



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

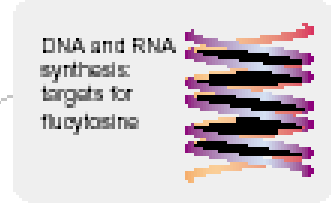
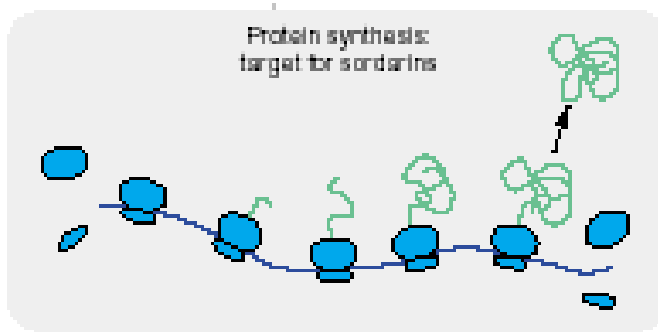
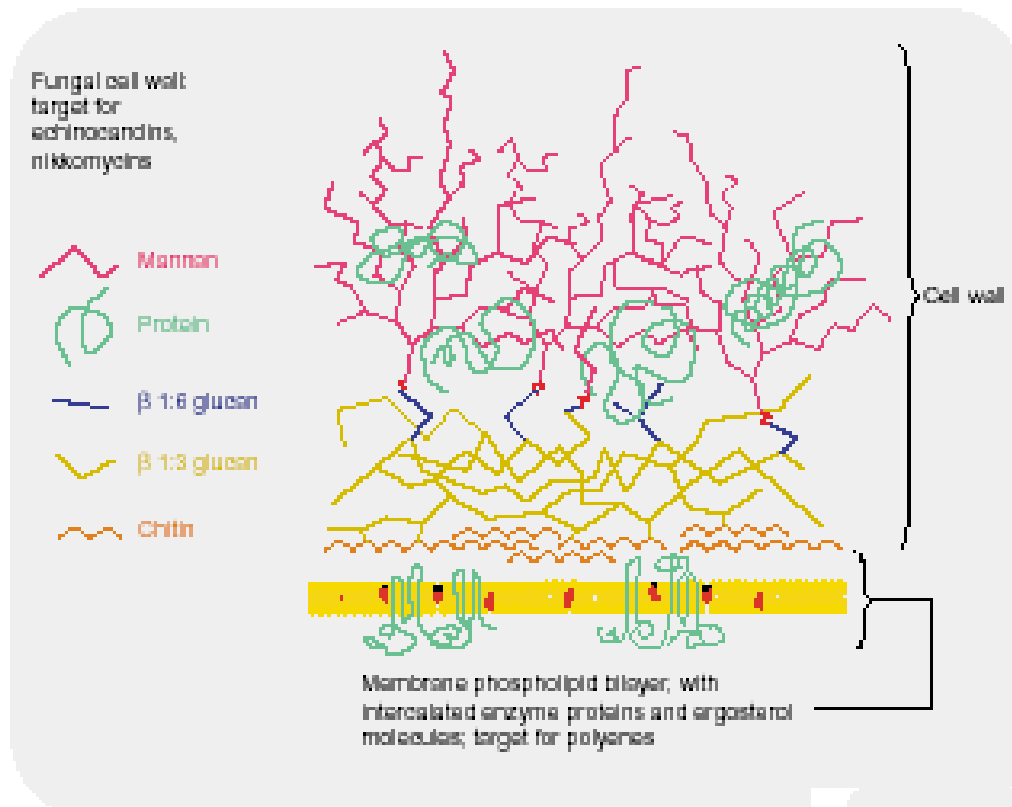
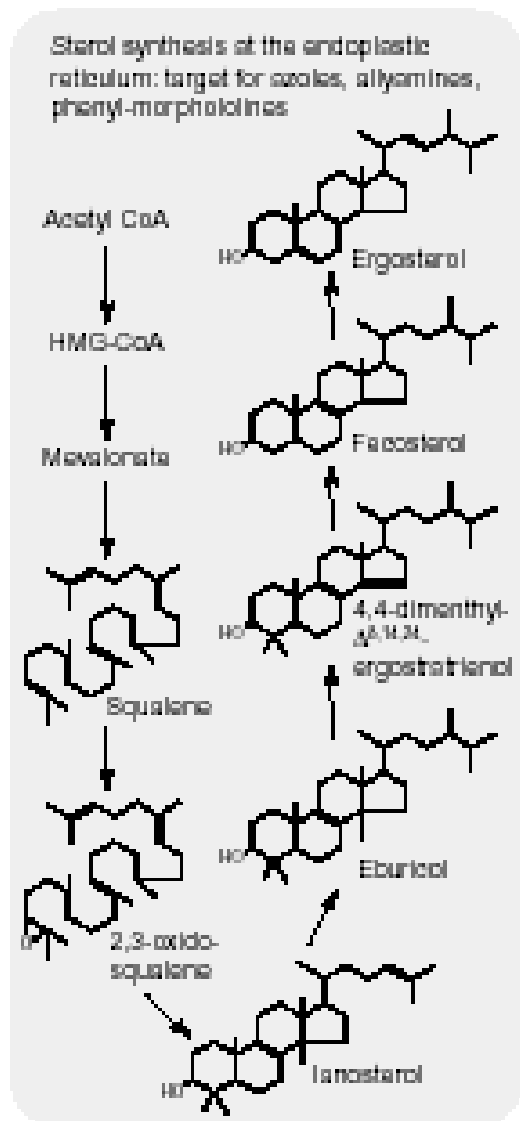
## Antimycotics

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

# Classification of antimycotics

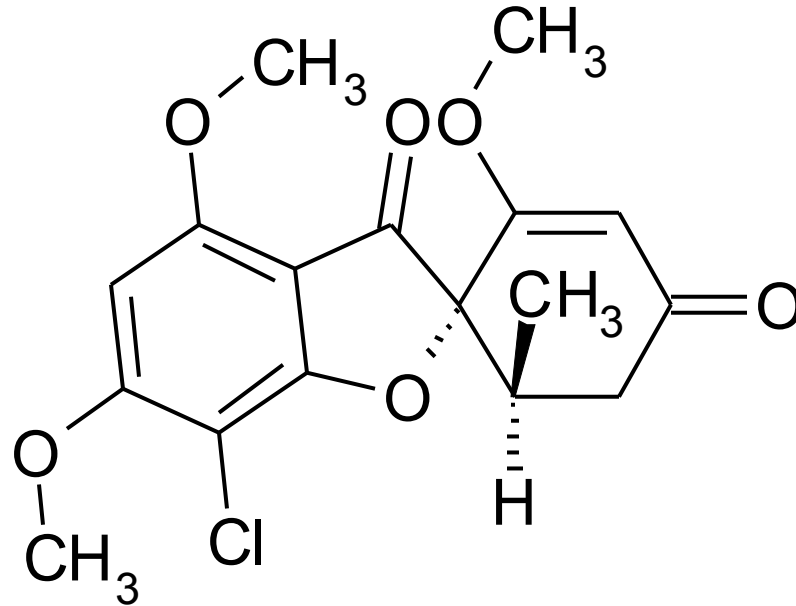
1. Antimycotic antibiotics
  - 1.1 Griseofulvine
  - 1.2 Polyene antibiotics
  - 1.3 Echinocandins
  - 1.4 Sordarins
2. Flucytosine
3. Azoles
  - 3.1 Imidazole derivatives
  - 3.2 Triazole derivatives
4. Allylamines
5. Morpholines
6. Ciclopirox olamin
7. Unsaturated fatty acids and their salts
8. Esters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

