Anti-infectieux:
6. antifongiques

Paul M. Tulkens, Dr Med. Lic. Sc. Biomed., Agr. Ens. Sup.

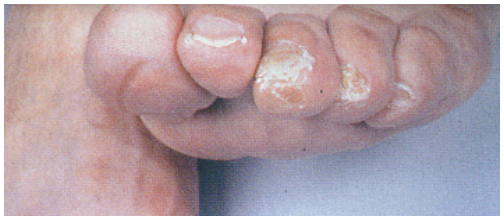
Faculté de pharmacie et sciences biomédicales
Faculté de médecine et de médecine dentaire
Université catholique de Louvain
Bruxelles, Belgique

Université d'Abomey-Calavi
Cotonou, Bénin

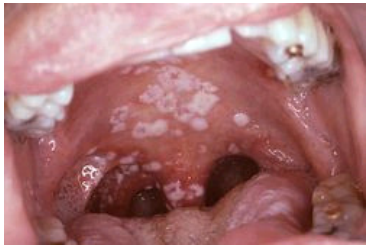
Ces diapositives sont reprises du cours des Prof. F Van Bambeke et P. Tulkens

Le soir au coin du bois …

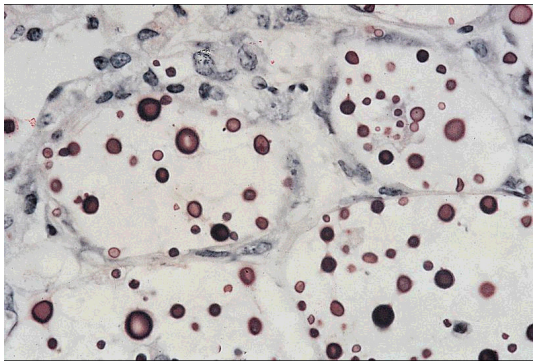
Il y a champignon …et champignon



oncomycose



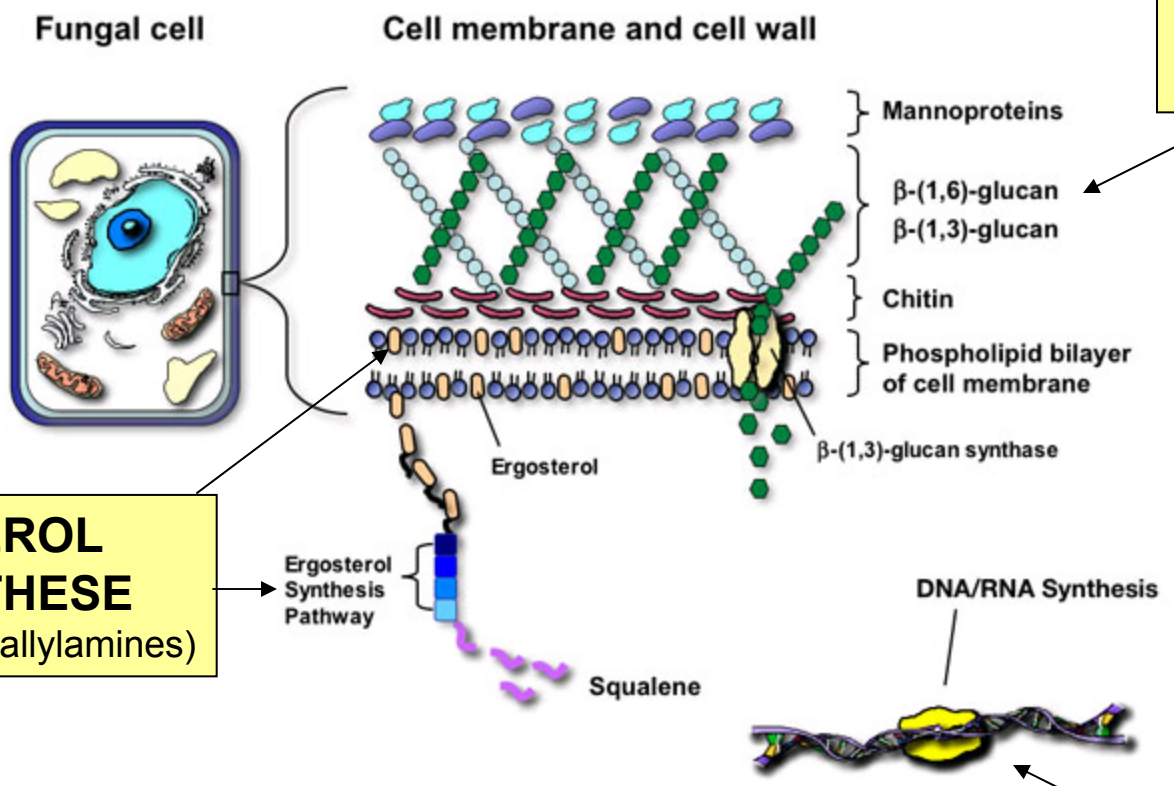
candidose



cryptococose pulmonaire

Cibles des médicaments antifongiques

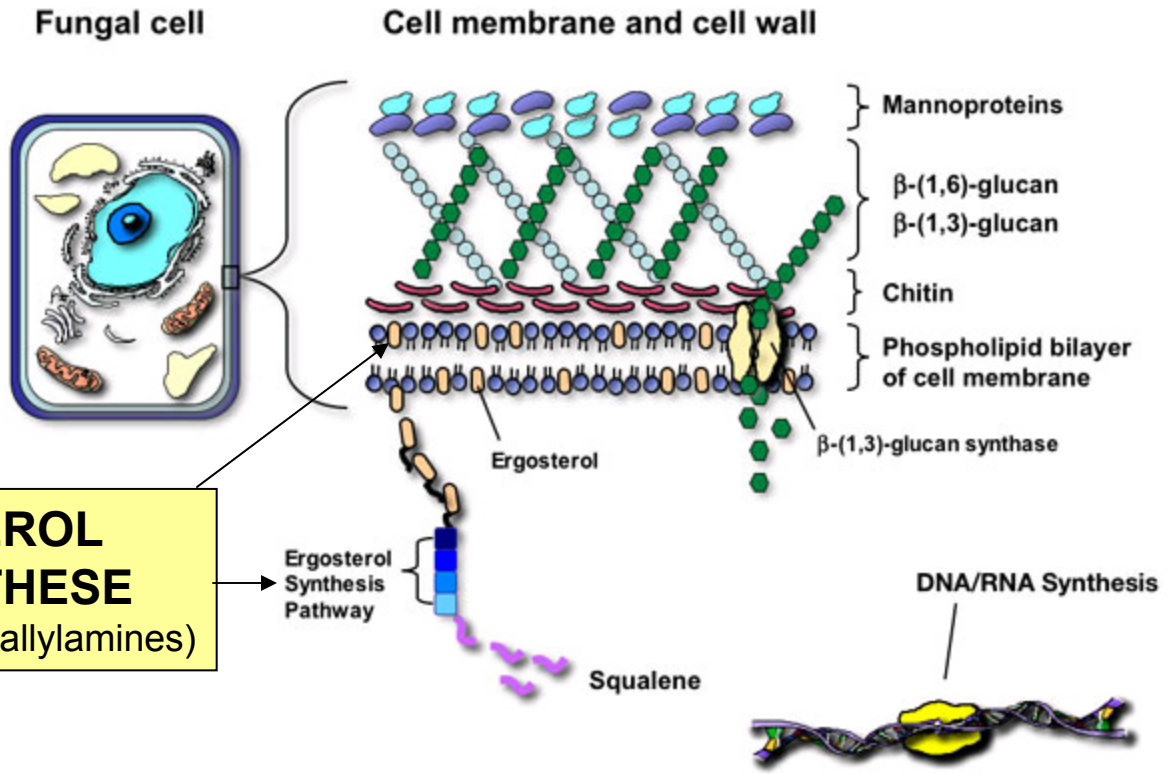
SYNTHESE des GLYCANS
(échinocandines)



ERGOSTEROL et sa SYNTHESE
(polyènes, azoles, allylamines)

SYNTHESE des Ac. Nucl.
(5-fluorocytosine, griséofulvine)

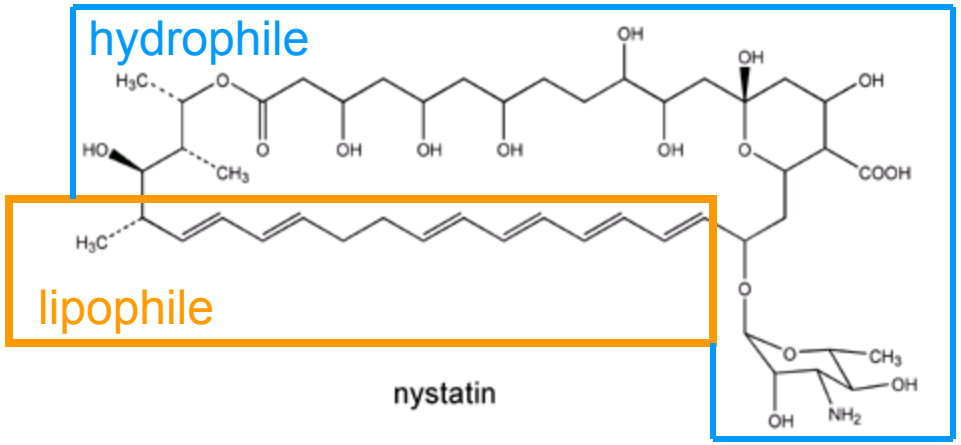
Cibles des médicaments antifongiques

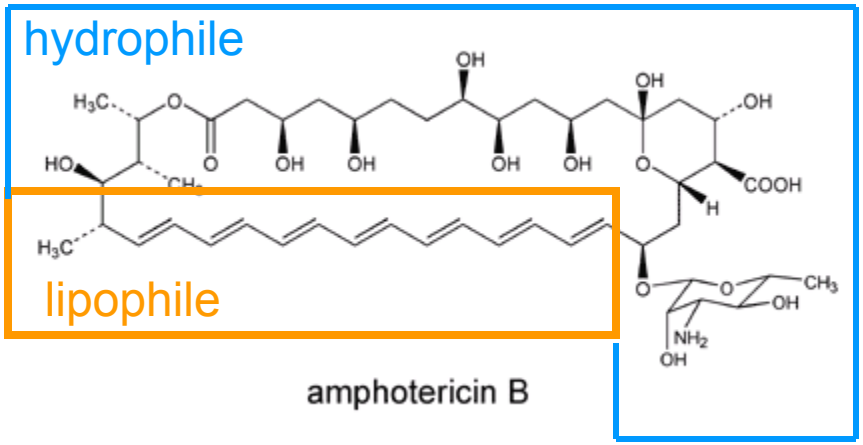


ERGOSTEROL
et sa SYNTHESE
(polyènes, azoles, allylamines)

Polyènes antifongiques

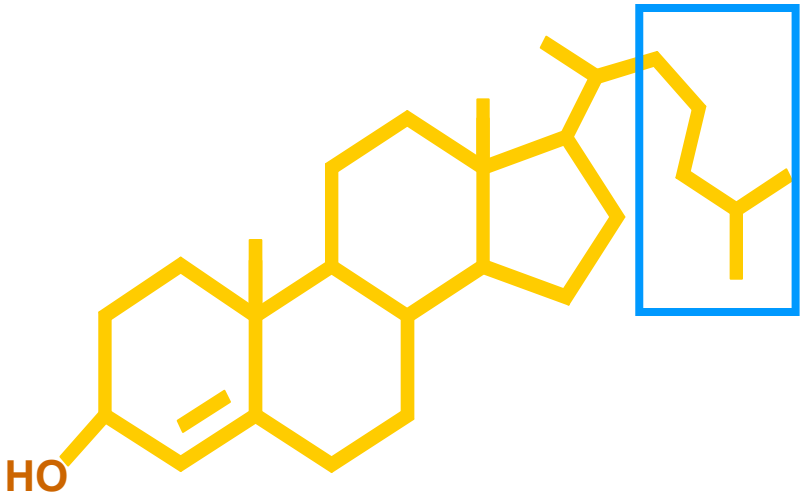
Molécules amphiphiles mais volumineuses
→ mal résorbées





