Pharmaceutical Chemistry

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Synthesis of Essential Drugs

By *R.S. Vardanyan* and *V.J. Hruby*, Elsevier, 2006

35. Antifungal Drugs

In comparison with bacteria or viruses, fungi are more complex organisms. They have ribosomes, cellular membrane components, and a nuclear membrane.

Therefore, antibacterial antibiotics are ineffective against pathogenic fungi.

Fungal infections (mycoses) occur less than bacterial or viral infections.

A few fungal infections can spread to the surface of the body and cause local disturbances, while others can be systemic and life threatening.

Some of these organisms (for example, *Candida*) can spread from a superficial location to internal organs, leading to systemic diseases with serious complications.

Fungal (mycotic) infections cause a lot of discomfort, and as a rule, are difficult to cure.

Fungal infections are conventionally divided into three categories: dermatophylic, mucocutaneous, and systemic.

1. **Dermatophytic infections** are the most widespread, which include skin, hair, and nails.

Most infections can be cured by using topical drugs, such as tolnaftate, undecylenic acid, haloprogin, clotrimazole, and miconazole. Griseofulvin is used orally for deep infections, in particular for infections of the nail bed. Ketoconazole is widely used for treating chronic dermatophytes.

2. **Mucocutaneous infections** caused primarily by the fungus *Candida albicans* occur in regions of moist skin and mucous membranes (i.e. gastrointestinal tract, perianal, and vulvovaginal areas).

Amphotericin B, miconazole, clotrimazole, and nystatin are used topically to treat such infections. For chronic infections, ketoconazole is taken orally.

3. **Systemic infections** are very rare, although they do present a serious problem since they are naturally chronic and difficult to diagnose and treat. So, antifungal drugs are medications used to treat fungal infections such as athlete's foot, ringworm, and candidiasis (thrush) as well as serious systemic infections like cryptococcal meningitis.

Antifungals work by exploiting differences between mammalian and fungal cells to kill the fungal organism and without significantly harming the host.

From the **medical point of view**, antifungal drugs are considered dermatophytic, mucocutaneous, and systemic.

From the **chemical point of view**, antifungal drugs can be divided into polyenes, imidazole and triazole derivatives, allylamines, and others.

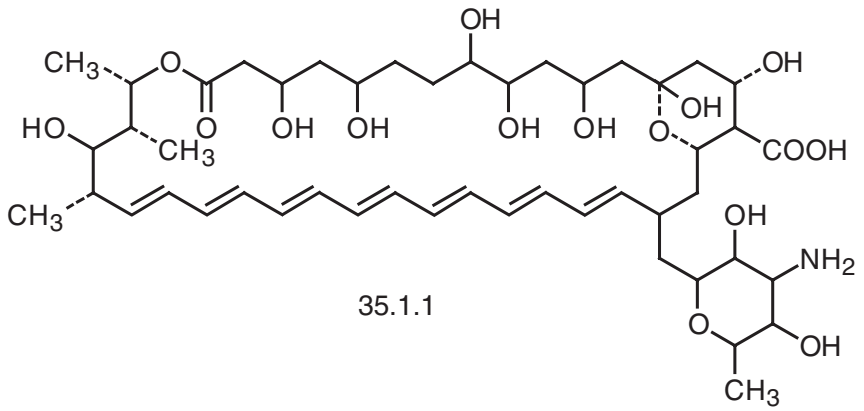
35.1 POLYENE ANTIFUNGAL DRUGS

Drugs included in this group—amphotericin B, nystatin, natamycin, are used for treating systemic and superficial infections. Polyenes bind with sterols in the fungal cell wall (ergosterol), causes the cell's contents to leak out and the cell dies.

Human (and other animal) cells contain cholesterol rather than ergosterol so are much less susceptible.

Amphotericin B

is made from the cultural fluid of the actinomycete *Streptomyces nodosus*. This compound has a broad spectrum of antifungal activity, including *Candida albicans*, *Leishmania brasiliensis*, *Mycobacterium leprae*, *Histoplasma capsulatum*, *Blastomyces dermatitidus*, and *Coccidioides immitis*.



35.1.1

It possesses **fungistatic** and **fungicidal** activity depending on the dose used. The antifungal activity of amphotericin B is exhibited because it binds with ergosterol in the cellular membrane of sensitive fungi.

This reaction makes pores in the membrane and increases the permeability of the membrane to small molecules, thus reducing the function of the membrane as an osmotic barrier and making the cells more sensitive to being destroyed.

Amphotericin B is active against growing cells and cells that are dormant.

Side effects: this compound is not highly selective and reacts with host mammalian cells.

Amphotericin B remains the primary drug for treating severe, acute systemic fungal infections, such as candidomycosis, aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis, and pulmonary mycoses.

Synonym: amphocyclin, fungisone, and fungilin

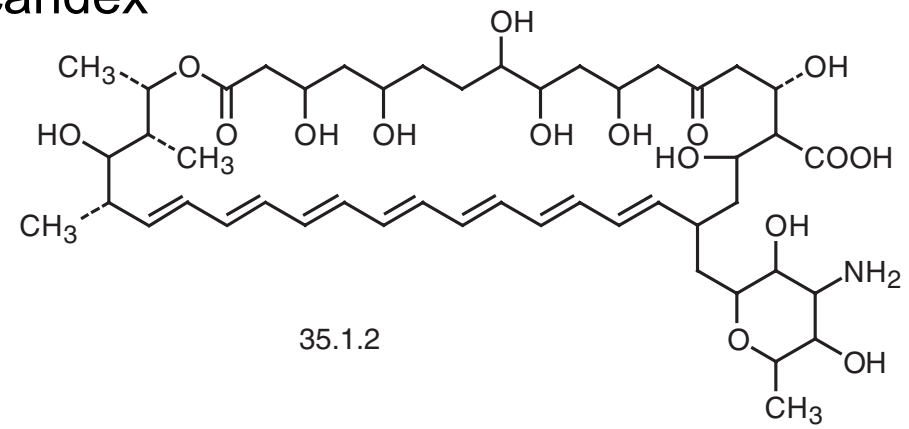
Nystatin

was isolated in 1949 from the products of the vital activity of the actinomycete *Streptomyces noursei*, and it was the first antifungal antibiotic to be discovered. It has a broad spectrum of activity.

