

Antimycotics

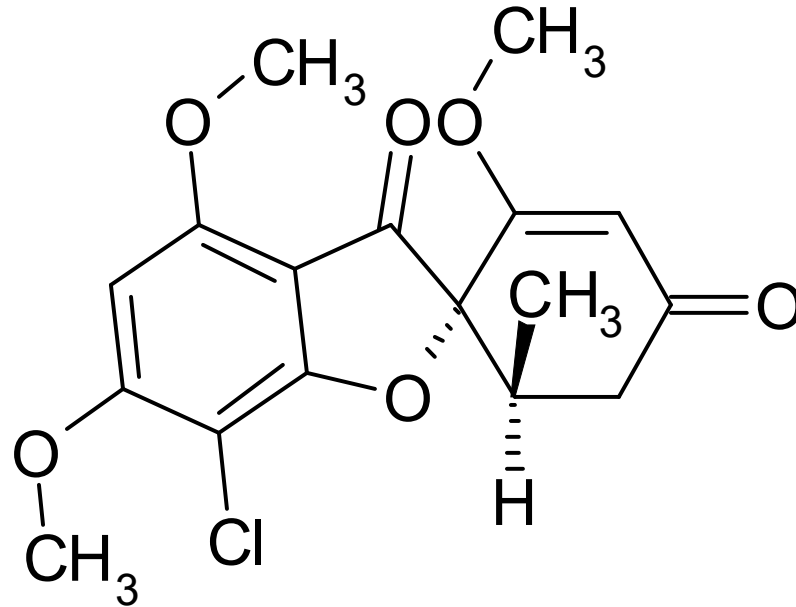
= compounds used for treatment of diseases caused by fungi
(moulds or yeasts)

Classification of antimycotics

1. Antimycotic antibiotics
 - 1.1 Griseofulvine
 - 1.2 Polyene antibiotics
 - 1.3 Echinocandins
 - 1.4 Sordarins
2. Flucytosine
3. Azoles
 - 3.1 Imidazole derivatives
 - 3.2 Triazole derivatives
4. Allylamines
5. Morpholines
6. Ciclopirox olamin
7. Unsaturated fatty acids and their salts
8. Esters of glycerole

1. Antimycotic antibiotics

Griseofulvine

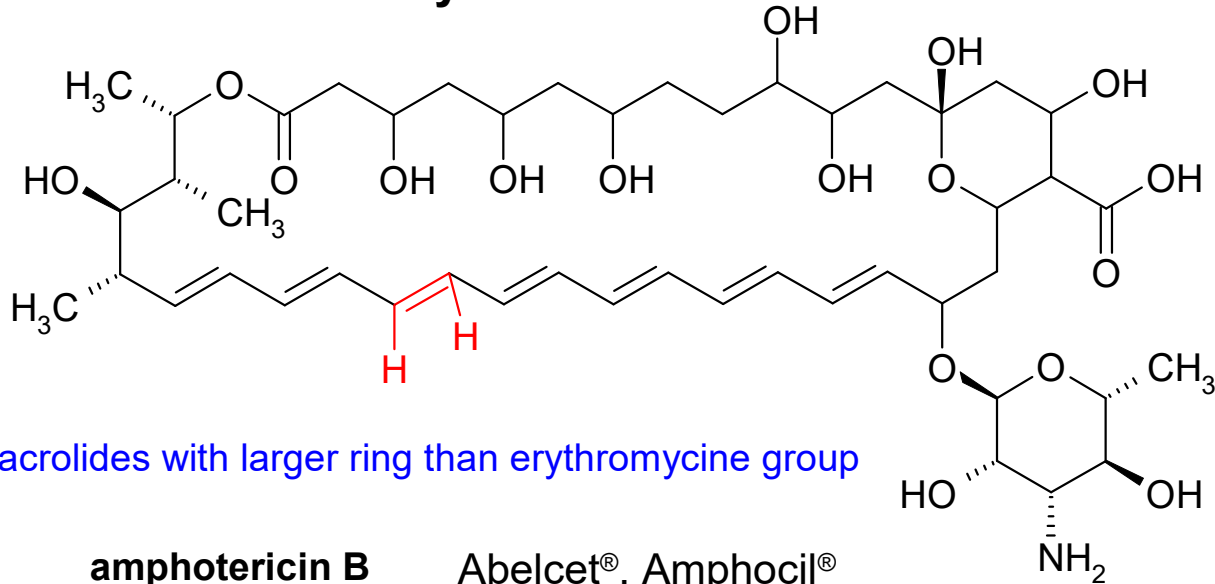


- antibiotic isolated from *Penicilium griseofulvum* in 1939
- site of action: microtubules formation
- high toxicity (liver)
- spectrum: dermatophytes

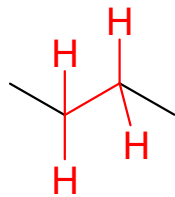
Griseofulvinum PhEur

Antimycotic antibiotics

Polyene antibiotics



- systemic candidoses and aspergiloses, sepses caused by fungi



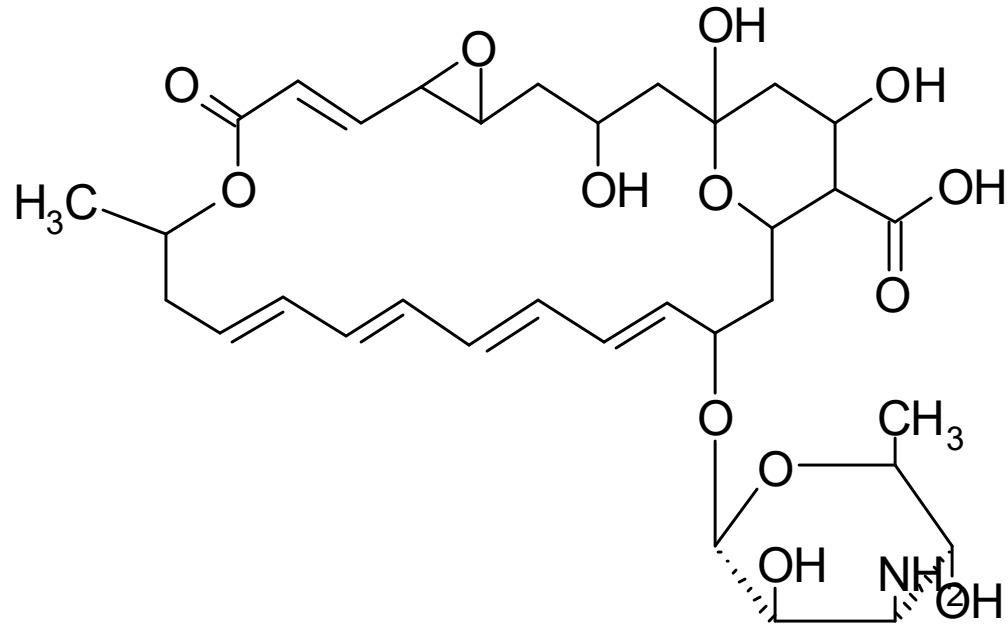
nystatin

Fungicidin[®] ung., Macmiror complex[®] ung., sup. (+ furazolidone)

•efficient to species *Aspergillus*, *Rhodotamba*, *Torulopsis*, *Trichosporon*, *Candida*, *Malassezia*, *Geotrichum* etc.