# Sites of action of particular types of antimycotics



## 1. Antimycotic antibiotics

### Griseofulvine

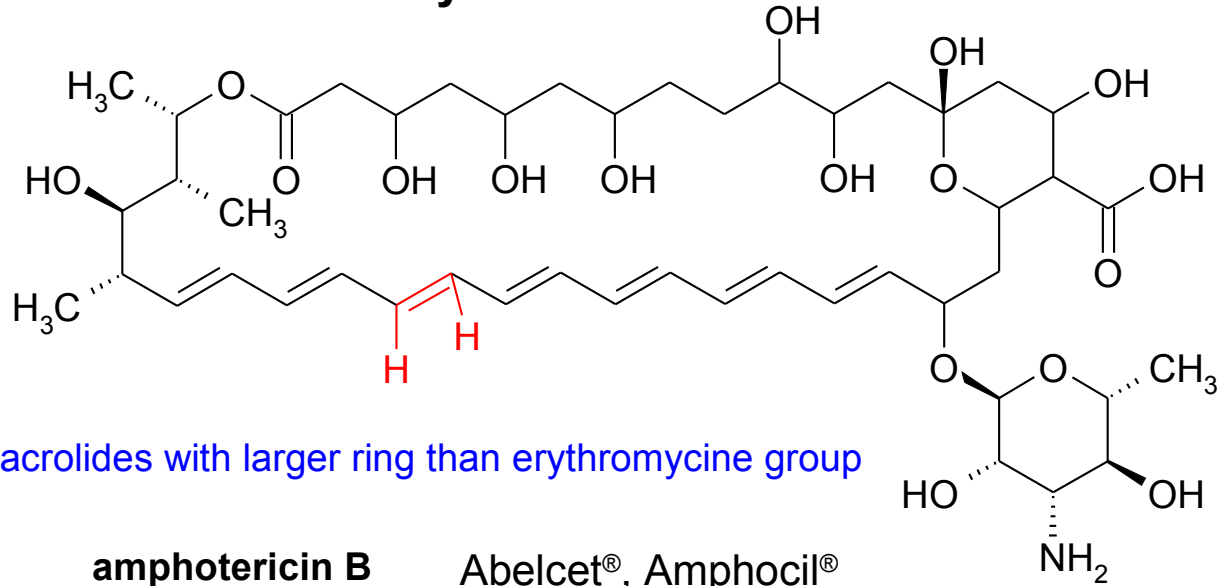


- antibiotic isolated from *Penicilium griseofulvum* in 1939
- site of action: microtubules formation
- high toxicity (liver)
- spectrum: dermatophytes

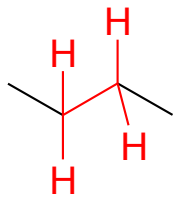
*Griseofulvinum PhEur*

# Antimycotic antibiotics

## Polyene antibiotics



- systemic candidoses and aspergiloses, sepses caused by fungi



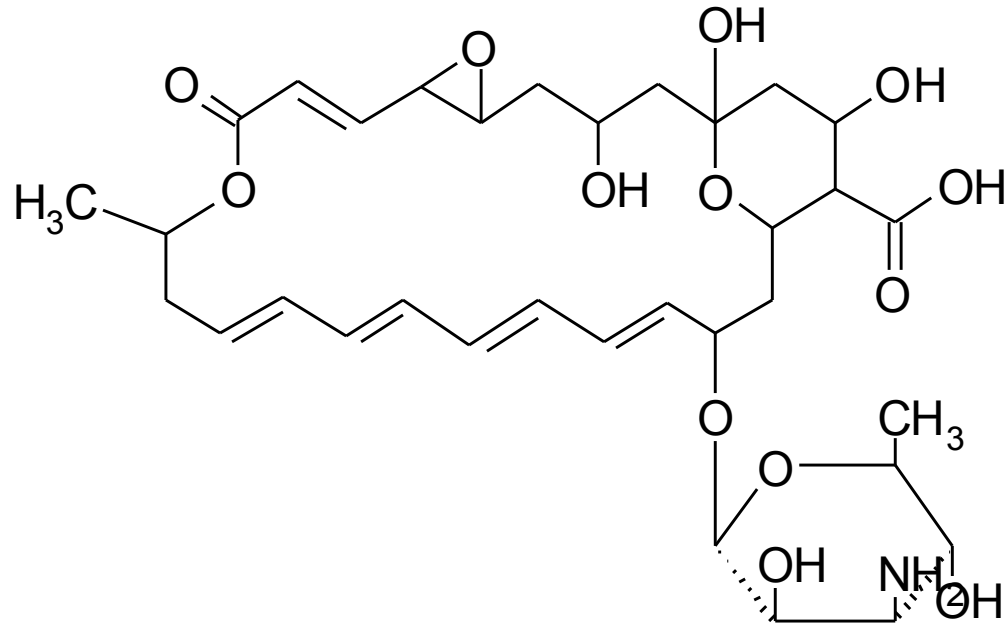
**nystatin**

Fungicidin<sup>®</sup> ung., Macmiror complex<sup>®</sup> ung., sup. (+ furazolidone)