The mechanism of antifungal activity is similar to the mechanism of action of amphotericin B. It is used for preventing and treating candida infections of the skin and mucous membranes.

It is also used for preventing the development of candidomycosis during prolonged treatment with penicillin drugs and antibiotics of other group, especially during oral use of tetracycline antibiotics, levomecytin, and others.

Synonym: biofanal, moronal, nicporil, fazigin, and candex



35.1.2

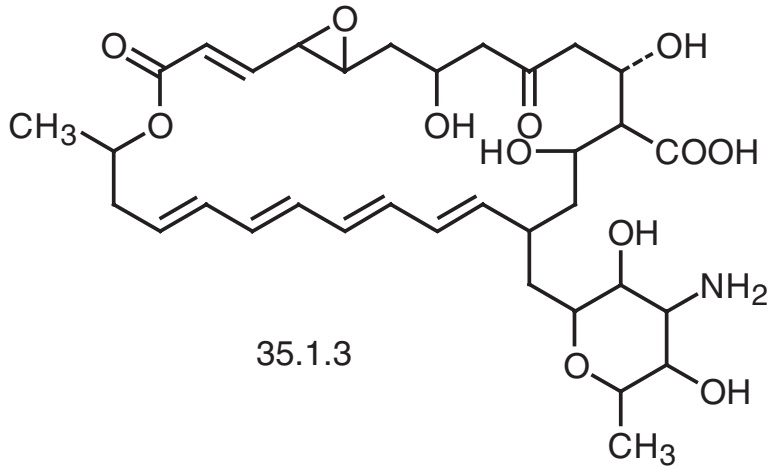
Natamycin

is a polyene antibiotic that is isolated from the products of the vital activity of the actinomycete Streptomyces natalensis.

The spectrum of its activity is somewhat narrower than that of amphotericin and nystatin, but at the same time, it is **less toxic**. It exhibits especially pronounced activity against a few strains of *Fusarium* and *Cefalosporium*.

Natamycin is a drug for treating superficial fungal infections, and it is used only for ophthalmologic purposes.

Synonym: pimafucin, pimaricin, and tennecetin



35.1.3

35.2 IMIDAZOLES (TRIAZOLES)

Some imidazole derivatives have turned out to be extremely beneficial for treating fungal infections. They are ketoconazole, miconazole, clotrimazole, econazole, butoconazole, mebendazole, fluconazole, and others.

The antifungal activity of imidazole derivatives is currently explained by their ability to selectively raise the permeability of the membrane of fungal cells by interfering with the biosynthesis of sterins (ergosterin), by inhibiting its synthesis and by changing the lipid content of the membrane.

Imidazole and triazole groups inhibit the enzyme cytochrome P450 14α-demethylase. This enzyme converts lanosterol to ergosterol, which is required in fungal cell-wall synthesis. These drugs also block steroid synthesis in humans.

Unlike amphotericin B, benzimidazole derivatives are active only against growing cells. This drug does not affect host cells because mammals use exogenic sterols for their vital functions.

