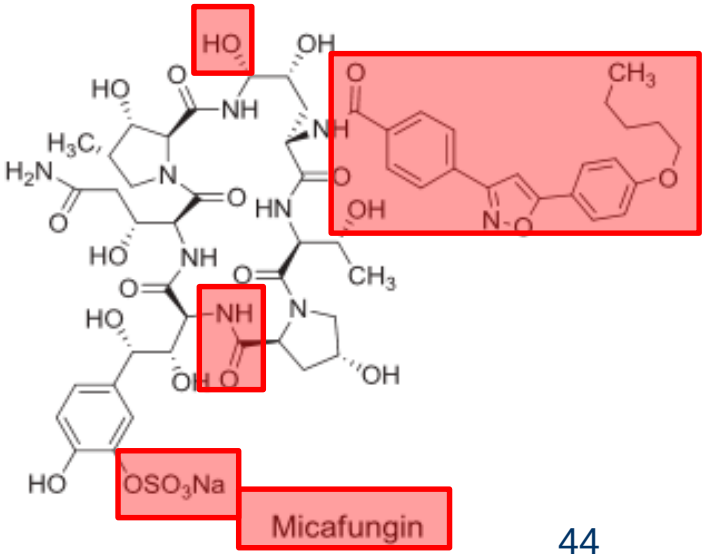
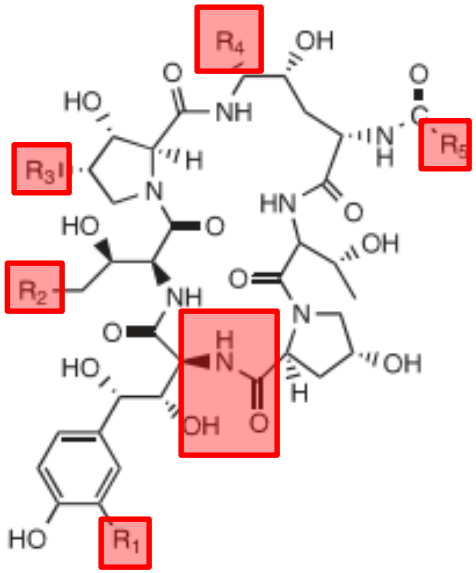


Figure 3. Chemical structures of echinocandins in clinical use.

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 (Ph-iso-oxazole-Ph)



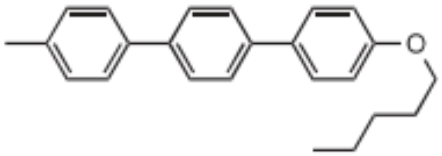
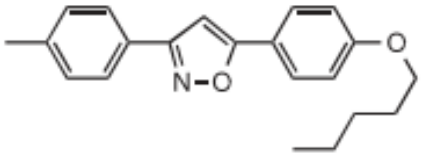
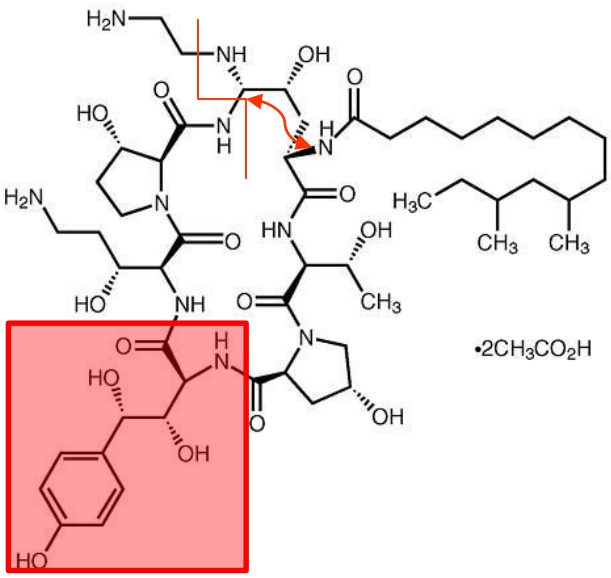
Drug	R_1	R_2	R_3	R_4	R_5
Caspofungin (Cancidas)	H	CH_2NH_2	H	$NHCH_2CH_2NH_2$	
Anidulafungin (Eraxis)	H	H	CH_3	OH	
Micafungin (Mycamine)	OSO_3H	$CONH_2$	CH_3	OH	

Figure 31.8 Echinocandins.