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

- in most externally

Antimycotic antibiotics  
Polyene antibiotics



**natamycin**

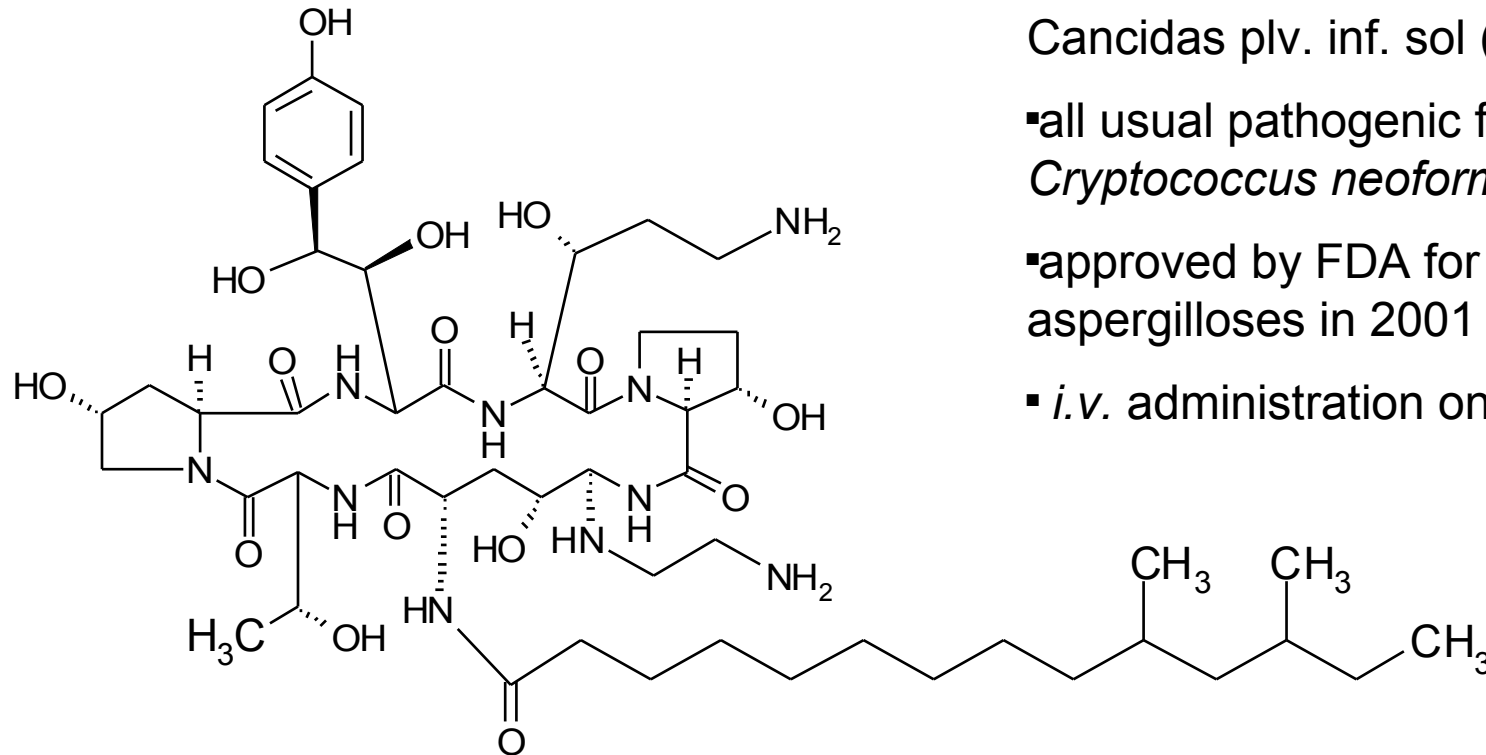
Pimafucin ® , Pimafucort ®

•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  $\beta$ -1,3-glucans of the cell wall



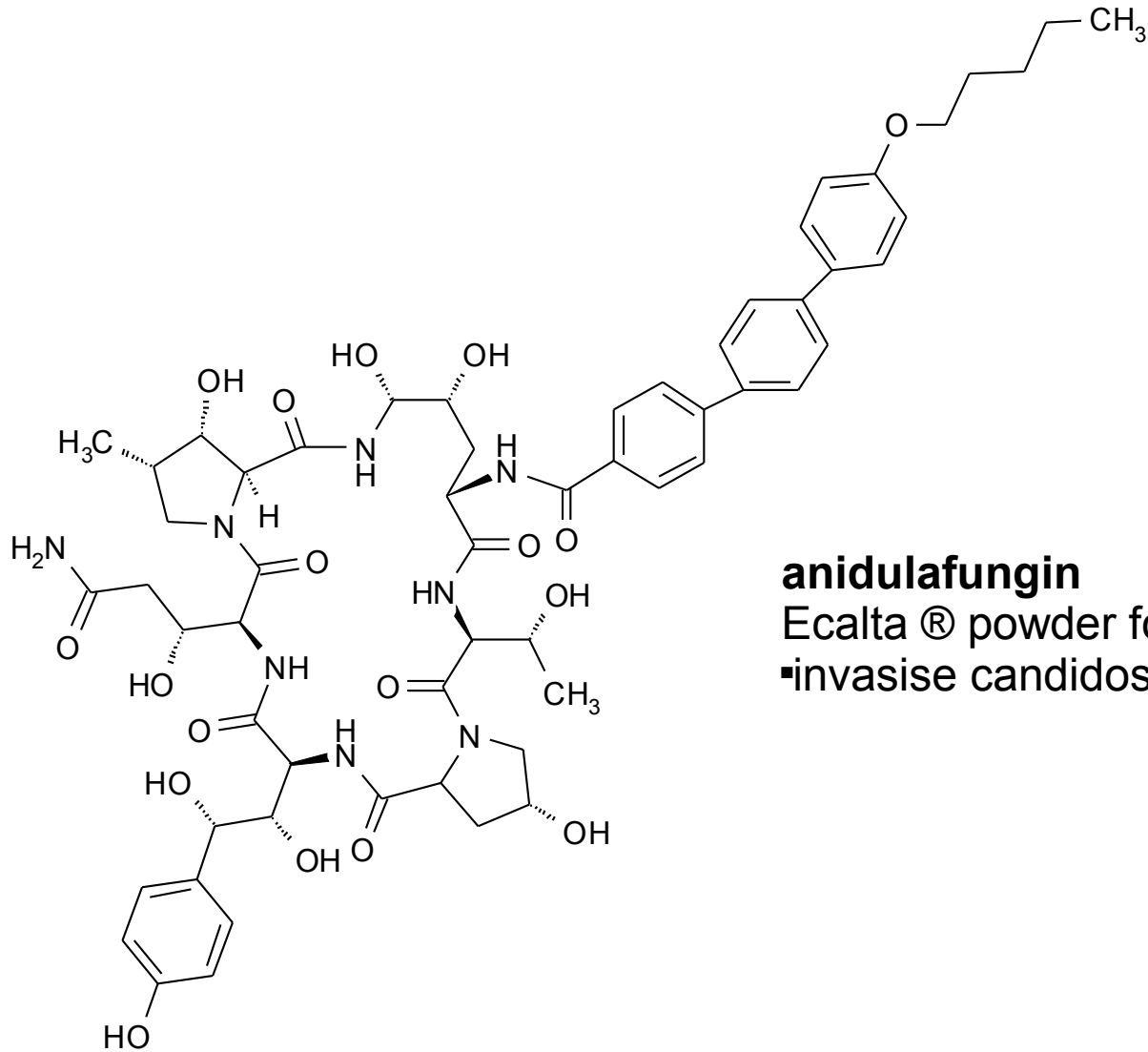
### caspofungin

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

- preparation of semi-synthetic micafungin (FK 463)