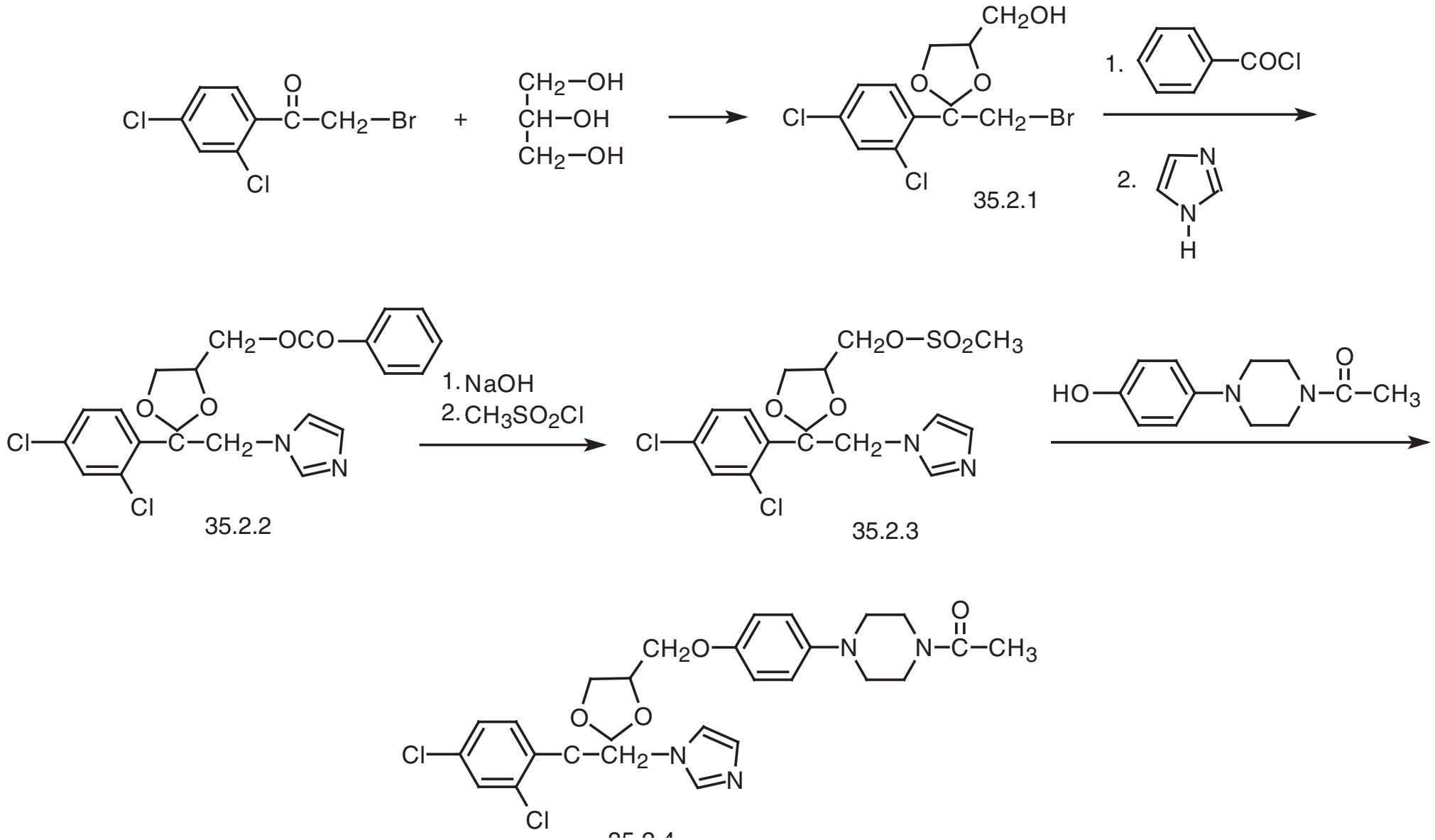
Ketoconazole

It has a broad spectrum of antifungal activity, including many candida infections. It possesses fungicidal and fungistatic activity with respect to dermatophytes, yeast fungus, dimorphous fungi, and eumycetes.

It is also active with respect to staphylococci and streptococci. It is effective for chronic diseases, treating fungal infections of the gastrointestinal tract, sex organs, skin, hair, and nails.

It is used in combination with shampoo for treating and preventing mycelial fungi, seborrheic dermatitis, and dandruff.

Synonym: nizoral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35.2.1
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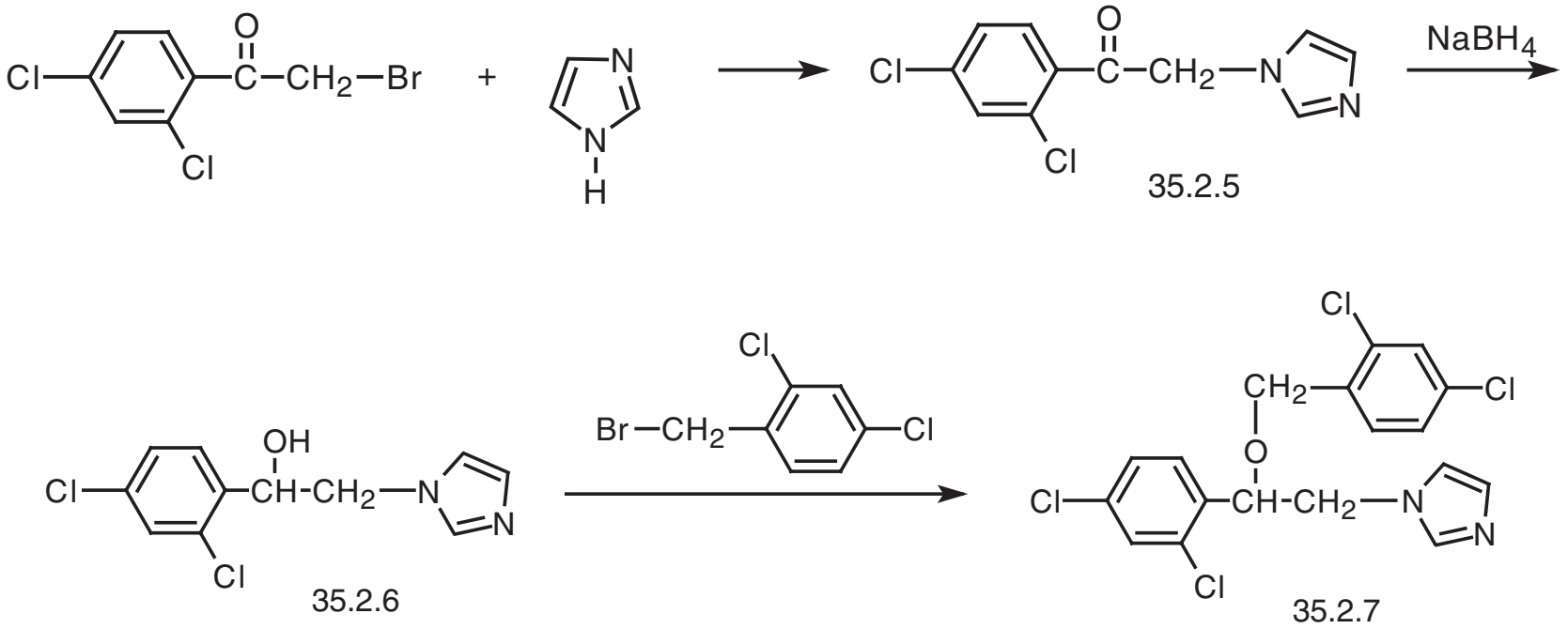
35.2.3

Miconazole

It is primarily used externally for candida and dermatophyte infections of the skin and vaginal candidosis as well as for acute internal mycoses.

