Synthetic Compounds for Antifungal Chemotherapy

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Abstract

Systemic fungal infections are major problems in phytopathology and infections caused by fungal species and to treat this various antimicrobial agents have been applied clinically, which is known as antifungal chemotherapy. Amongst various natural antifungal drugs, few are currently used in clinical practice to treat essentially systemic fungal infections because of their low spectrum of activity, toxicity and immunosuppressive nature. These limitation open up a market for new synthetic antifungal drugs or structural modifications of inactive molecules, which will provide a broad spectrum of activity with less toxicity. In this chapter, synthetic compounds for antifungal chemotherapy including various derivatives of azole, fluoropyrimidine, thiocarbamate, allyamines, morpholine, carabrol ester and carboline along with their mechanism, broad spectrum of activity, advantages and limitations have been discussed.

8.1 Introduction

We all are concerned about the coexistence of different microorganisms such as bacteria, viruses, and fungi with other living beings, i.e. humans, plants, and animals in the environment. Although some of these microorganisms are beneficial, many are pathogenic and are responsible for many life-threatening diseases. The therapeutics or therapy term deals with the treatment of these diseases, which may be done either by prevention or cure. The methods used in the therapy fall into three main categories: (i) physiotherapy, (ii) surgery, and (iii) pharmacological therapy (Loevenhart 1926). Pharmacology deals with the study of drugs and its action in the living systems to understand the properties of drugs and their actions, including the interactions of drug molecules with receptors and its effect. Chemotherapy (Northey 1943) is a phase of pharmacology and is broadly defined as the treatment of disease through administration of chemical agents or drugs that are highly toxic to the diseases but have low toxicity to the host. The 'chemotherapy' term was first introduced by Paul Ehrlich based on the affinity of a particular chemical to

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certain living cells. Classification of chemotherapy is not easy as it has a broad field of application. However, on the basis of types of diseases or the nature of pathogen, they can be classified majorly in three categories: (i) anticancer, (ii) antimalarial, and (iii) antimicrobial chemotherapy. The antimicrobial chemotherapy is the clinical application of antimicrobial agents to treat the infectious disease caused by microscopic organisms and which may be categorised into three specific types like antibacterial, antiviral, and antifungal chemotherapy.

In this chapter, we will mainly focus on the available synthetic antifungal drugs for the treatment of various types of fungal infection. Various fungal species are widely distributed in soil, plant debris, and other organic substrates and causes a range of illnesses (mycoses) ranging from the chronic to the serious and can manifest themselves in a variety of ways. These infections can be *superficial*, that is, situated at or close to the surface of the skin, which can affect the body as a whole, instead of individual parts or organs. Diseases such as athlete's foot (tinea pedis), jock itch (tinea cruris), tinea manus (infection of the hand), thrush (oral and vaginal), and onychomycosis (affecting the nails) are some of the specific examples of superficial infections caused by the dermatophytes from the *Trichophyton*, *Microsporum*, *Candida*, and *Epidermophyton* species. The classifications of these diseases are difficult as infections may be caused by one or more of these organisms collectively and they can be developed in such a way that similar symptoms can be caused by different organisms. At the same time, detection of the disease from its symptom caused by a particular fungal agent is difficult because symptoms may vary depending upon the host immunity and physiological condition.

Systemic fungal infections are major problems in phytopathology, and infections caused by fungal species are most common in immune-compromised patient cases such as AIDS, cancer, old age, diabetes, cystic fibrosis, and organ transplants and other invasive surgical procedures. It is estimated that invasive fungal infections develop in 10–25 % of patients with acute leukaemia and those receiving bone marrow transplants (Sahin and Akova 2005). In the USA, *Candida* spp. is the fourth most common nosocomial pathogen with the highest crude mortality rate (40 %). In addition to *Aspergillus* spp., novel and emergent fungal pathogens such as zygomycetes, *Fusarium* spp., or *Scedosporium* spp. have become increasingly important pathogens. Their exposure to presently available antifungals may be limited, and resulting mortality rate is $\geq$70 % in patients with haematological malignancies. So, fungal infections are emerging as a major cause of morbidity and mortality in immune-compromised patients. Still, fungi are one of the most neglected pathogens, as demonstrated by the fact that the amphotericin B, a polyene antibiotic discovered as long ago as 1956, is still used as a 'gold standard' for antifungal therapy. The appearance of AIDS, the re-emergence of TB (including multidrug-resistant strains), and an overall increase in infectious disease mortality during the 1980s and early 1990s provide additional evidence that as long as microbes can evolve, new diseases will emerge. The advent of new diseases underscores the importance of disease prevention through antifungal chemotherapy and continual monitoring of underlying factors that may encourage the emergence or re-emergence of diseases (Spellberg et al. 2004). Following these problems, effort has been given in the hope of finding a substance that will be less toxic to the host and more potent in its particular type of pharmacological activity. In order to get success to treat a particular type of infection by using a synthetic compound, a collective effort of chemists, pharmacologists, and physicians are required.

8.2 Available Drugs in the Market

The growth of antifungal drugs was slow paced despite the knowledge of their existence well before that of bacteria. This is exemplified by the fact that the first antibacterial agent, penicillin, came into use in 1941, whereas the first antifungal agent, nystatin, was not discovered

until 1949. The main reason believed for the slow development of broad-spectrum agents can be heaped on the nature of these fungal diseases; they are eukaryotic species which are biochemically similar to human hosts on contrary to prokaryotes like bacteria. This means that development of a drug to combat fungal infections leaving the human host unaffected is a very difficult job. The natural and synthetic drugs have been developed over the years to treat mycotic infections. Recognition of the rapid expansion of the fungal market has spurred efforts to discover alternative structural classes of antifungal agents. Despite extensive research on the development of new therapeutic strategies, there are few drugs available in the market to cure the invasive mycoses.

During the past two decades, a wide array of antifungal agents have been discovered, which have been or are currently being evaluated for use in treating invasive mycoses and are categorised by their site of action in fungal cells (Dismukes et al. 2000). Indeed, only four molecular classes, namely, (i) fluoropyrimidine analogues, (ii) polyenes, (iii) azoles, and (iv) echinocandins, are currently used in clinical practice to treat essentially systemic fungal infections, which are mainly targeted to three distinct fungal metabolic pathways. Several other classes of antifungal drugs, such as morpholines, allylamines, etc., are used only as topical agents due to either poor efficacy or severe adverse effects when administered systemically. These drugs acted upon fungal strains by three general mechanisms, which are inhibition of cell wall biosynthesis, disruption of the cell membrane, and inhibition of cell division. Inhibition with fungal cell wall biosynthesis has not been as successful and operative as penicillins or cephalosporins against bacteria. Till date, various chemicals have been discovered that interfere with numerous stages in fungal cell wall synthesis with excellent antifungal activity in vitro. Unfortunately, development of these agents into useful drugs has proven to be very difficult. Antifungal agents disrupt the cell membrane by targeting ergosterol, either by binding to the sterol with the formation of pores and effecting the membrane to become leaky (as with polyene antifungals) or inhibiting ergosterol biosynthesis (as seen with azole antifungal agents). Ergosterol is comparable to mammalian cholesterol; thus, agent-binding ergosterol may have a cytotoxic effect in the host tissue. A summary of various classes of antifungal drugs and their mechanism of action has been provided in Table 8.1.

Amongst various available classes of compounds, imidazoles such as clotrimazole, miconazole, sulconazole, and bifonazole work by binding to cytochrome P450, thus blocking ergosterol synthesis in the fungal cell membrane. The development of triazole antifungal agents that were less likely to cause hepatotoxicity possibly due to their diminutive effects on cytochrome P450-dependent enzymes. On the other hand, amongst various triazoles, terconazole was first developed, followed by itraconazole and finally fluconazole. Before the development of fluconazole, the two major antifungal agents existing were amphotericin B and flucytosine. The problems related with amphotericin B are that it has to be given intravenously and had harsh side effects, whereas flucytosine was orally active but had a limited range of action and resistance was easily developed. Later on, amphotericin B (AMB) was incorporated in three lipid formulations to reduce toxicity, while the first-generation triazoles (fluconazole and itraconazole) changed the epidemiology of *Candida* infections and presented a new treatment opportunity. A lot of these antifungals have proven to be less toxic and in some cases more effective than amphotericin B. However, most of the azole antifungals are highly lipophilic and are not effective orally because of their metabolic degradation. In this regard, Janssen Pharmaceutica had developed ketoconazole in mid-1978, which was proven to be effective orally, but it still degraded metabolically. Later on, Pfizer replaced the imidazole unit with 1,2,4-triazole derivative to get better activity. But they are not able to overcome the susceptibility to metabolism with those derivatives, and they found more activity in vivo but four times less potent in vitro. Various substituted