Metabolism of Caspofungin

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



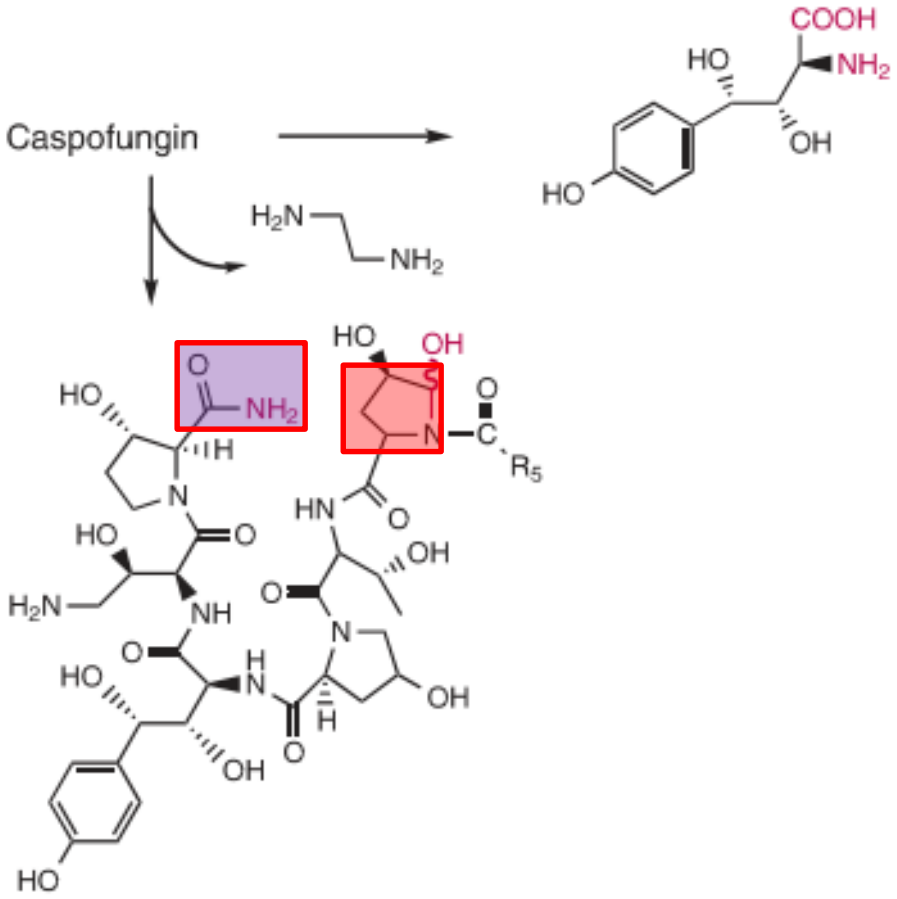


Figure 31.9 Metabolic products formed from caspofungin.

Novel Echinocandins: Rezafungin

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

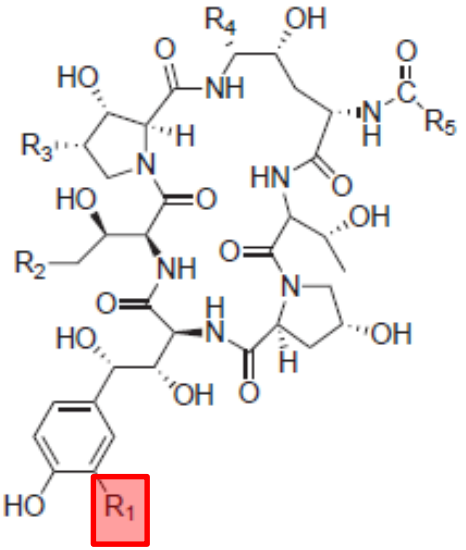


FIGURE 35.9 Echinocandins.

