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Review

The biology and chemistry of antifungal agents: A review

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ABSTRACT

In recent years their has been an increased use of antifungal agents and has resulted in the development of resistance to drugs. Currently, use of standard antifungal therapies can be limited because of toxicity, low efficacy rates. Different types of mechanisms contribute to the development of resistance to antifungals. This has given raise to search for a new heterocycle with distinct action or multitargeted combination therapy. This review addresses the areas such as the underlying mechanisms, eight different targets such as ergosterol synthesis, chitin synthesis, ergosterol disruptors, glucan synthesis, squalene epoxidase, nucleic acid synthesis, protein synthesis, microtubules synthesis. The clinically employed drugs along with the current research work going on worldwide on different heterocycles are discussed. In recent advances various heterocycles including imidazole, benzimidazole etc., twenty three scaffolds and their lead identification are discussed.

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Contents

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1. Introduction

Fungal infections pose a continuous and serious threat to human health and life.[1] These fungal infections in humans can be classified into (a) allergic reactions to fungal proteins, (b) toxic reactions to toxins present in certain fungi and (c) infections (mycoses). Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and in certain instances, systemic infections that cause a variety of conditions ranging from Athletes foot and nail infections to severe life-threatening disseminated disease (e.g., histoplasmosis).[2] Many fungal infections are caused by opportunistic pathogens that may be endogenous (*Candida* infections) or acquired from the environment (*Cryptococcus*, *Aspergillus* infections).[1]

The other type of fungal infection, that is, invasive fungal infections and dermatomycoses produced by fungal organisms in the individuals with increased vulnerability such as neonates, cancer patients receiving chemotherapy, organ transplant patients, and burns patients, apart from those with acquired immunodeficiency syndrome (AIDS). Other risk factors include corticosteroid and antibiotic treatments, diabetes, lesions of epidermis and dermis, malnutrition, neutropenia and surgery.[3–6] In recent years, the incidence and severity of fungal diseases has increased, particularly in patients with impaired immunity. The growing number of cases of fungi involved in sepsis is a consistent trend.[7]

There is considerable alarm amongst the medical profession regarding fungal disease. Dermatophyte infections such as tinea pedis and candidiasis, although rarely fatal, are common and widespread throughout the world. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* are the causes of considerable morbidity and mortality in immuno-compromised patients.[8]

Aspergillus and *Candida* spp. account for the majority of documented infections. Recent epidemiological trends indicate a shift towards infections by *Aspergillus* spp., non-albicans *Candida* spp. and previously uncommon fungi that often have diminished susceptibility to current antifungal agents.[9–13] Clinically, candidiasis and aspergillosis account for between 80% and 90% of systemic fungal infections in immunocompromised patients.[14]

Although, the arsenal of antifungal drugs has expanded, currently available antifungal drugs do not meet the increasing requirements of managing infection in the complex patient populations. The development of new antifungal drugs has been constantly required in the clinical therapy.[15]

1.1. *Candida albicans*

The major pathogen has been *C. albicans*, normally a commensal of the oral cavity and gastrointestinal tract of humans. Non-albicans *Candida* spp. (e.g., *C. glabrata*, *C. tropkalis*, *C. krusei*), however, are

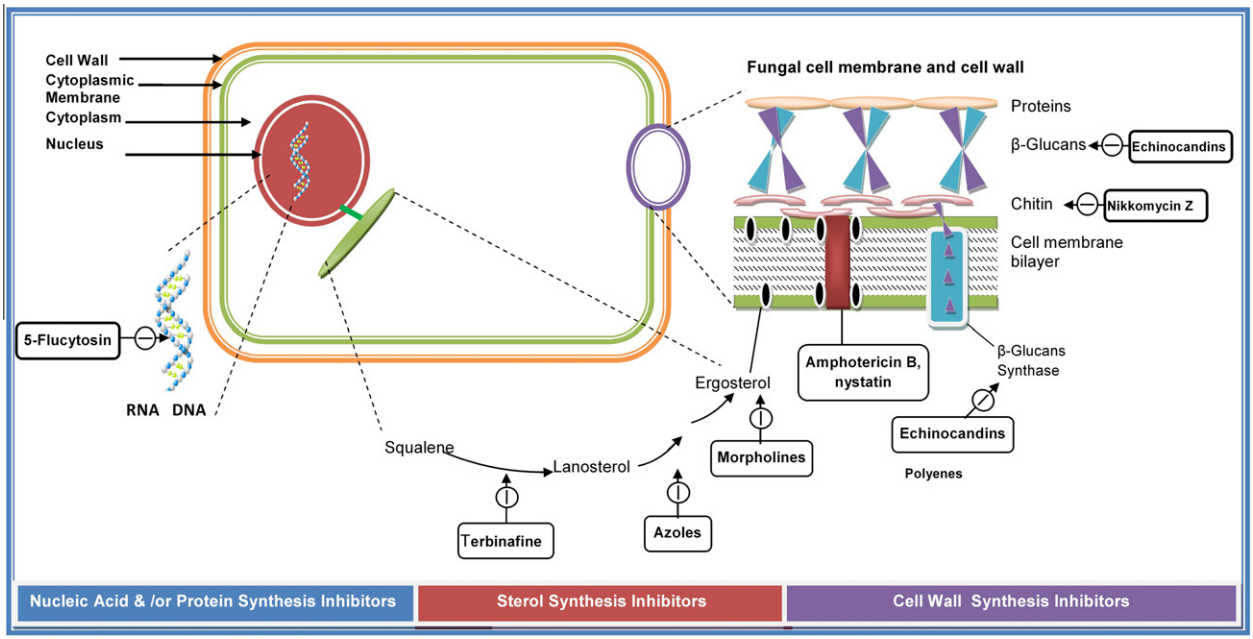

Figure 1. Targets for antifungal therapy.

also found with increasing frequency.[16] *C. albicans* and other *Candida* spp. are regarded as common constituents of the body microbiota in healthy humans.[17] *Candida* inhibits the mucosal surfaces of the human body.[18] There are seven *Candida* spp. of major medical importance, the most important being *C. albicans*, the one most frequently isolated. It is believed to be the most virulent in man. The other *Candida* spp. encountered in human infections is *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida stellatoidea*, *Candida krusei*, and *Candida kyfer*.[19]

The incidence of infections caused by non-albicans *Candida* spp. such as *C. glabrata* and *C. parapsilosis* is also more and more frequently reported.[20–24] *C. albicans* can cause chronic, superficial infections in otherwise healthy individuals; a prime example is vaginal candidiasis. Although, *C. albicans* is recognized as the most common pathogen among the *Candida* spp., in recent years other *Candida* spp., have been isolated with increasing frequency from clinical disease.[20]

Among the five common *Candida* spp., *C. albicans*, *C. parapsilosis* and *C. tropicalis* remain susceptible to polyenes, flucytosine, the azoles and the echinocandins. *C. glabrata* is inherently either dose-dependently susceptible or resistant to fluconazole. *C. krusei* is known to show intrinsic resistance to fluconazole, and decreased susceptibility of *C. krusei* to amphotericin B has also been reported. New triazoles, such as voriconazole and posaconazole, and the echinocandins are active against these two species, although cross-resistance was noted within the azoles in some *C. glabrata* strains.[25]

1.2. *Aspergillus niger*

Aspergillus niger Van Tieghem causes a disease called black mould.[26] It is a filamentous fungus growing aerobically on organic matter.[27] The *Aspergilli* are a large and diverse genus (~180 species) of filamentous fungi including several well known species with substantial commercial value (*Aspergillus oryzae and A. niger*) and medically significant molds; both as pathogens (*Aspergillus parasiticus and Aspergillus fumigatus*) and toxin-producing contaminants of food and feed (*Aspergillus flavus*), as well as lesser-known but valuable species such as *Aspergillus terreus*.[28]

Aspergillus is virtually ubiquitous. The microorganism acts as opportunistic pathogen in severely debilitated patients. Penetration of the skin for placement of a catheter, the use of cytostatic drugs that damage the mucosa, neutropenia and malabsorption pave the way for IFIs.[18] *A. fumigatus* is the most common aetiological agent, although other species, such as *A. flavus*, *A. niger* and *A. terreus*, are increasingly reported.[29,30]

Non-albicans *Candida*, non-fumigatus *Aspergillus* and moulds other than *Aspergillus* have become increasingly recognised causes of invasive diseases. The majority of *Aspergillus* spp. is susceptible to amphotericin B, extended-spectrum triazoles and the echinocandins. Whereas, *A. terreus* is considered to be particularly resistant to amphotericin B, it remains susceptible to extended-spectrum triazoles and the echinocandins.[25,31] The epidemiology of invasive aspergillosis indicates an increasing number of infections in immunosuppressed patients/individuals undergoing transplantation of bone marrow, hematopoietic stem cells, or organ transplantations, and those receiving intensive chemotherapy or other immunosuppressive treatment[32].

2. Targets for antifungal therapy

Different targets for antifungal therapy is shown in (Fig. 1)

2.1. Fungal ergosterol synthesis inhibitors

Ergosterol is the major component of the fungal cell membrane. It is as a bioregulator of membrane fluidity, asymmetry and integrity. Inhibition of the 14α-demethylase will result in a decreased ergosterol synthesis and a concomitant accumulation of 14-methylated sterols. They prevent the 14-α demethylation of lanosterol into ergosterol in the ergosterol synthetic pathway.[33,34] Thereby preventing the post-squalene synthesis segments such as the oxidosqualene cyclase methyltransferase.[35] Ergosterol plays a hormone-like role in fungal cells, which stimulates growth, the net effect of azoles is the inhibition the fungal growth.[36–38]

2.1.1. Azoles

The azole antifungal agents block the synthesis of ergosterol, a major component of fungal cytoplasmic membranes.[7,39]

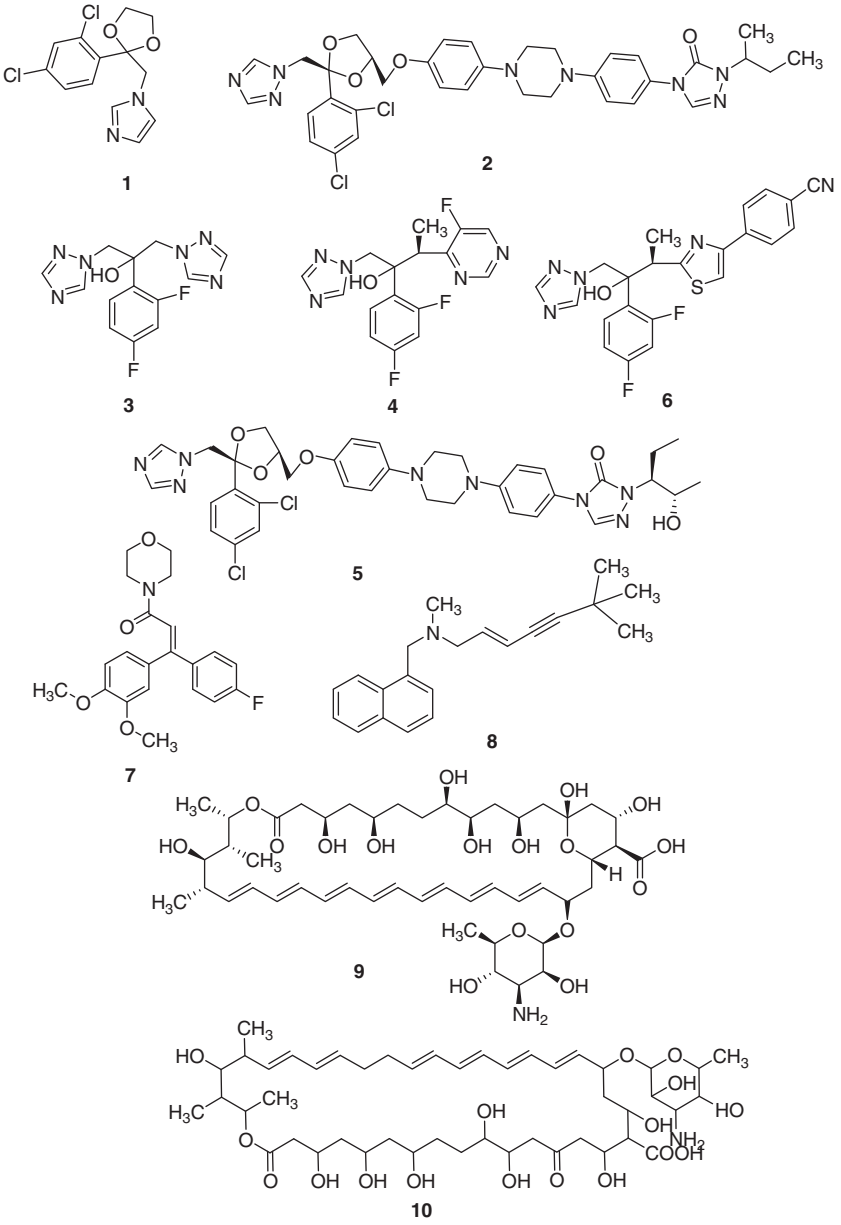

Figure 2. Anti fungal agents: Azoles, squalene epoxidase inhibitors and ergosterol disruptors.

2.1.2. Ketoconazole

Ketoconazole 1 (Fig. 2) was the first orally bioavailable imidazole.[40] and is a first significant broad spectrum antifungal azole. It is effective in patients with candidiasis, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis and cutaneous dermatophyte infections.[41] Ketoconazole revolutionised the treatment of oral candidiasis, coccidioidomycosis, endemic mycoses, dermatophyte infections and veterinary fungal infections,[42] but has been now replaced.[39] The most frequently reported adverse side effects are gastrointestinal in origin, but these are usually relieved with concomitant food administration,[43] fatal toxic hepatitis.[44]

2.1.3. Itraconazole

Itraconazole 2 (Fig. 2) was the first orally bioavailable agent with anti-Aspergillus activity[39,45,46] and useful in treatment of nonmeningeal, non-life threatening pulmonary and extrapulmonary blastomycosis, including chronic cavitary pulmonary disease and disseminated nonmeningeal histoplasmosis[47,48] chronic pulmonary aspergillosis, allergic syndromes related to *Aspergillus spp*, onychomycosis, histoplasmosis, blastomycosis and sporotrichosis.[49] It is not as good as fluconazole in acute cryptococcal infection and as maintenance therapy for cryptococcal meningitis in AIDS patients.[39,46] Itraconazole is licensed in the United States for salvage therapy of IA[50] and approved for treatment of allergic bronchopulmonary aspergillosis[50,51]

2.1.4. Fluconazole

In 1994, fluconazole 3 (Fig. 2) was approved for use as a single oral dose treatment for vaginal candidiasis.[52] Fluconazole is effective for treating oropharyngeal, oesophageal and vaginal candidiasis, as well as peritonitis, non-neutropenic patients with candidaema, disseminated candidiasis (including neutropenic patients), hepatosplenic candidiasis, funguria and focal urinary tract

infections. Fluconazole is also effective in pulmonary or disseminated cryptococcosis, acute cryptococcal meningitis, for life-long maintenance therapy, as primary prophylaxis for cryptococcal infections, in treating coccidioidal meningitis,[39] oropharyngeal candidiasis.[53] After induction therapy with Amphotericin B and flucytosine, fluconazole is used for suppression of cryptococcosis.[54] It is extensively used for the prevention and treatment of superficial and invasive *Candida* infections.[55,56] The bioavailability of fluconazole is very high compared with other azoles, likely to its higher water solubility and low affinity for plasma proteins.[39]

2.1.5. Voriconazole

Voriconazole 4 (Fig. 2) is the first available low molecular weight, water soluble second generation triazole and approved for first-line treatment of invasive aspergillosis, *Oesophageal candidiasis*.[57–59] It is active against *Aspergillus spp*, *Fusarium* spp. and *Candida* spp. (including the fluconazole resistant or less susceptible spp. of *C. glabrata* and *C. krusei*).[59] It also shows activity against the Fusarium and Scedosporium infections which are hard to treat.[60] Side effects of Voriconazole therapy include skin rash and transaminase elevation,[61] encephalopathy or hallucinations.[62–64]

2.1.6. Posoconazole

Posoconazole 5 (Fig. 2) was approved by the FDA in 2006 for prophylaxis against invasive *Aspergillus* and *Candida* infections.[65] Posaconazole is a lipophilic second-generation antifungal triazole with a similar molecular structure to that of itraconazole.[66] It has in vitro activity against a variety of pathogenic fungi, including *Aspergillus*, *Candida* spp., *Cryptococcus* spp., and *Histoplasma* spp. It is good against infections caused by the zygomycetes than voriconazole. [67,68] The most frequent side effects of posaconazole therapy are gastrointestinal (14%), with transaminase elevation and hyperbilirubinemia occurring in 3%,[69] gastrointestinal complaints (nausea, vomiting, abdominal pain or diarrhoea) and headache,[70,71] elevation of liver enzymes and skin rash.[70]

2.1.7. Ravuconazole

Ravuconazole 6 (Fig. 2) is highly active against a wide range of fungi, including *Candida* spp., even isolates that are resistant to fluconazole.[57,71,72] The efficacy of ravuconazole in *O. candidiasis* in human immunodeficiency virus (HIV) patients has been compared with that of Fluconazole.[57]

2.2. Squalene epoxidase inhibitors: morpholines and allylamines

Squalene epoxidase, an enzyme which together with squalene cyclase, converts squalene to lanosterol, which when inhibited prevents the conversion of lanosterol to ergosterol.[39,45]

2.2.1. Morpholines

Morpholines 7 (Fig. 2) was discovered in the 1970s, are completely synthetic compounds. Most of them have been used successfully in agricultural applications and amongst them only amorolfine is used in the topical treatment of nail infections.[1,59]

2.2.2. Amorolfine

It possesses both fungistatic and fungicidal activity in vitro. Two sites of antifungal action have been indicated the Δ^7–Δ^8 isomerase and the Δ^{14} reductase, two further enzymes in ergosterol biosynthesis. Inhibition by amorolfine leads to hyperfluidity of the membrane, which causes changes in membrane permeability and, in addition, induces abnormal chitin deposition leading to growth abnormalities.[47]

2.2.3. Terbinafine

Terbinafine 8 (Fig. 2) is an allylamine that has been available in the United States since May 1996. Terbinafine has good in vitro activity against *Aspergillus* spp., *Fusarium* spp. and other filamentous fungi but has variable activity against yeasts.[39] Terbinafine has been shown to be fungicidal against dermatophytes, *Sporothrix schenckii*, dimorphic fungi, *Scopulariopsis brevicaulis* and *Hendersonula* and *Acremonium* species.[36] Amorolfine can be used only for topical treatment of superficial mycoses, and neither of its targets has attracted recent research interest.[72]

2.3. Ergosterol disruptors (polyenes antibiotics)

Ergosterol is the main component of the fungal cell. Polyenes antibiotics form complex with ergosterol and disrupt the fungal plasma membrane that results in increased membrane permeability, the leakage of the cytoplasmic contents and ultimately death of the fungal cell. Thus, the polyenes are fungicidal and have the broadest spectrum of antifungal activity of any of the clinically available agents.[39,52,54]

2.3.1. Amphotericin B

Amphotericin B 9 (Fig. 2) was isolated from *S. nodosum* bind to sterols in cell membranes and cause them to leak cellular constituents. Because they bind with up to 10 times more avidity to ergosterol, the sterol in fungal membranes, than to cholesterol the human membrane sterol they show selective antifungal activity.[59]Amphotericin B have broad spectrum of activity against *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Paracoccidiodes brasiliensis*, *Sporotrichium* species *and Torulopsis glabrata.* Adverse side effects associated with amphotericin B are infusional toxicity, nephrotoxicity and low blood potassium.[39,75]

2.3.2. Nystatin

Nystatin 10 (Fig. 2) was discovered in 1950 from the fermentation broth of *Streptomyces noursei*, and is still used as a topical antifungal agent.[50] It is nonabsorbable after oral administration but is effective topically in the treatment of oropharyngeal candidiasis.

2.4. Glucan synthesis Inhibitors

Glucans are the major components that strengthen the cell wall.[33,58] The glucan polysaccharide consists of D-Glucose monomers attached to each other by β-(1,3)-glucan or β-(1,6)-glucan linkages. This component is essential for the cell wall assuring important physical properties.[33,73] The blockage of glucan synthase causes a decreased incorporation of glucose to the glucan polymer, hence the inhibitors cause the lysis of the susceptible fungal cells. The fungal cell wall has no counterpart in the mammalian cells.[75] β-(1,3)-Glucan synthase is inhibited noncompetitively by papulacandins and echinocandins.[72] Depending on the concentration, it can either induce or inhibit the macrophage release of tumor necrosis factor-α.[33,76,77] The mode of action of echinocandins is based on the inhibition of cell wall β-glucan synthesis, a specific noncompetitive inhibition (β-glucan synthase).[33,78–82]

2.4.1. Echinocandins

Echinocandins 11 (Fig. 3) are amphiphilic lipopeptides, products of cyclopentamine, which is formed during the fermentation of some fungi such as *Zalerion arboricola* or *Aspergillus nidulans var. echinulatus*.[63,83] The mechanism of action include inhibition of (1,3)-β-D-glucan synthase, which produces an important component of the cell wall of many pathogenic fungi such as *Candida* spp. and *Aspergillus* spp. Inhibition leads to disruption of the structure of the growing cell wall, resulting in osmotic instability and death

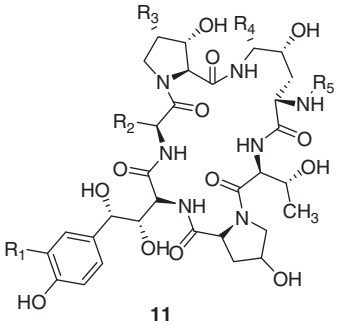

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Figure 3. Echinocandins.

of susceptible yeast cells.[84] The target of echinocandins does not exist in mammalian cells, so their toxicity is minimal.[57] The general structure for echinocandin series is shown in Table 1. [85,86]

2.4.2. Caspofungin

Caspofungin 12 (Table 1) was approved by FDA for the treatment of patients with IA.[57]Caspofungin 12 has potent in vitro inhibitory activity against *Aspergillus* spp. and moderate activity against some other moulds such as *H. capsulatum*, *C. immitis* and *B. dermatitidis*. It is also active against *P. carinii* and moderately against dematiaceous fungi. But it has no activity against *C. neoformans*, *Trichosporon* spp., *Fusarium* spp., *S. schenckii*, zygomycetes and hyalohyphomycetes.[82,83] Caspofungin has few significant interactions as it is neither a substrate nor an inhibitor of the cytochrome P-450 system.[57] Caspofungin has few side effects, consisting mainly of headache, fever, nausea, rash, phlebitis at the site of infusion and reversible elevation of hepatic enzyme levels.[57]

2.4.3. Micafungin

Micafungin 13 (Table 1) was approved for the treatment of *O. candidiasis* as well as prophylaxis in patients undergoing stem cell transplantation.[57] Micafungin is found to be effective against *O. candidiasis* and shown to be superior than fluconazole when given as prophylaxis in stem cell transplantation. Micafungin is shown less drug interaction than capsofungin. [80,87]

2.4.4. Anidulafungin

Anidulafungin 14 (Table 1) was approved for use in the treatment of *O. candidiasis*, candidaemia, peritonitis and intraabdominal abscesses due to *Candida* spp.[57] It is unique in echinocardins because it slowly degrades in humans, undergoing a process of biotransformation rather than being metabolized.[57,88] It is highly active in vitro against a wide range of *Candida* spp., including species that are resistant to azoles (*C. krusei*), amphotericin B (*C. lusitaniae*) or other echinocandins (*C. parapsilosis*)[74,89] and also against *Aspergillus* spp.[53] The most common adverse effects reported from clinical trials were hypotension, vomiting, constipation, nausea, fever, hypokalaemia and elevated hepatic enzymes.[57,90]

2.5. Chitin synthesis inhibitors

Chitin is an important polysaccharide in the fungal cell wall that is important in determining cell shape, although percentage of chitin in the cell-wall is only about 1%.[33,91–93] Chitin is practically insoluble polymer consisting of β-(1,4)-linked *N*-acetylglucosamine units. It is well separated from the glucan in the cell-wall, but it is covalently linked to it in order to strengthen the cell-wall. Chitin is essential for the fungi, it is absent in human organism. Therefore chitin synthase signifies an attractive target of the research for antifungal agents.[33]

2.5.1. Nikkomycin

Nikkomycin 15 (Fig. 4) is active toward the highly chitinous dimorphic fungal pathogens, for example, *C. immitis*, *B. dermatitidis* and *H. capsulatum*.[91] It has little to no activity against *C. albicans*, *C. tropicalis*. It can be used in combination with caspofungin showing fungicidal activity against *A. fumigates*.[33]It can be used in combination with caspofungin showing fungicidal activity against *A. fumigates*. [92,94]

2.5.2. Polyoxins

Polyoxins 16 (Fig. 4) show marked selective antifungal effect against the phytopathogenic fungi, however they are inactive toward bacteria, plants and animals.[33]

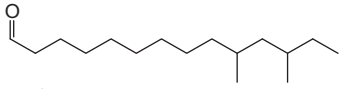
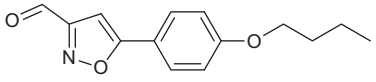
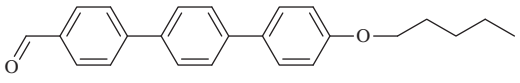
2.6. Nucleic acid synthesis inhibitors

Flucytosine interfares with pyrimidine metabolism, RNA/DNA and protein synthesis.[84] Flucytosine is converted to 5-fluorouracil by a cytosine deaminase, and later, by UMP pyrophosphorylase into 5-fluorouridylic acid, which is further phosphorylated and incorporated into RNA, resulting in disruption of protein synthesis. 5-Fluorouracil is converted to 5-fluorodeoxyuridine monophosphate, a potent inhibitor of thymidylate synthase.[84,88] This enzyme is involved in DNA synthesis and the nuclear division process.[89]

2.6.1. Flucytosine

Flucytosine 17 (Fig. 4) was first developed as anticancer agent but lateron it was screened for antifungal agent and today it is used in adjunctive therapy with Amphotericin B like *Cryptococcus neoformans*.[95] It works as an antifungal agent through conversion to 5-fluorouracil within target cells. Fluorouracil becomes incorporated into RNA, causing premature chain termination, and it inhibits its DNA synthesis through effects on thymidylate synthase. Most filamentous fungi lack these enzymes and hence useful spectrum of flucytosine is restricted to pathogenic yeasts (*Candida* spp. and

Table 1
Showing substitution for echinocandin (**11**)

Name of compound	R_1	R_2	R_3	R_4	R_5
Capsofungin (12)	H	$NH_2(CH_2)_2CHOH$	H	$NH(CH_2)_2NH_2$	
Micafungin (13)	$HOSO_3$	$NH_2(CO)CH_2CHOH$	CH_3	OH	
Anidulafungin (14)	H	CH_3CHOH	CH_3	OH	

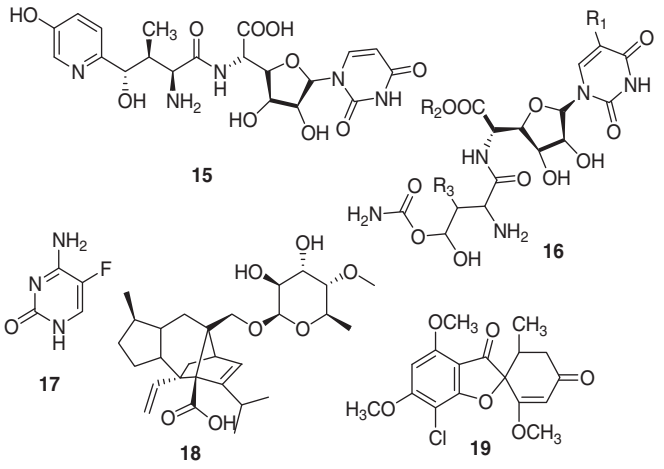


Figure 4. Anti fungal agents: Chitin synthesis inhibitors, nucleic acid synthesis inhibitors, protein synthesis inhibitors, & microtubules synthesis inhibitors.

Candida neoformans).[95] Flucytosine is used as adjunctive, rather than primary therapy in clinic because of development of registence.[73]

2.7. Protein synthesis inhibitors: sordarins

Sordarins, 18 (Fig. 4) has been identified as selective inhibitors of fungal protein synthesis. Sordarin was isolated from *Sordaria araneosa* in 1971.[47] The sordarins group are protein synthesis inhibitors that work by blocking the function of fungal translation. Sordarins are absent in mammalian cells or electron transport chain.[38]

2.8. Microtubules synthesis inhibitors

Microtubules are dynamic polymers of α- and β-tubulin dimmers.[96] They form a highly organized cellular skeleton in all eukaryotic cells. The agents like griseofulvin, vinblastin interact with β-tubulin, a protein highly conserved in eukaryotes. There may be differences between mammalian and fungal tubulins, for example, colchicine binds preferentially to mammalian tubulin.[97]

2.8.1. Griseofulvin

Griseofulvin 19 (Fig. 4) was the earliest chemical that could be claimed to have a selective inhibitory activity against fungi.[90] Griseofulvin interferes with intracellular microtubule production, which inhibits fungal mitosis.[98,99] The selective toxicity of griseofulvin for fungi is only moderate (liver toxicity is recognised as an occasional hazard) and its spectrum of action is restricted mainly to the dermatophyte fungi causes of ringworm and athlete's foot.[45,95,99] The classification of antifungal agents are listed in Table 2

3. Recent advances in antifungal agents

3.1. Imidazole

A series of compounds belonging to nitroimidazole were synthesized, evaluated for antibacterial and antifungal activity. The results indicate that alkyl substitution at R in 20 showed good antibacterial activity whereas piperazino alkane showed antifungal activity like miconazole. The compound with triazole attached to sulphur has also shown antibacterial activity. The best activity among the series is the compound bearing phenyl piperidine at R position in 20 (Fig. 5) against *Trichophyton tonsurans* with minimum inhibitory concentration (MIC 3 μg/mL), exerting about

Table 2
Classification of antifungal agents.

Class	Agent	Mechanism of action	Indication	Toxicity
First generation triazole	Fluconazole	A	Active against most *Candida* spp.	Gastrointestinal intolerance
	Itraconazole	A	Anti-*Aspergillus* activity	Fluid retention, left ventricular dysfunction, gastrointestinal intolerance
	Ketoconazole	A	Candidiasis, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis and cutaneous dermatophyte infections	Gastrointestinal, hepatitis
Second generation triazole	Voriconazole	A	Invasive aspergillosis	Elevation of transaminases and visual disturbances, rash and gastrointestinal symptoms
	Posoconazole	A	Prophylxis of invasive aspergillosis and *Candida* infection	Nausea, vomiting, headache, abdominal pain and diarrhea
	Ravuconazole	A	Active against a wide range of fungi, including *Candida* spp., *C. neoformans* and other yeast species,	Gastrointestinal
Echinocardin	Caspofungin	B	Potent activity against *Aspergillus* spp., *Oesophageal candidiasis*	Headache, fever, nausea, rash, phlebitis
	Micafungin	B	Treatment of *Oesophageal candidiasis*	Nausea, vomiting, headache,diarrohea, phlebitis and leukopenia
	Anidulafungin	B	Active against Candida spp., *Oesophageal candidiasis*	Hypotension, vomiting, constipation, nausea, fever, diarrhoea hypokalemia and elevated hepatic enzymes
Antibiotics	Nystatin	C	Superficial (mucosal) *candida* infections of the oropharynx, oesophagus and intestinal tract	Nephrotoxicity
	Amphotericin B	C	Broad-spectrum of antifungal activity	Nephrotoxicity, Infusional toxicity, low blood potassium
	Griseofulvin	D	For the treatment of cutaneous mycoses	Liver toxicity
Nucleoside analogues	Flucytosine	E	Active against *Candida* and *Aspergillus* spp.	Bone marrow toxicity
Allylamine	Terbinafine	F	Used for fungal nail infections	Mild rash, nausea, loss of taste

A = interact with cytochrome *p*-450; inhibit C-14 demethylation of lanosterol, thereby causing ergosterol depletion and accumulation of aberrant sterols in the membrane, B = the Δ^7–Δ^8 isomerase and the Δ^{14} reductase inhibition, C = glucan synthase inhibitors, D = Interact with ergosterol, thereby disrupting the cytoplasmic membrane, F = inhibits thymidylate synthase and thereby DNA synthesis, G = inhibit squalene epoxidase.

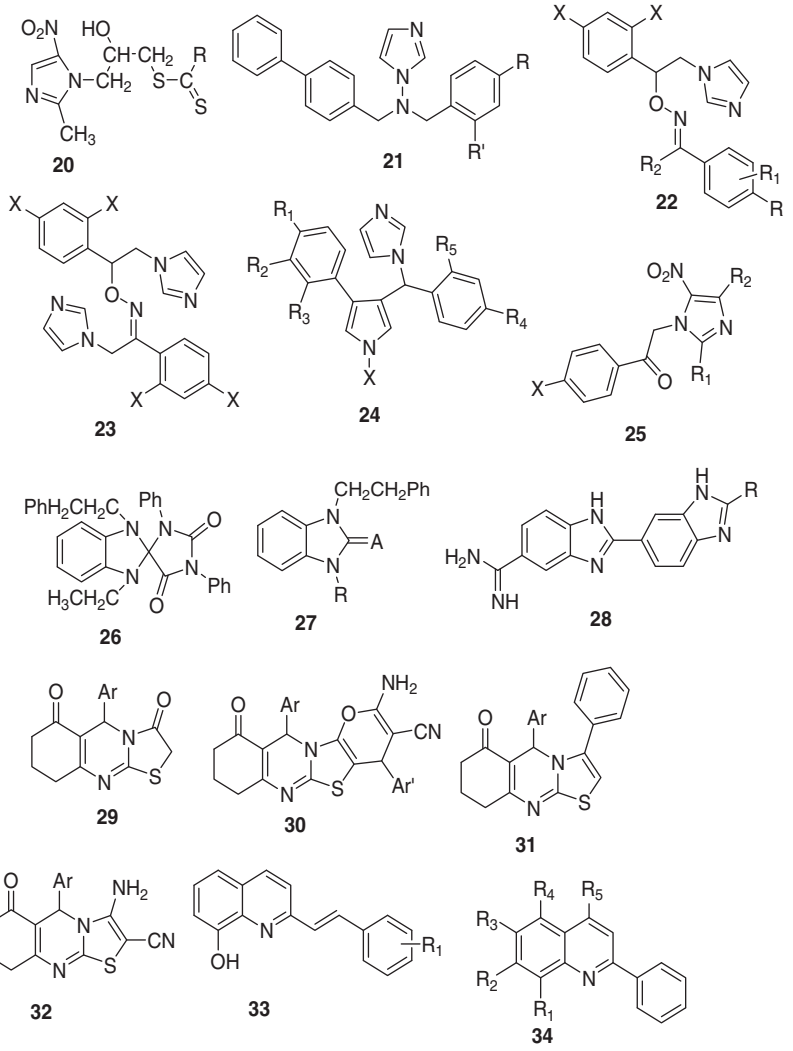


Figure 5. Anti fungal agents with various nulceous like imidazole, benzimidazole, quinazoline & quinoline.

one half the activity of onidazole, however none were as effective as miconazole (MIC 0.2 μg/mL) or ornidazole (MIC 0.8 μg/mL).[100]

Derivatives of 1*H*-imidazol-1-amine were synthesized and evaluated in vitro against several pathogenic fungi and compared with Miconazole. In 21 (Fig. 5) 2-Substituted phenyl compounds showed better results than 4-substituted phenyl, especially against *Candida neoformans*. Inhibition of dermatophytes was less influenced by the aryl portion. The potent compound has R = R′ = Cl, with MIC 0.8 μg/mL and miconazole 0.4 μg/mL, against *Trichophyton rubrum*. Test pathogens included representatives of yeasts (*C. albicans*, *C. parapsilosis*, *Cryptococcus neoformans*) dermathophytes (*T. verrucosum*, *T. rubrum*, *Microsporum gypseum*) and molds (*A. fumigatus*).[101]

The series of inverted oxime ethers of oxiconazole were synthesized 22, 23 (Fig. 5) and evaluated against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *A. fumigates*, *A. flavus*, *Trichophyton mentagrophytes*, *T. rubrum.* In 22 substitution at X = Cl, F and R = Ethoxy, morpholine, Cl and R_1 = Cl, F, H and R_2 = H, Me, Et, Pr. showed better results. In fact the most potent against all of the strains tested, both yeast fungi, such as *C. albicans* and filamentous fungi and dermatophytes, such as *Aspergillus* and *Trichophyton* with MIC 0.25–128 μg/mL. In 23 the substitution at X = Cl, F shows antifungal activity.[102]

The N-substituted 1-[(aryl)-(4-aryl-1*H*-pyrrol-3-yl)methyl]-1*H*-imidazole derivatives were synthesized and tested against 12 strains of *Candida* spp. In 23 (Fig. 5), monochloro derivatives were more potent than N-unsubstituted compound. Introduction of a methyl or a pyrrolyl groups on the phenyl rings or replacement of the phenyl with a naphthalene ring leads to less active compounds. The introduction of one, two, or three chlorine atoms on compounds lowers potency on R_3, R_4 R_5. The most active compound are those bearing substitution at X = C_3H_7, $CH_2 = CH_2$, $CH_2CH = CH_2$, $CH_2CH = C(CH_3)_2$, Ph, CH_3, C_2H_5, H and R_1 = Cl, H, 1-pyrrolyl $R_2 = R_3$ = H, Cl and R_4 = H, Cl, CH_3 and R_5 = H, Cl. The compound where R_1 = Cl, $R_2 = R_3 = R_4 = R_4$ = H, X = C_3H_7 found to be most potent amongst the series with MIC 0.016 μg/mL.[103]

Nitroimidazole derivatives have been synthesized and evaluated against sclerophomapityophila. High effectiveness was observed with the introduction of nitro group at 4-position on the imidazole ring in 25 (Fig. 5) bearing morpholine or piperidine and by the presence with substitution R_1 = H, R_2 = morpholine, piperidine ans X = H shows antifungal activity of a chlorine atom at 4-position on the phenyl ring. The compounds.[104]

3.2. Benzimidazole

Benzimidazole derivatives containing electron-rich olefines were synthesised. All compounds were screened in vitro against the *C. albicans* and *C. tropicalis*. Most potent compound 28 and

29 (Fig. 5) with following structures and MIC 50 μg/mL against *C. albicans* and *C. tropicalis*. The antifungal activity of this series were related to spiro structure and hydantoin moiety. The structure 29 with A = selenium moiety, R = CH_3, C_2H_5 also showed good antifungal activity.[105]

A series of 18 molecules belonging to 20-arylsubstituted-1*H*,10H-[2,50]-bisbenzimidazolyl-5-carboxamidines were synthesized and tested against *C. albicans* and C. krusei. Introduction of 1-napthyl (*R*) showed MIC 0.78 μg/mL in 28 (Fig. 5), greator activity than fluconazole 0.74 μg/mL and introduction of 2 napthyl leads to eightfold reduction in activity with MIC 6.25 μg/mL against *C. albicans*.[106]

3.3. Quinazoline

Quinazolines have broad spectrum of biological activities. Three compounds reported in a series of 15 have good antifungal activity against *Aspergillus ochraceus*, *C. albicans*. The substitution bearing Ar = *p*-FC_6H_4 in 29 (Fig. 5) and Ar = *p*-FC_6H_4, Ar′ = *p*-ClC_6H_4 in 32 (Fig. 5), showed marked antifungal activity but less than reference drug Ticonazole (trosyd).[107]

Fused quinazolin-5-one compounds were synthesized and evaluated for antifungal activity. The compounds containing both the quinazoline and pyrimidinothiazole moieties were found to be the most active against *A. ochraceus* and *A. flavus* when compared to trosyd with MIC 40 μg/mL. The most active compounds amongst the series were 31 and 32 (Fig. 5) with Ar = aromatic ring.[108]

3.4. Quinoline

A series of quinoline derivatives were prepared and tested for in vitro antifungal activity on eight pathogenic fungi. The results indicate that substitution in the C_4 position of the phenyl ring by polar group (phenolic or nitro moiety) seems to be very important for antifungal effect, as well as the presence and position of the nitrogen atom in the connecting linker between the quinoline and phenyl ring. The substitution with 2 and 3 OH group at R_1 in 33 (Fig. 5) showed in vitro antifungal activity comparable than that of the standard fluconazole.[109]

A new series of quinoline derivatives possessing an aromatic substituent (carbocyclic or heterocyclic) at C2 position were synthesized and screened for antifungal properties against a panel of standardized fungi including yeasts, hyalohyphomycetes and dermatophytes. The most active quinoline molecules were then tested against a panel of clinical isolates. Results showed that the most active compounds were 2-hetaryl quinolines particularly those containing a γ-pyridyl ring, α-Furyl (α-thienyl) derivatives were devoid of antifungal properties. The different substituents were tried in 34 (Fig. 5) like R_1 = H, CH_3, OCH_3, *i*-Pr. and R_2 = H, C_2H_5, CH_3 and R_3 = H, C_2H_5, CH_3, F, Cl, NO_2, OH and R_5 = H, CH_3. The activity could be related to the C-4 and/or C-8 substitution on the quinoline ring and would be related neither to the lipophilicity nor to the basicity of compounds.[110]

A series of 28 molecules belonging to 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7(1-piperazinyl)quinoline-3-carboxylic acid (norfloxacin) derivatives (Fig. 6) were synthesized and tested for fungicidal action against *Xanthomonas oryzae*, *Xanthomonas axonopodis*, *Erwinia aroideae*, *Ralstonia solanacearum* a plant pathogenic fungi. The inhibition of growth by Compound 36 and 37 (Table. 3) *R. solani* reached 83% and 94%, respectively, at a concentration of 200 mg/L which indicated that their activities were relatively close to carbendazim (its inhibition of growth was 100%), a commercial fungicide.[111]

Benzothieno[3,2-*b*]quinolinium and 3-(phenylthio)quinolinium compounds were synthesized and evaluated against *C. neoformans*, *C. albicans*, *A. fumigates*, *C. krusei*. In 38 (Fig. 7) substitution with R = 3OCH_3, 4-Cl and Y = OTf demonstrated significant in vivo efficacy against *C. albicans* and *C. neoformans* comparable to that of amphotericin B. The opening of the benzo[b]thiophene ring and replacing the *N*-methyl group with *N*-5-phenylpentyl or 5-cyclohexylpentyl groups in **39** (Fig. 7) to form substituted 3-(phenylthio)quinolinium compounds produced as high as 50-fold increases in potency without increasing cytotoxicity.[112]

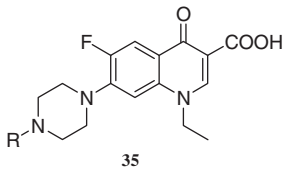


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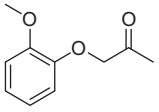
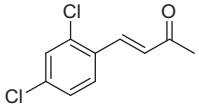
Figure 6. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7(1-piperazinyl) quinoline-3-carboxylic acid (norfloxacin) derivatives.

Table 3
Different substitution at 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7(1-piperazinyl)quinoline-3-carboxylic acid (norfloxacin) derivatives

Compound	R (Substitution at 35)
36	
37	

3.5. Quinazolinone

Derivatives of 4(3*H*)-quinazolinone were synthesized and evaluated for antifungal activity against *A. niger*, *C. albicans* and *Fusarium oxysporum*. The presence of the OCH_3 group in **40** (Fig. 7) at the phenyl ring does not impart any activity, but the presence of an alkyl group CH_3 at the phenyl ring leads to better outcomes than for compounds with an unsubstituted phenyl ring. The presence and position of the chlorine atom plays a crucial role, the order of activity being 4-Cl > 3-Cl > 2-Cl. The MIC range showed the best MICs 0.016–0.125 μg/mL, against *C. albicans*, *C. neoformans*, *A. fumigates* with Fluconazole 0.5–4 μg/mL.[113]

3.6. Isoquinoline

A series of novel pyrazino[2,1-*a*]isoquinolin compounds were designed, synthesized and evaluated for antifungal activity against *C. albicans*, *Cryptococcus neoformans*, *T. rubrum*, *M. gypseum*, *A. fumigates*. The substitution with R_1 = H, R_2 = F, R_3 = $(CH_2)_8CH_3$ in **41** (Fig. 7) found to be most potent with MIC (4–16 μg/mL) against *Cryptococcus neoformans*, *T. rubrum*, *M. gypseum*, *A. fumigates* with fluconazole (2–64 μg/mL). Methoxy and hydroxyl substitution at R_1 and R_2 shows good antifungal activity.[114]

3.7. Analogues to flucanazole and triazole

Novel fluconazole/bile acid conjugates were designed and evaluated for antifungal activity against *C. albicans*, *S. schenckii*, *C. parapsilosis*. The substitution attempted were benztriazole, benzimidazole, triazole, tetrazole in place of fluconazole in **42** (Fig. 7) but did not show any significant antifungal activity. Substitution with R = H, OH shows good antifungal activity in the range

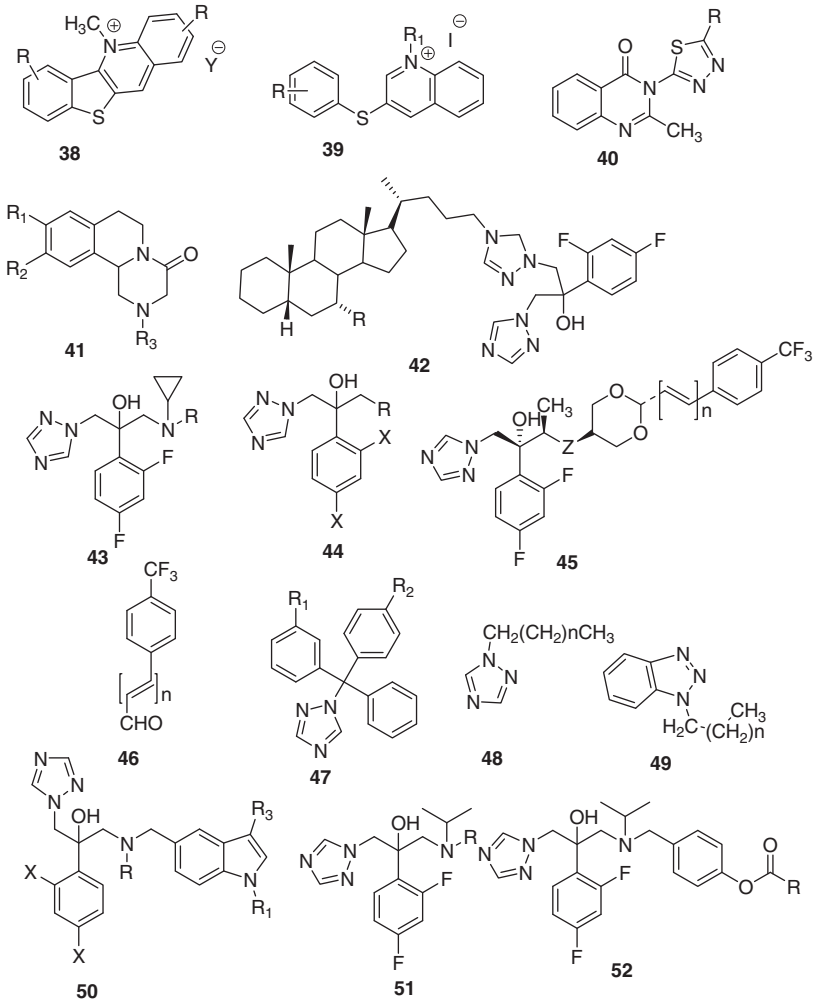


Figure 7. Anti fungal agents with various nulceous link quinolinium, quinazolinone, isoquinoline & anti fungal analogues of flucanazole and triazole.

2.18–25 μg/mL. It is thought that bile acid part acts as a drug carrier and fluconazole part acts as an inhibitor of 14α-demethylase enzymes in fungal cell.[115]

Twenty three derivatives belonging to 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-(*N*-cycloproyl-N-substituted-amino)-2-propanols were designed, synthesized and evaluated for antifungal activity. The title compounds had higher antifungal activity and broader antifungal spectrum than fluconazole with MIC values less than 0.125 μg/mL. The substitution in **43** (Fig. 7) with R = CH_3, 4-C_6H_5CN showed potent activity 0.125-2 μg/mL against *C. albicans*, *C. parapsilosis*, *C. neoformans*, *C. tropicalis*, *T. rubrum*, *A. fumigatus*, *Microsporum canis*, *Fonsecaea compacta*.[116]

A series of fluconazole analogues were synthesized and evaluated in vitro against two clinically important fungi, *C. albicans* and *A. fumigates.* Heterocycles were introduced in place of R in **44** (Fig. 7) such as indole, azaindole, benzimidazole, benztriazole. The MIC_{80} values for azaindole derivatives indicate that the most active compounds were the 2,4-dichloro phenyl with azaindole in place of R. This particular compound showed remarkable activities against *C. albicans* in particularly (IC_{80} = 0.0007 and 0.0031 μg/mL) which were much more potent than fluconazole (IC_{80} = 0.020 μg/mL).[117]

A new series of triazole compounds possessing a sulfur atom in place of Z were efficiently synthesized and their in vitro antifungal activities were investigated against *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *Cryptococcus neoformans*, *A. fumigatus*, *A. flavus*. Among compounds in **45** (Fig. 7) *n* = 0, 1, 2, 3 and in **46** (Fig. 7) *n* = 2, which has a side chain with two olefinic double bonds, showed excellent in vitro activity against *Candida*, *Cryptococcus*, and *Aspergillus* spp. The substitution of *n* = 2 gives most potent compound in the series with the MIC 0.016–0.125 μg/mL, against *C. albicans*, *Cryptococcus neoformans*, *A. fumigates* with fluconazole 0.5–4 μg/mL.[118]

A series of 1,2,4-triazole and benzotriazole derivatives were synthesized and evaluated. The azole compounds plus fluconazole were characterized by a docking mode in the active site of the cytochrome P450 14α-sterol demethylase. SAR study showed that the antifungal activity is dependent on the heterocyclic moiety as well as on the nature of the substituents. Small sized compounds may be attributed to the better penetration into fungi cell. The benzotriazoles compounds had low antifungal activity and may be because of the presence of methoxy group on the triazoles and benzotriazoles moiety.[119]

The design and synthesis of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols, were reported showing various degrees of antifungal activity against *C. albicans* and *A. fumigatus.* The 1-[(1*H*-indol-5-ylmethyl)amino] derivatives exhibited potent MIC 65 ng/mL against *C. albicans*. The best result was obtained with fluorinated compound **50** (Fig. 7) bearing a *N*-Boc protective group on the indole moiety, introduction of a *N*-methyl group in the linker would not play a major role on the two tested strains. Compound with X = F, R = H, R_1 = Boc exhibited moderate antifungal activities against all fungi tested with MIC values ranging from 3.8 to 33.0 ng/mL, lower than those of fluconazole (190 ng/mL).[120]

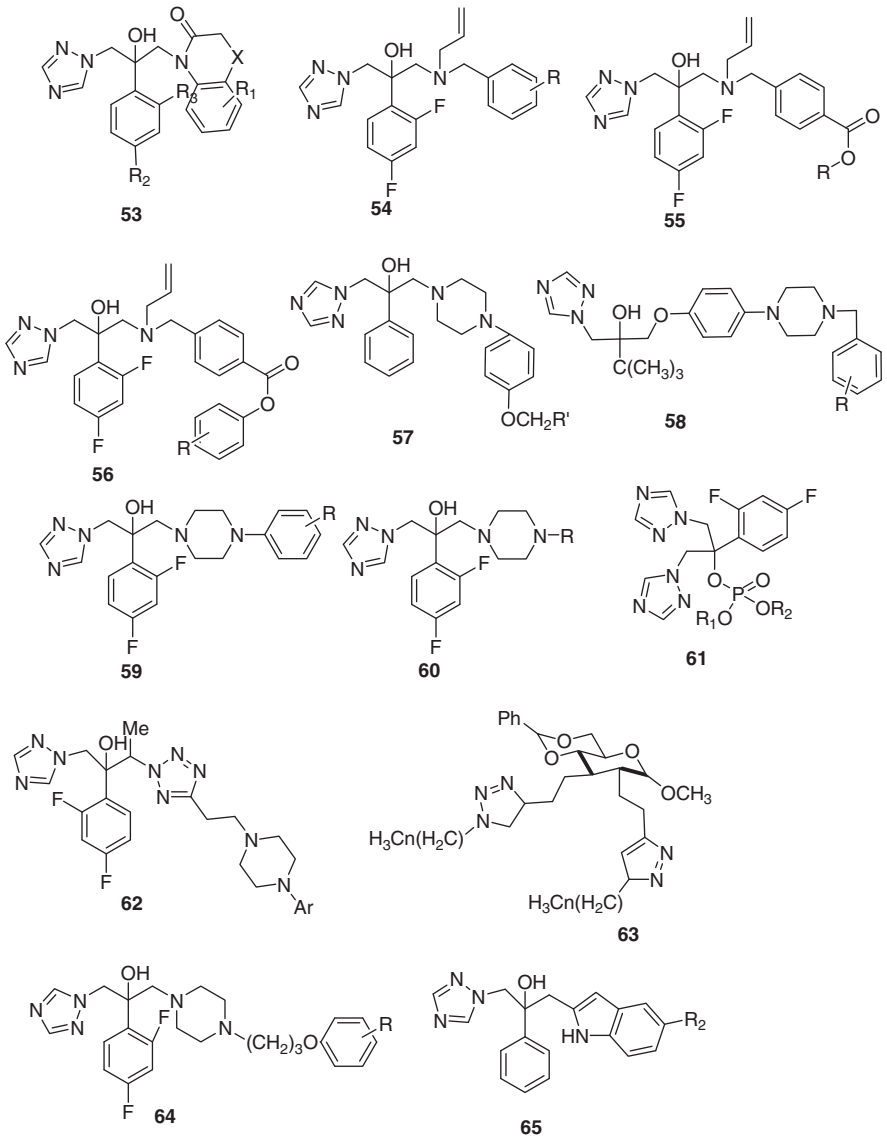


Figure 8. Anti fungal analogues of flucanazole and triazole.

A series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-(*N*-isoproyl-N-substituted-amino)-2-propanols have been designed and synthesized on the basis of the active site of lanosterol 14α-demethylase (CYP51). The substitutions with R = 4-$H_3COC_6H_4$, 4-$H_5C_2OC_6H_4$ showed MIC_{80} 0.0156–1 μg/mL in **51** (Fig. 7) and R = CH_3, CH_2CH_3, $CH_2CH_2CH_3$ in **52** (Fig. 7) (MIC_{80} 0.0156–64 μg/mL) exhibit stronger antifungal activity.[121]

A series of fluconazole analogues were designed and tested on *C. albicans* and *C. tropicalis*.The compounds containing benzothiazinone moiety are more active than those containing benzoxazinone. In the benzothiazinone series, replacement of fluorine by hydrogen atomo reduces the activity. The same is true for the benzoxazinone series, where halogen substituent at C_7 position is tolerated with slight decrease in activity while substituents like methoxy or methyl decrease the activity considerably. The potent compounds in this serieswere X = S, R_1 = H, R_2 = R = F (0.25 μg/mL) and X = O, R_1 = H, R_2 = R_3 = F (0.5 μg/mL) against fluconazole (1 μg/mL) in **53** (Fig. 8).[122]

QSAR analysis of a series of 50, 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols analogues of fluconazole were performed with **54**, **55**, **56** (Fig. 8.).[123]

LogMIC80 (μM) = 1.077(+0.1074)T_N_O_3
+0.5117(+0.1074) K3alpha
1.2944(+0.2248) T_N_Cl_6
−0.1459(+0.0263) T_C_F_5-6.1136

Based on the active site of *A. fumigatus* lanosterol 14α-demethylase (AF-CYP51), novel triazole compounds were designed, synthesis and antifungal activity were reported. All the target compounds exhibited excellent activities, with broad spectrum in which compounds with R′ = 4-FC_6H_4, 4-$CONH_2C_6H_4$, 4-C_5H_4N in **57** (Fig. 8). showed comparable activities *against A. fumigatus*, *C. parapsilosis*, *C. tropicalis*, *Cryptococcus neoformans*, *A. fumigatus*, *Microsporum lauosum*, *T. rubrum*. 0.0625–0.5 μg/mL to the control drug itraconazole 1–2 μg/mL.[124]

A novel triazole compounds structurally different from the current triazole drugs were designed, synthesized and screened for antifungal activity. In **58** (Fig. 8), strongly hydrophobic substituents with R bearing 4-phenyl moiety could help the side chain interact firmly with the residues in hydrophobic region of the enzyme, the CN group could form hydrogen-bonding interaction with the enzyme. The most active compounds were, R = 3,4-$(CH_3)_2$, 4-tBu, CN. Substitution with CN was potent compound (0.125–64 μg/mL), fluconazole (1–64 μg/mL) and itraconazole (0.125–1 μg/mL). The most active compound was docked into the

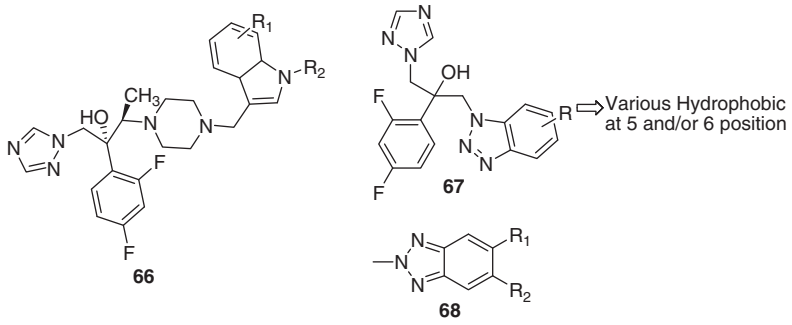


Figure 9. Anti fungal analogues of indole derivatives.

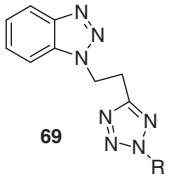


Figure 10. Benztriazole.

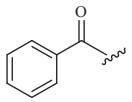
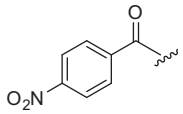
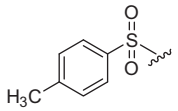
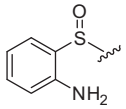
active site of CACYP51 by the affinity module within Insight II software package. Docking results revealed that the compound binds to the active site of CACYP51 through the formation of a coordination bond with iron of heme group. The tert-butyl group is located in the hydrophobic binding cleft lined with A114, F126, L139, M140, F145, I304 and M306, which is similar to the difluorophenyl group of fluconazole. The long side chain of the potent compound is oriented into substrate access channel 2 and forms hydrophobic and van der waals interactions with the residues. The phenyl group attached to oxygen atom of the side chain interacts with the phenol group of Y118 through the formation of pi–pi face-to-edge interaction. [125]

1-(1*H*-1,2,4-triazolyl)-2-(2,4-diflurophenyl)-3-(4-substituted-1-piperazinyl)-2-propanolol derivatives were evaluated against *C. albicans*, *C. paropsilosis*, *C. tropicalis*, *Cryptococcus neoformans*, *A. fumigates*, *Fonsecaea pedrosoi*, *T. rubrum*. The substitution with R = 4-$COCH_3$, 3-CF_3, 4-C $(CH_3)_3$ and R = 2-pyridine, 2-Cl, 4-CF_3, 2-pyridine in **59**, **60** (Fig. 8) were found to be more potent than fluconazole MIC less than 0.125 μg/mL.[126]

Fluconazole derivatives possessing carbohydrate phosphate esters, were synthesized and evaluated in vitro against *Cryptococcus neoformans*, *C. albicans* and *A. niger*. All compounds were less active in vitro in comparison to Fluconazole. The in vitro antifungal activities of several fatty alcohol phosphate diester and triester derivatives of Fluconazole were stronger against *C. albicans* and *A. niger* than those of Fluconazole. The more potent compound in this series were compounds bearing substitutioin at $R_1 = C_2H_4CN$, $R_2 = n$-$CH_2 = CH–C_9H_{18}$, in **61** (Fig. 8). Substitution at $R_1 = CH_3$ also shows antifungal activity with MIC 258–1628 μg/mL.[127]

Triazole derivatives with 5-substituted tetrazole structure were prepared and evaluated for antifungal activity against *Candida spp*, *Cryptococcus neoformans* and *Aspergillus* spp. in vitro. The location of the methyl group at the C_3 of compounds has been demonstrated to be a key structural element of antifungal potency. In **62** (Fig. 8), the compound having 2-butoxy substitution on the phenyl ring of piperazine, is the most active with MIC value of 1.0–2.0 μg/mL, against *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. neoformans*. Other compounds showed moderate activity against most of the Candida species with MIC value of 2.0–8.0 μg/mL however, none of the compounds showed significant activity against *Aspergillus* spp. up to 8.0 μg/mL.[128]

Table 4
Different substitution at tetrazolo **69**

Compound	R
70	
71	
72	
73	

A series of D-Glucose-derived benzyl and alkyl 1,2,3-Triazoles were synthesized and evaluated against *C. albicans*, *A. fumugatus*. The length of alkyl chain to the triazole is responsible for antifungal activity. In **63** (Fig. 8) when $n = 8$, showed 14 times more potent than fluconazole but in compound when $n = 12$ show no obvious inhibition. Hence, the introduction of linear alkyl chain with proper lengths into 1,2,3-triazole ring could enhance antifungal activities.[129]

A series of new azoles with substituted phenoxypropyl piperazine side chains were designed and synthesized. The study describes the design, synthesis and evaluation of a novel series of 1,2,4-triazole and benzotriazole derivatives as inhibitors of cytochrome P450 14α-demethylase. Furthermore, they were found to have in vitro activity against *M. canis*, *T. mentagrophytes*, *T. rubrum*, *Epidermophyton floccosum* and *C. albicans* comparable to fluconazole and clotrimazole. The substitution when R = 4-C$(CH_3)_3$, 4-Cl, 3-NO_2,4-Br in **64** (Fig. 8) shows good antifungal activity. The 4 and 3-substituted derivatives showed higher antifungal activity compared to 2-substituted ones. The compound with $n = 3$ was found to be potent among the series against *C. albicans* with MIC 0.0156 μg/mL.[130]

Conazole antifungals, in the series of triazole alcohols containing an indole moiety substituted at 5-position by halogens, a cyano or 4-methoxyphenyl group by Corey–Chaykovsky reaction under microwave irradiation shows marked antifungal activity. The various substitutions were tried like 2,4-diF, 2,4-diCl on R_1 and F, Cl, Br, CN, 4-OMePh on R_2 in **65** (Fig. 8.).[131]

A series of 1-Halogenobenzylindole were synthesized and evaluated against *C. albicans*, *C. krusei*, *C. neoformans*, *A. fumigates*. The substitution at **66** (Fig. 9) with R_1 5-Cl, 5-F, 5-CN, 6-Cl, 6-CN

showed activity equal to reference drugs amphotericin B, itraconazole, fluconazole. The presence of 2,4-difluorobenzyl group on R_2 of indole moiety showed better activity than compounds with mono-dichlorobenzyl or mono-fluorobenzyl substituents on R_2 position of indole.[132]

A series of 5-substituted benzotriazole were prepared and evaluated for antifungal activity against various species of *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *Saccharomyces cerevisiae*, *A. niger*, In **67** (Fig. 9) substitution at 5- and 6-position of benztriazole **68** (Fig. 9) with $R_1 = R_2 = CH_3$ showed MIC 12.5–100 μg/mL and when $R_1 = NO_2$. MIC were 1.6–100 μg/mL, are most potent compounds amongst the series.[133]

3.8. Benztriazole

A series of triazolo bearing tetrazolo type were synthesized and evaluated for antifungal activity against *C. albicans*. The following substitution at R shows antifungal activity. Also **69** (Fig. 10) was found to be most potent activity against fungi with 15 mm zone of inhibition. The compounds **72–77** in Table 4. were also active against fungi.[134]

3.9. Indole

1*H*-Indole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. It appears that a 2-thioxothiazolidin-4-one ring and an enone linkage are indispensable for activity. In addition, results indicate that compounds possessing both a relatively high log*P* value and a weakly polarized ring were the most active compounds in this series. The structure bearing **78**, **79** and **80** (Fig. 11) bearing $R_1 = CH_3$, C_2H_5; $R_1 = CH_3$, H and R_2 = H, Cl, Br, I, OCH_3, CH_3; R_1 = H, CH_3, F, Cl and R_2 = H, Cl, Br, F, OH showed potent antifungal activity. The marked antifungal activity against *C. albicans*, *C.tropicalis*, *C. krusei*, *Cryptococcus neoformans*, *A. niger* (0.8–100 μg/mL), may be due to an electronegative atom at R.[135]

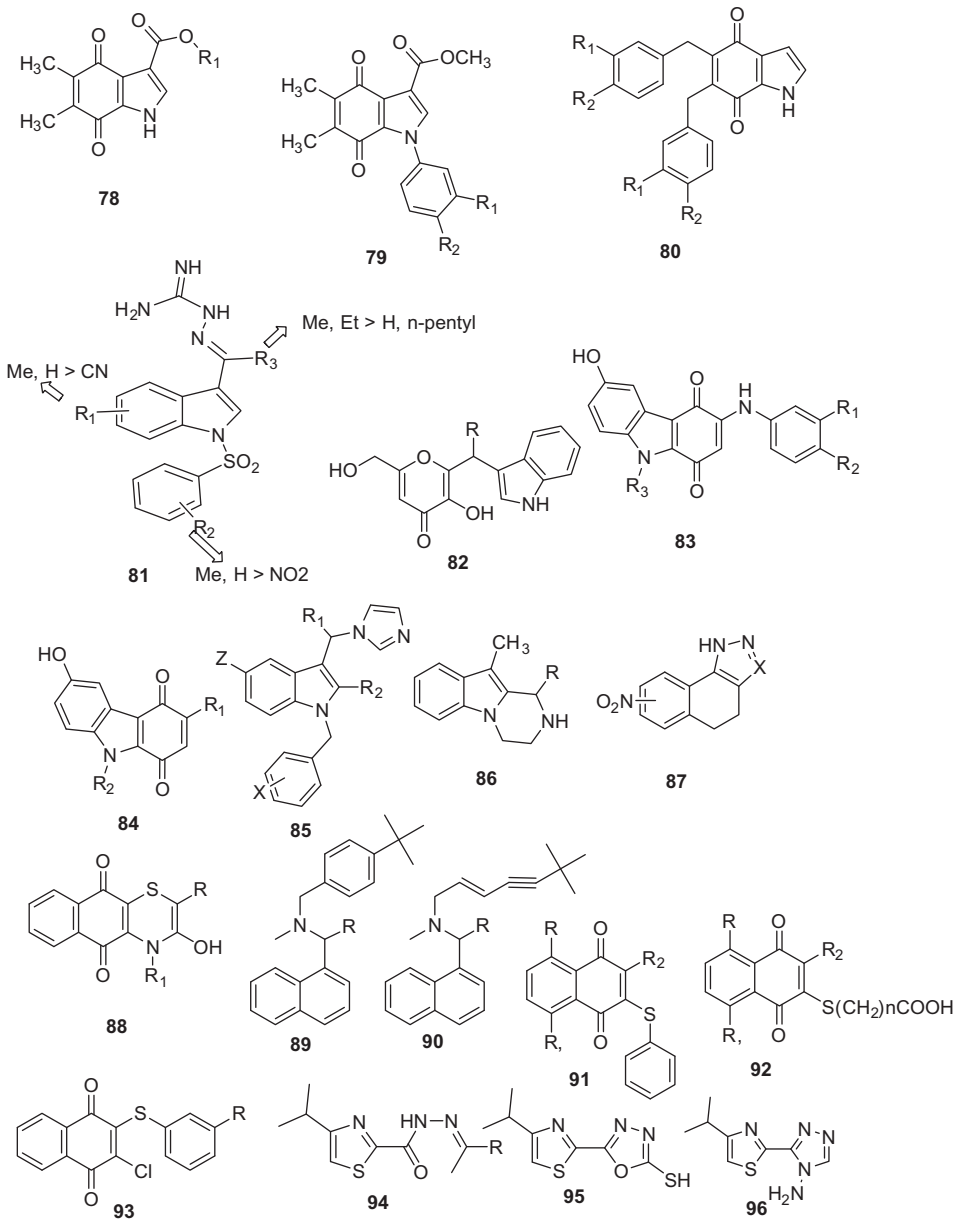


Figure 11. Anti fungal analogues of indole, benztriazole, napthalene, napthoquinone, & thiazole.

A series of aminoguanidine derivatives of *N*-arylsulfonyl-3-acylindoles were prepared and evaluated in vitro for their antifungal activities against seven phytopathogenic fungi. *Fusarium oxysporium*, *P. oryzae*, *A. alternate*, *A. brassicae*, *Fusarium graminearum*, *Bipolaris sorokinianum*, *F. oxysporium*. Preliminary SAR study demonstrated that introduction of electron donating substituents at R_1 and R_2, introduction of electron-withdrawing group (R_1) on the indolyl ring ON **81** (Fig. 11) would lead to less potent compounds than those with electron-donating group. When R_2 bearing electron-withdrawing group was introduced the corresponding compound exhibited less potent activities than that possessing electron-donating one. The proper length of substituent R_3 was found to be important for their antifungal activities. Substitution with R_1 = 4-Me, R_2 = H, R_3 = Me and R_1 = R_2 = 4-Me, R_3 = Me exhibited more potent antifungal activity.[136]

2-substituted aryl(indolyl)oic acid derivatives were synthesized and tested against *Rhizopus oryzae*, *A. niger*, *Candida rugosa C. albicans*, *S. cerevisiae*. The substitution with R = Ar in **82** (Fig. 11) is active against all five strains. Substitution with R = C_2H_5 and introduction of Aryl moiety on indole ring shows activity against all five fungi with zone of inhibition 11–21 mm at a concentration of 150 μg/mL.[137]

6-Hydroxy-1*H*-carbazole-1,4(9*H*)-diones were synthesized and tested for in vitro antifungal activity against *C. albicans*, *C. tropicalis*, *C. krusei*, *C. neoformans*, *A. niger*, *A. flavus*. The presence of arylamino, arylthio or alkyl moiety to the quinones was considerably an important factor to affect antifungal activity. In **83** (Fig. 11), when R_1 = H, OH, F; R_2 = CH_3O, H, CH_3, Br, Cl, I, F, OH, R_3 = C_2H_5, CH_3, *n*-Pr shows potent antifungal activity with MIC 6.3–100 μg/mL. In **84** (Fig. 11), R_1 = CH_3CH_2S, H; R_2 = C_2H_5, CH_3, *n*-Pr were also potent compounds with MIC 1.6–100 μg/mL.[138]

A series of 26, 1-benzyl-3-(imidazol-1-ylmethyl)indole derivatives **85** (Fig. 11), were screened as antifungals. The SAR study revealed that replacement of hydrogen atom by methyl group exerted a favourable effect which is 10-fold as active (3 and 27 μg/mL) and this level of activity could be maintained with a bulky group such as *i*-Pr, *n*-Bu, *t*-Bu, *n*-Pr. Their analogues were devoid of activity at 100 μg/mL. Replacing the 4-chloro at the benzyl moiety by a fluorine atom, exerted a positive effect and increased after dihalogenation (2, 4-dichloro or 2, 4-difluoro, but compared with the 1-(4-chlorobenzyl) subseries, the parent methyl R_1 counterparts, were less active. The presence of a bromine atom at C_5 of indole exerted a constant detrimental effect. The most potent compound contains Z = Br, R_1 = H, R_2 = H, X = 2-Cl, exhibited MIC value 8 μg/mL 16-fold higher than that of itraconazole.[139]

A series of substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles derivatives were screened for their activity against pathogenic strains of *A. fumigatus*, *A. flavus*, *A. niger* and *C. albicans*. The substitutions such as nitro, methoxy, bromo, fluoro benzene were tried on **86** (Fig. 11). The most active compound in series was R = *p*-ClC_6H_4 but potency of compound was less than that of amphotericin B, exhibited a MIC value of 5.85 μg/mL, against *A. fumigatus* 11.71 μg/mL. The toxicity of the synthesized compound is less than amphotericin B.[140]

3.10. Napthalene

Mono nitrated dihydronaphthalenes were synthesized and evaluated for antifungal activity. In **87** (Fig. 11) when X = S, Se showed moderate activity and substitution of SO_2NH_2 in place of nitro group showed potent activity against *Cryptococcus neoformans*. The presence of NO_2 at 7 and 8-position shows good activity against *S. cerevisiae* 0.53–12.5 μg/mL, comparable to to flucanazole. The most active compound in series was X = S and SO_2NH_2 in place of NO_2 exhibited significant antifungal activity against *Cryptococcus neoformans* (MIC 0.53 μg/mL, compared with 0.53 μg/mL, for fluconazole and 0.13 μg/mL for amphotericin B).[141]

A series 3-substituted-1,4-dioxo-1,4-dihydronaphthalen-2-ylthio-alkanoate derivatives were synthesized and evaluated for antifungal activity. The compound bearing CH_3 at R_1 and R on **88** (Fig. 11) (MIC 1.56-12.5 μg/mL) shows marked activity against *Cryptococcus neoformans*, *S. schenckii* and *T. mentagraphytes* when compared with fluconazole.[142]

Two groups of chiral amines structurally related to Butenafine and Terbinafine have been synthesised and tested as potential antifungal agents against *C. neoformans*. In both series **89** and **90** (Fig. 11), the antifungal activity was strongly dependent on both the steric bulk and the electronic nature of the substituents. Compared to the parent compounds (Butenafine and Terbinafine), the activity was maintained when the hydrogen atom was replaced with a methyl group. Testing of terbinafine towards *C. neoformans* gave a MIC_{50} value of 0.25 μg/mL, while compound second R = C_2H_5 was a less efficient inhibitor (MIC_{50} 0.5 μg/mL). Modifying the structure with a C_2H_5 substituent, reduced the antifungal properties further whereas the compounds containing fluorines or a cyano group, had no activity towards *C. neoformans*. The (*R*)-enantiomer was better (lower MIC values) than butenafine.[143]

3.11. Napthoquinone

A series of 1, 4-naphthoquinone derivatives were synthesized and tested for antifungal activity against *C. albicans*, *Cryptococcus neoformans*, *S. scenckii*, *T. mentagraphytes*, *A. fumigates*, *M. cannis*. In **91** (Fig. 11), R = R_1 = H, R_2 = CH_2OH and in **92** (Fig. 11) *n* = 2 are more potent compounds in the series with MIC 0.78–25 μg/mL.[144]

A series of naphthoquinones, were synthesized and evaluated for antifungal activity against *C. albicans*, *A. fumigates*, *Cryptococcus neoformans*. Presence of chlorine atom in 1,4-naphthoquinone nucleus seemed essential for potent antifungal activity. The substitution of R = C_6H_5 (1.56 μg/mL) in **93** (Fig. 11), show antifungal activity greator than fluconazole (2 μg/mL) against *S. schenckii*.[145]

3.12. Thiazole

A series of 4-isopropylthiazole-2-carbohydrazide analogs, were synthesized and tested against yeasts: *S. cerevisiae and C. tropicalis*, mould*: A. niger*. In **94** (Fig. 11), R = methyl, benzene, electronegative substitution on benzene like chloro, bromo, nitro, phenol but not showing any significant antifungal activity. In **95** (Fig. 11) MIC 16–31.5 (Fig. 11) μg/mL and **96** (Fig. 11) shows MIC 8–16 μg/mL.[146]

Novel 4-thiazolidinone derivatives incorporating three known bioactive nuclei such as thiazole, thiazolidinone and adamantine were synthesized and evaluated for antifungal activity. It is interesting to point out that for the isomeric chloro substituted compounds the meta substituted derivative is mostly endowed with higher activity with respect to ortho and para while for nitro substituted compound, the most active are para and meta derivatives. The most potent compound was reported where R = 4-OH, 3,5-CH_3 (MIC 1.05–2.09 μg/mL). The substitution of R = 3-Cl,2-Cl,4-NO_2, 2-NO_2, 3-NO_2, OH, OCH_3 in **97** (Fig. 12) shows marked antifungal activity with MIC 1.79-6.93 μg/mL.[147]

A new series of 28 derivatives of [4-(40-substituted-phenyl)thiazol-2-yl]hydrazine were synthesized and evaluated against *C. glabrata* (4 strains), *C. albicans* (8 strains), *C. kruzei* (3 strains), *C. sake* (2 strains), *C. tropicalis* (3 strains). All synthesized compounds (MIC 0.5–128 μg/mL) have a lower or similar antifungal activity with respect to clotrimazole (MIC 2–16 μg/mL) or fluconazole (MIC 4–64 μg/mL) against tested fungi. The substitution of the nucleus linked to the hydrazone moiety had a deep impact on the antifungal activity on this scaffold of derivatives. Based

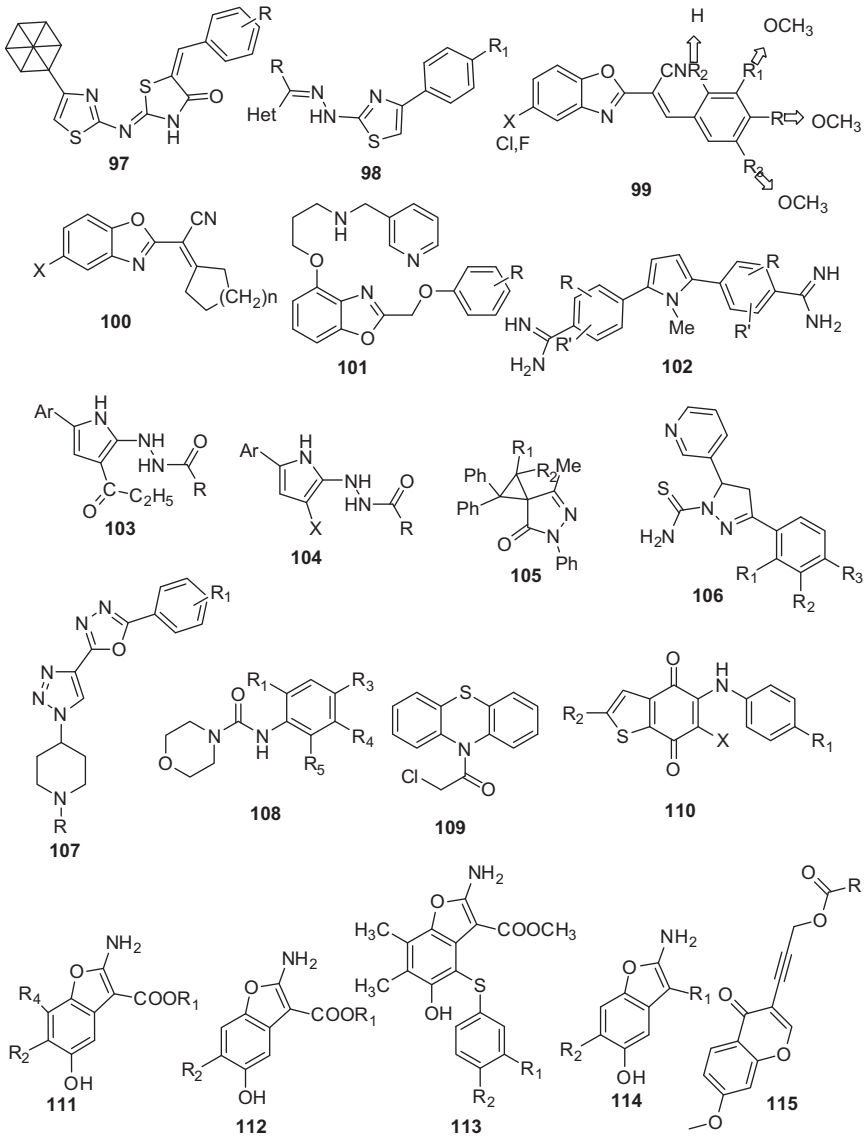


Figure 12. Anti fungal analogues of thiazolidinone, benzoxazole, benzisoxazole, pyrrole, pyrazole, pyrazoline, piperidine, morpholine, phenothiazine, thiophene, benzofuran and benzopyrone.

on the reported results, derivatives with substitution Het = thiophen-2-yl, pyridin-4-yl, naphthalen-2-yl, coumarin-3-yl and R = CH_3, H and R_1 = OCH_3, CH_3 in **98** (Fig. 12) represent good lead compounds for the development of novel broad-spectrum anti-*Candida* spp. agents and they could be used in association with azole derivatives to enhance their antifungal activity.[148]

3.13. Benzoxazole

Benzoxazole derivatives were synthesized and tested on *A. niger* and *A. fumigates*. The substitution with X = Cl and *n* = 1, 2 on **100** (Fig. 12) shows potent antifungal activity (60–75% zone of inhibition) against *A. flavus* and *A. niger*. Chloro and methoxy groups at the 4-position in the aromatic ring enhanced antifungal activity. The introduction of the fluoro group in place of the chloro at position 5 in the benzoxazole ring greatly enhanced antifungal activity against both *A. niger* and *A. flavus*, primarily due to the enhanced solubility of the fluoro substituent as well as due to the –I effect compared to the chloro group, which is electron withdrawing.[149]

A series of benzoxazole and indole derivatives were designed and synthesized as isosteric analogues of benzoheterocyclic *N*-myristoyltransferase Inhibitors. The substitution at R = 2,3,4-tri fluoro, (MIC 0.25–64 μg/mL) in **101** (Fig. 12) shows potent antifungal activity than fluconazole (0.25–4 μg/mL) amongst the synthesized compounds 0.25 μg/mL. A nitro group at position 3 of the phenyl group was unfavorable for the antifungal activity. When the phenyl group of compound was substituted with one or more fluorine atoms, the antifungal activity was increased. The antifungal activity increased as with the increase in the number of fluorine atoms on the phenyl ring. Fluorine substitutions at both position 2 and 6 of the phenyl group led to the decrease of the antifungal activity.[150]

3.14. Pyrrole

A series of novel 2, 5-bis(guanidino-aryl)-1-methyl-1*H*-pyrroles has been synthesized and evaluated for antifungal activity against *Candida* spp. and *Aspergillus* spp. The substitution at R = 2-Me in **102** (Fig. 12) shows activity comparable or more potent than fluconazole whereas R′ = 2-Cl, comparable to fluconazole. 4-Guanidino compound having methyl substituents on the phenyl ring was the most active compound with an MIC value of 1–4 μg/mL for *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. glabrata* and *C. tropicalis*.

Complete loss of antifungal activity was observed in compounds having guanidine groups at 2- and 3-positions, respectively.[151]

On the series of 2-Acylhydrazino-5-arylpyrroles were synthesized, SAR study reveals that activity of this series of **103**, **104** (Fig. 12) in compounds was dependent on the substituent present at 5-position of the pyrrole ring. Furthermore the presence at 2-position of the pyrrole ring of butyrylhydrazino, isobutyrylhydrazino, or (4-methoxyphenyl)acetylhydrazino moieties led to compounds with poor activity, a certain degree of lipophilicity is necessary for the compound to penetrate the fungal cell wall, the presence of a hydrophilic moiety can play a most vital role in binding to its biological target molecule. Pyrroles show a general enhancement in antifungal activity with MIC values of 0.39–6.25 μg/mL and 0.78–50 μg/mL. The compound with X = CN, Ar = 4-OMePh, R = Et was showed the highest activity of the whole series, MIC data reveals a 2- to 32-fold inhibition potency against *C. albicans*, *C. glabrata* and *C. krusei* as compared to fluconazole. Replacing the 3-COOEt or 3-COOMe with a 3-cyano group, to produce pyrrole, led to an approximate 8- to 32-fold increase in activity (4- to 32-fold).[152]

3.15. Pyrazole

A series of new spiro[cyclopropane-1,4′-pyrazol-3-one] derivatives were synthesized and tested *in vitro* against *C. albicans*. The **105** (Fig. 12) shows weak in vitro antifungal activity at R_1 = H, CH_3 and R_2 = CO_2Me, CO_2Et, CO_2iPr, CO_2tBt, CN, $CONEt_2$. All spiro compounds were active against *Candida* spp. with MIC 25 μg/mL. None of the test compounds showed superior activity to the standard drugs Miconazole and Itraconazole (2 μg/mL) which display moderate or weak antifungal activity against *Candida* spp.[153]

3.16. Pyrazoline

A new series of 3-aryl-5-(pyridin-3-yl)-1-thiocarbamoyl-2-pyrazoline derivatives were prepared. None of the synthesized compound shows significant antifungal activity. Electron rich group in para position of aromatic ring produced highest efficacy and exhibited >90% inhibition the primary screen at 6.25 ug/mL, against bacterial strains. The compound in **106** (Fig. 12) with substitution R_1 = H, R_2 = H, R_3 = Cl and R_1 = H, R_2 = CH_3, R_3 = H active against *Mycobacterium tuberculosis* at 6.25 μg/mL, and *Staphylococcus aureus* at 128 μg/mL.[154]

3.17. Piperidine

2,5-disubstituted 1,3,4-oxadiazole were synthesized and evaluated against *C. albicans*, *F. oxysporum*, *A. flavus*, *A. niger*, *C. neoformans*. The substitution with SO2CH3 on R and OH, Cl in R1 in 107 (Fig. 12) are most potent compounds in the series. Changes in piperidine nucleus: Protection in R position show less antifungal activity and deprotection of same show significant aantifungal activity. Substitution of Me and Et, OMe, NO2 shows significant activity.[155]

3.18. Morpholine

A series of *N*-alkyl substituted urea derivatives have been synthesized and evaluated for antifungal activities against *A. niger* and *T. rubrum*. Compounds having fluoro substituent at ortho and para positions of the phenyl ring exhibited potent antimicrobial activities against fungi. However R_3 = F, R_1 = R_2 = R_4 = R_5 = H (3.5 μg/mL) and R_1 = F, R_2 = R_3 = R_4 = R_5 = H (3.1 μg/mL) in **108** (Fig. 12), show potent antifungal activity against the above strains ketoconazole (3.4 μg/mL).[156]

3.19. Phenothiazine

Several α-chloro-*N*-acetyl phenothiazines were synthesized and their antifungal activity was evaluated. It was observed that the presence of an electron withdrawing group in the 2-position of the tricycle system is essential for neuroleptic activity. Several modification were done on phenothiazine **109** (Fig. 12), ring like isosteric replacement of sulphur, contraction of phenothiazine ring but none have shown antifungal activity. Only phenothiazine ring is responsible for antifungal activity. The following compound was found with MIC 4-512 μg/mL, ineffective against tested fungi.[7]

3.20. Thiophene

5-Arylamino-4, 7-dioxobenzo[b]thiophenes were synthesized and evaluated against *C. albicans*, *C. tropicalis*, *C. krusei*, *A. niger*, *A. flavus*. However the substitution bearing R_1 = CH_2OH, $COOCH_3$ and R_2 = H, Cl, Br, I, OCH_3, CF_3, OH, F and X = H, Cl in **110** (Fig. 12), are active antifungal agents. The potent compound have MIC 1.6–50 μg/mL, against 5-fluoro cytosine 12.5 μg/mL. Although substitution at Se in place of S was more potent compound in the series. The substitution with electronegative groups on R_2 may be responsible for activity.[157]

3.21. Benzofuran

Benzofuran-5-ol derivatives were synthesized and tested for in vitro antifungal activity against *C. albicans*, *C. tropicalis*, *C. krusei*, *C. neoformans*, *A. niger*, *A. flavus*. In **111** (Fig. 12), At R_1, R_2, R_4 = CH_3 (6.3–50 μg/mL) shows activity greator than fluconazole (6.3–50 μg/mL) and 5-fluoro cytosine (6.3–12.5 μg/mL). In **112** (Fig. 12.), R_1 = CH_3 and R_2 = H, CH_3 are active against all tested fungi. In **113** (Fig. 12), R = CH_3, F and R_2 = H, shows good antifungal activity (1.6–50 μg/mL). In **114** (Fig. 12), R_1 = CN, R_2 = CH_3 (0.8–50 μg/mL) shows antifungal activity superior to or comparable than 5-fluoro cytosine (6.3–12.5μg/mL) and fluconazole (6.3–50 μg/mL).[158]

3.22. Benzopyrone

A series of new 18 benzopyrone derivatives were designed and synthesized and evaluated aganist the five tested human pathogenic fungi *C. albicans*, *Cryptococcus neoformans*, *C. parapsilosis*, *T. rubrum*, *M. gypseum*. The results indicate that when R = alkyl chain in **115** (Fig. 12) with 2–5 carbon atoms exhibited better effective than the others. The introduction of substituted phenyl and benzyl groups on the terminal hydroxyl, marginal activity was found. Moreover, the length of the alkyl group attached with the terminal hydroxyl played an important role in the antifungal activity. One of the compound with an isopropyl alkyl substituent showed best antifungal activity among the synthesized compounds 12.5 μg/mL against *C.parapsilosis* Fluconaole as standard 32 μg/mL. The substitution of ethyl, butyl on same position shows good antifungal activity.[159]

3.23. Lactone

Derivatives of carabrone were synthesized and tested in vitro against *Colletotrichum lagenarium*. Substituents on the C-4 position could significantly affect the antifungal activity. For example, introducing the hydrazone substituents on the C-4 position lead to the most potent compounds in **116** (Fig. 13), while substituents, such as the hydroxy, chloro, and ester (except isobutyryloxy group), shows the less potent activity. The γ-lactone is necessary

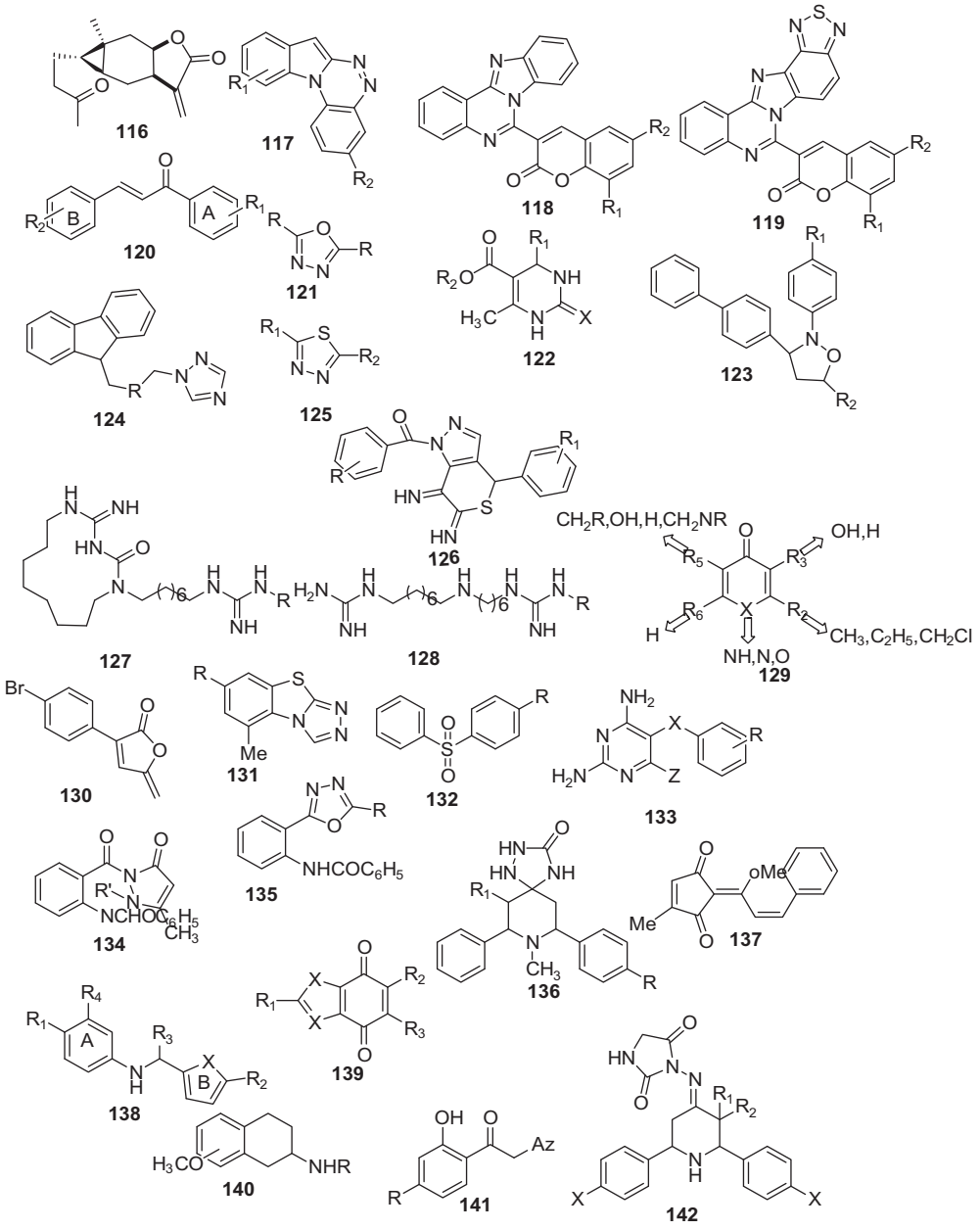


Figure 13. Anti fungal analogues of lactone, benzotriazine, chromane, chalcone, oxadiazole, pyrimidinone, isoxazolidine, carbazole, acetazolamide and some miscellaneous analogues.

for the antifungal activity and opening the lactone would lead to a less potent compound.[160]

3.24. Benzotriazine

A series of novel indole[1,2-*c*]-1,2,4-benzotriazine derivatives were obtained by a modified Sandmeyer reaction. The synthesized compounds were evaluated against *F. graminearum*, *Pyricularia oryzae*, *F. oxysporum*, *Alternaria alternate*, *Alternaria brassicae*. The most potent compound in series was substitution at R_1 = H, R_2 = H in **117** (Fig. 13) shown potent activity than hymexazol.[161]

3.25. Chromane

A 2 series of chromene-2-one were synthesized as shown in structure and evaluated against, *A. niger*, *C. albicans*, *A. flavus*. Substitution of lipophilic electron withdrawing bromo or chloro substituents at the R_2 or at the both the R_2 and R_1 positions of the coumarin ring afforded molecules with potent antifungal compound. In **118** (Fig. 13) substitution of R_2 = H, R_1 = Br shows MIC 15 μg/mL against *C. albicans*, in **119** (Fig. 13) substitution of R_2 = R_1 = Br shows MIC 15 μg/mL.[162]

3.26. Chalcone

The synthesis, in vitro antifungal evaluation, SAR study of 41 chalcones were reported. The synthesized compounds were evaluated against *C. albicans*, *S. cerevisiae*, *Cryptococcus neoformans*. All active structures were tested for inhibiting of β(1,3)-glucan synthase and chitin synthase. Chalcones **120** (Fig. 13) with substituents bearing electron donating and withdrawing groups on both rings, found to be active against dermatophytes and not against

other group of fungi. Chalcones with R_2 = H, 4-NO_2, 2-NO_2 and R_1 = H, 4-Br showed good antifungal activity. Electron withdrawing groups in the para position increased the potency, a nitro substituent enhances 2–4 times the activities in three of the fungi tested.[163]

3.27. Oxadiazole

A series of novel 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized by A. Rauf et al. In **121** (Fig. 13) when R is substituted by large alkyl skeleton, shows some antifungal activity against *Candida* spp. of Nystatin 20–30 mm zone of inhibition. Substitution at R = $CH_2(CH_2)_{13}CH_3$ and $CH_2(CH_2)_6CH$ = $CHCH_2CHOH(CH_2)_5CH_3$ shows excellent inhibitory action against *C. albicans*, *Trichoderma viridae*, *F. oxysporium*, *A. niger* with 15–27 mm zone of inhibition.[164]

3.28. Pyrimidinone

Singh et al. synthesized dihydropyrimidinones by the Biginelli reaction. Six compounds were selected and examined their antifungal activities against the radial growth of three fungal species viz *Trichoderma hammatum*, *Trichoderma koningii* and *A. niger*. In **122** (Fig. 13) substitution at R_1 = C_6H_5, 2-OH C_6H_5, 4-$Me_2NC_6H_5$ and R_1 = C_2H_5 and X = O,S shows antifungal activity. The radial growth of *T. koningii* after 24 and 48 h were found to be inhibited completely (100%) by compounds and were most potent against *A. niger*, with MIC value of 0.35 μg/mL each.[165]

3.29. Isoxazolidine

A series of novel 5-substituted isoxazolidine derivatives have been synthesized and screened against *A. flavus*, *Fusarium moniliforme* and *Botrydiplodia theobromae*. The compounds showed good antifungal activity against the above described strains in the range 2.5–12 μg/mL. In **123** (Fig. 13) the presence of R_2 = CH_2OH, C_6H_5 and introduction of R_1 = F, OMe to the phenyl ring enhanced the antifungal activity, introduction of one more phenyl ring to the isoxazolidine ring further resulted in increased antifungal activity.[166]

3.30. Carbazole

A series of N-substituted carbazole derivatives were synthesized and evaluated for antifungal activities against *C. albicans* and *A. fumigates*. Introduction of azole moiety (imidazole or 1,2,4-triazole) and electropositive group in carbazole derivatives could improve the activities which is most potent one in series against fungi and bacteria. The substitution where R = C_4H_8, C_2H_4 in **124** (Fig. 13) shows good antifungal activity 2–4 μg/mL with fluconazole 5 μg/mL. The substitution of R = benzene and dichlorobenzene to triazole show excellent activity 32 and 64 μg/mL against *C. albicans* and *A. fumigates*.[167]

3.31. Acetazolamide

A series of 22 numbers of acetazolamide derivatives **125** (Fig. 13) were synthesized and evaluated against *A. fumigates*. Increasing the size of the acetamide moiety by adding an extra methyl or a chloro substituent leads to a reduction in activity, while substitution with a trifluoroacetamide group on R_2 decreases activity. Also deacetylation of R_2 abolishes activity. Replacement of the sulphonamide is generally tolerated. SH, Ph, CF_3 and Br substituents as R_1 produce compounds with similar activity to acetazolamide.[168]

3.32. Miscellaneous

1-Aroyl-3 methyl-4-substituted phenyl-6-imino1,4,7-trihydro(1,3)-thiazino(5-4*D*) series of 10 compounds were synthesized as **126** (Fig. 13). A general trend of enhancement in activity is observed by the presence of chlorine group. Presence of two chlorine atoms in the either phenyl ring impart much fungitoxicity than one chlorine atom. But the change of position of chlorine atom from ortho and meta to para increases fungidical properties. The most potent compound of this series is position R and R_1 is replaced by 4-Cl with zone of inhibition 60% and 61% against *A. niger* and *A.fumugatus* with standard Carbendazim 90% and 92%, respectively.[169]

Guanidine derivatives were synthesized and tested in vitro for their antifungal activity toward clinically relevant strains of *Candida* spp. Guazatine components and linear and cyclic guanidino derivatives compounds **127**, **128** (Fig. 13). showed a minimum inhibitory concentration in the micromolar range and a biological activity (6.25 μg/mL) better than that of fluconazole (0.8–418 μg/mL).[170]

A series of 2-alkyl-3-hydroxy-pyridine-4-ones, were synthesized and evaluated against *C. albicans*, *A.niger*, *A. flavus*. The representative structure is **129** (Fig. 13) showing different substitutions. Geometrical parameters (J3D, ASP), functional group descriptor (*n*Cs) and topological parameter (SPI) have important roles in the antimicrobial activity against *C. albicans*. This equation has a good statistical quality (R_2 = 0.81, SE = 0.14, Q^2 = 0.73). All the synthesized compounds have MIC 16–512 μg/mL.[171]

5-Acetoxymethyl-3-(4-bromophenyl)-2,5-dihydrofuran-2-one was antifungally active, in **130** (Fig. 13) substituent in the allylic position was necessary for a compound to retain high activity. Presence of exocyclic double bond is necessary for activity, further substitution to the exocyclic double bond diminishes activity, is proved by antifungal assay. The representative compound shown below active against *Candida*, *Aspergillus*, *Trichphyton* spp. with MIC 0.49–31.25 μmol/L.[172]

The study was done by Garibotto et al. to develop new antifungal peptides possessing a length as short as possible while maintaining their antifungal activity. The RQKK sequence was selected as the starting structure, since RQKK was the smallest peptide so far showing at least a moderate antifungal effect against *C. neoformans*.[173]

New cobalt(II) and nickel(II) complexes of N-substituted thiosemicarbazones derivatives of 2 methylcyclohexanone of general composition ML_2X_2 (where, M = Co(II) and Ni(II),X = Cl^-, SCN^- and ½SO^{2-}) have been prepared and characterized by elemental analysis, molar conductance, magnetic susceptibility measurements and spectral (IR, electronic, mass and EPR) techniques. They were tested against *A. niger*, *Macrophomina phaseolina*, *F. oxysporum* by taking Chlorothalonil as standard (MIC 52–64 μg/mL).[174]

The synthesis of new pyrazolo-thiazolo-triazole compounds, analogues of tricyclazole (a commercial antifungal product that acts by inhibiting melanin synthesis), and their biological activity was studied on some dermatophytes and phytopathogens. The compounds poorly inhibited the growth and pigmentation of fungi tested and were less efficient than tricyclazole. Substitution in **131** (Fig. 13) at R = CH_3, H shows antifungal activity.[175]

Inhibitors of folate-synthesizing enzymes were designed and synthesized. The target enzymes used was dihydrofolate reductase (DHFR). Several series of 30 new 2, 4-diaminopyrimidines and new 15 sulfonamide were synthesized and tested. The following ranking in activity toward DHFR of *C. albicans* –OCH_2– > –CH_2CH_2– > –CH = CH– > –$NHCH_2$– > –CH_2NH– > –CH_2– in **132**, **133** (Fig. 13). Introduction of a methyl group in the 6-position of the pyrimidine ring led to an increase in toxicity. Introduction of the 1-naphthyl group reduced toward *C. albicans* DHFR. Substitution by methoxy

groups led to an increase in activity. This was in contrast to the positive influence of methoxy groups observed so far on 5-benzyl-2, 4-diaminopyrimidines when tested against other species. [176]

1,3,4-oxadiazoles and pyrazolones have been synthesized and evaluated for activity against *A. niger* and *A. flavus* using salicylic acid as a standard. The substitution with R = C_6H_5, *p*-OHC_6H_4 on **134**, **135** (Fig. 13) shows excellent antifungal activity with zone of inhibition (20–22 mm) against both *A. niger* and *A. flavus.* Compound second showed better activity (15–17 mm) against *A. niger* as compared to activity (11–13 mm) against *A. flavus* on same substitution. The diazole and triazole were responsible for the activity. [177]

Some novel spiropiperidinyl-1, 2, 4-triazolidin-3-thiones have been synthesized and studied for their antifungal activity against *C. albicans*, *A. niger and A. flavus*. **136** (Fig. 13) without any substituent at the para position of the aryl groups present at C_2 and C_6 positions of the six membered heterocyclic moiety did not show any in vitro anti fungal activity even at a maximum concentration of 200 μg/mL against *C. albicans* and *A. niger*. The compounds with Cl or OCH_3 functions at the para position of the aryl moieties present at C_7 and C_9 positions of the six membered heterocyclic ring along with or without CH_3 group at C_6 play an important role in eliciting its antifungal potency. Substitutions on **136** (Fig. 13) at R_1 = CH_3, H and R_2 = Cl, OCH_3 shown antifungal activity.[178]

A series of analogues of Coruscanone A have been synthesized and evaluated against *C. albicans*, *C. albicans*, *C. albicans*, *C. neoformans*, *A. fumigates.* It was postulated that introduction of the bulky phenyl group that extends conjugation might have a significant impact, O-methylation of the enolic hydroxyl group plays a key role in the antifungal activity of coruscanone A, the antifungal mechanism of coruscanone A regarding its reactive site to the target would be on the cyclopentenedione ring, which may be considered as the warhead of the molecule. SAR indicate that in **137** (Fig. 13) the 2-methoxymethylenecyclopent-4-ene-1,3-dione structural moiety is the pharmacophore responsible for the antifungal activity of this class of compounds while the side chain styryl-like moiety plays an important complementary role, presumably contributing to target binding.[179]

Based on computational studies the homoallylamine type of compounds were synthesized and screened for antifungal activity against *M. canis*, *M. gypseum, T. rubrum*, *T. mentagrophytes*, *E. floccosum*. In **138** (Fig. 13) the change of the phenyl ring B by heterocyclic rings such as a-, b- or c-pyridine gives very active compounds MIC 3.25–50 μg/mL. The lengthening of the flexible connecting chain caused a dramatic decrease in the antifungal activity. It appears that the presence of a non-substituted phenyl ring A leads to antifungal compounds. The presence of different substituents like CH_3 or halogen as R_1 enhances the antifungal activity, Presence of a heteroatom (with electronic lone pairs) or CH_3O groups on ring B, a particular length of the connecting chain, Presence of a halogen atom (particularly Br or Cl) as R_1 on ring A.[180]

A three-dimensional quantitative SAR studies for a series of compounds 74 using comparative molecular field analysis (CoMFA) was performed. The results for CoMFA were $n = 55$, $q^2 = 0.683$, $r^2 = 0.87$, standard error of estimation (SEE) = 0.152, $F = 89.50$, Steric (%) = 65.1, electrostatic (%) = 34.9. The recursive partitioning analysis showed that the number of nitrogen atoms at aromatic ring, hydrogen bonding donors and kappa-3 were essential features to classify the antifungal activity. In **139** (Fig. 13) a change from a methoxy to a hydrogen atom at the R_2-para-substituents decreases the potency, which may be due to a suitable increase in the electronegative groups. The introduction of pyridinyl on R_1 leads to decrease in activity. The substitution of N, S, CH = CH showed good activity.[181]

A series of 2-amino tetraline were synthesized, in **140** (Fig. 13) methoxy substituted and R containing long alkyl chain upto 10 shows activity more potent than fluconazole. The substitution of OH in place of OCH_3 at 5, 6, 7, 8 of napthol ring shows activity comparable to fluconazole (0.6–16 μmol/L). Same compounds exhibits better antifungal activities against fluconazole-resistant strains (MIC <0.125 μmol/L) than amphotericin B. Same compound was evaluated in vivo by a rat vaginal candidiasis model, and it was found to have a marked acceleration of clearance of the yeast, as demonstrated by a statistically significant decrease in colony forming unit (cfu) counts. The infection was cleared in one week with all dose regimens, the compound without alkyl substitution are low acting compounds.[182]

2-Hydroxyphenacyl azole and 2-hydroxyphenacyl azolium compounds have been described as a new class of azole antifungals. In **141** (Fig. 13) substitution at R = OMe, Cl and Az = triazole, diazole,amino triazole shows significant antifungal activity. Substitution of triazolium bromide in place of Az and substitution R = Cl and OMe was the most potent against *C. albicans*, with MIC values of 2 and 4 μg/mL. Methoxy substituted compounds shows activity comparable or more potent than reference drug fluconazole. Bisphenacyl triazolium derivative showed greater toxicity with IC_{50} values of 47 ± 5 μg/mL. [183]

3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones derivativeswere synthesized and evaluated for antifungal activity against *C. albicans*, *A. flavus*. In **142** (Fig. 13). Substitution of electron donating methoxy and methyl on the same position shows significant antifungal activity. Substitution of electron donating monomethyl substitution at third position on piperidine ring shows reasonable antifungal activity 12.5 μg/mL. Substitution at para position electron donating substitution of phenyl ring shows potent antifungal activity against *Aspergillus* and *Candida* spp. 12.5 μg/mL. [184]

4. Conclusion

Fungal infections pose a continuous and serious threat to human health and life in recent years their has been an increased use of antifungal agents and has resulted in the development of resistance and toxicity, low efficacy rates. This has given raise to search for a new heterocycle with distinct action or multitargeted combination therapy. In recent advances various heterocycles including imidazole, benzimidazole etc., twenty three scaffolds and their lead identification are discussed.

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