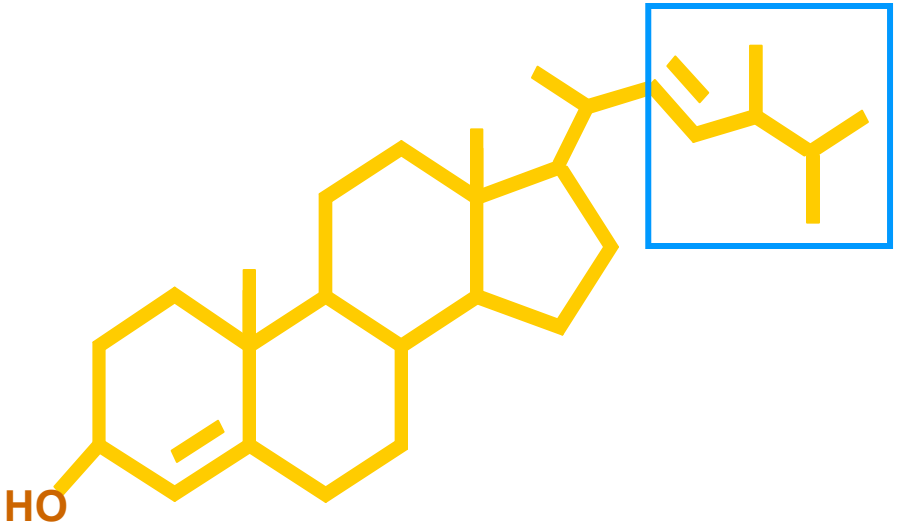
Cible pharmacologique: les stérols membranaires

eucaryotes supérieurs



cholestérol

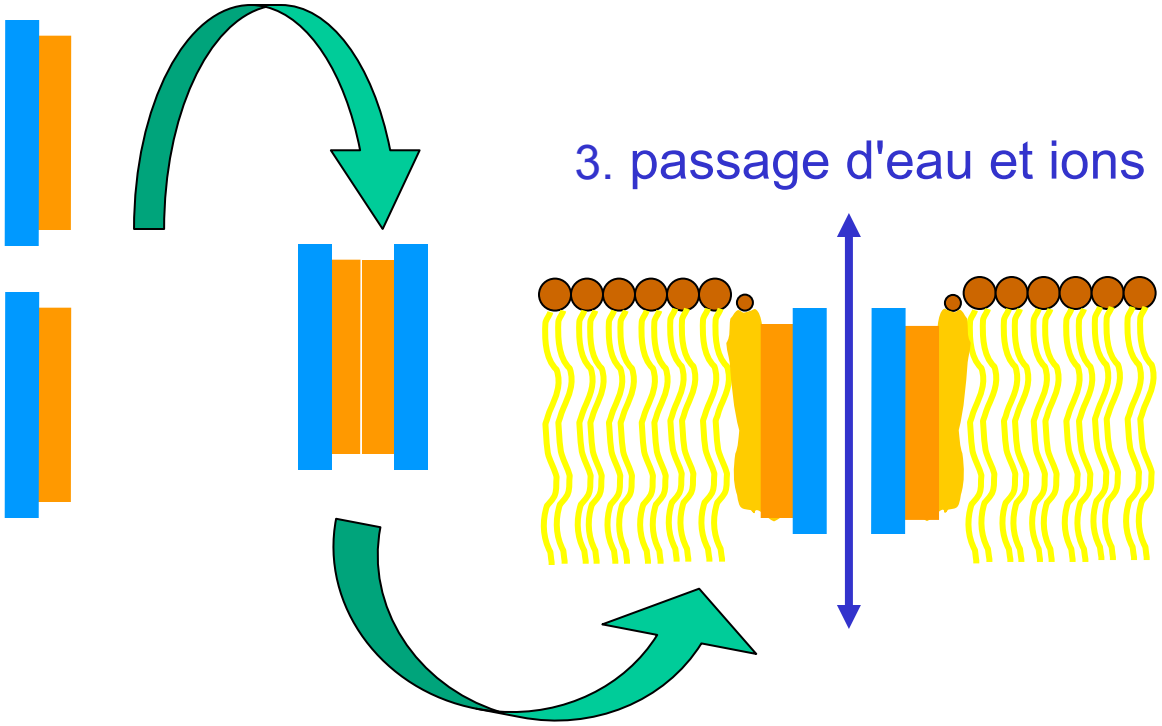
champignons



ergostérol

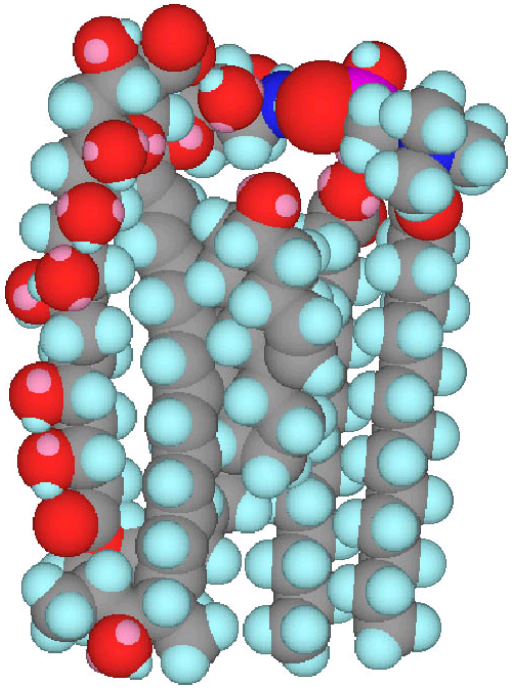
Mécanisme d'action des polyènes antifongiques

1. formation de dimères peu solubles...



3. passage d'eau et ions

2. Insertion dans la membrane au niveau de l'ergostérol



Asemblage moléculaire entre amphotéricine B, stérol et phospholipide dans une membrane

Mécanisme d'action des polyènes antifongiques

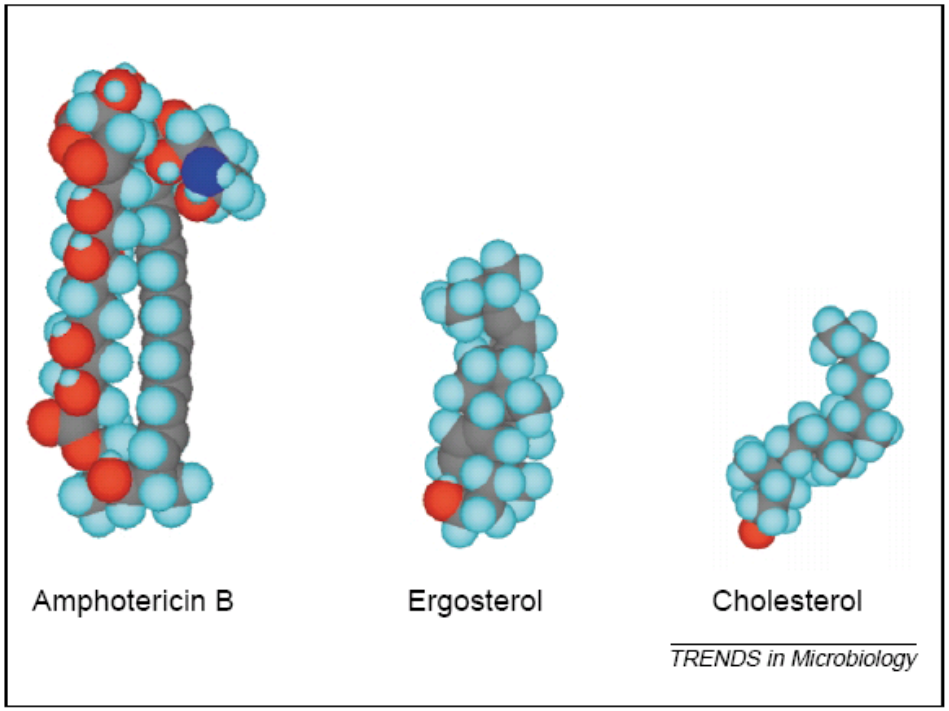
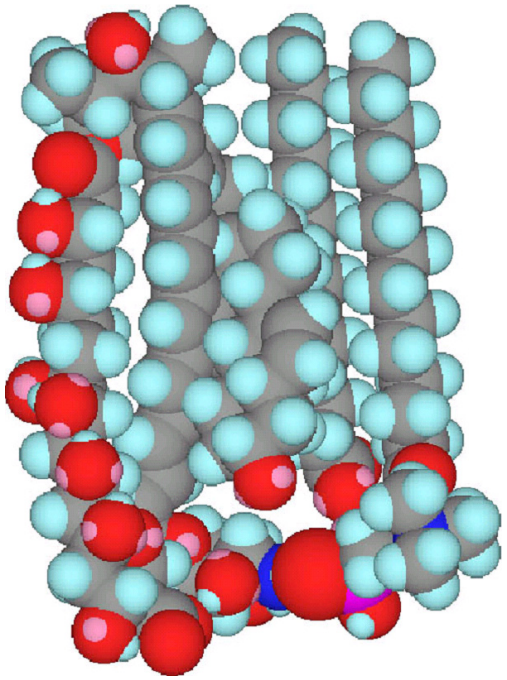


Fig. 3. The polyene antifungal agent, amphotericin B, ergosterol and cholesterol, visualised in three dimensions. Ergosterol, the sterol found in fungal cell membranes, retains a cylindrical shape in all rotations and binds better to the hydrophobic (right-hand) side of the amphotericin B molecule than does cholesterol, with its sigmoid structure. Cholesterol is the membrane sterol found in mammalian cells; the differential binding affinity of amphotericin B for the two sterols is the basis of its selective antifungal action.



Asemblage moléculaire entre amphotéricine B, stérol et phospholipide dans une membrane

Odds, Trends in Microbiology (2003) 11:272-279

Polyènes antifongiques: propriétés pharmacologiques

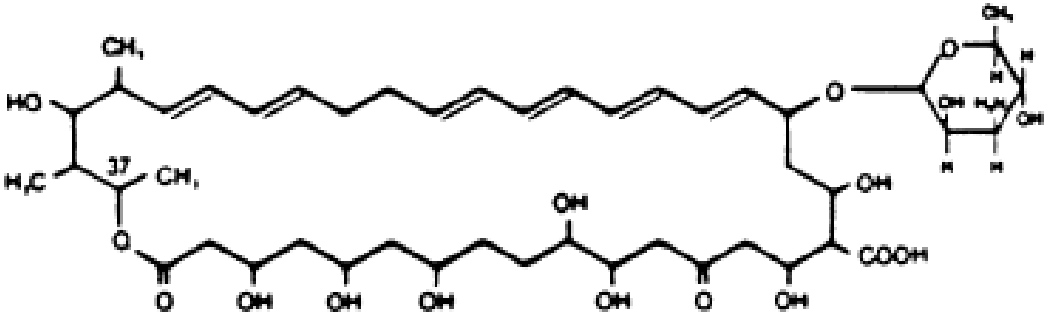
+	-
Fongicides Spectre large, peu de résistance	Résorption mauvaise voire nulle (nystatine)
	Antagonisme avec les azolés
	Faible spécificité → toxicité: • immédiate: fièvres, frissons, nausées, vomissements, hypotension, arythmies, … • à court terme: néphrotoxicité • à moyen terme: anémie

nystatine	Amphotéricine B
usage topique • oral: candidoses, dermatophyties • décontamination intestinale	• mycoses systémiques • mycoses oropharyngées et digestives graves

Nystatine: usage oral

DRUG DESCRIPTION

Nystatin (nystatin oral) is an antimycotic poly-ene antibiotic obtained from *Streptomyces noursei*. Structural formula:



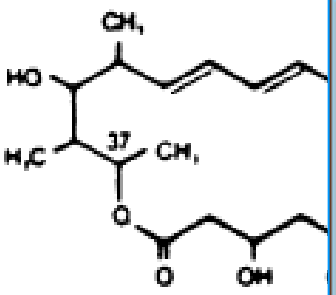
$C_{47}H_{75}NO_{17}$ MW = 926.13

Nystatin (nystatin oral) Oral Suspension, for oral administration, is cherry/mint flavored, containing 100,000 USP Nystatin (nystatin oral) Units per mL. Inactive ingredients: alcohol (≤ 1% *v/v*), 49.8% (*w/v*) sucrose, purified water, glycerin, sodium citrate, magnesium aluminum silicate, flavors, saccharin sodium, xanthan gum, benzaldehyde, edetate calcium disodium, meth-ylparaben and propylparaben.