Table 8.1 Various marked antifungal drugs and their mechanism of action

Polyenes
Mechanism of action: binds to ergosterol in the fungal membrane causing the cell membrane to become leaky
Available drug: amphotericin B, nystatin, natamycin
Azoles (mainly imidazoles, triazoles, and thiazole)
Mechanism of action: inhibits ergosterol synthesis, thereby disrupting membrane permeability and also function of membrane-bound proteins
Available drug: ketoconazole, miconazole, clotrimazole, tioconazole, econazole, fenticonazole, sulconazole, sertaconazole, oxiconazole, tinidazole, enilconazole (Imazalil), parconazole, eberconazole, lanoconazole, bifonazole, lombazole, voriconazole, itraconazole, butoconazole, fluconazole, terconazole, posaconazole, abafungin
Allylamines
Mechanism of action: inhibits conversion of squalene to squalene-2,3-epoxide by squalene epoxidase. Squalene is toxic to the cell wall causing P^H imbalances and therefore membrane protein malfunction.
Available drug: amorolfin, butenafine, naftifine, terbinafine, tolnaftate
Echinocandins
Mechanism of action: inhibit the synthesis of glucan in the cell wall, via noncompetitive inhibition of the enzyme 1,3-β glucan synthase
Available drug: pneumocandins, echinocandin B, cilofungin, caspofungin, micafungin, anidulafungin
Thiocarbamate
Mechanism of action: inhibit squalene epoxidase, an important enzyme in the biosynthetic pathway of ergosterol
Available drug: tolnaftate, tolciclate
Other available drugs:
Flucytosine (inhibits cell division via incorporation into RNA leading to faulty RNA synthesis)
Griseofulvin (inhibits microtubule polymerisation, thus inhibiting the formation of mitotic spindle)
Tavaborole (inhibition of leucyl-tRNA synthetase)
Undecylenic acid (inhibition of fatty acid biosynthesis which disrupts germ tube (hyphae) formation)
Ciclopirox (disrupts various enzyme activities including cytochromes, catalase, peroxidise, Na-K ATPase, etc.)
Amorolfine (disrupts the ergosterol biosynthetic pathway by inhibiting δ14 reductase and D8-D7 isomerase enzymes)

bis-triazoles were synthesised and tried to get better activity. Finally, water-soluble fluconazole was discovered for intravenous administration and was found to be very effective for a wide variety of fungal infections and marketed in various countries.

8.3 Synthetic Compounds for Antifungal Chemotherapy

It has been found that the previously discovered natural antifungal drugs have very low spectrum of activity and their applications are limited due to their toxicity and immunosuppressive nature (e.g. amphotericin B). These limitation leads to the development of synthetic drugs. That is why people are giving constant effort to develop structurally new classes of antifungal agents with novel mechanisms of action as well as structural modifications to improve their spectrum of activity. Towards the search for a new antifungal agent, various groups of compounds have been tried. Amongst these various compounds, success has been achieved with some selected groups of compounds like imidazoles, triazoles and thiazole, echinocandins, fluoropyrimidine, morpholine, thiocarbamate, etc. In addition, a good number of synthetic drugs which are designed to bind independently to different biological targets are reported in literature. But due to lack of sufficient biological data, they remain ineffective for clinical trial. Herein, we will discuss various classes of synthetic compounds for antifungal chemotherapy along with their mechanism of action. In this regard, their broad spectrum of activity, advantage, and limitation will also be discussed.

8.3.1 Azoles

In the first place, azoles (mainly imidazoles, triazoles, and thiazole) are by far the most commonly used systemically acting synthetic antifungals in clinical practice. Although imidazoles, triazoles, and thiazole function under a similar mechanism, they behave differently with respect to their fungal spectrum, pharmacokinetics, and toxicities. These agents primarily inhibit the ergosterol biosynthesis by inhibiting the cytochrome P450-dependent enzyme 14-α-demethylase within the fungal cell (Bossche 1997; Andriole 1999; Sheehan et al. 1999). This inhibition occurs through the binding of the free nitrogen atom of the azole ring to the iron atom of the haem group in the enzyme. The subsequent accumulation and metabolism of 14-alpha-methylated sterol species causes the synthesis of toxic compounds, which are unable to successfully replace ergosterol (Carrillo-Munoz 2006). All azoles are fungistatic at their MIC, but some are fungicidal at higher concentrations. This class of compounds includes imidazoles (e.g. econazole, miconazole, bifonazole, butoconazole, tioconazole, ketoconazole, etc.), triazoles (e.g. terconazole, fluconazole, itraconazole, voriconazole, posaconazole, etc.), and thiazole (e.g. abafungin). In addition, many other azole-based antifungal drugs have been synthesised, of which a few are licensed for use in human therapy. Azoles possess very broad activity, with effects on dermatophytes, *Trichophyton*, *Microsporum*, and *Epidermophyton*; dimorphic fungi, *Histoplasma*, *Blastomyces*, and *Coccidioides*; filamentous fungi (moulds), *Aspergillus*; and yeasts, *Candida*, *Cryptococcus*, etc.

8.3.1.1 Imidazoles

Imidazole is an important member of the azole family. Till date, various imidazole compounds have been synthesised and tried for antifungal chemotherapy. Amongst various imidazole derivatives, some compounds fall in the first generation.

First generation: miconazole, econazole, isoconazole, bifonazole, eberconazole, lombazole, sertaconazole, tioconazole, lanoconazole, clotrimazole (Pelletier et al. 2000), fenticonazole, sulconazole, and tinidazole

These early imidazoles have very poor aqueous solubility because of the lipophilic nature and are generally ineffective for oral or systemic therapy. However, they have exceptional skin/mucous membrane compatibility and hence are beneficial for topical application. They are normally applied either as creams for dermatophyte infections or as 'nail varnish' formulations for onychomycosis. Amongst various first-generation imidazoles, miconazole provides an exception to the others because it is absorbed in the gut slightly better. Thus, a gel formulation of miconazole is available for oral and intestinal fungal infections. However, miconazole has strong binding affinity to lipoproteins (up to 95 % is protein bound and only 20–30 % of a dose is detectable in the blood). So, its 'effective' concentration is hence much decreased. The incidences of secondary resistance were uncommon with these drugs, but are now rising from 1990s onwards. Some of the common disadvantages associated with these drugs are (i) potential hepatotoxic effects in long-term therapy, (ii) possible teratogenic/embryotoxic effects, and (iii) that they may affect testosterone/corticosteroid synthesis (acting against other cytochrome P450 enzymes).

Janssen sought to improve upon miconazole and econazole, but keeps hold of the important advantages of the early imidazoles, namely, high antimycotic activity and broad spectrum of activity. Their main aim was to provide a drug that was bioavailable, i.e. that was more soluble in water and could be used for systemic infections either by injection or as a tablet. In 1979, ketoconazole (Bossche 1997), a *second-generation* drug containing imidazole group, was found to be suitable to treat fungal infections of the skin such as athlete's foot, jock itch, ringworm, and seborrhoea (dry, flaking skin) and is available as a cream, gel, and shampoo. Some of the drawbacks associated with the ketoconazole are (i) limited efficacy against *Aspergillus*, (*ii*) metabolically vulnerable (<5 % excreted unchanged), (iii) 95–99 %

of drug bound to lipoproteins in serum (activity drops 10–1,000-fold in the presence of serum with in vitro tests), (iv) poor penetration into CSF, and (v) best absorbed by the gut in acid conditions, so antacids should not be prescribed at the same time as ketoconazole. Some of the selected structure along with their MIC value against the fungal strain was described in Table 8.1.

