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Antifungal agents: Synthesis of Griseofulvin, Fluconazole.

- Fungal infections are caused by microscopic organisms that can invade the epithelial tissue.
- The fungal kingdom includes yeasts, molds, rusts and mushrooms. Fungi, like animals, are hetrotrophic, that is, they obtain nutrients from the environment, not from endogenous sources (like plants with photosynthesis).
- Most fungi are beneficial and are involved in biodegradation; however, a few can cause opportunistic infections if they are introduced into the skin through wounds, or into the lungs and nasal passages if inhaled.
- Diseases caused by fungi include superficial infections of the skin by dermatophytes in the Microsporum, Trichophyton or Epidermophyton genera. These dermophytic infections are named for the site of infection rather than the causative organism.

Dermophytic Infection	Causative Organism
Tinea corporis (ringworm)	*Microsporum canis, Trichophyton mentagrophytes*
Tinea pedis (athlete's foot)	*T. rubrum, T. mentagrophytes, Epidermophyton floccosum*
Tinea cruis (jock itch)	*T. rubrum, T. mentagrophytes, E. floccosum*
Tinea capis (scalp)	*M. canis T. tonsurans*
Tinea barbae (beard/hair)	*T. rubrum, T. mentagrophytes*
Tinea unguium (nails)	*T. rubrum, T. mentagrophytes, E. floccosum*

- Systemic infections are caused by the inhalation of spores and cause fungal pneumonia. This pneumonia cannot be transmitted from human to human. These infections can occur in otherwise healthy individuals. Many of the organisms that cause systemic fungal infections are confined to specific geographic locations due to favorable climates for their proliferation.

Systemic Infections	Causative Organism	Geographic Location
Coccidioidomycosis	*Cocidioides immitis*	Southwestern U.S. and parts of Latin America
Histoplasmosis	*Histoplasma capsulatum*	Central and Eastern U.S
Brazilian Blastomycosis	*Paracoccidioides brasiliensis*	South America
Blastomycosis	*Blastomyces dermatitidis*	Southeastern U.S. and Mississippi River valley

- Organisms that cause opportunistic infections will not gain a foothold in healthy individuals, but in the immunocompromised they can cause serious, sometimes life-threatening infections. Patients especially susceptible to these infections include individuals with leukemia and other blood diseases, cancer, HIV and other immunodeficiencies, and diabetes. These organisms can be found throughout the U.S.

Systemic Infections	Causative Organism	Geographic Location
Candidaisis, Thrush, Vulvovaginitis	*Candida albicans*	GI tract and vagina
Cryptococcal meningitis	*Cryptococcus neoformans*	Through inhalation, may cause mild lung infection. Mainly affects CNS
Aspergillosis	*Aspergillus sp.*	Lung, brain, sinuses and other organs
Mucormycosis	*Murcor sp.*	Sinuses, eyes, blood and brain
Pneumocystis carinii pneumonia	*Pneumocystis carinii*	Lungs (especially prevalent in HIV patients)

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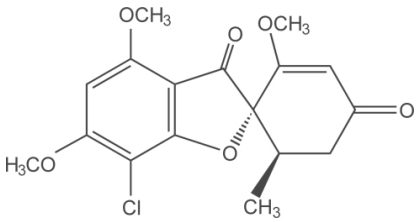
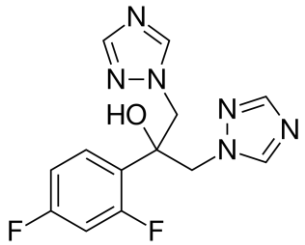
- **Chemical Classification of Anti-fungal agents**

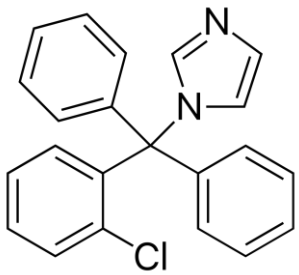
Antibiotics	Amphotericin B, Nystatin, Griseofulvin
Triazoles	Fluconazole, Itraconzole, Terconazole
Imidazoles	Clotrimazole, Ketoconazole, Miconazole, Bifonazole, Butoconazole, Zinoconazole
Fluorinated pyrimidines	Flucytosine
Chitin synthetase inhibitors	Nikomycin Z
Peptides/proteins	Cispentacin
Miscellaneous	Ciclopirox, Tolnaftate, Naftifine, and Terbinafine