- in most externally

Antimycotic antibiotics
Polyene antibiotics



natamycin

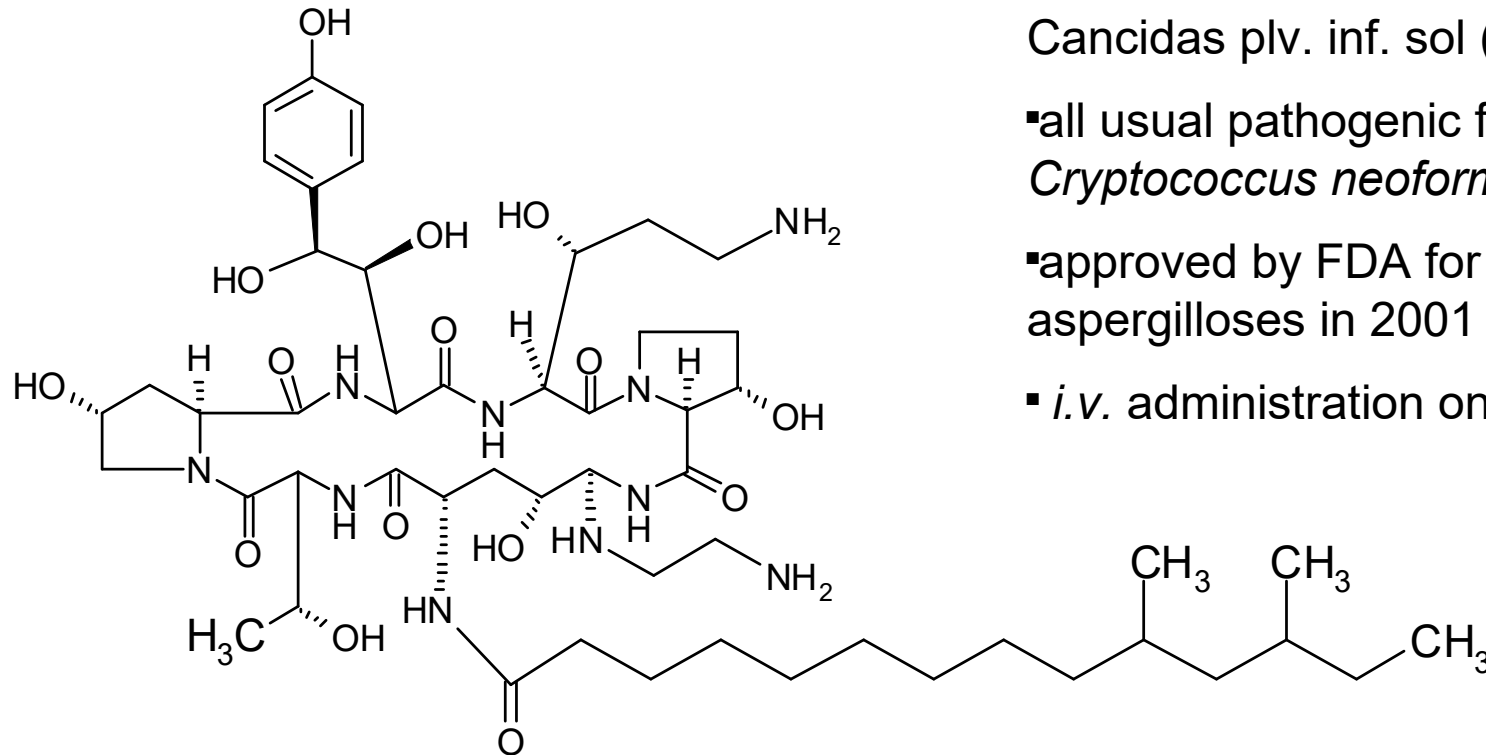
Pimafucin ® , Pimafucort ®

•external application

Antimycotic antibiotics

Echinocandins

- cyclic hexapeptides, OH-Pro dominates in their sequence, a lipophilic side acyl chain
- site of action: protein complex responsible for synthesis of β -1,3-glucans of the cell wall



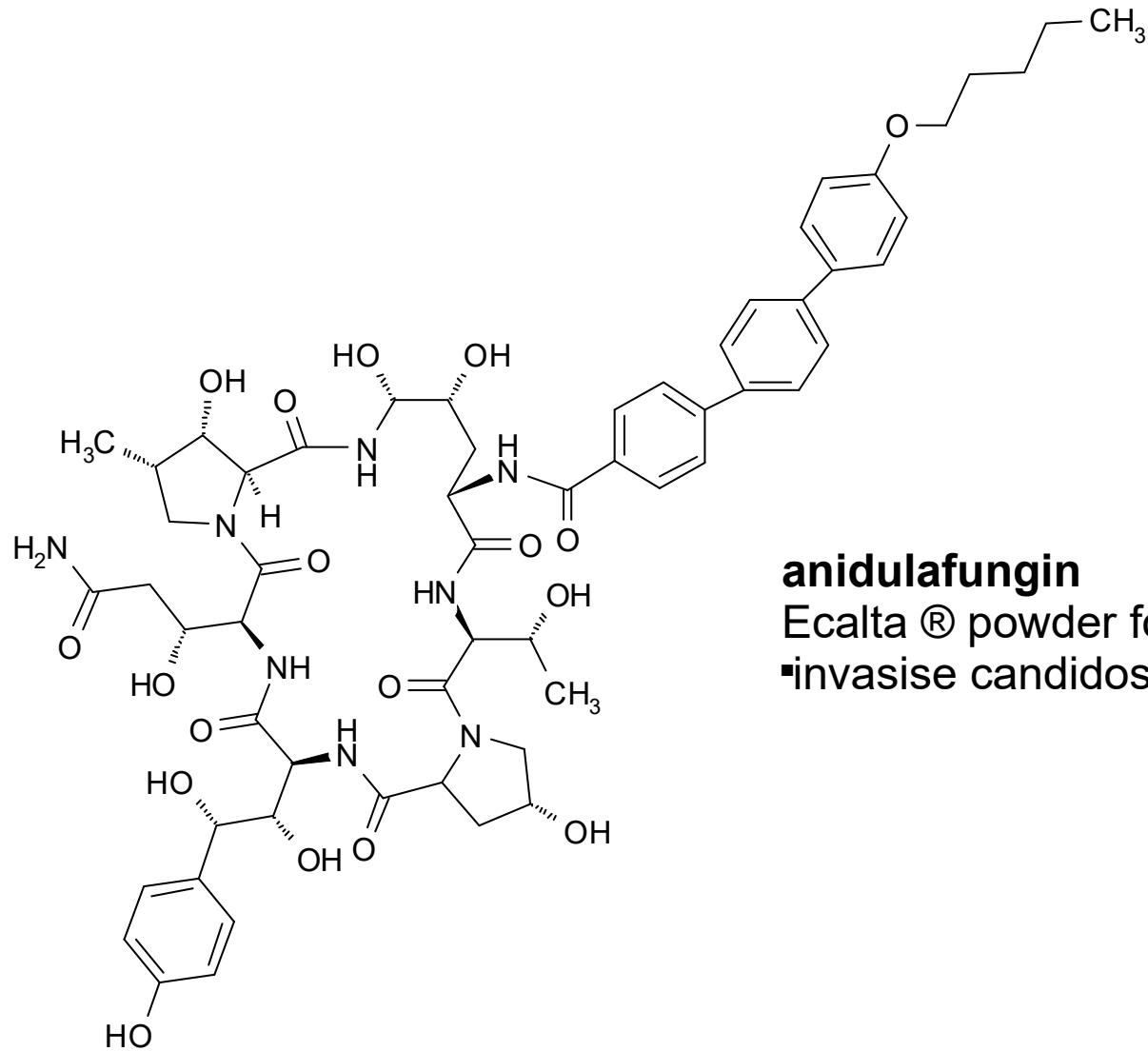
caspofungin

Candidas plv. inf. sol (acetate)

