Hindawi

Review Article

A Recent Overview of 1,2,3-Triazole-Containing Hybrids as Novel Antifungal Agents: Focusing on Synthesis, Mechanism of Action, and Structure-Activity Relationship (SAR)

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A pharmacophore system has been found as 1,2,3-triazole, a five-membered heterocycle ring with nitrogen heteroatoms. These heterocyclic compounds can be produced using azide-alkyne cycloaddition processes catalyzed by ruthenium or copper. The bioactive compounds demonstrated antitubercular, antibacterial, anti-inflammatory, anticancer, antioxidant, antiviral, and antidiabetic properties. This heterocycle molecule, in particular, with one or more 1,2,3-triazole cores has been found to have the most powerful antifungal effects. The goal of this review is to highlight recent developments in the synthesis and structure-activity relationship (SAR) investigation of this prospective fungicidal chemical. Also there have been explained drugs and mechanism of action of a triazole compound with antifungal activity. This review will be useful in a variety of fields, including medicinal chemistry, organic chemistry, mycology, and pharmacology.

1. Introduction

One of the most important fields of medicinal chemistry is the study of heterocyclic bioactive molecule containing nitrogen atoms [1, 2]. Triazole have been found as a potential heterocyclic component in a wide range of drug scaffolds. It has a five-membered nitrogen heterocycle core with three nitrogen atoms and two carbon atoms. The core has a substantial impact on biological activity [3]. The influences of the nitrogen heteroatom on the reactivity of the lead compound target medication pharmacokinetics and metabolism are affected by interactions between the lead chemical and several target inhibitors [4].

A fungus is one of the most diverse organisms in the world. Since eukaryotes share many potential drug-receptor targets with humans [5], the synthesis of the new fungicidal compounds with high selectivity is essential for fungal receptors and low affinity for human receptors [6, 7]. There are approximately recognized two million fungi types and 600 fungi species as human fungal pathogens with only 3-4% of these species leading to fungal infection [8]. Unfortunately, this kind of invasive fungal infections resulted in a high mortality rate [9]. Fungal infections have recently risen and are responsible for 1-2 million fatalities annually [10]. Most of the deaths (~90%) are assigned to the *Aspergillus* and *Candida* species [11]. Invasive candidiasis species including *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida albicans* enhanced rate of mortality (75%). Furthermore, the Aspergillosis family containing *fumigatus*, *niger*, *flavus*, *terreus*, and *parasiticus* caused mortality rate of 50–90% [12]. Azole derivatives achieved antifungal activity by linking ergosterol in the

active site of the cell membrane [13]. Researchers confirm that azoles with inhibiting the lanosterol 14α-demethylase enzyme inhibit the synthesis of ergosterol [14]. Certain 1,2,3-triazole derivatives have been generated and evaluated for antifungal activity in the last few years, with some potential activity against different fungi. This review is focused on the latest papers (2015–2021) on the synthesis of new series of 1,2,3-triazole antifungal agents and the evaluation of structure-activity relationship (SAR) to provide insight into the logical synthesis of more effective 1,2,3-triazole antifungal candidates. The process of selecting publications for this review is reported in the diagram below (Figure 1).

2. Synthesis of 1,2,3-Triazoles

2.1. Click Chemistry (Azide-Alkyne Cycloaddition). Huisgen introduced the first azide-alkyne cycloaddition in 1960 [15], which reported the 1,3-dipolar cycloaddition between alkyne (terminal) and azide to produce 1,2,3-triazoles. Unfortunately, high temperatures were required for this type of reaction, which resulted in low yield mixture of the two regioisomers consisting of 1,4- and 1,5-substituted triazoles [16] (Scheme 1).

Sharpless proposed the term "click chemistry" in 2001, which is explained as "chemistry tailored to produce a substance by linking small molecules together very quickly and simply" [17, 18]. Separately, Tornøe et al. [19] and Rostovtsev et al. [20] used Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) as one of the most reliable click reactions to generate 1,2,3-triazole derivatives. Sharpless demonstrated reactions with high yields, moderate reaction conditions, the generation of stereospecific products without the need of chromatography, and ease of use.

The copper-catalyzed reaction, in particular, leads to the synthesis of 1,4-disubstituted regioisomers; this suitable reaction can be accomplished in aqueous solutions, even at room temperature [21, 22]. However, researchers discovered that ruthenium-catalyzed reaction yields 1,5-disubstituted triazoles with opposite regioselectivity [23] (Scheme 2).

2.1.1. Mechanism of the Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition. Huisgen cycloaddition is a type of Diels-Alder reaction which is a 1,3-dipole reacting with a dipolarophile to produce 1,2,3-triazole in a $(3 + 2)$ cycloaddition (Scheme 3) [24].

This exothermic reaction occurs at high temperatures, as illustrated in Scheme 4, despite the fact that the rate of reaction is insignificant. Since the layers' two potential HOMO-LUMO interactions are nearly dependent in terms of energy, this results in almost 1 : 1 mixes in both the 1,5-substituted and 1,4-substituted regioisomers [20].

2.1.2. Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC). The reliable click reaction, copper-catalyzed azide-alkyne cycloaddition (CuAAC), has been expanded in medicinal and organic chemistry [25]. In this method for preparing Cu(I) in solution, *in situ* reduction of $CuSO_4 \cdot 5H_2O$ by sodium ascorbate was performed in

1,2,3-triazole of water/alcohol (MeOH, EtOH, or BuOH) mixtures. The product was separated by easy purification without the use of chromatography (Scheme 5) [26].

The mechanism of CuAAC is described in Scheme 6. Firstly, sodium ascorbate as a reducing agent can produce active Cu(I) from Cu(II) salts. Homocoupling products are not produced by adding a small amount of sodium ascorbate. In addition, DFT computations confirmed that the coordination of an alkyne to Cu(I) is somewhat endothermic in MeCN but exothermic in water. The rate of reaction then increased in water. DFT analysis showed that acetylene coordination to Cu does not catalyze a 1,3-dipolar cycloaddition. As shown in Scheme 6, a π-bound copper coordinates with the azide. The intermediate copper metallacycle is then prepared. The second copper atom acts as a stabilizing donor ligand. Finally, the catalytic cycle is closed with the generation of a triazolyl-copper derivative. As a result, 1,2,3-triazole derivatives are synthesized by Proteolysis [27].

2.1.3. Mechanism of the Ruthenium-Catalyzed Azide-Alkyne Cycloaddition (RuAAC). The researchers confirmed that pentamethylcyclopentadienyl ruthenium chloride [Cp∗RuCl] complexes may be used as effective catalysts in the reaction of terminal alkynes with azides, resulting in 1,5-disubstituted 1,2,3-triazoles (Scheme 7) [28].

The mechanism of the ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) is shown in Scheme 8; therefore, RuAAC appears from an oxidative coupling of the alkyne and the azide, yielding a six-membered ruthenacycle. The initial carbon-nitrogen bond is formed between the terminal nitrogen of alkyne and azide in the next step. The product 1,2,3-triazole is then formed by reductive elimination [28].

2.2. Synthesis and Structure of 1,2,3-Triazole-Based Marketed Drugs. Only a few 1,2,3-triazole-containing hybrids have been developed as therapeutic agents in the medicine industry in recent years, with a wide range of pharmacological applications. The antibiotics Tazobactam/Ceftolozane [29], Radezolid [30], Cefatrizine [31], Tertbutyldimethylsilylspiroaminooxathioledioxide (TSAO) [32], and the Carboxyamidotriazole (CAI) [33] are examples of pharmaceutical drugs containing 1,2,3-triazoles scaffold (Scheme 9). We discuss the synthesis process of these pharmaceutical medicines in this study.

2.2.1. General Synthetic Pathway for the Preparation of Pharmaceutical Drugs Containing 1,2,3-Triazole

(1) Synthesis of Tazobactam. Tazobactam is a pharmaceutical that inhibits the bacterial activity of β-lactamases, particularly those attached to the SHV-1 and TEM groups. In other words, it is a substance that can be added to some antibiotics to make bacteria more vulnerable to antimicrobial resistance. Tazobactam is coupled with the broad-spectrum β-lactam piperacillin antibiotic to form the drug piperacillin/tazobactam, which is used to treat *Pseudomonas aeruginosa* infections [34]. This medication was developed in 1982 and
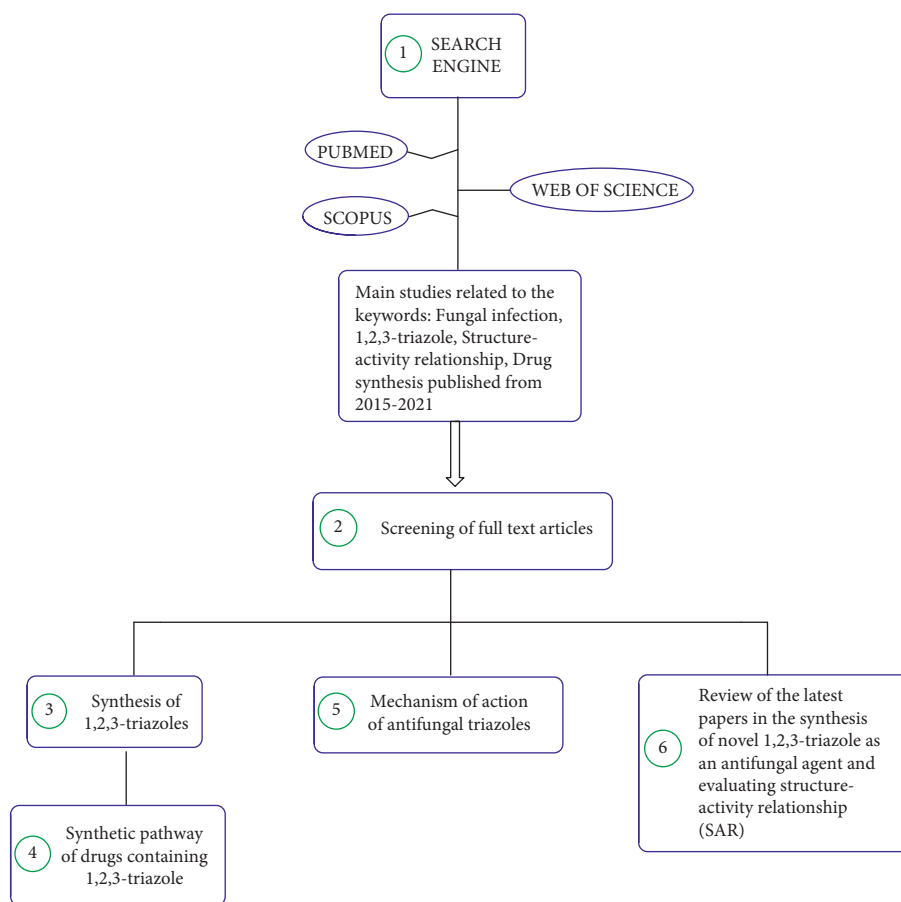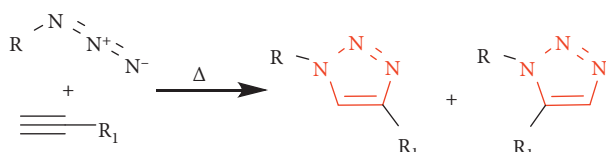
FIGURE 1: Diagram of identification of the provided content in this review.

SCHEME 1: Azide-alkyne Huisgen cycloaddition.

SCHEME 2: Copper-catalyzed and ruthenium-catalyzed reaction on azide-alkyne cycloaddition.

SCHEME 3: Huisgen cycloaddition.

SCHEME 4: Thermal reactions and mixtures in both 1,4- and 1,5-substituted regioisomers.

SCHEME 5: Copper-catalyzed azide-alkyne cycloaddition.

used in medicine for the first time in 1992. It is a combination of a penicillin and a sulfone [35].

Micetich et al. [36] described a novel route to the synthesis of Tazobactam, which resulted in the cycloaddition of the synthetic intermediate **1** with acetylene gas **2** in water and the dissociation of **1**. Finally, the reaction in MIBK without the excess sodium ascorbate supported Tazobactam yields ranging from 4 to 91% (Scheme 10).
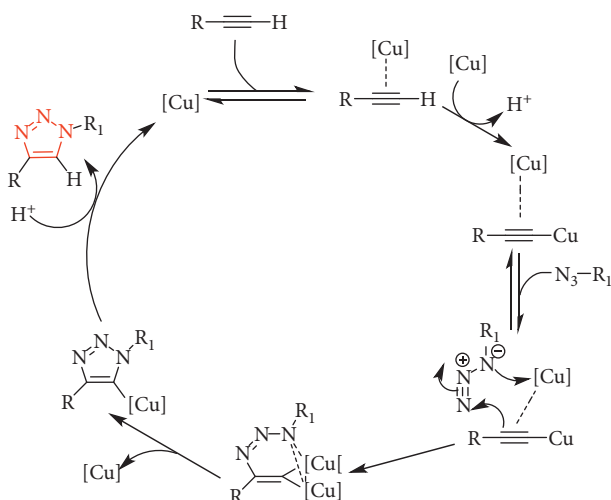
Scheme 6: Mechanism of the copper-catalyzed azide-alkyne cycloaddition (CuAAC).
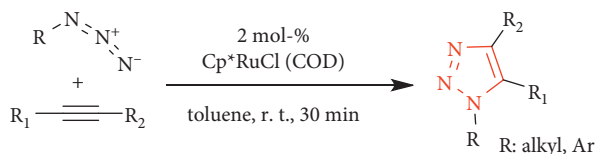
Scheme 7: Ruthenium-catalyzed azide-alkyne cycloaddition.
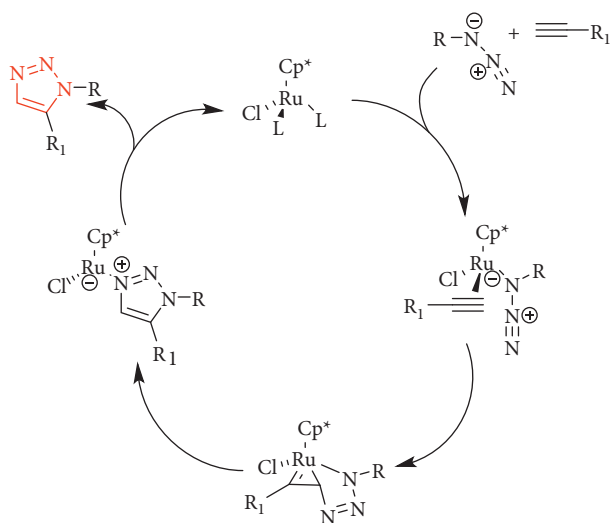
Scheme 8: Mechanism of the ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC).

(2) Synthesis of Radezolid. Oxazolidinones are an antimicrobial agent with a wide range of activity toward important Gram-positive and nosocomial pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci, and pneumococci [37]. *N*-{[(5S)-3-[3-Fluoro-4-(4-{[(1*H*-1,2,3-triazole-5-ylmethyl)amino]methyl}phenyl)phenyl]-2-oxo-1,3-oxazo-lidin-5-yl]methyl}acetamide (Radezolid) is a new antibacterial agent of biaryl oxazolidinone that is in clinical expansion; the first clinical experiments were performed on simple skin and skin structure infections (uSSSI)

and the second on community-acquired pneumonia (CAP) [38–40].

The most significant stage in Radezolid synthesis is the cross-coupling reaction of the iodooxalidinone derivative **13** and boroorganic acid derivative **18** catalyzed by tetrakis-(triphenylphosphine)palladium(0) relying on Suzuki reaction mechanism. Compound **18** was acquired by combining 4-methoxybenzyl chloride with the triazole ring. Intermediate **13** was provided from R-glycidyl butyrate and an introduced starting material to be used in the reaction of a carbamate, *N*-carboxyloxy-3-fluoroaniline, an oxazolidinone ring, allowing only one, enantiomerically pure, desired oxazolidinone derivative to be produced in four simple steps. Gravestock and coworkers [41] proposed critical modifications to the synthesis of Radezolid that focused on the phase leading to compound **19**. Other changes included raising the number of solvents and increasing the amount of a novel one, extending the reaction time and temperature, and using a contemporary approach including crystallization of the terminal product **21** (Schemes 11 and 12) [42].

(3) Synthesis of Carboxyamidotriazole (CAI). Carboxyamidotriazole (CAI) was initially developed as a noncytotoxic anticancer drug. Numerous studies [43–46] show that carboxyamidotriazole (CAI) has moderate anticancer efficacy *in vitro* and *in vivo*. Despite this, many preclinical investigations have revealed its antiproliferative, antiangiogenic, and antimigratory properties [44, 45, 47, 48].

In the proposed synthesis scheme, compound **22** is reacted with **24** to produce compound **25** after the alcohol group is shielded as the tert-butyldimethylsilyl (TBDMS) ether step (**23**). To form 3,5-dichloro-4-(4-chlorobenzoyl) benzyl azide, benzophene is reacted with thionyl chloride **26** and then with sodium azide (**27**). The reaction of cyanoacetamide with this azide constructs L651582 (**29**). Compounds **29** and **30** were produced by the interaction of component **29** with orotic acid (Scheme 13) [49].

(4) Synthesis of Cefatrizine. Cefatrizine is a wide-spectrum cephalosporin antibiotic [50] and one of the first 3-heterocyclic thiomethylcephalosporins produced in the laboratories [51]. Cephalosporin compounds are replaced at the 3-situation by a heterocyclic thiomethyl group and at the 7-position by free or substituted *α*-aminophenylacetamido. They are synthesized by combining a 3-acetoxymethyl ring to a mercaptoheterocycle. Antibacterial factors are found in products (Scheme 14) [51].

(5) Synthesis of Tertbutyldimethylsilylylspiroaminooxathioledioxide (TSAO). TSAO reported a completely novel class of HIV-1-particular factors in 1992 [52–56]. Human replication of immunodeficiency virus type 1 (HIV-1), simian immunodeficiency virus (SIV), or RNA viruses, and other DNA are inhibited by TSAO nucleoside analogs. They are designed to interact with RT-virus encoding at a nonsubstrate binding position [57, 58].

The 5-*N*-alkyl carbamoyl substituted TSAO triazoles were synthesized in two phases, with the aim of obtaining the 5-substituted 1,2,3-triazole derivative **36** [59] by reacting the
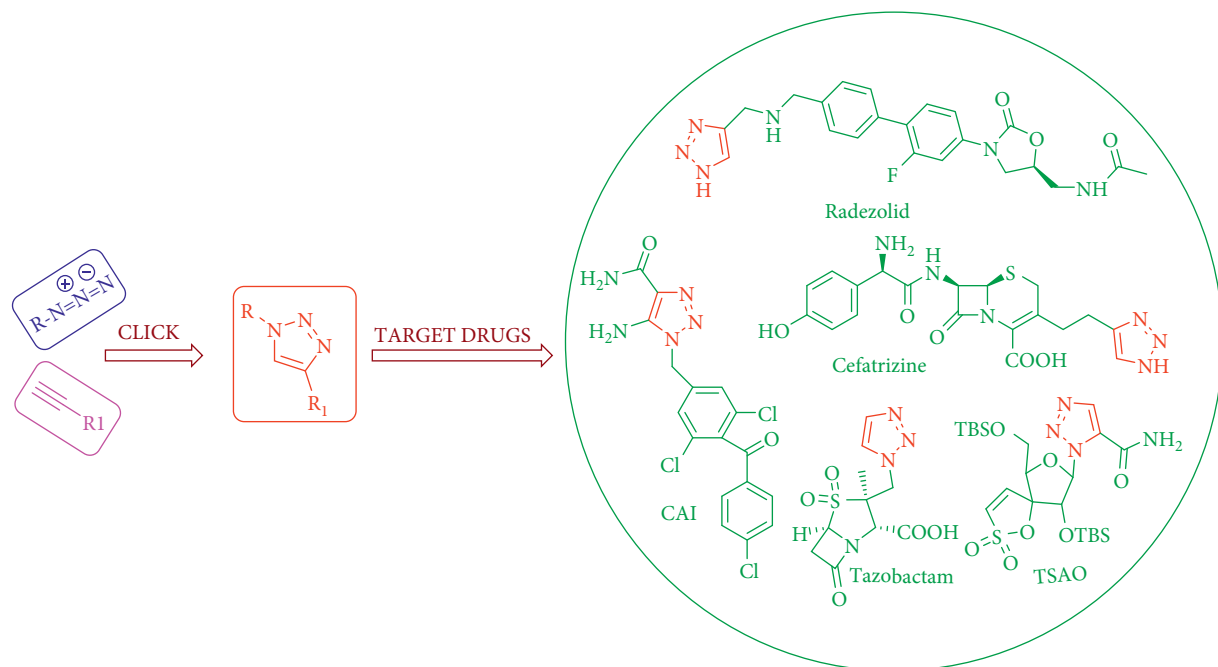
Scheme 9: Chemical structure of 1,2,3-triazole-based marketed drugs.
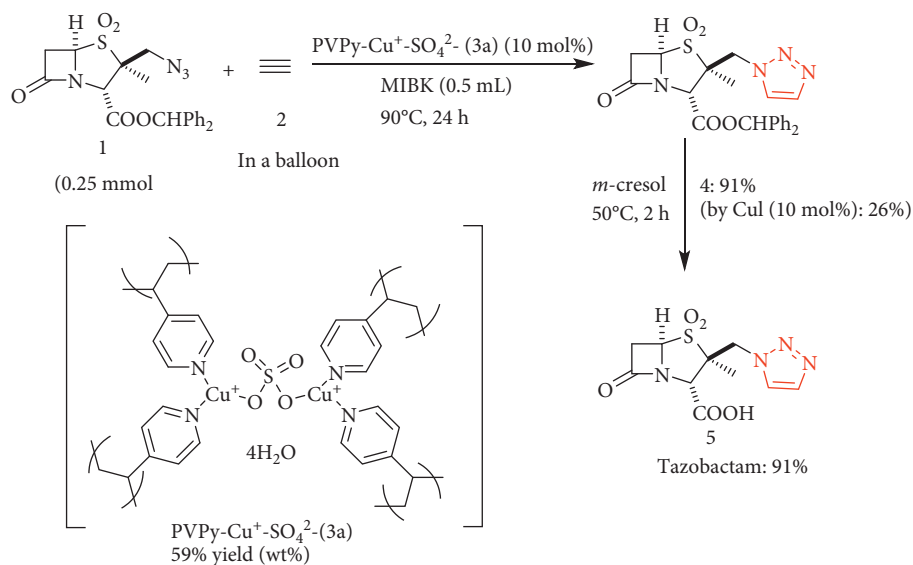
Scheme 10: Synthesis of tazobactam.

azide intermediate **34** [59] with 2-oxo-alkylidentriphenyl-phosphorane **35** [60] in refluxing xylene. Compound **37** was synthesized by aminolyzing these ester derivatives with the proper amine (Scheme 15) [61, 62].

2.3. Mechanism of Action of Antifungal Triazoles. Woolley originally reported the antifungal activity of an azole derivative in 1944 [63], but it was not until the early 1970s that this drug was subjected to a comprehensive assessment. Fluconazole (FLC), Itraconazole (ITC), Voriconazole (VCZ), Posaconazole, and Ravuconazole are examples of

synthetic compounds that include one or more azole rings with three nitrogen atoms in a five-membered ring (as antifungal triazoles) (Figure 2). In general, azoles have become a more important antifungal drug, since they are less toxic than Amphotericin B (AmB), act against different types of fungi, and have clinical effects in many cases. By inhibiting the fungus cytochrome P-450 3A-dependent enzyme lanosterol 14-alpha-demethylase, the antifungal azoles disturb the conversion of lanosterol to ergosterol [64]. The conversion of lanosterol to ergosterol, which is used in cell wall synthesis, is one of the important functions of this enzyme. The essential nitrogen of the azole ring binds firmly to the
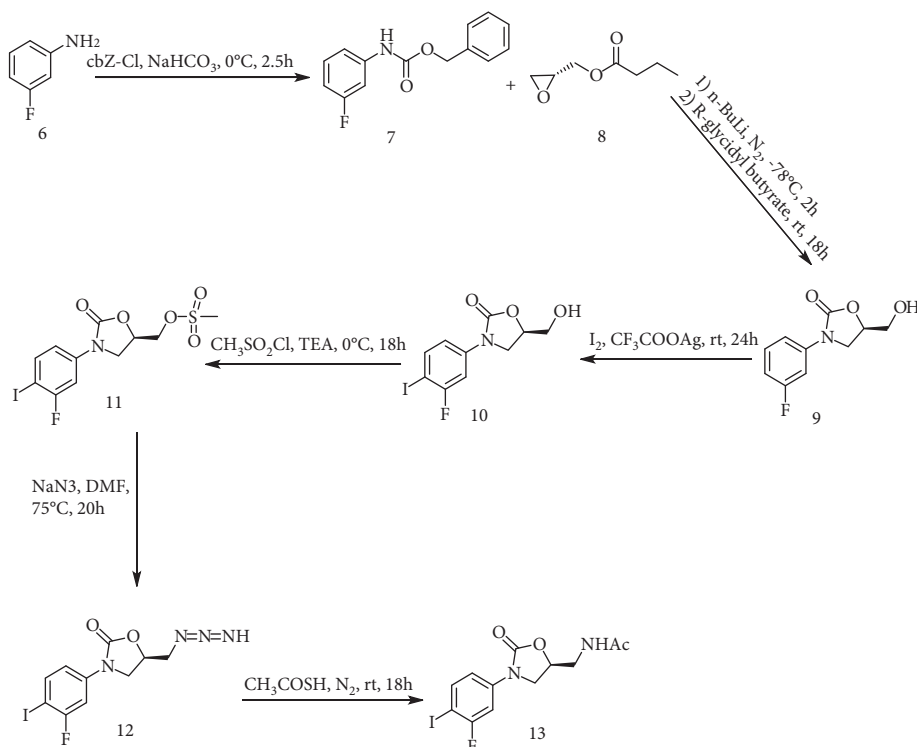
Scheme 11: Pathways of intermediate 13 synthesis.

fungus cytochrome P450 hemiron in this mechanism, preventing the bond between the substrate and oxygen. Accumulation of sterols, alteration of permeability, and dysfunction of membrane proteins are the result of 14α-demethylase inhibition. The inhibitory pathway of ergosterol biosynthesis is shown in Scheme 16 [65].

Azole antifungal drugs have shown a modern period in antifungal chemotherapy. Despite sharing a similar mechanism, they vary in pharmacokinetics, toxicity, and fungal spectrum (Table 1) [66]. Other key factors in the early steps of development may increase the options available in this significant group of compounds. The addition of broad-spectrum triazoles provides physicians with more effective and less toxic alternatives to Amphotericin B [67].

2.4. Review of the Latest Papers in the Synthesis of Novel 1,2,3-Triazole as an Antifungal Agent and Evaluating Structure-Activity Relationship (SAR)

2.4.1. 1,2,3-Triazole-Coumarin, Chromene, and Pyrane Hybrids. A series of novel 1,2,3-triazole-tethered coumarin conjugates linked by *N*-phenyl acetamide were effectively generated in high yields. Investigation of antifungal effect was performed against *Fusarium oxysporum, Candida albicans, Aspergillus niger, Cryptococcus neoformans,* and *Aspergillus flavus.* As shown in Figure 3, Compounds **39a**, **39b**, **39c**, **40a**, and **40b** showed a high antifungal activity compared with Miconazole [68].

Dharavath et al. [69] reported a method for synthesizing several coumarin-based 1,2,3-triazole compounds using a copper(I)-catalyzed click reaction between different substituted aryl azides and the end alkynes. All of the synthesized compounds were investigated for *in vitro* fungistatic effect against three fungus strains, *Aspergillus flavus, Fusarium oxysporum,* and *Aspergillus niger*, and the results were compared with standard drug (Clotrimazole). Six compounds (**41a–f**) showed better efficacy in contrast with the three pathogenic fungi (Figure 4).

A series of new 1,2,3-triazole derivatives of quinolinone, benzyl, and coumarin were synthesized and tested for antifungal activity (Figure 5). All of the azole derivatives were tested for antifungal activity against 8 different fungal strains, four of which were *Candida* species (yeast samples) and the other four were *Aspergillus* species (filamentous fungi). Almost all of the compounds demonstrated excellent antifungal efficacy. According to the findings of SAR investigations, electron withdrawing or donating groups do not seem to be a main factor in decreasing or increasing antifungal activity [70].

A novel class of 1,2,3-triazole based on coumarin was synthesized and assessed for antifungal behavior against three fungi (*Penicillium chrysogenum, Curvularia lunata,* and *Aspergillus niger*). All of the compounds displayed modest to good activity toward *P. chrysogenum, C. lunata,* and *A. niger* strains (Figure 6) [71].

