

Chapter 12: Antifungal Agents

Antifungal agents:

Antifungal antibiotics: Amphotericin-B, Nystatin, Natamycin, Griseofulvin.

Synthetic Antifungal agents: Clotrimazole, Econazole, Butoconazole, Oxiconazole, Tioconazole, Miconazole*, Ketoconazole, Terconazole, Itraconazole, Fluconazole, Naftifine hydrochloride, Tolnaftate*.

12.1. ANTIFUNGAL DRUGS

These are drugs used for superficial and deep (systemic) fungal infections

1. Antibiotics

A. *Polyenes:* Amphotericin B (AMB), Nystatin, Hamycin

B. *Echinocandins:* Caspofungin, Micafungin, Anidulafungin

C. *Heterocyclic benzofuran:* Griseofulvin

2. Antimetabolite Flucytosine (5-FC)

3. Azoles

A. *Imidazoles*

Topical: Clotrimazole, Econazole, Miconazole, Oxiconazole

Systemic: Ketoconazole

B. *Triazoles (Systemic):* Fluconazole, Itraconazole, Voriconazole, Posaconazole

4. Allylamine Terbinafine

5. **Other topical agents:** Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sod. thiosulfate.

Pharmacology

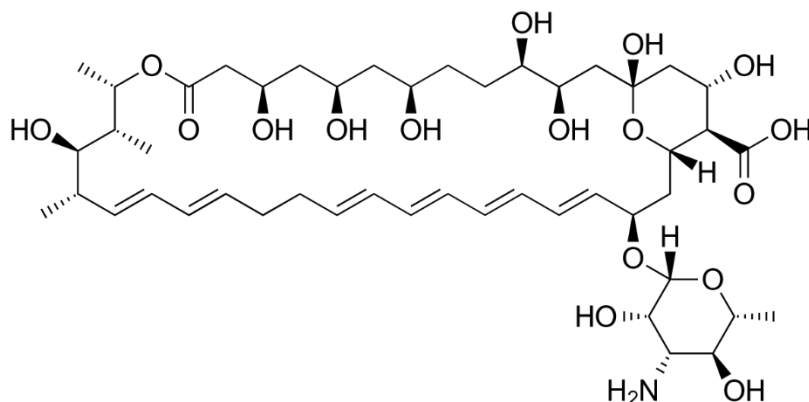
Antifungal Drugs and MOA: https://youtu.be/87NZK8XW_Fg

Amphotericin-B Pharmacology: <https://youtu.be/y6AYRpZ0uW0>

Griseofulvin Pharmacology: <https://youtu.be/sga-LYUP8f4>

Ketoconazole and Itraconazole Pharmacology: <https://youtu.be/iYvNCRYVygj>

B) Nystatin

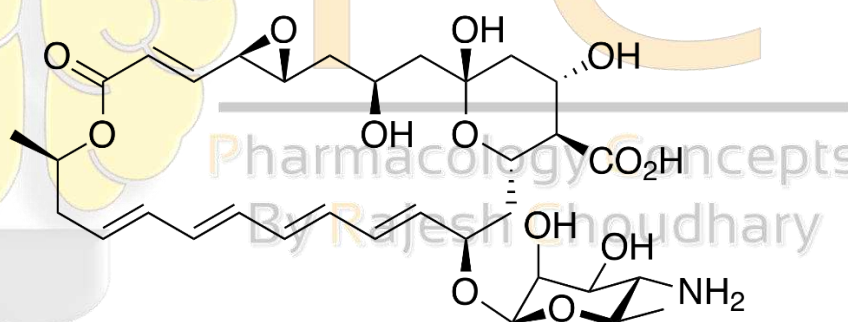


Obtain from *Streptomyces noursei*

MOA: Similar as Amphotericin-B (Ionophore)

Uses: It is used to treat *Candida* infections of the skin including diaper rash, thrush, esophageal candidiasis, and vaginal yeast infections. It may also be used to prevent candidiasis in those who are at high risk. Nystatin may be used by mouth, in the vagina, or applied to the skin.