8.3.1.2 Triazoles

The triazoles (Shalini et al. 2011) are also an important member of azole family, which are active against *Candida albicans*, non-*albicans Candida* spp., *Cryptococcus neoformans*, and the dimorphic fungi. Amongst non-*albicans Candida* spp., they are less active against *Candida glabrata* and inactive against *Candida krusei* with the exception of voriconazole and some investigational triazoles. Various *Aspergillus* spp. and dematiaceous patterns are only affected by itraconazole and voriconazole. The *first-generation* triazoles are fluconazole and itraconazole (Loevenhart 1926). Fluconazole, a fungistatic agent, is active against *Candida albicans*, *Candida tropicalis*, and *Candida glabrata*. Fluconazole is also used for the treatment of meningitis, cryptococcal meningitis, and systemic and mucosal candidiasis in both normal and immune-compromised patients. It is also used to treat coccidioidal meningitis, histoplasmosis, and infections due to chemotherapy or radiation therapy prior to a bone marrow transplant. Fluconazole circulates in plasma as the free form and is excreted unchanged through the kidneys. It is also orally bioavailable because it shows negligible hepatic metabolism. Almost 94 % fluconazole is absorbed and its oral bioavailability is not affected by food or gastric pH. On the other hand, itraconazole is largely metabolised in the liver by cytochrome P450 3A4, an active metabolite produced which is excreted in an inactive form via the liver and kidneys. It has strain-dependent fungicidal activity against filamentous fungi with the exception of some strains of *Cryptococcus neoformans*. It is taken orally as a capsule to treat fungal infections that start in the lungs and spread throughout the body. It can also be used to treat fungal infections of the nails and its oral solutions are useful to treat oral candidiasis. The most common side effects associated with itraconazole are constipation, heartburn, bleeding gums, headache, and dizziness. The more severe side effects with itraconazole can include excessive tiredness, nausea, vomiting, loss of appetite, tingling or numbness in the extremities, and difficulty in breathing or swallowing. The second-generation azole derivatives are voriconazole, posaconazole, and ravuconazole (Northey 1943). In 2002, voriconazole was first marketed and accepted as a first-line cure of oesophageal candidiasis; candidaemia; invasive aspergillosis; candidal infections of the skin; infections in the abdomen, kidney, and bladder wall and wounds; and infections caused by *Scedosporium apiospermum* and *Fusarium* spp. It is available for both oral and intravenous (i.v.) administration. Although it is orally bioavailable, it exhibits nonlinear pharmacokinetics. Voriconazole is metabolised in the liver, and, in case of renal failure, its excretion is not affected. Voriconazole interacts with drugs that are substrates of cytochrome P450 3A4 (terfenadine, cisapride, etc.), by increasing their serum levels. Its intake should be avoided in those patients who are taking cyclosporine, rifampicin, carbamazepine, ritonavir, and long-acting barbiturates.

Posaconazole is a hydroxylated analogue of itraconazole, which became available in Europe in 2005 and was approved by the Food and Drug Administration (FDA) in 2006. It has a wide range of antifungal activity against various fungal strains, viz. *Candida* spp. resistant to older azoles, *Cryptococcus neoformans*, *Aspergillus* spp., *Rhizopus* spp., *Bacillus dermatitidis*, *Candida immitis*, *Histoplasma capsulatum*, and other opportunistic filamentous and dimorphic fungi (Andriole 1999). Posaconazole is available only for oral administration, and it is 8–47 % bioavailable on an empty stomach, which increases by 400 % with the ingestion of a fatty meal. It is primarily metabolised by the liver, and approximately 77 % of the unaltered drug is excreted in

the faeces and small amount in the urine. The posaconazole shows good efficiency for the treatment of zygomycosis, invasive fusariosis, cryptococcal meningitis, coccidioidomycosis, and other central nervous system fungal infections. A few common side effects associated with posaconazole are nausea, vomiting, headache, abdominal pain, and diarrhoea. Ravuconazole is another second-generation azole antifungal agent, which is highly active against a wide range of fungi, including *Candida* spp., *Candida neoformans*, and other yeast species, as well as isolates that are resistant to fluconazole (Gomez-Lopez et al. 2004). An in vitro study evaluating the activity of ravuconazole against 923 clinical isolates of non-dermatophyte filamentous fungi showed that the drug is highly active against *Aspergillus* spp. and has inhibitory activity against other species of hyaline filamentous fungi and zygomycetes and black moulds. The study further indicated that it is active against 56.2 % of *Mucorales* tested, whilst itraconazole was active only against one-third of the isolates, and voriconazole was inactive against almost the whole collection of *Mucorales*. Ravuconazole shows linear pharmacokinetics over the anticipated dosage range and undergoes hepatic metabolism, and it also has a significant potential for drug-drug interactions through the cytochrome P450 enzyme system (Table 8.2).

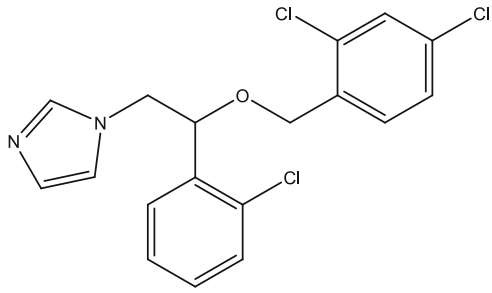
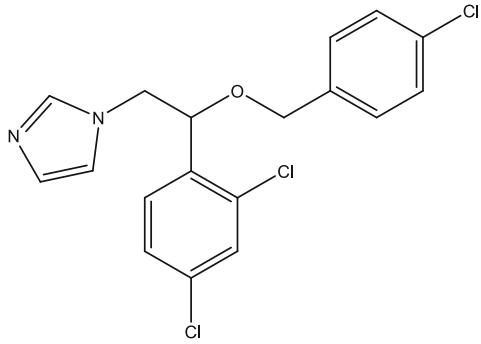
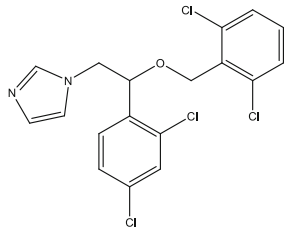
8.3.1.3 Other Imidazole Derivatives

In addition to the marketed imidazole antifungal drugs, several other imidazole derivatives have been synthesised so as to extend the spectrum of antifungal chemotherapy. Amongst various synthesised imidazoles, some selected compounds were found active against different fungal strains, which are summarised in Table 8.3. In this regard, Rauf et al. reported a series of two-substituted imidazole derivatives, which were found potent against fungal strains, *A. niger*, *C. albicans*, *Penicillium* spp., *T. viride*, and *Helminthosporium oryzae*, with MIC of 75–150 μg/ml when evaluated via disc diffusion method. All compounds are good antimycotics against yeasts and dermatophytes and are more active than bifonazole. The unsubstituted derivative of **1b** has MIC value ranging from 0.4 to 33 μg/ml which appeared to be most active in this series. On the other hand, Ogata et al. reported 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1H-imidazole hydrochloride (**1e**) that was found to be active against typical dermatophyte species with MIC 0.16–1.25 μg/ml and *Aspergillus* spp. and *Penicillium* spp. with MIC 0.63–5 μg/ml. Mamolo et al. reported 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives (**1h**) which show better in vitro antifungal activity than miconazole. Karaburan et al. reported aryl[3-(imidazol-1-ylmethyl)benzofuran-2yl] ketoximes (**1l**) with moderate antifungal potency of MIC 5–25 μg/ml. On the other hand, Na et al. reported a series of 1-benzyl-3-(imidazol-1-ylmethyl)indole derivatives (**1m**), and all the compounds were tested against two human fungal pathogens, *C. albicans* and *A. fumigatus* with good activity. Mullen et al. also reported 3,5-diphenyl-3-(1H-imidazol-l-ylmethyl)-2-alkylisoxazolidine derivatives (**1o**) which were found to be the most potent compounds in vitro with MIC values ranging between 0.2 and 7.0 μg/ml (Rani et al. 2013).

8.3.1.4 Fluoropyrimidines

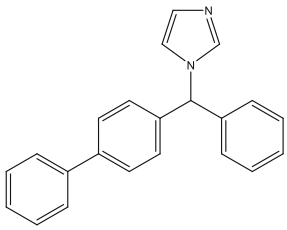
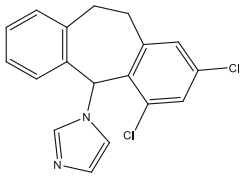
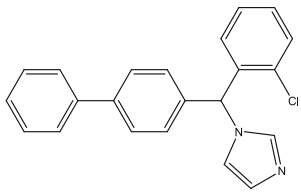
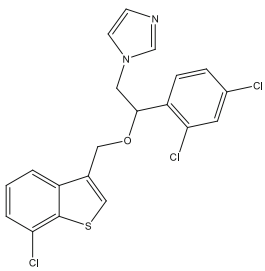
Fluoropyrimidines (Vandeputte et al. 2011) are a class of compounds, of which only 5-fluorocytosine (5-FC) and 5-fluorouracil (5-FU) are used in human drugs and are synthetic structural analogues of the DNA nucleotide cytosine of candidiasis. It inhibits pyrimidine metabolism via intrusion with RNA and protein synthesis in the fungal cell (Spellberg et al. 2004). In 1964, 5-FC was shown to be active in vivo (mice) against experimental cryptococcal and candidal infections. Its spectrum of activity is narrow and 8–10 % of *Candida* strains are resistant, which is a major drawback for this compound and is limited to yeast infections. Thus, it is used for cryptococcal meningitis and in case of dissemination in combination with