Shaikh et al. [72] reported a class of new ethyl-7-((1-(benzyl)-1*H*-1,2,3-triazole-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates as a possible fungicide. The fungicidal property assessed the impact of five human pathogenic fungal strains, like *Candida albicans, Aspergillus flavus, Aspergillus niger, Fusarium oxysporum,* and *Cryptococcus*
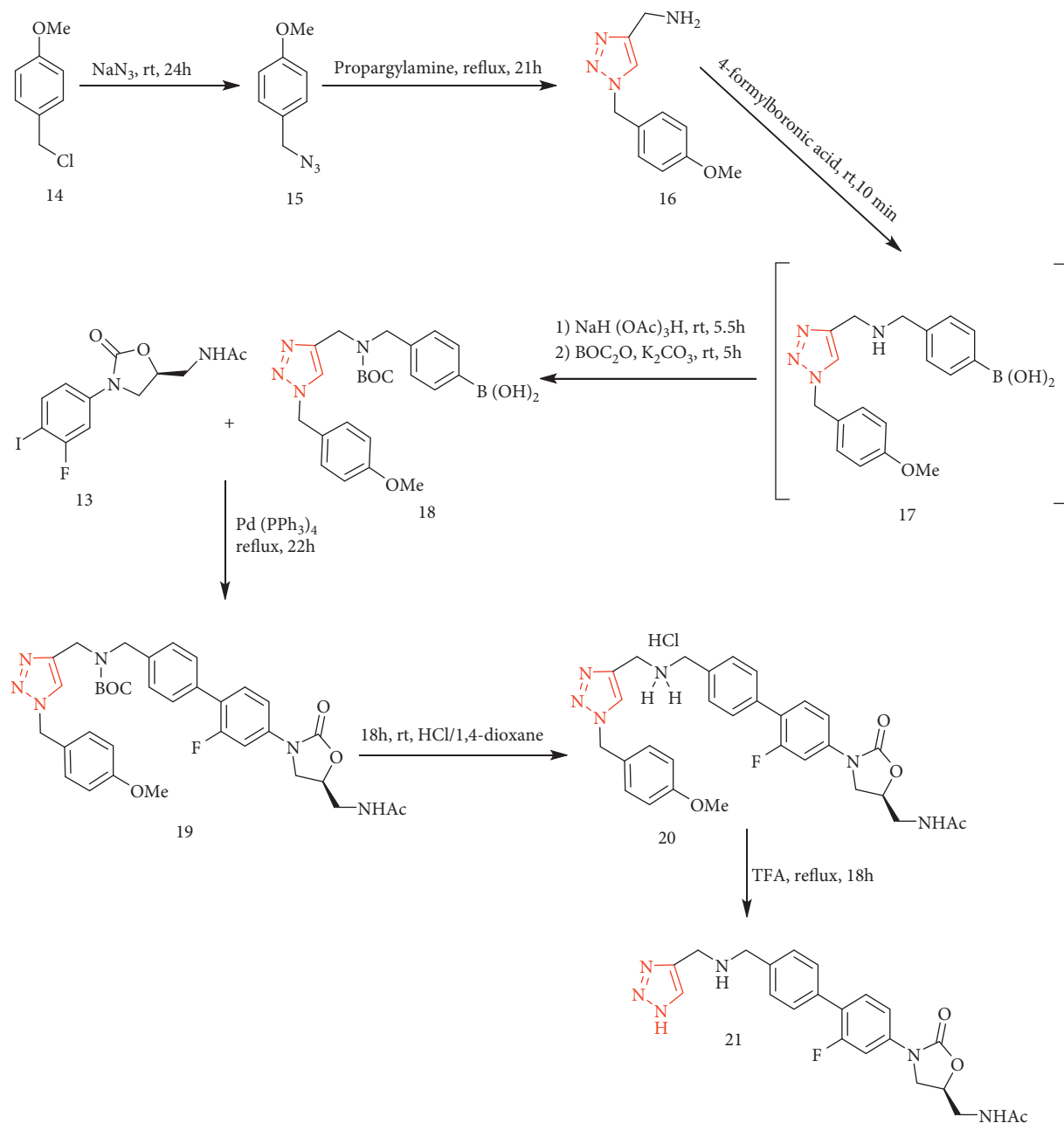
Scheme 12: Pathway of Radezolid synthesis.

neoformans. As shown in Figure 7, compounds **46a**, **46b**, **46c**, and **46e** had comparable activity against *Candida albicans* to Miconazole, while compound **46d** was twofold more active than the standard drug, which is similar to Fluconazole against *Candida albicans*. When compared to Miconazole, compounds **46b** (R_2 = Cl) and **46d** (R_3 = F) displayed equivalent effectiveness against the fungal strain *A. niger*. The addition of a triazole ring to coumarin increased the antifungal activity of the synthesized compounds. The addition of a triazole ring to coumarin improved the antifungal activity of the synthesized compounds.

Gondru et al. [73] developed a new series of triazole-thiazole hybrids using the multicomponent reaction approach. *In vitro* antimicrobial activity investigations were evaluated. The results showed that, among the synthesized compounds, **48a–d** and **48e** were active and exhibited activity that is equal to or more than that of the conventional medicine against several *Candida* strains. Although the compounds did not have a broad antifungal range, they were less active than the standard drug against some pathogenic strains (Figure 8).

The 1*H*-1,2,3-triazole-tethered 4*H*-chromeneD-glucose conjugates were synthesized using click chemistry of tetra-O-acetyl-b-D-glucopyranosyl azide and propargyl ethers. As it is seen in Figure 9, the antifungal activities of 1*H*-1,2,3-triazoles against *Aspergillus flavus* (ATCC 204304), *Aspergillus niger* (ATCC439), *Saccharomyces cerevisiae* (SH 20),

Scheme 13: Path of CAI synthesis.

Scheme 14: Path of Cefatrizine synthesis.

and *Candida albicans* (ATCC7754) were evaluated. Fluconazole and Miconazole were used as standard drugs. Surprisingly, nearly all tested diazoles were more active against fungi *C. albicans*, *S. cerevisiae*, and *A. flavus*. Nonetheless, the triazoles were more resistant to *A. niger* than standard drugs. In fungi *A. niger*, approximately all of the compounds were less active than common medicines, with the exception of triazole **49c**, with an MIC value of 1.56 μM. Compound **49a** was more active against *C. albicans* than Miconazole but less active than Fluconazole, and compounds **49f** and **49g** against *S. cerevisiae* were more active than Miconazole. In total, triazoles with big groups (methyl, methoxy, and

isopropyl) in their phenyl ring were less active. Nevertheless, there are several unusual compounds (**49b**, **49c**, and **49e**) [74].

Khare et al. [75] developed a green and impressive protocol for the synthesis of new 1,2,3-triazole-chromene conjugates using ultrasound-assisted and NaHCO$_3$-catalyzed reactions. Triazole-chromene compounds were evaluated for fungicidal activity against five different fungal strains: *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, *Cryptococcus neoformans*, and *Candida albicans*, and several of them (**50a–f**) showed stronger activity (MIC = 6.25–25 μg/mL) compared to the standard drug

Scheme 15: The path of TSAO synthesis.
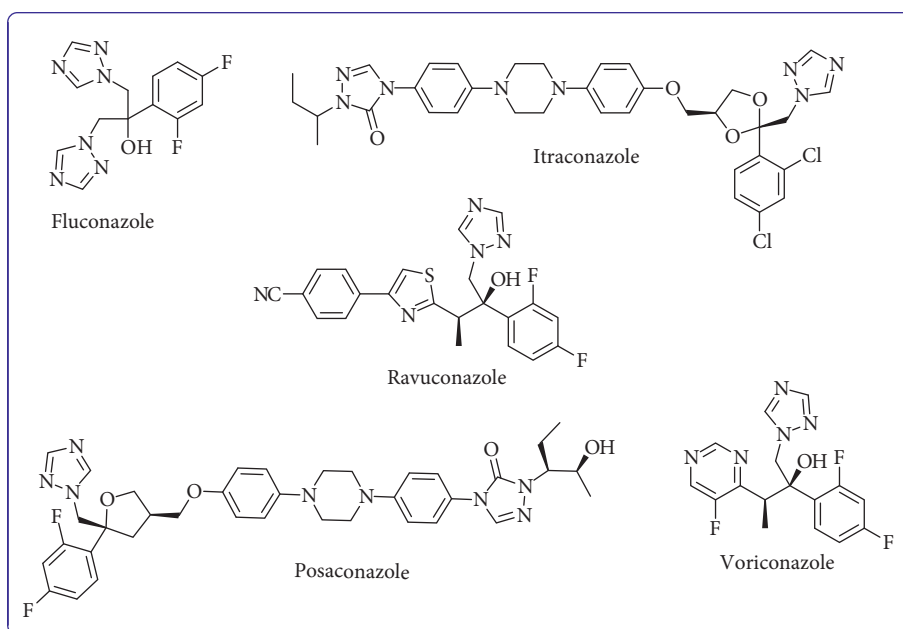
Figure 2: A few examples of antifungal triazoles.

Miconazole. Compound **50d** (with $R = 2$-OMe) was more active than Miconazole against *C. albicans* and displayed less antifungal activity against remaining fungal strains. Only compound **50f** has displayed greater activity against *A. flavus* as compared to the other strains (Figure 10).

Dofe et al. [76] prepared a sequence of 3-((1-benzyl-1*H*-1,2,3-triazole-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-ones (**51**) via click chemistry. As shown in Figure 11, all of the compounds were tested for *in vitro* fungicidal activity toward *Candida albicans*, *Candida tropicalis*, and *Candida glabrata*. Significantly, 1,2,3-triazole-based chromones are more sensitive to *C. glabrata* and *C. tropicalis* fungal strains. When compared to the reference drug

Miconazole, compounds **51a** and **51b** displayed equivalent activity against *C. albicans*. Compounds **51a** and **51b** with an MIC of 12.5 μg/mL are very strong antifungal agents against *C. glabrata* and *C. tropicalis*, respectively.

Kant et al. [77] described the synthesis of 1,2,3-triazole-connected chalcone and flavone hybrids. The recent synthesized compounds were screened for their antifungal behavior toward *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, *Dermatophyte*, and *Candida albicans* and also molds *Aspergillus fumigatus* and *Aspergillus niger*. Figure 12 shows that compounds **52b**, **53a**, **53b**, **54a**, **55a**, **55b**, **55c**, **56a**, and **56b** displayed good antifungal behaviors as compared to the corresponding reference
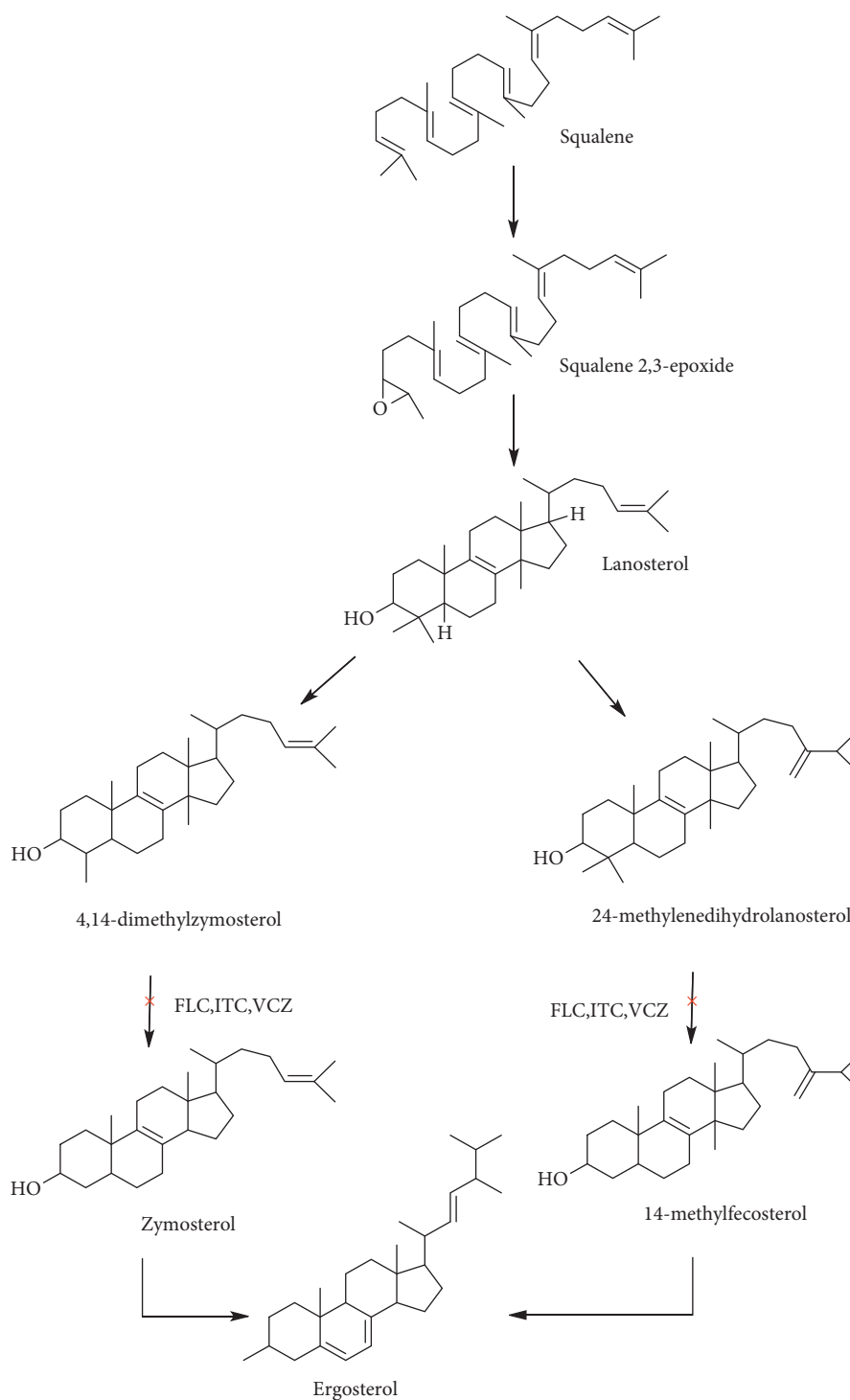
SCHEME 16: Ergosterol biosynthesis inhibitor pathway.

medications. Compound **52a**, including 2-chloro-4-fluoro-substituted benzene ring, displayed modest to good activity with MIC ranges of 25–100 μg/mL and 100 μg/mL compared to Fluconazole in the range of 0.5–4.0 μg/mL against all examined strains. Flavone compounds **55a** and **55b** containing 2-chloro-4-fluoro- and 3-chloro-4-fluoro-substituted benzene ring in order displayed good activity against four strains. Amalgamation of chloro and fluoro

atoms in benzene ring has greater antifungal activity than monohalogen compounds in one-triazole-connected flavones. But the existence of 2-chloro or its composition with fluoro group in phenyl ring displayed stronger activity than other groups and their combinations in flavones included two triazole units.

A new model has been proposed and synthesized, consisting of the development of double pharmacophores of

TABLE 1: Mechanism of action of 1,2,3-triazole-based marketed drugs.

Name	Type of triazole	Mechanism of action	Ref.
Cefatrizine	4-monosubstituted	Second-generation cephalosporin. Cefatrizine is utilized to treat many types of infections, including respiratory tract, skin, ear, and urinary tract infections.	[51] [66]
Tazobactam	1-monosubstituted	Powerful irreversible β-lactamase (SHV-1 and TEM) inhibitory activity and very low antibacterial activity. Tazobactam is combined in the drug piperacillin/tazobactam, which is used in infections caused by *Pseudomonas aeruginosa*.	[34, 66]
Carboxyamidotriazole (CAI)	1,4,5-trisubstituted triazole	CAI has antiangiogenic, antimetastatic, and antitumor properties owing to its ability to indirectly participate in the Store-Operated Calcium Entry.	[66]
Radezolid	4-monosubstituted	Antibiotic, active against bacteria (Gram-negative and Gram-positive) that connect to the 50S ribosomal subunit. Radezolid has been used in the treatment of abscess and infectious skin diseases.	[40, 66]
TSAO	4- or 5-substituted 1,2,3-triazoles	TSAO nucleoside analogs inhibit human replication of immunodeficiency virus type 1 (HIV-1), simian immunodeficiency virus (SIV), or RNA viruses and other DNA	[61]

The Compounds 39a,39b respectively with having CH₃ group at ortho and para situations of the phenyl ring and compound 39c with Cl group at ortho position exhibited an equal or twice more powerful than Miconazole against all the fungal strains

Coumarin

1,2,3-triazole motif

N-phenylacetamide-linked 1,2,3-triazole

The Compounds 40a and 40b having CH₃ and Cl groups at ortho situation of the phenyl ring showed an great anti-fungal properties against all the fungal strains

39

40

39a: R = 2-Me
  (MIC,12.5 - 25 μg/ml)
39b: R = 4-Me
  (MIC,12.5 - 25 μg/ml)
39c: R = 2-Cl
  (MIC,12.5 - 25 μg/ml)

40a: R = 2-Me
  (MIC,12.5 - 25 μg/ml)
40b: R = 2-Cl
  (MIC,12.5 - 25 μg/ml)

FIGURE 3: Chemical structure of new N-phenylacetamide-linked 1,2,3-triazole-coumarin conjugates.

pyrano-[2,3-d]-pyrimidine-attached 1,2,3-triazole derivatives in an exceptional molecular hybrid with antimicrobial activity (bacteria and fungi). The antifungal efficacy of the target compounds toward *Aspergillus flavus* and *Candida albicans* is outstanding. Ketoconazole (zone of inhibition 14.0–20.5 μg/mL) was applied as the standard medicine for antifungal activity (Figure 13). Meanwhile, three compounds (57a–c) exhibited significant fungicidal activity against all of the studied fungi when compared to ketoconazole owing to groups (nitro and fluoro) linked to the 1,2,3-triazole of the pyranopyrimidine ring [78].

A class of dehydroacetic acid chalcone-1,2,3-triazole hybrids were synthesized as possible antibacterial agents. All of the compounds were screened *in vitro* toward two fungal strains (*Candida albicans* and *Aspergillus niger*) and four bacterial strains (Figure 14). Almost all of the compounds performed better than DHA, which is an antimicrobial agent. The antifungal activity of combination 58h (R_1 = OCH₃) against *A. niger* and *C. albicans* showed MIC values of 0.0068 and 0.0034 μM/mL, respectively. When compared to *A. niger*, compounds 58a–h were more potent than the standard drug, but in the case of *C. albicans*,
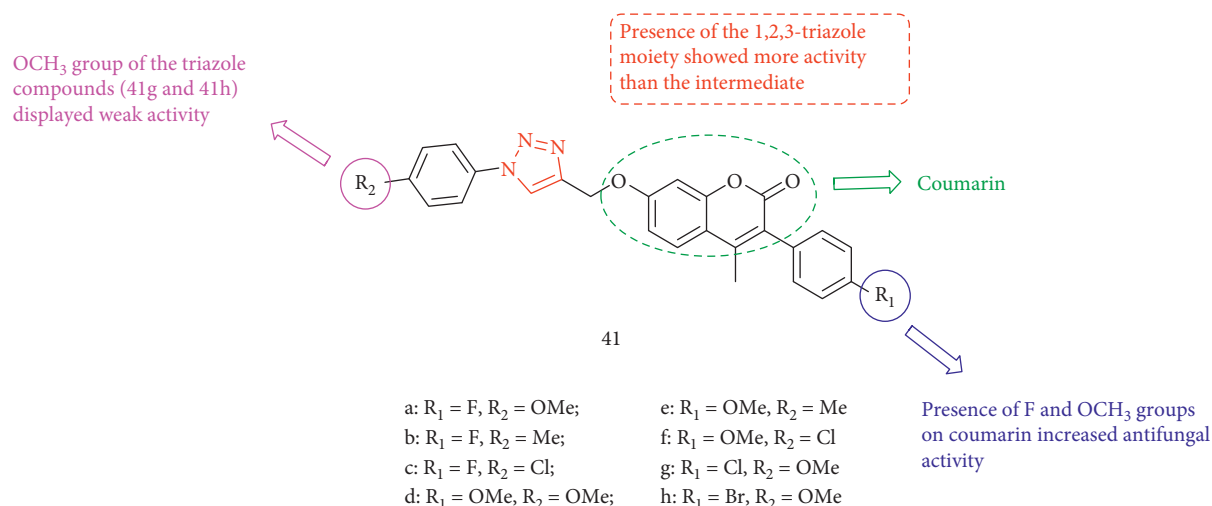
FIGURE 4: Chemical structure coumarin-based 1,2,3-triazole compounds.
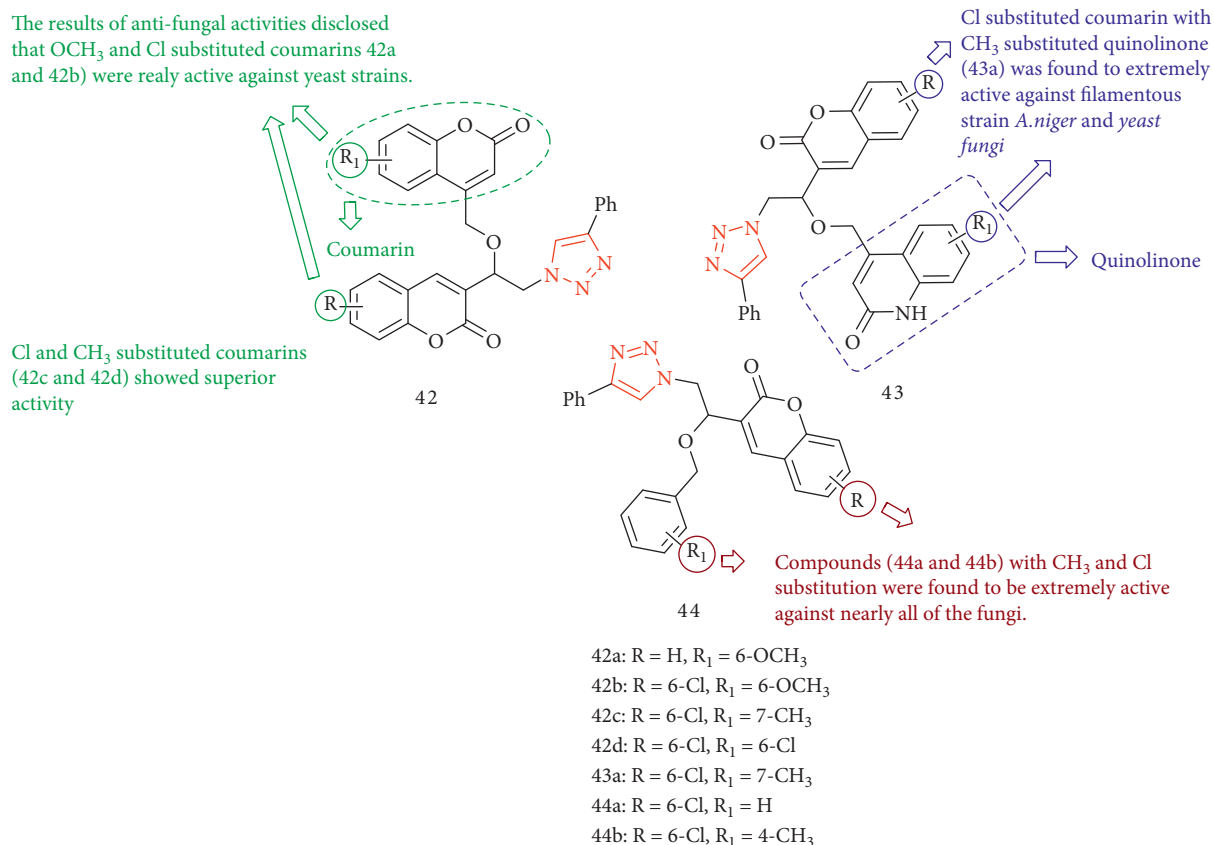
FIGURE 5: Chemical structure of coumarin, quinolinone-linked 1,2,3-triazoles.

compounds **58g** and **58h** revealed significant activity among all synthesized triazoles [79].

2.4.2. 1,2,3-Triazole-Amide Hybrids.
González-Calderón et al. [80] used a one-pot method to synthesize new benzylic 1,2,3-triazole-4-carboxamides with passable yields. As shown in Figure 15, the sequence of compounds was

evaluated for antifungal activity *in vitro* toward four filamentary fungi and four *Candida* species. Compounds **59b** and **59c** were the most impressive fungal factors (of all the trial compounds) against *R. oryzae*, even better than the standard medicine (MIC = 0.017 μmol/mL for **59b** and **59c**; MIC = 0.14 μmol/mL for Itraconazole). The SAR for compounds **59b** and **59c** showed that the 4-phenyl-4-carboxamide triazole was accountable for the antifungal result,

Almost all of the synthesized compounds are more active against the fungi strain *C. lunata* as compared to reference medicines Miconazole and Amphotericin B.

Coumarin moiety ⇐

45

a: R = H, R$_1$ = NO$_2$
b: R = Cl, R$_1$ = H

The compound 45b containing chloro-substituent at meta situation of phenyl ring exhibited favorable activity as compared to the reference drugs Miconazole and Amphotericin B.
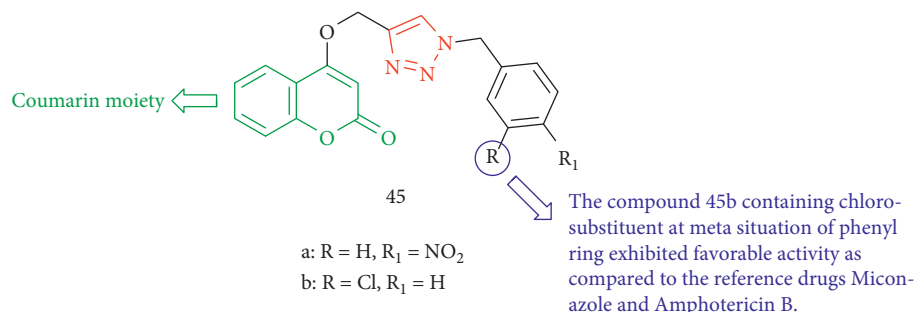
FIGURE 6: Chemical structure of novel coumarin incorporated triazoles.

Most of the compounds were inactive against the fungal strain *A. niger*, *A. flavus* and *C. neoformans*

Compounds with (chloro-group at para, meta and ortho), and 46e with MIC amounts 25 μg/mL displayed equal power for fungal strain *C. albicans* compared to the Miconazole.

Ethyl-2-oxo-7-(prop-2-yn-1-yloxy)-2*H*-chromene-3-carboxylate

Coumarin

46

a: R$_1$ = H, R$_2$ = H, R$_3$ = Cl
b: R$_1$ = H, R$_2$ = Cl, R$_3$ = H
c: R$_1$ = Cl, R$_2$ = H, R$_3$ = H
d: R$_1$ = H, R$_2$ = H, R$_3$ = F
e: R$_1$ = H, R$_2$ = H, R$_3$ = H

Compound 46d containing fluoro-group at para situation of phenyl ring has been showed good stopper of C. albicans with MIC amounts 12.5 μg/mL and double active as compared to the Miconazole and similar to Fluconazole.

FIGURE 7: Chemical structure of 1,2,3-triazole incorporated coumarin derivatives.

The compounds 48a and 48b dis- played antifungal activity against *C.albicans* MTCC 854 and *Issatchenkia hanoiensis* MTCC 4755 at MIC amount of 7.1 μM and 6.5 μM in order that is smaller than the reference drug.

47

H$_3$C

Coumarin moiety

48

H$_3$C

The compound 48d (6-bromo-8-methoxycoumarinyl; MIC, 5.9 μM) was found to be a very strong hybrid of the examed sequence against most of the Candida spp when compared to Miconazole (MIC,18.7 μM).

48a: R$_1$ = R$_2$ = R$_3$ = H
48b: R$_1$ = H, R$_2$ = R$_3$ = C$_4$H$_4$
48c: R$_1$ = OCH$_3$, R$_2$ = R$_3$ = H
48d: R$_1$ = OCH$_3$, R$_2$ = Br, R$_3$ = H
48e: R$_1$ = R$_2$ = NO$_2$, R$_3$ = H

FIGURE 8: Chemical structure of synthesis of 1,2,3-triazole-thiazole hybrids.
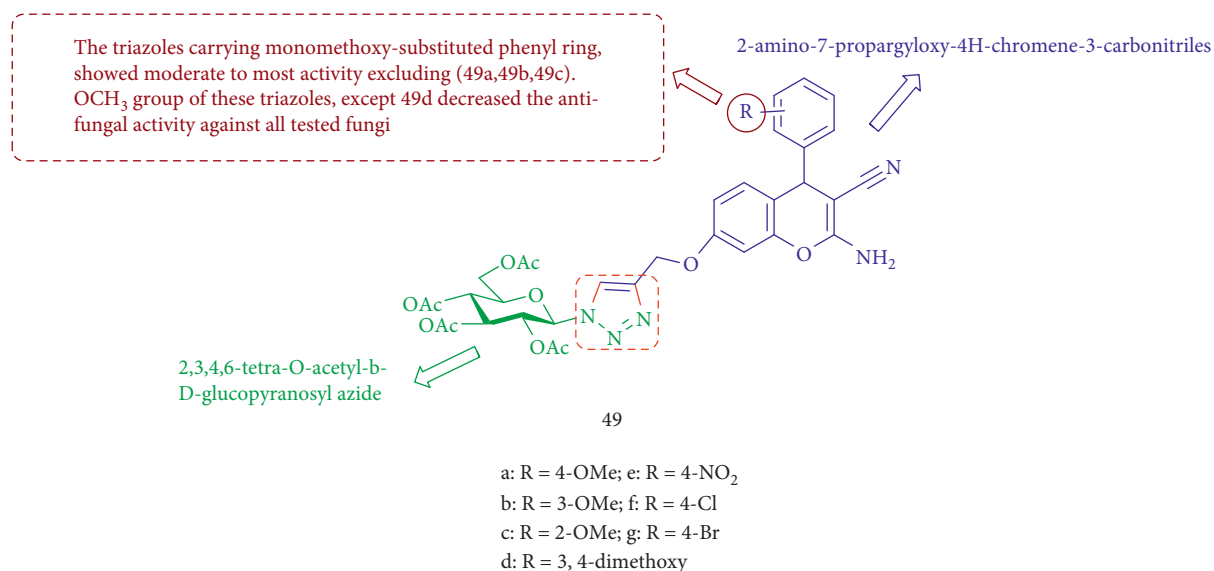
Figure 9: Chemical structure of novel 1H-1,2,3-triazole-tethered 4H chromene-D-glucose conjugates.