- all usual pathogenic fungi except *Cryptococcus neoformans*
- approved by FDA for treatment of aspergilloses in 2001
- *i.v.* administration only

Antimycotic antibiotics

Echinocandins



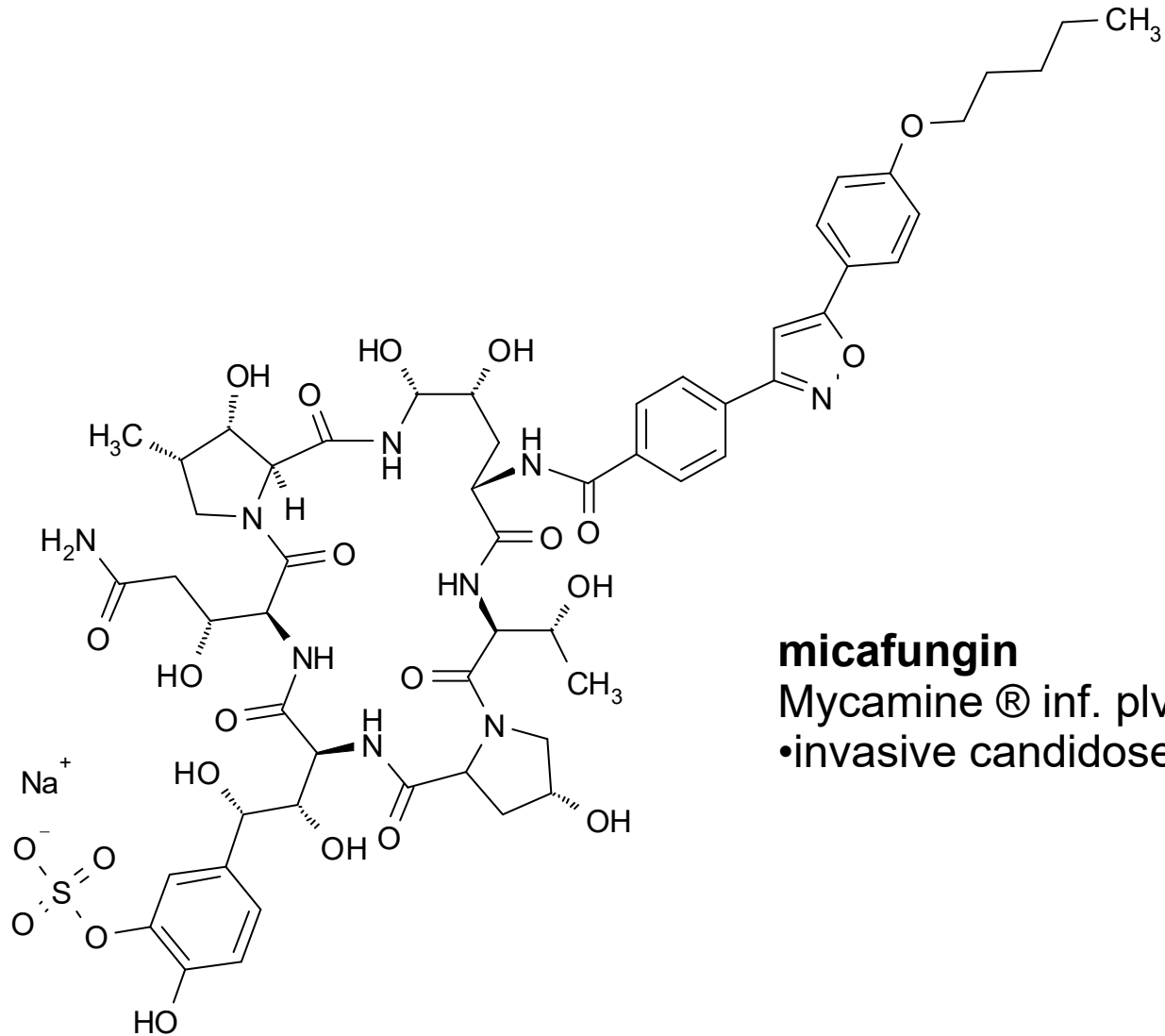
anidulafungin

Ecalta® powder for inf. sol.

▪invasive candidoses

Antimycotic antibiotics

Echinocandins



micafungin

Mycamine ® inf. plv. sol.

•invasive candidoses

Antimycotic antibiotics

Echinocandins

- preparation of semi-synthetic micafungin (FK 463)