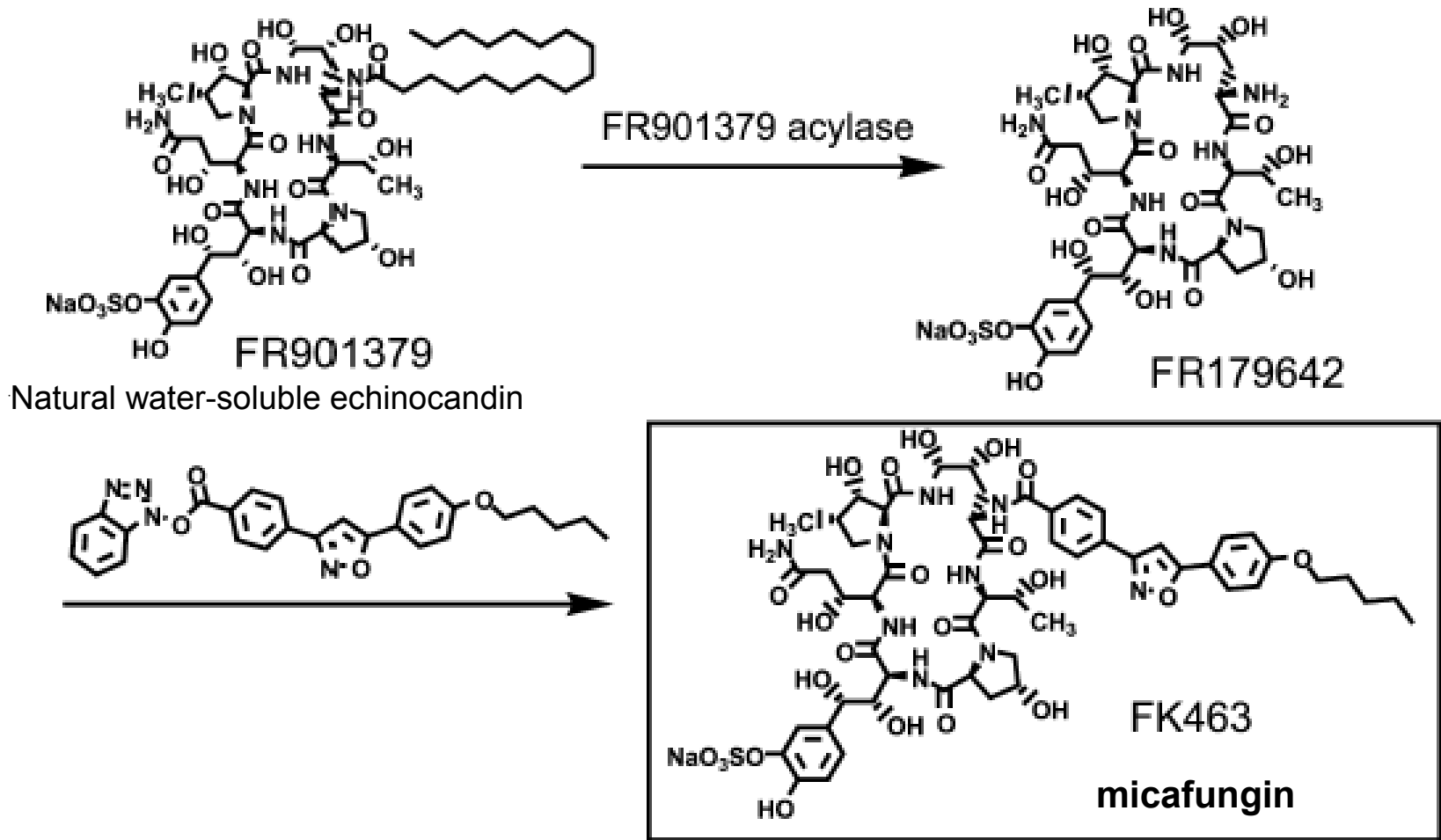
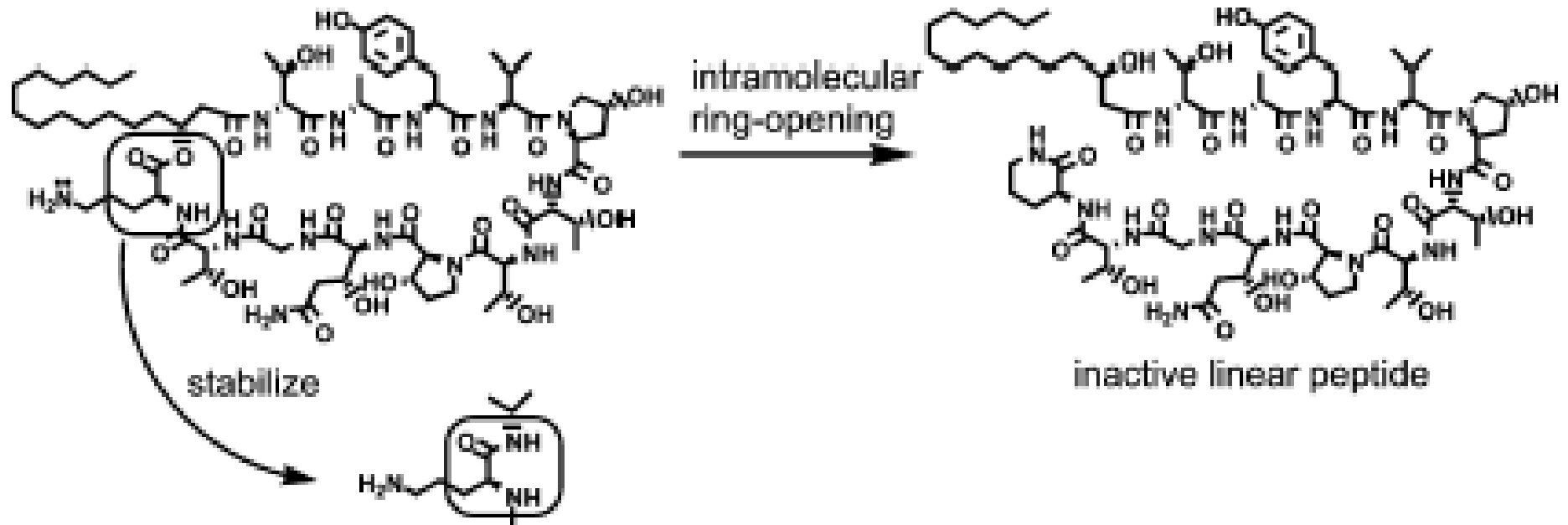


Fig. 8. Deacylation of FR901379 and synthesis of FK463.