The triazoles carrying monomethoxy-substituted phenyl ring, showed moderate to most activity excluding (49a,49b,49c). OCH₃ group of these triazoles, except 49d decreased the anti-fungal activity against all tested fungi

2-amino-7-propargyloxy-4H-chromene-3-carbonitriles

2,3,4,6-tetra-O-acetyl-b-D-glucopyranosyl azide

49

a: R = 4-OMe; e: R = 4-NO₂
b: R = 3-OMe; f: R = 4-Cl
c: R = 2-OMe; g: R = 4-Br
d: R = 3, 4-dimethoxy

NO₂ group at meta position of phenyl ring showed equipotent activity to standard drug against *A.flavus*, *C. albicans* and *C. neoformans* and lower active versus *A. niger* and *F. oxysporum*

Cl group at para position of phenyl ring displayed resistance against all the examed fungal strains except *A. niger*

50

a: R = H; d: R = 2-OMe
b: R = 4-Me; e: R = 4-Cl
c: R = 3-OMe; f: R = 3 = NO₂

Figure 10: Chemical structure of novel triazole-chromene conjugates.

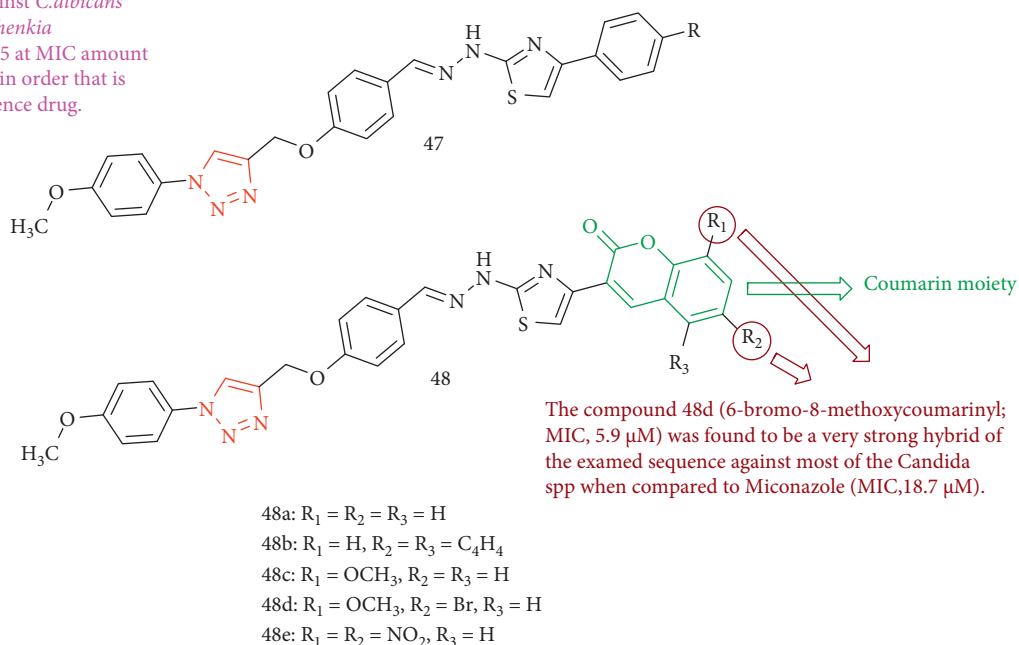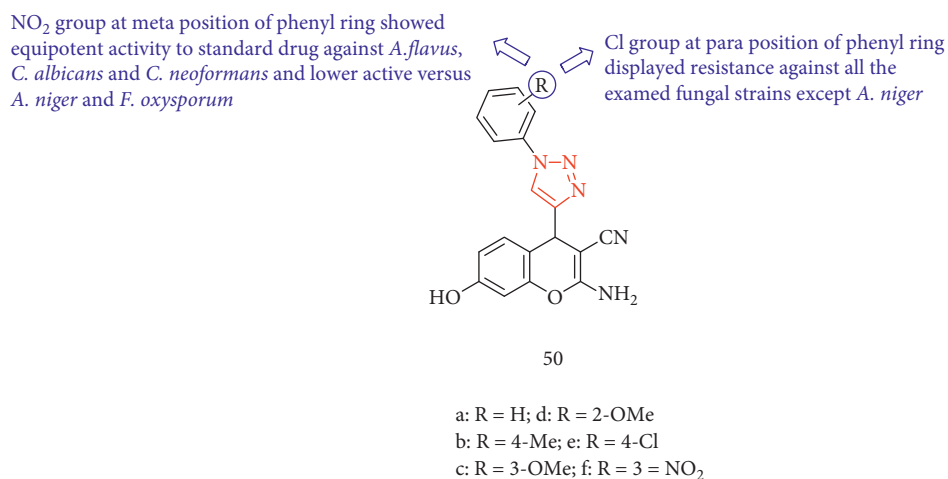while neither the electron-wealthy ring (including piperonyl in **59c**) nor the electron-needy ring (substituted with 2,6-dichloro to form **59b**) was related. Compounds with the largest functional groups in their structure exhibit lower activity than standard drug, indicating the need for a modest substituent in positions 1 and 5 of triazole to interact positively with the active site of the fungus.

A new class of *N*-Boc L-Leucine-connected 1,2,3-triazoles were synthesized and evaluated the fungicidal activity against *A. niger* and *Candida albicans* fungus strains using an MIC value of $0.0102 \, \mu$mol/mL. In case of both fungal strains, compounds **60a** and **60b** had approximately comparable activity with Fluconazole. Compounds **60a** and **60c** found a remarkable activity as compared to Fluconazole in the case of *C. albicans* (Figure 16) [81].

Kaushik et al. [82] reported a novel library of 1,2,3-triazoles bridged with amine-amide functionalities from *N*-substituted (prop-2-yn-1-yl)amines and sodium azide

and 2-bromo-*N*-arylacetamides by copper(I)-catalyzed. Antifungal assessment of recent derivatives was carried out against *Aspergillus niger* and *Candida albicans*. All compounds of synthesized 1,2,3-triazoles showed modest to good antifungal activity against fungi strains. Compounds **61a–f** displayed good activity against *C. albicans*, while in case of *A. niger*, compounds **61b**, **61c**, and **61g** displayed significant activity (Figure 17).

The use of [Et₃NH][OAc] as a mediator in the performance of ultrasonic irradiation via click chemistry resulted in a simple, very impressive, and greener method for the preparation of novel 1,4-disubstituted-1,2,3-triazoles with high yields. These compounds were assessed *in vitro* for antifungal activity against five different fungus species: *Aspergillus niger, Aspergillus flavus, Fusarium oxysporum, Cryptococcus neoformans*, and *Candida albicans*. Some compounds have the same or greater power compared to the reference drug (Miconazole) (Figure 18) [83].
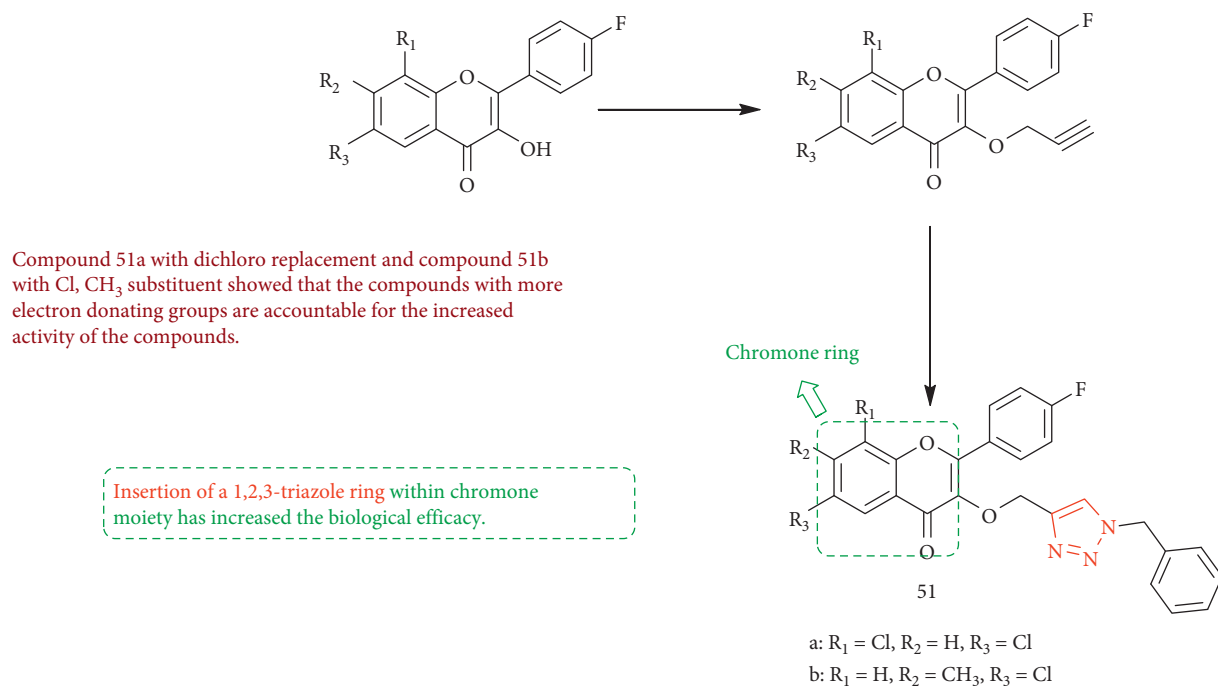
Compound 51a with dichloro replacement and compound 51b with Cl, CH$_3$ substituent showed that the compounds with more electron donating groups are accountable for the increased activity of the compounds.

Insertion of a 1,2,3-triazole ring within chromone moiety has increased the biological efficacy.

Chromone ring

51

a: R$_1$ = Cl, R$_2$ = H, R$_3$ = Cl
b: R$_1$ = H, R$_2$ = CH$_3$, R$_3$ = Cl

FIGURE 11: Chemical structure of novel chromone-based 1,2,3-triazoles.

Chalcone moiety

52

53

Existence of chloro group in phenyl ring of one triazole unit chalcones exhibited powerful antifungal property, while difluoro compounds increased antifungal activity in two triazole connected chalcones.

54

Flavone moiety

55

56

The flavone compounds having difluoro substituted phenyl rings were found to be slow versus antifungal and also antibacterial activity.

52a: R = 2-Cl,4-F
52b: R = 4-Cl
53a: R = 2-Cl
53b: R = 4-Cl
54a: R,R$_1$ = 2,4-di-F

55a: R = 2-Cl,4-F
55b: R = 3-Cl,4-F
55c: R = 4-Cl
56a: R,R$_1$ = 2-Cl,4-F
56b: R,R$_1$ = 2-Cl

FIGURE 12: Chemical structure of newer 1,2,3-triazole-linked chalcone and flavone hybrid compounds.

Aryloxy-linked dimeric 1,2,3-triazoles from azides and bis(prop-2-yn-1-yloxy)benzene were synthesized by Deshmukh et al. [84] using a Cu(I)-catalyzed click chemistry approach with good to excellent yields.

All of the compounds were tested for antifungal activity against five different fungal strains: *Cryptococcus neoformans*, *Fusarium oxysporum*, *Aspargillus flavus*, *Aspargillus niger*, and *Candida albicans*, and Miconazole
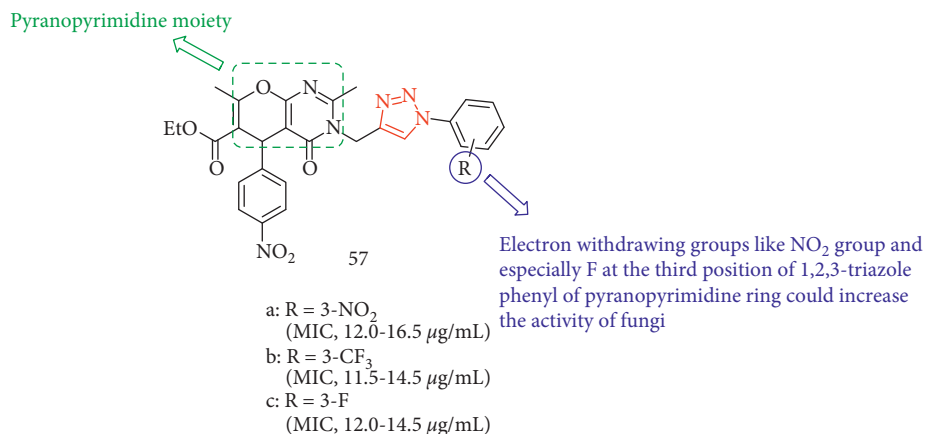
FIGURE 13: Chemical structure of pyrano-[2,3-d]-pyrimidine-attached 1,2,3-triazole derivatives.
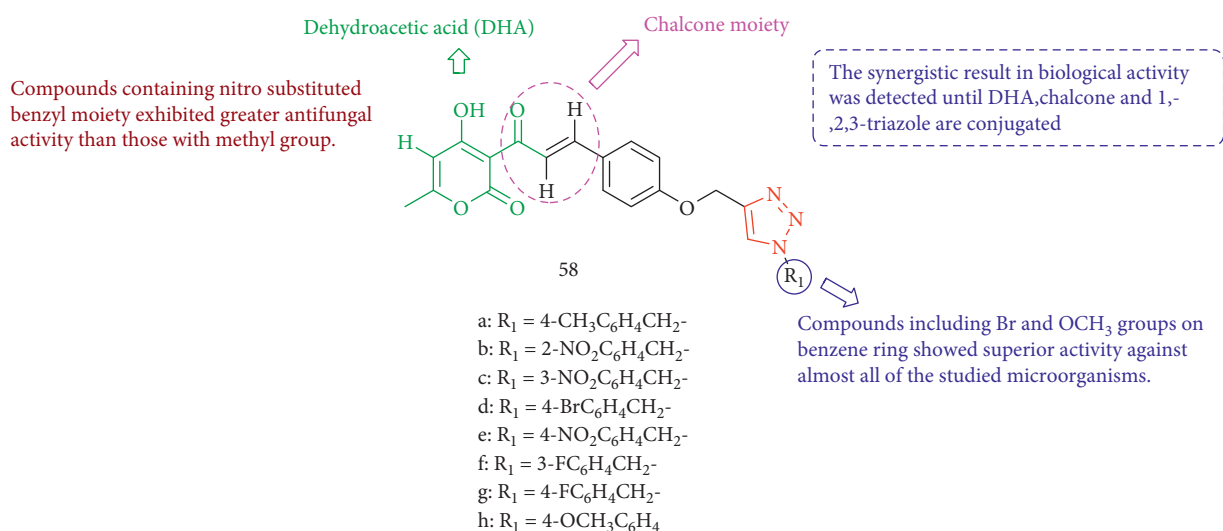
FIGURE 14: Chemical structure of dehydroacetic acid-chalcone-1,2,3-triazole hybrids.
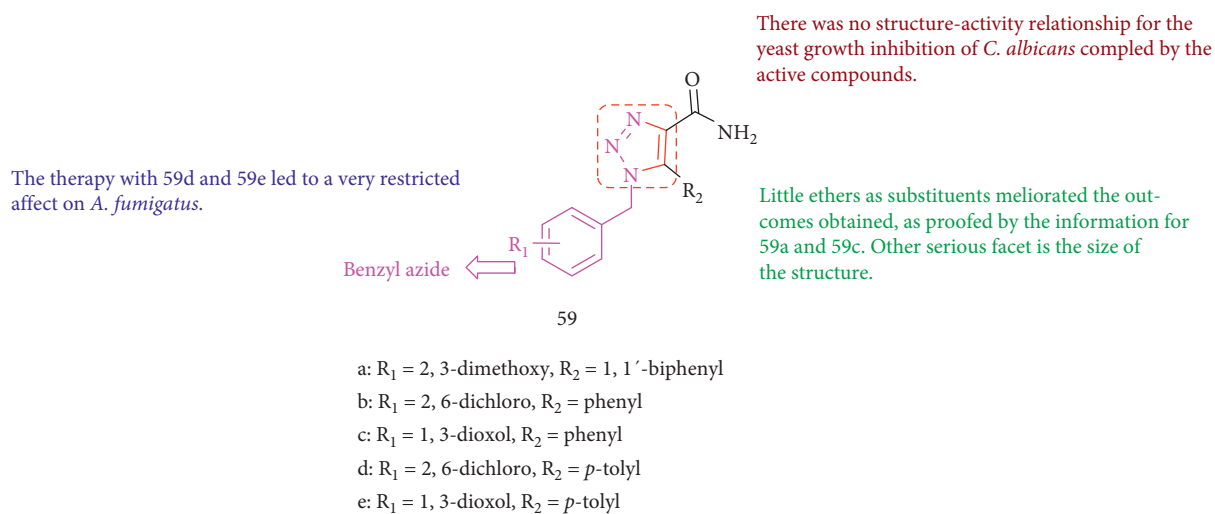
FIGURE 15: Chemical structure of novel benzylic 1,2,3-triazole-4-carboxamides.

is utilized as standard medicine. Most of the compounds showed moderate-to-great antifungal activity (Figure 19).

Yan et al. [85] synthesized 42 carboxamide derivatives, including a 1,2,3-triazole ring, and demonstrated antifungal activity against nine phytopathogens at $50 \, \mu g/mL$ boscalid as

N-Boc protected L-Leucine-linked alkyne

All N-Boc protected L-Leucine linked 1,2-3-triazoles displayed greater activity than N-Boc protected L-Leucine linked alkyne for *A.niger* and *C. albicans*, as compared to reference drug.

N-Boc protected L-Leucine linked 1,2,3-triazoles

6 0

a: R = *o*-Br; (MIC, 0.013 μmol/mL)
b: R = *p*-F; (MIC, 0.0148 μmol/mL)
c: R = *p*-Br; (MIC, 0.013 μmol/mL)

FIGURE 16: Chemical structure N-Boc-protected Leucine-linked 1,4-disubstituted 1,2,3-triazole.

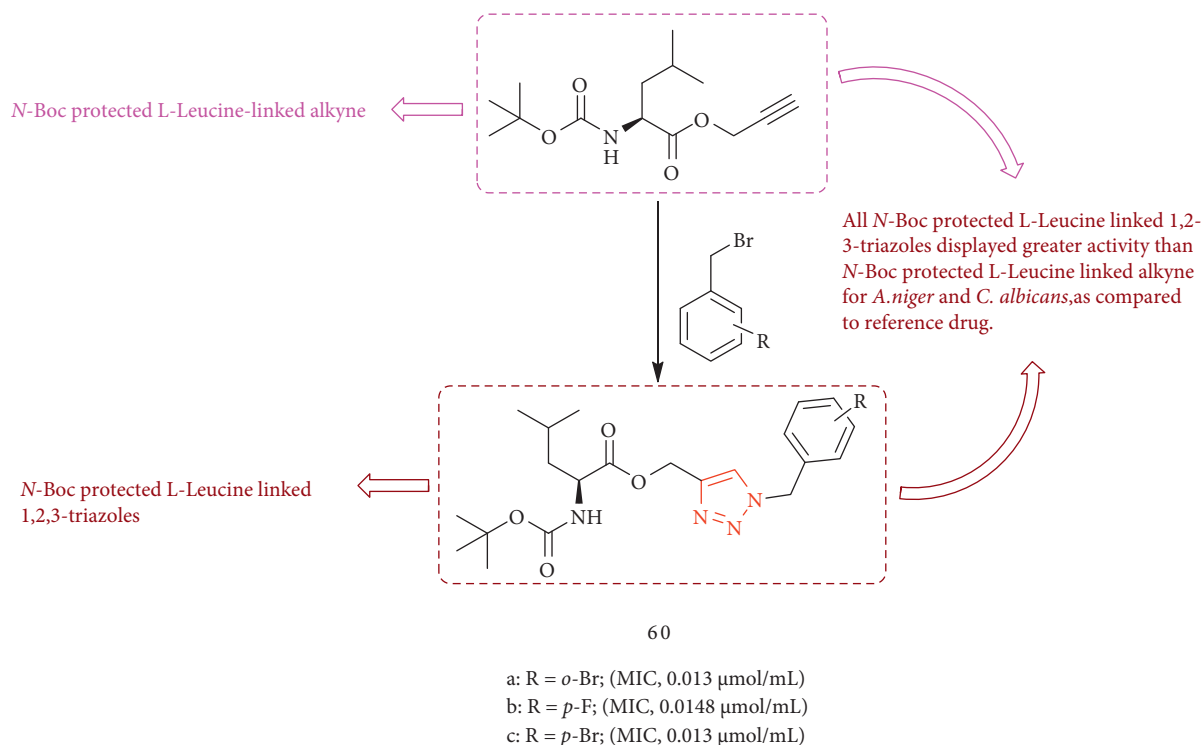The results showed that compounds having naphthyl moiety revealed premier activity in comparison to phenyl moiety.

61

a: $R_1 =$ [morpholine] $R_2 = 4\text{-NO}_2\text{C}_6\text{H}_4$ e: $R_1 =$ [phenyl-N] $R_2 = \alpha\text{-C}_{10}\text{H}_7$

b: $R_1 =$ [morpholine] $R_2 = \alpha\text{-C}_{10}\text{H}_7$ f: $R_1 =$ [phenyl-N] $R_2 = \alpha\text{-C}_{10}\text{H}_7$

c: $R_1 =$ [pyrrolidine] $R_2 = 4\text{-NO}_2\text{C}_6\text{H}_4$

d: $R_1 =$ [pyrrolidine] $R_2 = \alpha\text{-C}_{10}\text{H}_7$ g: $R_1 =$ [piperidine] $R_2 = 4\text{-NO}_2\text{C}_6\text{H}_4$
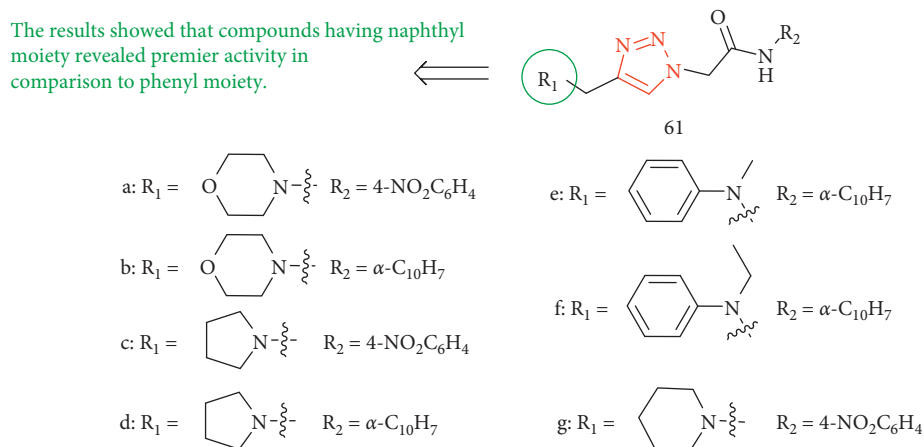
FIGURE 17: Chemical structure of amine-amide-linked 1,4-disubstituted 1,2,3-triazoles.

the positive control. The target compounds in sequence A displayed more extraordinary inhibitory activities against *G. graminsis*, *S. sclerotiorum*, *B. cinerea*, and *R. cerealis* compared to other fungus strains. In sequence B, compounds showed fewer antifungal activities than series A. Compound **65A3-1** revealed remarkable antifungal activity against *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Rhizoctonia cerealis*, and *Gaeumannomyces graminis*, and it was chosen as the best compound for further investigation. When R of the benzene was monosubstituted, the inhibitory rate of **65A1-1** (*p*-Cl) was preferred over **65A1-2** (*p*-F) and **65A1-3** (*p*-OCH₃), while R of the benzene was disubstituted; the activity of **65A1-4** (3,4-di-Cl) was superior to those of **65A1-5** (3-Cl-4-F) and **65A1-6** (4-Cl-3-OCH₃) (Figure 20).

Brahmi et al. [86] explored a novel sequence of semicarbazone-triazole hybrid derivatives with condensation among the commercial semicarbazide hydrochloride and heterocyclic aldehydes. The *in vitro* antifungal activities were examined against two fungus strains (*Fusarium oxysporum* and *Fusarium phyllophilum*) and showed the greatest inhibitory antifungal activity that was created for compound **66c** against *F. oxysporum* in comparison to the standard drug. The *ortho*-methoxy substitution in the aryl ring (**66e**) is more acceptable for activity than the *para*-methoxy substituent (**66d**) because of the structure's fixation by intramolecular H-bonds. The following antifungal activity levels were observed: **66c** > **66e** > **66d** against *F. oxysporum*. **66a** and **66b** had low-to-moderate activity (Figure 21).
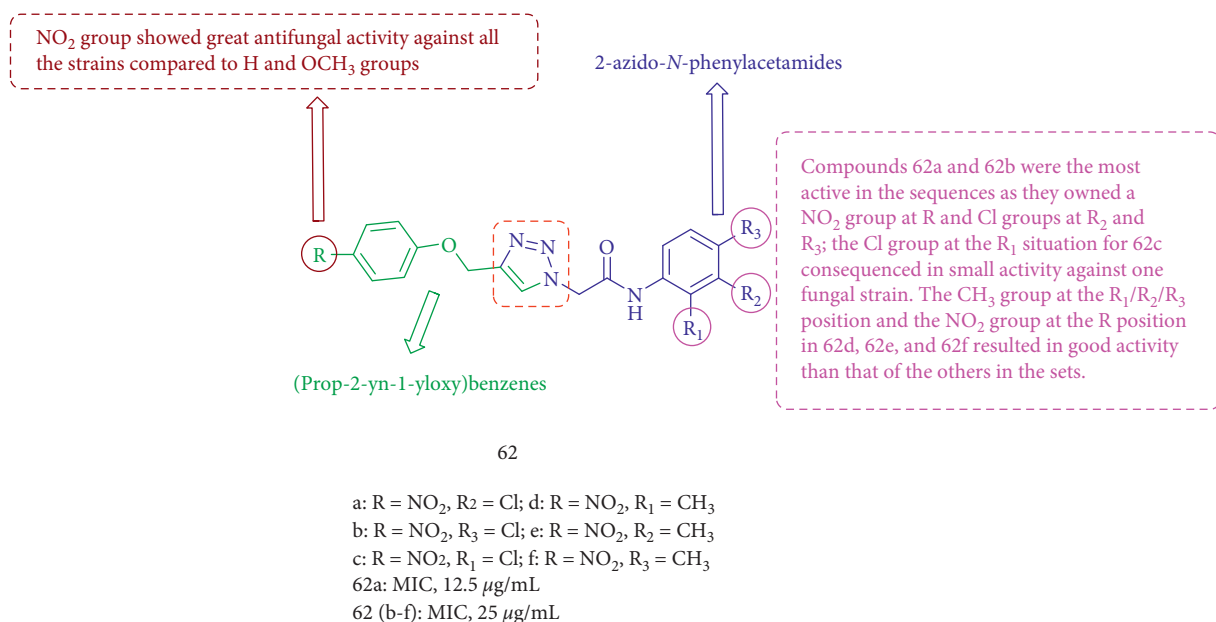
NO₂ group showed great antifungal activity against all the strains compared to H and OCH₃ groups

2-azido-*N*-phenylacetamides

Compounds 62a and 62b were the most active in the sequences as they owned a NO₂ group at R and Cl groups at R₂ and R₃; the Cl group at the R₁ situation for 62c consequenced in small activity against one fungal strain. The CH₃ group at the R₁/R₂/R₃ position and the NO₂ group at the R position in 62d, 62e, and 62f resulted in good activity than that of the others in the sets.

(Prop-2-yn-1-yloxy)benzenes

62

a: R = NO₂, R₂ = Cl; d: R = NO₂, R₁ = CH₃
b: R = NO₂, R₃ = Cl; e: R = NO₂, R₂ = CH₃
c: R = NO₂, R₁ = Cl; f: R = NO₂, R₃ = CH₃
62a: MIC, 12.5 μg/mL
62 (b-f): MIC, 25 μg/mL

FIGURE 18: Chemical structure of new N-phenylacetamide-incorporated 1,2,3-triazoles.

1,3-bis (prop-2-yn-1-yloxy)benzene

Among all compounds, 64f and and 64g exhibited the greatest antifungal activity.