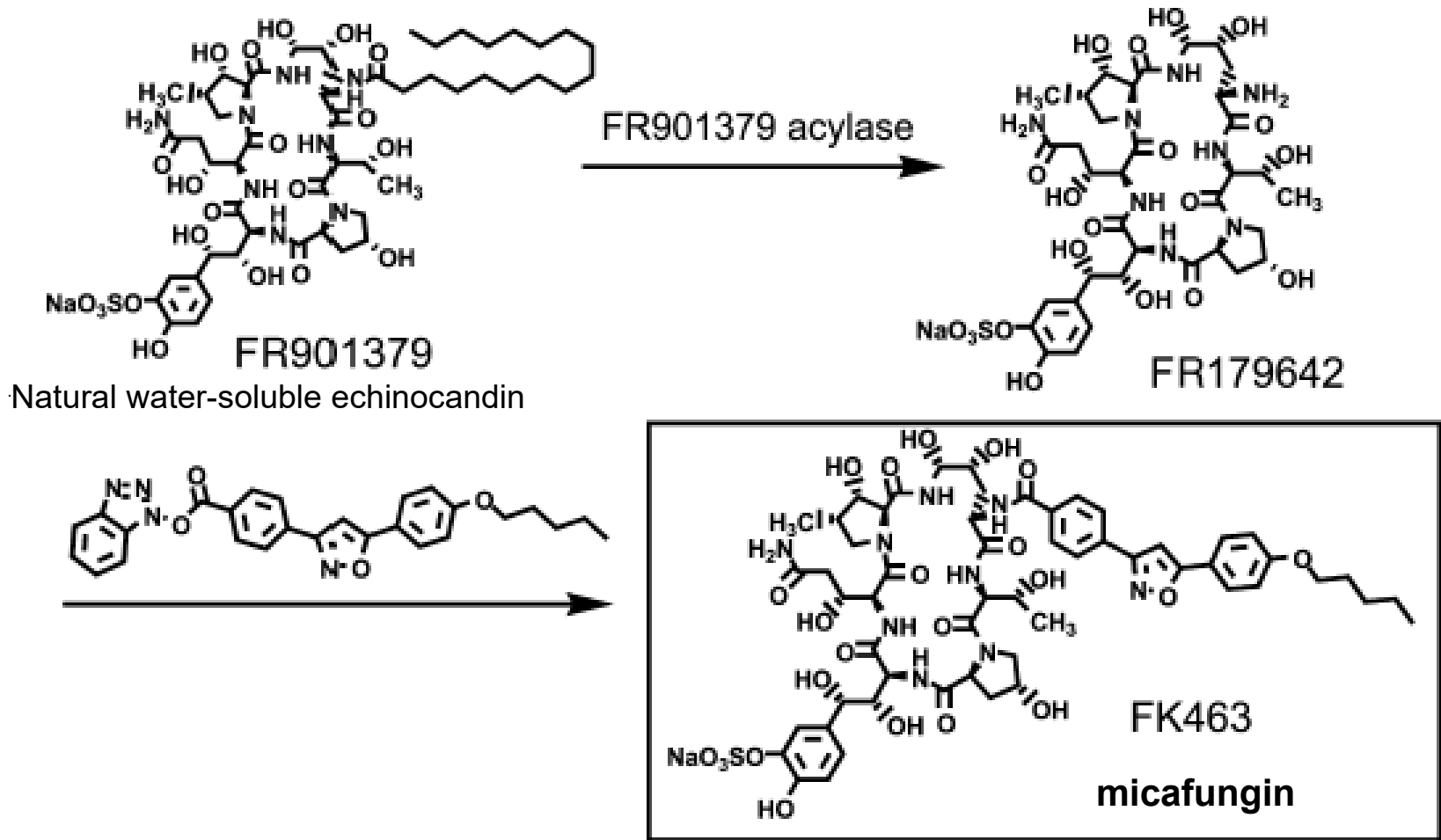
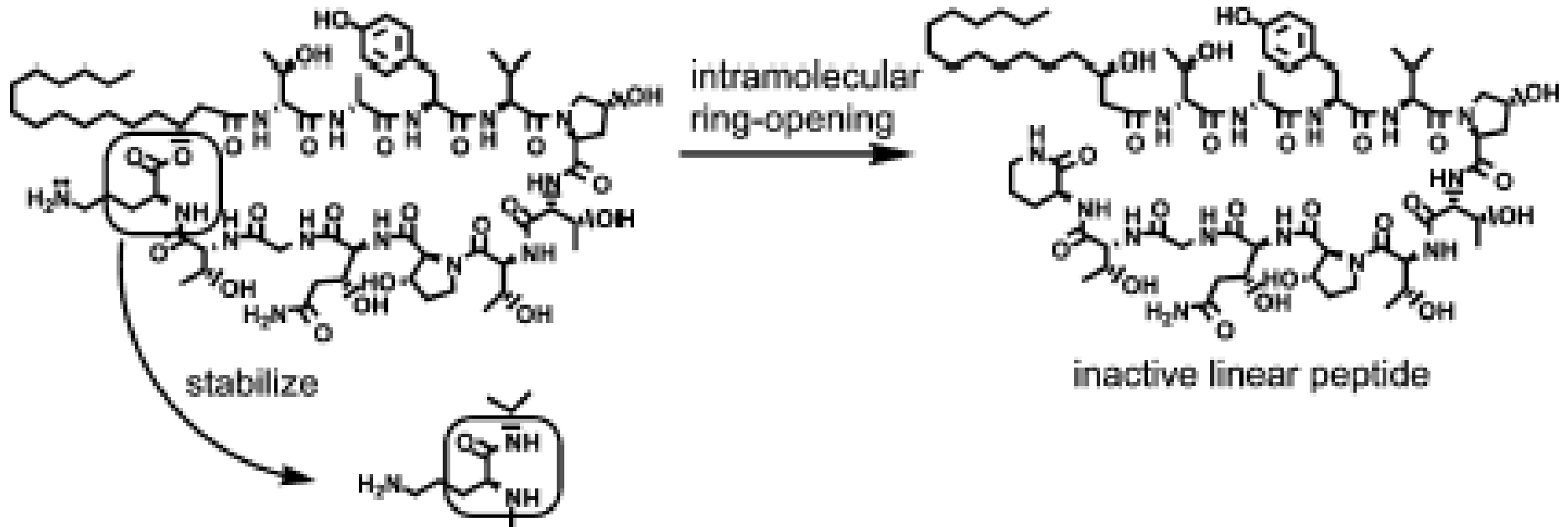


Fig. 8. Deacylation of FR901379 and synthesis of FK463.

Antimycotic antibiotics

Echinocandins

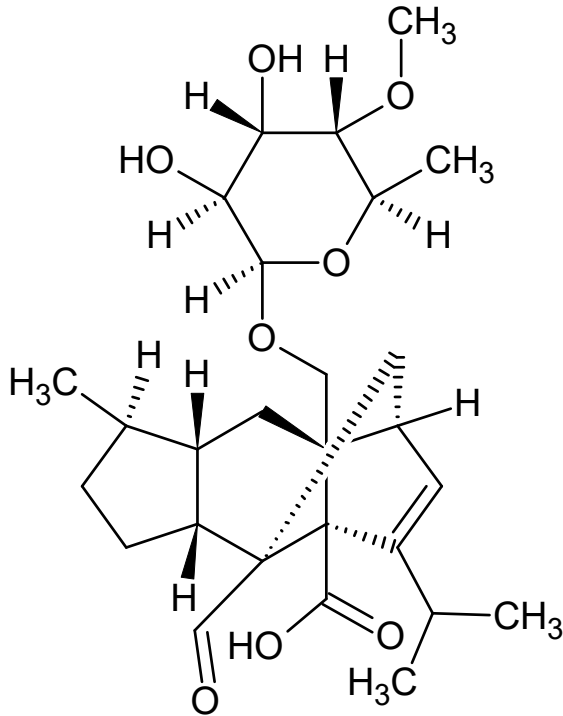
Intramolecular cleavage of the lactone ring –
lactone aminolysis – in compound FR901469