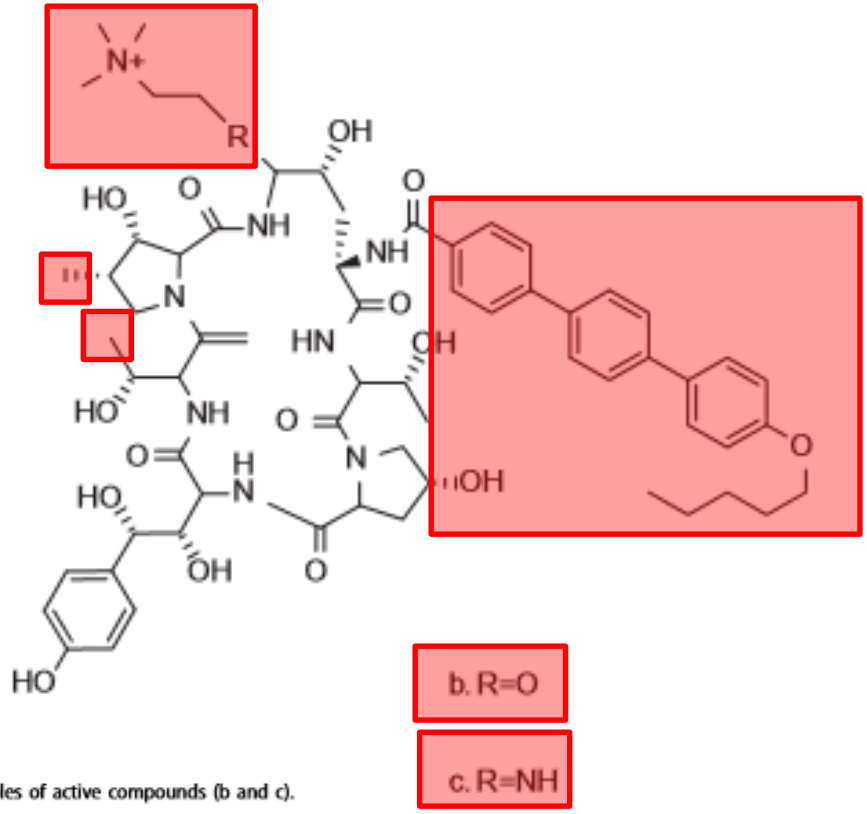
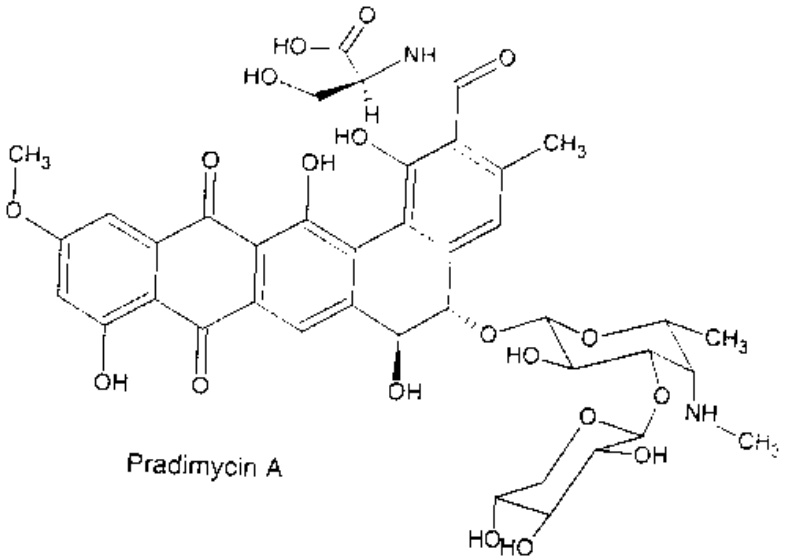


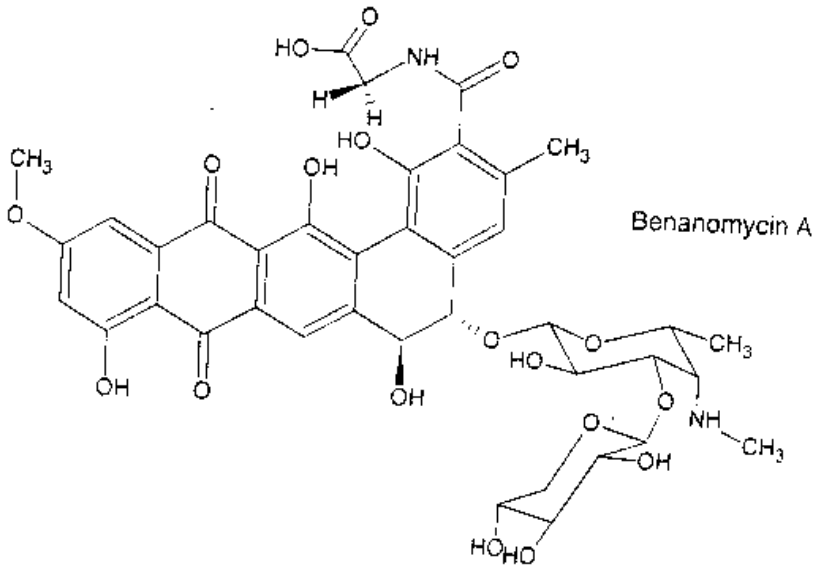
Figure 4. Echinocandin derivatives disclosed by Cidara Therapeutics Inc. General formula (a) and examples of active compounds (b and c).