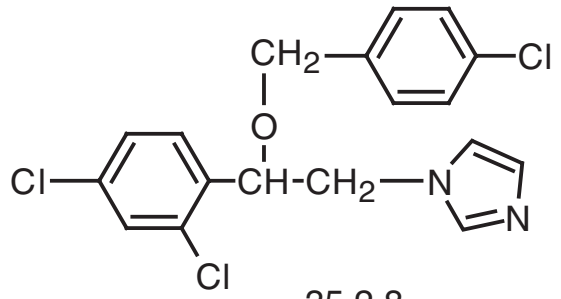
Synonym: acnidazil, dactar, and dermonistate



Econazole

It is also used externally (only superficially) to treat ringworm and candidoses caused by flora that are sensitive to this drug (*Trichophiton rubrum, Trichophiton menta-grophytes, Trichophiton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum, Candida albicans*). When used locally, it kills fungi in three days.

Synonym: pevaryl, exostatin, and dermazol



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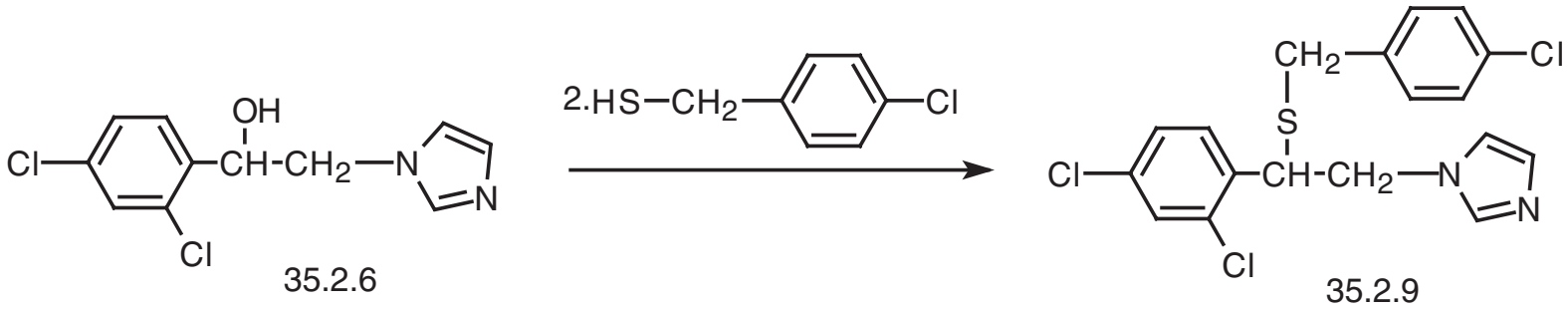
Sulconazole

Like econazole, it is used externally for the same indications as econazole.

Synonym: exelderm



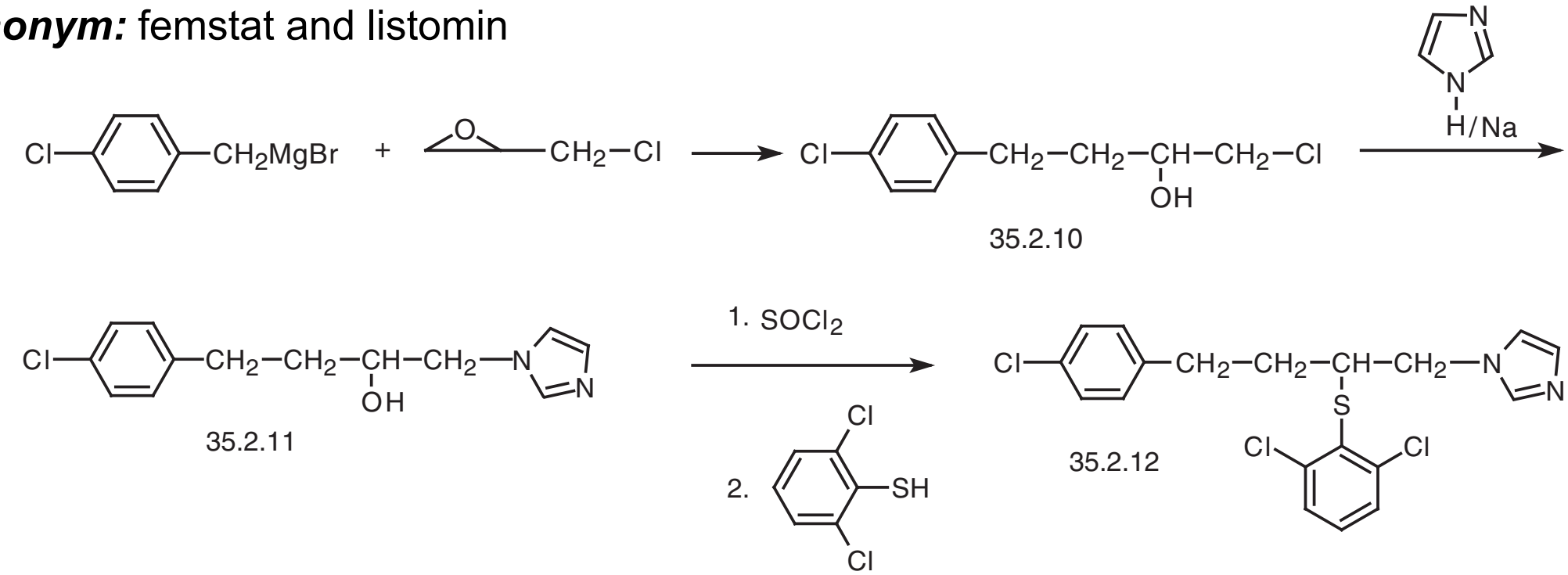
35.2.6 35.2.9

Butoconazole

It is a fungostatic drug, inhibits the biosynthesis of estrosterin in the cytoplasmatic membrane of fungi.

