ATHENA
International Conference
Approaching The Severely Infected Patient
19-20 November 2015
Divani Caravel Hotel
Athens Greece

New or under development antibiotics and antifungals

Azoles-Echinocandins

George Dimopoulos MD, PhD, FCCP, FCCM

As. Prof Critical Care Medicine

Critical Care Department, University Hospital ATTIKON

Medical School, University of Athens, Greece

gdimop@med.uoa.gr

ATTIKON

Faculty disclosure (2012-15)

Advisory Boards

- MERCK USA, Bayer Europe, MSD Europe, Clinigen UK, Cardeas USA, Virogates Denmark, Cempra USA, Tetraphase USA, Gilead UK

Lectures fees

- Pfizer (Asian Pacific, USA, Korea, Taiwan, Australia)
- Astellas (UK, Japan)
- MediaHealth New Delhi –India
- Baxter France
- Bayer Germany

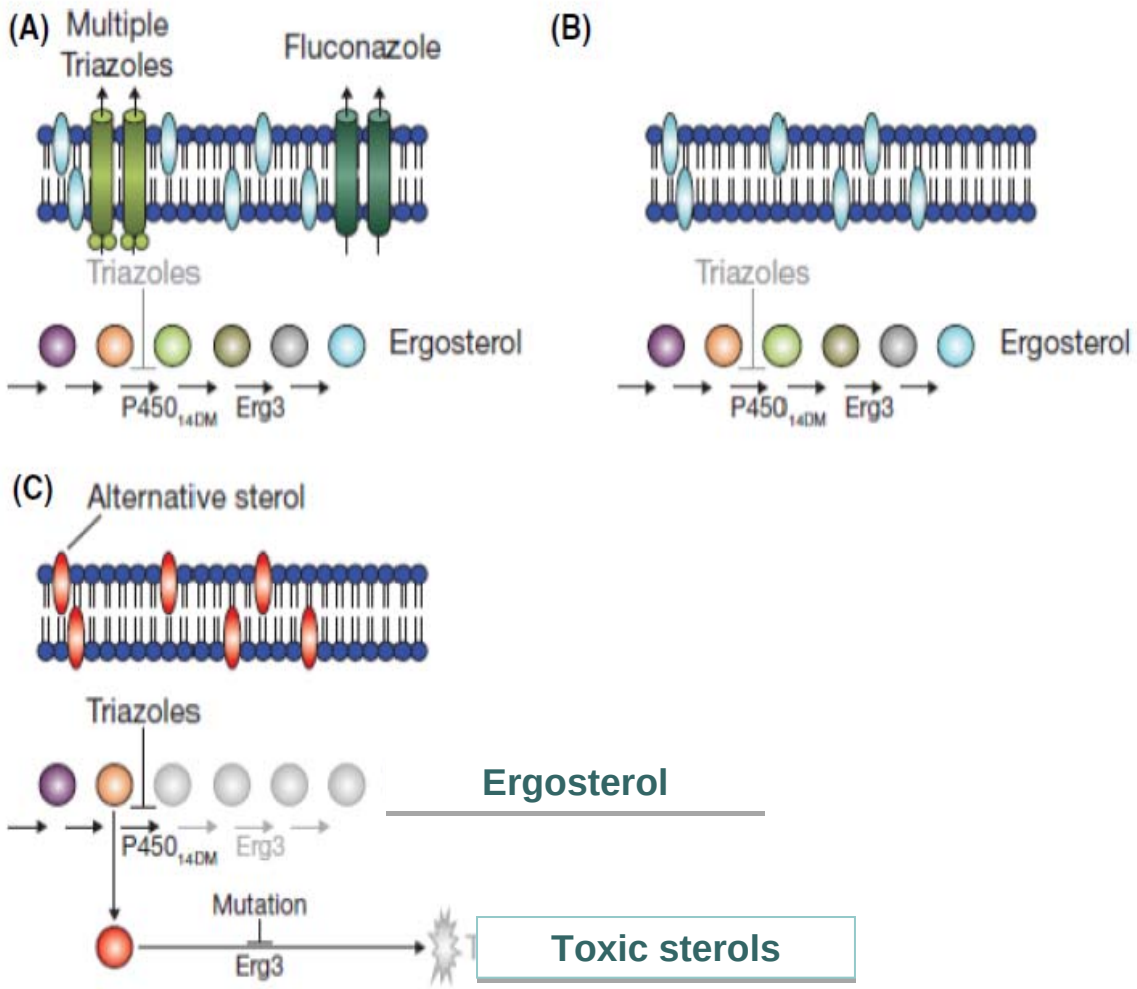
Research Grants

- EU-FP_7 Project
- EU-Horizon FP_8 Project

Societies

- ESICM, ERS, ESCMID, International Society of Chemotherapy Asian-Pacific Society of Infectious Diseases