Nystatine: usage oral

DRUG DESCRIPTION

Nystatin (nystatin oral) is an a
noursei. Structural formula:



Nystatin (nystatin oral) Oral Su
containing 100,000 USP Nyst
alcohol (≤ 1% w/v), 49.8% (w/
magnesium aluminum silicat
edetate calcium disodium, m

INDICATIONS

Nystatin (nystatin (oral)) Oral Suspension is indicated for the treatment of candidiasis in the oral cavity.

DOSAGE AND ADMINISTRATION

INFANTS: 2 mL (200, 000 units) four times daily (in infants and young children, use dropper to place one-half of dose in each side of mouth and avoid feeding for 5 to 10 minutes).

NOTE: Limited clinical studies in premature and low birth weight infants indicate that 1 mL four times daily is effective.

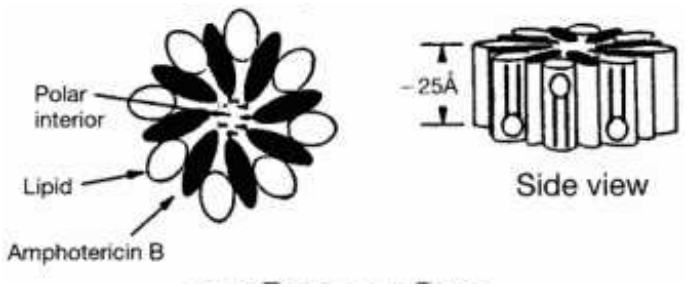
CHILDREN AND ADULTS: 4-6 mL (400,000 to 600,000 units) four times daily (one-half of dose in each side of mouth). The preparation should be retained in the mouth as long as possible before swallowing.

Continue treatment for at least 48 hours after perioral symptoms have disappeared and cultures demonstrate eradication of *Candida albicans*.

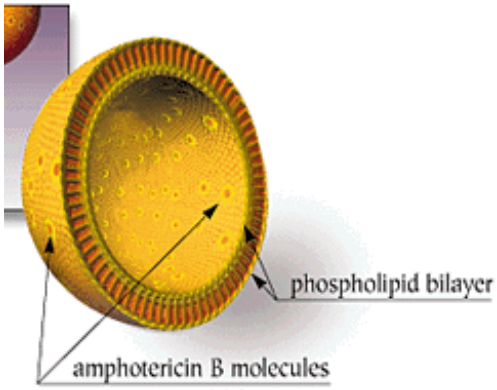
Compendium belge: Nystatine: usage local dans les infection à *Candida* de la bouche (muguet) et usage oral dans les infections gastro-intestinales à *Candida* et la candidose cutanée afin d'éliminer la source de contamination gastro-intestinale.

Formes lipidiques de l'amphotéricine

AMB$_{deoxycholate}$ **ABELCET**



AMPHOTEC **AmBisome**



The various lipid formulations of AMB have demonstrated antifungal efficacy at least equivalent to the conventional product with significantly reduced nephrotoxicity.
In: THE USE OF LIPID FORMULATIONS OF AMPHOTERICIN B IN CANCER PATIENTS -- Rod Quilitz, PharmD, Department of Pharmacy, H. Lee Moffitt Cancer Center & Research Institute, University of San Francisco, Cal.
http://www.moffitt.usf.edu/cancjrnl/v5n5/department3.html

Formes lipidiques: propriétés pharmacologiques

3 Drug profiles of amphotericin B (AMB) formulations

Parameter	AMB deoxycholate	AMB lipid complex	Liposomal AMB
Dosage* (mg/kg per day)	0.5–1.5	5	3–5 (or higher)
Maximum serum concentration†	—	Lower	Higher
Infusion-related toxicity‡	High (50%–60%)	Moderate (20%–40%)	Mild (10%–20%)
Decrease in serum potassium	++++	++	++
Anaemia	++++	+	+
Nephrotoxicity	++++ (up to 80%)	+ (15%–25%)	+ (10%–20%)
Prevention of infusion-related toxicity§	Required	Required	Generally not required

* Commonly prescribed treatment doses; dose varies with pathogen. High-dose liposomal AMB required for zygomycete infection (≥ 5 mg/kg per day). † In comparison with AMB deoxycholate. ‡ Includes fever, chills, headache, joint and muscle pain, and hypotension. Before therapy, a test dose is recommended to identify patients in whom severe infusion-related reactions might occur. § Usually comprises "cocktail" of antipyretic, antiemetic and antihistamine drugs. Value of corticosteroids not proven.

Mais cher et administration intraveineuse obligatoire
→ indications limitées

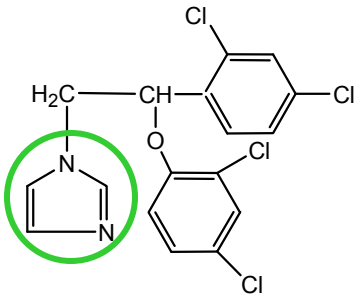
Chen et al. Med J Aust. (2007) 187:404-9.

Formes lipidiques: indications selon la notice

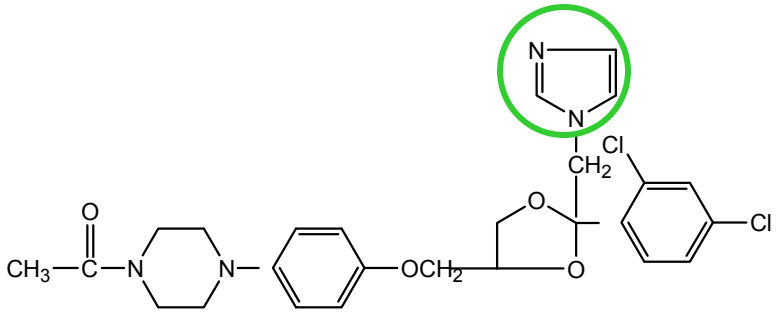
Abelcept	AmBisome
Infections fongiques généralisées: Abelcet est recommandé dans le traitement des infections fongiques graves, chez les patients n'ayant montré aucune amélioration avec l'amphotéricine B conventionnelle, ou chez les patients ayant développé une insuffisance rénale lors du traitement à l'amphotéricine B, même lorsque ce dernier avait été administré en même temps qu"un litre de solution saline physiologique par jour.	AmBisome est destiné au traitement des **formes graves de mycoses systémiques et/ou profondes** des patients ne répondant pas à l'amphotéricine B conventionnelle ou des patients représentant une contre-indication à l'administration de celle-ci due à l'existence de lésions rénales. Une réponse positive a été obtenue chez 80 % de ces patients traités pour une candidiase systémique, chez 70 % des patients traités pour une aspergillose et chez 100 % des patients traités pour une cryptococcose….