Table 8.2 The structure and activity against particular fungal strain of various azoles

Compound	Fungal strains	MIC (μg/ml)
Miconazole  Meerpoel et al. (2010)	*T. mentagrophytes*	0.312–80
	T. rubrum	0.312–0.55
	T. tonsurans	10
	T. verrucosum	8
	M. audouinii	9–10
	M. gypseum	10–12
	Epidermophyton floccosum	0.4–0.625
	C. albicans	0.25–32
	C. parapsilosis	0.12–0.5
	C. tropicalis	0.5–16
	C. krusei	2–4
	C. guilliermondii	0.25–1
	C. glabrata	<0.05–3.125
	Cryptococcus neoformans	0.625–1.95
	Geotrichum candidum	40
	Torulopsis glabrata	1.25
	Malassezia furfur	0.88–6.25
	A. fumigatus	33.1–160
	A. niger	22–40
	A. flavus	12
Econazole  Meerpoel et al. (2010)	*T. mentagrophytes*	0.60–0.80
	T. rubrum	0.58
	T. tonsurans	4
	T. verrucosum	10
	M. audouinii	10
	M. gypseum	1.3
	Epidermophyton floccosum	0.25–32
	C. albicans	0.25–4
	C. parapsilosis	0.5–16
	C. tropicalis	4–8
	C. krusei	0.5–4
	C. guilliermondii	<0.05–12.5
	C. glabrata	2.25–2.62
	Cryptococcus neoformans	40
	Geotrichum candidum	0.31
	Torulopsis glabrata	0.78–6.25
	Malassezia furfur	28
	A. fumigatus	18
Isoconazole  Meerpoel et al. (2010)	*C. albicans*	0.12–4
	C. parapsilosis	0.12–0.25
	C. tropicalis	0.12–2
	C. krusei	1–2
	C. guilliermondii	0.12–1

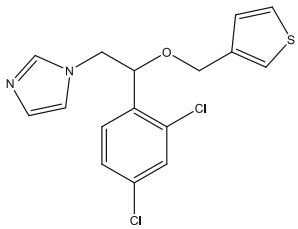
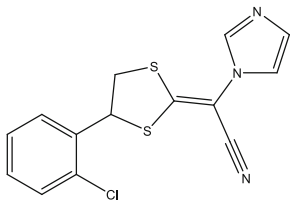
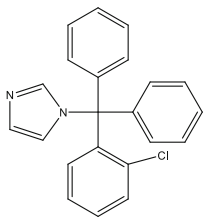
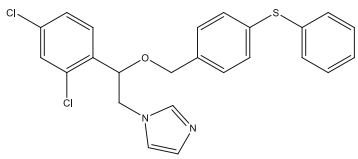
(continued)

Table 8.2 (continued)

Compound	Fungal strains	MIC (μg/ml)
Bifonazole  Baziard et al. (2011)	*A. niger*	4
	C. albicans	128
	C. krusei	128
	T. rubrum	4
	C. tropicalis	–
	C. glabrata	–
	Candida spp.	–
	Aspergillus spp., *Trichophyton* spp.	–
Eberconazole  Guarro et al. (2003)	*E. floccosum*	0.03–1
	M. audouinii	0.03–2
	M. canis	0.01–4
	M. canis	0.03–0.5
	M. ferrugineum	0.03–2
	M. fulvum	0.03–1
	M. gallinae	0.03–8
	M. gypseum	>16
	M. racemosum	0.03–2
	T. balcaneum	0.03–4
	T. rubrum	0.03–4
	T. tonsurans	0.125–>16
	T. simii	0.03–8
Lombazole 	*C. albicans*	–
Sertaconazole  Meerpoel et al. (2010)	*C. albicans*	0.03–1
	C. parapsilosis	0.06–0.5
	C. tropicalis	0.125–8
	C. krusei	0.06–4
	C. glabrata	0.125–0.5

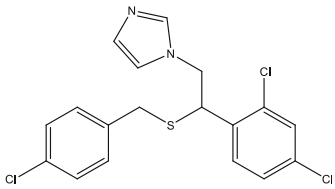
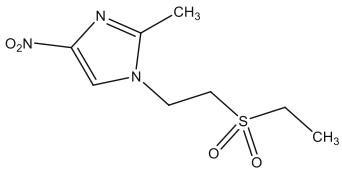
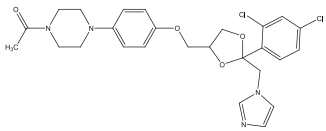
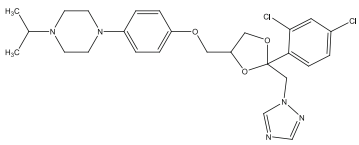
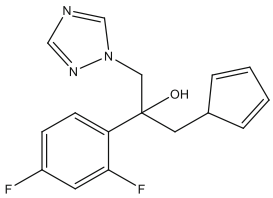
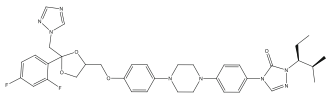
(continued)

Table 8.2 (continued)

Compound	Fungal strains	MIC (μg/ml)
Tioconazole  Jevons et al. (1979)	*C. albicans*	1.6–12.5
	Candida spp.	<0.01–6.3
	Cryptococcus neoformans	0.01–0.4
	Torulopsis glabrata	0.05–0.07
	Aspergillus fumigatus	3.1–9.4
	Aspergillus fumigatus	3.1–6.2
	Aspergillus fumigatus	0.08–0.18
	T. mentagrophytes	0.5
	T. rubrum	0.3–0.5
Lanoconazole  Koga et al. (2006) Niwano et al. (1995)	*C. albicans*	0.63–5
	Trichophyton rubrum	0.00024–0.016
	T. mentagrophytes	0.0005–0.004
	Epidermophyton floccosum	0.001
Clotrimazole  Borelli et al. (2007)	*C. albicans*	2–32
	C. glabrata	1–32
	C. guilliermondii	1–>64
	C. krusei	1–2
	C. tropicalis	2–8
	C. parapsilosis	1–>64
	T. rubrum	0.06
	T. mentagrophytes	0.06–1.0
	A. fumigatus	1–2
	A. niger	1–4
	M. gypseum	0.06
Fenticonazole 	*T. mentagrophytes*	0.28–20
	T. rubrum	0.33–0.625
	T. verrucosum	1.25
	T. tonsurans	0.25
	M. canis	5–20
	M. audouinii	8–9.2
	M. gypseum	5–8.8
	Epidermophyton floccosum	0.625–1.1
	C. albicans	0.25–32
	C. parapsilosis	0.25–1
	C. tropicalis	0.5–16
	C. krusei	4–16
	C. guilliermondii	2–8
	C. glabrata	0.03–2
	Cryptococcus neoformans	0.312–0.55
	Geotrichum candidum	40
	Torulopsis glabrata	40
	A. fumigatus	22.3–160
	A. niger	10–37.5
	A. flavus	10

(continued)

Table 8.2 (continued)

Compound	Fungal strains	MIC (μg/ml)
Sulconazole  Meerpoel et al. (2010)	*C. albicans*	0.12–8
	C. parapsilosis	0.12–8
	C. tropicalis	0.25–8
	C. krusei	4–8
	C. guilliermondii	0.5–2
Tinidazole X 	*B. fragilis* subsp. *fragilis*	0.4–1.6
Ketoconazole  Meerpoel et al. (2010)	*C. albicans*	0.03–0.25
	C. parapsilosis	0.03–0.06
	C. tropicalis	0.03–4
	C. krusei	0.03–
	C. guilliermondii	0.5–4
	C. glabrata	0.03–2
Terconazole 	*M. canis*	
	T. mentagrophytes	
	T. rubrum	
	Cryptococcus neoformans	
	C. albicans	
	C. tropicalis	
	Phialophora verrucosa	
	Sporothrix schenckii	
	A fumigatus	
	Mucor spp.	
	Saprolegnia spp.	
Fluconazole  Sanclemente et al. (2009)	*C. parapsilosis*	0.125–8
	C. albicans	0.125–4
	C. guilliermondii	0.125–64
	C. tropicalis	0.125–1
	T. rubrum	1–64
	T. mentagrophytes	16–64
	M. gypseum	64
Posaconazole  Pfaller et al. (2011)	*C. albicans*	0.007–2
	C. glabrata	0.007–8
	C. parapsilosis	0.007–1
	C. tropicalis	0.007–2
	C. krusei	0.015–1
	C. lusitaniae	0.007–1
	C. guilliermondii	0.015–2
	C. kefyr	0.007–25