Azole resistance mechanisms in *Candida albicans*



Sanguinetti M. Mycoses, 2015, 58 (Suppl. 2), 2–13

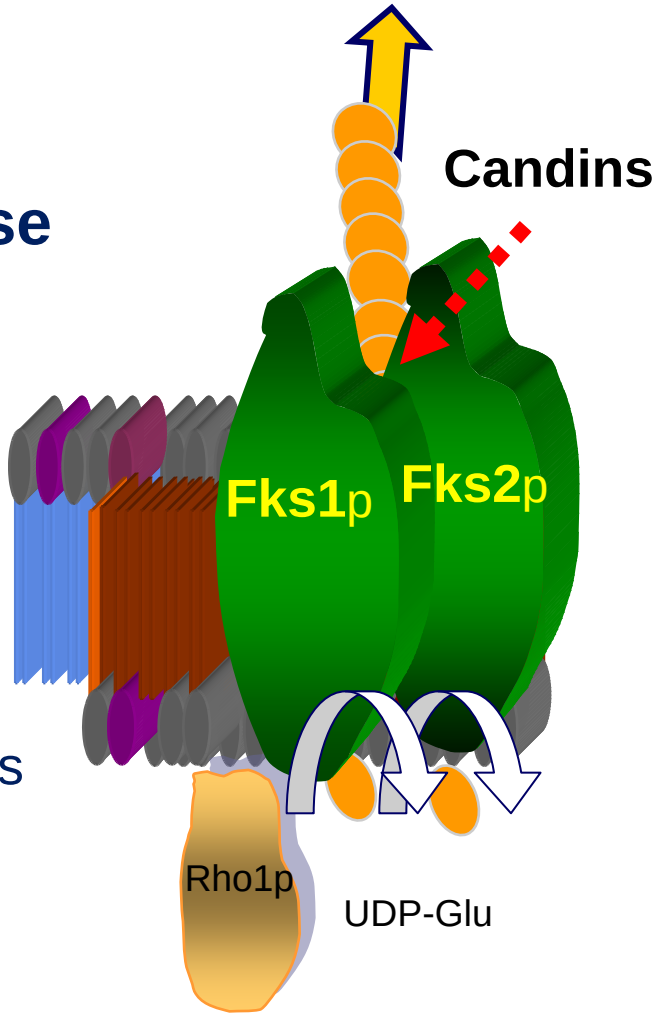
Echinocandins Inhibit Glucan Synthase

Inhibit β -1,3-D-glucan synthase

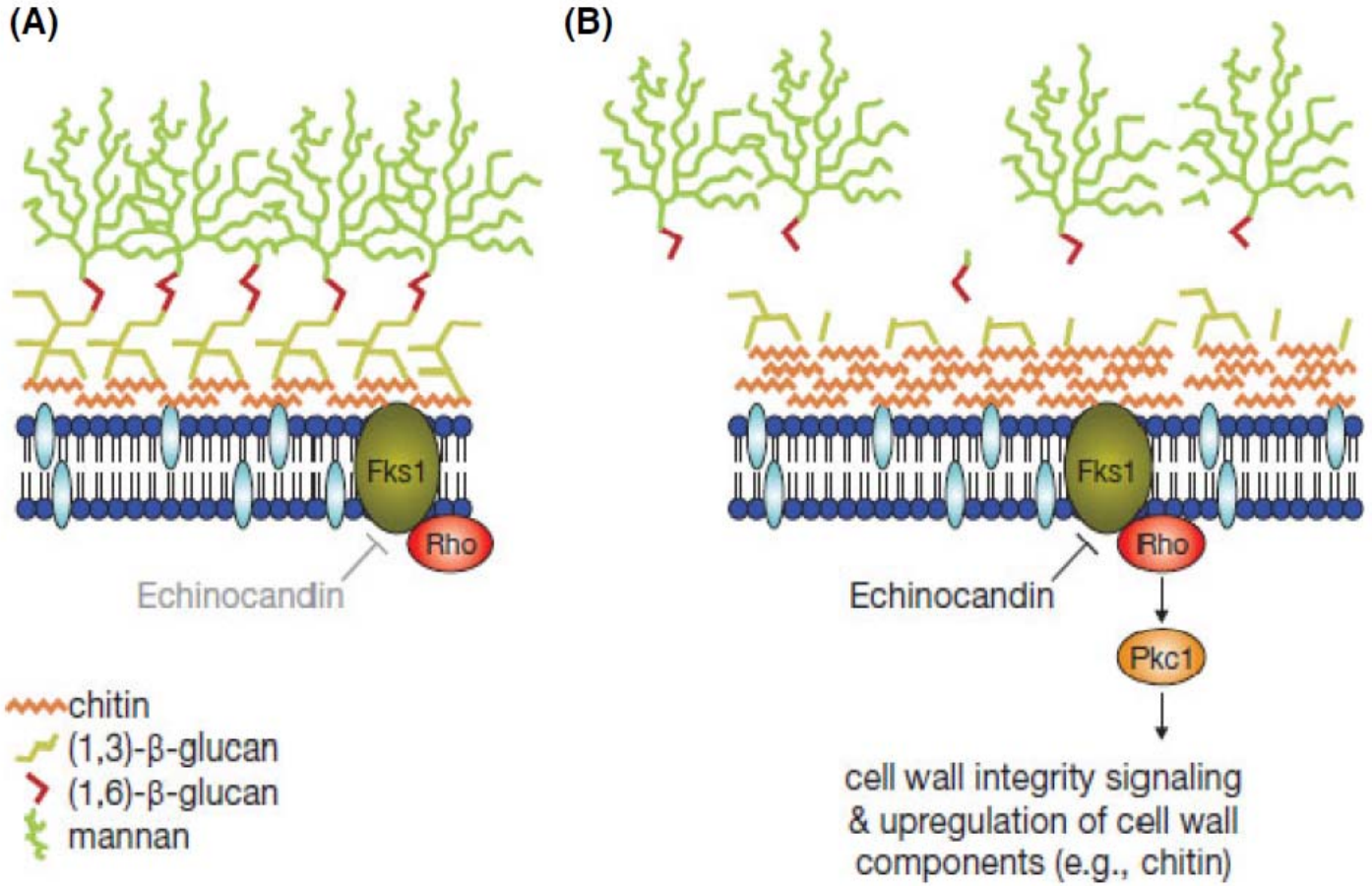
- Non-competitive with substrate
- Do not inhibit syn. of other glucans

β -1,3-D-glucan synthase

- Unresolved protein complex
- Catalytic subunit (Fks1/2)
- Regulatory subunit (Rho1)
- GS encoded by 3 FKS-related genes in *Candida* spp.



Echinocandin resistance mechanisms in *Candida albicans*



Sanguinetti M. Mycoses, 2015, 58 (Suppl. 2), 2–13

New triazoles

Drug	Mechanism	Via	Spectrum
Isavuconazole	Inhibition of ergosterol synthesis	Oral and IV	*Candida* *Aspergillus* spp Dermatophytes
Ravuconazole	Inhibition of ergosterol synthesis	Oral and IV	Similar to Isavuconazole + *Cryptococcus* spp. *Chaetomonium* spp, *Trypanosoma cruzi*
Albaconazole	Inhibition of ergosterol synthesis	Oral	*Candida* and *Aspergillus* spp + *Paecilomyces* spp., *Cryptococcus* spp., *Chaetomonium* spp, *Trypanosoma cruzi,* *Malassezia spp.*