Dérivés azolés

imidazoles

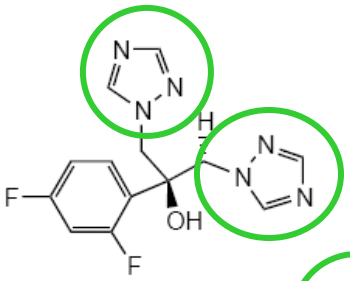


Miconazole

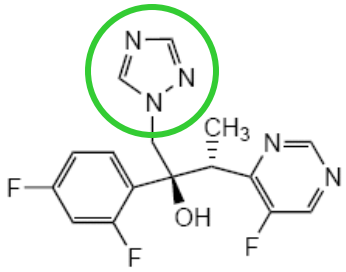


Ketoconazole

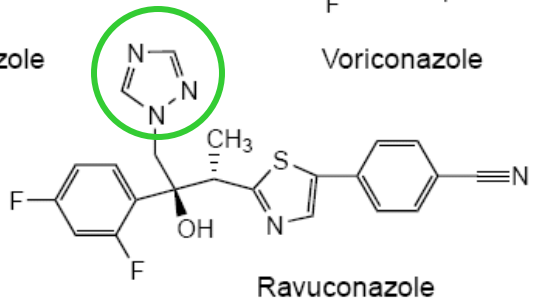
triazoles



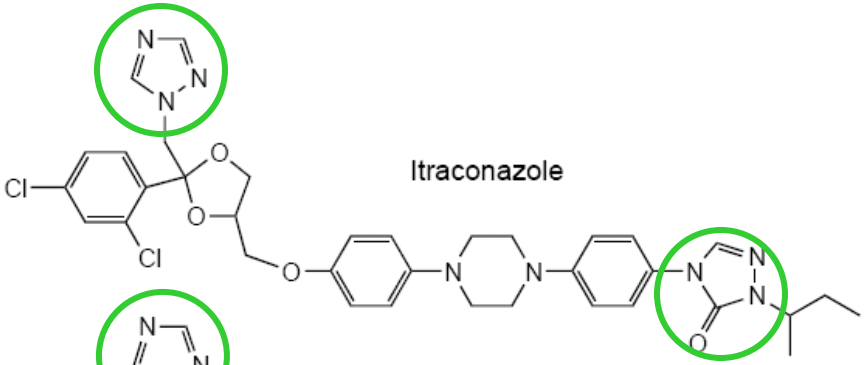
Fluconazole



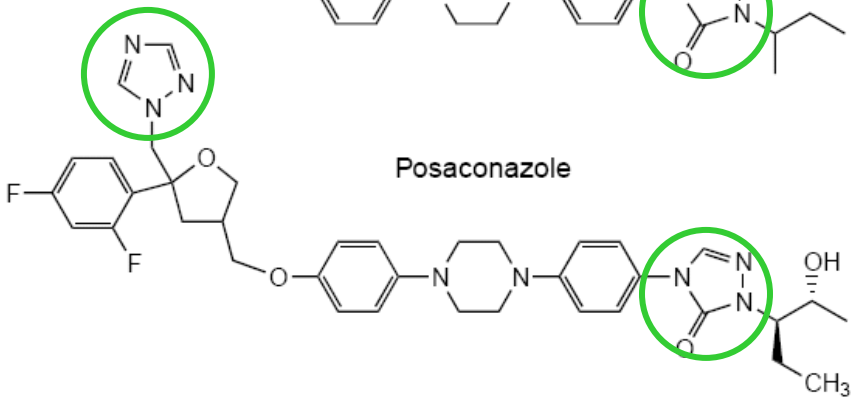
Voriconazole



Ravuconazole



Itraconazole



Posaconazole

Biosynthèse de l'ergosterol

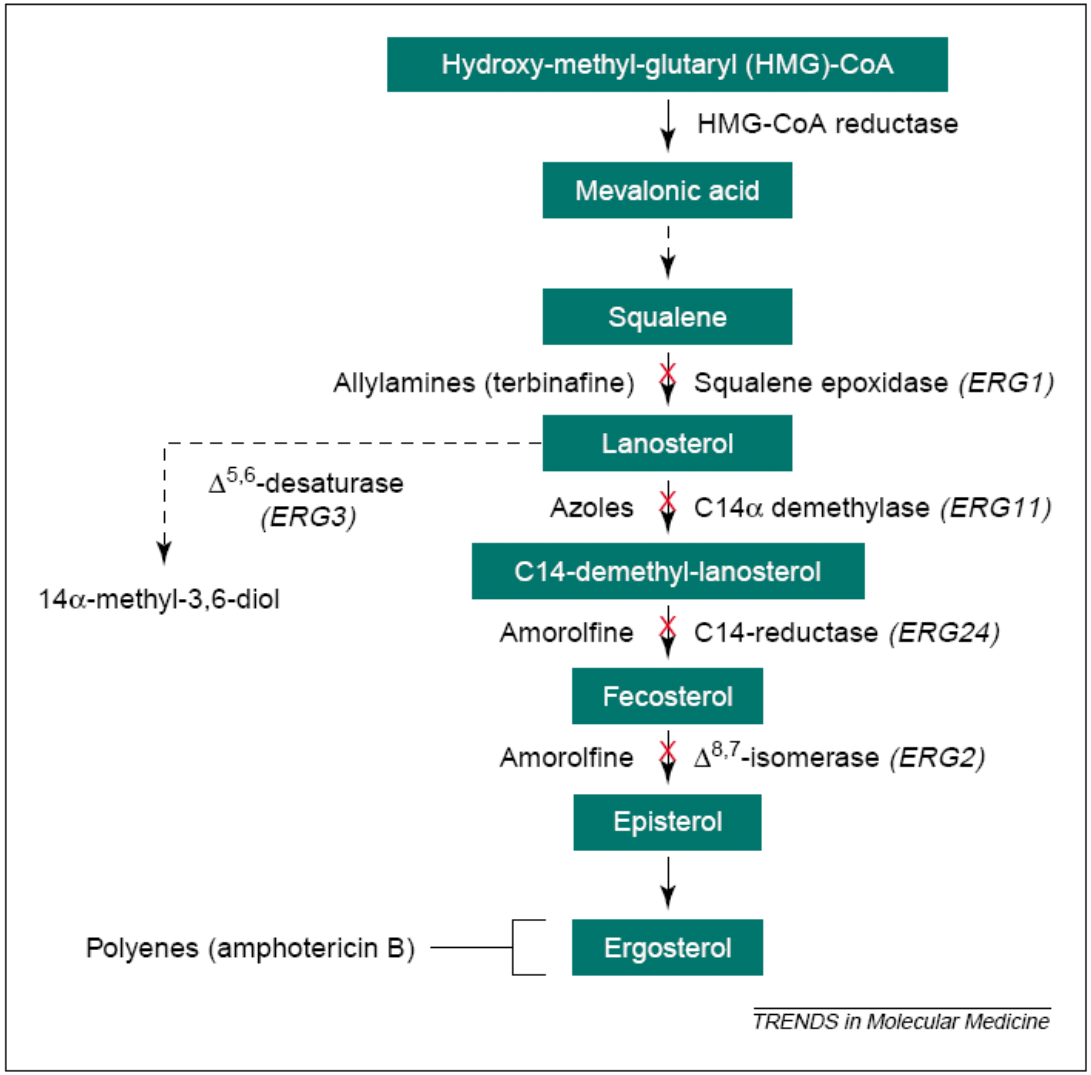
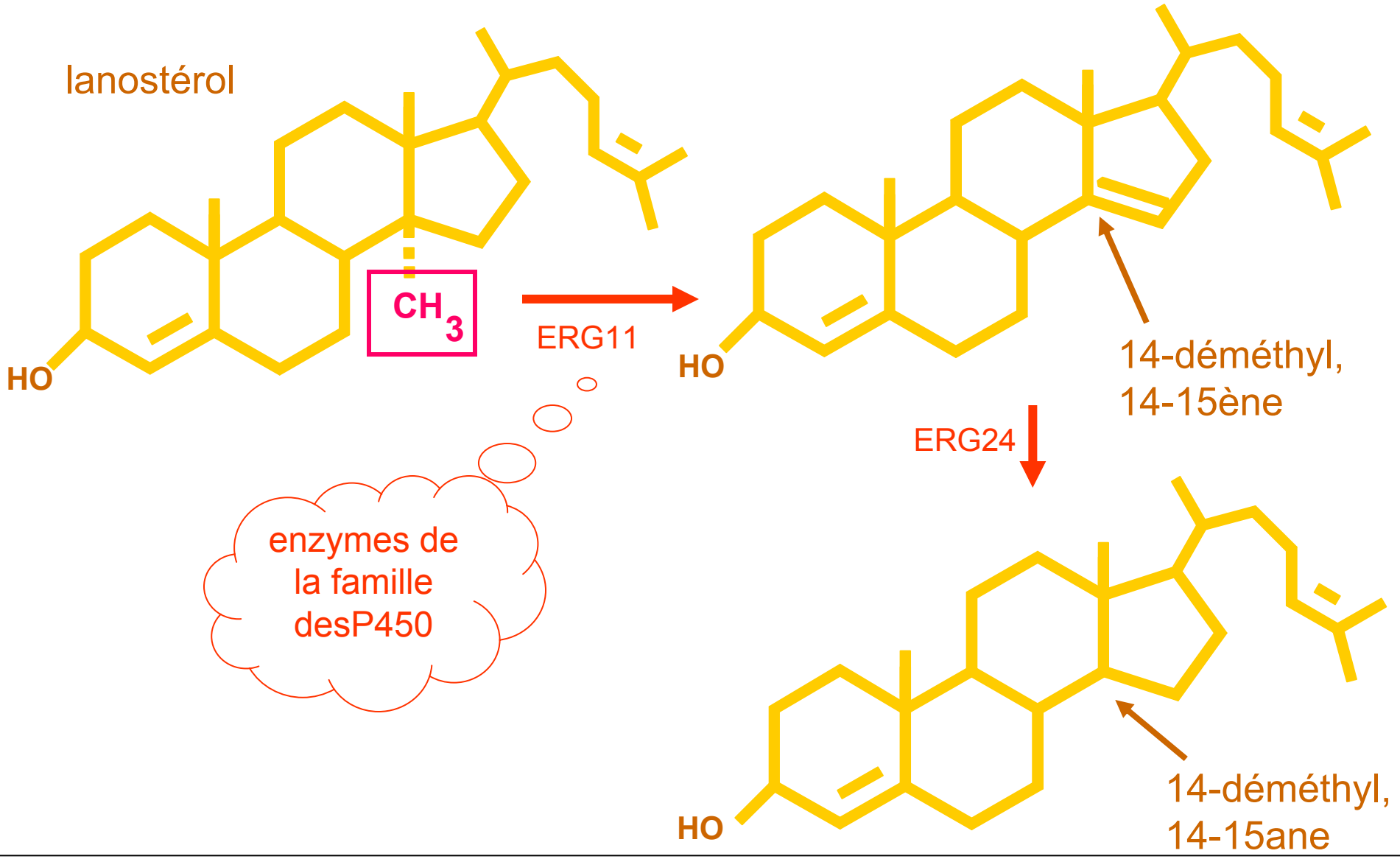


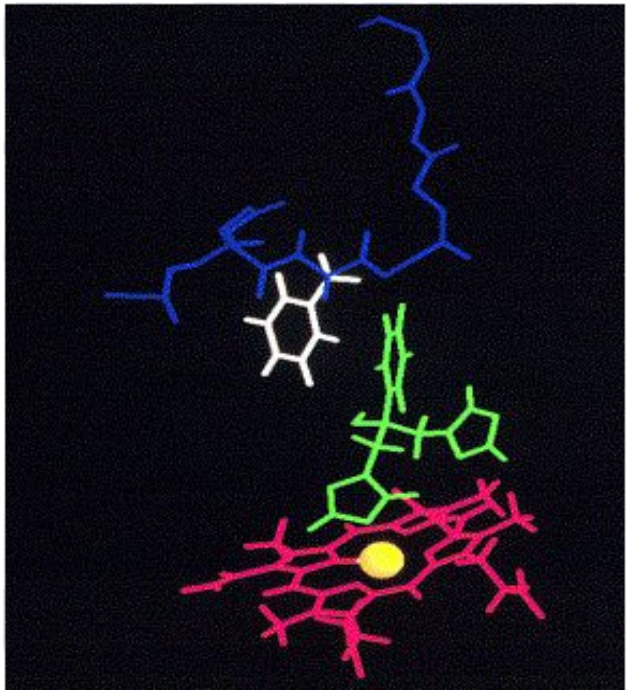
Fig. 2. Mechanism of action of antifungal drugs affecting the ergosterol biosynthetic pathway. The target enzymes are reported on the right with encoding genes in parentheses, whereas the antifungal drugs are reported on the left of the arrows indicating the sequential steps of sterol biosynthesis.

Biosynthèse de l'ergosterol



Dérivés azolés et site actif de Erg11p

Le cytochrome P450 possède un hème essentiel à l'activité oxydo-reductasique



Le cycle imidazole ou triazole se colle à l'hème …

http://users.aber.ac.uk/cca/p450/intro.html

Dérivés azolés et site actif de Erg11p

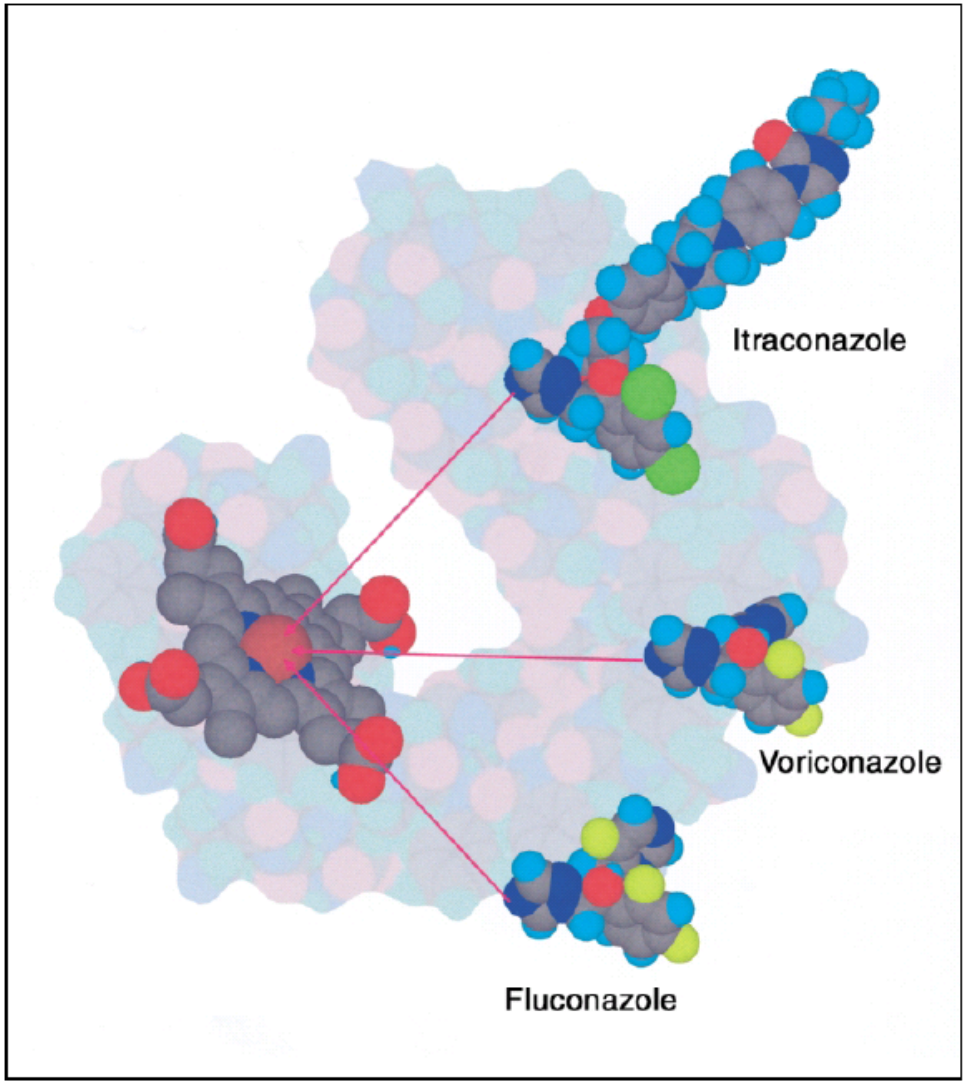
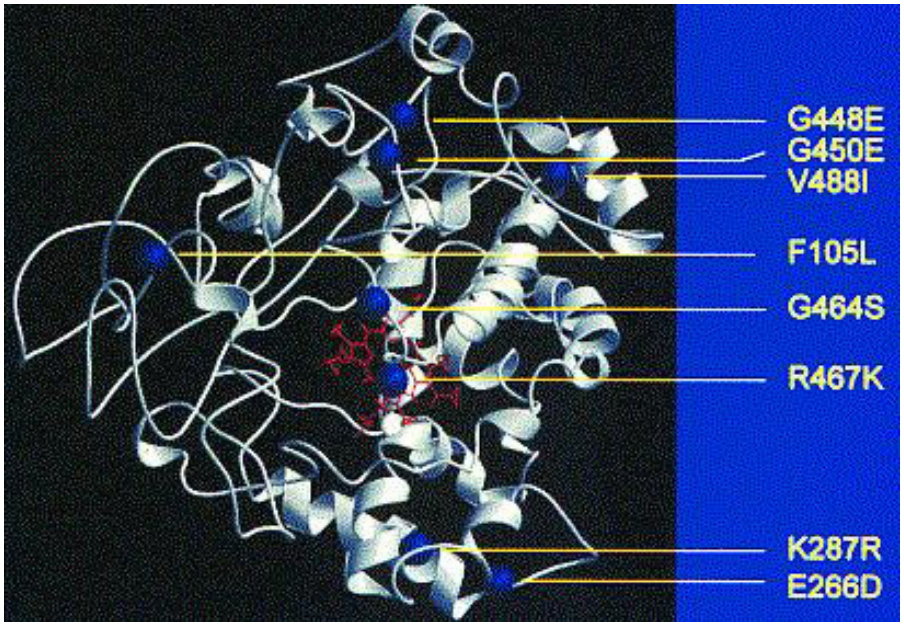


Fig. 4. Cartoon giving an approximate impression of the protoporphyrin moiety located at the active site of Erg11p (Cyp51p), the cytochrome P450 enzyme target for imidazole and triazole antifungals. Three triazole antifungals, itraconazole (top), fluconazole (centre) and voriconazole (bottom) are shown in comparable orientations. Arrows link the azole nitrogen atom to the iron atom where the azoles bind to block the active site of the enzyme. The different side chains attached to the common azole pharmacophore in the three examples shown will obviously bind differently to the surrounding regions of the whole P450 protein.