(continued)

Table 8.2 (continued)

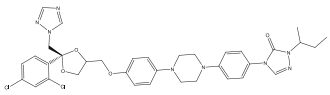
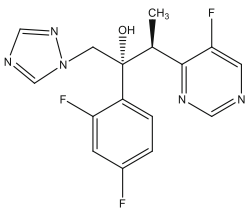
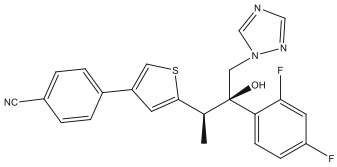
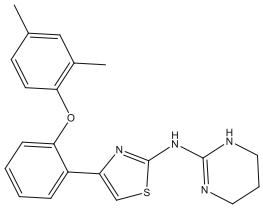
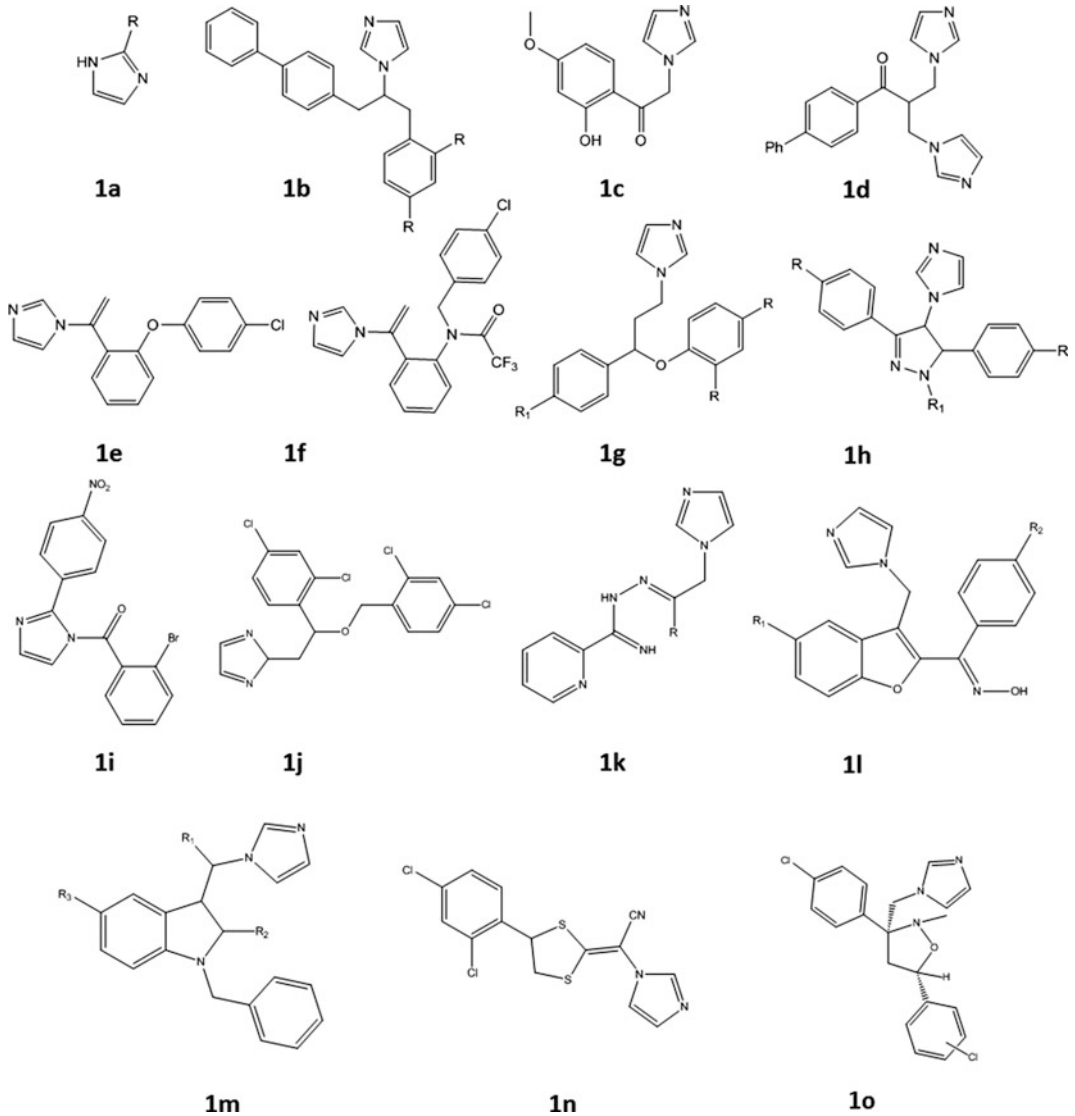
Compound	Fungal strains	MIC (μg/ml)
Itraconazole  Sanclemente et al. (2009)	*C. parapsilosis*	0.031–0.5
	C. albicans	0.031–0.5
	C. guilliermondii	0.031–16
	C. tropicalis	0.031–0.125
	T. rubrum	0.06–1
	T. mentagrophytes	0.03–0.5
	M. gypseum	0.25–1.0
Voriconazole  Cuenca-Estrella et al. (2004)	*C. albicans*	0.031–0.5
	C. glabrata	
	C. parapsilosis	
	C. tropicalis	
	C. Krusei	
	C. lusitaniae	
	C. guilliermondii	
Ravuconazole  Estrella et al. (2004)	*C. albicans*	0.031–16
	C. glabrata	
	C. parapsilosis	
	C. tropicalis	
	C. krusei	
	C. guilliermondii	
	C. lusitaniae	
	C. haemulonii	
	C. dubliniensis	
	C. rugosa	
	C. inconspicua	
	C. zeylanoides	
	D. hansenii	
	S. cerevisiae	
	Y. lipolytica	
	Arxiozyma telluris	
	T. delbrueckii	
Abafungin  C. Borelli et al. (2008)	*T. mentagrophytes*	0.031–0.125
	T. rubrum	
	T. equinum	
	C. albicans	
	C. glabrata	
	C. krusei	
	C. tropicalis	
	C. parapsilosis	
	A. fumigatus	
	A. niger	
	A. amstelodami	
	M. mycetomatis	

Table 8.3 Structures and activities against specific fungal strains of some imidazole derivatives

Compounds	Fungal strain	MIC (μg/ml)
		
1a	*A. niger*	0.06–1
	C. albicans	
	Penicillium spp.	
	T. viride	
	Helminthosporium oryzae	
1b	*C. albicans*	0.03–0.5
	C. parapsilosis	
	C. neoformans	
	T. verrucosum	
	T. rubrum	
	M. gypseum	
	A. fumigates	

(continued)

Table 8.3 (continued)

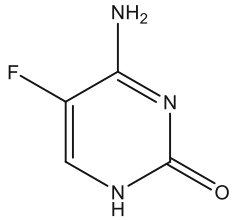
Compounds	Fungal strain	MIC (μg/ml)
1c	*C. albicans*	0.25–1.0
	C. parapsilosis	
	C. neoformans	
	T. verrucosum	
	T. rubrum	
	M. gypseum	
1d	*C. albicans*	2–4
1e	*Dermatophyte* spp.	0.16–1.25
	Aspergillus spp. and *Penicillium* spp.	0.63–5.0
	Candida spp. and other yeasts	10–80
1f	*C. albicans*	1.6–50
	A. fumigates	
	T. asteroids	
1g	*C. albicans*	0.125–128
1h	*C. albicans*	0.06
1i	*A. niger*	4
	C. albicans	16
1j	*E. floccosum*	25–100
	P. notatum	
	A. niger	
	A. fumigates	
	C. albicans	
	Torulopsis glabrata	
1k	*C. albicans*	0.125–2
1l	*Candida*	5–25
1m	*C. albicans*	1–6
	A. fumigatus	
1n	*T. mentagrophytes*	0.0093
	T. rubrum	0.0015
1o	*C. parapsilosis*	0.2–7.0
	C. neoformans	
	C. albicans	
	T. verrucosum	
	T. rubrum	
	M. gypseum	

amphotericin B. The structure along with the MIC value against fungal strain has been described in Table 8.4. In spite of its numerous pharmacological advantages, the use of 5-FC in clinical practice is shrinking because of the frequent incidence of innate or acquired resistance to this drug in fungal pathogens. The common side effect associated with 5-FC are mainly due to the long courses of therapy that include gastrointestinal (GI) disorders, nausea, and diarrhoea and in serious cases ulceration and enterocolitis. On the other hand, its excretion occurs through the kidneys, so renal function is sometimes impaired with extended dosing.

