1. Introduction

Heterocyclic organic chemistry is a main field in organic and medicinal chemistry [1–4]. Azoles are nitrogen-containing five-membered heterocyclic compounds [5, 6]. The presence of nitrogen in heterocycles has a major effect on biological activity. Recently,azole compounds have become hot topics around the world [2, 7]. Among the azoles fused as heterocyclic compounds, 1,2,4-triazole derivatives with molecular formula \((C_2H_3N_3)\) are the most stable compounds [8]. 1,2,4-Triazoles showed broad ranges of biological activities, such as antimalarial [9], antiurease [10], antiviral [11], anticonvulsant [12], antioxidant [13], and antifungal [14]. Some of the medicinal plants containing triazole scaffolds were demonstrated to be antifungal agents, including cyproconazole, triadimefon, metconazole, tebuconazole, propiconazole, epoxiconazole, and prothioconazole [15]. Annually, invasive fungal infections cause 1.7 million deaths in the world, which is a major public health issue [16]. One of the most serious issues is the rise of synthetic drug resistance to various fungal pathogens; thus, the synthesis and development of new 1,2,4-triazoles with low toxicity are essential worldwide [17]. This group of bioactive compounds acts by inhibiting the activity of cytochrome P450-dependent enzyme, the lanosterol 14α-demethylase (CYP51), which is an important enzyme in fungi ergosterol biosynthesis [18]. Azoles link to the iron in porphyrins, causing a blockade of the fungal ergosterol biosynthesis pathway resulting in the agglomeration of 14-demethylated sterols [19]. Recently, novel derivatives of 1,2,4-triazoles were prepared and evaluated for fungicidal activity and some of them showed potential activity against certain fungi. In previous years, many research articles have emphasized the importance of 1,2,4-triazoles as potent antifungal and antibacterial properties [20–31]. However, this review is focused on the latest papers (2015–2021) in the synthesis of new 1,2,4-triazole as an...
antifungal agent and evaluating structure-activity relationship (SAR) to provide an insight for the logical synthesis of more effective 1,2,4-triazole antifungal candidates. The diagram of choosing publications and the content of this review are illustrated in Figure 1.

2. Synthesis of 1,2,4-Triazoles

1,2,4-Triazoles are five-membered sp² hybridization compounds containing three nitrogen atoms at the 1-, 2-, and 4-positions of the ring. There are two tautomeric forms: 4H-1,2,4-triazole and 1H-1,2,4-triazole (Scheme 1) [32].

2.1. General Pathways. A simple method for preparing 1,2,4-triazoles has been introduced from the reaction of formamide and hydrazines without a catalyst using microwave irradiation (Scheme 2) [33].

A series of 1,3-disubstituted-1,2,4-triazoles were synthesized by reacting amidine and trialkyl amines with K₃PO₄ as a base in the presence of a copper (II) catalyst (Scheme 3) [34].

I₂-mediated oxidative N-S and C-N bond formations are an ecologically friendly and effective approach for synthesizing novel 1,2,4-triazoles from isothiocyanates (Scheme 4) [35].

1,5-Disubstituted-1,2,4-triazoles were prepared using copper (II) as the catalyst. This regioselective method makes it simple to produce 1,2,4-triazole moiety with wide substrate amplitude, high yield, and significant functional group compatibility (Scheme 5) [36].

The synthesis of 1,2,4-triazoles from aliphatic amines and hydrazones has been developed using a cascade C-H functionalization, oxidative aromatization sequence, and double C-N bond formation under iodine as the catalyst (Scheme 6) [37].

2.2. Synthesis by Substitution of 1,2,4-Triazole

2.2.1. Arylation Reactions. Under reflux circumstances in pyridine, 1-aryl-1,2,4-1H-triazole is arylated by an aryl halide with electron-withdrawing groups using CuO as the catalyst (Scheme 7) [38, 39].

2.2.2. Alkylation. When sodium methoxide in methanol is used as the base, 1,2,4-triazole is alkylated at the N1 position, yielding in a mixture of 1-methyl- and 4-methyl-1,2,4-triazole with methyl sulfate alkylation in NaOH (Scheme 8) [40].