Odds, Trends in Microbiology (2003) 11:272-279

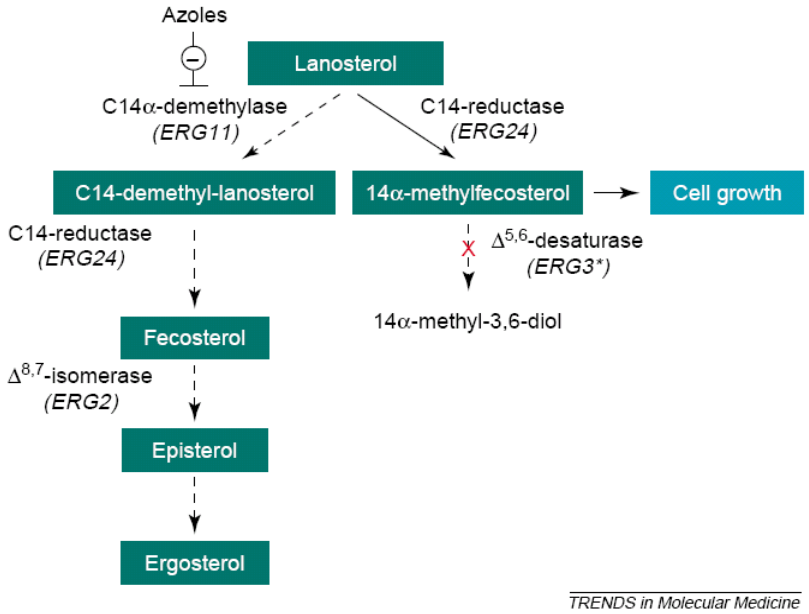
Mécanismes de résistance aux dérivés azolés



Mechanism	Caused by:	Comments
Alteration in drug target (14α-demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^{5(6)}$-desaturase	Results in accumulation of 14α-methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN^r)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

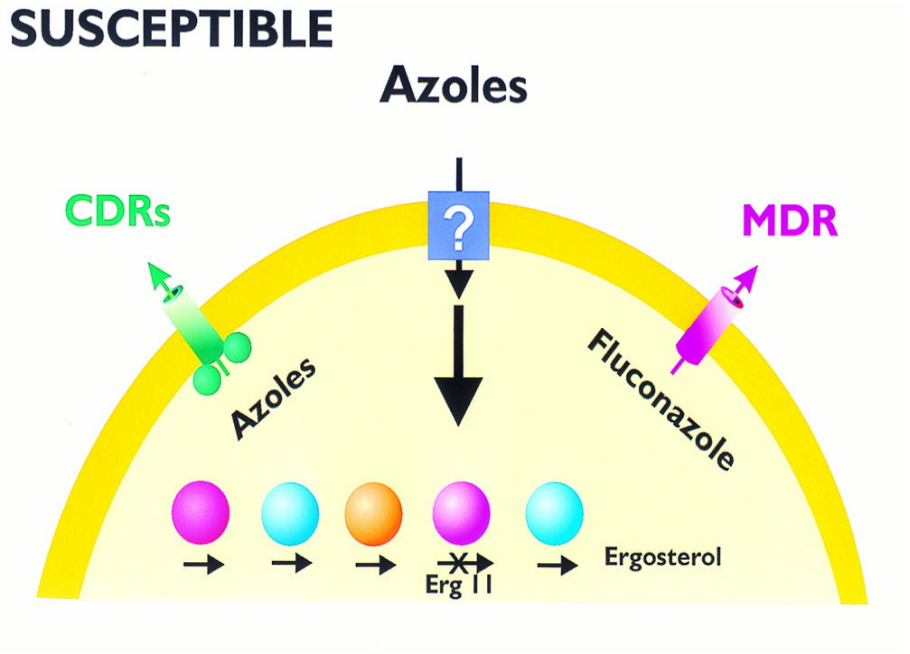
Lupetti et al, Trends Mol Medicine (2002) 8:76-81

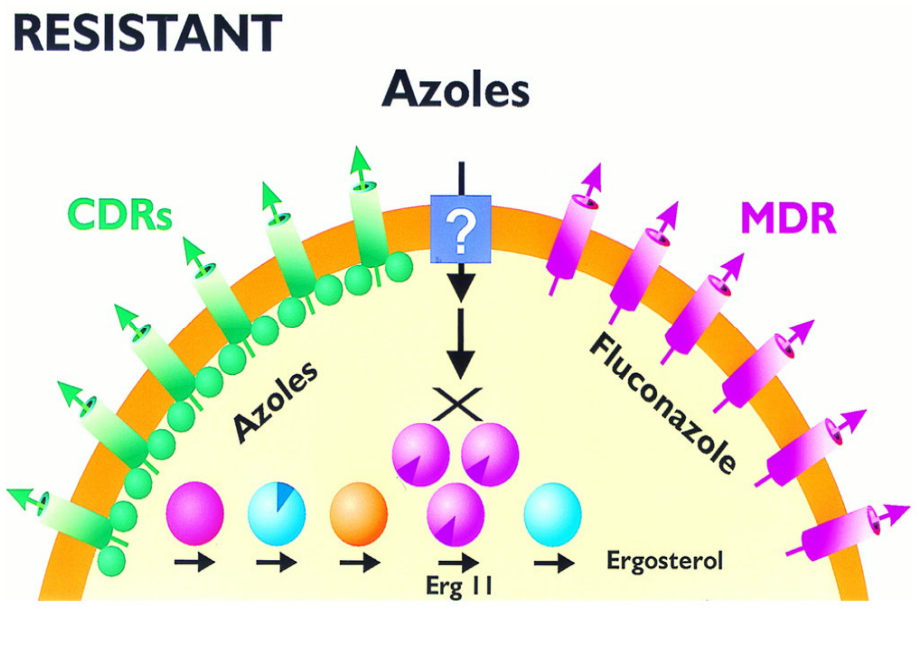
Mécanismes de résistance aux dérivés azolés



Mechanism	Caused by:	Comments
Alteration in drug target (14α-demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^{5(6)}$-desaturase	Results in accumulation of 14α-methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN^r)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

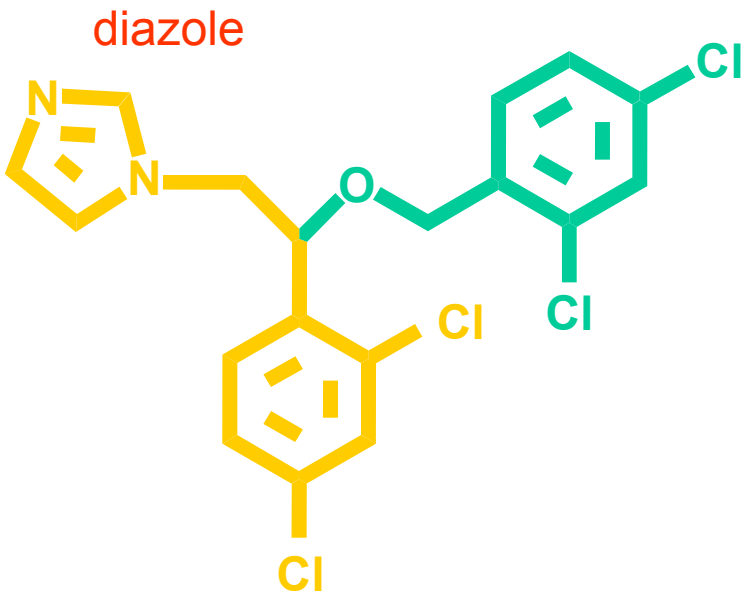
Mécanismes de résistance aux dérivés azolés





Mechanism	Caused by:	Comments
Alteration in drug target (14α-demethylase)	Mutations which alter drug binding but not binding of the endogenous substrate	Target is active (i.e., can catalyze demethylation) but has a reduced affinity towards azoles
Alteration in sterol biosynthesis	Lesions in the $\Delta^{5(6)}$-desaturase	Results in accumulation of 14α-methyl fecosterol instead of ergosterol
Reduction in the intercellular concentration of target enzyme	Change in membrane lipid and sterols; overexpression of specific drug efflux pumps (CDR1, PDR5, and BEN^r)	Poor penetration across the fungal membrane; active drug efflux
Overexpression of antifungal drug target	Increased copy number of the target enzyme	Results in increased ergosterol synthesis; contributes to cross-resistance between fluconazole and itraconazole

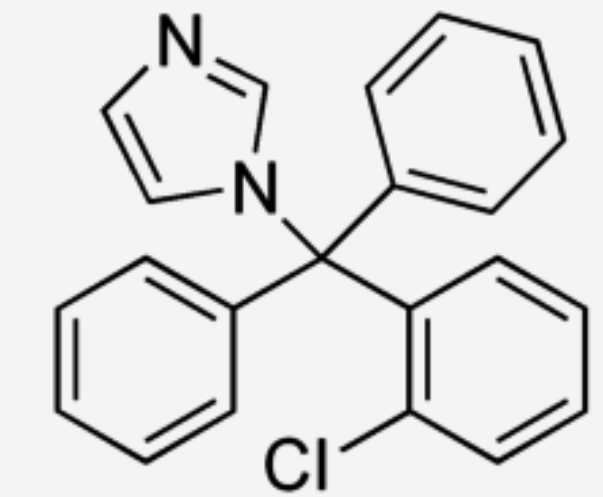
Miconazole



- premier antifongique azolé
- mauvaise résorption digestive
- usage essentiellement topique (candidoses)