# Antimycotic antibiotics

## Echinocandins

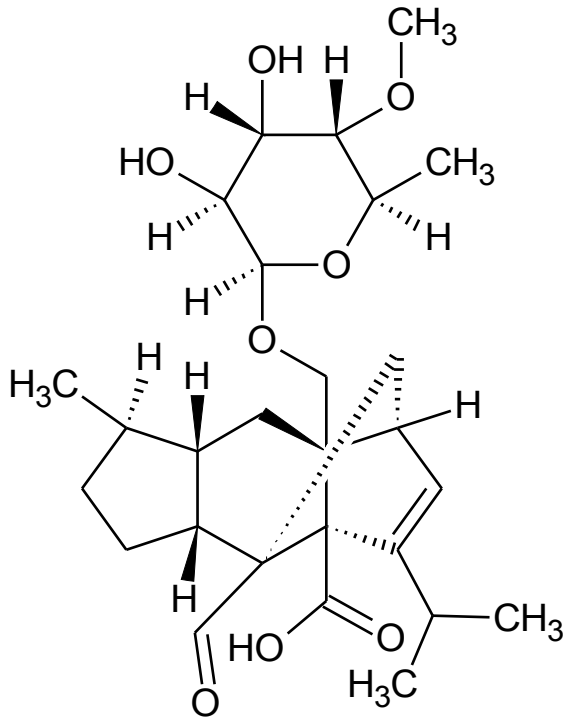
Intramolecular cleavage of the lactone ring –  
lactone aminolysis – in compound FR901469



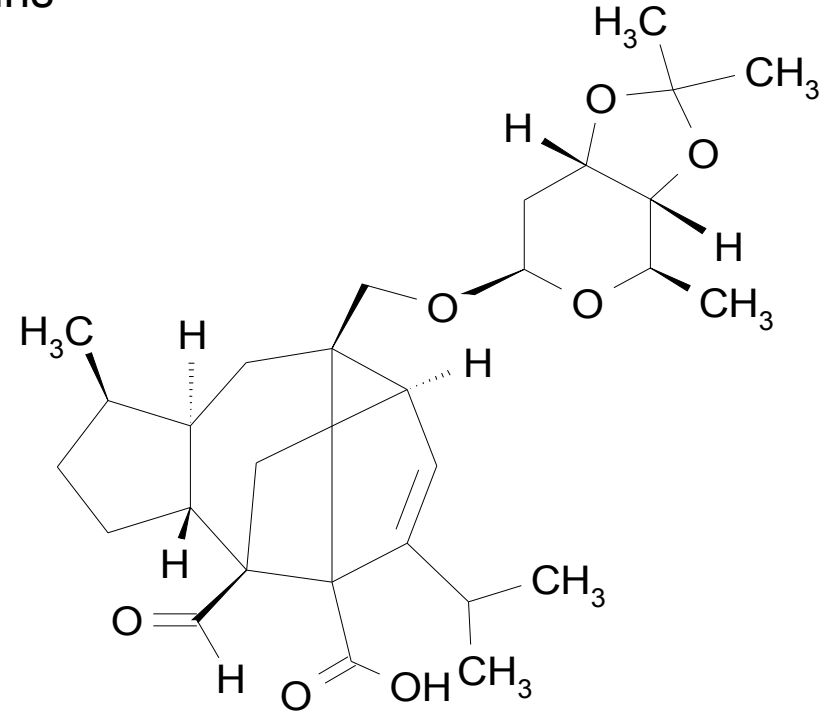
- replacement of the ester bond with the amide one avoids this peptide ring-opening

# Antimycotic antibiotics

## Sordarins



**sordarin**



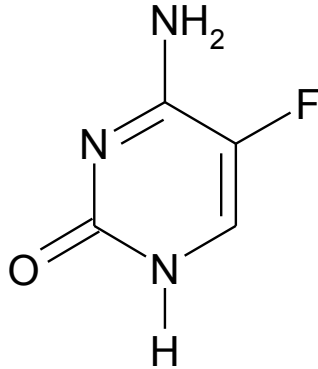
**GM 193663**

- metabolite of the mold *Sordaria araneosa*
- first isolated in Sandoz, Switzerland, 1969
  - mode of action: protein synthesis 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.

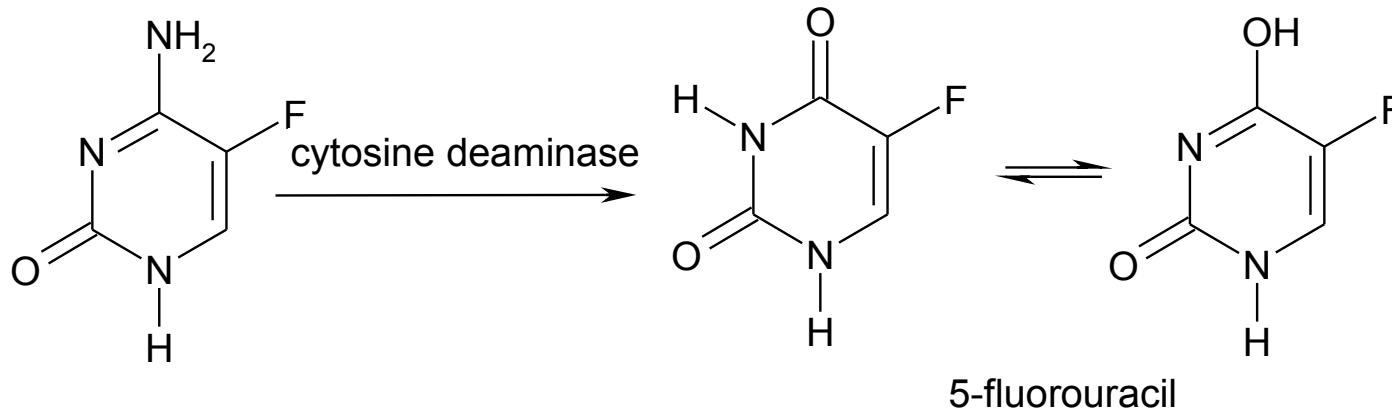
## 2. Flucytosine



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

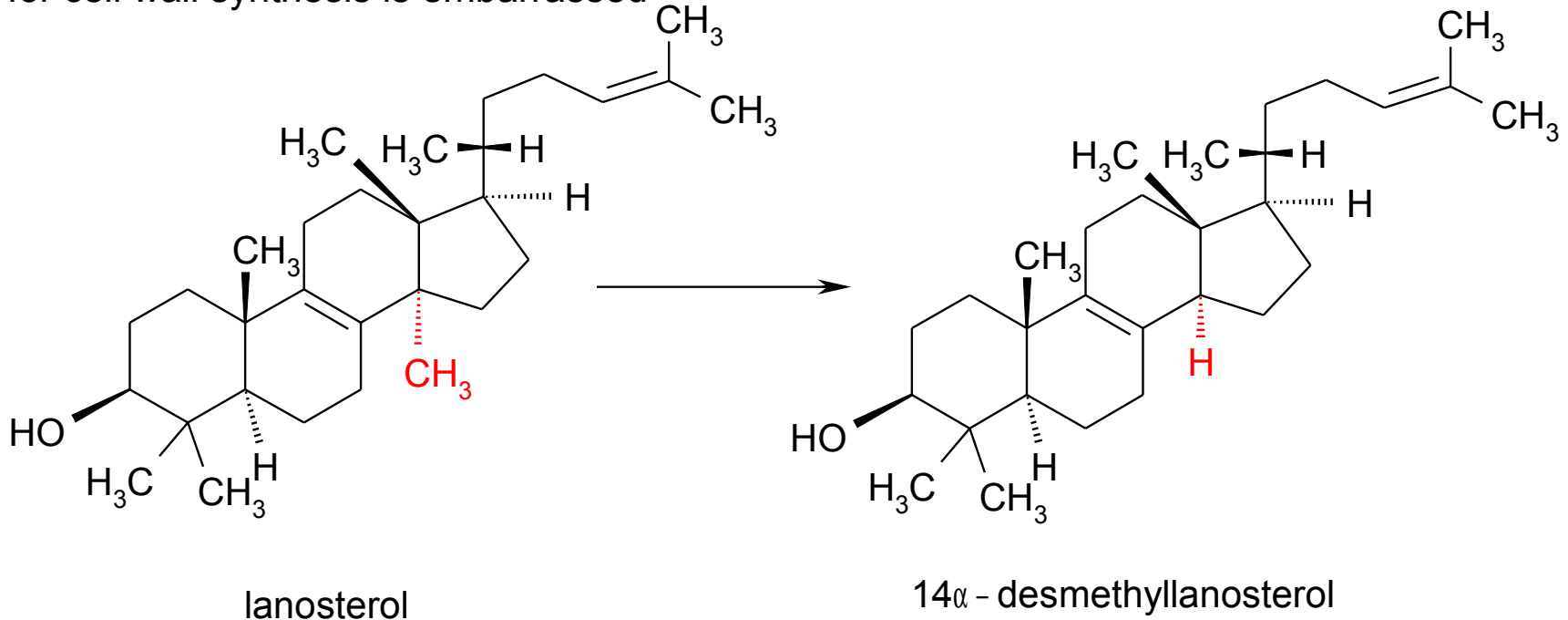
▪mechanism of action: inhibition of  $14\alpha$ -demethylation of lanosterol in biosynthesis of ergosterol