It is effective for vaginal infections caused by various types of candida. It is also used only externally and vaginally.

Synonym: femstat and listomin



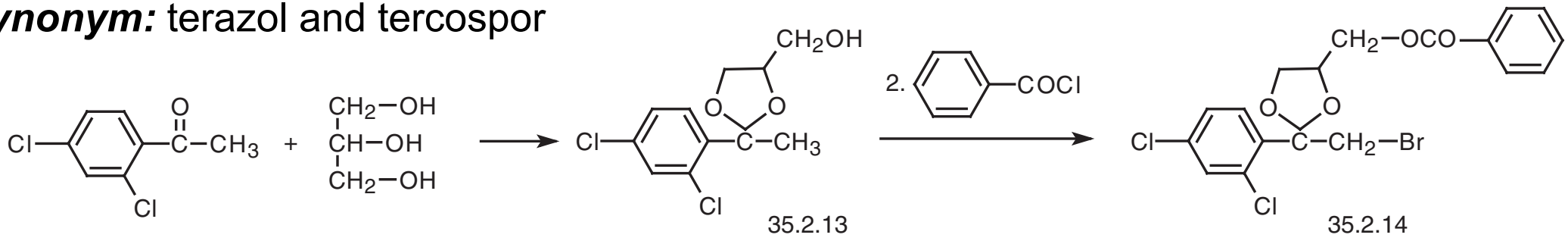
Terconazole:

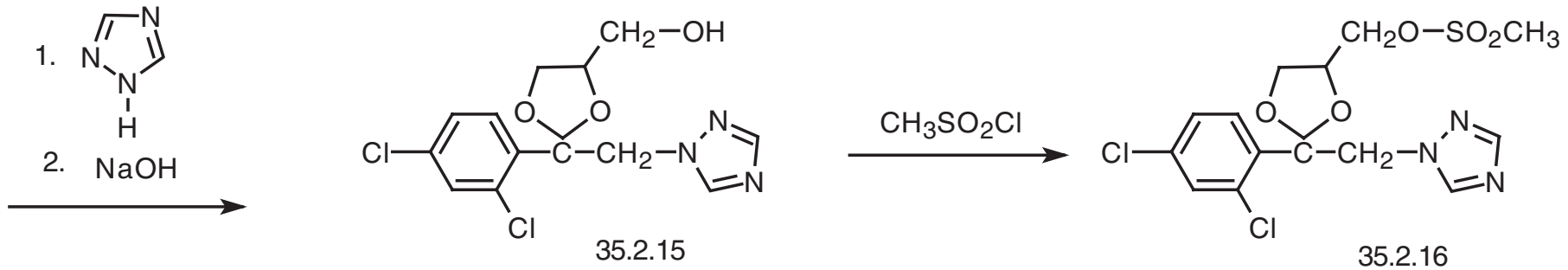
It is effective for fungistatic action for many strains of *Candida* and dermatophytes.

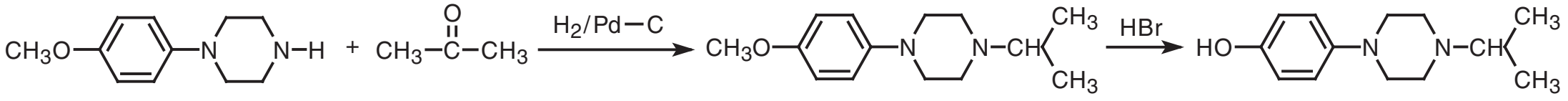
It inhibits the action of the enzyme lanosterol 1-demethylase of cytochrome P-450 of sensitive fungi, causing a reduction in the amount of ergosterin, which is necessary for the organisms to construct membranes and to retain the appropriate permeability.

It is only used externally for treating vulvovaginal candidoses.

Synonym: terazol and tercospor







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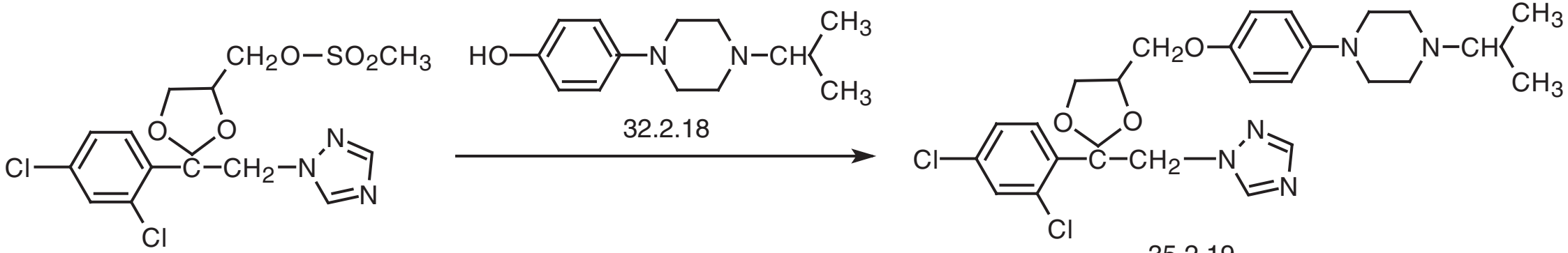

