ANTIFUNGAL AGENTS

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Fungal infections – MYCOSES

Superficial

Dermatomycoses

Trichophyton
Malassesia furfur
Microsporum

Epidermophyton
Candidiasis

Subcutan mycoses

Sporothrix schenkii

Systemic

Candidiasis

Candida albicans

Candida tropicalis
Candida kruzei

Aspergillosis

Aspergillus nidulans

Histoplasmosis
Blastomycosis
Coccidioidomycosis
Paracoccidioidomycosis

The underlined the opportunistic pathogens

Risk Factors for fungal diseases

Broad-spectrum antibacterial therapy

Reduced immune responses (phagocytosis, neutropenia, T4 ly, Th-1 cytokines)

- **Primary and secondary immundeficient syndromes**
- **AIDS**
- **Immunosuppressant drug therapy, transplantation**
- **Cancer chemotherapy**
- **Malignant hematological diseases**

Diabetes mellitus

Local factors

Intravenous or urogenital canules

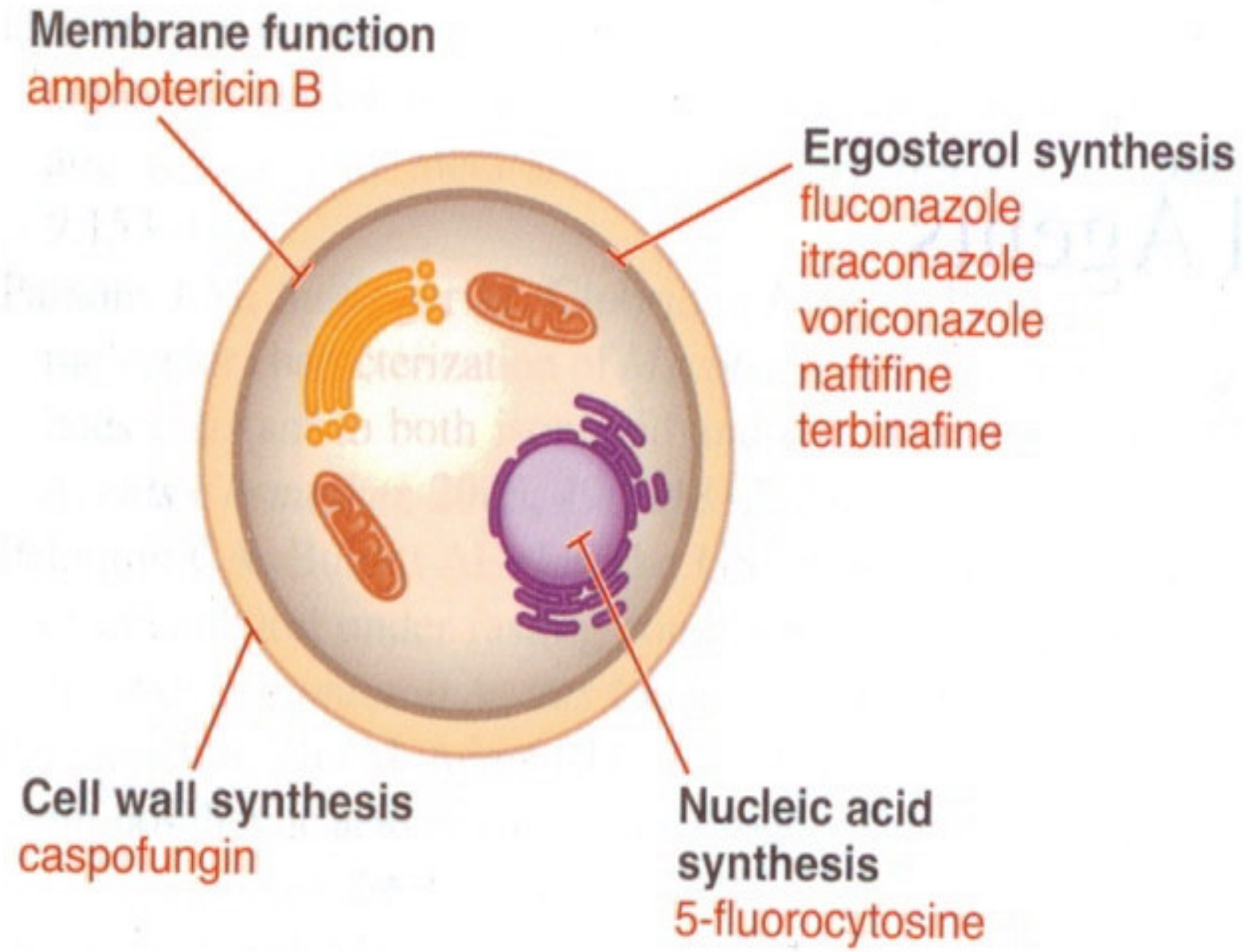

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Table 47.2 Discovery of antifungal drugs

Decade	Drug
1950s	Amphotericin
1960s	Griseofulvin
1970s	Flucytosine, clotrimazole, miconazole
1980s	Ketoconazole, fluconazole, itraconazole
1990s	Terbinafine, naftifine, different formulations[a] of amphotericin
2000s	Caspofungin
Under development	Voriconazole[b], posaconazol[b], ravuconazole[b], micafungin (FK463)[b], sordarins, pradimicin, nikkimycin

[a]Different formulations: liposomes, nanosomes, nanoparticles.
[b]Undergoing clinical trials.

Application

Superficial infections

Topical
Ointment

Solution
Nail lacquer

Powder
Eye/ear drop
Vaginal tablets

oral
tabl, caps

suspension

Systemic infections

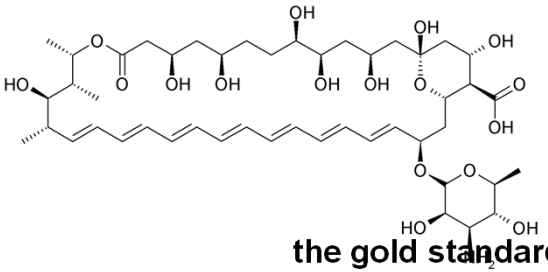
oral
tabl, caps

parenteral
infusion, injection

special
formulations:

liposomes

1. Polyene antifungal drugs from Streptomyces speciei, macrolide antibiotics I.



amphotericin B

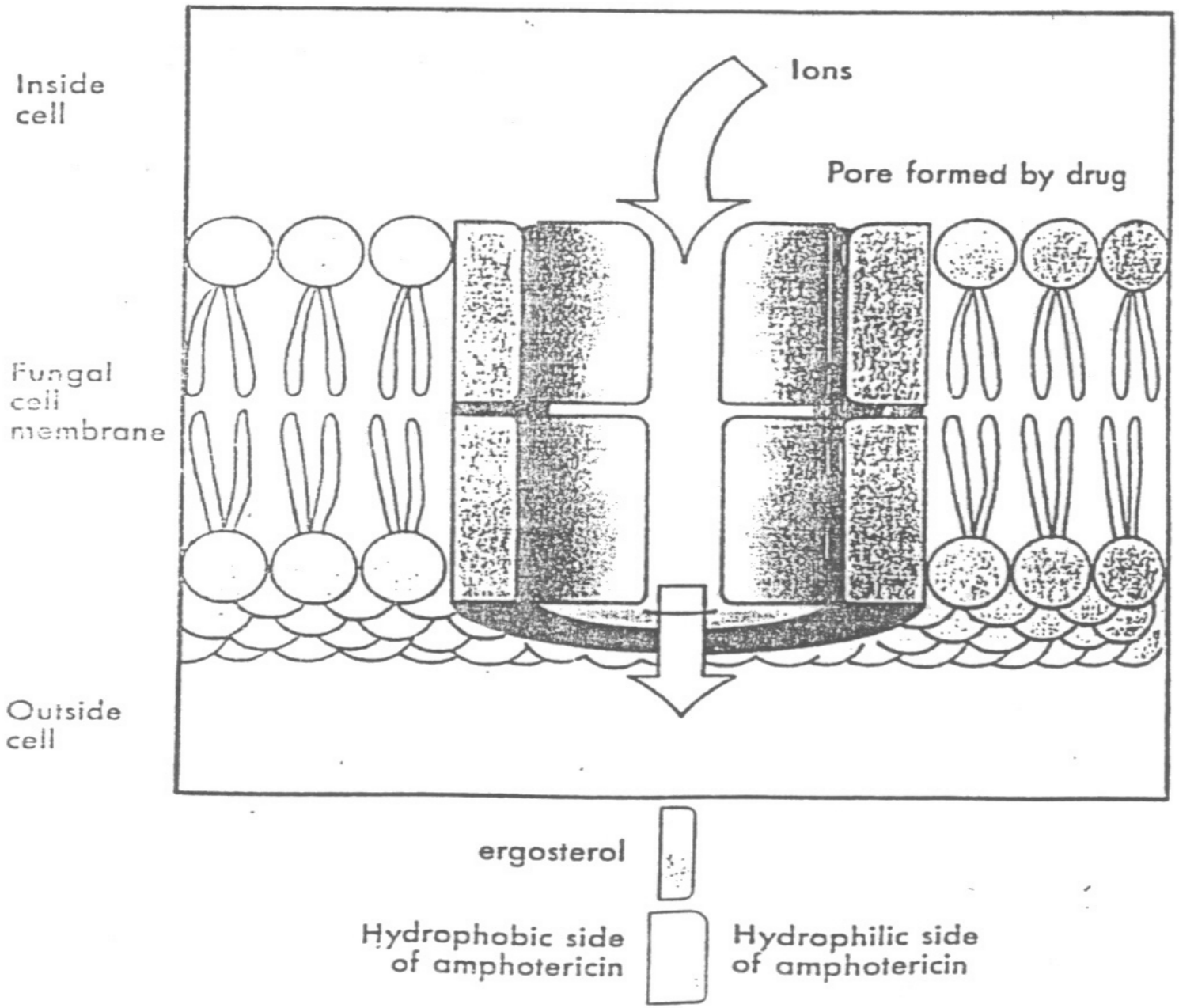
the gold standard for systemic fungal diseases

broad-spectrum

rare resistance

mechanism of action:

binding to ergosterol – pore formation ! in the membranes



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1. Polyene antifungal drugs from Streptomyces speciei, macrolide antibiotics II.

amphotericin B

resistance: RARE ! change in ergosterol content
combined with 5-FC

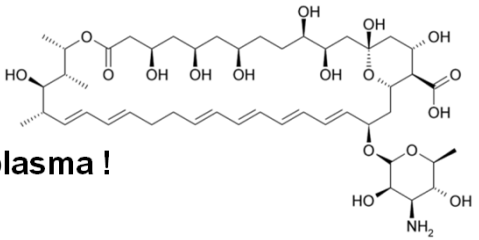
Pharmacokinetics:

Poorly absorbable , lipid soluble drug
Complexed with sodium deoxycholate → **suspension for slow iv. injection**
New formules:
Complexed with b-cyclodextrin or lipids
Encapsuled in liposomes or nanospheres (long-circulating)
Very slow elimination, excretion by kidney