C) Natamycin

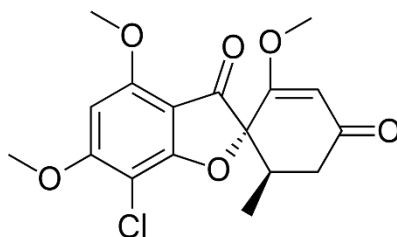


MOA: Natamycin inhibits the growth of fungi by specifically binding to ergosterol present in fungal cell membranes. Natamycin inhibits amino acid and glucose transport proteins leading to a loss of nutrient transport across the plasma membrane.

Uses:

- ✓ Used to treat fungal infections around the eye. This includes infections of the eyelids, conjunctiva, and cornea.
- ✓ It is used as eyedrops. Natamycin is also used in the food industry as a preservative

D) Griseofulvin



7-chloro-3',4,6-trimethoxy-5'-methylspiro[1-benzofuran-2,4'-cyclohex-2-ene]-1',3-dione
It was one of the early antibiotics extracted from *Penicillium griseofulvum*.

MOA:

The drug binds to tubulin, interfering with microtubule function, thus inhibiting mitosis. It binds to keratin in keratin precursor cells and makes them resistant to fungal infections. The drug reaches its site of action only when hair or skin is replaced by the keratin-griseofulvin complex.

Uses:

- ✓ Griseofulvin is used orally only for dermatophytosis. It is ineffective topically. It is reserved for cases in which topical treatment with creams is ineffective.
- ✓ Griseofulvin is fungistatic for most dermatophytes, including *Epidermophyton*, *Trichophyton*, *Microsporum*, etc., but not against *Candida* and other fungi causing deep mycosis. Bacteria are also insensitive.

2. SYNTHETIC ANTIFUNGAL AGENTS

AZOLES DERIVATIVES

A. Imidazoles

Topical: Clotrimazole, Econazole, Miconazole, Oxiconazole

Systemic: Ketoconazole

B. *Triazoles (Systemic):* Fluconazole, Itraconazole, Voriconazole, Posaconazole

MOA:

- ✓ The mechanism of action of imidazoles and triazoles is the same. They inhibit the fungal cytochrome P450 enzyme 'lanosterol 14-demethylase' and thus impair ergosterol biosynthesis and interfere the cell membrane integrity.

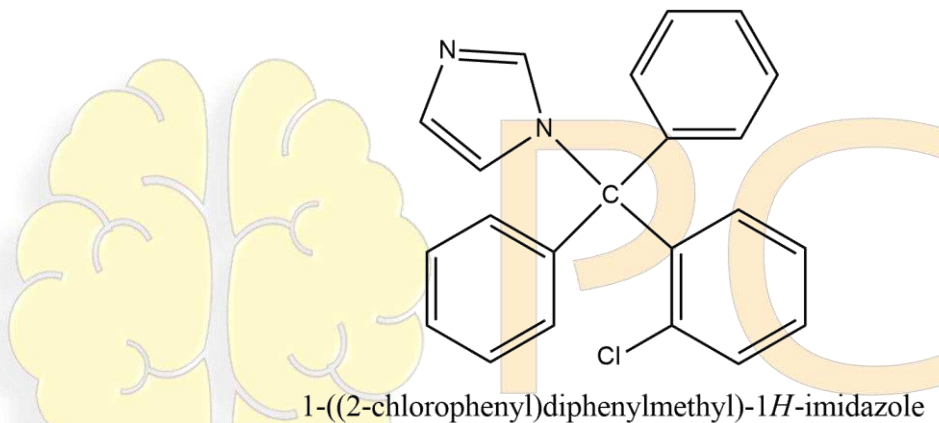


- ✓ Triazoles have higher selectivity for **lanosterol 14-demethylase** than imidazoles. Thus they have lower host toxicity (lower affinity to mammalian CYP450 enzymes) compared to imidazoles