8.3.1.5 Thiocarbamates

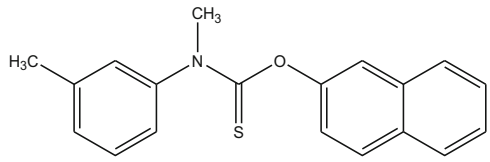
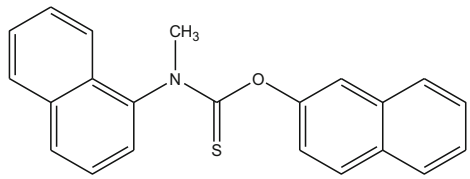
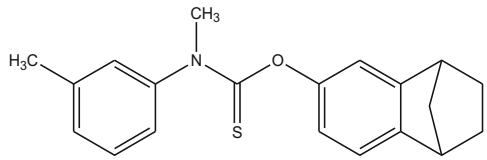
The thiocarbamates were found to have strong and selective in vitro antifungal properties against *Trichophyton* spp. They are mostly used for the topical treatment of skin mycoses like athlete's foot, but are not very effective against nail and scalp mycoses. However, they are very

Table 8.4 The structure and activity against particular fungal strain of 5-FC

Compound	Sensitive fungal strains with species	MIC (μg/ml)
Flucytosine	*C. albicans*	0.12–128.0
	FLZ-R	
Estrella et al. (2004)	FLZ-S	
	Candida parapsilosis	0.12–1.0
	FLZ-R	
	Candida tropicalis	0.12–16.0
	FLZ-R	
	Candida glabrata	0.06–4.0
	FLZ-R	
	Candida krusei	0.50–8.0
	FLZ-R	
	Candida lusitaniae	0.25–1.0
	FLZ-R	
	Candida dubliniensis	0.12
	FLZ-R	0.12
	FLZ-S	
	Candida rugosa	1.0
	FLZ-R	0.25–1.0
	FLZ-S	
	Candida inconspicua	1.0
	FLZ-R	0.25
	FLZ-S	
	Candida zeylanoides	0.25–1.0
	FLZ-R	
	Debaryomyces hansenii	0.12–0.25
	FLZ-S	
	Saccharomyces cerevisiae	0.25–4.0
	FLZ-R	0.12–16.0
	FLZ-S	
	Torulaspora delbrueckii	0.25
	FLZ-R	0.12–0.25
	FLZ-S	
	Pichia membranifaciens	0.50–4.0
	FLZ-R	
	Pichia norvegensis	1.0–16.0
	FLZ-R	
	Rhodotorula glutinis	0.25–1.0
	FLZ-R	

active against actively growing cells only. The thiocarbamates inhibit the activity of squalene epoxidase, a key enzyme in the biosynthetic pathway of sterol production (Ryder et al. 1986). For topical application, they are commonly administered as a 1 % solution or

Table 8.5 In vitro MICs of thiocarbamates against various fungal strains

Compound	Fungal strains	MIC (μg/ml)
Tolnaftate or napthiomate T	Dermatophytes	0.1–1
		
Boa et al. (course synopsis)		
Napthiomate N	Dermatophytes	–
		
Boa et al. (course synopsis)		
Tolciclate	*C. albicans*	–
	*C. parapsilosis*	
Ryder et. al. (1986)	*T. mentagrophytes*	

cream in polyethylene glycol. The structures of various thiocarbamate derivatives as well as their in vitro MIC values are provided in Table 8.5.

8.3.1.6 Allylamine Derivatives

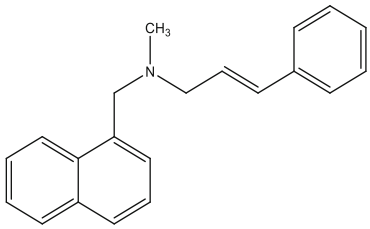
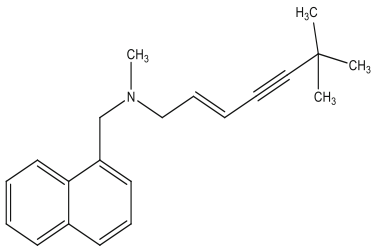
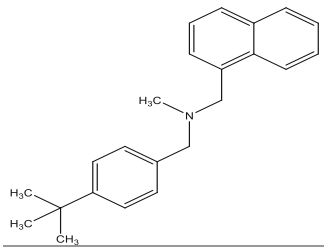
In this category, the general structural motif for all active compounds is a tertiary allylamine.

In this family, naftifine is topically active against dermatophytes and shows some activity against yeasts (Georgopoulos et al. 1981). On the other hand, terbinafine is active against a wider range of fungi including *Aspergillus*, *Histoplasma*, and *Candida* species. The *tert-butyl* side chain of terbinafine is essential for activity against these particular fungi, and it is most active against dermatophytes (Petranyi et al. 1987). Like thiocarbamates, allylamines also inhibit the squalene epoxidase (Ryder and Dupont 1985; Ryder 1989), a key enzyme in the biosynthetic pathway of sterol production, and activity appears to be due to the intolerance of the fungal cell to increased squalene levels. However, the fungicidal *Candida albicans* can tolerate higher levels of squalene and show only fungistatic susceptibility to allylamines, whereas terbinafine is 100-fold more active compare to naftifine and is used to treat for ringworm and nail infections where oral administration is considered appropriate. Terbinafine may also be administered topically as a 0.5–1.0 % cream. Moreover, groupings of azoles and terbinafine are predicted to exhibit positive result in the treatment of mycosis (Garcia-Effron et al. 2004; Andriole 1998). Terbinafine has been reported to cause gastrointestinal disturbance and nausea when used orally, and in rare cases serious skin reactions can be triggered (Table 8.6).

8.3.1.7 Morpholine Derivatives

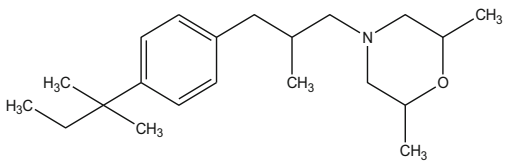
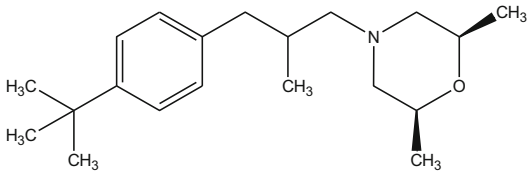
The morpholines were discovered in the late 1960s as a sequel from research into plant growth regulators and were initially used as agricultural fungicides. Tridemorph and dodemorph are the examples of the agricultural fungicides. Tridemorph has been used to treat yellow rust

Table 8.6 In vitro MICs of various allylamines against various fungal strains

Compound	Fungal strains	MIC (μg/ml)
Naftifine	*Trichophyton* spp.	0.1–0.2
	*E. floccosum*	0.1–0.2
Georgopoulos et al. (1981)	*Microsporum* spp.	0.1–0.2
	Aspergillus spp.	0.8–12.5
	Sporothrix schenckii	0.8–1.5
	Candida spp.	1.5–≥100
Terbinafine	*T. rubrum*	0.007–0.06
	*T. mentagrophytes*	0.007–0.06
Sanclemente et al. (2009)	*M. gypseum*	0.015–0.125
	C. albicans	8–>64
Borelli et al. (2008)	*C. glabrata*	32–>64
	C. krusei	>64
	C. guilliermondii	>64
	C. tropicalis	>64
	C. parapsilosis	>64
Butenafine	Dermatophytes	0.0015–0.05
	*Aspergillus*	0.025–0.78
	Cryptococcus neoformans	0.025–0.78
	Candida	0.78–1.56

in cereals, Dutch elm disease, and the banana fungal disease sigatoka. On the other hand, dodemorph was used to treat powdery mildews. The early morpholines were 4-alkyl-cis-2,6-dimethylmorpholines and were at first incorrectly believed to act in a similar fashion to the polyenes as the 4-alkyl group was most often a long or large-ring lipophilic alkyl group. These plant fungicides led the foundation for search of morpholines with applications in the field of human mycoses via fenpropimorph and culminating in the discovery of amorolfine in 1981. Amorolfine and fenpropimorph are strong inhibitors of fungal pathogens in both plants and humans and are highly active against dermatophytes. Depending upon the substituent,

Table 8.7 In vitro MICs of various morpholines against various fungal strains

Compound	Fungal strains	MIC (μg/ml)
Amorolfine	Dermatophytes	0.06
	Dimorphic fungi	0.1
Marcireau et al. (1990)	Dematiaceous fungi	0.07
	Yeasts	0.5
	Alternaria	0.3
	Scopulariopsis	0.3
Fenpropimorph	*S. cerevisiae*	0.1 for cholestenol
		0.1–0.3, lanosterol
Marcireau et al. (1990)		>60, ergosterol

morpholines act at multiple sites in the ergosterol biosynthetic pathway each to a different degree. The structure of various morpholines along with their in vitro MICs is provided in Table 8.7. Fenpropimorph and amorolfine are about 100-fold more active than tridemorph against the δ14 reductase, perhaps indicating this enzyme's significance to treat human mycoses with this class of drugs. Topical use of amorolfine can lead to temporary burning sensations, erythema, and pruritus.