Griseofulvin

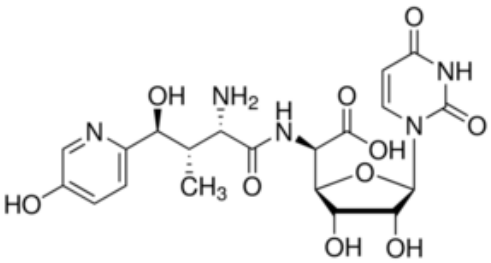


Fluconazole

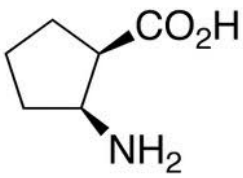


Clotrimazole

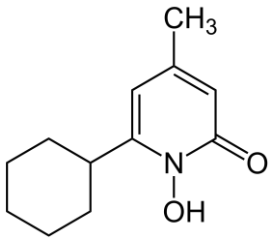
Flucytosine



Nikomycin Z



Cispentacin



Ciclopirox

- **Classification Based on the Route of Administration**

- ***Drugs for subcutaneous and systemic mycoses:*** Amphotericin B, Fluconazole, Flucytosine, Itraconazole, Ketoconazole.
- ***Drugs for superficial mycoses:*** Clotrimazole, Econazole, Griseofluvin, Miconazole, Nystatin.

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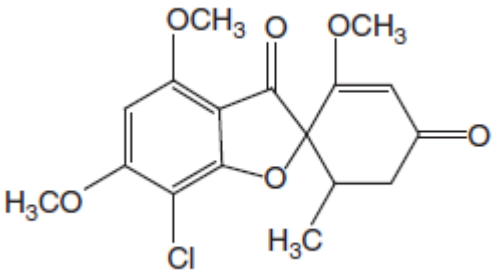
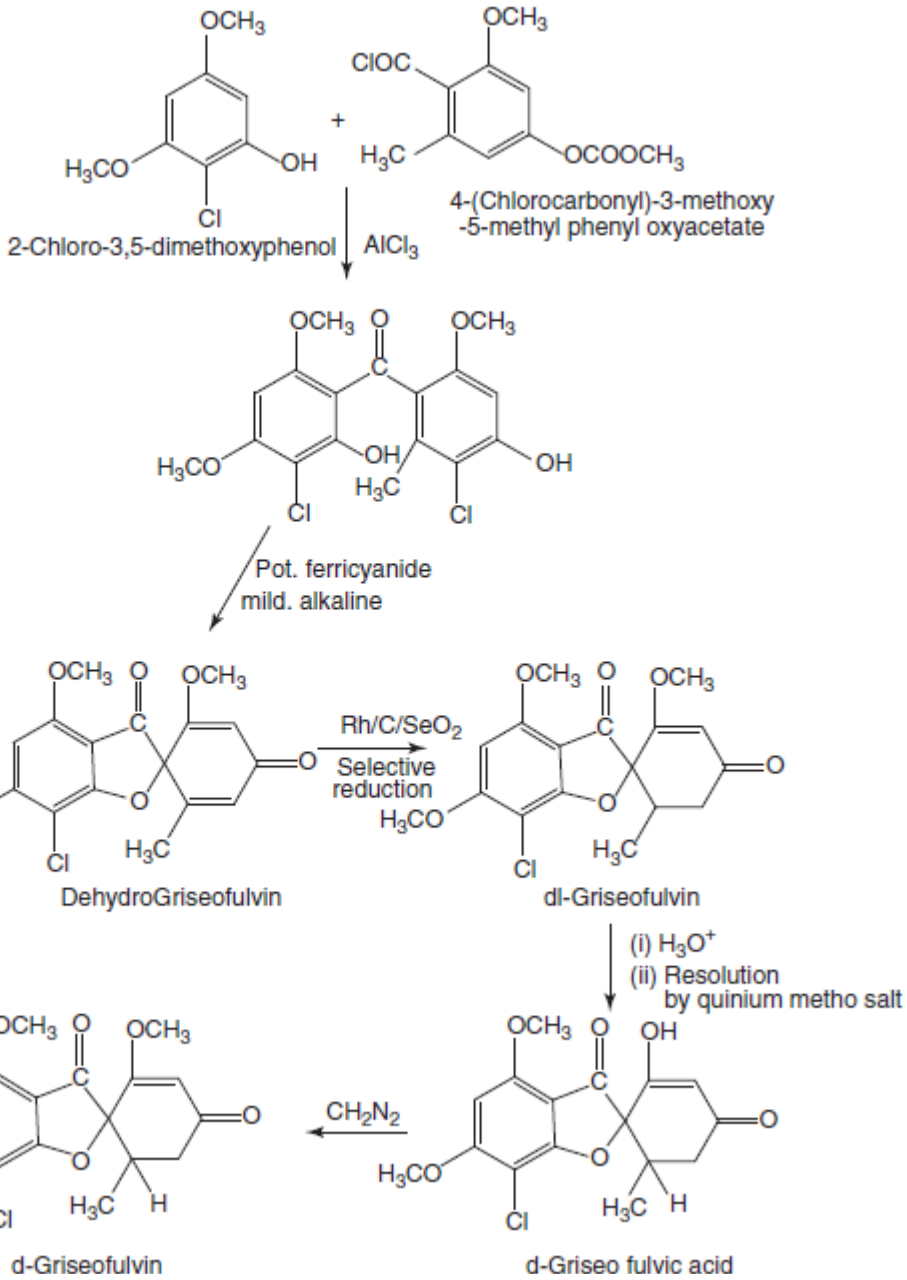
❖ Griseofulvin