USES:

- ✓ The imidazoles and triazoles have broadspectrum antifungal activity (Fungistatic).
- ✓ They active againts dermatophytes, *Candida*, other fungi involved in deep mycosis (except mucor), *Nocardia* and *Leishmania*.
- ✓ Development of fungal resistance to azoles has been noted among *Candida* especially Fluconazole. Many of fluconazole-resistant *Candida* respond to itraconazole or to voriconazole.

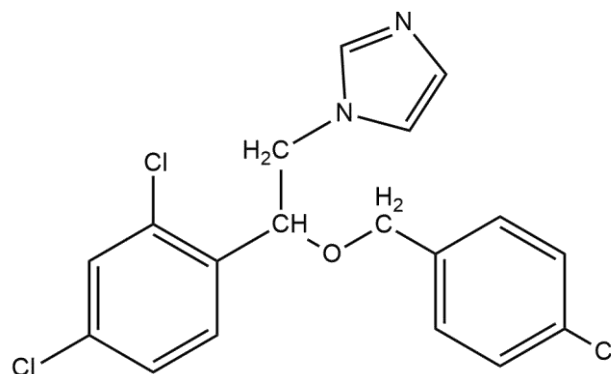
A) Clotrimazole



Uses:

- ✓ Effective against Dermatophytes, candida and yeast infection
- ✓ It is effective in the topical treatment of tinea infections like ringworm
- ✓ Also useful in Athletes' foot, otomycosis and oral/cutaneous/vaginal candidiasis

B) Econazole

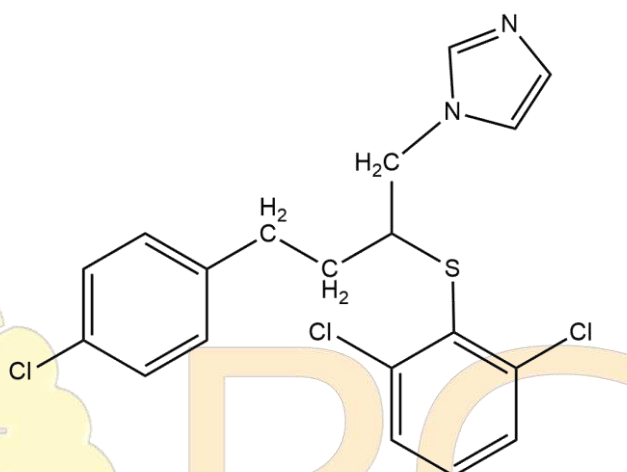


1-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole

Uses:

- ✓ Highly effective in dermatophytosis, otomycosis, oral thrush
- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm.
- ✓ Also used in cutaneous candidiasis

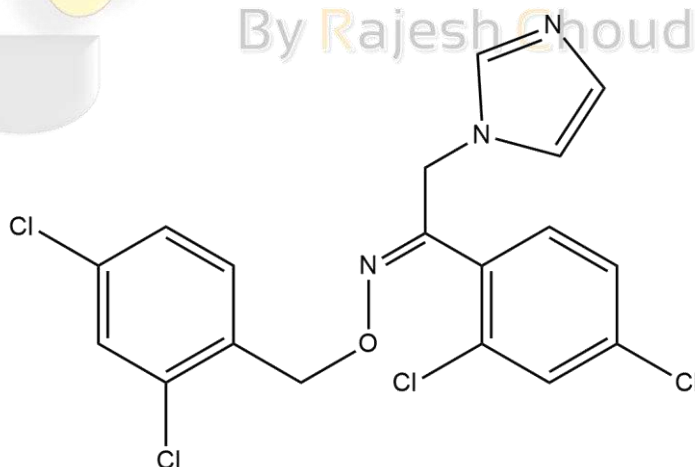
C) Butoconazole



1-(4-(4-chlorophenyl)-2-((2,6-dichlorophenyl)thio)butyl)-1H-imidazole

Uses: Used topically in treatment of vulvovaginal candidiasis and also usefull in vaginal yeast infection