8. Pentacyclic Chelators

- Pradimycin

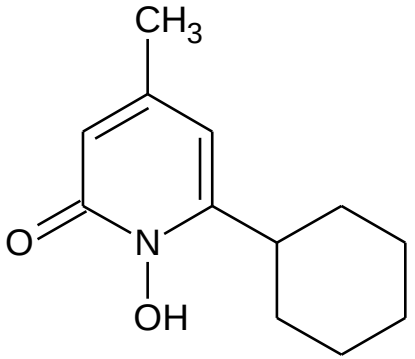


- Benanomycin



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:

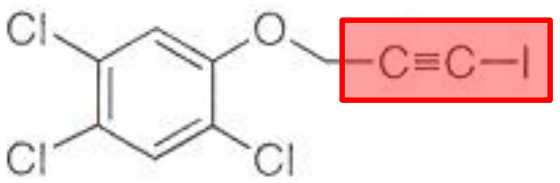
✓ superficial dermatophytes

✓ 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

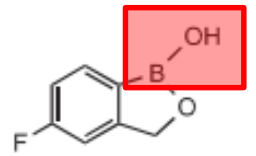


Haloprogin

- Clinical application: dermatophytes: topical

9. Miscellaneous: Tavaborole

- Chemistry: boron derivative
- FDA approved: 2014



Tavaborole (Kerydin)

- MOA: binds terminal Adenosine Leu tRNA

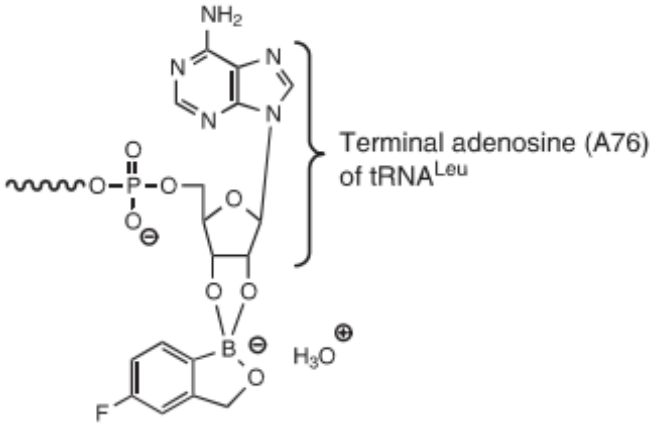
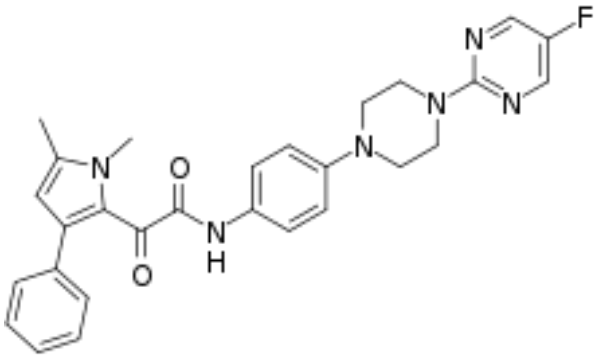


Figure 31.11 Binding between tavaborole and tRNA in the editing active site of leucine-tRNA synthetase (LeuRS).