Isavuconazole

- **Broad spectrum**

-*In-vitro* activity against *Aspergillus* spp, fluconazole susceptible and resistant *Candida spp*, *Cryptococcus* spp, *Coccidioides* spp and rare yeasts
-Limited activity against Mucorales
-Poor activity against *Fusarium* spp. and Scedosporium prolificans

- **PO and IV formulations**
- **Excellent bioavailability**
- **Highly protein bound (98%)**
- **Metabolized primarily by the liver and eliminated in the feces**
- **Dose adjustment : in patients with liver dysfunction**
- **Phase III studies : three different doses (50 mg/day, 100 mg/day, 400 mg/week) of isavuconazole compared with fluconazole**

Schmitt-Hoffmann A et al. Antimicrob Agents Chemother 2006; 50:279–285.

Isavuconazole
advantages and disadvantages

Drug	Company	Advantages	Disadvantages
Isavuconazole	Basilea Pharmaceutica Ltd	▪ broad spectrum ▪ water soluble - **no need to cyclodextrin** ▪ long acting - **once daily up to once weekly dosing** ▪ limited drug interactions	

Ravuconazole

Activity against

- *in vitro Candida* spp., including many fluconazole resistant non-albicans *Candida* spp, *Aspergillus* spp,

Variable activity against several other filamentous fungi

Poor activity against

-*Fusarium* spp. and *Scedosporium prolificans* but displays favorable activity against *Scedosporium apiospermum*

Combination

-with liposomal amphotericin B is antagonistic, but its efficacy against *Aspergillus* spp. in animal models increases when in combination with micafungin

PO and IV formulations, highly protein bound (98%), undergoes liver metabolism, dose 400mg/day

Hata K, Kimura J, Miki H, et al. In vitro and in vivo antifungal activities of ER-30346, a novel oral triazole with a broad antifungal spectrum. Antimicrob Agents Chemother 1996; 40:2237–2242.

Ravuconazole
advantages and disadvantages

Drug	Company	Advantages	Disadvantages
Ravuconazole	Eisai Co Ltd	- long acting - very similar to isavuconazole	Potential cross-resistance with other azoles

Albaconazole

Potent *in-vitro* activity against

- *Cryptococcus neoformans*
- *Cryptococcus gattii*
- *Scedosporium prolificans*
- *Scedosporium apiospermum*
- *Candida* spp. and
- *Aspergillus* spp.

Limited data are available regarding clinical use

Girmenia C. Expert Opin Investig Drugs 2009; 18:1279–1295, Paiva et al Curr Opin Infect Dis 2013, 26:168–174

Albaconazole
advantages and disadvantages

Drug	Company	Advantages	Disadvantages
Albaconazole	Laboratorios Uriach & Cia S.A.	- low toxicity - less drug interactions - potent anti- *Aspergillus* activity - long acting - more active than Mica- and Caspo- against *C. parapsilosis*	Cerebrospinal fluid - low concentrations Potential cross-resistance with other azoles

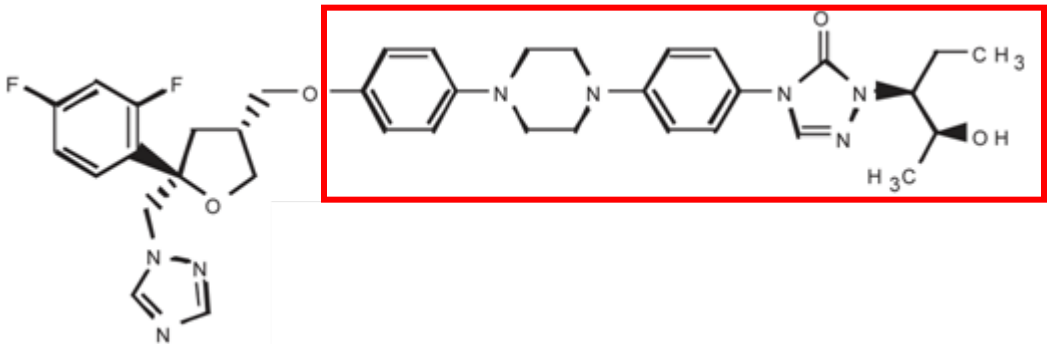
Posaconazole
the already released azole

- **Highly distributed to various site (also bone, CNS, eyes)**
- **⇧ Vd (Volume of Distribution)**
- **In poor renal function without dose adjustment**
- **Fungicidal Activity (*in vitro* and *in vivo*)**
  - against a variety of fungi
  - also in rare and resistant strains
- **Currently Oral suspension**
- **Recently approved the PO formualtion**
- **IV is coming**

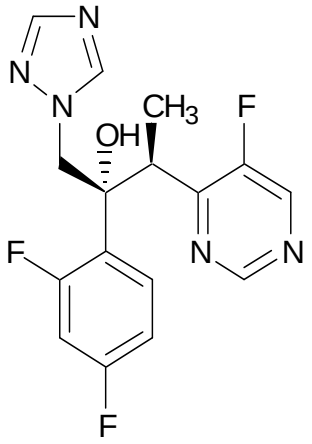
Schiller DS et al, Clin Ther 2007; 29:1862-1887

Posaconazole molecule

Posaconazole

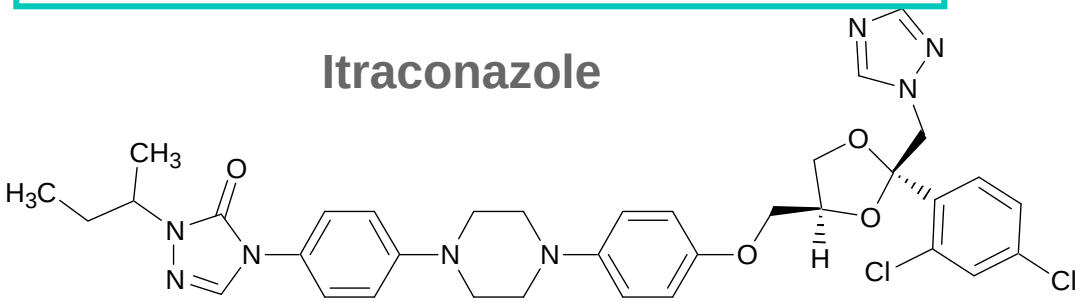


Voriconazole

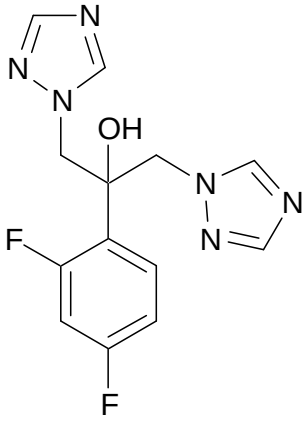


Itraconazole also has a long side chain; voriconazole and fluconazole do not and are sometimes considered compact azoles[2]

Itraconazole



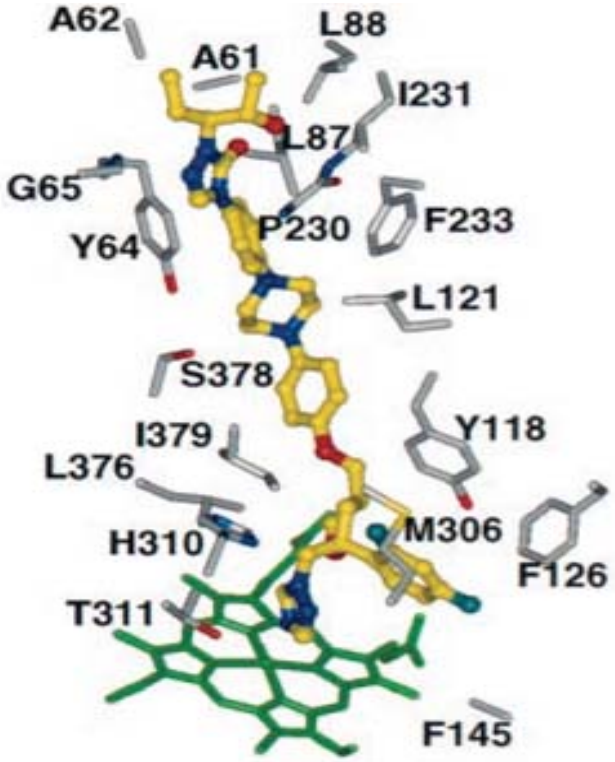
Fluconazole

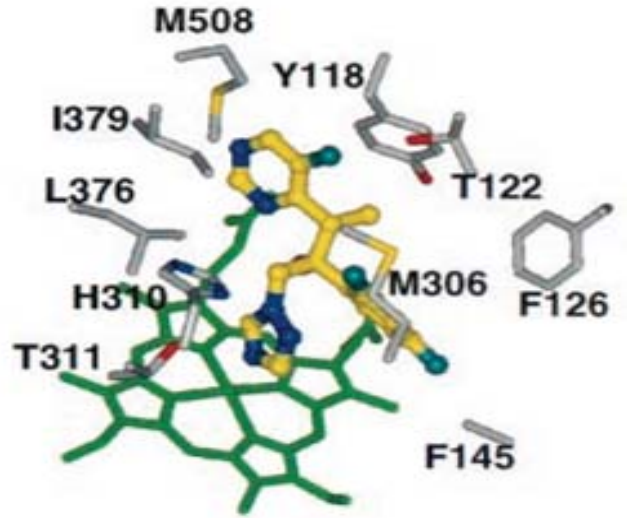


Xiao L et al. *Antimicrob Agents Chemother*. 2004:48;568–574.

Meaning of the extended side chain

- The extended side chain occupies a ligand channel in the target enzyme, which may stabilize the drug in the target and increase its overall binding affinity



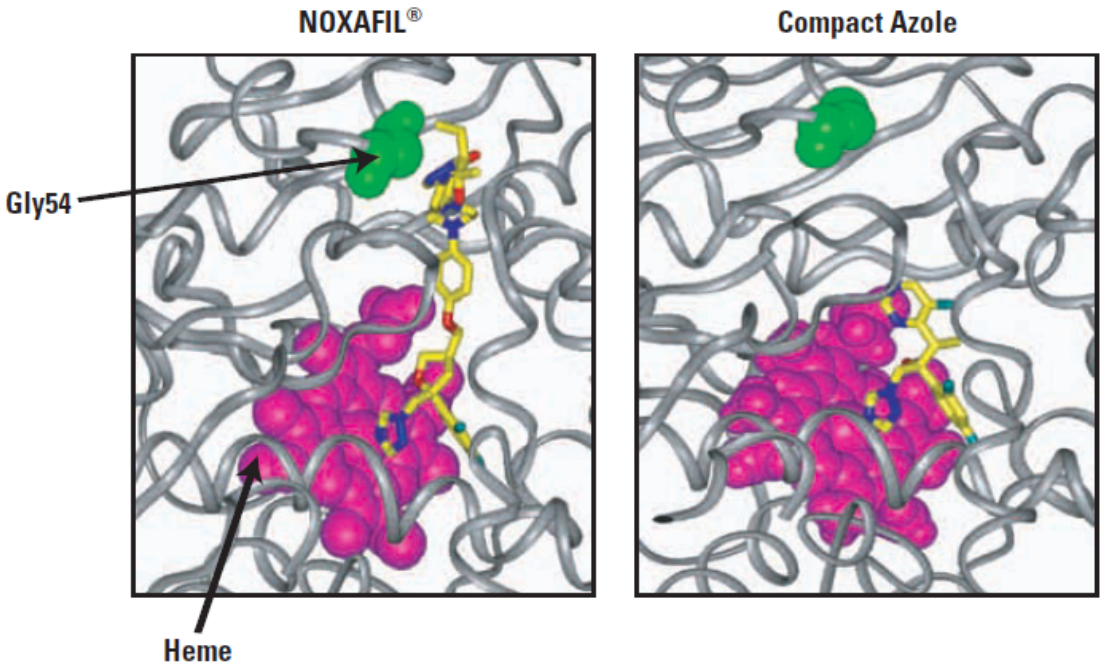


Xiao L et al. *Antimicrob Agents Chemother*. 2004;48:568–574.