1,2-bis (prop-2-yn-1-yloxy)benzene

63   64

63a: O⌷N-ξ-   64e: ⌷N-ξ-

63b: ⌷N-ξ-   64f: ⌷N-ξ-

63c: ⌷N-ξ-   64g: ⌷N-ξ-

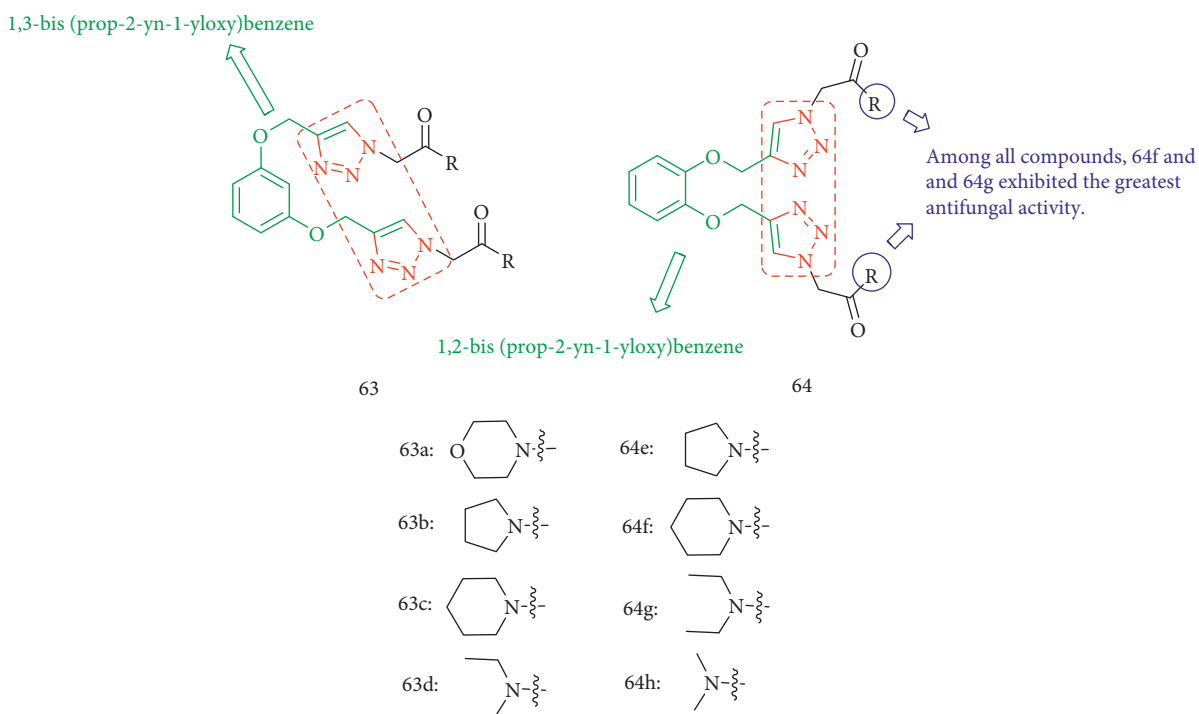63d: ⌷N-ξ-   64h: ⌷N-ξ-

FIGURE 19: Chemical structure of new aryloxy-linked substituted dimeric 1,2,3-triazoles.

Kaushik and Luxmi [87] examined a collection of 25 amides linked to 1,4-disubstituted 1,2,3-triazoles. The antifungal activity of two fungus strains was also studied using a serial dilution approach. Fluconazole was employed as a conventional treatment, and compounds **67a** and **67b** showed moderate intense activity (Figure 22).

Kaushik and Luxmi [88] synthesized 2-(4-(hydroxyalkyl)-1*H*-1,2,3-triazol-1-yl)-*N*-substituted propanamides using Cu(I) catalyzed reaction of 2-azido-*N*-substituted propanamide and terminal alkynes. Furthermore, the

antifungal activity of these triazoles was examined *in vitro* against two fungal strains (*A. niger* and *C. albicans*), with Fluconazole serving as a reference drug. Compounds **68a–c** revealed powerful fungicidal activity against *C. albicans* and displayed good activity against *A. niger* (Figure 23).

Amide-ester-connected 1,4-disubstituted 1,2,3-triazoles were synthesized by employing Copper(I)-catalyzed 1,3-dipolar cycloaddition of 2-azido-*N*-substituted acetamides and benzoic acid prop-2-ynyl esters. All of the compounds were evaluated for antifungal activity against two different
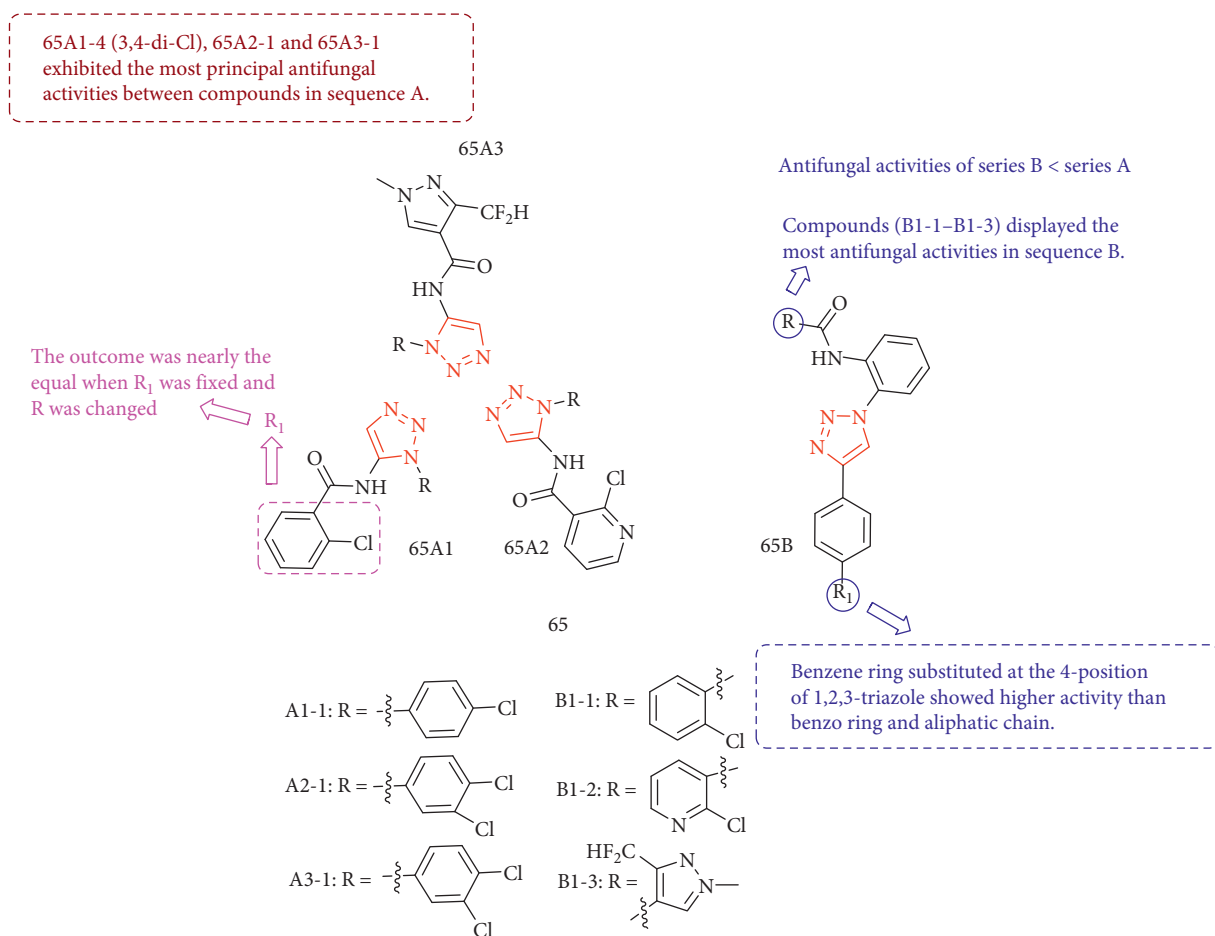
65A1-4 (3,4-di-Cl), 65A2-1 and 65A3-1 exhibited the most principal antifungal activities between compounds in sequence A.

The outcome was nearly the equal when R_1 was fixed and R was changed

Antifungal activities of series B < series A

Compounds (B1-1–B1-3) displayed the most antifungal activities in sequence B.

Benzene ring substituted at the 4-position of 1,2,3-triazole showed higher activity than benzo ring and aliphatic chain.

A1-1: R = ... Cl

A2-1: R = ... Cl Cl

A3-1: R = ... Cl Cl

B1-1: R = ... Cl

B1-2: R = ... Cl

B1-3: R = ...

FIGURE 20: Chemical structure of carboxamide derivatives containing 1,2,3-triazole ring.

Presence of two methyl groups in ortho-position of the aromatic ring (66c) increased fungul activity.

Powerful biological activities might be owing to the presence of the 1,2,3-triazole ring connected to the various substituents in the molecule.

The compounds 66a and 66b (methyl group in the para-position of the aryl ring) decreased activity because of their electron donating efficacy and the lowest size of the H atom.

a: R = H; d: R = 4-OMe
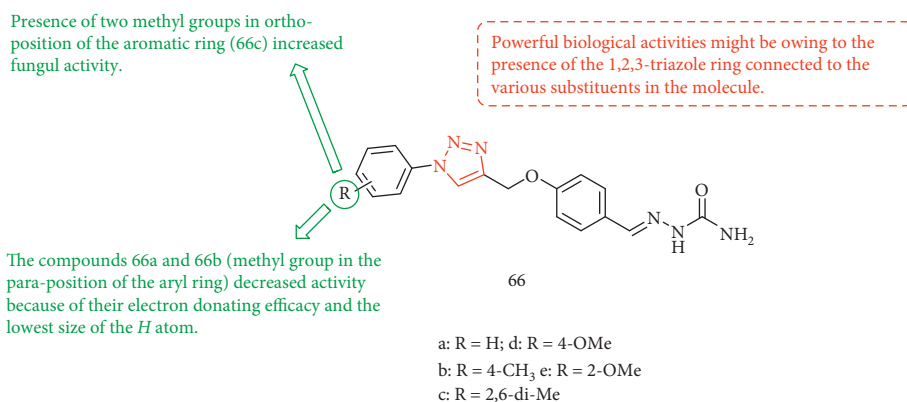b: R = 4-CH$_3$ e: R = 2-OMe
c: R = 2,6-di-Me

FIGURE 21: Chemical structure of new series of semicarbazone-triazole hybrid derivatives.

fungus strains, *Aspergillus niger* and *Candida albicans*. The antifungal activity results revealed that most of the synthesized compounds exhibited moderate-to-good antifungal efficacy against the named fungus strains. Compound **69e** including R_2 = electron-donating group and R_1 = p-Br-C$_6$H$_4$- had good antifungal activity against *A. niger*. R_1 and R_2 containing an electron-donating group, like methyl on both the benzoate and amino phenyl moieties (**69i**), showed good fungicidal activity against *C. albicans* (Figure 24) [89].

Wang et al. [90] synthesized and tested novel hydrazide derivatives of 1,2,3-triazole for fungicidal activity against *S. sclerotiorum*, *F. graminearum, M. oryzae,* and *R. solani.* The findings revealed that all of the target compounds have notable antifungal activity. Compound **70b** showed the most potent antiphytopathogenic activity, with EC$_{50}$ values of 0.18, 0.35, 0.37, and 2.25 μg/mL against the four fungi, respectively. Owing to the lower cost of fluorosubstituted aniline compared to chlorine-substituted aniline, **70b** was
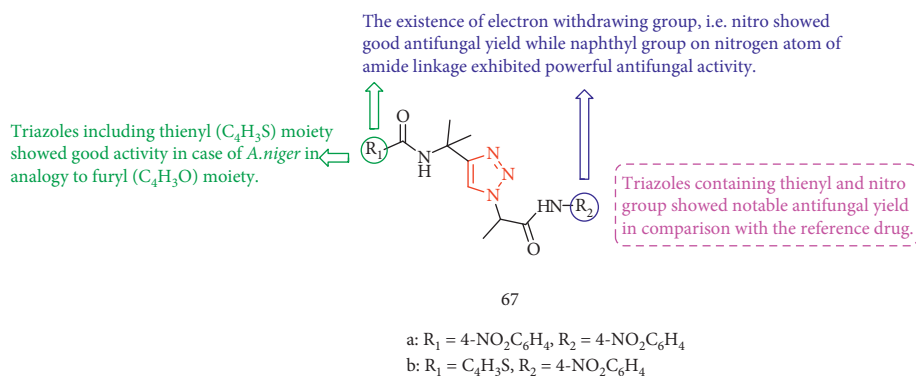
The existence of electron withdrawing group, i.e. nitro showed good antifungal yield while naphthyl group on nitrogen atom of amide linkage exhibited powerful antifungal activity.

Triazoles including thienyl (C_4H_3S) moiety showed good activity in case of *A.niger* in analogy to furyl (C_4H_3O) moiety.

Triazoles containing thienyl and nitro group showed notable antifungal yield in comparison with the reference drug.

67

a: $R_1 = 4\text{-}NO_2C_6H_4$, $R_2 = 4\text{-}NO_2C_6H_4$
b: $R_1 = C_4H_3S$, $R_2 = 4\text{-}NO_2C_6H_4$

FIGURE 22: Chemical structure of 1,4-disubstituted 1,2,3-triazoles.

The existence of the alkyl group on carbon having free hydroxyl group enhanced the antifungal activity against *A. niger* and *C. albicans*.

All the examed compounds with Br and NO_2 group on phenyl ring exhibited good antifungal activity against both the strains.

68

a: $R_1 = 4\text{-}BrC_6H4$, $R_2 = CH_3$, $R_3 = CH_3$
b: $R_1 = 4\text{-}BrC_6H_4$, $R_2 = CH_3$, $R_3 = C_2H_5$
c: $R_1 = 4\text{-}NO_2C_6H_4$, $R_2 = CH_3$, $R_3 = C_2H_5$
d: $R_1 = 4\text{-}BrC_6H4$, $R_2 = H$, $R_3 = H$
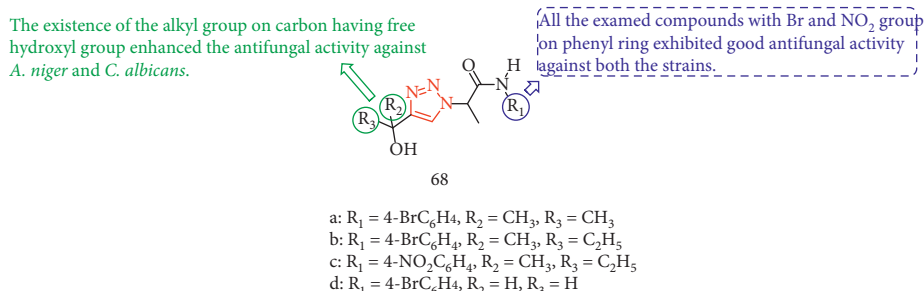
FIGURE 23: Chemical structure of amide-linked 1,4-disubstituted 1,2,3-triazoles.

R_2 = electron withdrawing group, like nitro and R_1 = *p*-methoxyphenyl (69f), *p*-flourophenyl (69g), and naphthyl (69h) revealed as strong fungicidal agents.

R_2 = flouro group on benzoate moiety with R_1 = phenyl (69a), *p*-toluyl (69d), *p*-nitrophenyl (69c) emerged as impressive antifungals against *A. niger*.

The triazoles containing *p*-flourobenzoate moiety with R_1 representing phenyl (69a), *p*-bromophenyl (69b), and *p*-nitrophenyl (69c) displayed greater antifungal potency against *C. albicans*.

69

a: $R_1 = C_6H_5\text{-}$, $R_2 = p\text{-}F\text{-}C_6H_4\text{-}$
b: $R_1 = p\text{-}Br\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}F\text{-}C_6H_4\text{-}$
c: $R_1 = p\text{-}NO_2\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}F\text{-}C_6H_4\text{-}$
d: $R_1 = p\text{-}CH_3\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}F\text{-}C_6H_4\text{-}$
e: $R_1 = p\text{-}Br\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}CH3\text{-}C_6H_4\text{-}$
f: $R_1 = p\text{-}CH_3O\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}NO_2\text{-}C_6H_4\text{-}$
g: $R_1 = p\text{-}F\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}NO_2\text{-}C_6H_4\text{-}$
h: $R_1 = \alpha\text{-}Naphthyl$, $R_2 = p\text{-}NO_2\text{-}C_6H_4\text{-}$
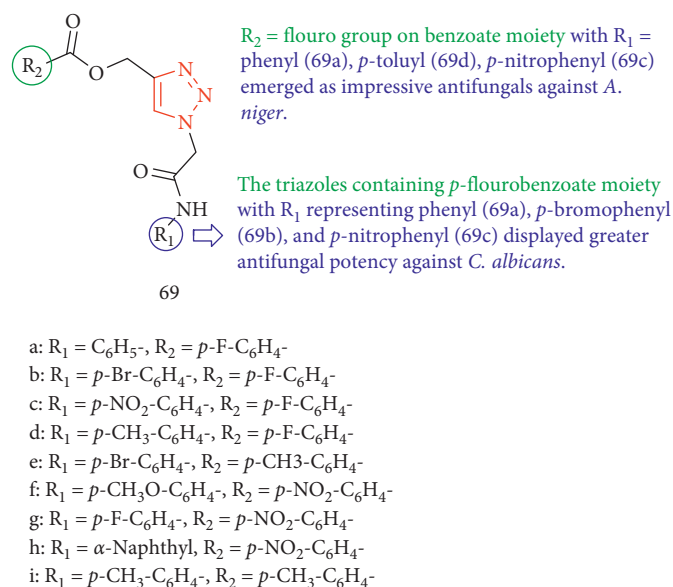i: $R_1 = p\text{-}CH_3\text{-}C_6H_4\text{-}$, $R_2 = p\text{-}CH_3\text{-}C_6H_4\text{-}$

FIGURE 24: Chemical structure of amide-ester-linked 1,4-disubstituted 1,2,3-triazoles.

chosen to experiment antifungal property *in vivo* despite the equal antifungal activity produced by other compounds. The EC50 values displayed that an electron-withdrawing group outperformed an electron-donating group for R_2 (Figure 25).

Saidugari et al. [91] synthesized new 1,2,3-triazolehydrazone derivatives with a 3,4-dimethoxy pyridine ring core. Different benzohydrazides and 2-(chloromethyl)-3,4-dimethoxypyridine 1,4-ethynylbenzaldehyde were produced using these compounds. They were tested for fungal stains such as *Aspergillus niger* and *Candida albicans* (Figure 26).

A series of 5-nitrofuran-triazoles were synthesized with appropriate structural corrections of the formerly reported

Halogen substituents of R_1 at the ortho situation and halogen substituents of R_2 at the para position (70b, 70c, 70d and 70e) created the optimal combinations.
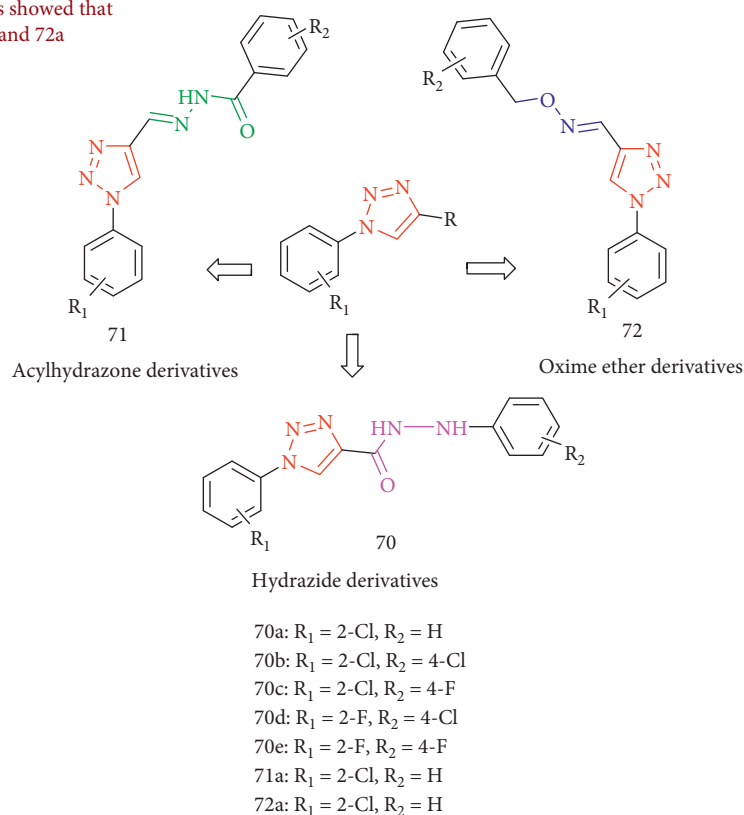
Antifungal activity experiments showed that 70a performed better than 71a and 72a

71
Acylhydrazone derivatives

72
Oxime ether derivatives

70
Hydrazide derivatives

70a: R_1 = 2-Cl, R_2 = H
70b: R_1 = 2-Cl, R_2 = 4-Cl
70c: R_1 = 2-Cl, R_2 = 4-F
70d: R_1 = 2-F, R_2 = 4-Cl
70e: R_1 = 2-F, R_2 = 4-F
71a: R_1 = 2-Cl, R_2 = H
72a: R_1 = 2-Cl, R_2 = H

FIGURE 25: Chemical structure of 1,2,3-triazole hydrazide derivatives exhibiting antiphytopathogenic activity.

Compounds 73a-c and 73d displayed very good anti-fungal activity.

73

a: R = 4-OH
b: R = 4-SO$_2$Me
c: R = 3,5-dichloro
d: R = 2,5-difluoro
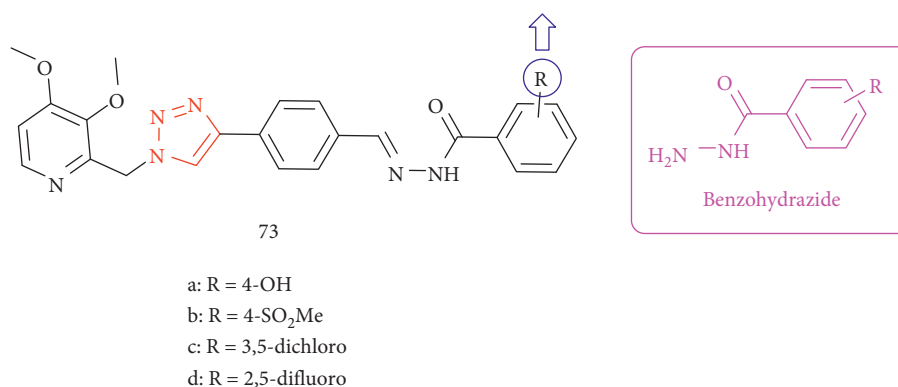
Benzohydrazide

FIGURE 26: Chemical structure of novel 1,2,3-triazole-carbohydrazide derivatives.

counterparts, and they were evaluated to examine 14 various fungal strains and were shown to have great antifungal activities. In comparison to one or more fungal strains examined, all compounds were comparable with Miconazole and showed good effectiveness against other equivalents. Compound **74a** displayed twofold better antifungal activity (MIC = 3.9 μg/mL) compared to Miconazole (MIC = 7.8 μg/mL) against *C. parapsilosis* and *C. albicans* (Figure 27) [92].

2.4.3. 1,2,3-Triazole-Sugar Hybrids. Tan et al. [93] used CuAAC and methylation to synthesize a new cationic chitosan derivative with 1,2,3-triazolium and pyridinium groups. The antifungal capabilities of all compounds were evaluated to study three plant-threatening fungi by hypha measurement *in vitro*. The research presented that *N*-methylation of pyridine and 1,2,3-triazole may successfully increase the antifungal properties of the synthesized chitosan derivatives. The results exhibited that chitosan
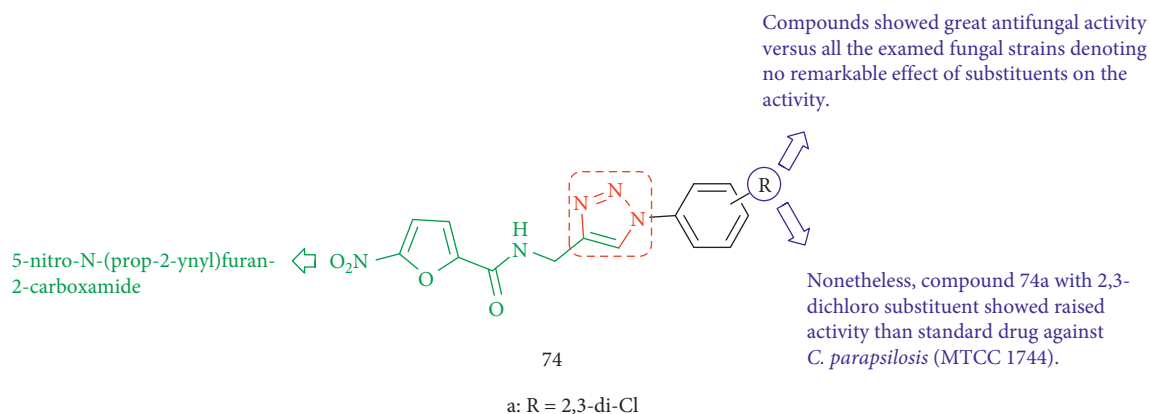
FIGURE 27: Chemical structure of 5-nitrofuran-triazole conjugates.

derivative containing 1,2,3-triazolium and pyridinium increased antifungal activity as compared with chitosan and chitosan derivations bearing 1,2,3-triazole and pyridine. All of the synthesized compounds displayed superior ability of inhibiting the growth of the examined phytopathogenic fungi than chitosan (Figure 28).

Li et al. [94] used click chemistry to design and synthesize reclaimed chitosan containing a 1,2,3-triazole scaffold with a different alcohol chain. To improve the antifungal activity of chitosan derivatives, molecules of varied lengths were used as functional dendrons. All of the derivatives showed great activity against the examed fungi (*P. asparagi* and *C. lagenarium*). The inhibitory indices of six chitosan derivatives **77** were greater than those of unmodified chitosan and quaternary ammonium chitosan **76** at the identical concentration. The results revealed that the triazolyl group linked to the synthesized chitosan derivatives contributed significantly to antifungal action, hence increasing their antifungal activity (Figure 29).

Tan et al. [95] synthesized the 1,2,3-triazolium-functionalized starch derivative, and the efficacy of quaternization of the 1,2,3-triazole section with benzyl bromide on the antifungal screen of the starch derivative was evaluated by looking at the percentage inhibition of mycelial growth. These derivations displayed notable reclaimed antifungal behavior than starch derivative bearing 1,2,3-triazole and starch. Electrostatic and hydrophobic interactions may have a greater antifungal activity tangency than hydrogen bond interactions and higher inhibitory indices of 1,2,3-triazolium-functionalized starch derivatives compared with starch derivative containing 1,2,3-triazole (Figure 30).

A novel group of inulin derivatives with 1,2,3-triazolium-charged parts by associating "click reaction" with impressive 1,2,3-triazole quaternization were synthesized. As shown in Figure 31, the antifungal tests revealed that compounds containing triazolium **80** inhibited the growth of tested phytopathogens more effectively than inulin derivatives, including triazoles **79**. However, 1,2,3-triazolium exhibited a higher cationic charge, which was affected more by the interactions with anionic fragments in the fungal cell wall [96].

Tan et al. [97] suggested a direct synthetic approach to novel starch derivatives with 1,2,3-triazolium- and pyridinium-charged units by linking CuAAC with impressive

alkylation of pyridine and 1,2,3-triazole. Fungicidal activity against three plant-threatening fungi (*Watermelon fusarium*, *Phomopsis asparagi*, and *Colletotrichum lagenarium*) was estimated *in vitro* by hypha measurement. The antifungal activity of synthesized starch derivatives having 1,2,3-triazolium and pyridinium was higher than that of starch derivatives with 1,2,3-triazole and pyridine, implying that the alkylation of 1,2,3-triazole and pyridine was remarkable for raised antifungal activity (Figure 32).

Based on the pioneer starch compounds *N*-alkylated with 1,2,3-triazole and iodomethane, four novel 1,2,3-triazolium-functionalized starch derivatives were synthesized (CuAAC). The antifungal activities of compounds against *Fusarium oxysporum*, *Watermelon fusarium*, and *Colletotrichum lagenarium* were tested *in vitro* by hypha measurement. *C. lagenarium* is the most sensitive pathogenic fungus yeast to the examined compounds. The inhibitory indices of all cases increase with increasing concentration ($P < 0.05$) with 1.0 mg/mL exhibiting the greatest antifungal activity. Following a one-step alkylation with iodomethane, 1,2,3-triazolium-functionalized starch derivatives exhibit massively increased antifungal property with inhibitory indices of up to 60% at 1.0 mg/mL ($P < 0.05$), compared with 1,2,3-triazole-functionalized starch derivatives with inhibitory indices of less than 10% ($P < 0.05$). In general, the length of the alkyl groups was an effective determinant of 1,2,3-triazolium-functionalized starch derivative antifungal activity (Figure 33) [98].

Li et al. [99] investigated three new chitosan derivatives, including 1,2,3-triazole with or without halogen. Their antifungal activity toward three kinds of phytopathogens was evaluated via hyphal mensuration *in vitro*. The inhibitory effects and water solubility of the synthesized chitosan derivatives were significantly superior to chitosan. CTCTS and BTCTS, which include halogens at the polymer's edge, inhibited the development of the examined phytopathogens more impressively, with inhibitory indices ranging from 81 to 93% at 1.0 mg/mL (Figure 34).