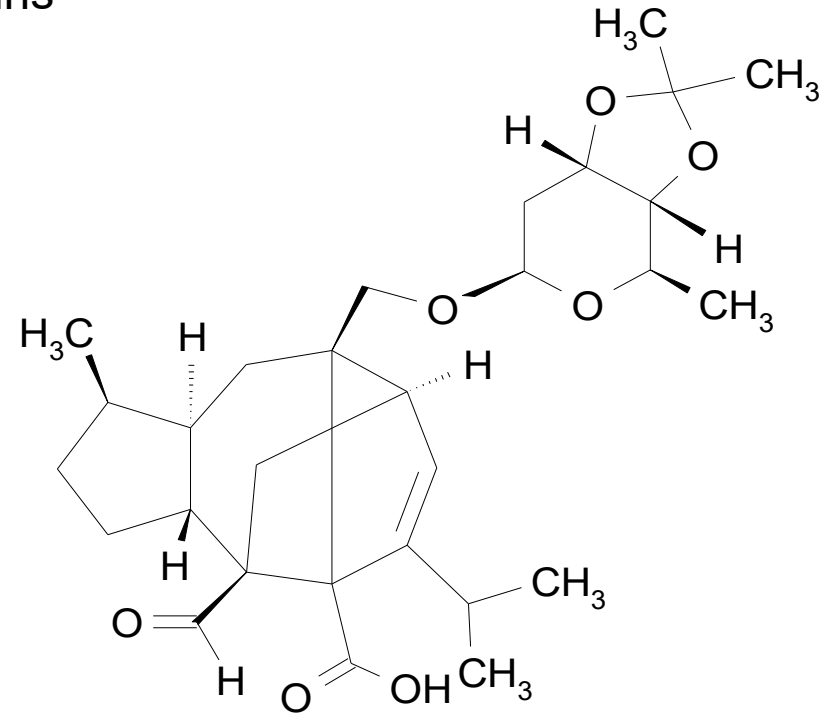
- replacement of the ester bond with the amide one avoids this peptide ring-opening

Antimycotic antibiotics

Sordarins



sordarin



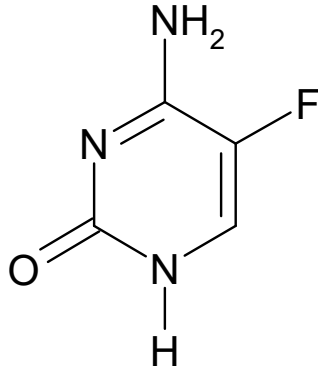
GM 193663

- metabolite of the mold *Sordaria araneosa*
- first isolated in Sandoz, Switzerland, 1969
 - mode of action: protheosynthesis inhibition by blocking of fungal elongation factor 2 (EF2) in translation

(the amino acids sequence of EF2 is in *Candida albicans* in 85 % equal to this in human)

Spectrum: *Candida albicans* etc.

2. Flucytosine

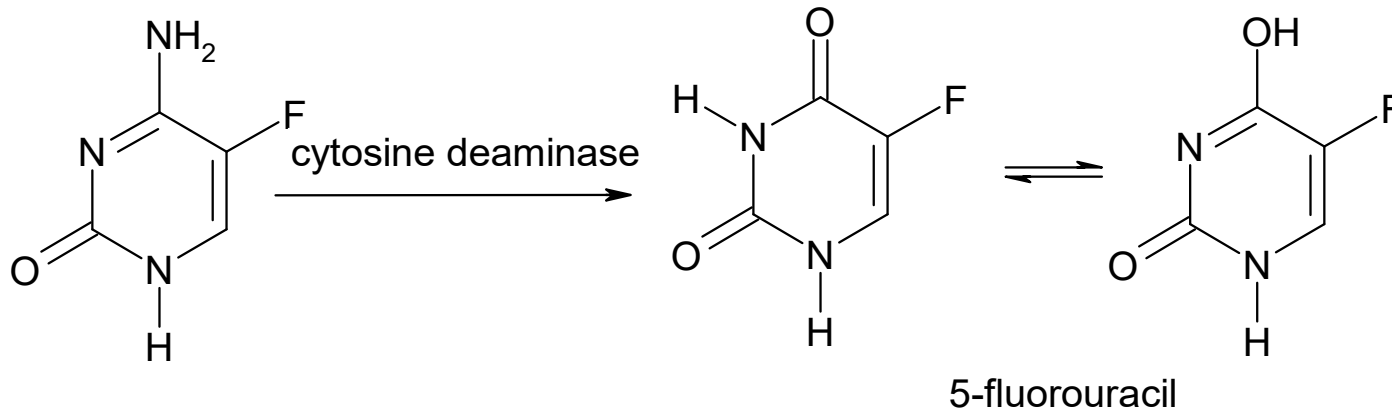


4-amino-5-fluoro-1H-pyrimidin-2-one

5-fluorocytosine
flucytosine
Ancotil®

- Spectrum: pathogenic yeasts (*Candida*, *Cryptococcus*), strains causing chromomycoses

- Mechanism of action: transformation into 5-fluorouracil by fungal cells \Rightarrow 5-fluorouracil inserted into RNA \Rightarrow inhibition of thymidylate synthase \Rightarrow blocking of DNA synthesis



3. Azoles

▪imidazole (= 1,3-diazole) derivatives

▪1,2,4-triazole derivatives

▪the most numerous group of antimycotics

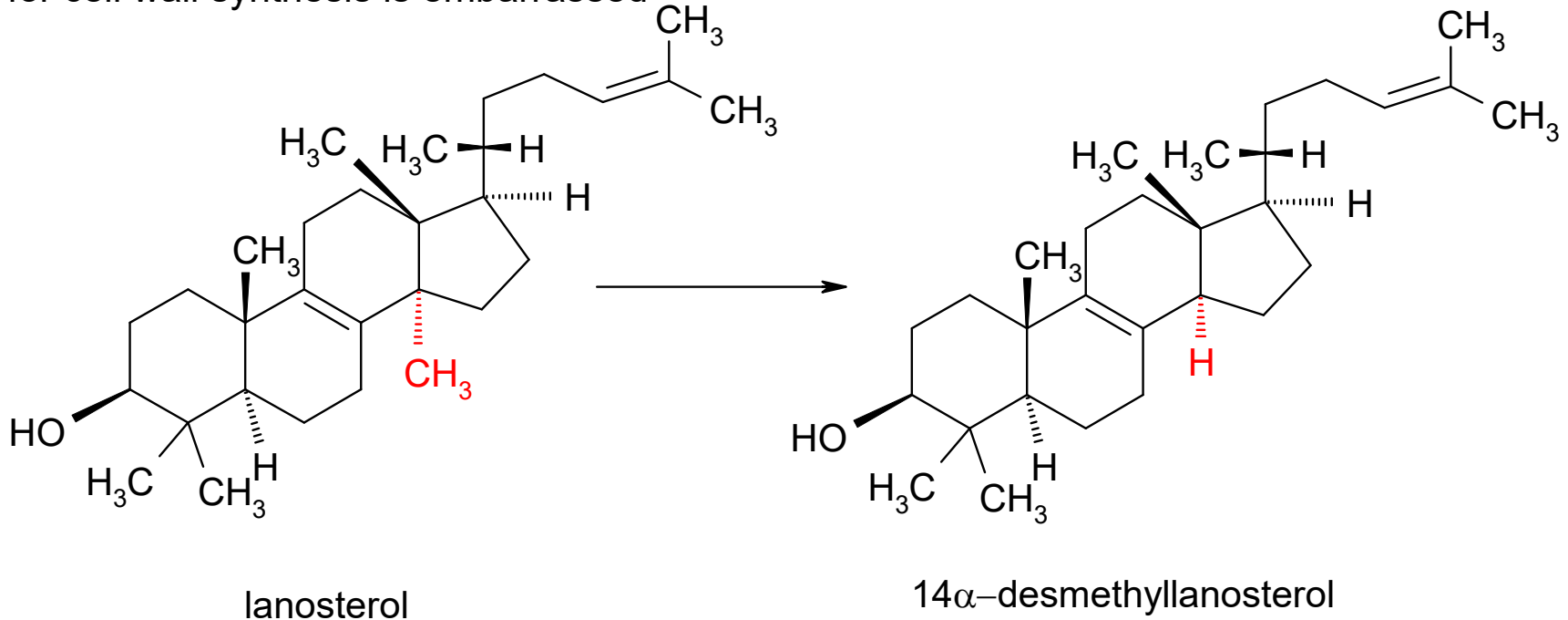
▪mechanism of action: inhibition of 14α -demethylation of lanosterol in biosynthesis of ergosterol