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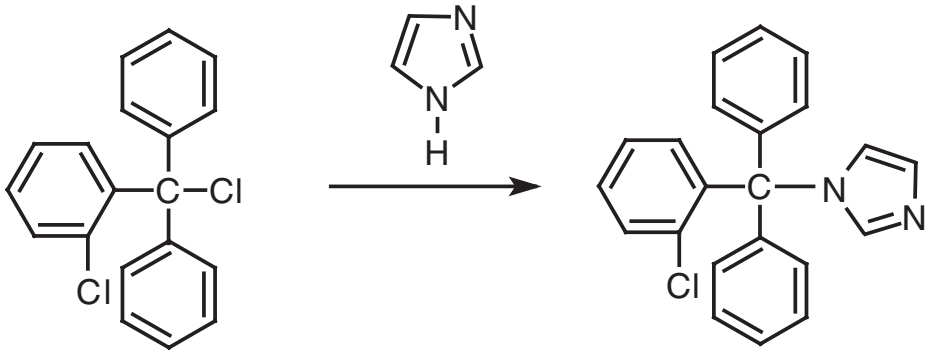
Clotrimazole

It also inhibits the biosynthesis of ergosterin in the cytoplasmatic membrane of fungi. In terms of pharmacological action, clotrimazole is very similar to miconazole.

It has a broad spectrum of antifungal activity. It is effective with respect to dermatophytes, and it also has an antimicrobial effect against streptococci and staphylococci. It is also effective with respect to trichomonases. It is very widely used, both externally and vaginally for treating superficial infections.

Synonym: canesten, empecid, lotrimin, and micosporin



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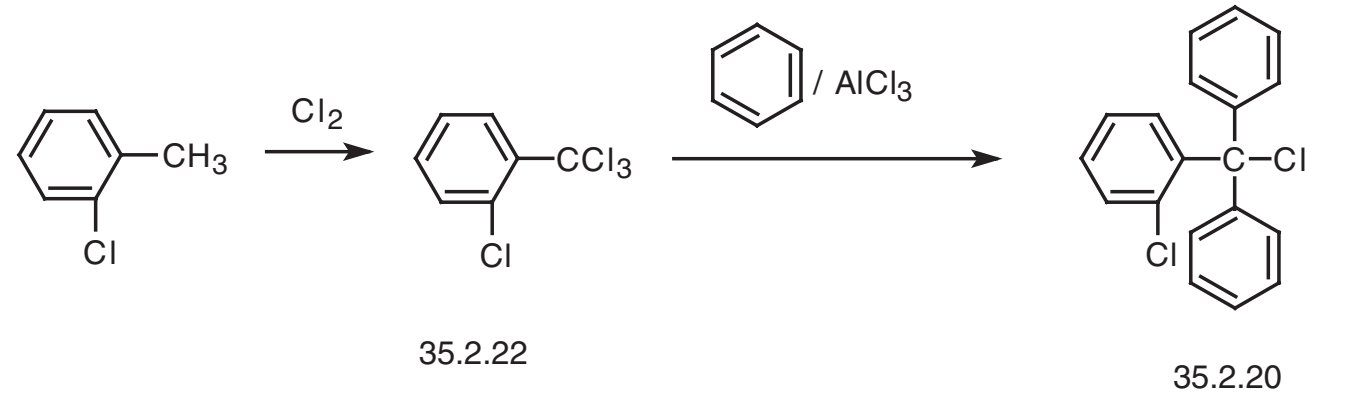

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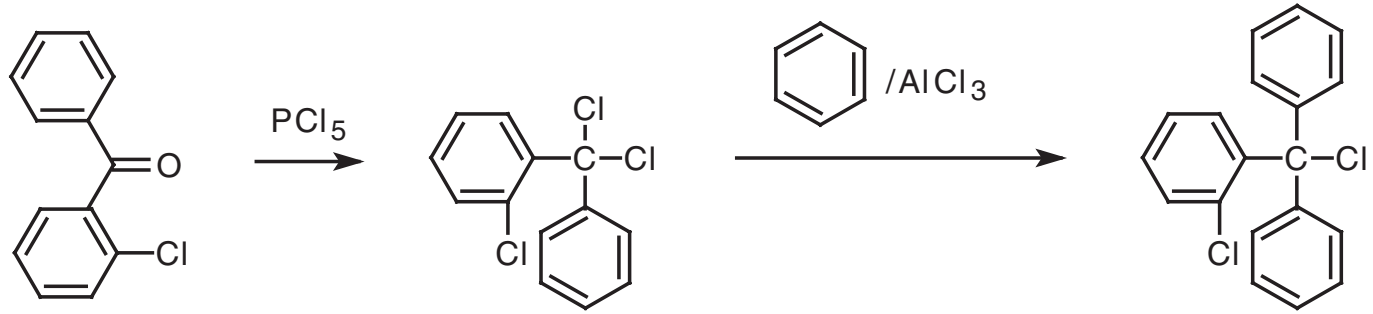