2.4.4. 1,2,3-Triazoles-Pyrazole, Imidazole, and Benzimidazole Hybrids.
Among the heterocycles containing nitrogen, imidazole, pyrazole, and triazole have many biological,

Amongst the three examed plant pathogenic fungi, all of the compounds manifested the fairly potent antifungal efficacy against *C. lagenariumbut* but the fairly fragile inhibition towards *F. oxysporum*
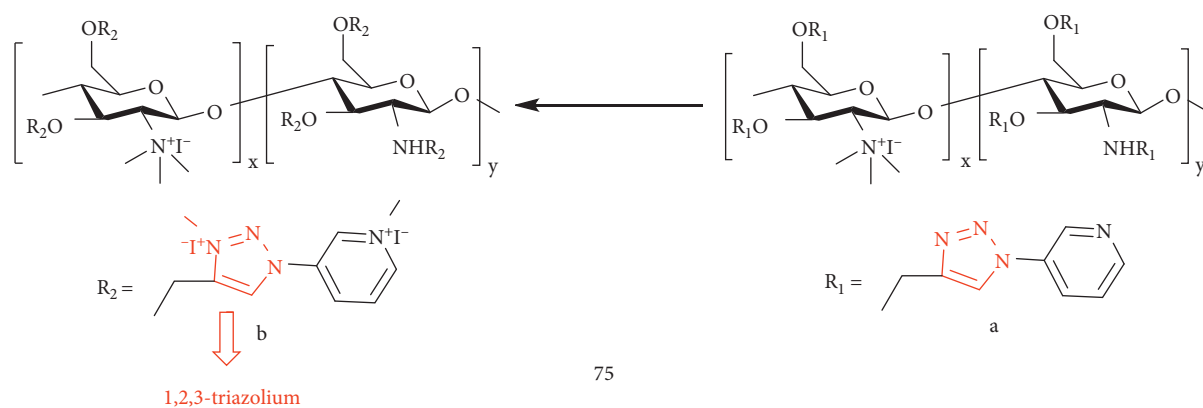

FIGURE 28: Chemical structure of novel cationic chitosan derivations bearing 1,2,3-triazolium and pyridinium.
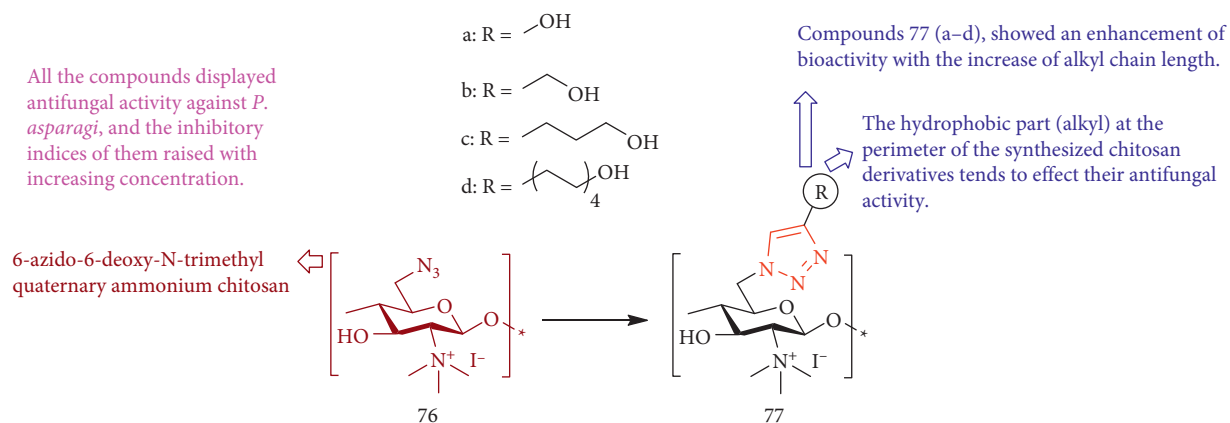

FIGURE 29: Chemical structure of novel triazolyl-functionalized chitosan derivatives with different chain lengths of aliphatic alcohol substituent.
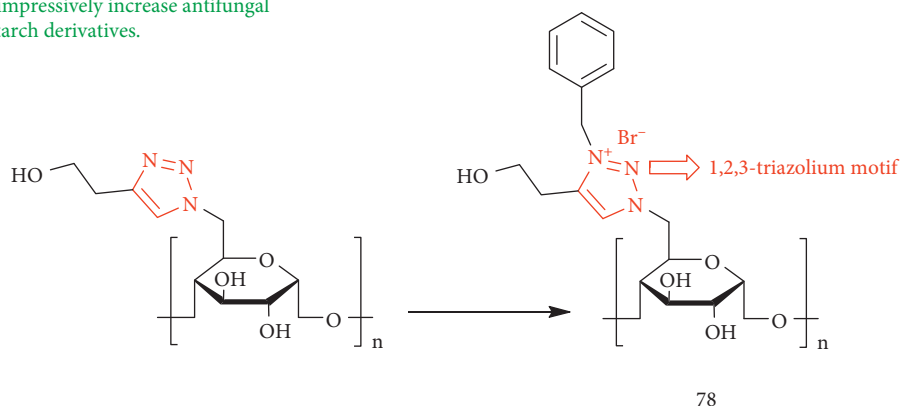
FIGURE 30: Chemical structure of novel 1,2,3-triazolium-functionalized starch derivative.

Inulin derivatives having triazolium 80 showed better inhibitory indices than those of inulin derivatives inclu- ding triazoles 79.

1,2,3-triazolium motif

Inulin derivatives

The 1,2,3-triazolium would be a more impressive anion captor than triazole after quaternarization, that may help fixate the free radicals figure.

79

80
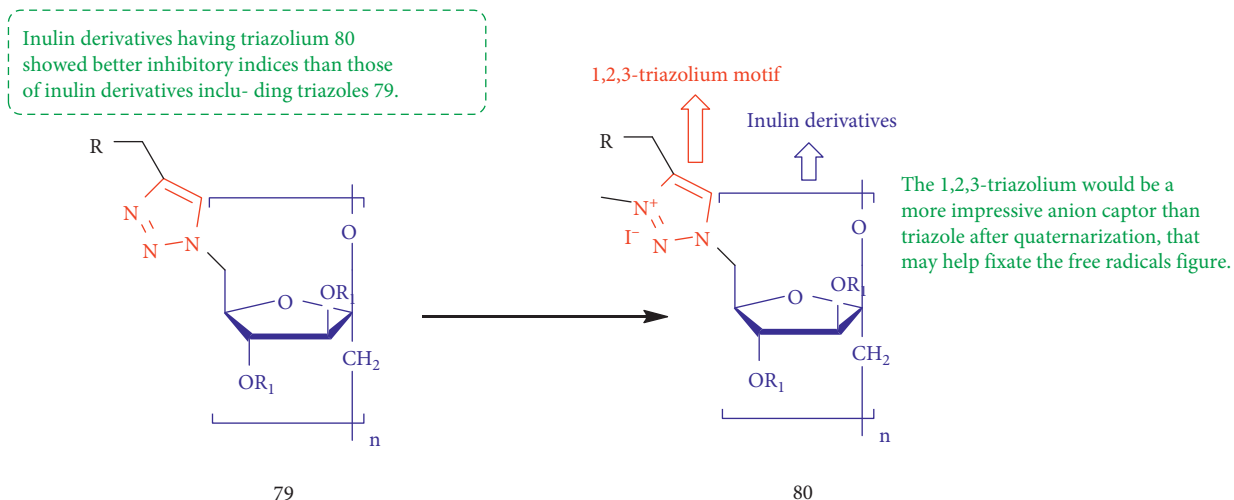
FIGURE 31: Chemical structure of inulin derivatives possessing 1,2,3-triazolium charged units.

The antifungal examination results showed that all the compounds reveal antifungal activity against *P. asparagi*, and the antifungal activity of starch derivatives is concentration-affiliate.

Pyridine moiety

Pyridinium moiety

1,2,3-triazolium motif

Starch

81

Antifungal activity respectively: share of 1,2,3-triazolium and pyridinium groups > share of 1,2,3-triazole and pyridine groups > starch
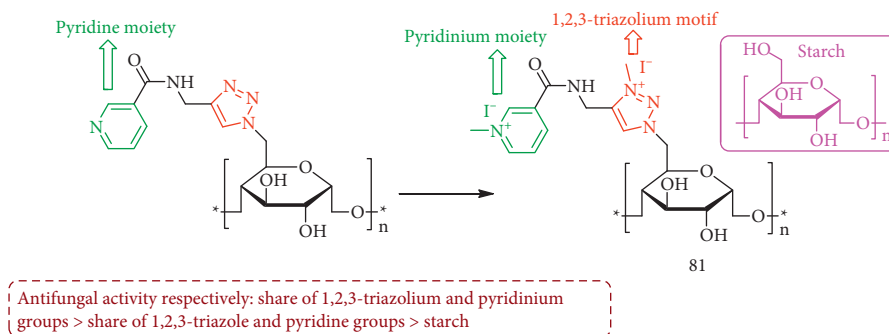
FIGURE 32: Chemical structure of novel starch derivative bearing 1,2,3-triazolium and pyridinium.

The results showed that increasing the length of the alkyl chain on the 1,2,3-triazolium rings reduced the antifungal activity of starch derivatives ($P < 0.05$) against all the fungi strains and the antifungal activity increased respectively: 83a > 83b > 83c > 83d > 82a ~ 82d > starch.

Starch

1,2,3-triazolium motif

82

83

a: R =   OH

b: R =   OH

c: R =   OH

d: R =   OH
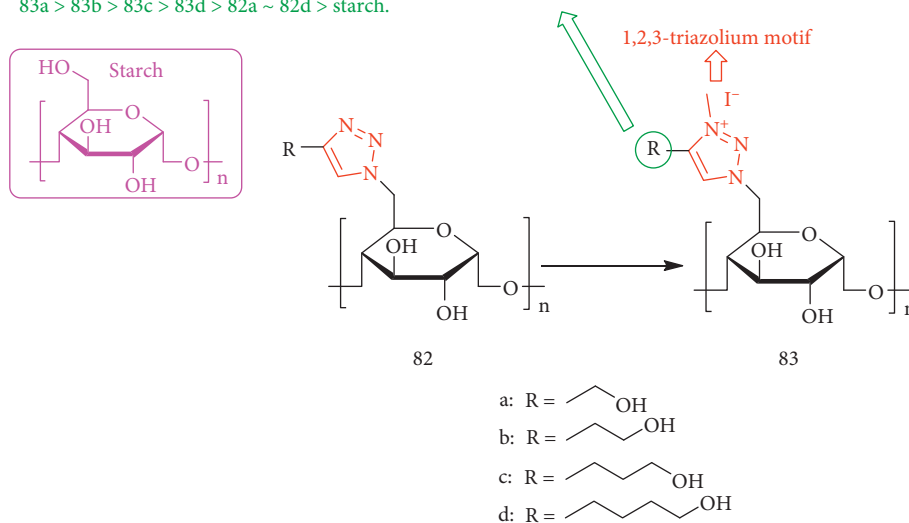
Antifungal activity respectively: 1,2,3-triazolium- functionalized starch derivatives > starch derivatives bearing 1,2,3-triazole > starch

FIGURE 33: Chemical structure of novel 1,2,3-triazolium-functionalized starch derivatives.

This study offeres that the synergistic affect of halogens and triazole will enhance the antifungal activity of chitosan derivatives.
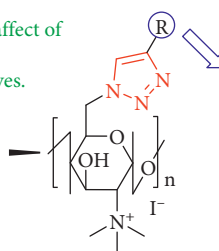
The outcomes showed that the chitosan derivatives with powerful electron-withdrawing valency dis- played greater antifungal activity.

84

CTCTS: R = Cl

BTCTS: R = Br

Figure 34: Chemical structure of water-soluble chitosan derivatives with halogeno-1,2,3-triazole.

agrochemical, chemical, and medicinal characteristics. A set of eighteen imidazole amide-linked 1,2,3-triazole hybrids (Figure 35) were synthesized, and their antifungal activities against *C. albicans* and *A. niger* were examined. The derivative, **85e** (MIC = 0.0064 μmol/ml), was approximately twice active compared to Fluconazole (MIC = 0.0102 μmol/ml) against *A. niger*. Six hybrids **(85a–f)** (MIC = 0.0246–0.0282 μmol/mL) were found to have remarkable influence on *C. albicans*. The research showed that triazole derivatives with OMe and Cl groups at the anilide ring had better antifungal activity than NO$_2$. Among the synthesized compounds, most of the methyl derivatives in the pyrazole ring had higher activity than the **H** analogs. In general, these compounds have been shown to be more effective against *A. niger* than against *Candida albicans* [100].

Nalawade et al. [101] demonstrated the formation of a series of 1-substituted benzyl-4-[1-phenyl-3-(4-methyl-2-aryl-1,3-thiazol-5-yl)-1*H*-pyrazol-4-yl]-1*H*-1,2,3-triazole. Almost most of the compounds showed good-to-high antifungal activity toward *R. glutinis* and *A. niger*. The antifungal activity suggests that these compounds can be preferred for improved optimization and spread, since they have the potential for behaving against fungal infections (Figure 36).

Khare et al. [102] synthesized new 1,2,3-triazolyl pyrano[2,3-c]pyrazole derivatives in high yield using NaHCO$_3$ as a catalyst under ultrasonic irradiation. The observations showed that the antifungal activity was different from the substituent present on an aromatic unit of 1,2,3-triazolyl pyrano[2,3-c]pyrazole. Compound **87e** revealed high antifungal activity, and it was more potent than Miconazole against *C. albicans* with MIC = 12.5 μg/mL; moreover, only this compound displayed equivalent activity against *A. niger* with MIC = 25 μg/mL (Figure 37).

Bhat et al. [103] explained the synthesis of a new sequence of 1,2,3-triazolyl pyrazole derivatives, as well as antifungal investigations on the synthesized compounds against *A. flavus*, *C. keratinophilum*, and *C. albicans*. When compared to other fungal species, *C. albicans* was the most vulnerable. *A. flavus* and *C. keratinophilum* responded differently to each organic compound. Compounds **88a** and **88b** exhibited significant activity compared to the reference

drug Fluconazole. The SAR also revealed the existence of multi-electron-withdrawing, liphophilic, and electronegative groups on phenyl rings, such as fluorine, chlorine, nitro, and trifluoromethyl, and electron-donating groups like quinyl and phthalazinyl, which may be more useful than the less substituted or unsubstituted groups on phenyl rings (Figure 38).

Sindhu et al. [104] reported a new molecule sequence of pyridinone, 1,2,3-triazoles, and pyrazole. Two yeast strains, *Saccharomyces cerevisiae* and *Candida albicans*, were studied *in vitro* for fungicidal activity. As it is shown in Figure 39, all compounds had excellent antifungal activity, with MICs ranging from 64 to 256 μg/mL for *C. albicans* and from 64 to 256 μg/mL for *S. cerevisiae*. Compounds **89b** and **89a** displayed MIC values of 64 μg/mL against *S. cerevisiae*, which were lower than the reference Amphotericin B (APT-B).

Dubovis et al. [105] designed and developed a novel and fundamental method for synthesizing 1-(1*H*-imidazole-4-yl)-1*H*-1,2,3-triazoles. As shown in Figure 40, antifungal screening of these compounds on a variety of phytopathogenic fungus has been explored. A significant alteration of the triazole ring of the halogen-substituted aromatic remainders displayed an enhancement of fungicidal activity in the final compounds. Compound **90a** was substantially more active than its nonsubstituted or alkyl-substituted counterparts.

Seven miconazole analogs, including 1,4,5-tri and 1,5-disubstituted triazole moieties, were developed and synthesized by azide-enolate 1,3-dipolar cycloaddition. The antifungal properties of these compounds were screened *in vitro* for three different *Candida* spp. as yeast samples and four penicillate fungi: *Rhizopus oryzae*, *Mucor hiemalis*, *Trichosporon cutaneum*, and *Aspergillus fumigatus*. Compound **91b** was shown to be better than or equivalent to Itraconazole in its antifungal activity against the filamentous fungi *R. oryzae*, *M. hiemalis*, and *T. cutaneum*. When compared to the reference drug (MIC = 0.25 g/mL), compound **91c** inhibited *A. fumigatus* growth only little (MIC 0.5 μg/mL) (Figure 41) [106].

Rezki [107] described the synthesis and antimicrobial evaluation of new polyheterocyclic molecules based on the benzimidazole core of 1,2,3-triazole and 1,2,4-triazoles. As shown in Figure 42, triazoles **92a–c** gave the most potent
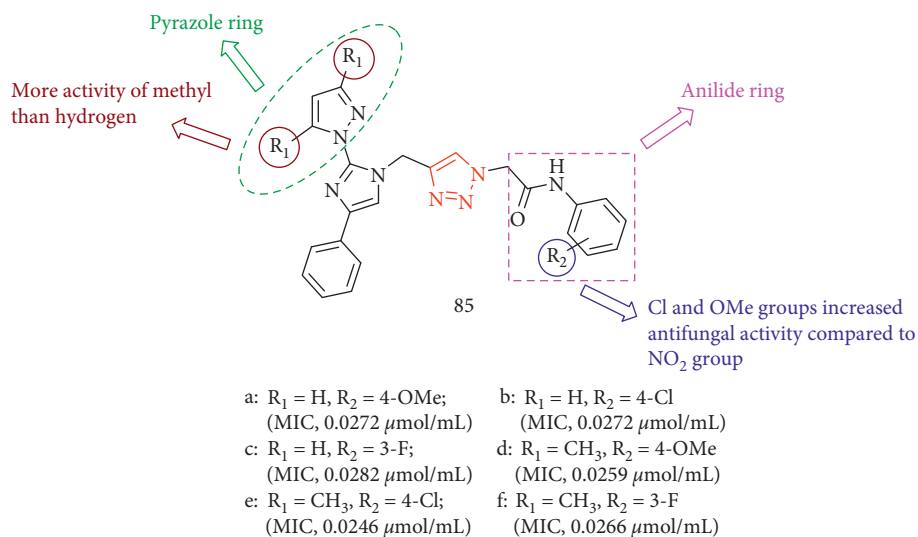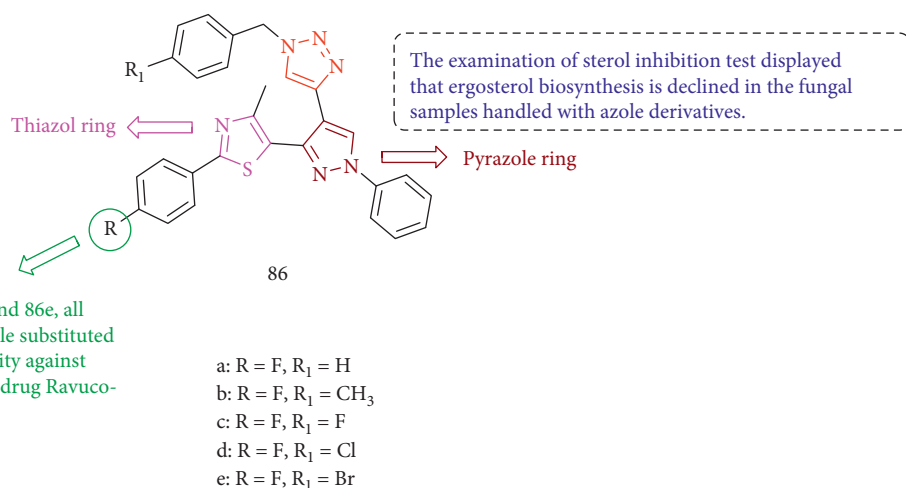
a: R_1 = H, R_2 = 4-OMe;   b: R_1 = H, R_2 = 4-Cl
   (MIC, 0.0272 μmol/mL)   (MIC, 0.0272 μmol/mL)
c: R_1 = H, R_2 = 3-F;   d: R_1 = CH_3, R_2 = 4-OMe
   (MIC, 0.0282 μmol/mL)   (MIC, 0.0259 μmol/mL)
e: R_1 = CH_3, R_2 = 4-Cl;   f: R_1 = CH_3, R_2 = 3-F
   (MIC, 0.0246 μmol/mL)   (MIC, 0.0266 μmol/mL)

FIGURE 35: Chemical structure of pyrazole-imidazole-triazole hybrids.

a: R = F, R_1 = H
b: R = F, R_1 = CH_3
c: R = F, R_1 = F
d: R = F, R_1 = Cl
e: R = F, R_1 = Br

FIGURE 36: Chemical structure of new thiazolyl-pyrazolyl-1,2,3-triazole derivatives.

a: 4-OMe;   d: 4-Cl
b: 3-OMe;   e: 3-NO_2
c: 2-OMe;
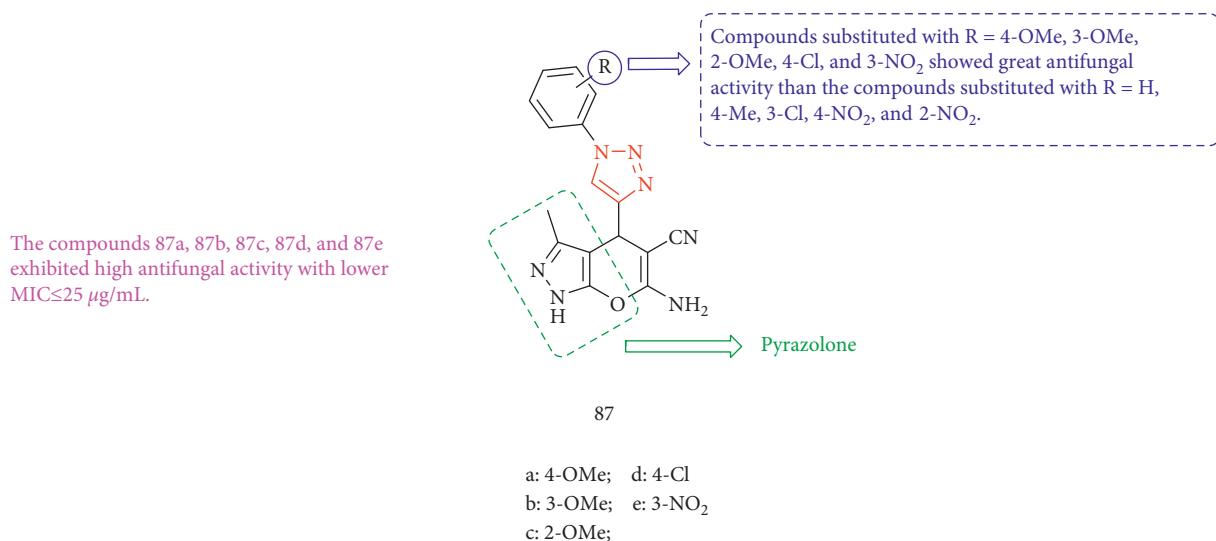
FIGURE 37: Chemical structure of new 1,2,3-triazolyl pyrano[2,3-c]pyrazole derivatives.

Compounds 88a and 88b bearing 4-chloro phenyl and 2,4-dinitro phenyl substituents in the 2nd situation of the pyrazole ring, respectively, were showed to be more powerful antifungal agents than the other compounds.

88

a: R_1, R_2 = H; Ar = 4-Cl-phenyl
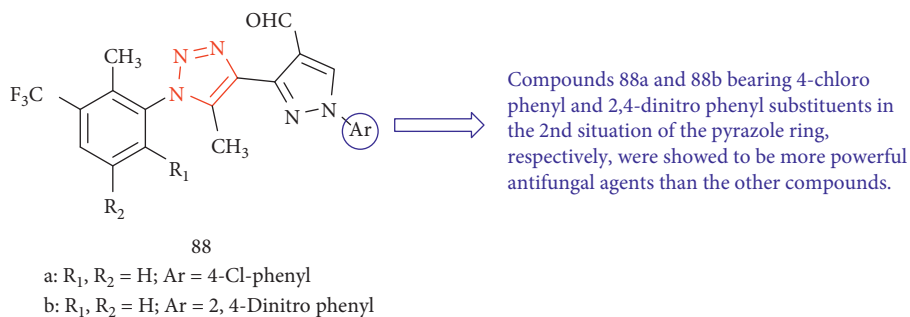b: R_1, R_2 = H; Ar = 2, 4-Dinitro phenyl

FIGURE 38: Chemical structure of new 1,2,3-triazolyl pyrazole derivatives.

Compound 89a exhibited greatest activity against *C. albicans* with MIC value of 64 μg/mL and Also was most active against *S. cerevisiae* with MIC value of 64 μg/mL

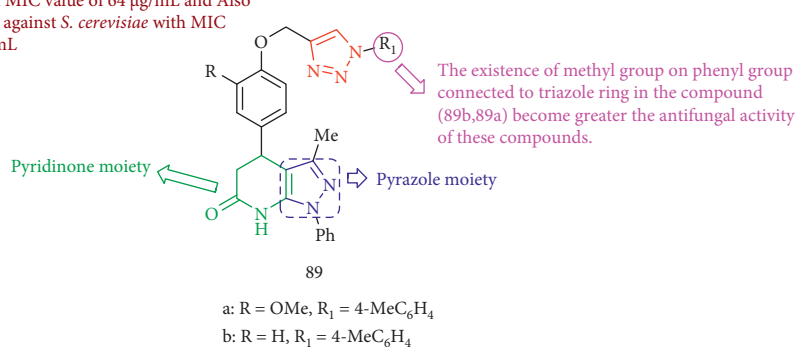The existence of methyl group on phenyl group connected to triazole ring in the compound (89b,89a) become greater the antifungal activity of these compounds.

Pyridinone moiety

Pyrazole moiety

89

a: R = OMe, R_1 = 4-MeC$_6$H$_4$
b: R = H, R_1 = 4-MeC$_6$H$_4$

FIGURE 39: Chemical structure of some functionalized 1H-1,2,3-triazole tethered pyrazolo[3,4-b]pyridin-6(7H)-ones.

The presentation of OCH$_3$ group in phenyl ring decreased the fungicidal activity of compound 90b.
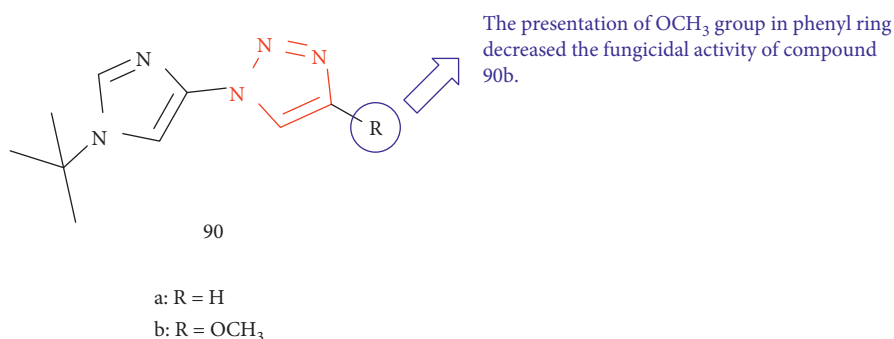

90

a: R = H
b: R = OCH$_3$

FIGURE 40: Chemical structure of substituted 1-(1H-imidazole-4-yl)-1H-1,2,3-triazoles.

Compounds 91a, 91b and 91c displayed good activity against *C. albicans* and *C. tropicalis* (MIC 0.03 - 0.06 μg/mL) as compared to standard drug (Itraconazole, MIC 0.03 μg/mL).

1-(2-Azido-2-(2,4-dichlorophenyl) ethyl)-1H-imidazole

Results indicate that an alkyl group in the 5-substituted triazole raised the biological activity of this type of compound.

91

a: R_1 = Ph, R_2 = COPh
b: R_1 = CH$_3$(CH$_2$)$_4$-, R_2 = SO2Ph
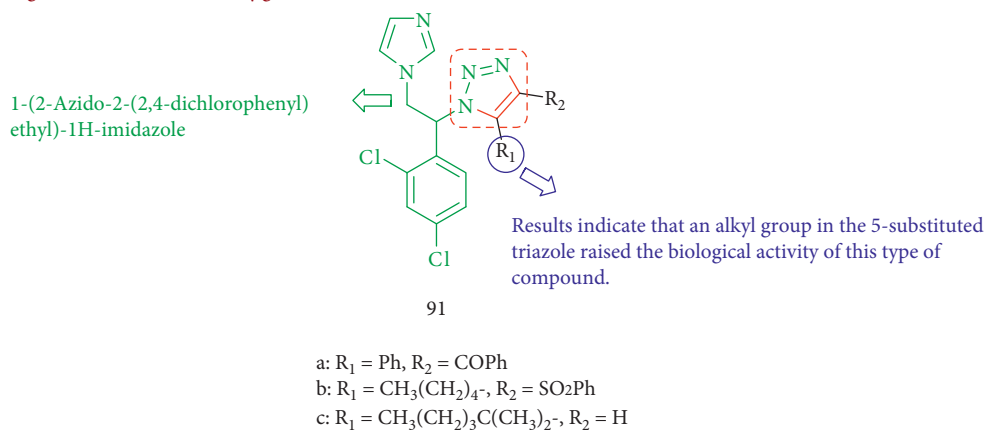c: R_1 = CH$_3$(CH$_2$)$_3$C(CH$_3$)$_2$-, R_2 = H

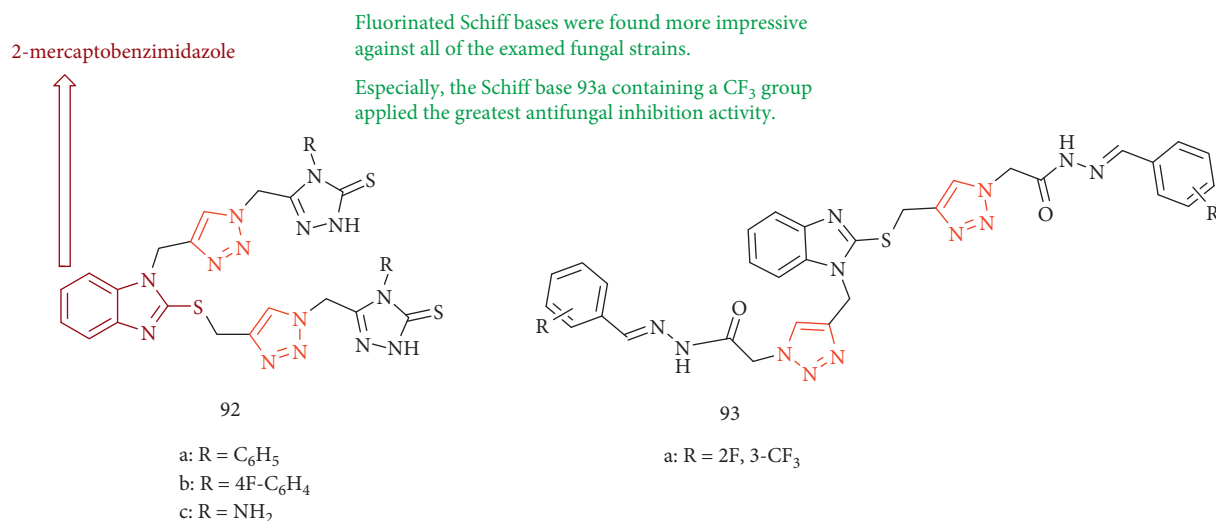FIGURE 41: Chemical structure of novel triazole-based miconazole analogs.

FIGURE 42: Chemical structure of new polyheterocyclic molecules by clubbing the benzimidazole reliance.

inhibition toward all of the tested fungal strains that were more powerful than the standard drug Fluconazole.

2.4.5. 1,2,3-Triazole Core with 1,2,4-Triazoles.

The click reaction of aromatic azides with various benzo-fused *N*-heteroaromatic alkynes resulted in the synthesis of 1,4-di-substituted 1,2,3-triazoles with benzo-fused *N*-hetero-aromatic scaffolds. As it is shown in Figure 43, all of the synthesized compounds were screened for antifungal behavior toward two fungi (*Aspergillus niger* and *Candida albicans*). All of the compounds revealed modest-to-good antifungal activity toward the examined fungal strains. Compounds **95a** (MIC = 2.15 μmol/cm$^3 \times 10^{-2}$), **95b** (MIC = 2.05 μmol/cm$^3 \times 10^{-2}$), and **96b** (MIC = 1.63 μmol/cm$^3 \times 10^{-2}$) displayed nearly twofold antifungal activity against *A. niger* as compared to the reference drug. Some of the compounds, like **95b** (MIC = 2.05 μmol/cm$^3 \times 10^{-2}$) and **96a** (MIC = 1.77 μmol/cm$^3 \times 10^{-2}$), showed antifungal effect comparable to standard drug against *C. albicans* [108].

2.4.6. 1,2,3-Triazloe-Indole and Oxindole Hybrids.

Xu et al. [109] explored a class of new 1,4-disubstituted 1,2,3-triazoles with an indole ring using CuCl$_2$/Zn-catalyzed Huisgen cycloaddition. The fungicidal activities of all the collected compounds against *cotton physalospora* pathogens *(CPP)* and *Colletotrichum capsici* pathogens *(CCP)* were evaluated, and the results displayed that these compounds, mainly **99a** and **99f**, exhibited remarkable inhibitory effects for fungi. Compounds revealed greater activity toward *CCP* than toward *CPP* (Figure 44).

Soltani Rad et al. [110] described a new class of fungicidal compounds known as 1,2,3-triazolyl β-hydroxy alkyl/carbazole hybrid molecules. The 'Click' Huisgen cycloaddition reaction was carried out in the present of copper-doped silica cuprous sulfate. Compound **101a** demonstrated strong antifungal activity against all fungal studies (*Candida albicans* (*ATCC 10231*), *Aspergillus niger* (*ATCC 16404*), *Candida krusei* (*ATCC 6258*), and *Trichophyton rubrum*

(*PTCC5143*)) compared with Fluconazole and Clotrimazole as standard drugs. From the SAR viewpoint, since all of the studied compounds differ only in side chains, the differences in antifungal activity are ascribed to these changes (Figure 45).

Huo et al. [111] reported two series of new aryl-1,2,3-triazole-β-carboline hybrids, and their antifungal activities were appraised *in vitro* against phytopathogenic species containing *Fusarium oxysporum*, *R. solani*, *Botrytis cinerea* Pers., sunflower sclerotinia rot, and rape sclerotinia rot using a 50 μg/mL mycelia growth inhibition test. *In vitro*, none of the target compounds displayed antifungal activity, with an inhibition rate of less than 20% against *F. oxysporum* (Figure 46).

5-Fluoroindoline-2,3-dione-1-aryl-1*H*-triazole-4-yl methyl hybrid molecules were synthesized in aqueous conditions using a well-known CuAAC reaction applying Cell-CuI-NPs as a novel heterogeneous catalyst [112]. All synthesized compounds were analyzed against two fungal pathogens of *Candida Albicans* and *Aspergillus niger* and then Fluconazole (MIC = 0.0051–0.0102 μmol/mL) drug was applied. All synthesized compounds showed moderate-to-high antifungal activity (Figure 47).

Sakly et al. [113] investigated a wide range of novel functionalized spirooxindole-pyrrolidine and spirooxindole-pyrrolizidine-connected 1,2,3-triazole conjugates. The compounds were examined *in vitro* for antifungal and antibacterial activity using the agar dilution procedure and showed appropriate activity. Compounds **106a** and **107a** were similarly potent against *C. albicans* as griseofulvin (Figure 48).

Aouad [114] reported the discovery of new isatin-1,2,3-triazoles attached by morpholines, piperazines, or piperidines through a methylene or acetyl linkage and tested for antifungal activity against a panel of pathogenic fungal strains. Antimicrobial activity ensured the association of the action on the nature of the cyclic secondary amine added to the 1,2,3-triazole ring. The isatin-1,2,3-triazole hybrids including a piperazine unit were found to be the most active of
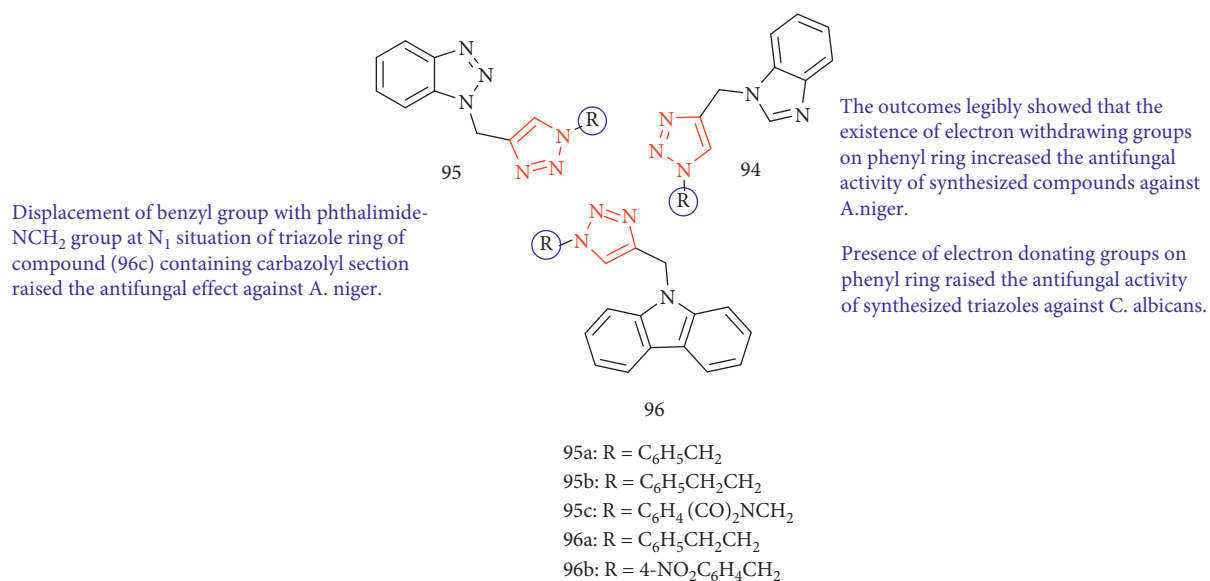
The outcomes legibly showed that the existence of electron withdrawing groups on phenyl ring increased the antifungal activity of synthesized compounds against A.niger.

Presence of electron donating groups on phenyl ring raised the antifungal activity of synthesized triazoles against C. albicans.

Displacement of benzyl group with phthalimide-NCH$_2$ group at N$_1$ situation of triazole ring of compound (96c) containing carbazolyl section raised the antifungal effect against A. niger.

95a: R = C$_6$H$_5$CH$_2$
95b: R = C$_6$H$_5$CH$_2$CH$_2$
95c: R = C$_6$H$_4$(CO)$_2$NCH$_2$
96a: R = C$_6$H$_5$CH$_2$CH$_2$
96b: R = 4-NO$_2$C$_6$H$_4$CH$_2$

FIGURE 43: Chemical structure of 1,4-disubstituted 1,2,3-triazoles containing benzo-fused N-heteroaromatic moieties.
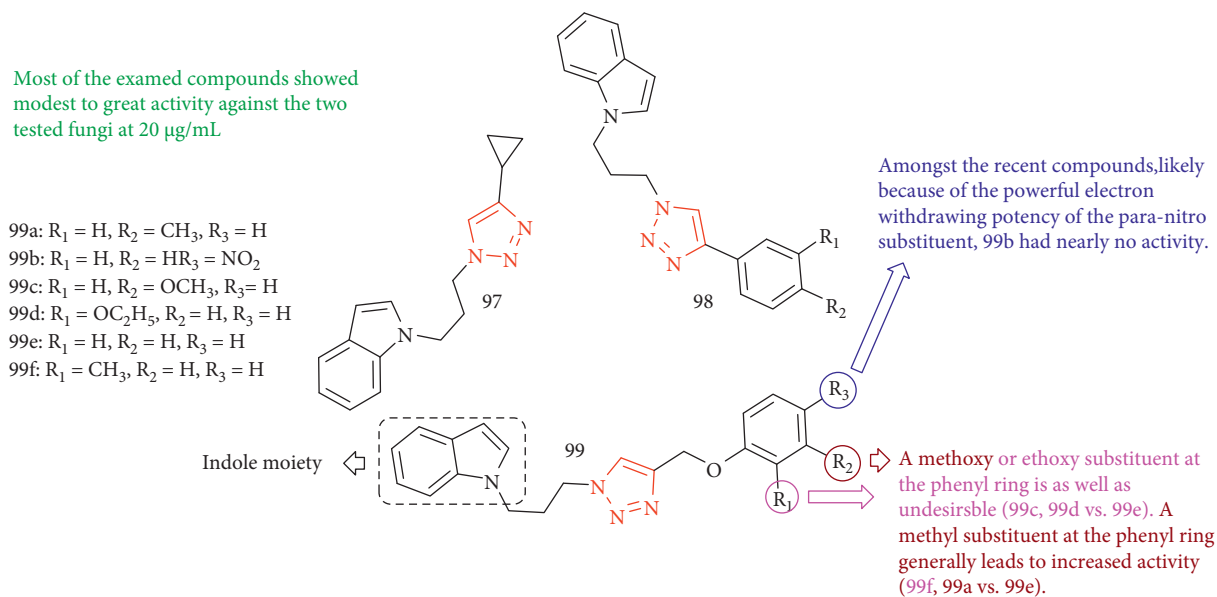

Most of the examed compounds showed modest to great activity against the two tested fungi at 20 μg/mL

Amongst the recent compounds,likely because of the powerful electron withdrawing potency of the para-nitro substituent, 99b had nearly no activity.

99a: R$_1$ = H, R$_2$ = CH$_3$, R$_3$ = H
99b: R$_1$ = H, R$_2$ = HR$_3$ = NO$_2$
99c: R$_1$ = H, R$_2$ = OCH$_3$, R$_3$= H
99d: R$_1$ = OC$_2$H$_5$, R$_2$ = H, R$_3$ = H
99e: R$_1$ = H, R$_2$ = H, R$_3$ = H
99f: R$_1$ = CH$_3$, R$_2$ = H, R$_3$ = H

Indole moiety

A methoxy or ethoxy substituent at the phenyl ring is as well as undesirsble (99c, 99d vs. 99e). A methyl substituent at the phenyl ring generally leads to increased activity (99f, 99a vs. 99e).

FIGURE 44: Chemical structure of novel 1,4-disubstituted 1,2,3-triazoles containing indole framework.

101a was the strongest compound against all examed fungal pathogens.

The attendence of aliphatic side chains displayed more adequate result in comparison with aryl sections even bearing various substituents.

Except that of C. Krusei, 101b showed same reactivity to 101a against all examed fungal strains.

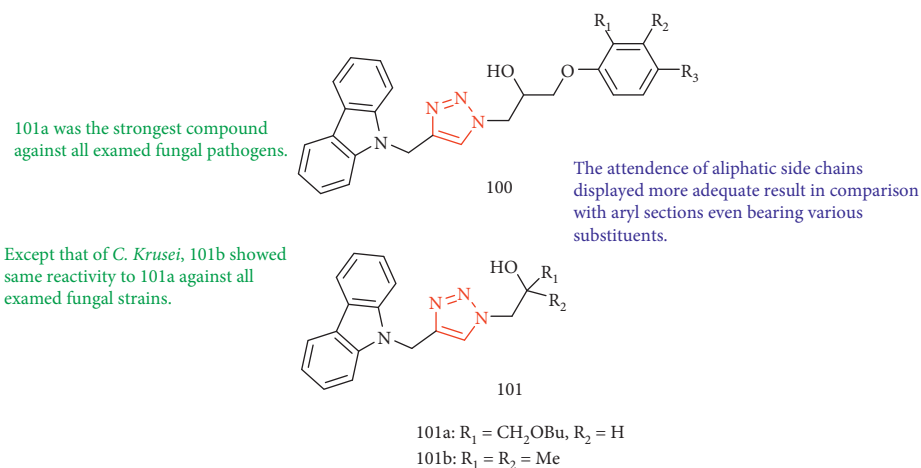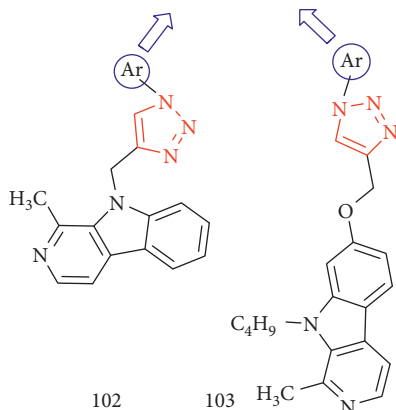101a: R$_1$ = CH$_2$OBu, R$_2$ = H
101b: R$_1$ = R$_2$ = Me

FIGURE 45: Chemical structure of novel 1,2,3-triazolyl β-hydroxy alkyl/carbazole hybrid molecules.

The compounds (102a), (102b), (102c), and (103a) displayed reasonable antifungal activity against sunflower sclerotinia rot.
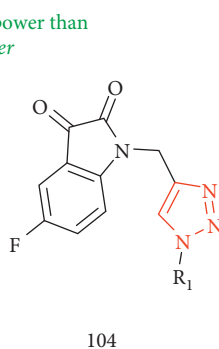
In total, compound (103a) also showed great broad-spectrum fungicidal activity against all the examed fungi.

102

103

102a: Ar = phenyl; 102c: Ar = 3, 4, 5-trifluorophenyl
102b: Ar = 4-trifluoromethylphenyl; 103a: Ar = 3, 4, 5-trifluorophenyl

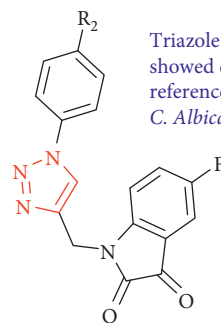FIGURE 46: Chemical structure of two series of new aryl-1,2,3-triazole-β-carboline hybrids.

104a, 104b and 105a exhibited higher power than antifungal drug Fluconazole for *A. Niger*

Presence of the 1,2,3-triazole moiety showed more activity than the intermediate

Triazole hybrids 104a, 104b and 104c showed comparable activity to the reference drug Fluconazole in the case of *C. Albicans*

104

105

104a: R$_1$ = 3-BrC$_6$H$_4$CH$_2$ (MIC, 0/0075 μmol/mL)
104b: R$_1$ = 4-NO$_2$C$_6$H$_4$CH$_2$ (MIC, 0/0082 μmol/mL)
104c: R$_1$ = 2-CH$_3$C$_6$H$_4$CH$_2$ (MIC, 0/0090 μmol/mL)

105a: R$_2$ = 4-F (MIC, 0/0092 μmol/mL)

FIGURE 47: Chemical structure of 5-fluoroindoline-2,3-dione-triazoles derivatives.

the examined compounds (**108a–c**). Compounds with a piperazine moiety (**109a–c**) displayed the biggest antifungal inhibition activity (Figure 49).

Shaikh et al. [115] described novel triazole-based isatin derivatives that were evaluated for biological activity using click chemistry. The 1,2,3-triazole-based isatin compounds showed good-to-moderate activity against all five human pathogenic fungal strains tested. The activity of **110b** and **110c** with chloro-group at *meta* and *ortho* situations in the phenyl ring displayed strong activity as compared with the standard drug against *Fusarium oxysporum*. Compound **110a** with nitro-group at *para* position in the phenyl ring displayed equal activity against the fungicidal strain *Candida albicans* as compared with the reference medicine Miconazole (Figure 50).

2.4.7. 1,2,3-Triazole-Quinoline Hybrids.
Nesaragi et al. [116] described a new sequence of quinolin-3-yl-methyl-1,2,3-triazolyl-1,2,4-triazol-3(4*H*)-ones synthesized via click

chemistry as a final tactic in which azides with final alkynes were tested for antifungal properties against four various pathogenic fungi (*C. albicans*, *A. flavus*, *A. fumigatus*, and *A. niger*). Fluconazole was employed as a standard drug. The antifungal results of synthesized derivatives announced favorable activity. According to the *in silico* and *in vitro* studies, these additional quinolines triazoles may acquire the arbitrary structural prerequisites for secondary synthesis of novel restorative components (Figure 51).

Shaikh et al. [117] investigated the biological activity of tetrazoloquinoline derivatives based on 1,4-disubstituted 1,2,3-triazole (Figure 52). All of the synthesized 1,4-disubstituted 1,2,3-triazole-based tetrazoloquinoline derivatives displayed good-to-moderate activity toward *C. albicans*, *P. chrysogenum*, *C. lunata*, *A. niger*, *A. flavus*, and *C. neoformans* strains. Compounds **113a–c** revealed four times the activity against *C. albicans* strain compared to the standard medicine Miconazole and Amphotericin B and twice the activity compared to Fluconazole.
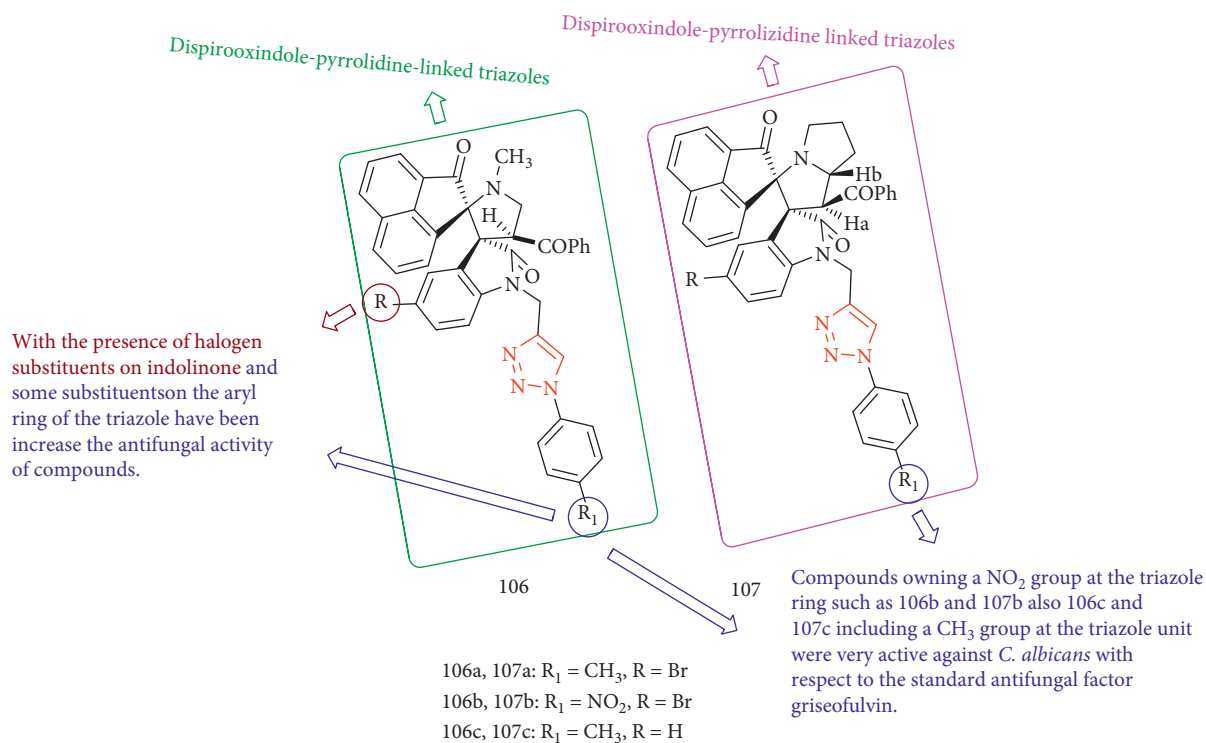
Dispirooxindole-pyrrolidine-linked triazoles

Dispirooxindole-pyrrolizidine linked triazoles

With the presence of halogen substituents on indolinone and some substituentson the aryl ring of the triazole have been increase the antifungal activity of compounds.

Compounds owning a NO$_2$ group at the triazole ring such as 106b and 107b also 106c and 107c including a CH$_3$ group at the triazole unit were very active against *C. albicans* with respect to the standard antifungal factor griseofulvin.

106a, 107a: R$_1$ = CH$_3$, R = Br
106b, 107b: R$_1$ = NO$_2$, R = Br
106c, 107c: R$_1$ = CH$_3$, R = H

FIGURE 48: Chemical structure of novel spirooxindole-pyrrolidine/pyrrolizidine-linked 1,2,3-triazole conjugates.

The existence of the acetyl group among the indole and the 1,2,3-triazole moieties plays a notable role in increasing antifungal activity.

Propargylated isatin moiety

1-(2-Azidoacetyl)Indoline-2,3-Dione moiety

Piperazine moiety

108

a: —N◯ = —N⬠N—CH$_3$

b: —N◯ = —N⬠N

c: —N◯ = —N⬠N
           |
           CH$_3$

109

a: —N◯ = —N⬠N—CH$_3$

b: —N◯ = —N⬠N

c: —N◯ = —N⬠N
           |
           H$_3$C
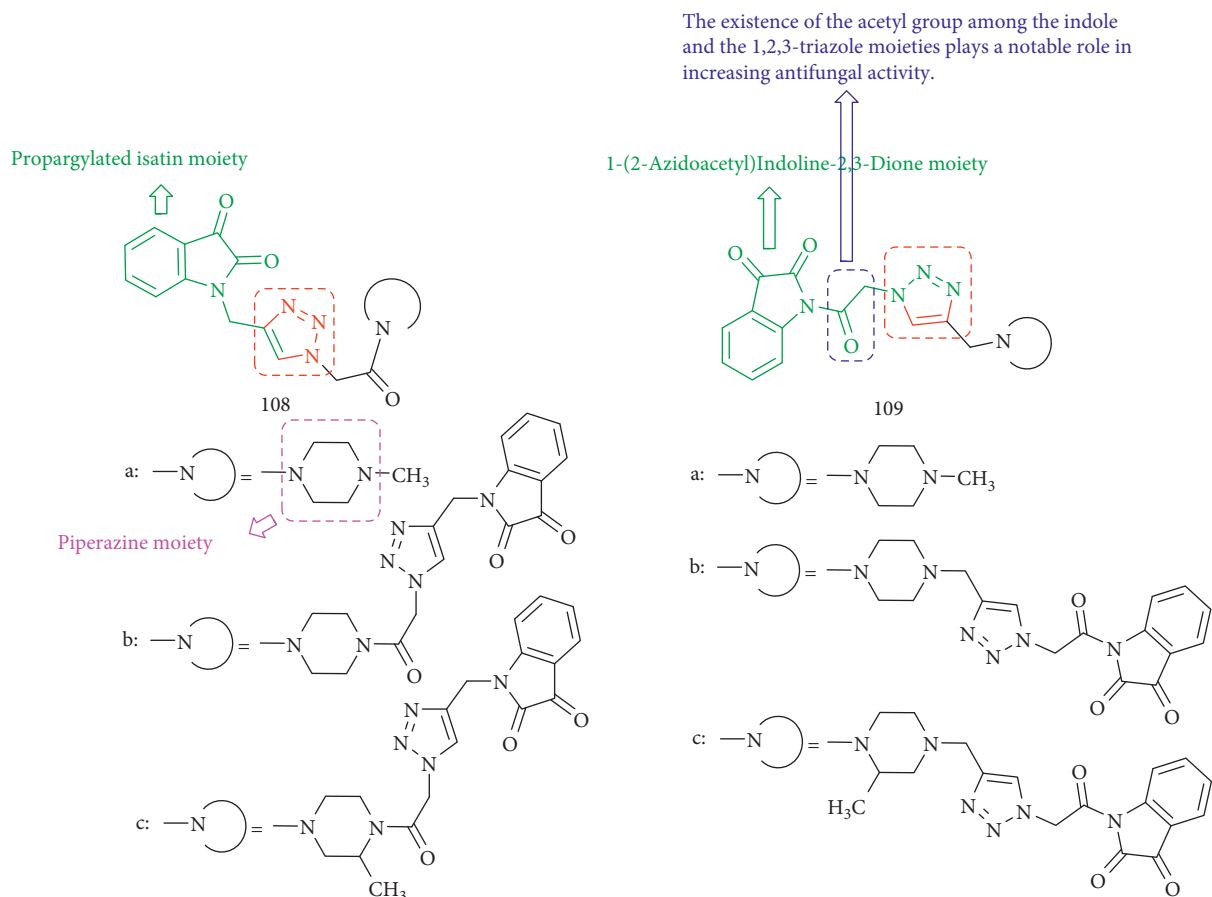
FIGURE 49: Chemical structure of novel isatin-1,2,3-triazoles with piperidine, morpholine, or piperazine moieties.

Compounds 110a for *Aspergillus flavus*, with nitro- group at para, 110b with chloro- group at meta, and 110e with fluoro- group at para position of phenyl ring displayed comparable activity as compared with reference drug.

Aafter presentation of 1,2,3-triazole ring on isatin, it gave notable antifungal property.

Compounds 110d and 111a containing nitro- substituentat meta situation of phenyl ring displayed favorable activity as compared with the Miconazole.
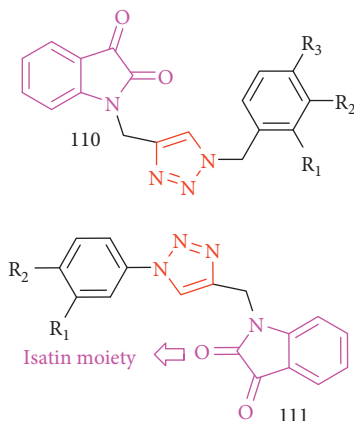
110a: R_1 = H, R_2 = H, R_3 = NO_2
110b: R_1 = H, R_2 = Cl, R_3 = H
110c: R_1 = Cl, R_2 = H, R_3 = H
110d: R_1 = H, R_2 = NO_2, R_3 = H
110e: R_1 = H, R_2 = H, R_3 = F
111a: R_1 = NO_2, R_2 = H

FIGURE 50: Chemical structure of novel triazole-incorporated isatin derivatives as antifungal agents.

The antifungal outcomes disclosed that all the compounds have showed great activity against the examed fungal strains.
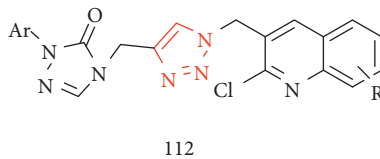
a: Ar = C_6H_5, R = H
b: Ar = C_6H_5, R = 6-Br
c: Ar = C_6H_5, R = 6-CH_3
d: Ar = 4-H_3CO-C_6H_4, R = H

FIGURE 51: The chemical structure of quinoline-appended triazoles as potent antitubercular and antifungal agents.

The starting material 4-(azidomethyl)-8-methoxytetrazolo[1,5-a]quinoline showed very smaller antifungal activity

The 1,2,3-triazoles obtioned from the azide, displayed great antifungal activity compared to three standard antifungal drugs Miconazole, Amphotericin B and Fluconazole.
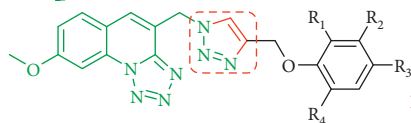
In total, all the synthesized compounds showed great antifungal activity against *C. albicans* and *A. niger*.

a: R_1 = H, R_2 = H, R_3 = Cl, R_4 = H
b: R_1 = H, R_2 = CH_3, R_3 = Cl, R_4 = H
c: R_1 = Cl, R_2 = H, R_3 = Cl, R_4 = Cl
113a, 113b, 113c (MIC, 4 μmol/mL)

FIGURE 52: Chemical structure of tetrazoloquinoline-1,2,3-triazole derivatives.

Irfan et al. [118] reported the synthesis of 1,2,3-triazole derivatives that were evaluated on three various fungal strains, *C. glabrata* ATCC 90030, *Candida tropicalis* ATCC 750, and *Candida albicans* ATCC 90028, and the findings were compared with the reference drug (Fluconazole). The results of anticandidal activity were obtained from three various *Candida* strains. They showed that compound **114a** outperformed Fluconazole with IC_{50} values of 12.022 μg/mL against *Candida glabrata*, 0.044 μg/mL against *Candida albicans*, and 3.60 μg/mL against *Candida tropicalis*. Also, compounds **114a** and **114b** exhibited <5% hemolysis at their IC_{50} values, demonstrating the nontoxic treatment of these inhibitors (Figure 53).

2.4.8. bis-Triazole Derivatives. Novel series of bis-1,2,3- and 1,2,4-triazoles as potential antimicrobial agents were synthesized by Bitla et al. [119] also, and all of them screened for their antifungal effect against *Saccharomyces cerevisiae* and *Aspergillus niger*. The majority of the synthesized compounds displayed favorable antifungal activity with the zone of inhibition (1.5–8.2 mm). The studies showed that **(115a–d)** compounds displayed an impressive antifungal effect among all the other synthesized compounds (Figure 54).

The click reaction catalyzed by Cu(I) used a class of 1,2,3-triazole containing oxime products under both conventional and microwave irradiation conditions. The compounds were evaluated against two fungi (*Aspergillus flavus* and *Aspergillus niger*) using Nystatin as a standard medicine. Compounds **116a** and **116b** showed a better zone of inhibition, whereas compounds **116c–f** exhibited a similar zone of inhibition comparable to the standard drug against the tested fungal strains (Figure 55) [120].

A new class of 1,3-bis-(1,2,3-triazole-1-yl)-propan-2-ol derivatives were synthesized using various alkynes and 1-aryl-1,3-diazidopropan-2-ol derivatives, with the critical step including click reaction. When compared to Itraconazole and Fluconazole (MIC = 2.56 and 1.28 μg/mL, respectively), almost all of the synthesized compounds displayed great activity against *Candida* spp. strains in 0.04–0.5 μg/mL concentration ranges. The effect of cyclopropyl groups and fluorine atom in molecule **117a** suggested a great selectivity in this compound to inhibit these type of *Candida* strains (Figure 56) [121].

A new class of 1,2,4-triazole thione derivatives including substituted piperazine portions and 1,2,3-triazole were described by Wang et al. [122]. The results of the bioassay showed that several compounds have significant fungicidal activity toward a variety of plant fungi at 50 μg/mL. In most cases, trifluoromethyl-including triazole thione derivatives displayed desirable fungicidal activities that could be due to the great effects (like hydrophobicity and permeability) of the trifluoromethyl group reported on the parent structure (Figure 57).

Pertino et al. [123] synthesized 24 novel triazole derivatives from the abietane diterpenes carnosic acid and carnosol through using click chemistry. The length of the linker and the substituent on the triazole portion differed among compounds. The compounds varied in the length of the linker and the substituent on the triazole section. Antifungal activity was determined against *Cryptococcus neoformans* (ATCC 32264) and *Candida albicans* (ATCC 10231). In terms of antifungal action, *C. neoformans* was the most susceptible fungus, with some compounds inhibiting more than 50% of its fungal growth at doses as low as concentrations ≤250 μg/mL. Compound **123b** containing a *p*-Br-benzyl substituent on the triazole ring had the best activity (91% growth inhibition) at 250 μg/mL. In turn, six compounds prevented 50% *C. albicans* growth at concentrations further ess than 250 μg/mL. When comparing **122a** and **122b** with **122c** and **122d** (R_1: *p*-bromobenzyl), the existence of a Br in the aromatic ring did not shift the activity until the length of the linker was three CH_2 units; however, it decreased when the linker possessed two CH_2 units. Comparing the activities of **122a** and **122b** with those of **122e** and **122f**, introducing a nitro group in the aromatic ring (R_1: *p*-nitrobenzyl), the activity of the nitro compounds is lower (Figure 58).

2.4.9. 1,2,3-Triazole Linked to Other Heterocyclic Pharmacophores. As it is shown in Figure 59, a series of novel derivatives of 1-(4-methyl-2-aryl-1,3-thiazole-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl) ethanol were synthesized and their antifungal properties screened *in vitro* against *Candida albicans*, *Aspergillus niger*, *Rhodotorula glutinis*, and *Penicillium chrysogenum*. Most of the compounds have moderate-to-good antifungal activity against *A. niger* in comparison to the standard medicine Ravuconazole [124].

Thotla et al. [125] synthesized a new series of Benzo[*b*]thiophene triazoles with high yields from various azides with propargyl derivatives of benzothiophene, and most of them displayed significant antifungal activity against the fungi tested (*Sclerotium rolfsii* and *Aspergillus niger*) (Figure 60).

Costa et al. [126] explained a new route for synthesizing a series of glycerol-derived 4-alkyl-substituted 1,2,3-triazoles using glycerol as the starting substance. *Colletotrichum gloeosporioides*, a causal factor of papaya anthracnose, were tested for fungicidal activity. All compounds inhibited mycelial development less effectively than the positive control Tebuconazole. Compounds **126a** and **126b** were the most active (ED50 values below 20 ppm), with **126b** exhibiting the widest power (ED50 10.14 ppm) (Figure 61).

Seventeen new benzoxazole derivatives, containing a 1,2,3-triazole scaffold, were generated in order to discover contemporary bioactive compounds with outstanding antifungal properties. The antifungal activities of the synthesized compounds were screened toward *Fusarium verticillium* (FV) and *Botrytis cinerea* (BC), with hymexazol serving as a positive control. The results of the tests showed that compounds **127a–d** had good inhibitory effects on fungus. In these compounds, when the benzotriazole and benzoxazole moiety were without substituents at aromatic ring, they revealed the best antifungal activity against BC (**127b**). The compounds were more active against BC than against FV (Figure 62) [127].

The raised anticandidal activity of compounds 114a and 114b might be happened owing to existence of quinoline ring and free aldehyde group, in order along with 1,2,3 triazole ring in their buildings.
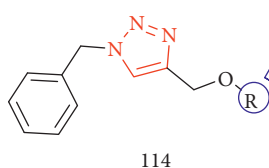
Compound 114b with free-CHO group and 1,2,3-triazole ring displayed good to modest activity with IC_{50} amount of 44.67 µg/mL against *C. albicans*, 92.68 µg/mL versus *C. tropicalis* and 215.77 µg/mL against *C. glabrata*.

114

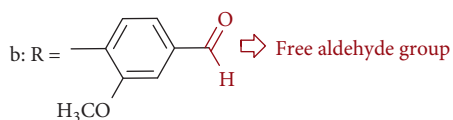a: R = ⇨ Quinoline ring

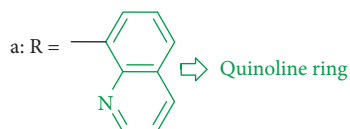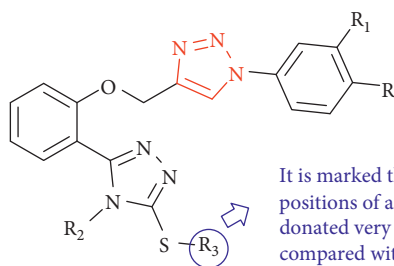b: R = ⇨ Free aldehyde group

H₃CO

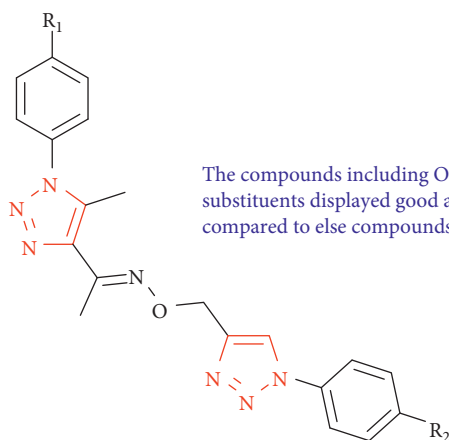FIGURE 53: Chemical structure of novel 1,2,3-triazole derivatives.

115

It is marked that Cl and Br substitutes at -para and -meta positions of aryl group linked to –CH₂CO (for example –R₃) donated very well biological inhibitory activities when only compared with –CH₂COPh and –COPh group.

a: R = Cl, R_1 = H, R_2 = PhCH₂-, R_3 = PhCOCH₂-
b: R = Cl, R_1 = H, R_2 = PhCH₂-, R_3 = PhCO-
c: R = H, R_1 = H, R_2 = PhCH₂-, R_3 = *p*-BrPhCOCH₂-
d: R = H, R_1 = H, R_2 = PhCH₂-, R_3 = *m*-BrPhCOCH₂-

FIGURE 54: Structure of *bis*-(1,2,3- and 1,2,4)-triazole derivatives as potential antimicrobial and antifungal agents.

a: R_1 = OCH₃, R_2 = OCH₃
b: R_1 = OCH₃, R_2 = C₄H₉
c: R_1 = CH₃, R_2 = OCH₃
d: R_1 = OCH₃, R_2 = CH₃
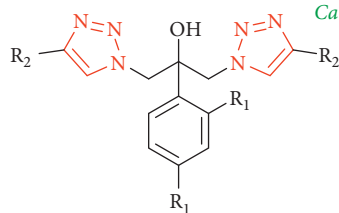e: R_1 = OCH₃, R_2 = Br
f: R_1 = H, R_2 = OCH₃

The compounds including OCH₃ substituents displayed good activity compared to else compounds.

116

FIGURE 55: Chemical structure of some new 1,2,3-triazole derivatives.

The compounds 117a and 117b demonstrated to be efficient for the inhibition of strains of *Candida spp.*

Compound 117a displays an inhibitory efficasy on strains of *Candida albicans* and *Candida krusei* under 0.0075 μg/mLwhilst antifungal properties against other Candida strains is alike, and in some instances, less (*Candida glabrata*, *Candida tropicalis*, MIC = 2.56 μg/mL).

117

a: R₁ = F, R₂ = Cyclopropyl
b: R₁ = OCH₃, R₂ = Cyclopropyl

FIGURE 56: Chemical structure of 1,3-*bis*-(1,2,3-triazol-1-yl)-propan-2-ol derivatives.

The activity of most compounds, whereas R was firmed as H, showed the tendency Ph > Py, and 4-methylpyrimidyl > 4,6-dimethylpyrimidyl in the aryl group of piperazine 4-situation.
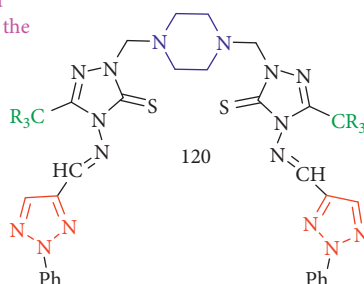
When R was firmed as F, displayed the tendency benzyl > 2,4-dichlorobenzyl, Ph ≈Py, and 4-methylpyrimidyl > 4,6-dimethylpyrimidyl in the class of piperazine 4-situation.

119a exhibited wide fungal activity.
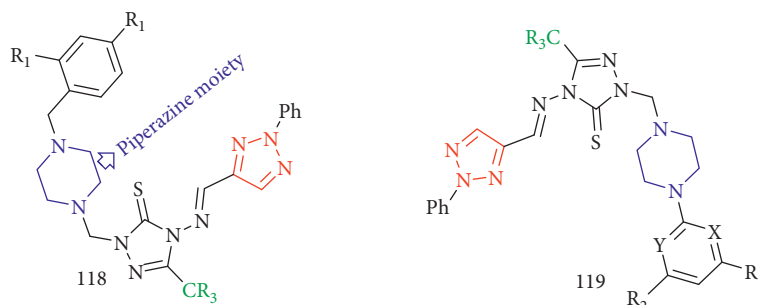
119a: R=F,R1=H, R2=CH3, X=Y=N.

FIGURE 57: Chemical structure of novel 1,2,4-triazole thione derivatives containing 1,2,3-triazole and substituted piperazine moieties.

Straight and adaptive azide-enolate (3 + 2) cycload-dition was used to synthesize modern oxazolidin-2-one-connected-1,2,3-triazole derivatives. As it can be seen in Figure 63, the sequence of compounds was tested for fungicidal activity toward four penicillate fungi as well as six yeast species of *Candida* spp., and Itraconazole used as the reference antifungal drug. Compounds **128a–c** showed higher activity against *C. glabrata* (MICs of 0.12, 0.25, and 0.12 μg/mL, respectively) than Itraconazole (MIC = 1 μg/ml). The activity of compound **128a** (MIC = 2 μg/mL) against *Trichosporon cutaneum* was better than that of Itraconazole (MIC = 8 μg/mL), while compound **128c** showed a great antimycotic activity in *Mucor hiemalis* (MIC = 2 μg/mL versus 4 μg/mL for Itraconazole) [128].

González-Calderón et al. [129] reported the first synthesis of a new kind of compound, using 1′-homo-*N*-1,2,3-triazole-bicyclic carbonucleosides **129a** and **129b** that exhibited good activity against some of the yeast strains examined (Figure 64).

The new benzofuran-triazole hybrids were generated using click reaction. The antifungal effect of goal compounds toward five strains of pathogenic fungi was assessed using the microdilution broth technique. The results showed that the lead compounds were active in a moderate-to-acceptable range. Some compounds only have a mild antifungal activity against *Candida albicans* and *Rhodotorula rubra*. With the exception of compounds **130a** and **130b**, most of the compounds displayed antifungal activity against *Cryptococcus neoformans* in concentrations ranging from 32 to 128 μg/mL. The primary SARs were supported by the

The outcomes showed some selectivity for the various fungi and that the assignment of the lactone is serious for the effect.
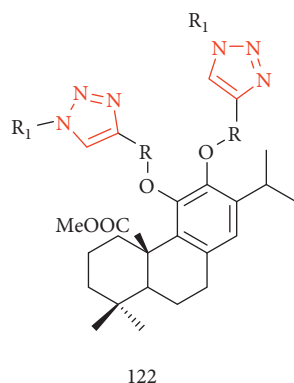
For compound 121a and 121b the γ-lactone emerges to be significant for activity.

122

121
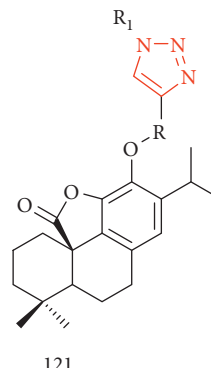
Compounds 121a, 121b, 122b and 123a, that displayed the best activities against *C. albicans*, containing the following usual properties:
1: the linker to the diterpene part included three CH₂ units.
2: in the triazole rings, R₁ was either a methyl phenyl sulfide (compounds 121a and 123a) or a benzyl (compounds 121b and 122b);
3: the activity was nearly the identicalfor the four compounds
4: when R₁ connected to the triazole ring was *p*-bromobenzyl or *p*-nitrobenzyl, the equivalent derivatives were passive.

123

121a: R = CO (CH₂)₃, R₁ =   122c: R = CO (CH₂)₂, R₁ = Br

121b: R = CO (CH₂)₃, R₁ =   122d: R = CO (CH₂)₃, R₁ = Br

122a: R = CO (CH₂)₂, R₁ =   122e: R = CO (CH₂)₂, R₁ = O₂N

122b: R = CO (CH₂)₃, R₁ =   122f: R = CO (CH₂)₃, R₁ = O₂N

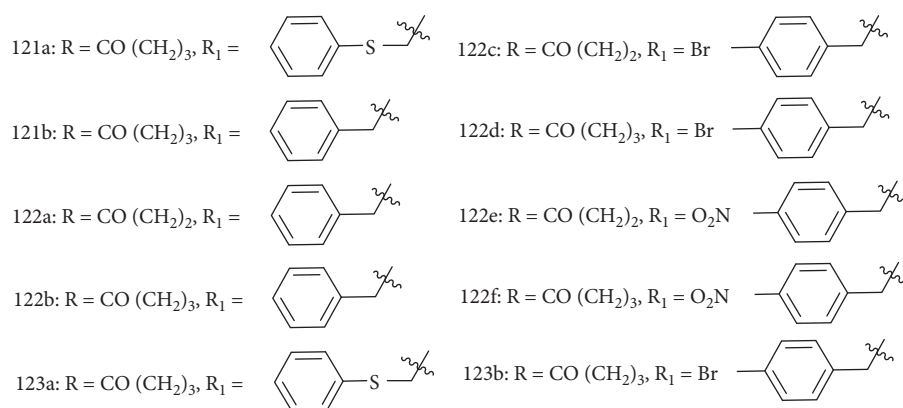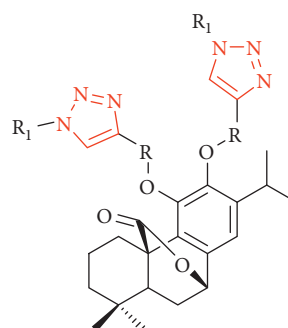123a: R = CO (CH₂)₃, R₁ =   123b: R = CO (CH₂)₃, R₁ = Br

FIGURE 58: Chemical structure of 1,2,3-triazole-substituted carnosic acid and carnosol derivatives.

excellent bioactivities of **130f** and **130g** among all the goal compounds (Figure 65) [130].

2.4.10. Miscellaneous 1,2,3-Triazole Hybrids. Yadav et al. [131] synthesized novel fluorinated-chalcone-1,2,3-triazoles. The antimicrobial assessment revealed that most of the compounds displayed unusual activity. When 1,2,3-triazole and chalcone were added to the antimicrobial screening results, the activity increased. Compound **131c** containing *p*-nitro group displayed superior power against *A. niger* and *C. albicans* with MIC value of 0.0032 mmol/mL compared to Fluconazole (MIC = 0.0102 mmol/mL). Compound **131b** with a bromine group demonstrated comparable activity to the standard with MIC values of 0.0054 mmol/mL against

C. albicans. Compounds having nitro and methoxy groups on the benzene ring displayed better activity against most of the microorganisms tested (Figure 66).

A sequence of 4-((1-benzyl/phenyl-1*H*-1,2,3-triazole-4-yl) methoxy) benzaldehyde derivatives were generated in high yield. All compounds were examined for fungicidal activity against *Aspergillus niger* and *Candida albicans in vitro*. The majority of the compounds demonstrated good-to-outstanding antifungal activity. Compounds **132a** and **132b** were more potent against *A. niger* with MIC value of 0.0084 μM/mL compared to Fluconazole (MIC = 0.0102 μM/ mL) (Figure 67) [132].

Jiang et al. [133] explored a series of new paeonol derivatives linked to a 1,2,3-triazole moiety for obtaining modern bioactive compounds with remarkable fungicidal

Thiazol ring

4-chlorophenyl and 4-fluorophenyl at situation-2 of thiazole ring showed more active against *A. niger*

Compounds 124a and 124g established relatively active and compounds 124b,124c,124d, 124e, 124f, and 124h were established twice less active compared with Ravuconazole against *A. niger*

124

a: R_1 = H, R_2 = H;
   (MIC, 31.25 µg/ml)
b: R_1 = Cl, R_2 = H;
   (MIC, 62.5 µg/ml)
c: R_1 = Cl, R_2 = 4-CH$_3$;
   (MIC, 62.5 µg/ml)
d: R_1 = Cl, R_2 = 4-OCH3;
   (MIC, 62.5 µg/ml)

e: R_1 = F, R_2 = H
   (MIC, 62.5 µg/ml)
f: R_1 = F, R_2 = 4-CH$_3$
   (MIC, 62.5 µg/ml)
g: R_1 = F, R_2 = 4-OCH$_3$
   (MIC, 31.25 µg/ml)
h: R_1 = F, R_2 = 4-F
   (MIC, 62.5 µg/ml)

FIGURE 59: Chemical structure of 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1- yl)ethanol.

Benzo[b]thiophene ring

The compounds 125e, 125f and 125g showed very well antifungal activity against examed fungi

Full observation of the results displayed that compounds 125a, 125b, 125c and 125d showed superior antifungal activity against both organism.

125

a: R = 4-COCH$_3$; b: R = 4-OH
c: R = Cl; d: R1 = cyclohexyl
e: R = 4-NO$_2$; f: R = 3-Me
g: R = 3-OMe
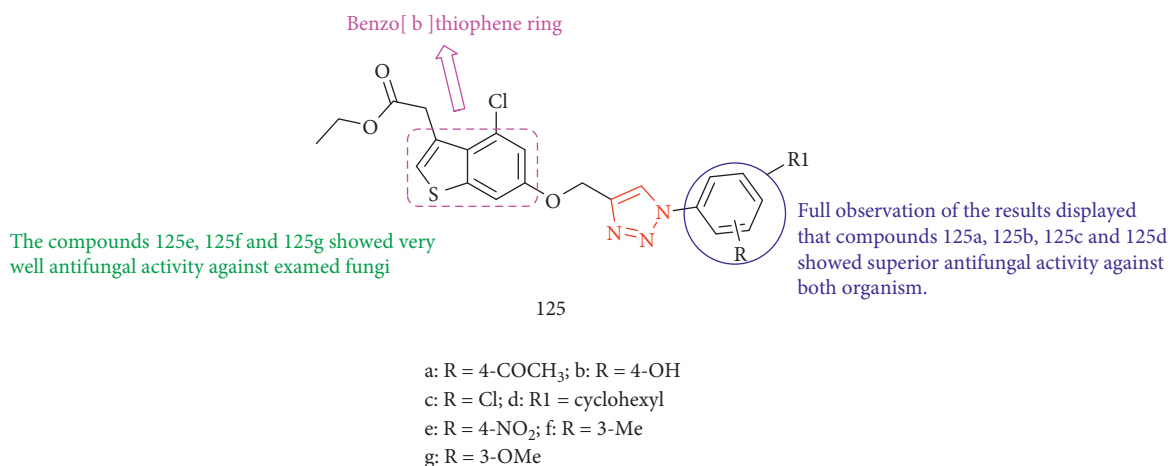
FIGURE 60: Chemical structure of benzo[b]thiophenes-1,2,3-triazole derivatives.

These 4-alkyl-substituted triazoles might show a framework to be explored for the growth of novel fungicidal agents.

All compounds presented large yield (comparable to the industrial fungicide tebuconazole) in inhibiting *C. gloeosporioides sporulation* and all compounds dis- played a lower output inhibiting mycelial growth than the positive control Tebuconazole.

126

a: R = CH$_3$[CH$_2$]4CH$_2$-
b: R = CH$_3$[CH$_2$]8CH$_2$-

FIGURE 61: Chemical structure of glycerol triazolic derivatives.

Benzotriazole

Compounds 127b and 127d (R_1 = 2-CH_3), showed good inhibitory activity against BC,

Benzoxazole moiety

Compound 127c (R_1 = 3-Cl, R = 5-CH_3) revealed the inhibition ratio 81.9% for BC

127

Compounds with R_1= 2-F or 4-CH_3 displayed medium inhibitory activity toward BC.

a: R_1 = H, R = H
b: R_1 = 2-CH_3, R = H
c: R_1 = 3-Cl, R = 5-CH_3
d: R = 2-CH_3, R = 4-Cl
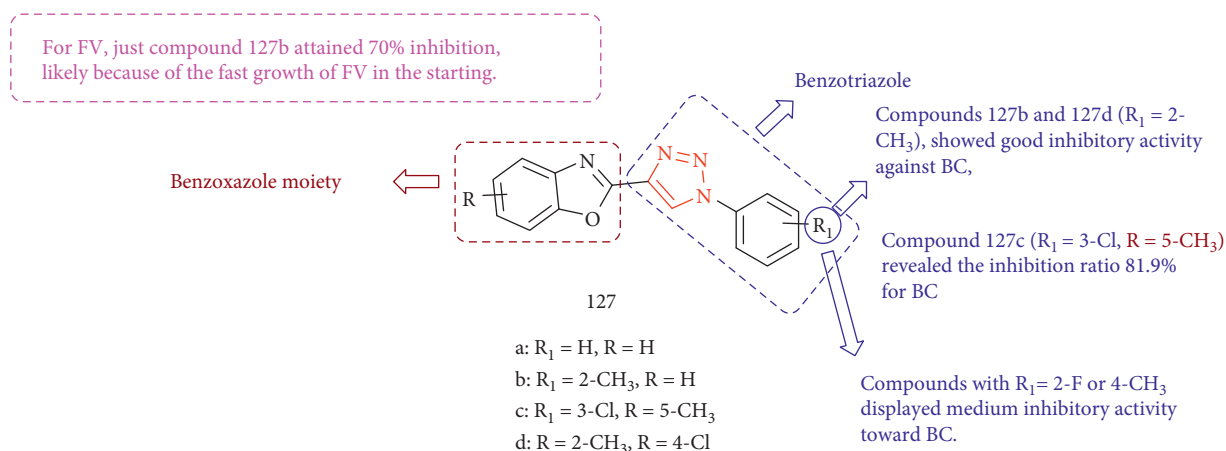
FIGURE 62: Chemical structure of novel benzoxazole derivatives containing a 1,2,3-triazole moiety.

Oxazolidin-2-one moiety

Ph   Ph

The results expressed that the existence of either a -CN or p-NO_2Ph group at situation 5 of the triazole rings incremented the biological activity of these compounds in both filamentous fungi and yeast.

128

a: R_1 = SO_2-p-TOl, R_2 = m-NO_2Ph
b: R_1 = SO_2Ph, R_2 = Pentyl
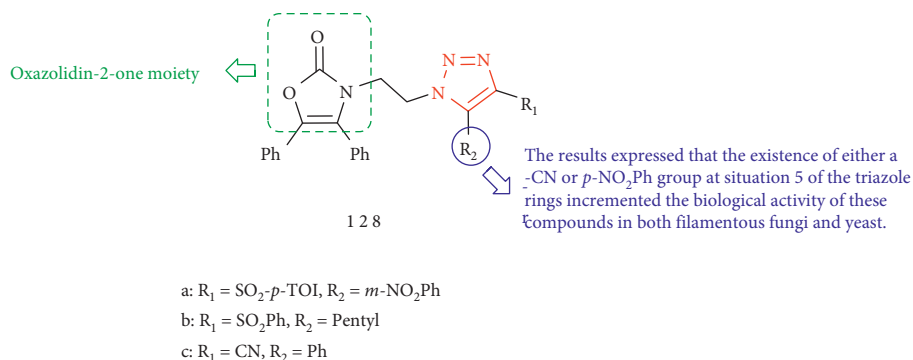c: R_1 = CN, R_2 = Ph

FIGURE 63: Chemical structure of oxazolidin-2-one-linked-1,2,3-triazoles.

Compounds 129a and 129b displayed good activity in some of the yeast strains, containing *C. utilis*, *C. lipolytica*, *C. glabrata* and *C. famata*.
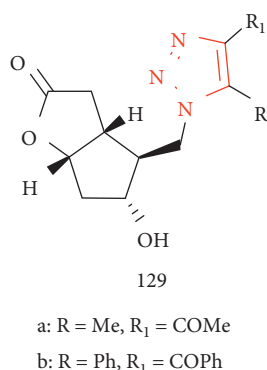
129

a: R = Me, R_1 = COMe
b: R = Ph, R_1 = COPh

FIGURE 64: Chemical structure of 1'-homo-N-1,2,3-triazole-bicyclic carbonucleosides.

activity using $Cu(OAc)_2 \cdot H_2O$/sodium ascorbate as a catalyst and under mild conditions. The antifungal properties of all the target compounds were assessed *in vitro* against two plant pathogenic fungi: *Rhizoctonia cerealis* and *Colletotrichum capsici*. The outcomes of antifungal activities showed that several of the compounds had acceptable

activity *in vitro* against the examined fungi at $20\,\mu g/mL$ (Figure 68).

He et al. [134] investigated the activity of 5-iodo-1,4-disubstituted-1,2,3-triazole compounds that were evaluated to study their *Escherichia coli* PDHc-E1 and fungicidal activity. Compound **135b** had the most inhibitory activity ($IC_{50} = 4.21 \pm 0.11\,\mu M$) and was shown to be an aggressive PDHc-E inhibitor. Fungicidal activity findings exhibited that compounds **135a–c** had almost good activity against *Botrytis cinerea* and *Rhizoctonia solani* even at $12.5\,\mu g/mL$. The SAR resolution showed that the 4-situation in the benzene ring significantly influenced the antifungal effect and inhibitory strength against *E. coli* PDHc-E1. It exhibited that an acceptable electron-withdrawing substituent in the 4-position of the benzene ring was useful for the binding interaction with the active region of PDHc-E1. The introduction of replacement R in the 4-position of the benzene ring could dramatically raise both enzyme inhibition and antifungal property compared with R in other situations or no substituent on the benzene ring (Figure 69).

Ren et al. [135] described a successful protocol for direct *ortho*-C-H alkoxylation of 1,4-di-substituted 1,2,3-triazoles utilizing alcohol as the alkoxyl source. Furthermore, alkoxylated products exhibited potent antifungal activity in combating the root-rot disease of *Panax notoginseng* (Figure 70).

The substituted groups on the phenyl ring connected to the triazole also had an effect on the activity.

Attenting the antifungal assay outcomes, it can be datumed that the derivatives with a di-fluorine substituted phenyl ring at the benzofuran C-2 side chain are more impressive than the mono fluorine ones (e.g., 130d vs. 130f).

The alkyl-substituted compounds are more powerful than the halogenated derivatives (e.g., 130c vs. 130d) and the ortho-substituted derivatives are stronger than the para isomers (e.g., 130e vs. 130d).
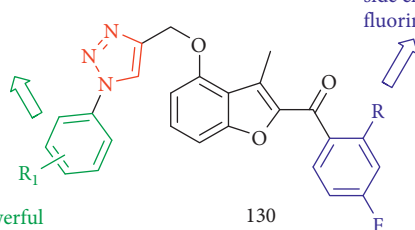
130

a: R = H, R_1 = 4-Cl
b: R = H, R_1 = 4-Br
c: R = H, R_1 = 2-Cl
d: R = H, R_1 = 2-CH$_3$
e: R = H, R_1 = 4-CH$_3$
f: R = F, R_1 = 2-CH$_3$
g: R = F, R_1 = 2, 5-di-CH$_3$

FIGURE 65: Chemical structure of novel benzofuran-triazole hybrids.