- **Synthesis**



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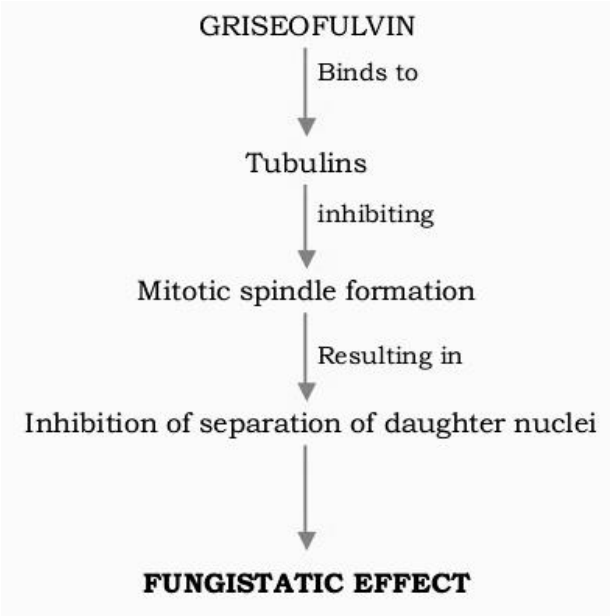
- **Mode of action**

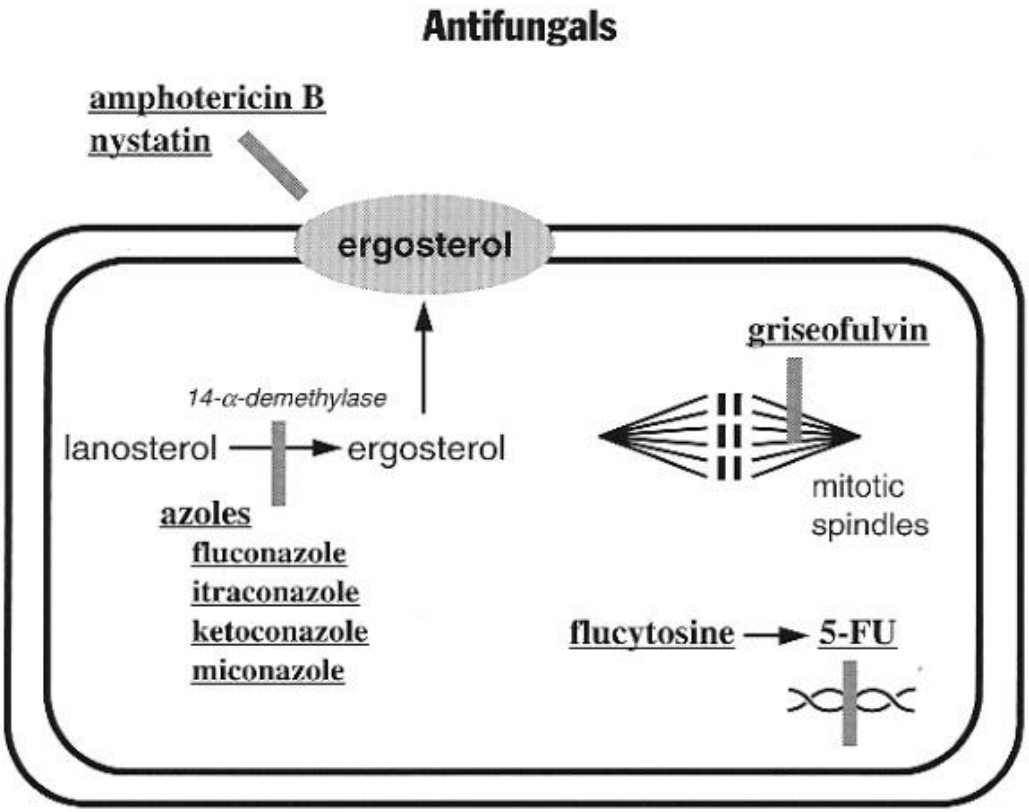
- Griseofulvin is a fungi-static drug that causes disruption of the mitotic spindle by interacting with polymerized microtubules.



- **Dose**

- As an oral suspension, the administered dose is 125 mg/5 ml; as capsules, 250 or 500 mg as tablets. For adults, in divided doses, the dose is 500 mg/day.