▪in some species also inhibition of following  $\Delta^{22}$  desaturation

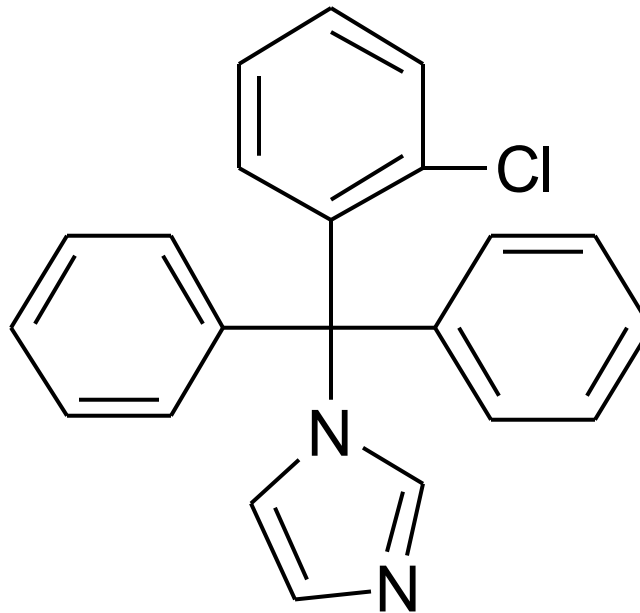


▪ergosterol is replaced with non-functional sterols  $\Rightarrow$  permeability and fluidity of the cell

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<sup>®</sup> , Candibene<sup>®</sup> ...

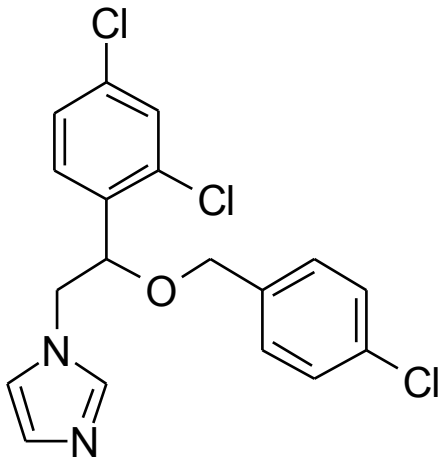
▪mostly external use

# Azoles

## Imidazole derivatives

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

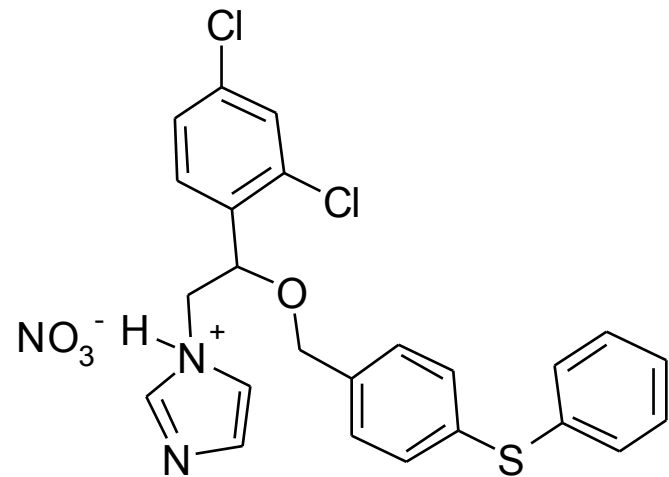
- spectrum: dermatophytes, *Candida*, *Malassezia*, *Geotrichum* ...
- skin and vaginal candidoses
- mostly external use



### econazole

Gyno-Pevaryl® supp.  
vag.

- nitrate



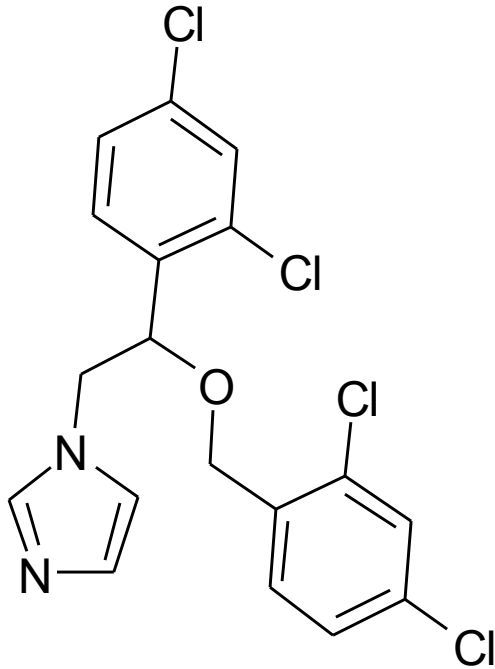
### fenticonazole

(fenticonazolium nitrate)

Lomexin® crm. vag.



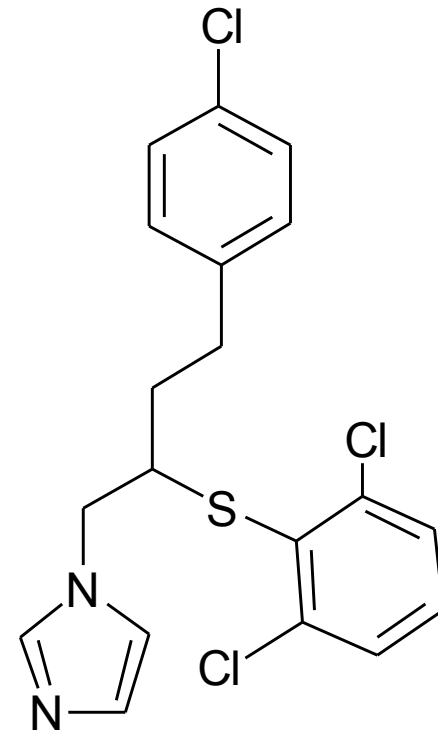
## Azoles Imidazole derivatives



### **miconazole**

Klion-D® vag. tbl., Loramyc® tbl.