Naphthaldehyde-chalcone alkynes

The synthesized triazole analogues with a substituted benzene displayed superior activity than naphthaldehydechalcone alkynes

Compounds with electron withdrawing substituents on benzene exhibited more activity than having electron donating groups

Screening results showed the increasable effect of activity when that 1,2,3-triazole and chalcone are attached.

Nearly all of the fluorinated triazoles showed nice results than the non-fluorinated compound 131a.

131

a: R_1 = Br, R_2 = $C_6H_5CH_2$-
b: R_1 = Br, R_2 = 4-$FC_6H_4CH_2$-
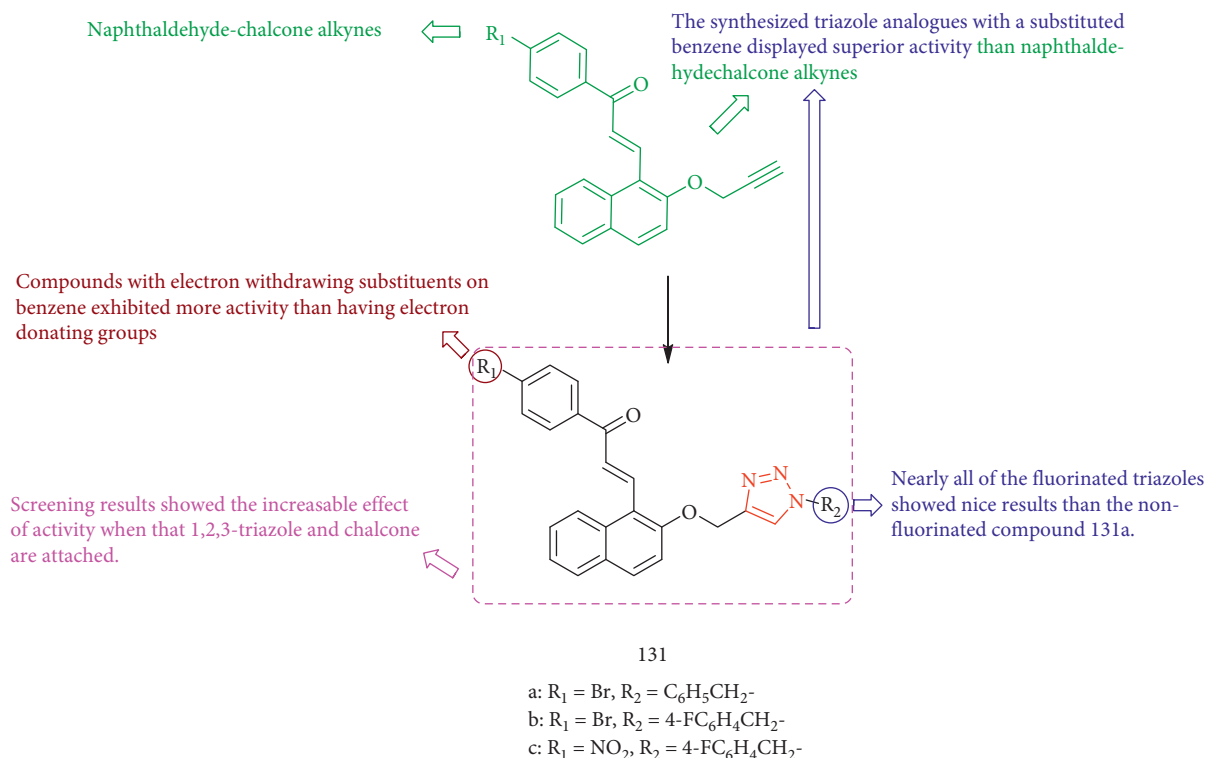c: R_1 = NO_2, R_2 = 4-$FC_6H_4CH_2$-

FIGURE 66: Chemical structure of chalcone-1,2,3-triazole hybrids.

A new 4-(1-phenyl-1-hydroxyethyl)-1-(o-hydroxyphenyl(-1H-1,2,3-triazole was designed by integrating the constructional properties of triazole PITENIN anticancer factors and the azole class of antifungal drugs. Their evaluation of a wide spectrum of human fungal pathogens resulted in the identification of several possible antifungal strains, some of which demonstrated stronger antifungal activity than standard drug against *Aspergillus fumigatus*, *Candida glabrata*, *Cryptococcus neoformans*, and *Aspergillus niger*. Many of these compounds demonstrated strong antifungal activity against several of the examined pathogen. Compounds **138d** and **138e** were the most effective against all fungal infections, with MICs ranging from 4 to 32 μg/mL. Compounds **138i**, **138j**, **138f**, **138g**, and **138h** displayed very good antifungal activity excluding *A. niger* (MIC > 128 μg/mL) as shown in Figure 71. Surprisingly, all derivatives exhibited greater activity than Fluconazole against *Candida glabrata* NCYC 388. In general, dichloro- or *bis*-trifluoromethyl groups on the scaffold are expected to enhance lipophilicity while simultaneously polarizing the sample molecule [136].
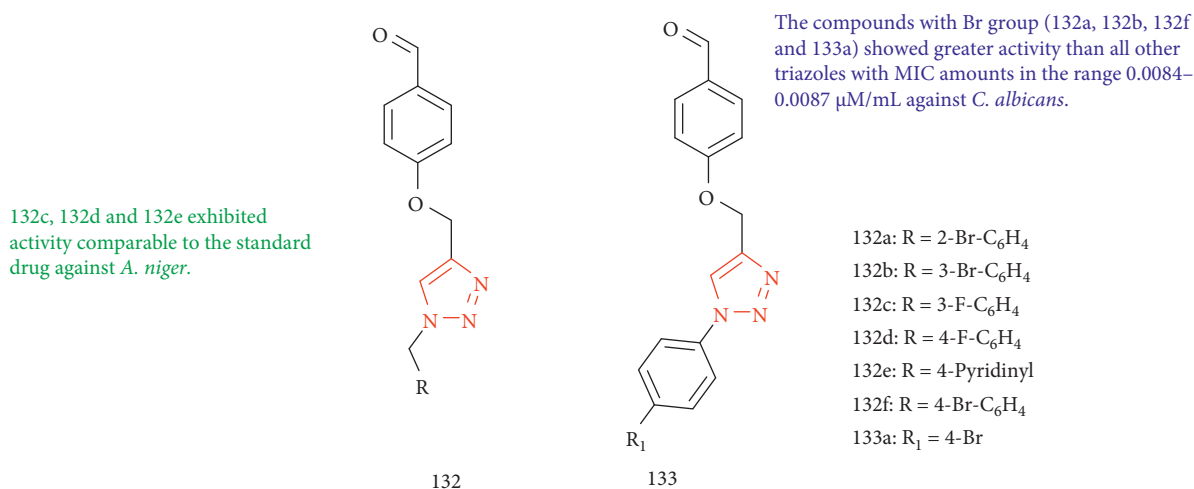
132c, 132d and 132e exhibited activity comparable to the standard drug against *A. niger*.

The compounds with Br group (132a, 132b, 132f and 133a) showed greater activity than all other triazoles with MIC amounts in the range 0.0084–0.0087 μM/mL against *C. albicans*.

132a: R = 2-Br-C_6H_4
132b: R = 3-Br-C_6H_4
132c: R = 3-F-C_6H_4
132d: R = 4-F-C_6H_4
132e: R = 4-Pyridinyl
132f: R = 4-Br-C_6H_4
133a: R_1 = 4-Br

FIGURE 67: Chemical structure of 4-((1-benzyl/phenyl-1H-1,2,3-triazole-4-yl)methoxy)benzaldehyde analogs.

Paeonol moiety

The compounds having *o*-fluorophenyl, *o*-trifluoromethylphenyl, *o*-tolyl and *p*-methoxyphenyl groups in order, displayed more powerful antifungal activities than other novel compounds.
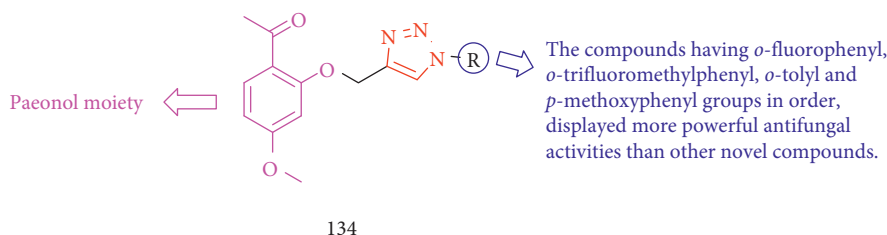
FIGURE 68: Chemical structure of novel paeonol derivatives linked with 1,2,3-triazole moiety.

R = (4-Br, 3-NO_2, 4-Cl, 4-F, 4-CN, and 4-OCH_3) had desirable result on both antifungal activity and enzyme inhibition (IC$_{50}$ <12 μM).

When 4-CO_2Et as R was presented into the benzene ring, both activities of compound 139b notably reduced.

For the di-substituents, R = 3-CH_3-4-Cl or R = 2-Cl-4-NO_2 was most useful to both antifungal activity and enzyme inhibition.

a: R = 4-CN
b: R = 4-Br
c: R = 4-Cl

Comparing the inhibitory power versus E. coli PDHc-E1, (R = 4-Br, IC$_{50}$ = 4.21 ± 0.11 μM) > (R = 2-Br, IC$_{50}$ = 15.69 ± 0.85 μM); (R = 4-NO_2, IC$_{50}$ = 5.33 ± 0.1 μM) > (R = 2-NO_2, IC$_{50}$ = 8.73 ± 0.34 μM); (R = 4-Cl, IC$_{50}$ = 11.86 ± 1.01 μM) > (R = 2-Cl, IC$_{50}$ = 14.83 ± 0.91 μM).
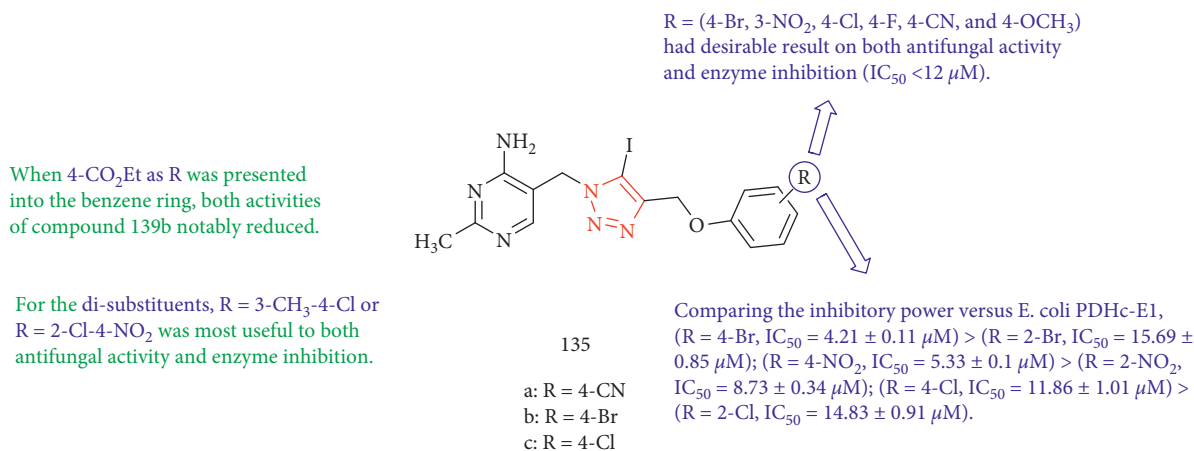
FIGURE 69: Chemical structure of the new 5-iodo-1,4-disubstituted-1,2,3-triazole derivatives.

A series of novel strobilurin derivatives with various 1,2,3-triazole side chains were synthesized. As shown in Figure 72, all of the compounds were evaluated *in vitro* for fungicidal activity against *Phytophthora capsici, Alternaria alternate, Gibberella zeae, Sclerotinia sclerotiorum*, and *Botrytis cinerea,* with some displaying medium-to-high fungicidal activity against *Alternaria alternate* and *Phytophthora capsici*. Difenoconazole was used as a standard medicine. Amid the goal compounds X = Br and R = 4-OCH_3, R = 4-CH_3 was preferred for the advancement of antifungal activities, which were surprisingly better than **139e** ($R = 3$-NO_2) and compounds

including ($X = $ Cl) with different halogen atoms on the benzene ring displayed comparable inhibition rates against the examined fungi, for example, **139f, 139g**, and **139b** [137].

Pyta et al. [138] used the click reaction to enhance the antifungal agent gossypol by adding a triazole moiety. The biological assessment of the new gossypol-triazole conjugates, as shown in Figure 73, revealed that the potency of **140g** and **140h** compounds containing triazole-benzyloxy portion was equivalent to that of conventional medication against *Fusarium oxysporum*. Antifungal tests were applied on some plant pathogens that cause serious difficulties in
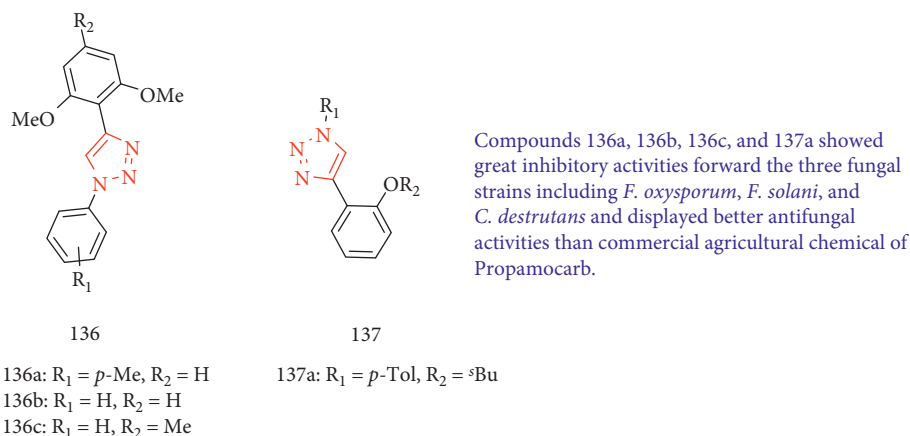
Compounds 136a, 136b, 136c, and 137a showed great inhibitory activities forward the three fungal strains including *F. oxysporum*, *F. solani*, and *C. destrutans* and displayed better antifungal activities than commercial agricultural chemical of Propamocarb.

136

137

136a: R_1 = *p*-Me, R_2 = H
136b: R_1 = H, R_2 = H
136c: R_1 = H, R_2 = Me

137a: R_1 = *p*-Tol, R_2 = *s*Bu

FIGURE 70: Chemical structure of 1, 4-disubstituted 1,2,3-triazole.

The presence of a halo-substituent on aryl ring, for-example 138a, 138b etc, showed modest progress in the antifungal activity.

The presence of two trifluromethyl groups on this aromatic motif (that are chief in case of the PITENIN analogues), displayed great antifungal activity.

When two Cl and F atoms were sited on this ring, like 138c and 138d, antifungal activity revealed notable increase

The antifungal activity for many of compounds was not remarkable when there was no substituent on the left side aromatic ring.

In the azido portion of the structure, the activity modified from no substitution<5-fluoro<4-chloro<5-chloro with respect to –OH.

138

a: R = CH_3, R_1 = 4-F, R_2 = 4-Cl
b: R = CH_3, R_1 = 4-Cl, R_2 = 4-Cl
c: R = CH_3, R_1 = 4-F, R_2 = 3-Cl
d: R = CH_3, R_1 = 4-Cl, R_2 = 3-Cl
e: R = CH_3, R_1 = 4-Cl, R_2 = 3-F
f: R = H, R_1 = 1,4-di-CF_3, R_2 = 4-Cl
g: R = CH_3, R_1 = 1,4-di-CF_3, R_2 = 4-Cl
h: R = nBu, R_1 = H, R_2 = 4-Cl
i: R = H, R_1 = 1,4-di-CF_3, R_2 = 3-Cl
j: R = CH_3, R_1 = 1,4-di-CF_3, R_2 = 3-Cl

FIGURE 71: Chemical structure of novel 4-(1-phenyl-1-hydroxyethyl)-1-(o-hydroxyphenyl)-1H-1,2,3-triazole.

agriculture. In microbiological investigations, compounds **140a–f**, as well as gossypol, were found to be ineffective against *Aspergillus brasiliensis*.

A new series of 1,2,3-triazole phenylhydrazone derivatives were synthesized, and most of the derivatives displayed vigorous activity against *F. graminearum*, *R. solani*, and *S. sclerotiorum*. Compounds **141d–f**, **142d**, **142e**, **143d**, and **143e** depicted the most excellent antifungal activity against *F. graminearum* with EC50 values ranging from 0.28 to 1.06 mg/mL. Compound **143d** showed the biggest and second most inhibitory activity against *R. solani* and *S. sclerotiorum* with EC50 values of 0.86 and 1.66 mg/mL, respectively. When comparing all compounds with similar halogen substituents, it has an unfavorable effect on antifungal activities, since the methylene group is found among the 1,2,3-triazoles and aromatic rings (Figure 74) [139].

Santos et al. [140] tested nine synthetic 1,2,3-triazole derivatives against four *Candida* spp. strains of clinical significance like *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. albicans*. The two compounds displayed antifungal activity containing **144d** against *C. tropicalis* (MIC > 64 μg/mL) and **144b** against *C. albicans* (MIC = 8 μg/mL) with some stereoelectronic properties allied to the activity. When compared to compounds **144a** and **144b**, the existence of an aldehyde group in place of alcohol in compound **144c** was not desirable for antifungal activity, since compound **144b** with methanol as a substituent showed antifungal activity, while compound **144c** with aldehyde did not (Figure 75).

Structure-based design was used to create a novel derivative of 5-substituted benzotriazole as inhibitors of fungal cytochrome P450 lanosterol 14-a demethylase in response to the demand for new antifungal medicines with better

Influence of the substituent X (Br or Cl) on the antifungal activity for all test fungi, showed nearly identical power,like the inhibition speeds of compounds 139a and 139b against *P.capsici* were up to 69.1%, 139c and 139d for *A. alternate* were 61.3% and 69.0%.

Methoxyacrylate moiety

The inhibitory rates of 139h (R = 3-NO$_2$) and 139d (R = 4-CH$_3$) against *P. capsici* were 69.1% and 55.5%, and against *A. alternate* were 53.6% and 69.0% in series and the inhibition rate of 139h was 69.1% against *P. capsici*, that was better than 139i (R = OCH$_2$Ph).

Presence of methoxyacrylate on N^2-position of triazole affected the fungicidal power and The preface of methoxyacrylate greatly frailed the inhibition activities all of compounds against fungi strains

139

a: R = 4-F, X = Br; f: R = 4-Cl, X = Cl
b: R = 4-F, X = Cl; g: R = 4-Br, X = Cl
c: R = 4-CH$_3$, X = Br; h: R = 3-NO$_2$, X = Cl
d: R = 4-CH$_3$, X = Cl; i: R = 4-OCH$_2$Ph, X = Cl
e: R = 3-NO$_2$, X = Br
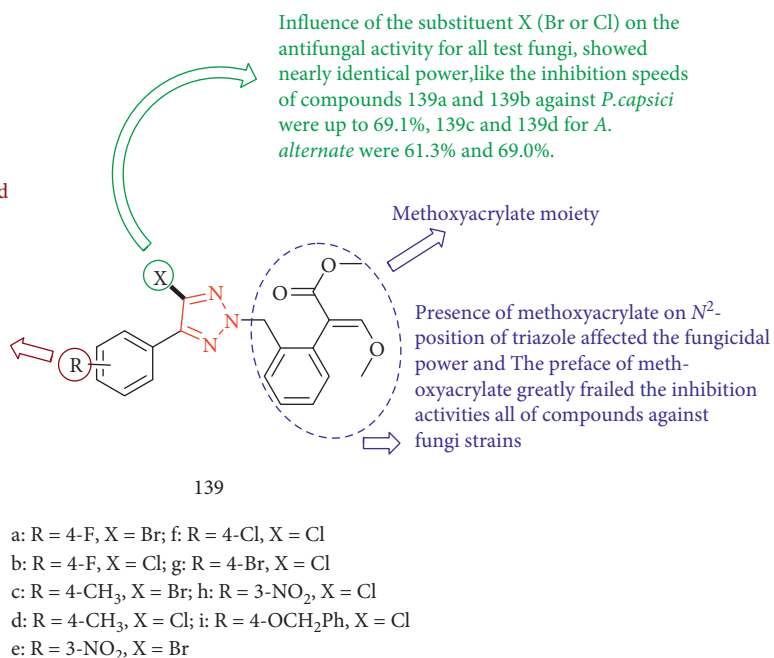
FIGURE 72: Chemical structure of novel 1,2,3-triazole-functionalized strobilurins.

Presentation of triazole–benzyloxy section to gossypol skeleton amended antifungal activity of compound 140g, against to its antibacterial power.

The most compelling results were recieved for *Fusarium spp.*
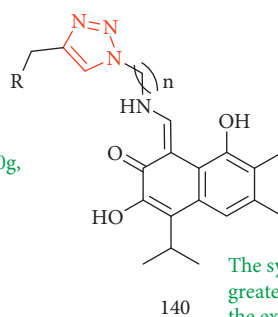
The synthesized compounds 140a–140h displayed the greatest activity against *Fusarium spp.* strains, with the exclusion of *F.acuminatum*.

140

a: n = 2 R = ethyl
b: n = 3 R = ethyl
c: n = 2 R = n-propyl
d: n = 3 R = n-propyl
e: n = 2 R = n-butyl
f: n = 3 R = n-butyl
g: n = 2 R = benzyloxy
h: n = 3 R = benzyloxy

FIGURE 73: Chemical structure of new gossypol-triazole conjugates including aliphatic chains and benzyloxy groups.

potency and a broader range of activity. The antifungal assessment was performed on the fungus *Candida albicans* (ATCC 10231). At concentration of 100 μg/mL, compounds **145a** and **145b** displayed larger antifungal activities as compared to the standard drug Fluconazole (Figure 76) [141].

Phosphonates, quinones, and azoles are examples of drugs found in bioactive compounds. In 3-4 steps, a series of phosphonates linked to quinones and azoles with changing carbon chain lengths were prepared to be in high yield. The antifungal activity of these azole derivatives against the phytopathogenic fungus *Fusarium graminearum* was found to be extremely high in ethyl preserved phosphates. Free-base phosphates have great antifungal training toward *Candida albicans* and *Aspergillus flavus* which are human pathogenic fungi. In terms of cytotoxicity and antifungal activity, compound **146f** is the most active with the smallest cytotoxicity, followed by **146d** and **146e** (Figure 77) [142].

All the compounds (n = 0 or n = 1) with halogen substituents of R_3 at the para position, particularly for p-F and p-Cl, display remarkable results and the stronger the electron withdrawing potency of the R_3 substituent, the higher the activities.
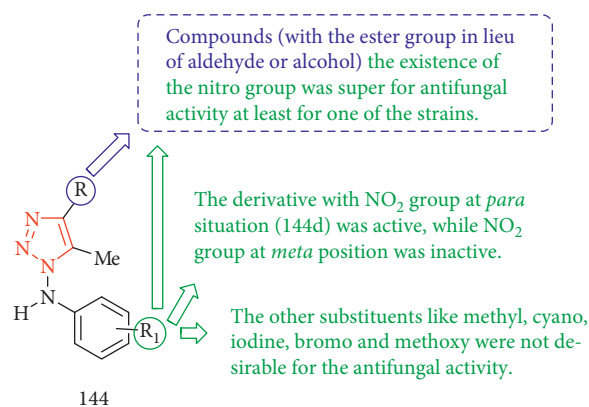
When n = 0, comparing the all compounds (141~143), methyl substitution at the R_1 or R_2 positions has no notable results on antifungal activity, whiles when n = 1, methyl substitution seems have an effect on activity, but there is no clear tendency.

141-143

141(a-f): n = 0, R_1 = H, R_2 = CH_3, R_3 = -2F, -2Cl, -3Cl, -4F, -4Cl, -4Br
142(a-f): n = 0, R_1 = CH_3, R_2 = H, R_3 = -2F, -2Cl, -3Cl, -4F, -4Cl, -4Br
143(a-f): n = 0, R_1 = CH_3, R_2 = CH_3^-, R_3 = -2F, -2Cl, -3Cl, -4F, -4Cl, -4Br

FIGURE 74: Chemical structure of 1,2,3-triazole phenylhydrazones as fungicide candidates.

Compounds (with the ester group in lieu of aldehyde or alcohol) the existence of the nitro group was super for antifungal activity at least for one of the strains.

The derivative with NO_2 group at *para* situation (144d) was active, while NO_2 group at *meta* position was inactive.

The other substituents like methyl, cyano, iodine, bromo and methoxy were not desirable for the antifungal activity.

144

a: R = CH_3OH, R_1 = 4-Br
b: R = CH_3OH, R_1 = H
c: R = CHO, R_1 = H
d: R = CO_2Et, R_1 = 4-NO_2

FIGURE 75: Chemical structure of N-substituted-phenylamino-1,2,3-triazole derivatives.

On doing SAR study it was seen that all 5-substituted phenylaminomethyl or phenoxymethyl derivatives of benzotriazole displayed powerful activity against *C. albicans* as compared to Fluconazole.
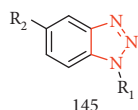
Hence, 5-substitution with phenylaminomethyl or phenoxymethyl side chain is needful for protecting the power of benzotriazole derivatives.
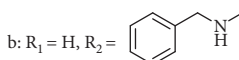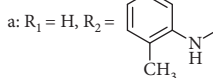
145

a: R_1 = H, R_2 =

b: R_1 = H, R_2 =

FIGURE 76: Chemical structure of benzotriazole derivatives as novel antifungal agents.

The collation of MICs and IC50 showed that with longer carbon chain length among phosphonate and anthraquinone analogs consisting of azole and quinone moieties (146a-146f) raises antifungal activity

There was a notable drop in antifungal activity for potassium phosphonate analogs, (147a–147e) against *F.graminearum*

Naphthoquinone analog

Phosphonate analog

146

146a: n = 1
146b: n = 2
146c: n = 3
146d: n = 5
146e: n = 7
146f: n = 9

147

147a: n = 1
147b: n = 2
147c: n = 5
147d: n = 7
147e: n = 9

FIGURE 77: Chemical structure of phosphonates conjugated to azoles and quinones with variable carbon chain lengths.

3. Conclusion

1,2,3-Triazole-hybrids with broad antifungal activity have garnered worldwide attention. This lead compound will act as a potent drug candidate in the future. The CuAAC reaction for the regioselective synthesis of 1,2,3-triazole-hybrids has been proven to be an excellent tool in organic and medicinal chemistry. Fungal infections have a big challenge on the global health system. Fungal infections were the primary cause of death for more than 1.35 million people globally. Treatment of this type of infection is complicated owing to the toxic side effects of antifungal medications; on the other hand, since drug resistance in chemotherapy is one of the most significant hurdles in fungal treatment, the development of novel antifungal agents is critical. The present review explains the recent advantage of 1,2,3-triazole-hybrids as an effective antifungal agent and the mechanism of action and then it evaluates the structure-activity relationship. The versatile synthetic applicability and antifungal activity of these *N*-heterocycles will aid medicinal chemists in organizing, planning, and executing new drugs with higher activity and lower toxicity.

Abbreviations

AmB:	Amphotericin B
CAI:	Carboxyamidotriazole
CAP:	Community-acquired pneumonia
CCP:	*Colletotrichum capsici* pathogens
[Cp∗RuCl]:	Pentamethylcyclopentadienyl ruthenium chloride
CPP:	Cotton physalospora pathogens
CuAAC:	Copper-catalyzed azide alkyne cycloaddition (CuAAC)
DFT:	The density functional theory
DHA:	Dehydroacetic acid
DNA:	Deoxyribonucleic acid
EC50:	Effective concentration
FLC:	Fluconazole
HIV-1:	Human immunodeficiency virus type 1
HOMO:	Highest occupied molecular orbital
IC_{50}:	Inhibitory concentration
ITC:	Itraconazole
LUMO:	Lowest unoccupied molecular orbital
MIBK:	Methyl isobutyl ketone
MIC:	Minimum inhibitory concentration
MRSA:	Methicillin-resistant *Staphylococcus aureus*
PITENIN:	Anticancer agent
RNA:	Ribonucleic acid
RT:	Reverse transcriptase
RuAAC:	Ruthenium-catalyzed azide-alkyne cycloaddition
SAR:	Structure-activity relationship
SIV:	Simian immunodeficiency virus
TBDMS:	Tert-butyldimethylsilyl
TEM-1 and SHV-1:	Class A-lactamases commonly found in *Escherichia coli* and *Klebsiella pneumoniae* pathogens responsible for urinary tract, respiratory tract, and bloodstream infections
TSAO:	Tertbutyldimethylsilylspiroaminooxathio ledioxide
VCZ:	Voriconazole.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. All data are presented in the form of figures.

Ethical Approval

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

EZ designed, wrote, and finalized the manuscript and supervised. The first draft of the manuscript was written and revised by MM. Also, MF, ZK, AS, and AK helped in writing and revising the manuscript. All authors approved the final manuscript.

Acknowledgments

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