Side effects

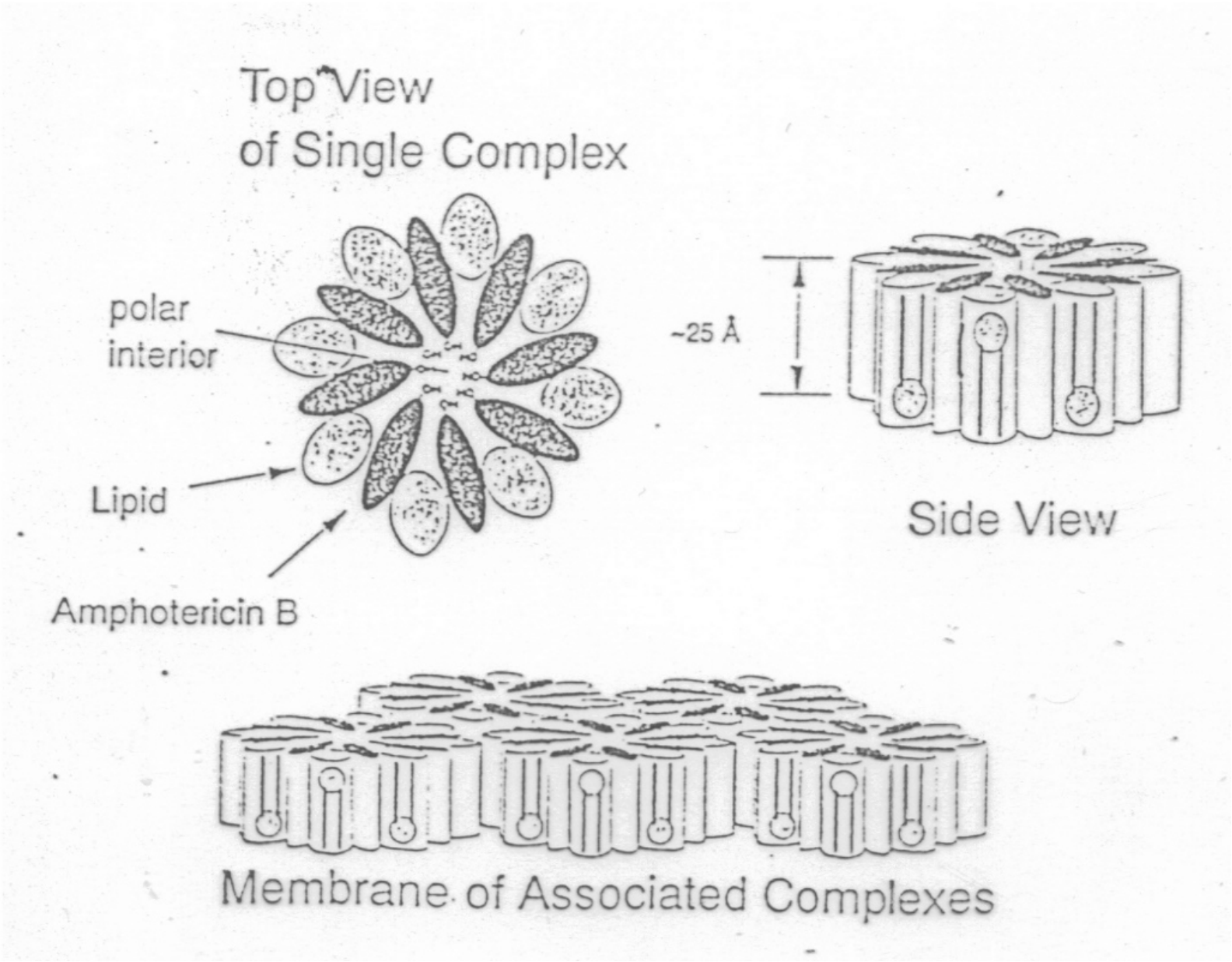
Renal toxicity
Myelotoxicity
Hypokalemia
Impaired hepatic function
Anaphylactic reactions
Chills, fever, tinnitus, haedache, vomitus - intrathecal injection neurotoxicity

nystatine



Nystatine is stable in dry form but decomposes quickly in the presence of water and plasma !

Orally against intestinal Candida infections, NO ABSORPTION from mucous membranes and skin (no significant blood or tissue level)



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Drug	Physical Form	Dosing (mg/kg/d)	C_{max}	Clearance	Nephrotoxicity	Infusional Toxicity	Daily Cost ($)
Conventional formulation							
Fungizone	Micelles	1	...	...	...	...	24
Lipid formulations							
AmBisome	Spheres	3–5	↑	↓	↓	↓	1300
Amphotec	Disks	5	↓	↑	↓	↑(?)	660
Abelcet	Ribbons	5	↓	↑	↓	↓(?)	570

[1]Changes in C_{max} (peak plasma concentration), clearance, nephrotoxicity, and infusional toxicity are relative to conventional amphotericin B.

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2. flucytosine, 5-fluorocytosine

synthetic
converted to 5-FU by fungal deaminase

resistance: **change in deaminase**

Pharmacokinetics:

Water-soluble
Widely distribution, into CNS too
Half-life: 3-5 hours
Excretion via kidney