Clotrimazole

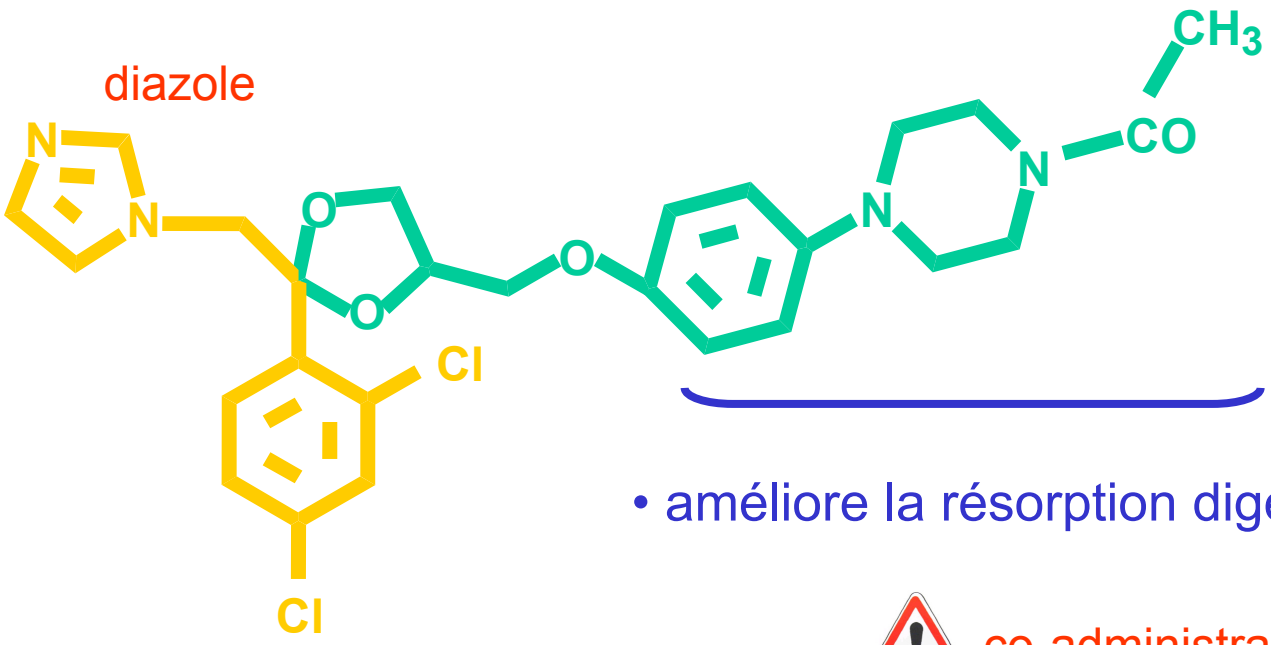
diazole



Indications :
- candidoses
- dermatophytoses

actif également dans le traitement de l'anémie falciforme par bloquage des canaux ioniques (maintien de la fome des globules rouges

Kétoconazole

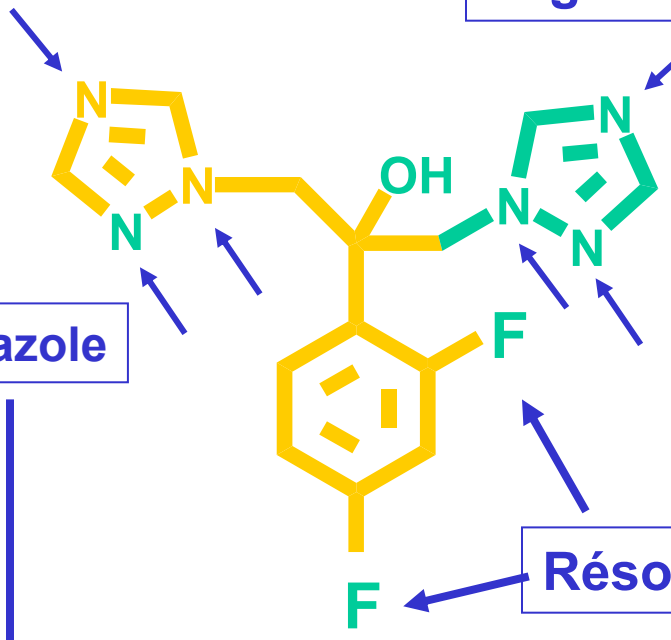


- améliore la résorption digestive en milieu acide

co-administration d'anti-acides ….

indications (peu utilisé aujourd'hui):
- candidoses (histoplasmose, coccidioïdomycose)
- prophylaxie des colonisations par levures chez les neutropéniques

Fluconazole



augmente l'activité

2ème triazole

1er triazole

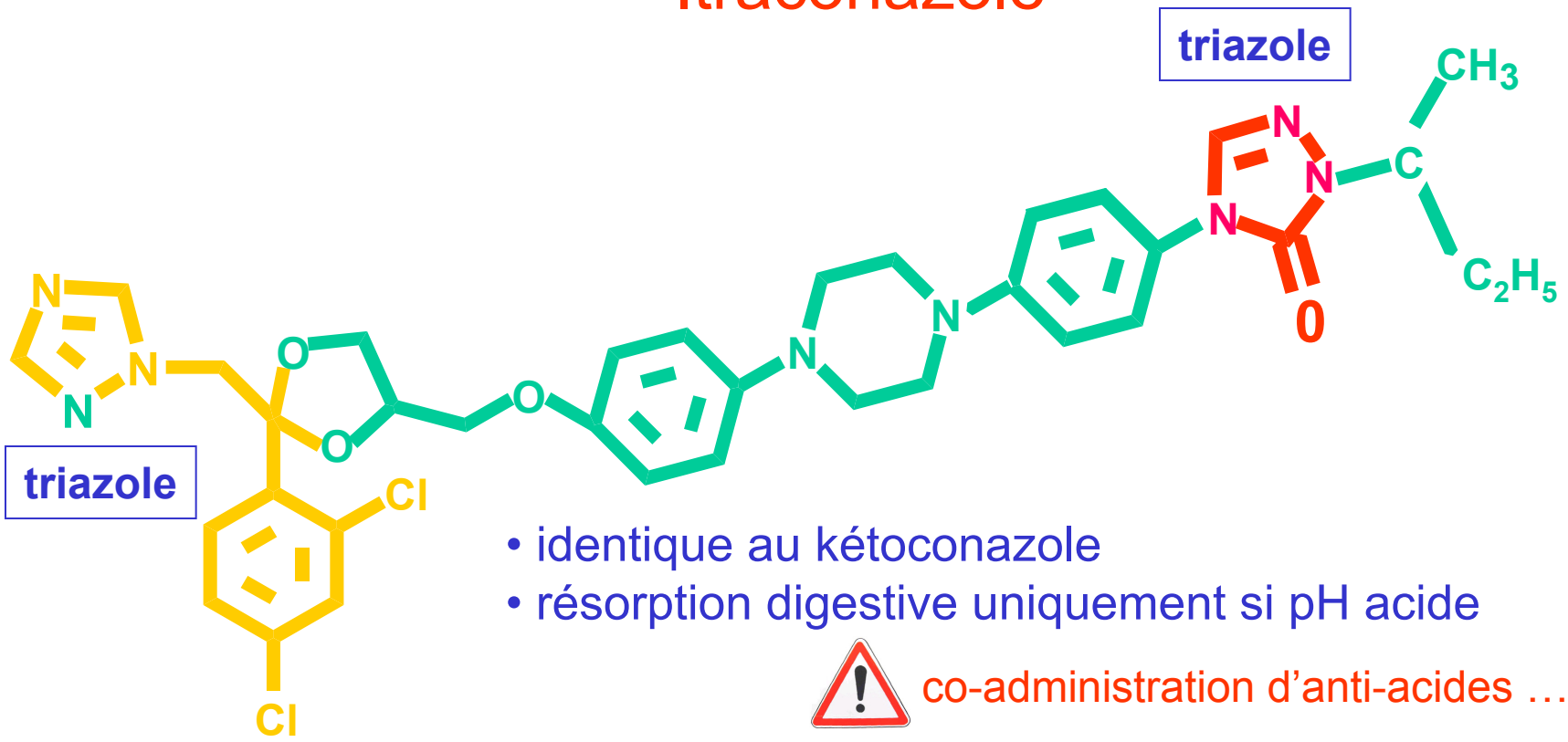
Résorption digestive même à pH neutre

augmente la spécificité et diminue la dégradabilité

Indications :

- méningites cryptococciques (pénétration dans LCR)
- candidoses.

Itraconazole



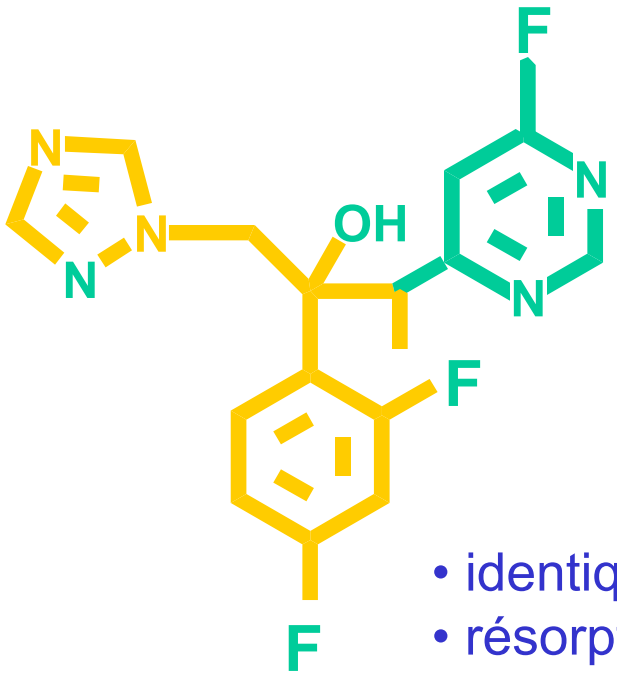
- identique au kétoconazole
- résorption digestive uniquement si pH acide

co-administration d'anti-acides ….

- 2 triazoles; meilleure activité

Indications :
- candidoses
- aspergilloses

Voriconazole



- spectre large; puissante activité
- pas de résistance croisée avec les autres azolés

- identique au fluconazole
- résorption digestive même à pH neutre

- **indications** :

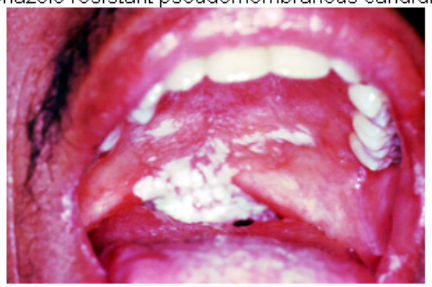
– aspergilloses invasives

– infections invasives graves à Candida **résistant au fluconazole.**

– Traitement des infections fongiques graves à Scedosporium spp. ou Fusarium spp.

- en <u>première intention</u> aux patients immunodéprimés, atteints d'infections évolutives, pouvant menacer le pronostic vital.

Fluconazole resistant pseudomembranous candidiasis



Dérivés azolés et interactions avec CYP (CYP2C19, CYP2C9 et CYP3A4)

2 Major drug interactions encountered with triazole agents

	Degree of interaction					
	FLU	ITC	VOR	POS	Effect	Clinically significant
Substrates of CYP3A4 and CYP2C9*	++	+++	+++	++	Increased plasma concentrations of other drug substrates	Yes (some contraindicated)
Inducers of CYP3A4 and CYP2C9†	++	+++	+++	++	Decreased plasma concentrations of triazoles	Yes (some contraindicated)
Warfarin	++	+++	+++	++	Increased prothrombin time	Yes
Phenytoin	+++	+++	+++	+++	Increased phenytoin levels, decreased triazole levels	Yes
Rifampicin	+++	+++	+++	+++	Decreased triazole levels	Yes (contraindicated with ITC, VOR, POS)
Proton-pump inhibitors	++	++	+++	++	Increased proton-pump inhibitor levels, decreased triazole absorption	Yes
Cyclosporine	++	++	+++	++	Toxicity, renal failure	Yes
Tacrolimus	++	++	+++	++	Toxicity, renal failure	Yes
Sirolimus	++	++	++++	++	Toxicity, renal failure	Yes (contraindicated with VOR)
Statins	++	+++	+++	++	Increased statin levels	Yes

FLU = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole. + = mild, ++ = moderate, +++ = high, ++++ = very high. * Includes but not restricted to cisapride (contraindicated with FLU, ITC, VOR POS), terfenadine, astemizole, pimozide, quinidine, ergot alkaloids (contraindicated with ITC, VOR), sirolimus (contraindicated with VOR), tacrolimus, cyclosporin, statins, warfarin, omeprazole, phenytoin, benzodiazapines, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and sulfonylurea oral hypoglycaemics. † Includes rifampicin (contraindicated with ITC, VOR, POS), rifabutin (contraindicated with ITC, VOR), long-acting barbiturates (contraindicated with VOR), phenytoin, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors.

- contre-indiqués: terfénadine, astémizole, cisapride, quinidine, alcaloïdes de l'ergot
- surveillance étroite : ciclosporine, tacrolimus, anticoagulants oraux, sulfonylurées
- adaptation de posologie : statines, benzodiazépines

Chen et al. Med J Aust. (2007) 187:404-9.