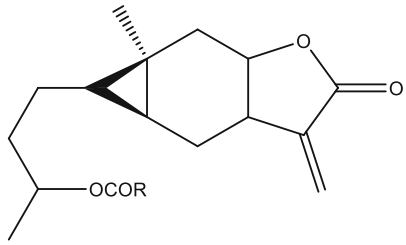
8.3.1.8 Carabrol Ester Derivatives

In an important contribution, Zhang et al. synthesised and characterised 38 new ester derivatives of carabrol (Feng et al. 2012). The antifungal activities of all the synthesised compounds were evaluated using a spore germination assay against the fungal pathogen *Colletotrichum lagenarium*. They observed that out of those 38 ester derivatives, 16 have higher antifungal activity than that of carabrol and 7 compounds have higher antifungal activity than that of carabrone. The study revealed that the C-4 position of carabrol was a key position for possessing its antifungal activity, which exhibited the deviation of 50 % inhibition concentration (IC50) from 2.70 to 52.33 μg/ml. The electron-withdrawing groups at the phenyl ring of carabrol ester derivative showed higher activity compared to electron-donating groups. Two ester derivatives, carabryl 4-cynaobenzoate (**2p**, IC50, 2.70 μg/ml) and carabryl 4-isopropylbenzoate (**2q**, IC50, 2.82 μg/ml), exhibited only somewhat lower antifungal activity than that of the positive control chlorothalonil (IC50, 0.87 μg/ml) and have been recognised as prospective leads for progress of new environmentally friendly fungicides (Table 8.8).

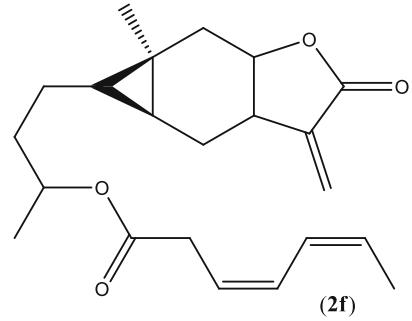
8.3.1.9 Carboline Derivatives

β-Carboline alkaloids (Cao et al. 2007) are a large collection of natural and synthetic indole alkaloids and are widely distributed in nature,

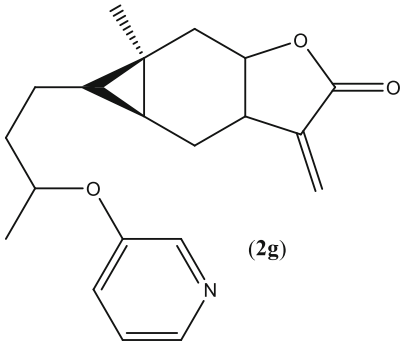
Table 8.8 The IC50 of some selected carabrol ester derivatives against spore germination of *C. lagenarium*



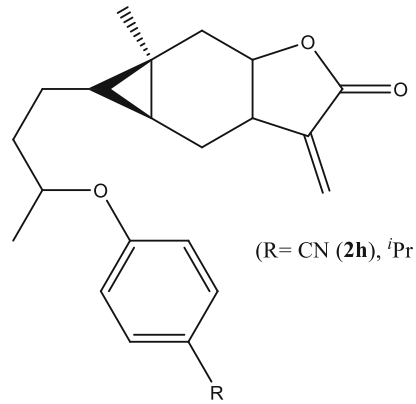
R= CH_3 (**2a**), CH_2Cl (**2b**), CH_2CH_3 (**2c**), $CH_2CH_2CH_3$ (**2d**), $CH_2(CH2)_2CH_3$ (**2e**)



(**2f**)



(**2g**)



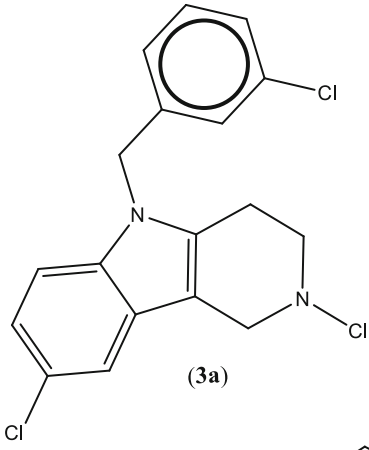
(R= CN (**2h**), ^{i}Pr (**2i**)

Fungal strain	Compounds	IC_{50}(μg/ml)[a]
C. lagenarium	**2a**	10.77 ± 0.09
	2b	4.51 ± 0.06
	2c	23.28 ± 0.57
	2d	28.84 ± 0.41
	2e	31.19 ± 0.59
	2f	8.41 ± 0.53
	2g	8.26 ± 0.25
	2h	2.70 ± 0.13
	2i	2.82 ± 0.12

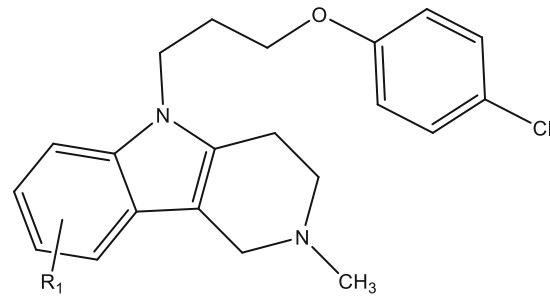
[a]All values are presented as means ± SD ($n = 3$). And chlorothalonil was used as the positive control

comprising various foodstuffs, plants, marine creatures, insects, mammalians as well as human tissues and body fluids. Most of these compounds are of great interest due to their diverse biological activities. In this regard, Zhang et al. have designed and synthesised a series of novel antifungal carboline derivatives which showed broad-spectrum antifungal activity. Particularly, compound **4d** showed comparable in vitro antifungal activity to fluconazole and showed almost negligible toxicity to human embryonic lung cells. It also showed good fungicidal activity against both fluconazole- sensitive and fluconazole-resistant *Candida albicans* cells. Moreover, **4d** exhibited good synergistic antifungal activity in combination with fluconazole against fluconazole-resistant *Candida* species. Preliminary mechanistic study revealed that **4d** might act by inhibiting the synthesis of fungal cell wall (Wang et al. 2014) (Table 8.9).

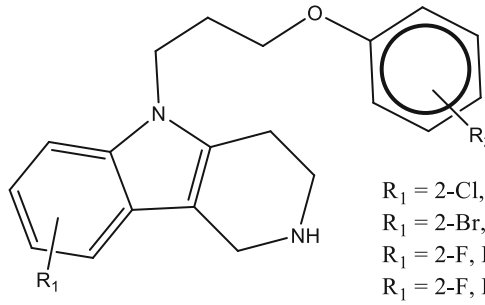
Table 8.9 Structure and activity against specific strains of some carboline derivatives



(**3a**)



R_1 = 2-CH_3 (**3b**); R_1= 2-OCH_3 (**3c**)



R_1 = 2-Cl, R_2 = 4-F (**4a**)
R_1 = 2-Br, R_2 = 4-F (**4b**)
R_1 = 2-F, R_2 = 4-^{t}Bu (**4c**)
R_1 = 2-F, R_2 = 4-Cl (**4d**)

Compounds	Fungal strain	MIC_{80} (μg/ml)
3a	*C albicans*	64
	C. parapsilosis	32
	C. neoformans	16
	C. glabrata	16
	A. fumigatus	32
	T. rubrum	8
	M. gypseum	16
3b	*C albicans*	32
	C. parapsilosis	16
	C. neoformans	8
	C. glabrata	16
	A. fumigatus	16
	T. rubrum	8
	M. gypseum	8
3c	*C albicans*	32
	C. parapsilosis	32
	C. neoformans	8
	C. glabrata	>64
	A. fumigatus	32
	T. rubrum	8
	M. gypseum	8

(continued)

Table 8.9 (continued)