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

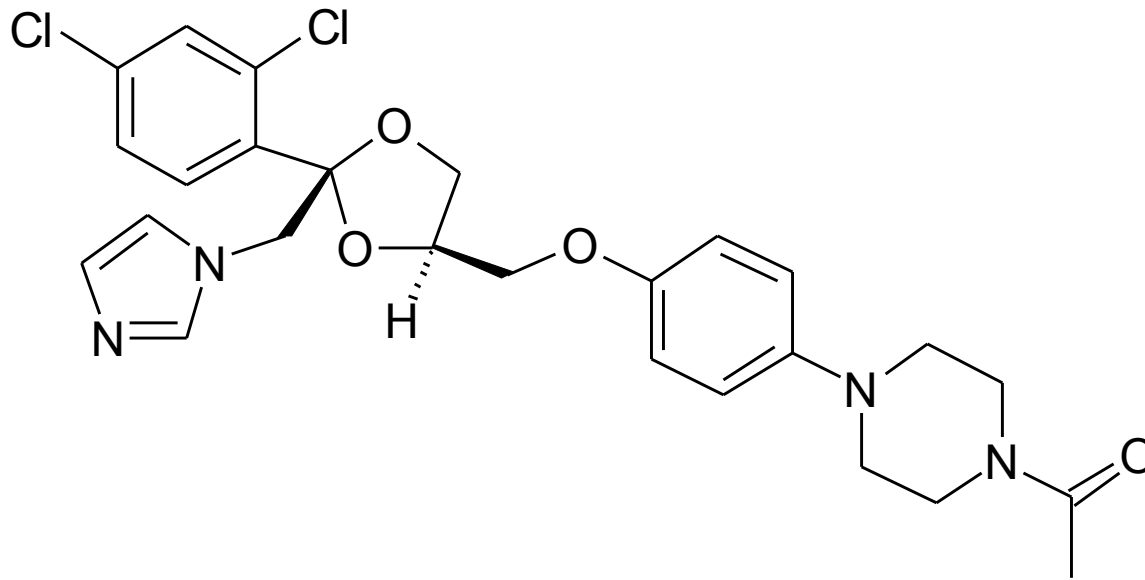


### **butoconazole**

Gynazol®

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

Azoles  
Imidazole derivatives



**ketoconazole**

Ketoderm<sup>®</sup> crm., Nizoral<sup>®</sup> tbl. (not authorised in ČR)

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

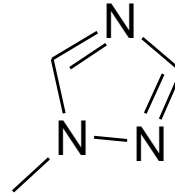
# Azoles

## 1,2,4-triazole derivatives

R<sup>1</sup>

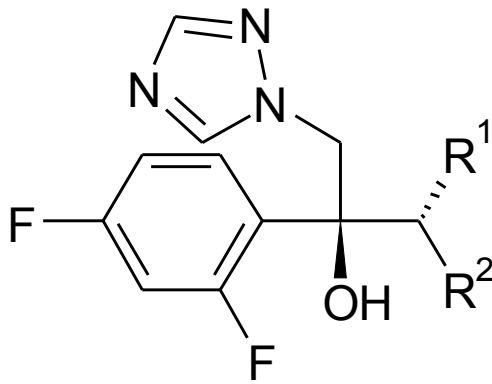
R<sup>2</sup>

H

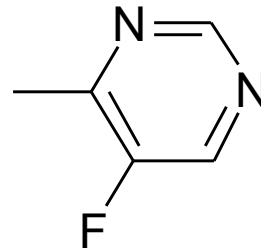


**fluconazole**

Diflucan cps. ...



CH<sub>3</sub>

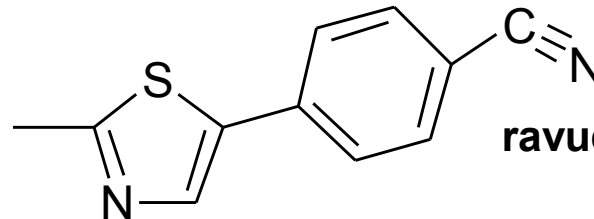


**voriconazole**

Vfend tbl.