Dérivés azolés : propriétés pharmacologiques

Pharmacocinétique

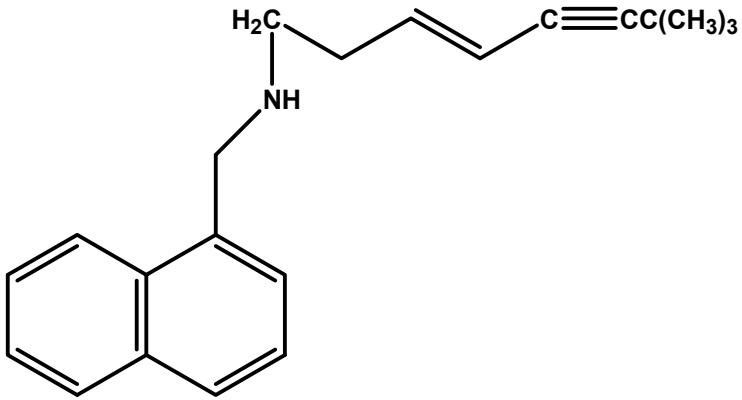
- absorption variable; parfois dépendante du pH.
- distribution variable; LCR : fluconazole
  voie orale: itraconazole, fluconazole, voriconazole
- demi vie longue (> 24 heures) sauf kétoconazole (8 h) et voriconazole (6 h)

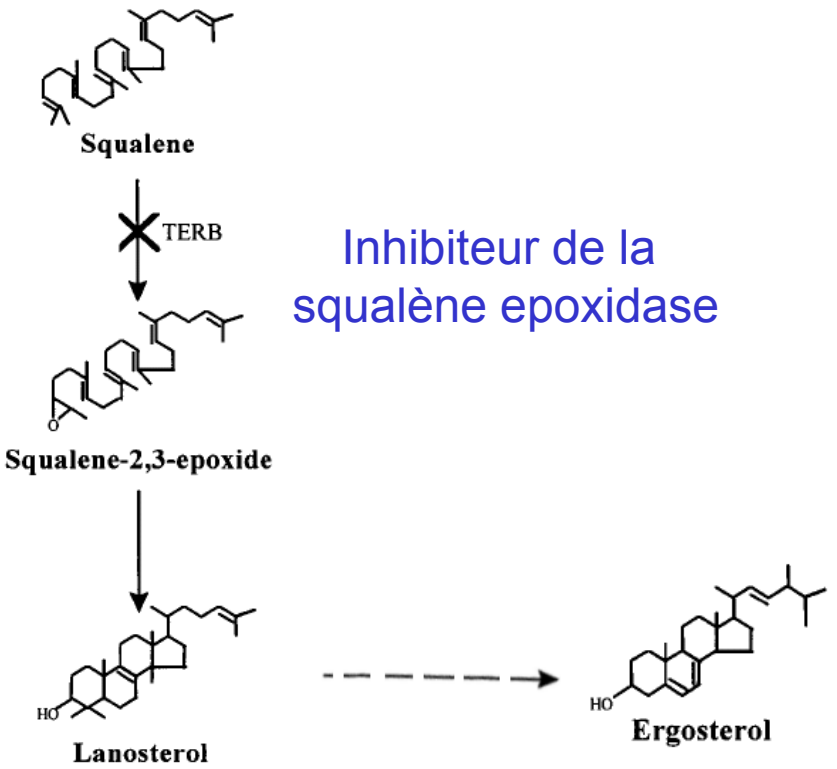
Effets secondaires

- toxicité hépatique (surtout kétoconazole)
- troubles digestifs (miconazole)
- intolérance cutanée par voie locale

Allylamines

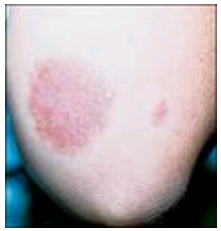
terbinafine



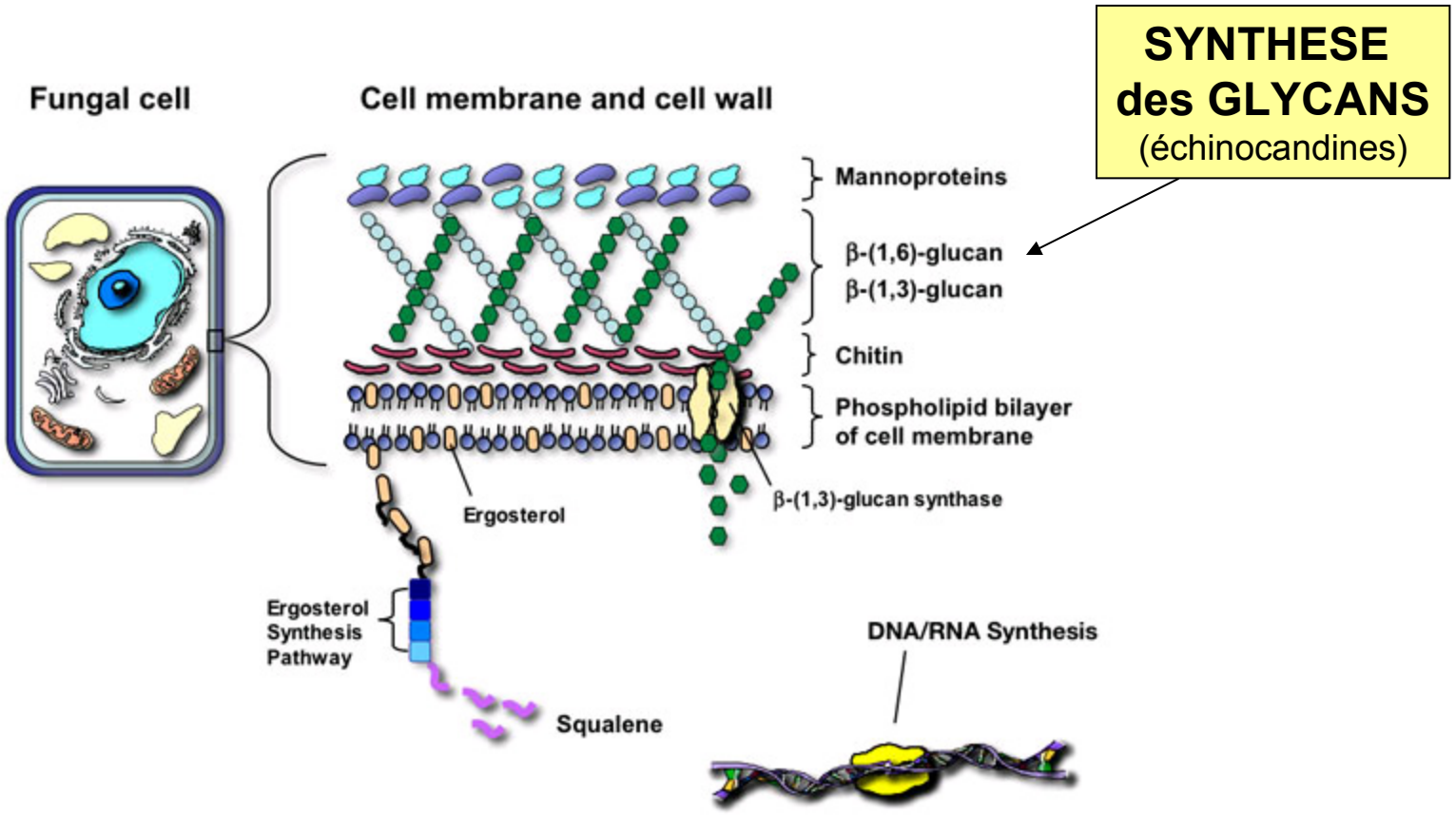


Inhibiteur de la squalène epoxidase

- actif uniquement sur les dermatophytes
- bien résorbée mais effet de premier passage important
- interaction avec inhibiteurs et inducteurs des cytochromes



Cibles des médicaments antifongiques



Echinocandines : caspofungine & anidulafungine

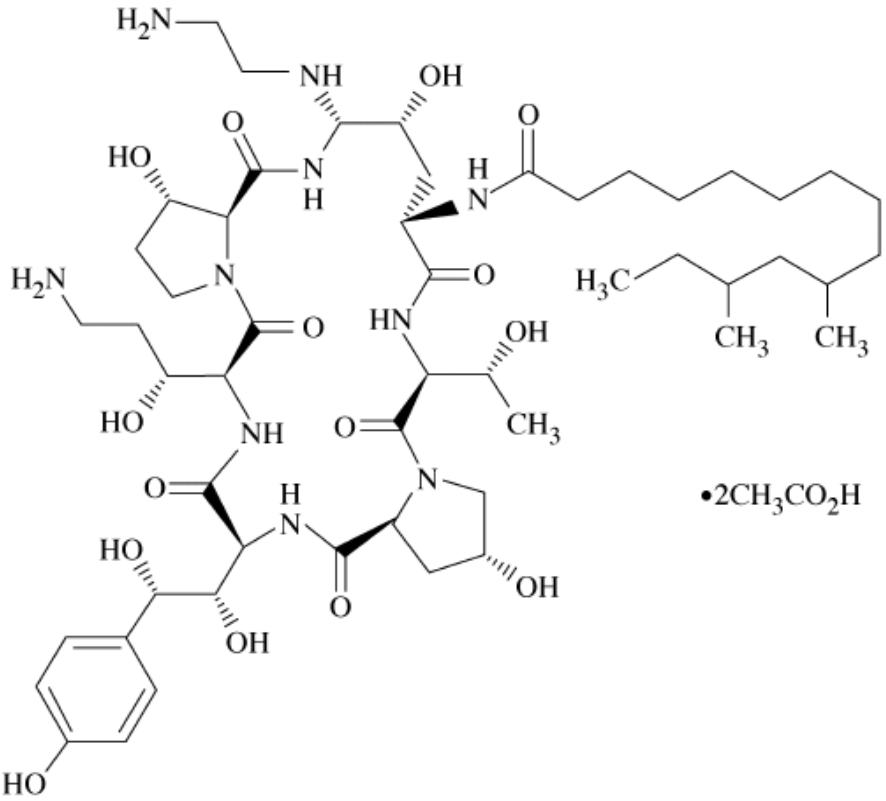
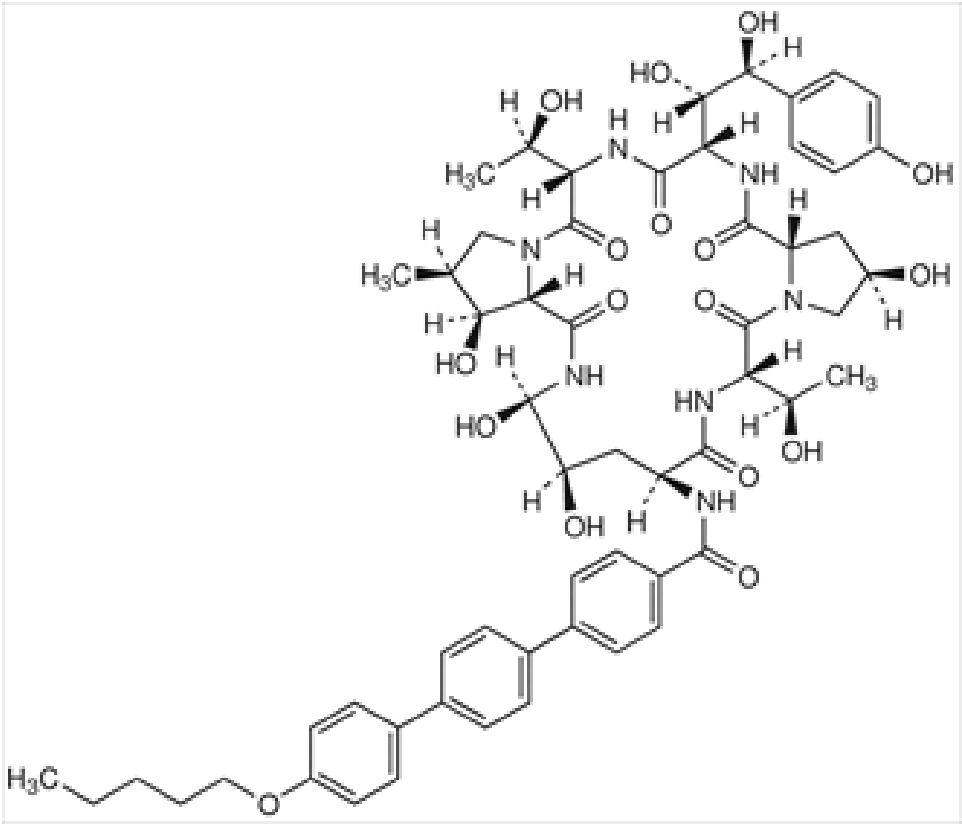


Figure 1. Structure of caspofungin.



Echinocandines

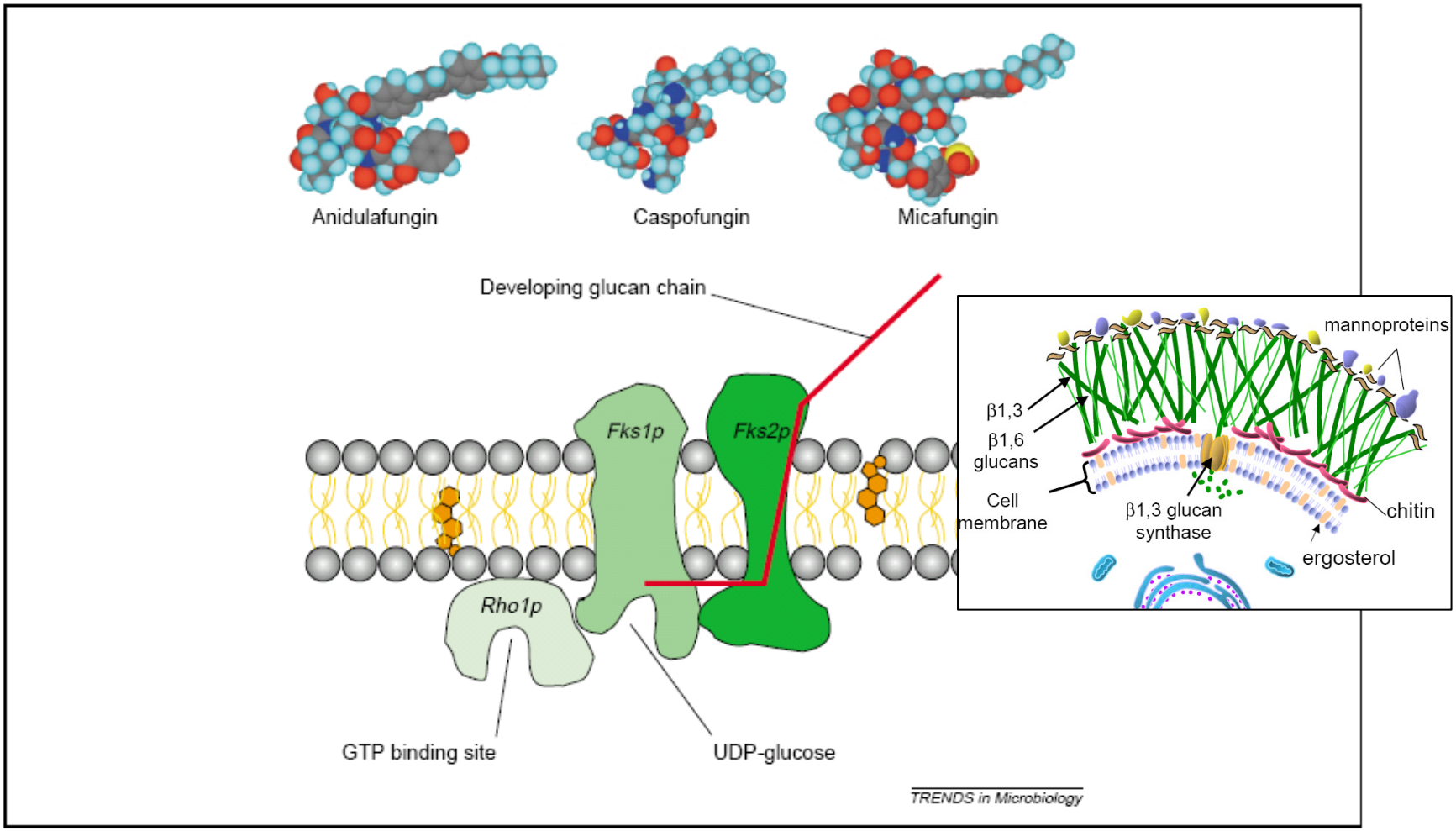


Fig. 5. Cartoon depicting the transmembrane complex of two proteins, Fks1p and Fks2p, involved in synthesis of β-1:3 glucan in the cell walls of *Saccharomyces cerevisiae*. Activity of the complex is regulated by the GTP-binding peptide, *Rho1p*. Fks1p is the target of the echinocandins, with the structures of the three agents now entering clinical use illustrated above. Evidence for *Candida albicans* suggests that the Fks2p homologue in this species might not be expressed in growing cells. Much remains unknown about the glucan synthase protein complex and the manner of interaction of echinocandins with the complex.

Odds, Trends in Microbiology (2003) 11:272-279

Caspofungine: propriétés pharmacologiques

Indications:

- candidoses (oropharyngées, oesophagiennes)
- aspergilloses invasives chez les patients qui ne répondent pas ou sont intolérants aux autres traitements

Pharmacocinétique:

- Mauvaise résorption orale
- Accumulation dans l'organisme lors d'un traitement prolongé (25-50 % d'augmentation de l'AUC après 2 à 3 semaines de traitement).
- Métabolisation par le foie; demi-vie, environ 10 h.

Effets secondaires

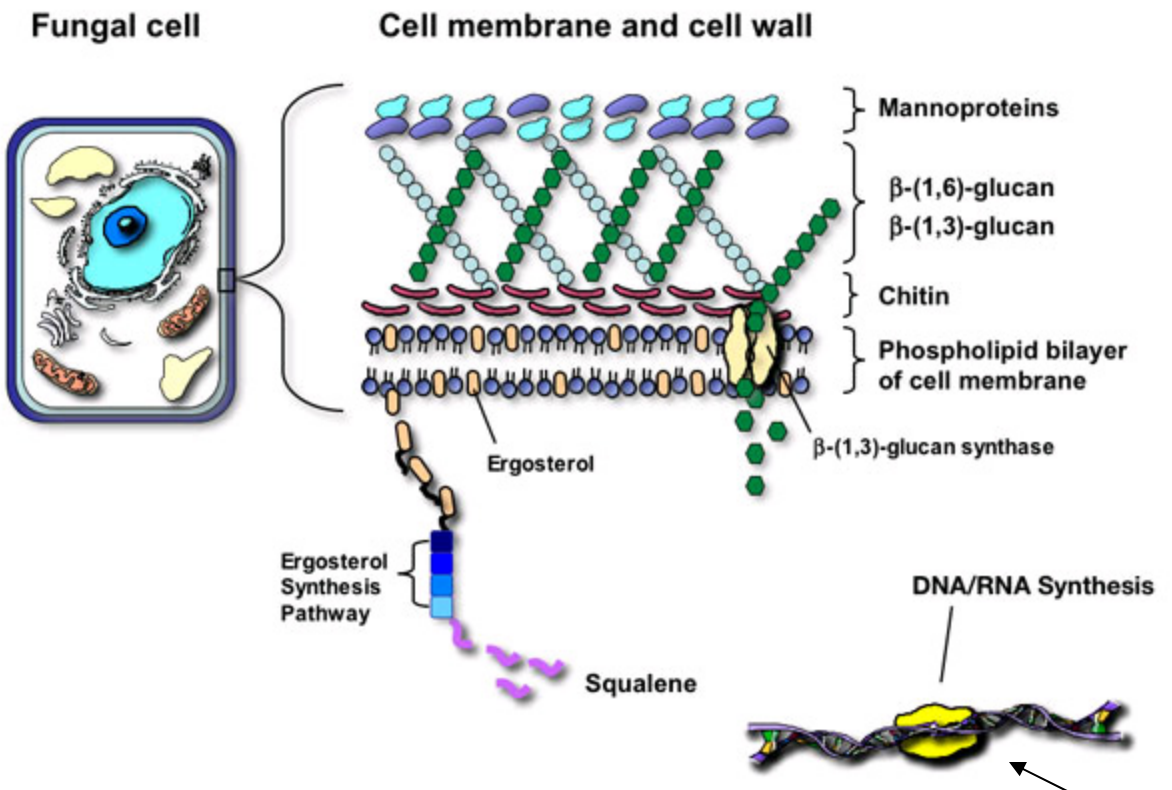
- phlébite au site d'injection
- fièvre, nausées et vomissements.

Interactions médicamenteuses

- ↗ AUC de la caspofungine par cyclosporine
- ↘ AUC par inducteurs des cytochromes P450 (rifampicine, inhib.protéases du HIV, phénytoïne, carbamazépine, dexaméthasone).

Patients à risque d'infection fongique!

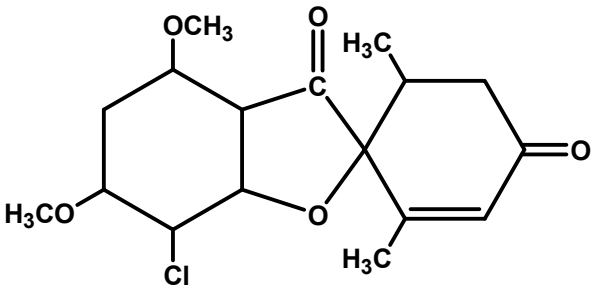
Cibles des médicaments antifongiques



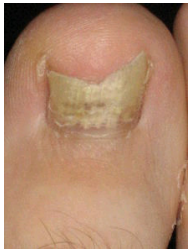
SYNTHESE des Ac. Nucl.
(5-fluorocytosine, griséofulvine)

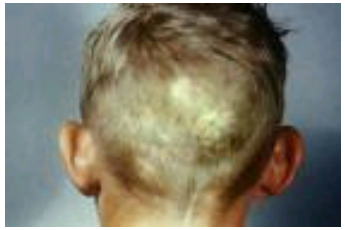
Inhibiteurs de synthèse des acides nucléiques

griséofulvine

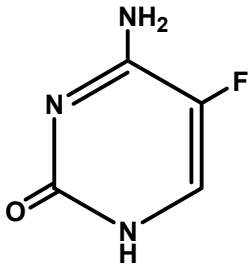


- infections à dermatophytes (cuir chevelu, peau, ongles)
- adm. orale, résorption ↗ par aliments riches en graisse
- réactions allergiques, maux de tête, troubles digestifs

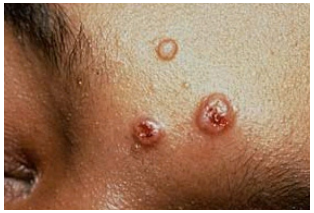




5-fluorocytosine



- inhibition de la thymidilate synthase; résistance fréquente
  → utiliser en association avec l'ampho B pour les candidoses et les cryptococcoses
- concentration dans l'urine → infection urinaire
- leuco- et thrombopénie



Et au Bénin ?

Médicaments essentiels génériques par classe thérapeutique et spécialités correspondantes

DESIGNATION (DCI)		VOIE D'ADMINISTRATION	D'UTILISATION						
	DESIGNATION	FORMES ET DOSAGES			Zones Sanitaires				SPECIALITES
			CNHU	CHD	HZ	CSC	CSA	UVS	
6.5 Antifongiques									
6.5. 1	Griséofulvine	250 mg comp	x	x	x	x	-		Griséofuline, Fulcine
		5% pommade	x	x	x	x	-		
6.5. 2	Nystatine	500000 UI comp	x	x	x	x(U)	-		Mycostatine
		100000UI comp gynécologique	x	x	x	x(M)	-		
6.5. 3	Miconazole	125 mg comp	x	x	x	x	x		Britane, Daktarin
		2% lotion	x	x	x	x	x		
		crème	x	x	x	x			
6.5. 4	Fluconazole	150 mg comp	x	x	x	x	X		Trifucan; flucazole
		100 mg comp	x	x	x	x	x		
		50 mg comp	x	x	x	x	X		
		2mg /ml inj	x	x	x	x			
		200 mg / 5 ml suspensuion buv	x	x	x	x	X		
		50 mg / 5 ml suspension buv	x	x	x	x	x		
6.5. 5	Clotrimazole	100 mg comp	x	x	x	x	x		canesten
		500 mg comp	x	x	x	x	x		
		1% crème	x	x	x	x			
		2% crème	x	x	x	x			