Side effects

Myelosuppression, alopecia, hepatitis, gastrointestinal

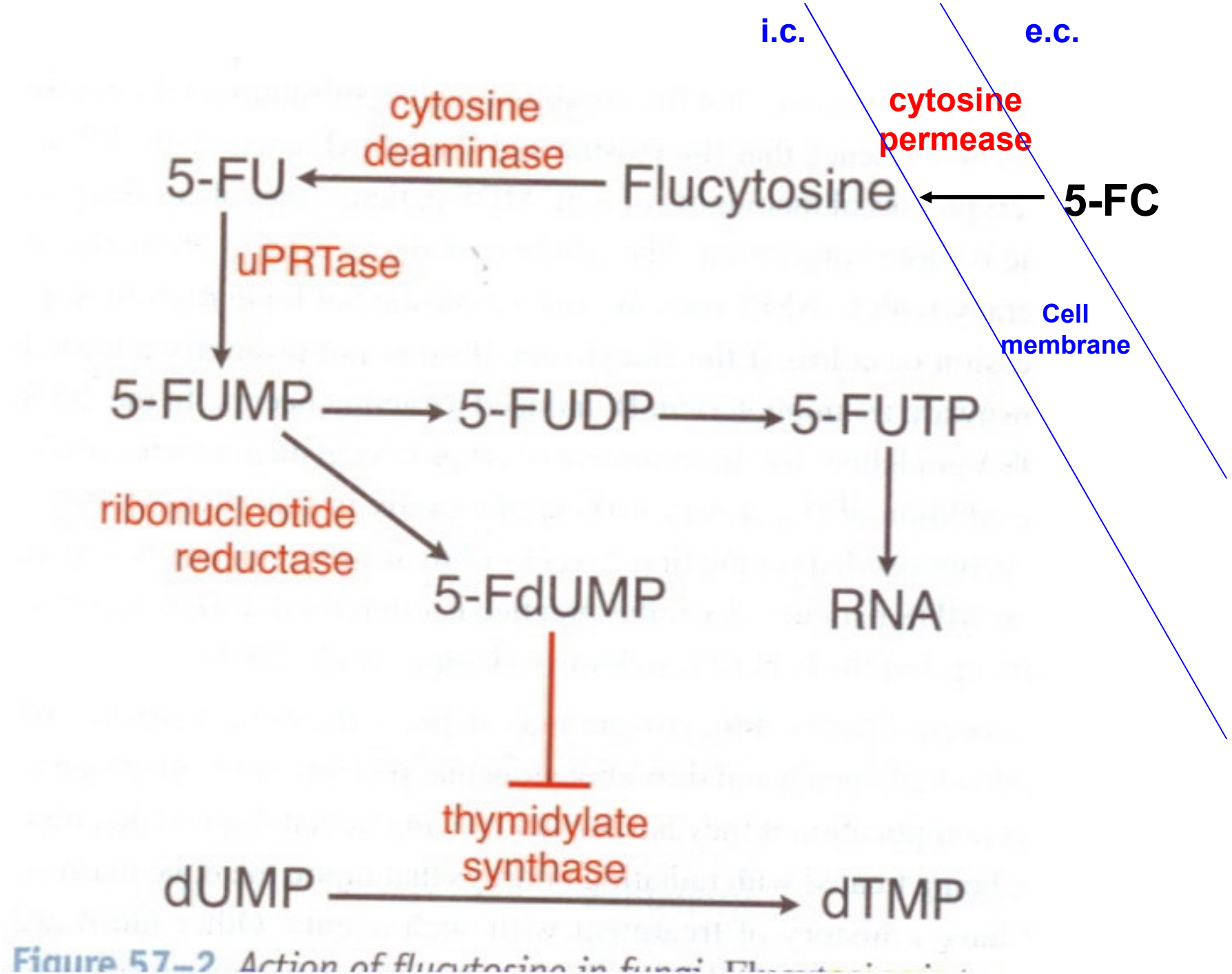
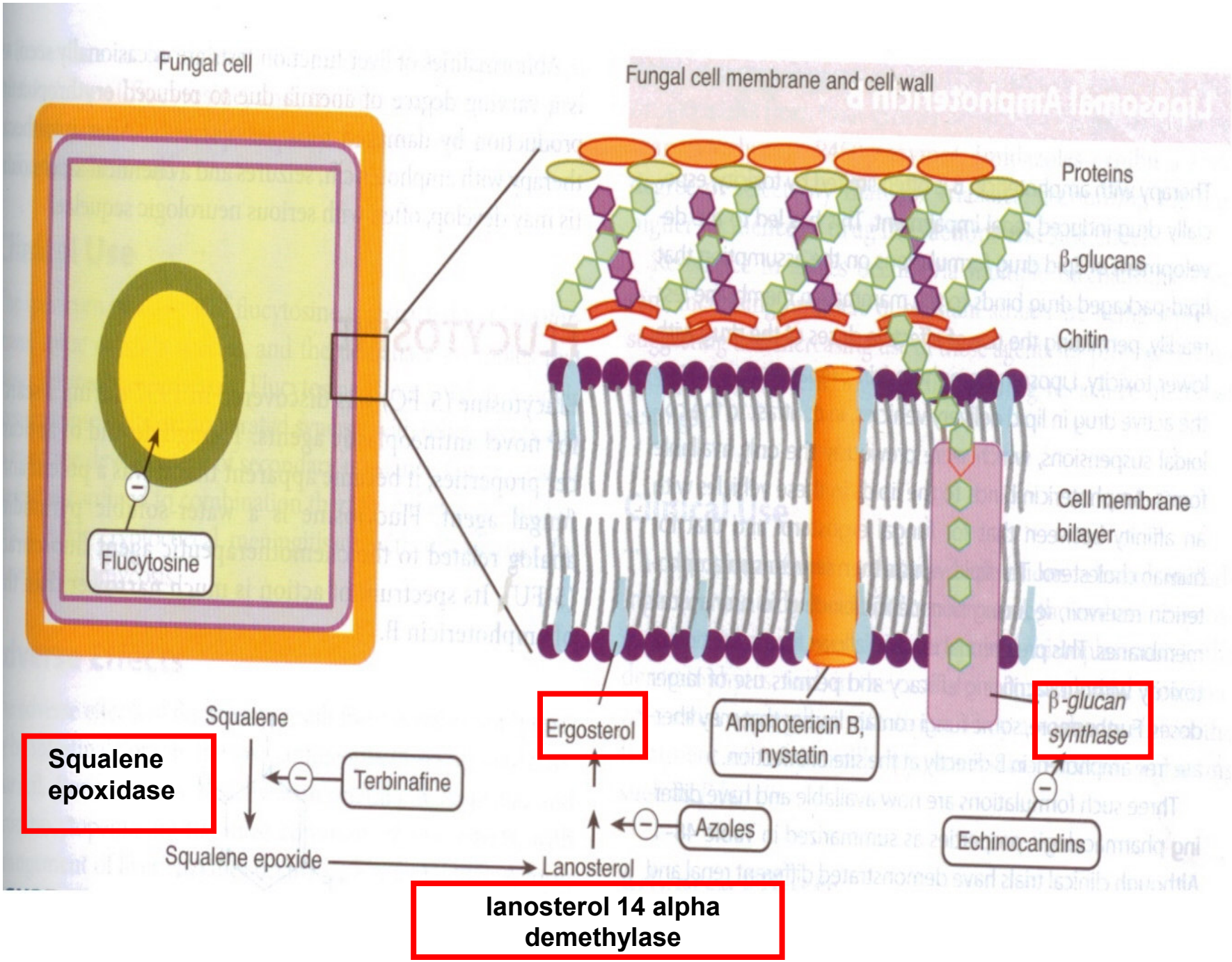


Figure 57–2 Action of flucytosine in fungi.



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3. AZOLES

imidazoles **triazoles**

synthetic
broad spectrum

mech. of action:

inhibition of P450 3A (CYP 3A) dependent lanosine 14alfa-demethylase

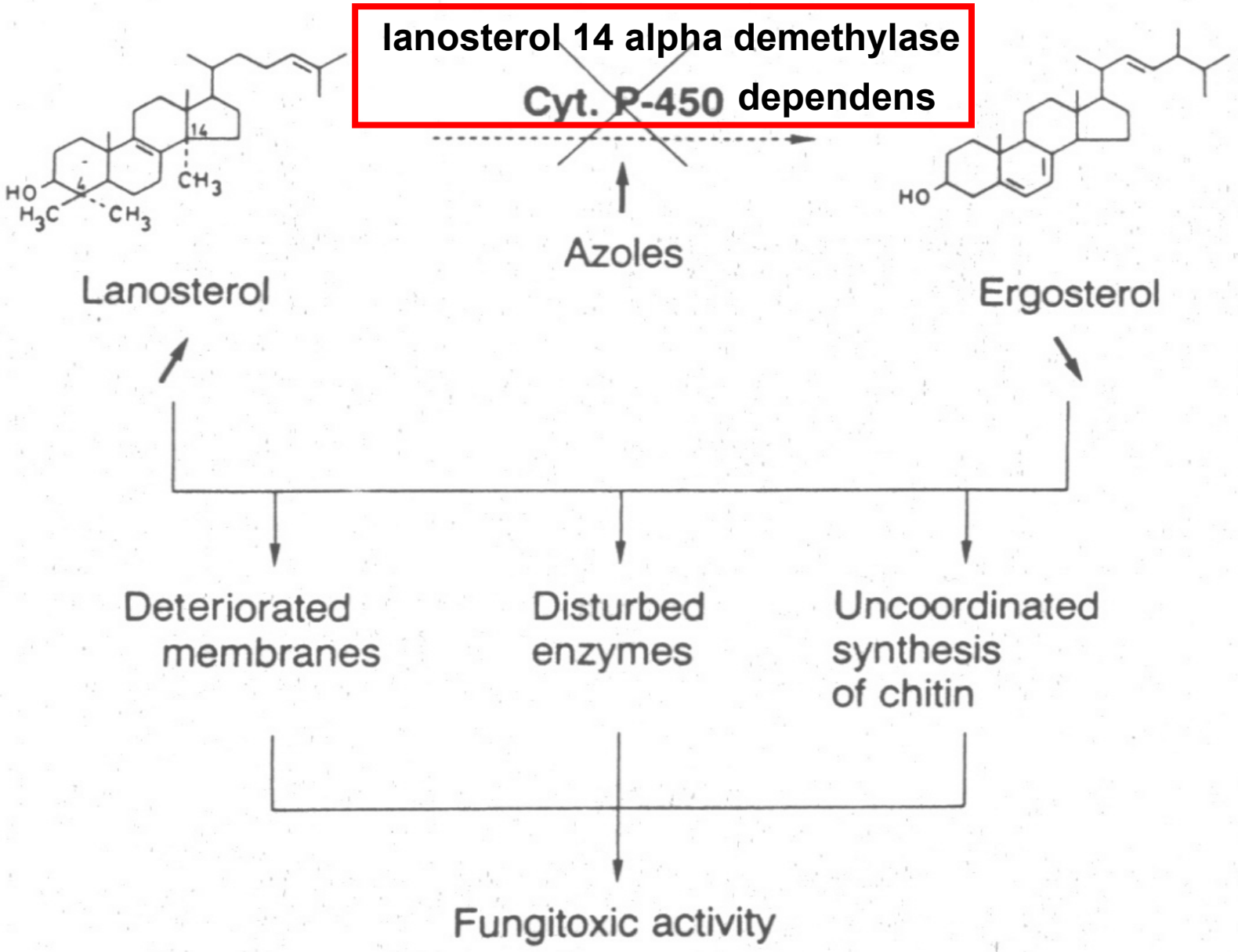
imidazoles
triazoles: specificity better, fluconazole water soluble, crosses blood-brain barrier

Toxicity:

liver, fulminant hepatitis, GI, pruritus
imidazoles block adrenocortical steroid and testosteron synthesis – gynecomastia

drug interactions:

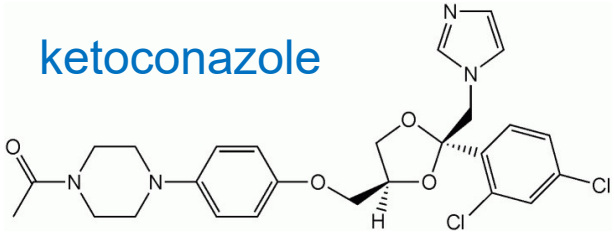
terfenadine, astemizole, ciclosporine
H2 receptor blocking drugs decrease ketoconazole's absorption


lanosterol 14 alpha demethylase
Cyt. P-450 dependens
Azoles
Lanosterol
Ergosterol
Deteriorated membranes
Disturbed enzymes
Uncoordinated synthesis of chitin
Fungitoxic activity

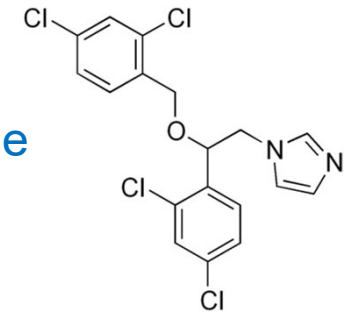
3. AZOLES

imidazoles

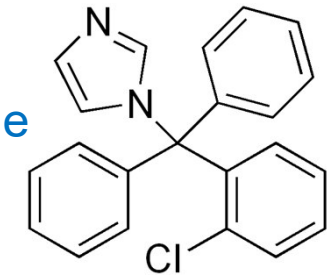
ketoconazole



miconazole

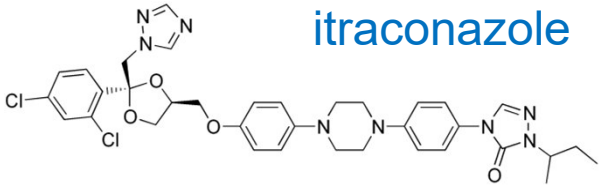


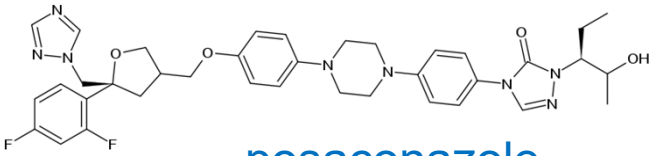
clotrimazole



triazoles

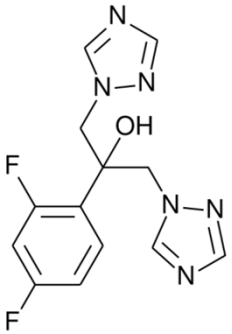
itraconazole

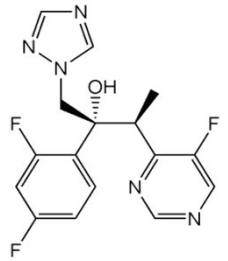




posaconazole

fluconazole





voriconazole

Contraindication in pregnancy !