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

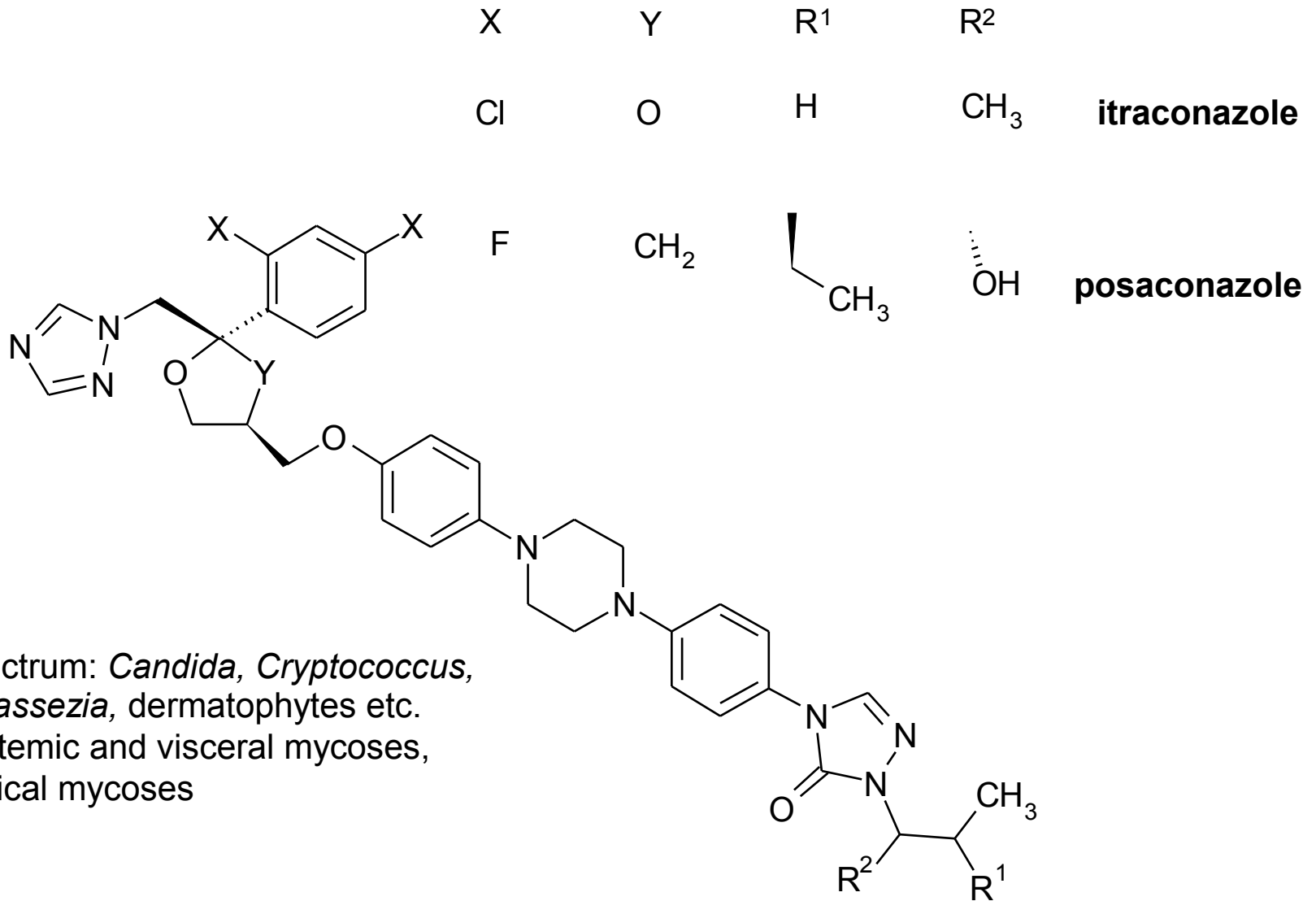
CH<sub>3</sub>



**ravuconazole**

# Azoles

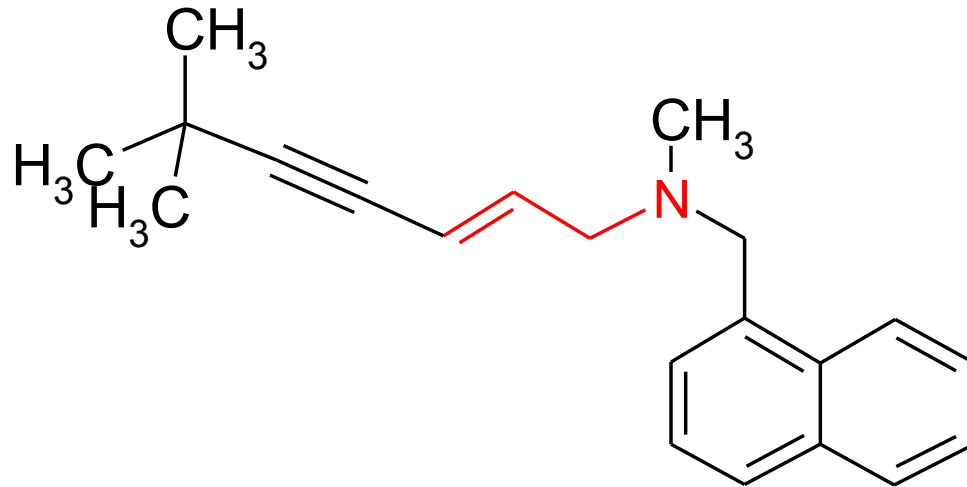
## 1,2,4-triazole derivatives



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

## 4. Allylamines

- mechanism of action: squalene epoxidase inhibition



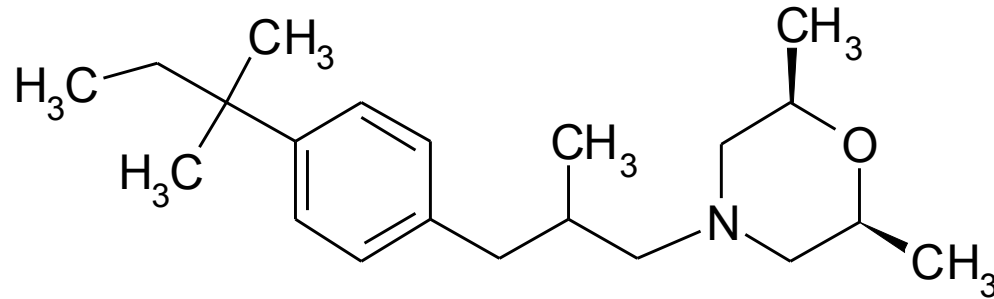
### terbinafine

Lamisil®

- spectrum: dermatophytes, *Candida parapsilosis*

## 5. Morpholine derivatives

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

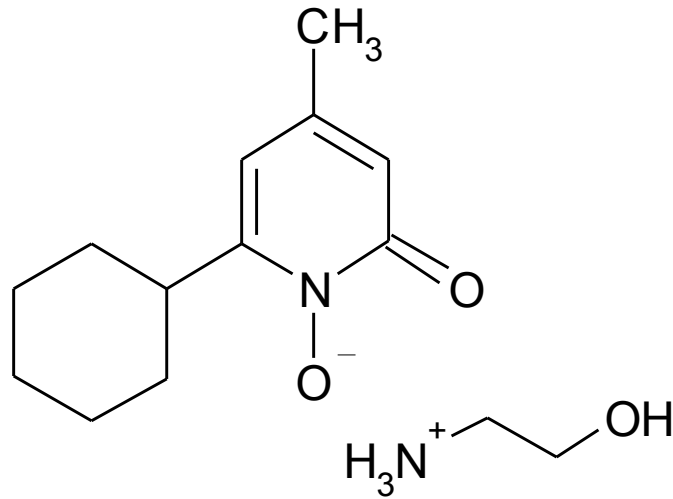


### amorolfine

Loceryl<sup>®</sup>

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

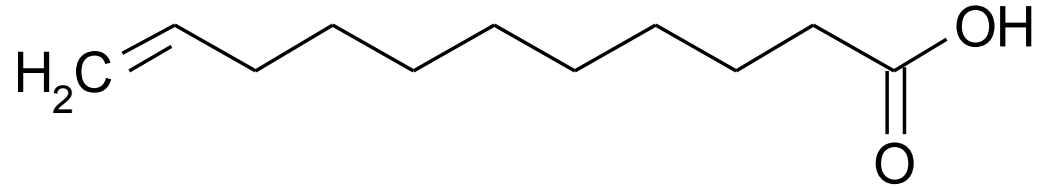
## 6. Ciclopirox olamine



Batrafen<sup>®</sup>, Mycooster<sup>®</sup>

- 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*

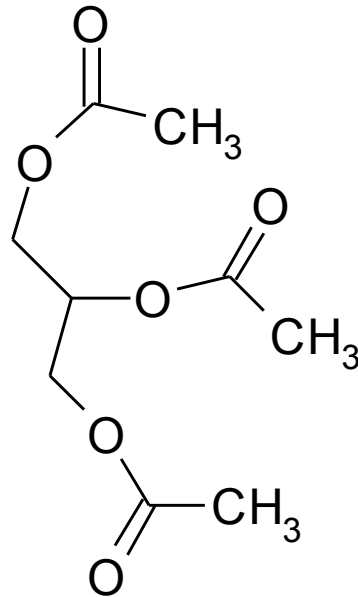
▪ traditional constituent of MS (*magistralliter* = pharmacy-made) antimycotic preparations

▪ zinc and copper salts also used

*Zinci undecylenas PhEur*



## 8. Esters of glycerole



### **triacetin**

propan-1,2,3-triyl triacetate

*Triacetinum PhEur*