Posaconazole long side chain

tighter binding and greater resistance to mutation in its target enzyme

- Additional hydrophobic interactions through its long side chain.
- These hydrophobic interactions may help posaconazole tolerate mutations in the heme binding site of its target enzyme (active site of the cytochrome P450 14α-sterol demethylase).



Xiao L et al. *Antimicrob Agents Chemother*. 2004:48;568–574.

Aminocandin (HMR-3270)

- Semi-synthetic fermentation product from *Aspergillus sydowi*
- Lipopeptide not metabolized by the liver
- Not a substrate, inhibitor or inducer *of* Cytochrome P450
- Potent activity against
  - *Aspergillus spp.* (itraconazole resistant strains)
  - *Candida spp.* (strains resistant to azoles and AMFO B)
- MICs of aminocandin
  - similar for yeasts (0.03-4 mg/L)
  - species-specific for filamentous fungi

MIC_{90} (mg/L)

Aspergillus fumigatus	*Scedosporium spp.*	*Fusarium spp.*	*Mucorales*
0.5	8	>256	>16

Warn PA, et al . Int J Antimicrob Agents 2010; 35:146–151.

Aminocandin (HMR-3270)

Linear PKs

- Cmax and AUC increase in proportion to its dose

Long half-life

-Single weekly dose or twice weekly, either for prophylaxis or treatment

-This strategy may be far from ideal when treating infections caused by isolates with reduced susceptibility

as higher doses are needed to maintain effectiveness

Najvar LK et al. Clin Microbiol Infect 2008; 14:595–600, Ghannoum MA et al J Antimicrob Chemother 2007; 59:556–559, Brzankalski GE et al J Antimicrob Chemother 2008; 62:1094–1100

Enfumafungin

Natural product with antifungal activity derived from endophytic fungi isolated from leaves of *Juniperus communis.*

The compound is a new triterpene glycoside, showing highly potent *in-vitro* antifungal activity against *Candida* and *Aspergillus* and moderate efficacy in an *in-vivo* mouse model of disseminated candidiasis

Synthetic products derived from enfumafungin, aiming to optimize in-vivo antifungal activity and absorption properties

IV and PO formulations ?

Pelaez F, Cabello A, Platas G, et al. The discovery of enfumafungin, a novel antifungal compound produced by an endophytic Hormonema species biological activity and taxonomy of the producing organisms. Syst Appl Microbiol 2000; 23:333–343

Iron chelators

- **Iron chelators (deferasirox and deferiprone)**
- **Adjunct of antifungal therapy**
  - ✓ iron is a key nutrient for fungi
  - **Have been investigated against IPA and mucormycosis**
  - **Deferasirox study : small open label trial**
    - ✓ diabetic and nonneutropenic patients with mucormycosis
    - ✓ well tolerated - effective
    - ✓ AEs : rashes
    - ✓ No changes in renal or liver function
- **DEFEAT Mucor trial (deferasirox + LAMPB)**
  - ✓ Randomized, double-blinded, placebo-controlled trial
  - ✓ Results were disappointing
  - ✓ Patients with mucormycosis treated with deferasirox had a higher mortality rate at 30 and 90 days,

Nikkomycins

- **Act by competitive inhibition of chitin synthase**
  - ✓ fungal enzyme forming chitin (component of fungal cell wall)
- **Nikkomycin Z**
  - ✓ *in-vitro* and *in-vivo* activity against *Histoplasma capsulatum and Blastomyces dermatitidis,* effective *in vitro* against *Coccidioides immitis*
- **Almost inactive against**
  - ✓ yeasts, *Cryptococcus neoformans, Aspergillus fumigatus*
- **Combination with azoles : *in-vitro* synergistic activity**
  - ✓against *Candida* spp, *Cryptococcus neoformans, Aspergillus fumigatus and in-vivo* activity against *Histoplasma capsulatum*
- **Combination with echinocandins**
  - ✓ Synergistic or additive interactions against *Aspergillus fumigatus* and *Coccidioides* spp

Instead of conclusions

Why we need new antifungal agents ?

Because of

a) the emergence of new pathogenic fungal species

b) the increased needs for drugs with

- better bioavailability
- less toxicity
- less drug interactions
- less resistance
- PO and IV formulations