	Water Solubility	Absorption	CSF: Serum Concentration Ratio	$t_{1/2}$ (Hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	...	6	Hepatic	Oral, IV
Posaconazole	Low	High	...	25	Hepatic	Oral

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4. Echinocandins

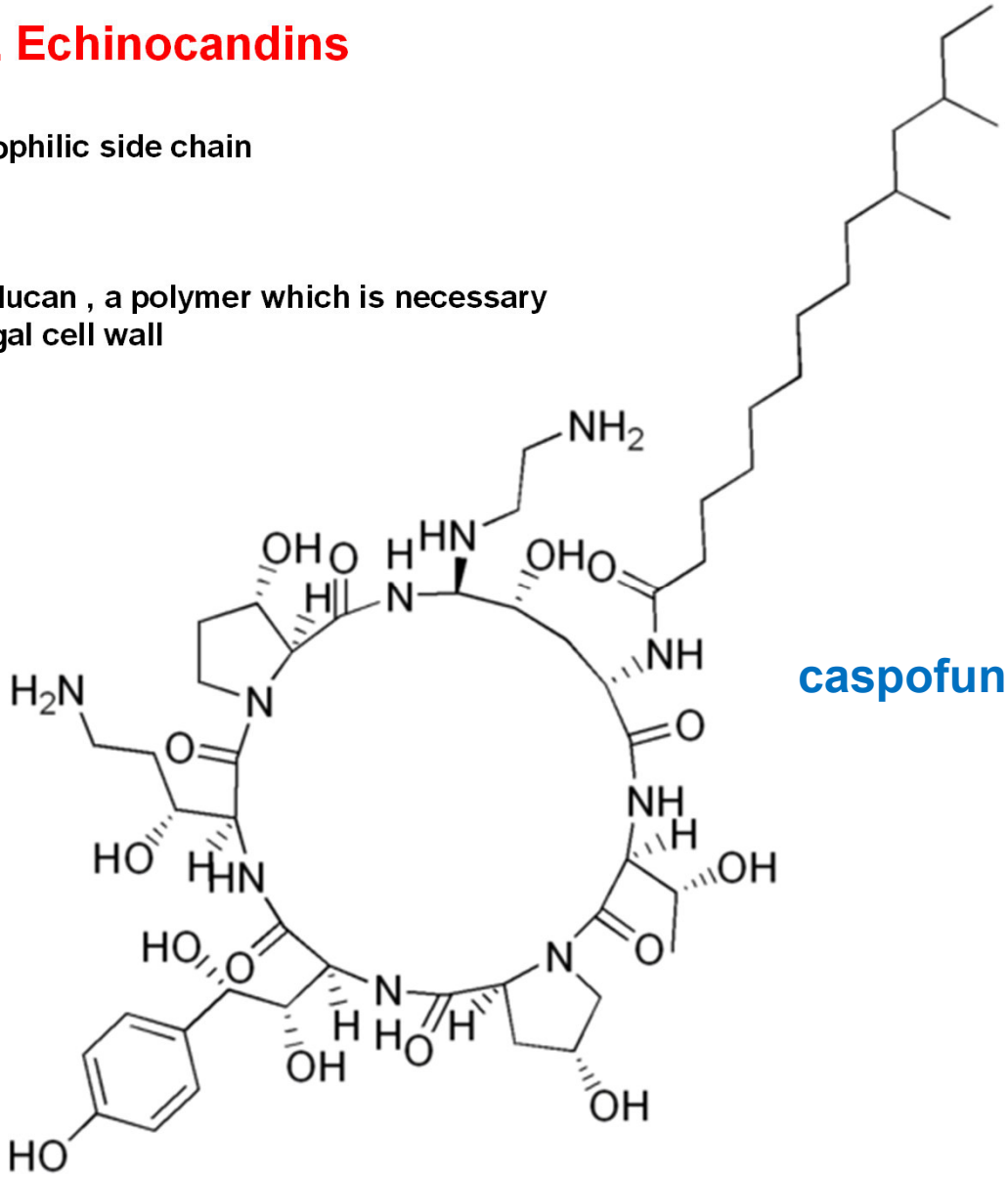
caspofungin
a ring of 6 amino acids linked to lipophilic side chain

mech. of action:

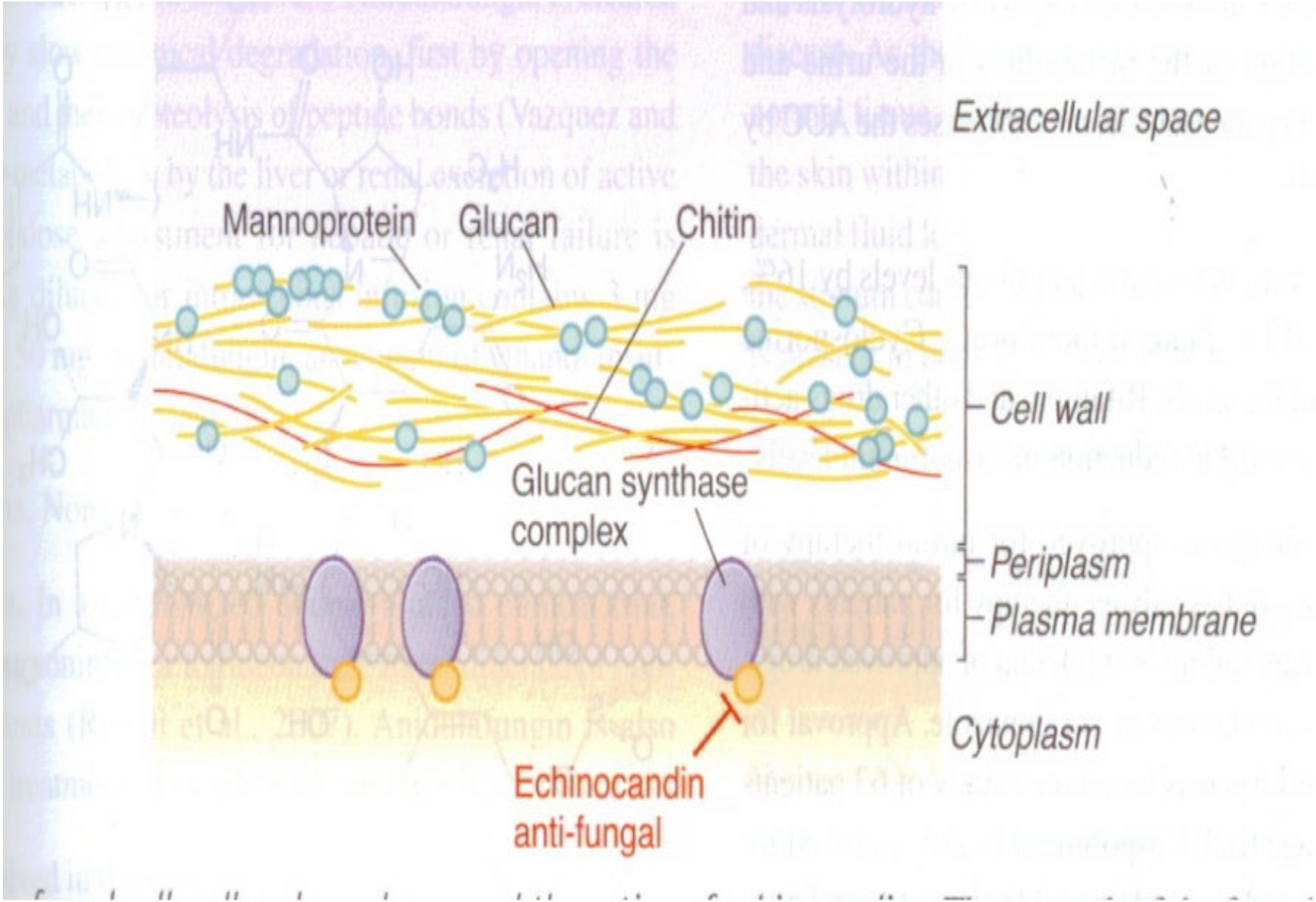
Inhibition of the synthesis of beta-glucan , a polymer which is necessary for maintaining the structure of fungal cell wall