2.3. Direct the Synthesis of N4-Substituted Triazoles. A group of 4-Arylsubstituted-1,2,4-4H-triazoles yields via the reaction of N, N-diformylhydrazine with primary amine at high temperatures (Scheme 9) [41]. Pellizzari and Soldi pioneered this system by reacting simple arylamines such as naphthylamine, aniline, or toluidine with N, N'-diformylhydrazine [42, 43], as well as downloading via slight changes in amino heterocycles containing 3-amino-1,2,4-4H-triazole to generate 3,4-bitriazoles [44–46].

3. Pharmaceutical Drugs

3.1. Chemical Structures of 1, 2, 4-Triazole-Based Marketed Drugs. Bladin were the first to synthesize 1,2,4-triazoles in 1885 [31]. The primary procedures, such as the reaction of formamide with formylhydrazine, produced low yields of 1,2,4-triazole [47, 48]. Later, it was found that condensation of formamide with hydrazine sulfate yielded 1,2,4-triazole in average yield. Various pharmacological activities of 1,2,4-triazoles as antifungal [42, 49, 50] have been observed which included fluconazole, isavuconazole, itraconazole, voriconazole, ravuconazole, and posaconazole (Figure 2). Several 1,2,4-triazole-based drugs are under clinical use for the treatment of different diseases. Some of the most effective drugs available in the market are described in the following Table 1.

3.2. Structure-Activity Relationship of Fluconazole. Fluconazole is well known as one of the most potent antifungal drugs with remarkable interest in medicinal chemistry. Due to the importance of fluconazole as a reference drug, the structure-activity relationship is shown in Figure 3.

4. 1,2,4 Triazole Scaffold for the Development of Antifungal Agents

This part of the review is classified into two parts based on the structural similarities of 1,2,4-triazole derivatives. First, we explained novel analogues of commercial 1,2,4-triazole drugs and then discussed 1,2,4-triazole-based scaffolds with various functional groups such as indole, benzimidazole, quinolone, quinazoline, amine, hydrazone, amide, sulfur, and oxime ether that showed remarkable antifungal properties, as well as SARs of all synthesized compounds.

4.1. Analogues of Commercial 1,2,4-Triazole Drugs. Most triazole compounds containing 1,2,3-benzotriazine-4-one demonstrated more antifungal activity against Candida albicans and Cryptococcus neoformans than reference drug with MIC values ranging from 0.0156 to 2.0 μg/mL. Furthermore, a strong SAR investigation revealed that derivatives with groups –NO₂ and CF₃ at the 7-position exhibited more effective antifungal activity than derivatives with groups at the 5-, 6-, and 8-positions. In addition, products containing halogens such as Cl and F demonstrated more excellent antifungal activity than those containing electron-withdrawing groups. Meanwhile, compound 1a (R = 7Cl) demonstrated remarkable antifungal activity specifically against Aspergillus fumigatus (MIC = 0.25 μg/mL) and moderate activity against fluconazole-resistant Candida albicans strains (Figure 4) [88].

Blokhina et al. [29] investigated the fungicidal activity of thiazolo[4,5-d] pyrimidine hybrids with (1H-1,2,4) triazole. All derivatives include the methyl-(2a), fluoro-(2b), and chloro-(2c) substituents at the para position. In vitro evaluation of various compounds with a potent alkylpiperazinyl linker demonstrated antifungal activity similar to the standard drug. The most active compounds are methyl-(2a), fluoro-(2b), chloro-(2c) methyl-(3a), and fluoro-(3b). Based
on MIC values, antifungal activity is classified as poor (≥32 μg/mL), modest (16–32 μg/mL), good (4–8 μg/mL), excellent (0.06–2 μg/mL), or outstanding based on MIC values (Figure 5).

Montoir et al. [89] reported a novel class ofazole antifungal compounds based on a pyrrolotriazinone scaffold. As a result, these compounds demonstrated fungicidal activity against pathogenic Candida species *in vitro* (fluconazole susceptible and fluconazole resistant) and were more active than voriconazole against two Candida *albicans* candidates. Compound 4e also showed promising *in vitro* activity against several filamentous fungi, including *Aspergillus fumigatus* (Figure 6).

Xie et al. [90] demonstrated that the entire series of triazole containing isoxazole compounds (5a-f) were antifungal against eight human pathogenic fungi. Compound 5a showed a strong inhibitory activity toward *Candida parapsilosis* and *Candida albicans* with MIC80 values of 0.0313 μg/mL. According to the SARs study, mono-fluorine on the phenyl ring possesses antifungal activity. On the other hand, enhancing the number of fluorine atoms (5c-d) may result in a reduction in antifungal activity (Figure 7).