D) Oxiconazole

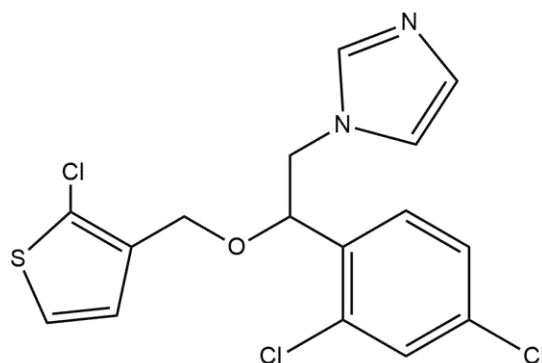


1-(2,4-dichlorophenyl)-N-[(2,4-dichlorophenyl)methoxy]-2-imidazol-1-yl-ethanimine

Uses:

- ✓ Newer topical imidazole antifungal effective in tinea and other dermatophytic infection, as well as vaginal candidiasis.
- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm

E) Tioconazole

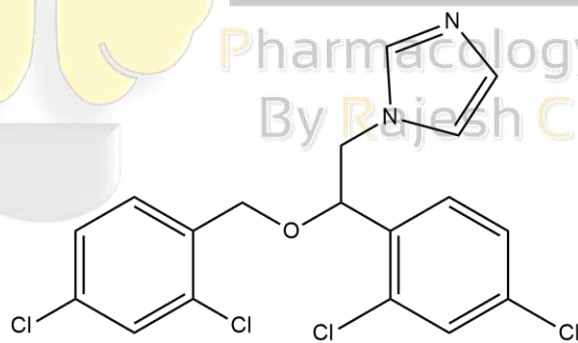


1-(2-((2-chlorothiophen-3-yl)methoxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole

Uses

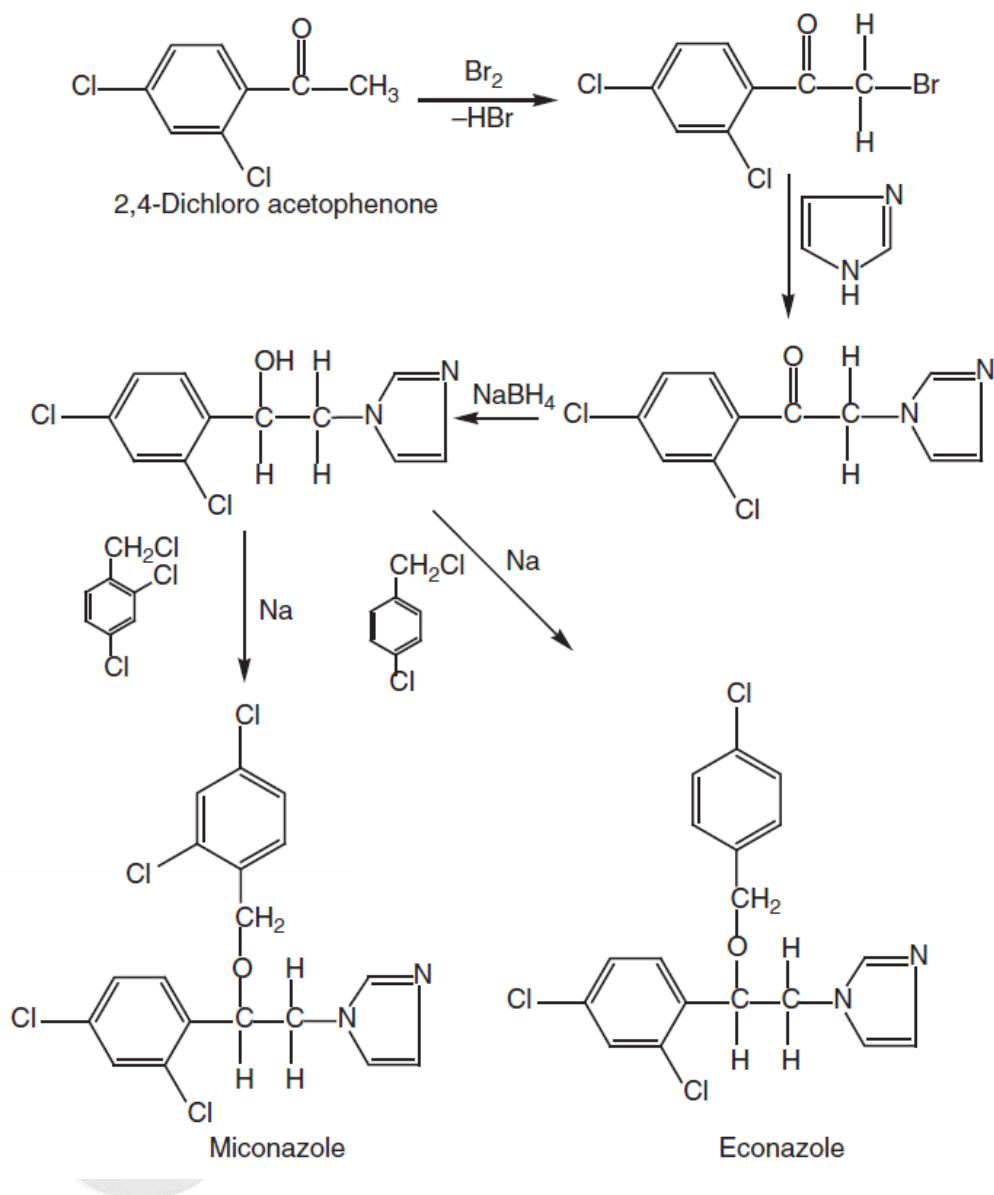
- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm.
- ✓ Also used in cutaneous candidiasis

F) Miconazole*



1-(2-((2,4-dichlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole

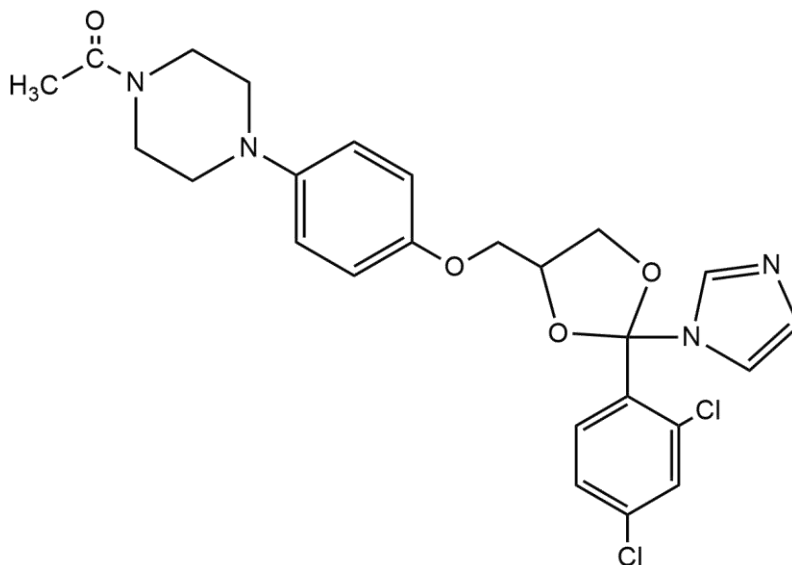
Synthesis



Uses:

- ✓ It is a highly efficacious (>90% cure rate) drug for tinea, pityriasis versicolor, otomycosis, cutaneous and vulvovaginal candidiasis. Because of its good penetrating power

G) Ketoconazole



1-(4-(4-((2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)ethanone

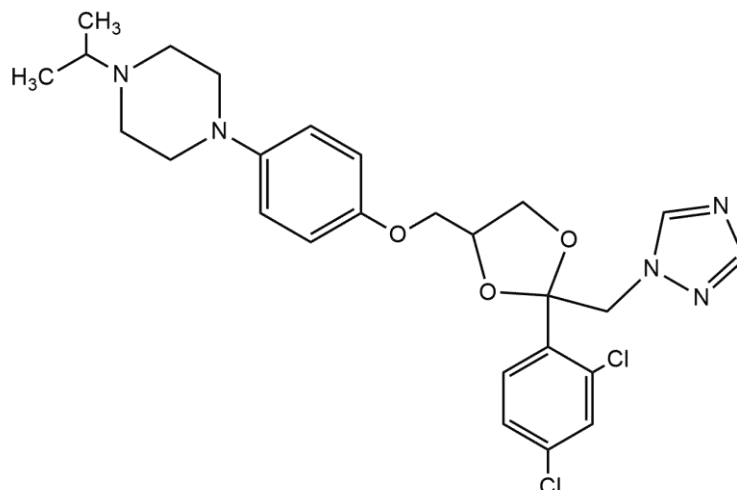
MOA: Ergosterol Biosynthesis inhibitor

Lanosterol-----**lanosterol 14-demethylase** -----> Ergosterol

Uses:

- ✓ It is the first orally effective broad-spectrum antifungal drug, useful in both dermatophytosis and deep mycosis
- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm.
- ✓ It is also used in treatment of Cushing Syndrome (Hypercortisolism), candida infection and dermatophyte infection