Compounds	Fungal strain	MIC_{80} (μg/ml)
4a	*C albicans*	4
	C. parapsilosis	4
	C. neoformans	4
	C. glabrata	4
	A. fumigatus	4
	T. rubrum	8
	M. gypseum	4
4b	*C albicans*	4
	C. parapsilosis	4
	C. neoformans	4
	C. glabrata	16
	A. fumigatus	4
	T. rubrum	8
	M. gypseum	4
4c	*C albicans*	8
	C. parapsilosis	8
	C. neoformans	4
	C. glabrata	4
	A. fumigatus	16
	T. rubrum	4
	M. gypseum	4
4d	*C albicans*	1
	C. parapsilosis	2
	C. neoformans	4
	C. glabrata	4
	A. fumigatus	4
	T. rubrum	2
	M. gypseum	1

8.3.1.10 Miscellaneous

8.3.1.10.1 5-Amino-6-arylamino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one Derivatives

Wang et al. synthesised some new 5-amino-6-arylamino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives (Wang et al. 2008) via tandem aza-Wittig and annulation reactions of iminophosphorane and aromatic isocyanates. From bioassay analysis, they found that both the derivatives (5a-5c and 6a-6d) possessed high antifungal activity against *Botrytis cinerea* Pers. and *Sclerotinia sclerotiorum*. Especially, compounds **6a**, **6b**, and **6c** shows 100 % inhibition against *Sclerotinia* at the concentration in 50 mg/L. At the same time, it shows almost 80–90 % inhibition activity against *Sclerotinia* at 10 mg/L. Both the derivatives were found to be active against *Botrytis* at 50 mg/L. For example, inhibitory rates of compounds **5a**, **5b**, **5c**, **6a**, **6b**, **6c**, and **6d** were 93 %, 87 %, 99 %, 91 %, 99 %, 99 %, and 97 %, respectively.

8.3.1.10.2 β-Trifluoroalkyl Aminovinyl Ketone Derivatives

Gellerman et al. synthesised ten β-trifluoroalkyl aminovinyl ketone derivatives and their inhibitory effect on several phytopathogenic fungi, an oomycete and plants were tested. The fungal strains used in their study were *Sclerotinia sclerotiorum*, *Alternaria alternata*, *Botrytis cinerea*, *Rhizoctonia solani*, *Penicillium digitatum*, *Pythium aphanidermatum*, and *Neurospora crassa*, and they were cultured on potato

dextrose agar. Almost all the synthesised compounds exhibited some degree of toxicity towards the filamentous fungi in different extent. Most of the compounds were found to be fungitoxic at the dose of 10–100 μg/ml. Amongst all the tested compounds, (Z)-3-amino-4,4,4-trifluoro-1-(4-chlorophenyl)but-2-en-1-one (**7a**) showed the highest inhibitory effect, whilst **7b** and **7c** were the less significantly toxic to the most of tested pathogens. From the study, they found that *Neurospora crassa* is the most sensitive fungi, whereas *Alternaria alternate* and *Penicillium digitatum* are the least susceptible fungi to most of the tested compounds (Gellerman et al. 2009).

8.3.1.10.3 Dithiocarbamate and Rhodanine Derivatives

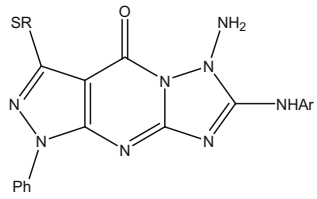
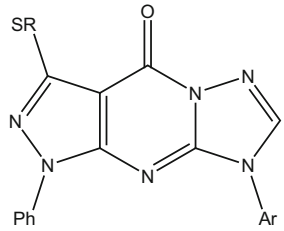
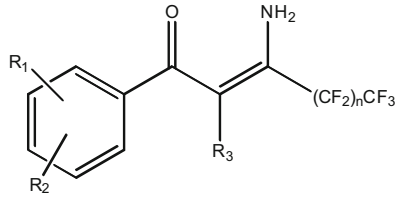
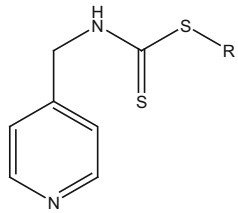
Chauhan et al. reported a series of 27 dithiocarbamate and the rhodanine derivatives containing pyridine moiety to check their antifungal activity. All the synthesised compounds (**8a–f** and **9**) were tested in vitro (Table 8.10) against the various fungal strains such as *Candida parapsilosis*, *Cryptococcus neoformans*, *Sporothrix schenckii*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, and *C. albicans*. Of all the compounds **8d**, **8e**, and **9** showed better antifungal potency than fluconazole against *Aspergillus fumigatus* and *Trichophyton mentagrophytes* against *Aspergillus fumigatus*. Compounds **8b** and **8d** showed almost 12-fold better activity compared to fluconazole and clotrimazole against *Sporothrix schenckii*. Further, these active compounds were tested for in vitro anti-candidal activity and amphotericin B-resistant strain of *Candida*.

Particularly compounds **8a–f** and **9** were found to be more effective (MIC = 0.39–3.12 μg/ml) against *Candida albicans* MTCC183. Further, these compounds except **8e** and **8f** showed significantly better activity against amphotericin B-resistant strain of *Candida albicans* in comparison to fluconazole (Chauhana et al. 2012).

8.4 Future Prospects

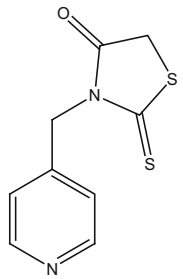
Invasive fungal infections are a principal problem in immunocompromised patients. They are found difficult to treat because their clinical manifestations are not specific unlike other infective diseases. The complete eradications of this invasive infection are not possible as the fungi are common in the environment. However, prevention can be achieved by detection and identification of the causal agent and using proper diagnosis techniques and therapeutic drug monitoring. Antifungal susceptibility testing is the one novel approach to understand the clinical significance of antifungal agents and has become an important medium for the recognition of microbiologically resistant organisms and for optimal selection of antimicrobial therapy. Many standardised methods for testing the in vitro susceptibility of fungi are now available, and concentration-effect relationships are increasingly explored. The availability of drugs with different molecular targets has opened new avenues for exploring combination therapies of two or even more drugs. The apparent aims of combination therapies are to extend the antifungal spectrum, to reduce the selection of resilient organisms, and to develop overall antifungal ability without conceding patient safety. However, combination therapy is not the universal approach for all established or alleged fungal infections but will be earmarked for selected subgroups. Of late, the increase of antifungal drug research has occurred because there is a crucial necessity for new antifungal agents to treat these fatal invasive infections. Although we have innovative, less toxic, antifungal agents that are present for clinical use, their clinical effectiveness in certain invasive fungal infections, such as aspergillosis and fusariosis, is not ideal. Many antifungal drugs targeting different molecules in the fungal cell have been developed. But route for identification of novel target and development of entirely new

Table 8.10 Structure and active strains of some miscellaneous antifungal agents

Structure	Fungal strain	Reference
	*Botrytis cinerea* Pers.	Wang et al. (2008)
5a, R=Me Ph= o-FC6H4 **5b**, R=Me Ph=m-FC6H4 **5c**, R= Me Ph=m-ClC6H4	*Sclerotinia sclerotiorum*	
	*Botrytis cinerea* Pers.	Wang et al. (2008)
6a, R=Me Ph=m-FC6H4 6b, R=Me Ph=C6H5 6c, R= Me Ph=m-ClC6H4 6d, R=Me Ph=m-MeC6H4	*Sclerotinia sclerotiorum*	
	*S. sclerotiorum* *B. cinerea*	Gellerman et al. (2009)
7a, R_1= *p*-Cl, R_2= H, R_3= H, n= 0	*Penicillium digitatum*	
7b, R_1= *p*-Cl, R_2= H, R_3= Et, n= 0		
7c, R_1= *p*-NHBoc, R_2= H, R_3= H, n= 0	*Pythium aphanidermatum*, *Alternaria alternate*, *Rhizoctonia solani* and *Neurospora crassa*	
	*C. albicans*	Chauhan et al. (2012)
8a-f, R = ethyl, n-propyl, n-butyl, allyl, benzyl, 4-trifluoromethylbenzyl	*C. parapsilosis* *S. schenckii* *T. mentagrophytes* *A. fumigatus* *C. neoformans* *C. albicans*	

(continued)

Table 8.10 (continued)

Structure	Fungal strain	Reference
	*C. parapsilosis*	
9	*S. schenckii*	
	T. mentagrophytes	
	A. fumigatus	
	C. neoformans	

therapeutics is difficult because of the eukaryotic nature of fungal cells. Thus, concerted effort in antifungal drug discovery is still required to develop more promising and effective antifungal agents for use in the clinical arena. Furthermore, developments of new methodology for antifungal susceptibility testing as well as laboratory and well-planned concerted clinical trials are essential in order to augment utility in clinical guidance of antifungal therapy.

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