▪in some species also inhibition of following Δ^{22} desaturation

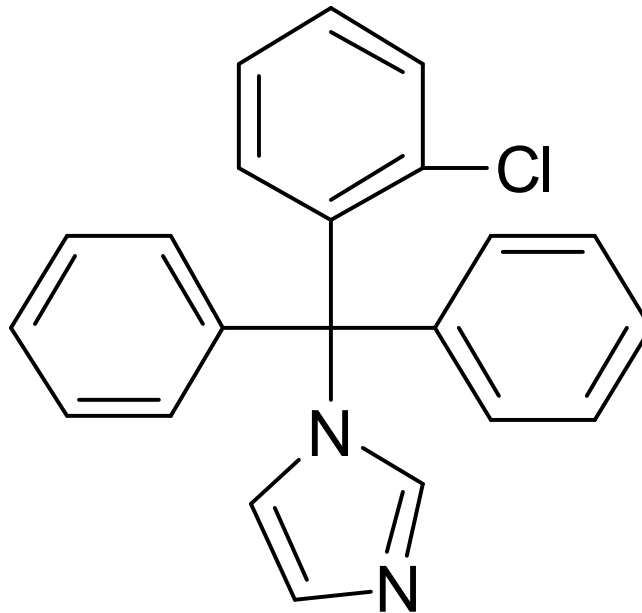


▪ergosterol is replaced with non-functional sterols \Rightarrow permeability and fluidity of the cell

membrane is altered \Rightarrow binding of membrane enzymes including those which are needed for cell wall synthesis is embarrassed



Azoles
Imidazole derivatives



1-[(2-chlorophenyl)diphenylmethyl]imidazole

clotrimazole

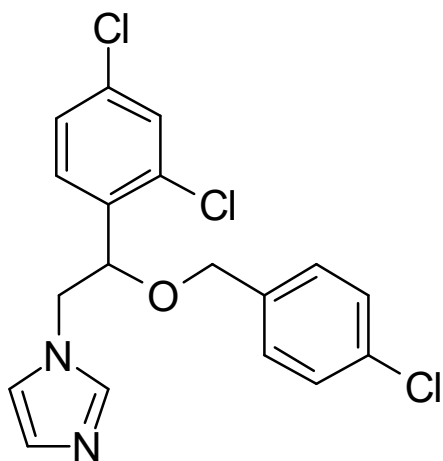
Canesten[®] , Candibene[®] ...

▪mostly external use

Azoles Imidazole derivatives

Compounds with 1-[2-(phenylmethoxy)-2-phenyl]ethylimidazole fragment

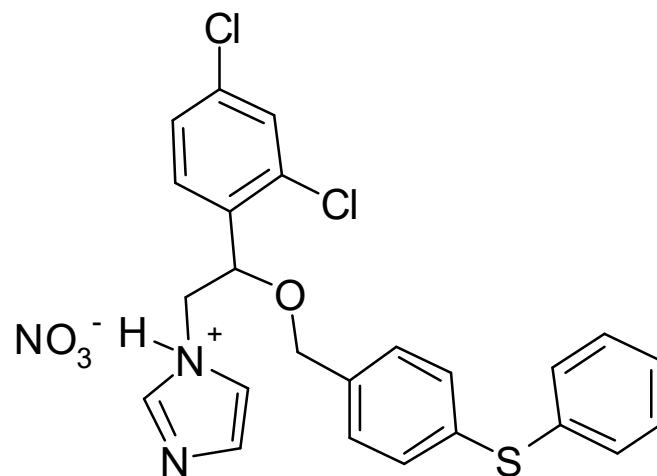
- spectrum: dermatophytes, *Candida*, *Malassezia*, *Geotrichum* ...
- skin and vaginal candidoses
- mostly external use



econazole

Gyno-Pevaryl® supp.
vag.

- nitrate

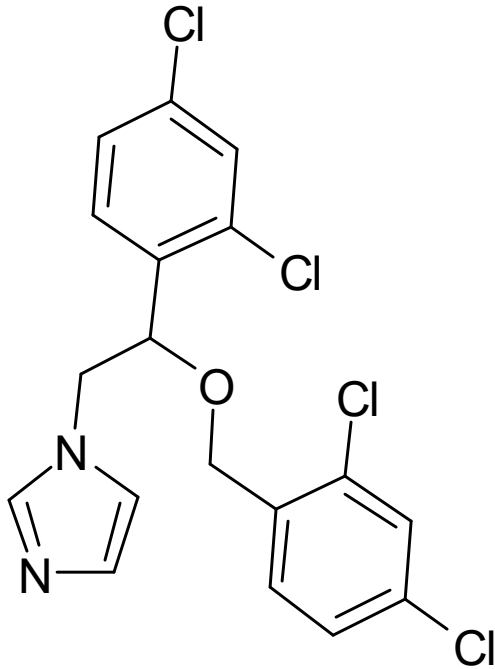


fenticonazole

(fenticonazolium nitrate)

Lomexin® crm. vag.

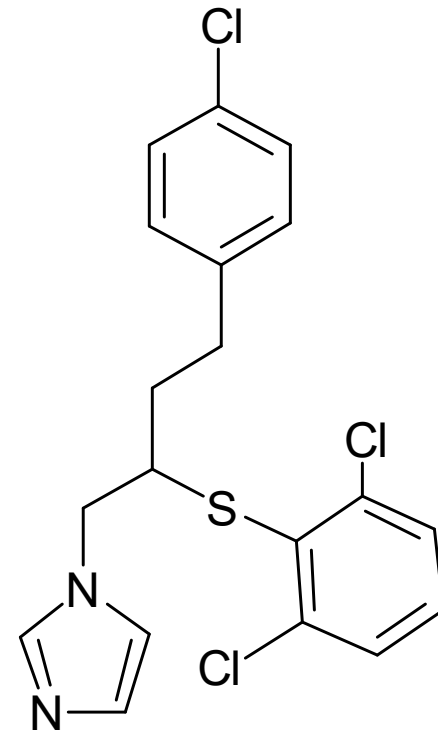
Azoles Imidazole derivatives



miconazole

Klion-D® vag. tbl., Loramyc® tbl.