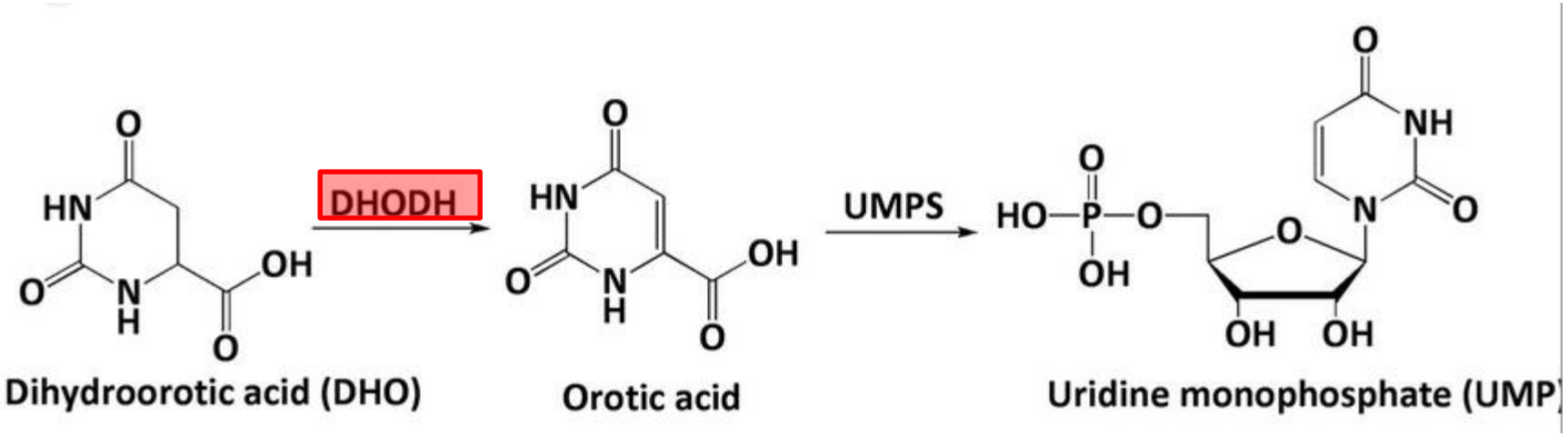
- Against onychomycosis:
- ✓ nail infections: lacquer formulation
- Dosage form: topical

9. Miscellaneous: Orotomide

- Chemistry: …
- Investigational: discovered in 2015



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



SCENARIO: OUTCOME AND ANALYSIS

Outcome

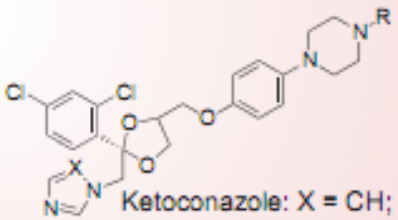
Douglas Slain, PharmD, BCPS

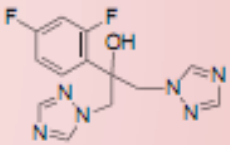
The patient was told to go to the emergency room at the hospital. They measured her plasma digoxin concentration, which was found to be very elevated (3.3 ng/mL). The pharmacist at the emergency department found reports in the medical literature of interactions between itraconazole and digoxin. The team monitored and stabilized the patient. They decided to lower her digoxin dose by 50%. A week later, digoxin concentration was again tested and was within the desired range (1.9 ng/mL), and there were no signs of toxicity. The patient was able to remain on the reduced digoxin dose while finishing the course of itraconazole. Fluconazole does not have an interaction with digoxin, but it is not as effective for treating histoplasmosis.

Chemical Analysis

Victoria Roche, PhD, and S. William Zito, PhD

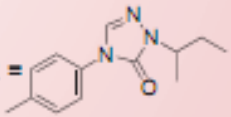
The interaction is due to the fact that itraconazole is a P-glycoprotein inhibitor. Digoxin is a substrate of P-glycoprotein. From a chemical standpoint, itraconazole and ketoconazole bind tightly to P-glycoprotein and serve as significant inhibitors and substrates. Structures that bind to P-glycoprotein are often lipophilic entities with molecular weights between 300 and 1,000. Conazole antifungal agents commonly have a structural pattern of three electron donor groups separated by 4.6 Angstroms, a motif known to be recognized by this efflux protein (73). Fluconazole does not appear to bind to P-glycoprotein. It is a much smaller structure than either itraconazole or ketoconazole, and it is significantly less lipophilic. As a result, it has been claimed to distribute ineffectively across membranes and experience difficulty reaching and interacting with the P-glycoprotein binding site (47). Therefore, a P-glycoprotein–mediated interaction with digoxin would not be expected from fluconazole.





Fluconazole

Itraconazole: X = N; R =



Agents that are CYP3A4 substrates and inhibitors are often P-glycoprotein substrates and inhibitors. Newer azoles like voriconazole and posaconazole appear to bind to P-glycoprotein but have not been as well studied.

From Foye's 2013