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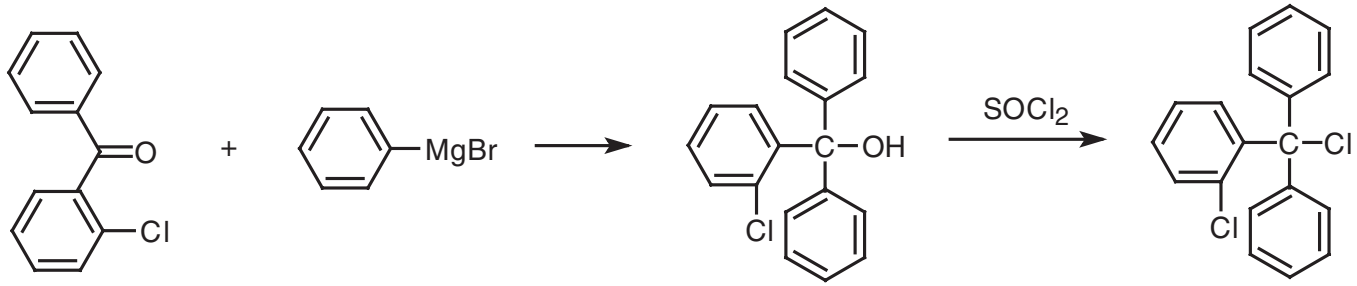

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35.2.20

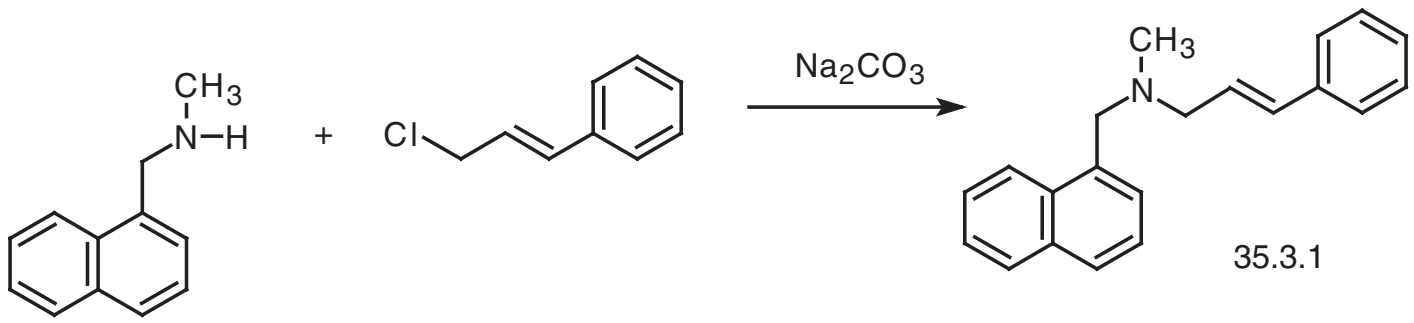
35.3 ALLYLAMINES

Allylamines (naftifine, terbinalfine, butenafine, amorolfine) inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis.

Naftifine

It is only permitted to be used externally and only superficially as a drug with a broad spectrum of action against dermatophytes and candida infections. It exceeds the activity of econazole. Moreover, it does not have a locally irritating effect.

Synonym: exoderil and naftin



35.3.1

35.4 OTHERS

Griseofulvin:

It binds to polymerized microtubules and inhibits fungal mitosis (causing the formation of multiple-nuclei, defective cells).

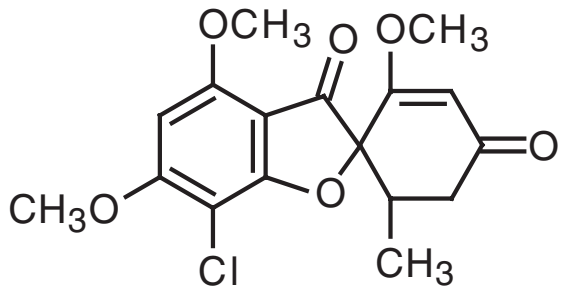
Flucytosine is an antimetabolite. It is used to treat superficial infections includes dermatophyte infections of the skin, nails, and scalp.

It has a fungistatic effect on various types of dermatophytes (trichophytes, microsporums, achoriones, epidermophytones).

It is ineffective against deep systemic mycotic infection, and for candidomycoses.

It is only used orally.

Synonym: fulcin, licuden, and grifulvin



35.4.1

Flucytosine

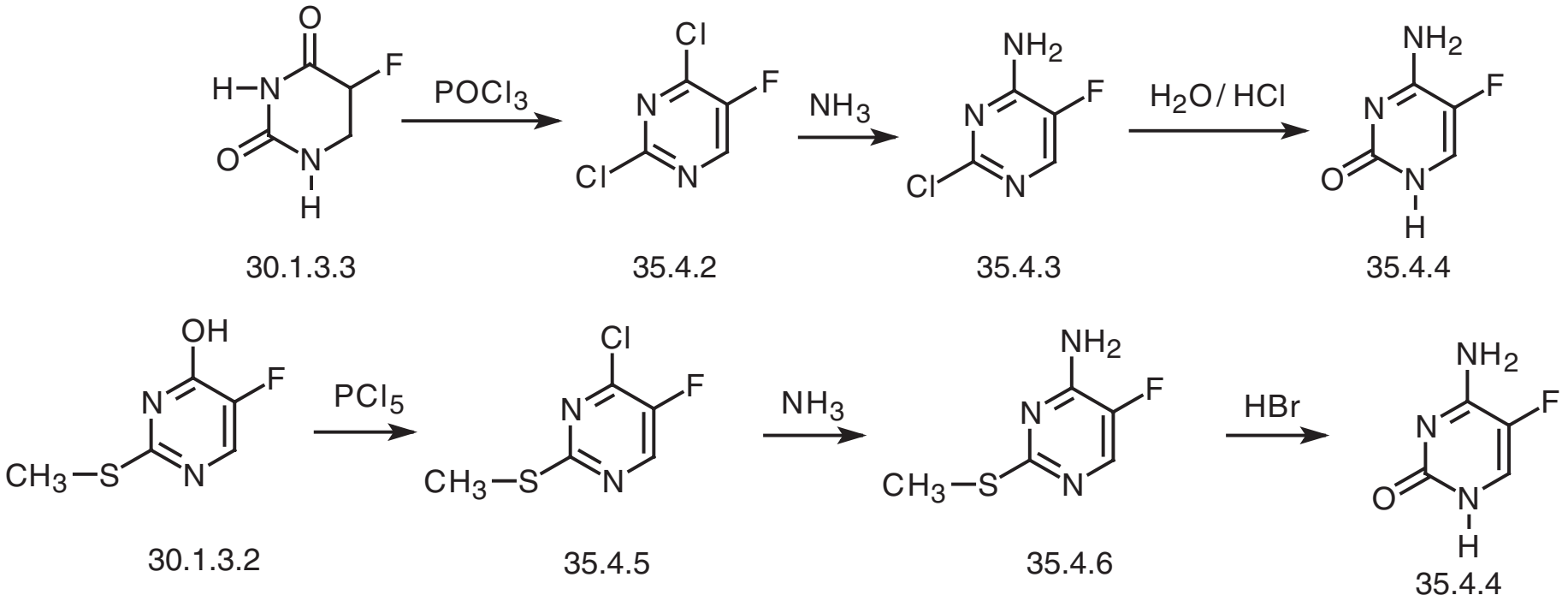
It is a fluorinated derivative of pyrimidine. Its spectrum of activity is narrower than that of amphotericin B. It exhibits a synergetic effect when used in combination with amphotericin B for treating certain systemic fungal infections (subcutaneous chromobastomycosis).