invasive aspergillosis:

amphotericin B
itraconazole
voriconazole
caspofungin



caspofungin



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5. Griseofulvin

from *Penicillium griseofulvum*
narrow spectrum

It concentrates in skin, nails, hair - orally but only for superficial infections !!!

mech. of action:

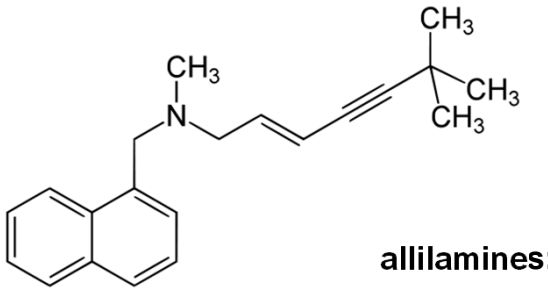
binds to microtubules and inhibits mitosis

Pharmacokinetics

poorly water solubility and variable absorption

Toxicity

Neurotoxicity, haedache, gastrointestinal upsets, photosensitivity



terbinafine

6. Allilamines

allilamines: terbinafine (Lamisil)

mech. of action: inhibition of squalen-epoxidase

Pharmacokinetics:
orally good absorption, high concentrations in fat, skin , nail, hair
metabolism in liver

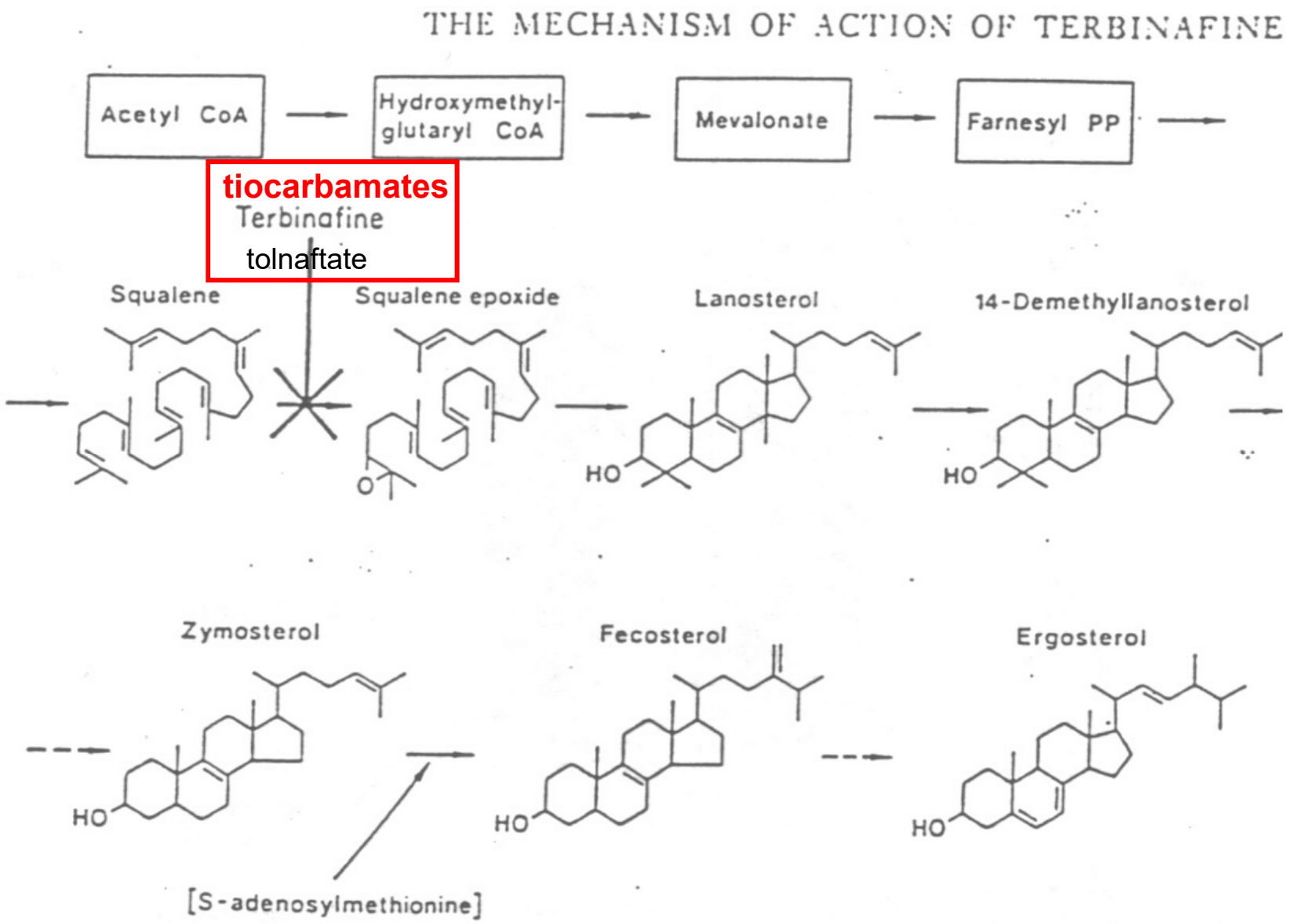
7. Thiocarbamates

tolnaphtate (Chinofungin)
mech. of action: inhibition of squalen-epoxidase

against dermatophytons

8. Morpholins

amorolfin (Loceryl)
mech. of action: inhibition of 14 reductase and 7-8 izomerase enzimes