❖ General Mechanism action of Antifungal agents



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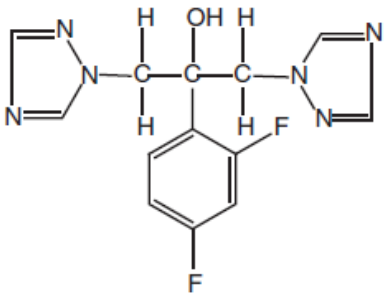
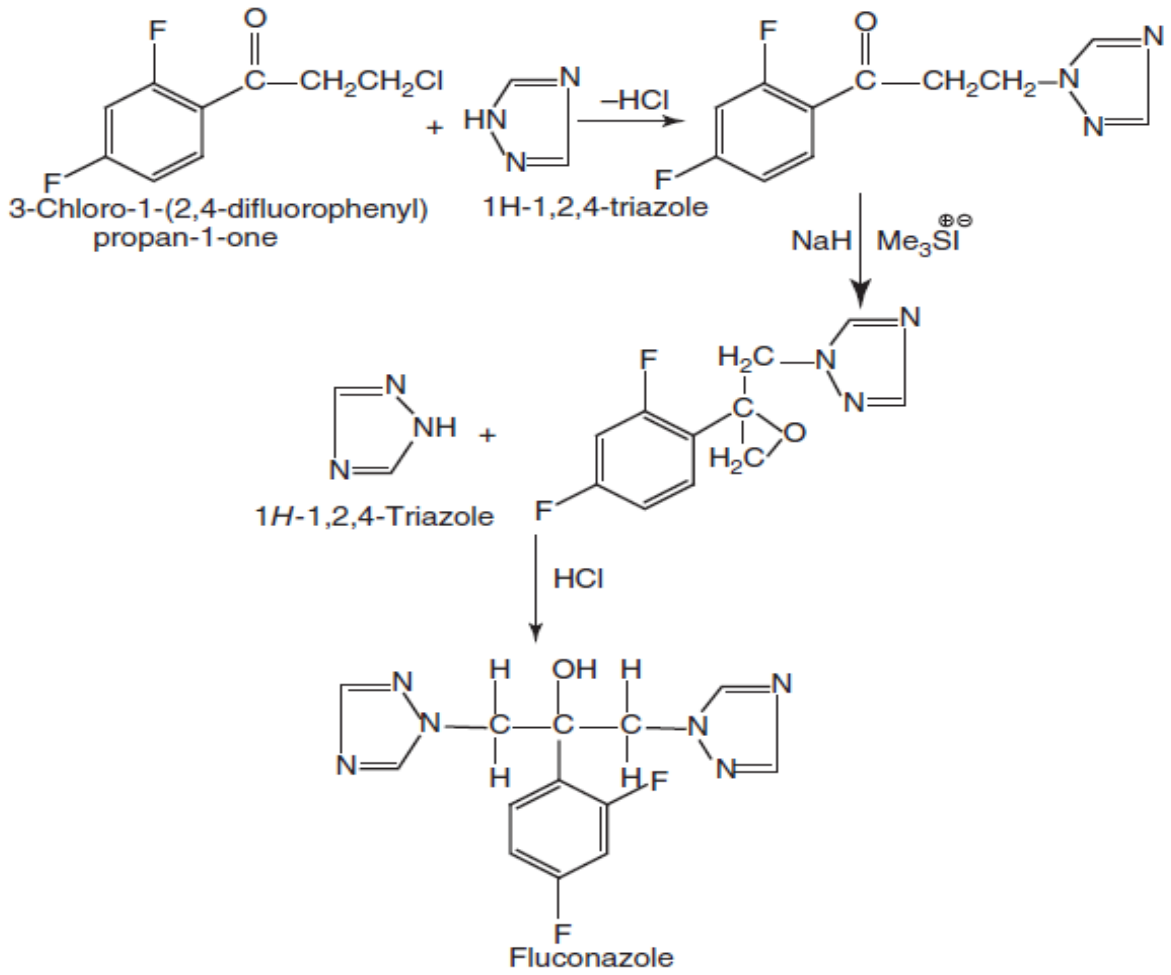
❖ Fluconazole



2-(2,4-Difluorophenyl)-1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol

- **Synthesis**



- **Dose**

- The administered dose for superfi cial mucosal candidiasis for adults is 50 mg daily, which is increased to 100 mg daily.
- Recommended treatment duration is 7–14 days; in the case of oropharyngeal candidiasis, 14 days for atrophic oral candidiasis associated with dentures, 14–30 days for other mucosal candidal infections, including oesophagitis.
- In the case of children, more than 4 weeks the loading dose is 6 mg/kg followed by 3 mg/kg daily.
- The administered dose for dermatophytosis, pityriasis versicolor, and candida infections for adults is 50 mg daily for up to 6 weeks.

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