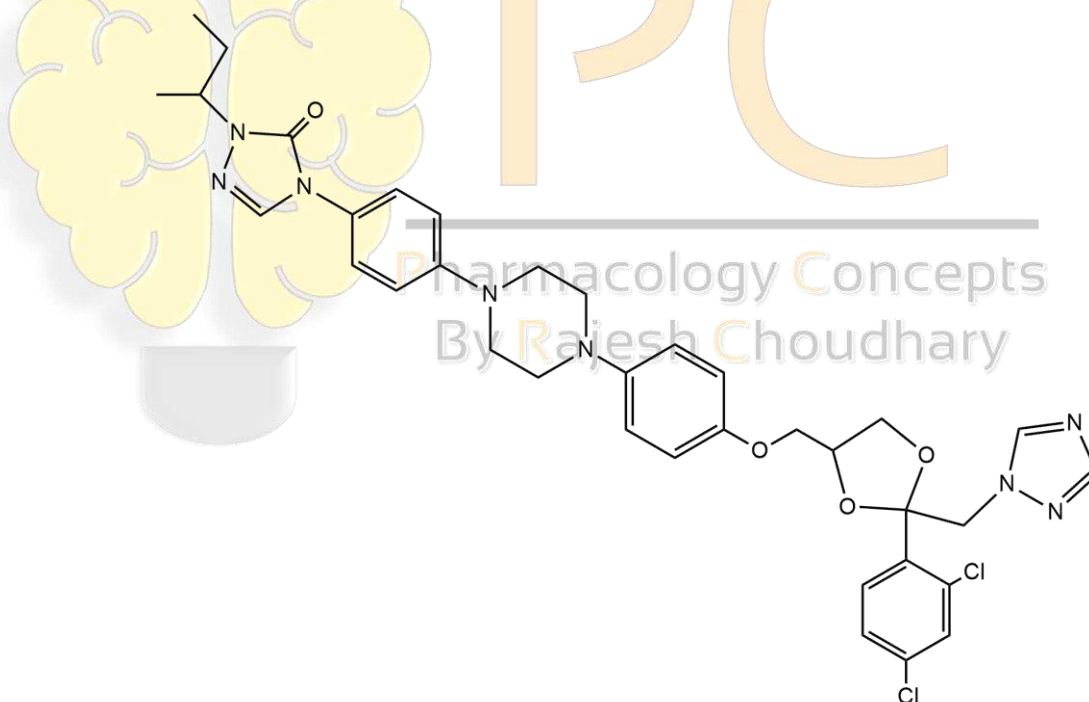
H) Terconazole



1-(4-((2-((1*H*-1,2,4-triazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-4-isopropylpiperazine

Uses: Used in vaginal yeast infection and also used in candida and dermatophytes infection.

I) Itraconazole



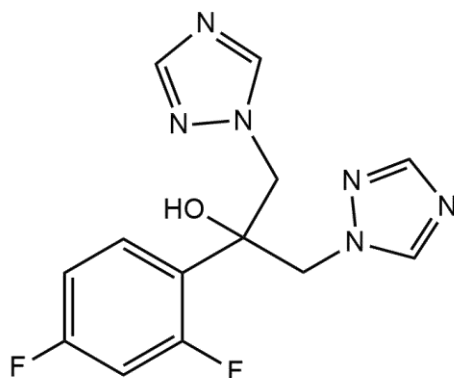
2-butan-2-yl-4-[4-[4-[4-[[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-1,2,4-triazol-3-one

Uses:

- ✓ Itraconazole is the preferred azole antifungal for most systemic mycosis.
- ✓ It is superior to fluconazole for histoplasmosis, blastomycosis, sporotrichosis and is the drug of choice for the rare fungal infections—paracoccidioidomycosis and chromomycosis

- ✓ Also useful in aspergillosis.

J) Fluconazole

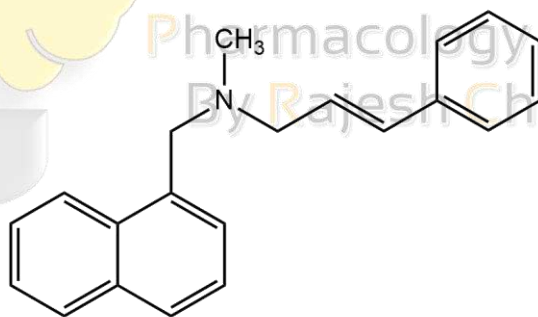


2-(2,4-difluorophenyl)-1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol

Uses

- ✓ It is a water-soluble triazole having a wider range of activity, include cryptococcal meningitis, systemic and mucosal candidiasis in both normal and immunocompromised patients, coccidioidal meningitis and some tinea infections (tinea manuum; ringworm in hand)

K) Naftifine



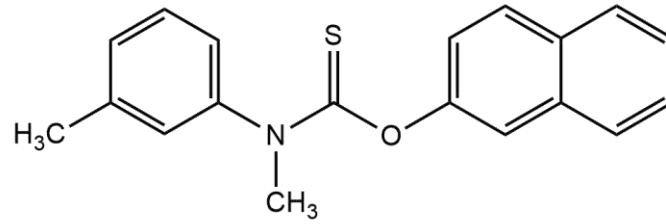
(*E*)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine

MOA: Inhibits the enzyme squalene 2,3-epoxidase (involve in sterol/ergosterol biosynthesis)

Uses:

- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm.
- ✓ Also used as an antibacterial and anti-inflammatory agents.

L) Tolnaftate*



O-naphthalen-2-yl methyl(*m*-tolyl)carbamothioate

MOA: Similar to Naftifine.

Uses:

- ✓ Used topically against variety of skin fungal infection like Athletes' foot, jock itch, and ringworm.
- ✓ It is effective for the treatment of most cutaneous mycoses, such as *Trichophyton rubrum* and *Microsporum canis*.

Synthesis:

