ANTIFUNGAL PROPERTIES OF 1,2,4-TRIAZOLES

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Five-membered sp^2 hybridization compounds known as 1,2,4-triazoles have three nitrogen atoms positioned at the ring's 1, 2, and 4 locations. 4*H*-1,2,4-triazole and 1*H*-1,2,4-triazole are the two tautomeric forms (Benson & Savell, 1950). 1,2,4-triazole compounds are getting a lot of interest due to their wide-ranging effects. Most importantly, due to their wide variety of biological activity, several ring structures with a 1,2,4-triazole nucleus have been included into a number of clinically approved medications (Lemke & Williams, 2008). In addition to all these, they exhibit many biological activities such as antimicrobial (Kotan, 2021), antioxidant (Çiftçi et al., 2018), antifungal (Mi et al., 2022), anticancer (Uddin et al., 2020), herbicidal (Zhang et al., 2014), anti-inflammatory (Ayaz et al., 2020), anticonvulsant (Küçükgüzel et al., 2004). In this regard, they are actively used both in pharmacology and in medicine. Therefore, the 1,2,4-triazole ring is important for creating novel chemical heterocyclic compounds entities with distinctive structural characteristics. Furthermore, Schiff bases containing 1,2,4-triazole show many biological activities (Sun et al., 2009; Wang et al., 2016; Sztanke et al., 2008; Hu et al., 2012). In recent years, Schiff bases containing 1,2,4-triazole with very high pharmacological properties have also been added to the literature (Chohan et al. 2010). In addition, a large number of 4-amino-5-substituted-1,2,4-triazole Schiff bases have been designed and synthesized (Aktaş Yokuş et al., 2017; Jin et al., 2018; Beytur et al., 2019). These compounds were compared with the triadimephone standard and it was seen that their antifungal activities were quite good. The molecules with antifungal activity such as Rizatriptan, fluconazole and terconnazole containing 1,2,4-triazole were obtained as products (Jin et al., 2014). For this reason, the synthesis of 1,2,4-triazole Schiff bases containing

imidazole ring, halogenated benzene ring, pyridine ring, furan ring has increased (Kotan, 2015; Gürbüz et al., 2020; Kotan et al., 2022).

Fungus

Fungi are thought to have formed with the evolution of eukaryotic creatures about 1.5 billion years ago (Rogozin et al., 2003). Since their fossilization is difficult compared to vertebrates, they cannot be followed easily. Mycology is the sub-discipline of biology that studies fungi. Mycology is a new science that was advancing with the development of the microscope in the 17th century. Fungal spores were first observed by Giambattista della Porta in 1588. The work titled "Nova plantarum genera", published by Pier Antonio Micheli in 1729, provided the development of Mycology. The Dutch Christian Hendrik Persoon (1761-1836) investigated the classification of fungi in modern mycology, and Elias Magnus Fries (1794-1878) improved the classification of fungi on spore colors and properties with his microscopic research, methods still used by toxonomists today. Taxonomists have suggested that there are about 120.000 fungal species, but in 2017 there are thought to be between 2.2 and 3.8 billion species (Murthy, 2021).

Fungi are unicellular or multicellular organisms (Niklas & Skalamera, 1997). These creatures can live in all habitats, such as on land, in the sea, in plants. Some fungi can benefit their environment, they are called decomposers and take part in the cycle of carbon and other elements in nature. For example, yeast used to make bread and beer is a type of fungus (Kavanagh, 2011). This is how they grow in soil and dead plants. Others are plant parasites that cause diseases such as rust, mold and thrush (Heath & Skalamera, 1997). Fungal diseases cause significant losses in plants and, cause disease in animals and humans.

Antifungal Activities

The type of stereols known as lipid particles in pathogenic fungi is argosterol. In the mammalian cell, the cell membrane is the lipid particle cholesterol. The difference in chemical properties of cholesterol and ergosterol allows us to use antifungals. The antifungal agents aim to inhibit the biosynthetic pathway of ergosterol, an important component of fungal membranes (Ozkirimli et al., 2009). Sterol 14α-demethylation constitutes an impact part of the Sterol biosynthetic pathway in eukaryotes (Nes & McKean, 1977). Cytochrome P450 sterol 14α-demethylases included in the CYP51 family within the fungal sequences were first purified from yeast in 1984 (*Sacharomyces cerevisiea*) (Yoshida& Aoyama, 1984). It has been

investigated that several plants and fungi contain more than one CYP51 gene and in recent years the CYP51 family participates in proteins found in 82 organisms (Lepesheva & Waterman, 2007). Therefore, Sterol 14α-demethylase is the primary drug target for a number of microbial infections in both plants and animals (Andes, 2004). CYP51-targeted drugs may be useful as an herbicide in crop cultivation and in the treatment of fungal diseases in humans (Warfield et al., 2014).

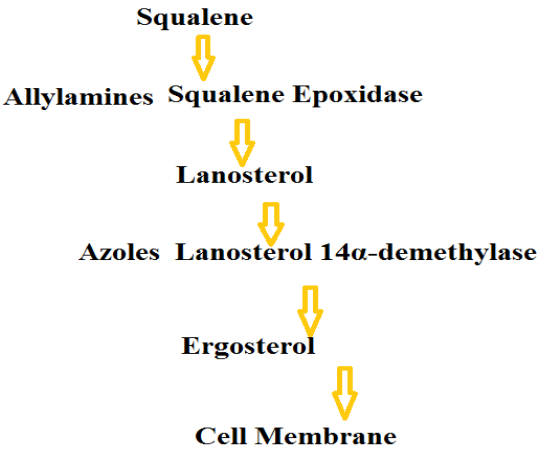


Figure 1. The biosynthetic pathway of ergosterol

Antifungal Drugs

In the synthesis of Ergosterol, firstly, Lanosterol is synthesized from squalene by the Squalene enzyme, and Ergosterol is synthesized from Lanosterol by the 14 alpha demethylase enzyme and shown in the Figure 1 (Aoyama, 2005). Allylamine (Terbinafine) blocking the Squalene Epoxidase enzyme, and Azoles (Imidazoles and Triazoles) blocking the 14 alpha-demethylase enzyme. Triazole-derived azole antifungals such as fluconazole and Voriconazole inhibit the CYP51 enzyme, thereby impairing Ergosterol synthesis (Aoyama, 2005). These antifungals are used to inhibit the growth of Ergosterol, the main Sterol found in the stolasma membrane of fungal cells. The sterol found in the animal cell membrane is called Cholesterol.

There are antifungals that inhibit the enzymes used during these transformations. The agents that effect Ergesterol synthesis are as follows. The polyene derivatives (Amphotericin B, Nystatin, Pimaricin), Azole group antifungals, i) the imidazole derivatives (such as miconazole, econazole and ketoconazole) and ii) the triazole derivatives (such as fluconazole and itraconazole, voriconazole, posaconazole), the allylamine derivatives (terbinafine, naftifine), Morpholine derivative (Amorpholine) (Sanati, 1997).

Azole group antifungals

Fungal diseases caused by pathogens are a medical problem in itself. The main ones of these pathogens are known as *Candida albicans, Aspergillus fumigatus* and *Cryptococcus neoformans (*Ostrosky-Zeichner et al., 2010; Kathiravan et al., 2012). Azole antifungals inhibit the biosynthesis of ergosterol in some fungal species such as Candida (Fringuelli et al.,1998). Because of their efficacy and lower price for most fungal infections, azoles are used worldwide as first-line antifungals for the management of systemic infections (Zavrel et al.,2017). Azoles are organic molecules consisting of a five-membered heterocyclic ring containing at least two nitrogens in their molecular structure. They are classified according to the number of nitrogen atoms in the azole ring. Azole antifungals are divided into two as imidazole and triazole derivatives (Castro et al., 2016; Chen & Sorrell, 2007; Odds et al., 2003). Imidazole and triazole antifungals were the most successful group in terms of affecting more agents in number (Ostrosky-Zeichner et al., 2010).

The triazoles (voriconazole, posaconazole, itraconazole and fluconazole,) are licensed agents used in the clinical use of invasive fungal disease. Voriconazole and Posaconazole, which represent specific advances in the understanding of structure-activity relationships, have an important place among the antifungal azoles (Ostrosky-Zeichner et al., 2010). The triazoles are effective against Cryptococcus neoformans, Candida albicans, non-albicans Candida species, and dimorphic fungus. With the exception of voriconazole and a few experimental triazoles, they are less efficacious against Candida glabrata and inert against Candida krusei among non-albicans Candida spp. Only itraconazole and voriconazole have any effect on different Aspergillus species and dematiaceous molds. Additionally effective against Fusarium spp. is voriconazole (Anaissie et al., 1995).

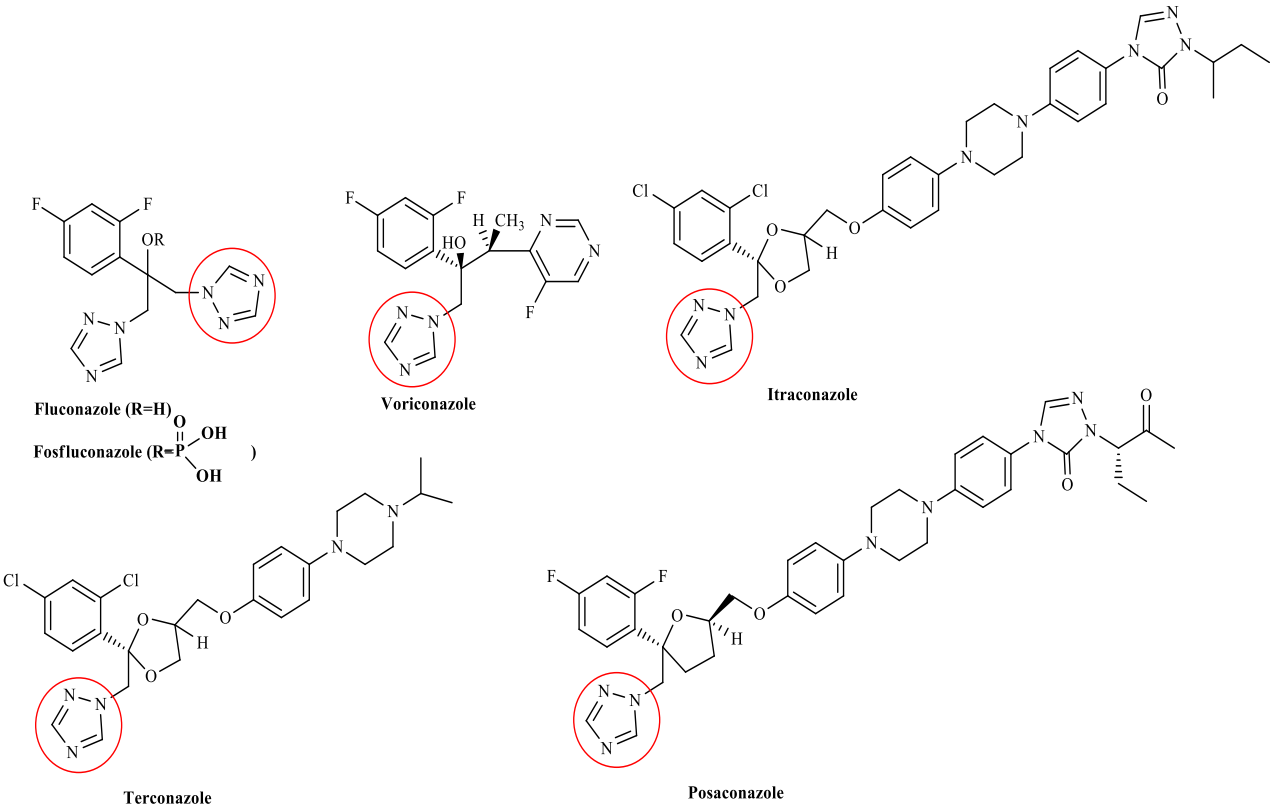
Voriconazole, a derivative of Fluconazole, is an important antifungal agent. It was first approved by the US Food and Drug Administration (FDA) in May 2002 (Jeu et al., 2003). The Voriconazole general formule is $C_{16}H_{14}F_3N_5O$ and its IUPAC name is (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol (Zhao et al., 2017) Voriconazole is highly active against fungal species such as Candida, Aspergillus and Cryptococcus and has proven to be an effective treatment for infections caused by these pathogens (Kullberg et al., 2005; Walsh et al., 2002; Herbrecht et al., 2002; Eiden et al., 2007; Singh et al., 2006; Barchiesi et al., 2015). The side effects of using voriconazole are few. The most common adverse events listed in clinical studies of a total of 1655 patients were rash

(5.3%), fever (5.7%), nausea (5.4%), visual disturbances (18.7%) and (Pfizer, New York, NY, USA).

Another antifungal agent derived from triazole is Posaconazole. It is an molecule with a broad antifungal spectrum that is widely used for the treatment of immunocompromised patients (Cornely et al., 2007; Walsh et al., 2007). The Posaconazole has antifungal activity against Candida species, the Zygomycetes species, Cryptococcus neoformans, Aspergillus and other some filamentous fungi. It is structurally a derivatives of itraconazole (Greer, 2007) The Posaconazole general formule is $C_{37}H_{42}F_2N_8O_4$ and its IUPAC name is 4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(2*S*,3*S*)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one (Chen et al., 2011). It contains three nitrogen atoms in its structure, thus forming the 1,2,4 triazole ring.

Itraconazole, a triazole antifungal derivative, primarily inhibits the biosynthesis of ergosterol, an essential component of fungal cell membranes (Grant & Clissold, 1989). The Posaconazole general formule is $C_{35}H_{38}Cl_2N_8O_4$ and its IUPAC name is 2-butan-2-yl-4-[4-[4-[4-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-1,2,4-triazol-3-one. It is used in the treatment of infections caused by fungi (Ahmad et al., 2001).

Fluconazole is a triazole antifungal agent that is part of the treatment for patients with a compromised immune system (Grant & Clissold, 1990). The presence of Triazole groups and 2 fluoride atoms in its structure increases the hydro-solubility and polarity of the drug, allowing it to be used in parenteral form (Debruyne & Ryckelynck, 1993) . Fluconazole is effective for treating oesophageal and vaginal candidiasis, disseminated candidiasis, oropharyngeal, as well as peritonitis, hepatosplenic candidiasis, non-neutropenic patients with candidaema, focal urinary tract infections and funguria (Kathiravan et al., 2012). The Fluconazole general formule $C_{13}H_{12}F_2N_6O$ is and its IUPAC name is 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol (Ruchita et al., 2007; Sanati et al., 1997).



Fungal microorganisms

Candida albicans

Classified as an opportunistic fungus, *Candida albicans* usually causes disease in immunocompromised individuals. Candida species are yeast-type fungi. Candida albicans is the most common of the similar species (Garber, 2001) *Candida albicans* produces white patches on the skin or mucous membranes. There are many species such as *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis* (Ellepola et al., 2000).

Aspergillus flavus

Aspergillus flavus is a saprophytic soil fungus that contaminates seed crops. It is an opportunistic fungal species that causes aspergillosis diseases as a pathogen in immunocompromised organisms. It can infect the cornea and upper tract of the eye. Like many molds, it can produce aflatoxin, a carcinogenic substance (Amaike & Keller, 2011).

Epidermophyton floccosum

It is a filamentous fungus that causes infections of the nail and skin in humans. The use of itraconazole, voriconazole, Terbinafine, and ketoconazole is effective against microorganisms that cause fungal diseases such as Epidermophyton floccosum (St-Germain & Summerbell., 2003).

Microsporum Canis

They are infectious fungi that have a low incidence in humans but are very common in animals. These fungi occur in cats and dogs. The Microsporum is the most common species in canine and feline ringworm cases (Mancianti et al., 2003).

Tricophyton mentagrophytes

Trichophyton mentagrophytes is a type of fungus that makes humans and animals sick. Such pathogenic fungi exist in different environments and infections can take all forms. T. mentagrohphytes is responsible for scaly, inflammatory fungal infections such as athlete's foot and ringworm (Gräser et al., 1999).

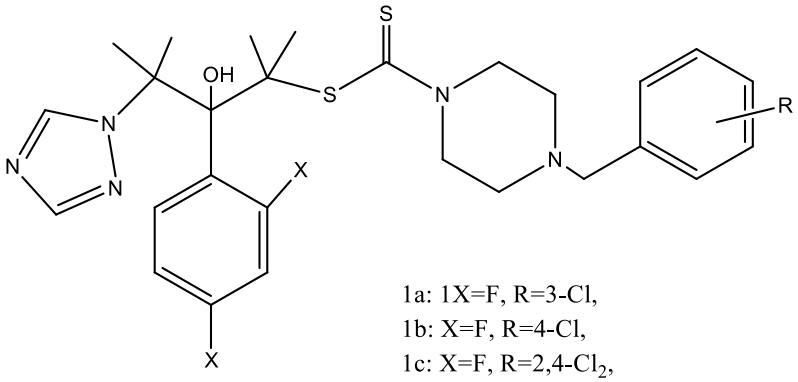
Aspelgillus fumigatus

The most frequent species isolated from the environment and found during postmortem exams is Aspelgillus fumigatus. It is primarily responsible for bone marrow transplant and cancer patients' nosocomial infections, which account for around 80% of all nosocomial infections. The remaining 20% of infections are brought on by A. j&zvus, A. niger, and A. teveus. The primary site of infection after inhaling fungal spores is typically the lung, and the chronic allergy to Aspergi/h spores and saprophytic growth (using dead or damaged tissue that has developed as a result of prior infections or injury) in pre-existing cavities, which results in the formation of so-called "fungus balls," are the most common manifestations of the disease (Koltin et al., 1997).

Antifungal Studies of 1,2,4-Triazoles

Mahmoudi et al. evaluated various 1,2,4-triazole alcohols bearing N-(halobenzyl) piperazine carbodithioate scaffold as effective antifungal agents in vitro bioassays against *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida tropicalis*; the best activity was shown by N-(4-chlorobenzyl) derivative 1b, which Additionally, the 3-

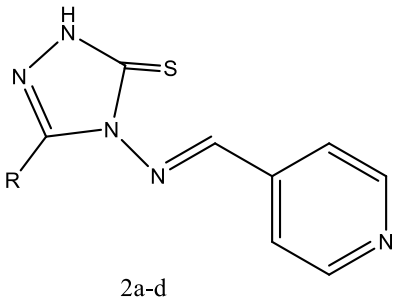
chlorobenzyl compound 1a showed high effectiveness against both Candida albicans and non-albicans species. In general, 2,4-difluorophenyl derivatives were more active than their dichlorophenyl counterparts, according to MICs. Furthermore, 2,4-difluorophenyl-carbinol was superior to the 2,4-dichlorophenyl-carbinol scaffold, according to SAR analyses. Additionally, testing against isolates resistant to fluconazole revealed that compound 21b was effective against isolates of *Candida albicans*, *Candida krusei*, and *Candida parapsilosis*, with MIC values ranging from 2 to 16 mg/mL (Mahmoudi et al.,2018)



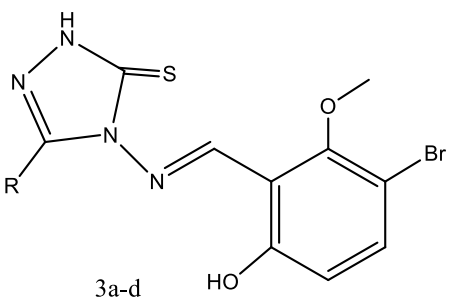
1

1a: 1X=F, R=3-Cl,
1b: X=F, R=4-Cl,
1c: X=F, R=2,4-Cl_2,
1d: X=F, R=3,4-Cl,
1e: X=F, R=4-Br,
1f: X=Cl, R=2,4-Cl_2

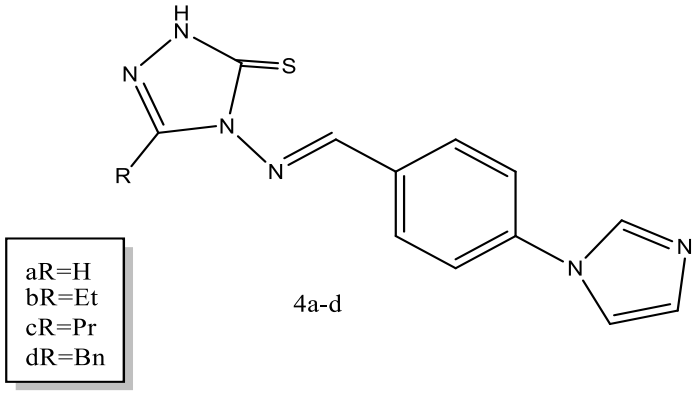
In a study by Jin et al. in 2018 (Jin et al., 2018), 1,2,4-Triazole Schiff Base derivatives were synthesized. Then, their antifungal activite test against "*Pythium solani*, *Cercospora arachidicola*, *Gibberlla saubinetii*, *Alternaria iycopersici*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla nicotiancola*, *Phytophthora capsici*, *Physalospora piricola*, *hori* and *Fusarium oxysporium* f. sp. cucumber" were performed. Triadimephone was chosen as the control. The activity test was performed using the procedure in the literature (Atlas et al., 1995). In this study, it was determined that only the 4a molecule showed antifugal activity.



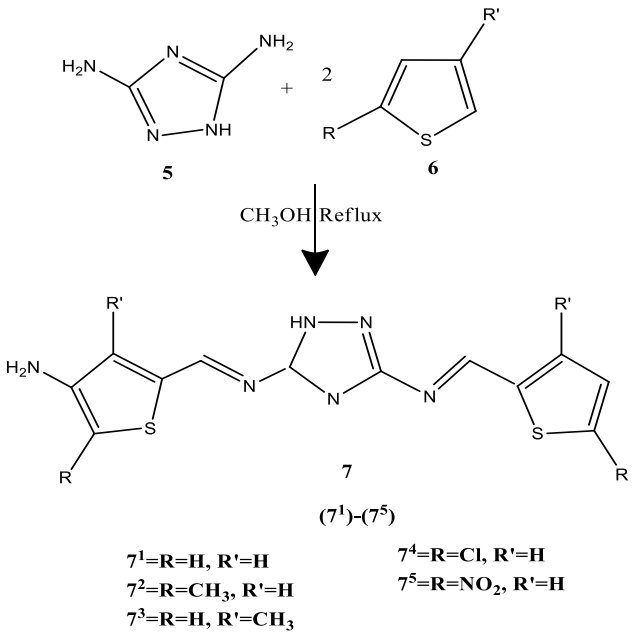
2a-d



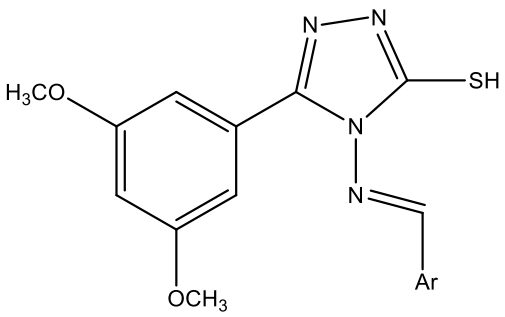
3a-d



In a study by Sumrra et al. in 2013 (Sumrra & Chohan, 2013) novel triazol-derivatives Schiff base were synthesized. The antifungal studies of compound were investigated against fungus such as *T. longifusus*, *C. albican*, *A. flavus*, *M. canis*, *F. solani* and *C. glabrata* fungal. The Miconazole and Amphotericin B were taken as standard. Antifungal test was performed according to the protocol found in the literature (McLaughlin et al., 1991). It has been determined that the ligands show different percentages of antifungal activity against different antifungal agents.



In a study by Morrthy et al. in 2017 (Moorthy et al., 2017), the antifungal activity was performed by MIC method. Amphotericin-B was determined as the standard antifungal. The antifungal activities of all the compounds were studied against *C. albicans* up to 512 µg/ml concentration. The results showed that 8a, 8b and 8f exhibit significant antifungal activity.

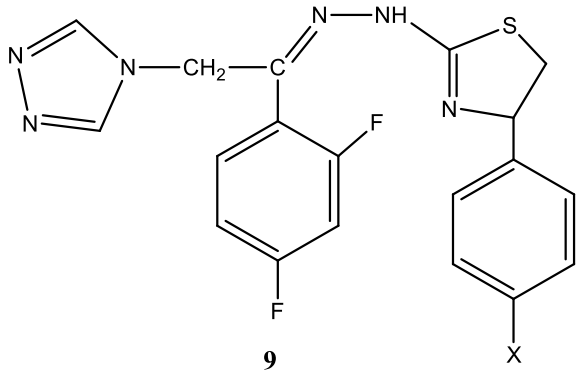


8

Ar

8a=4-Cl-C_6H_4
8b=2,4-Cl_2-C_6H_3
8c=4-OCH_3-C_6H_4
8d=C_4H_3O
8e=2,NH_2-3,4-di-CH_3-C_6H_2
8f=C_6H_4OH

In a study by Russell et al. in 2014 (Russell & Soiket, 2014) new six 1,2,4- triazol Schiff base was synthesized. The four fungal strains were selected for antifungal activity testing. These are *C. albicans*, *Colletotrichum spp*., *A. nigar* and *Fusarium spp*. The Sabouraud Dextrose Agar mediaby diffusion method (Batovska et al., 2007; Turan-Zitouni et al., 1999) was preferred for antifungal screening of compounds. Flucanazole was used as fungal control agent. The 2b and 4b were activited agains four micro-organisms. It was observed that 9b and 9d showed antifungal activity against four microorganisms and other compounds were inactive.

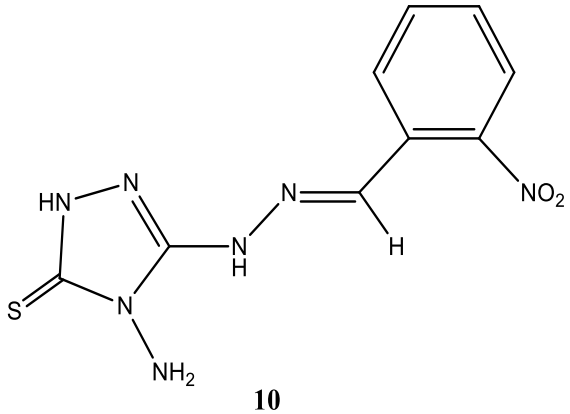


9

9a; X=Br,
9b; X=Cl,
9c; X=NO_2,
9d; X=H,
9e; X=OCH_3

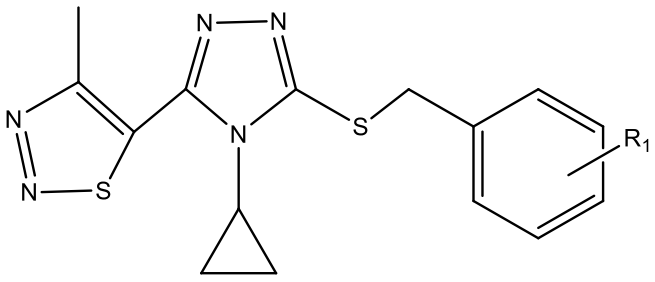
In a study by Joshi et al. in 2021 (Joshi, et al., 2018) (E)-4-amino-5-[N'-(2-nitro-benzylidene)-hydrazino]-2,4-dihydro-[1,2,4]triazole-3-thione molecule was synthesized. Antifungal activity was investigated using four fungal strains such as *Candida albicans* (ATCC 90028), *Candida tropicalis* (ATCC 750), *Candida krusei* (clinical strain) and *Candida glabrata* (clinical strain). The Agar disc diffusion test was done for activity determination (Kumar et al., 2011). The MIC results of the compound as compared with the reference fluconazole. The result of this study

showed us that, the new compound has important antifungal activity against *C. albicans* and moderate antifungal activity against *C. tropicalis*.



10

In a study by Tan et al. in 2014, triazole derivative compounds were synthesized and their antifungal activities were investigated. The *in vivo* fungicidal effects of the title compounds against *Fusarium oxysporum, Pseudoperonospora cubensis, Sphaerotheca fuligenea, Corynespora cassicola, Xanthomonas axonopod* were determined. As a control thiophanate methyl, jinggangmeisu, and zhongshengmycin were utilized. The fungicidal activity of compounds 7c, 7d, 7f, 7j, and 7k were greater than those of thiophanate methyl, jinggangmeisu, and zhongshengmycin against *P. cubensis*. Against R. solanii, none of these drugs showed overt fungicidal activity. The 7f, 7i, 7j, 7k showed fungicidal activity against F. oxysporum (Tan et al., 2014).



11a-k

R=2-ClPh, 3-ClPh, 4-ClPh, 2,4-Cl_2Ph, 3,4-Cl_2Ph, 4-BuPh, 4-OMePh, Ph, 3-CNPh, Propinyl, Heptyl

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To Cite This Chapter

Kotan, G. & Medetalibeyoğlu, H. (2022). Antifungal Properties of 1,2,4-Triazoles. In H. Yüksek & M. Beytur (Eds.), *Chemistry of 1,2,4-Triazoles in Current Science*, (82-98). ISRES Publishing.