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AZOLES				
• Ketoconazole	Blocks fungal P450 enzymes and interferes with ergosterol synthesis	Poorly selective • interferes with mammalian P450 function	Broad spectrum but toxicity restricts use to topical therapy	Oral, topical • *Toxicity and interactions:* Interferes with steroid hormone synthesis and phase I drug metabolism
• Itraconazole	Same as for ketoconazole	Much more selective than ketoconazole	Broad spectrum: *Candida, Cryptococcus,* blastomycosis, coccidioidomycosis, histoplasmosis	Oral and IV • duration, 1–2 d • poor entry into central nervous system (CNS) • *Toxicity and interactions:* Low toxicity
• *Fluconazole, voriconazole, posaconazole: Fluconazole has excellent CNS penetration, used in fungal meningitis*				
ECHINOCANDINS				
• Caspofungin	Blocks β-glucan synthase	Prevents synthesis of fungal cell wall	Fungicidal *Candida* sp • also used in aspergillosis	IV only • duration, 11–15 h • *Toxicity:* Minor gastrointestinal effects, flushing • *Interactions:* Increases cyclosporine levels (avoid combination)
• *Micafungin, anidulafungin: Micafungin increases levels of nifedipine, cyclosporine, sirolimus; anidulafungin is relatively free of this interaction*				
ALLYLAMINE				
• Terbinafine	Inhibits epoxidation of squalene in fungi • increased levels are toxic to them	Reduces ergosterol • prevents synthesis of fungal cell membrane	Mucocutaneous fungal infections	Oral • duration, days • *Toxicity:* Gastrointestinal upset, headache, hepatoxicity • *Interactions:* None reported

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Treatment of superficial infections:

For TOPICAL use

antiseptics	Polyene macrolides	azoles	allylamines and thiocarbamates	others
salicylic acide iodine, hexachlorophene, metals	nystatine natamycine candicidine	ketoconazole clotrimazole miconazole econazole bifonazole oxiconazole	Allylamine: terbinafine naftifine thiocarbamate: tolnaphtate	morpholine: amorolfine - cyclopyroxolamine undecylenic acid

Orally

azoles	polyenes	griseofulvin
ketoconazole fluconazole voriconazole	nystatine Only for GI infections !! No absorption	It concentrates in skin, nails, hair

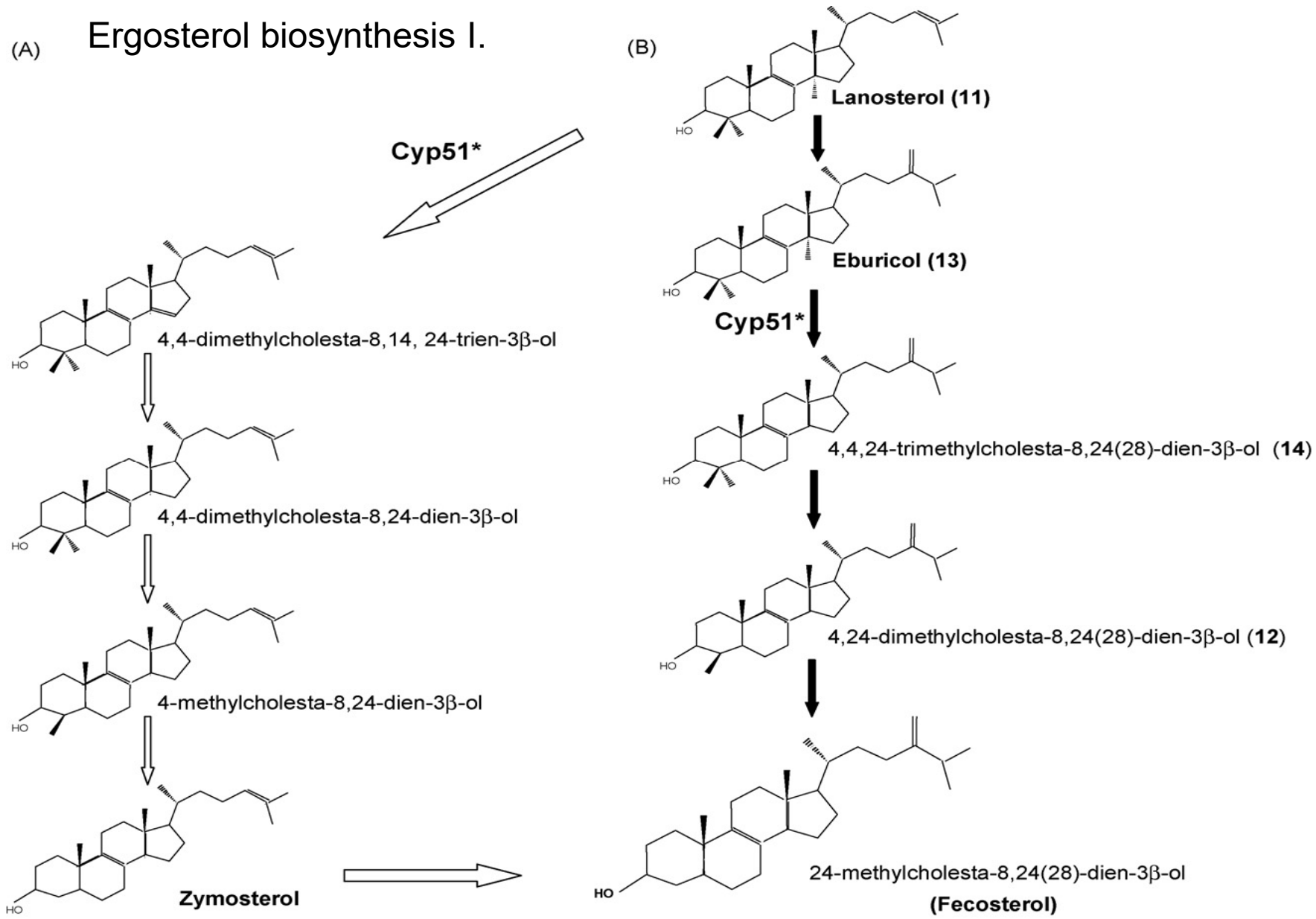
Treatment of systemic infections

polyenes	nucleotide	azoles	echinocandins
amphotericin B Liposomal amphotericine B	5-fluorocytosine	ketoconazole itraconazole fluconazole voriconazole	caspofungin micafungin cilofungin

invasive aspergillosis:

amphotericin B
itraconazole
voriconazole
caspofungin

Ergosterol biosynthesis I.



Ergosterol biosynthesis II.