It is used intensively for treating systemic infections of the urinary tract that are caused by various strains of *Candida*.

In sensitive fungi, flucytosine is transformed into 5-fluorouracil and then turned into 5-fluorodeoxyuracilic acid, an inhibitor of thymidylate synthetase and DNA synthesis. 5-Fluorouracil triphosphate, which causes the formation of defective RNA, may also be involved in this process.

The mechanism is highly selective because mammalian cells are not able to turn a large amount of flucytosine into 5-fluorouracil.

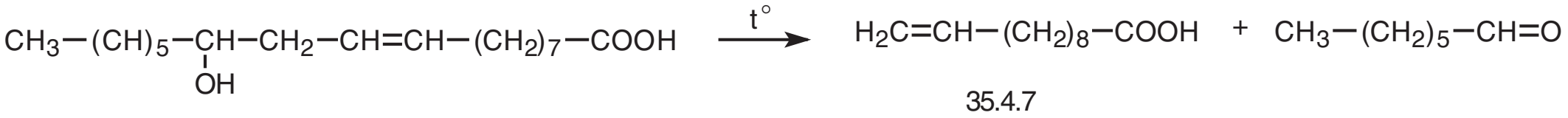
Synonym: ancobon and ancotil



Undecylenic acid

It is very effective as an external drug for treating moderate dermatophyte infections and yeast dermatitis, but it is not effective for shingles and for candida infections.

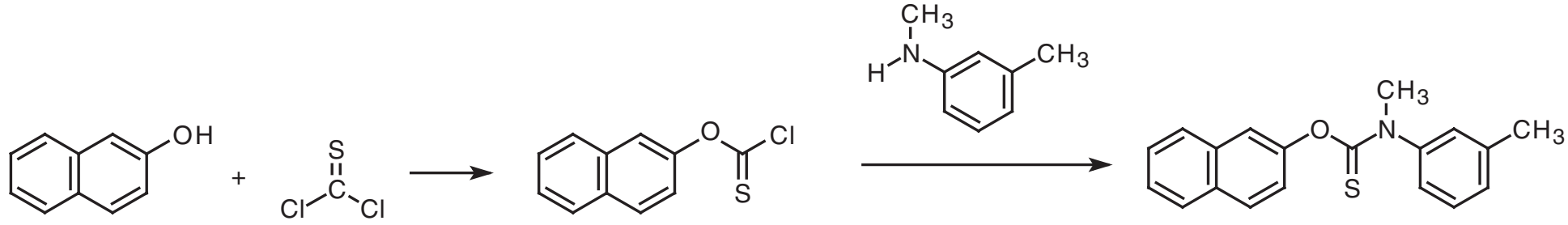
Synonym: benzevrine, micocid, and undetin,



Tolnaftate

It is used as an external drug for moderate dermatophyte infections (shingles), and it is not effective for treating candida infections.

Synonym: tinatox, tonoftal, timoped, tinaderm, and tinactin

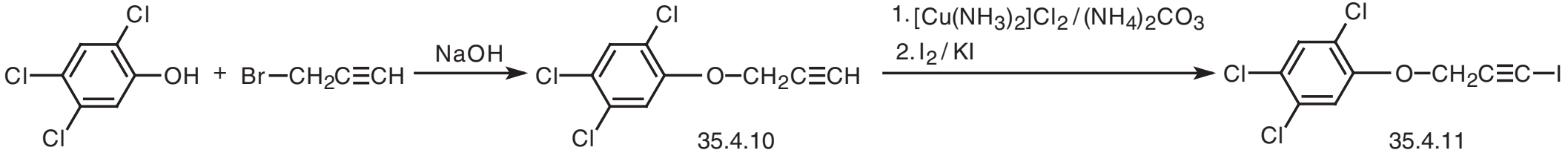


35.4.8 35.4.9

Haloprogin

It is used as an external drug for moderate dermatophyte infections (shingles), and it is effective for superficial candida infections.

Synonym: halotex, mycilan, and micanden



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