- spectrum: *Candida*
- vaginal mycoses and mycoses of GIT

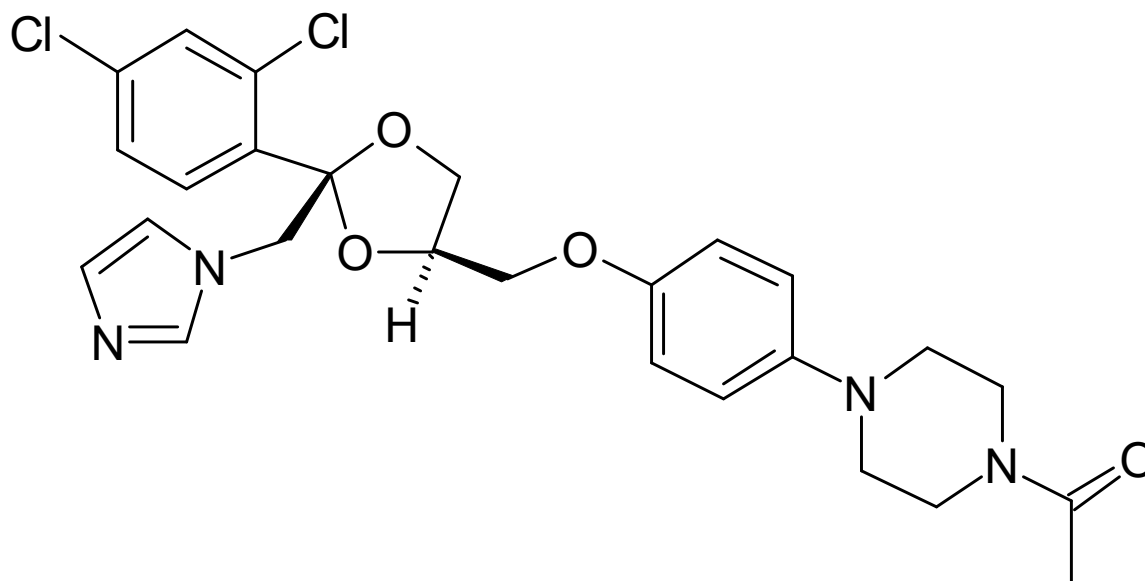


butoconazole

Gynazol®

- spectrum: dermatophytes, *Candida*, *Malassezia*, *Geotrichum* ...
- skin and vaginal candidoses

Azoles Imidazole derivatives



ketoconazole

Ketoderm[®] crm., Nizoral[®] tbl. (not authorised in ČR)

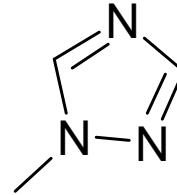
- spectrum: dermatophytes, *Candida*, *Malassezia*, *Geotrichum* ...
- skin, vaginal, GIT candidoses
- both external and internal use

Azoles
1,2,4-triazole derivatives

R¹

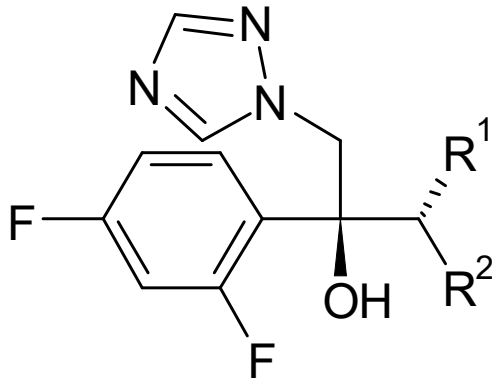
R²

H

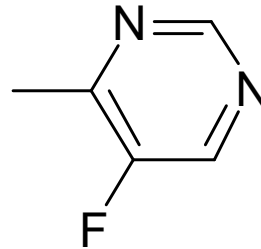


fluconazole

Diflucan cps. ...



CH₃

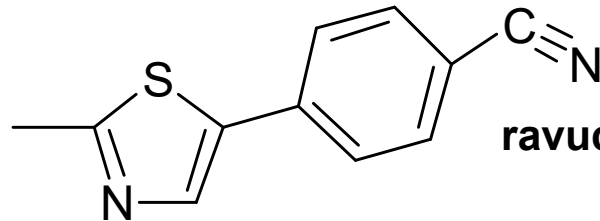


voriconazole

Vfend tbl.

- systemic mycoses, p.o. application
- namely *Candida*, *Cryptococcus*

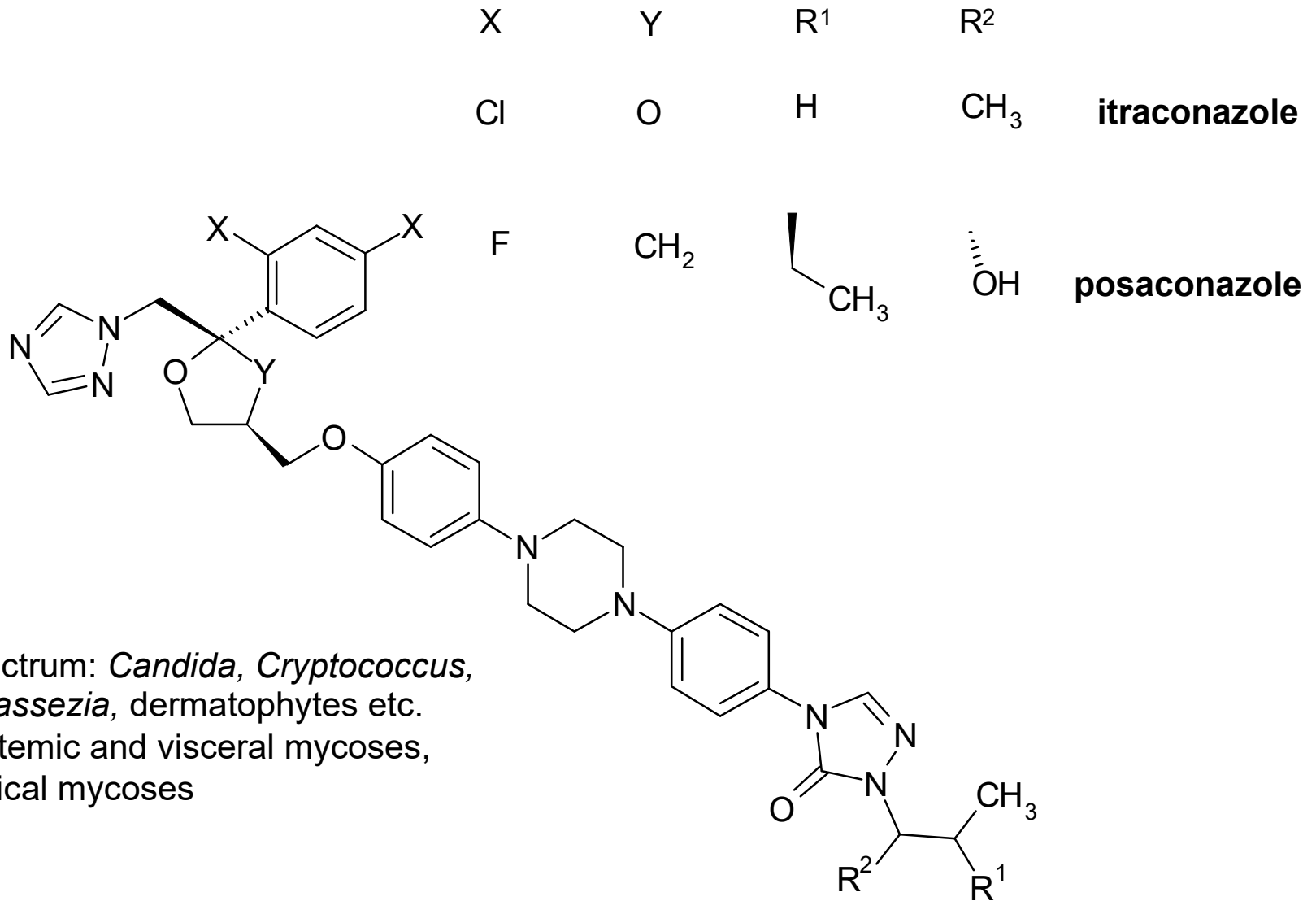
CH₃



ravuconazole

Azoles

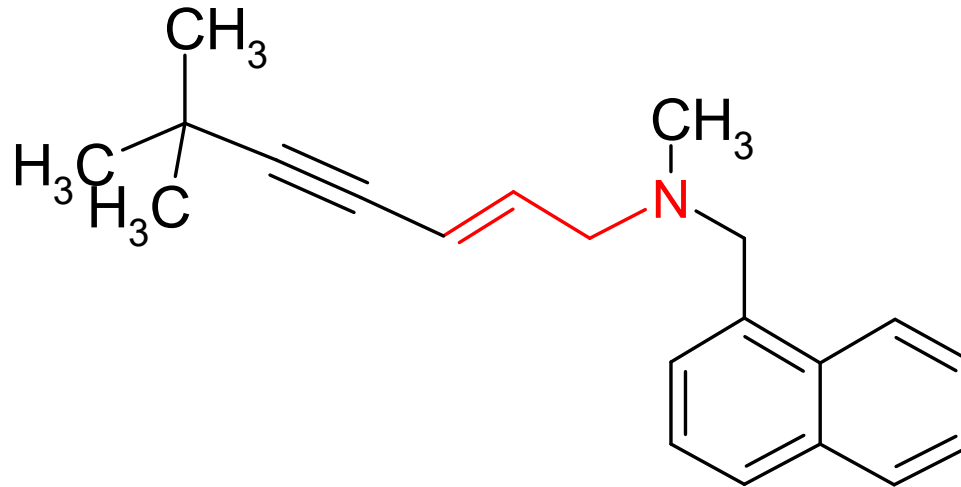
1,2,4-triazole derivatives



- spectrum: *Candida*, *Cryptococcus*, *Malassezia*, dermatophytes etc.
- systemic and visceral mycoses, tropical mycoses

4. Allylamines

- mechanism of action: squalene epoxidase inhibition



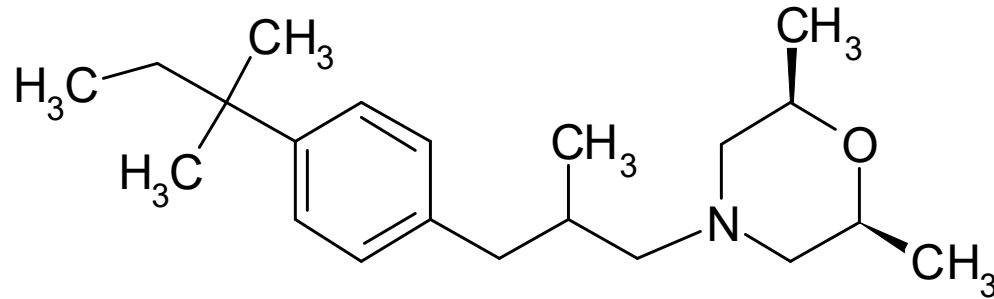
terbinafine

Lamisil®

- spectrum: dermatophytes, *Candida parapsilosis*

5. Morpholine derivatives

- mechanism of action: inhibition of 2 enzymes in final stage of ergosterole synthesis:
 Δ^{14} reductase and Δ^8 - Δ^7 isomerase

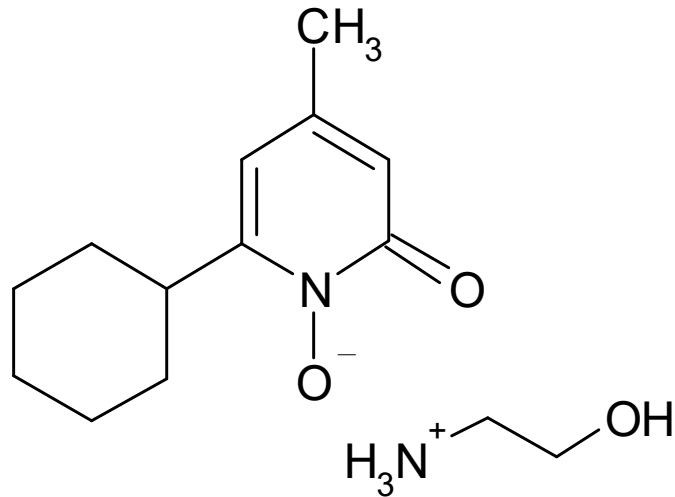


amorolfine

Loceryl®

- spectrum: dermatophytes, *Candida*
- topical treatment of superficial mycoses (including those of nails = onychomycoses)

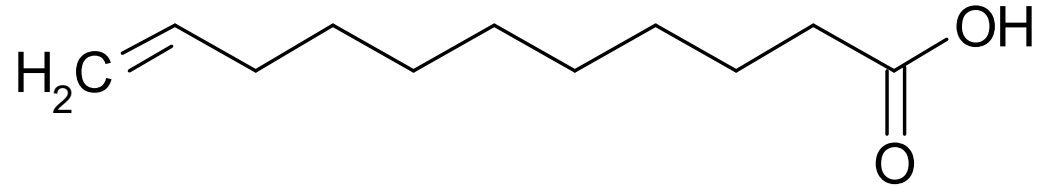
6. Ciclopirox olamine



Batrafen[®], Mycooster[®]

- spectrum: dermatophytes, *Candida*, *Malassezia*
- superficial skin and nail mycoses, candidoses, dermatophytoses

7. Unsaturated fatty acids and their salts



Undecylenic acid

undec-10-enoic acid

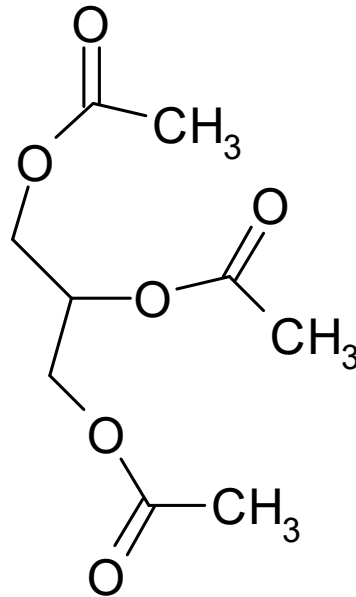
Acidum undecylenicum PhEur

▪ traditional constituent of MS (*magistralliter* = pharmacy-made) antimycotic preparations

▪ zinc and copper salts also used

Zinci undecylenas PhEur

8. Esters of glycerole



triacetin

propan-1,2,3-triyl triacetate

Triacetinum PhEur