In comparison to the reference drugs, voriconazole, fluconazole, and ravuconazole, an alkyne linked in the side
The antifungal efficacy of triazole alcohol derivatives toward 16 Candida isolates from five different species, including fluconazole-susceptible and fluconazole-resistant isolates, was investigated. All of these derivatives with MIC values of 0.063–1 mg/mL showed higher activity than fluconazole (MICs = 0.5–4 mg/mL) against fluconazole-susceptible isolates; significantly, compounds 7b and 7e were also active against fluconazole-resistant species. However, the effect of chloro substitution depends on the type of species. For example, the 2,4-dichloro substituent 7d was shown to be more effective against C. albicans than 3-Cl (7b) or 4-Cl (7c). In the case of C. krusei, however, the 3-chloro group was better than the 4-chloro or 2,4-dichloro substituents. The addition of fluoro or bromo groups to the benzyl residue, however, had no beneficial impact. Among the fluoro-benzyl regioisomers (7f-h), the 3-fluoro 7g analog was more active against Candida species (Figure 9) [91].

Chandrika et al. [93] investigated novel fluconazole (FLC) compounds for antifungal activity against the clinical strains of C. parapsilosis, C. glabrata, and Candida with azyl, alkyl, cycloalkyl, and dialkyl-amino substituents for neofarmans using MIC determination. The activity of the alkylamino FLC derivatives was shown to be directionally related to the length of the alkyl chains (Figure 10).

Tekale et al. [94] investigated the antifungal activities of triazole compounds, including imidazole. The impact of the imidazole side chain on the in vitro fungicidal activity of novel synthesized compounds toward various microorganisms such as aspergillus, niger, aspergillus fumigates, and Candida albicans was demonstrated. Compound 9e had the lowest activity against C. albicans, and compounds 9b & 9d had higher activity against A. niger than the other compounds (Figure 11).

The MIC<sub>80</sub> values of new triazole compounds containing 1,2,3-triazoles or substituted amines as side chain 10a-o derivatives demonstrated better antifungal properties than those of fluconazole on three significant fungal infections except for 10i. Furthermore, the considerable compounds 10d, 10k, 10n, 10m, and 10o were reported on the Aspergillus fumigatus strain (MIC<sub>80</sub> range: 0.125–1 μg/mL). In addition, 10k can be applied to almost all fungi tested, especially Aspergillus spp. In vitro biological assessments of the compounds 10d and 10k showed potent antifungal properties (Figure 12) [95].

Sadeghpour et al. [96] reported two classes of novel fluconazole-derivatives containing nitrotiazole or 2-(piperazin-1-yl) ethanol moieties, which were evaluated for antifungal activity against standards and clinically isolated yeasts, and their MIC structures were compared with those of fluconazole. Nitrotiazole derivatives 11a-d and compounds 12g and 11b containing two chlorine atoms exhibited good activity against the tested fungus, notably some fluconazole-resistant species. Compounds 11a, 11b, and 12g with 2,4-difluorophenyl or 2,4-dichlorophenyl groups had more excellent antifungal activity (Figure 13). In vitro antifungal activities of new triazole derivatives of ravuconazole and isavuconazole were demonstrated against eight fungal isolates. Compounds 13e (2-F), 13f (2, 3-diF), and 13g (2, 4-diF) in particular displayed activity to ravuconazole. In vitro biological assessments of the compounds 14j, 14k, 14l, 15a, and 15b (MIC = 0.125–0.5 μg/mL) were shown to be more effective than fluconazole (MIC = 0.25 μg/mL) against C. glabrata. SARs revealed that 3-substitutions (14d, 14e, and 14f) were more favorable than the 4-substitutions (14b, 14c), while electron-rich thiophene (14h, 14i) significantly outperformed the electron-deficient pyridinyl group in antifungal activity (14g). Antifungal activity may be enhanced by replacement of the phenyl group of compound 14a by a cycloalkyl group, namely, cyclopentyl (14j), cyclohexyl (14k), and cyclopropyl (14l). In contrast, tert-butyl substitution (14m) only showed modest activity (Figure 15).

Compared to fluconazole and 5-flucytosine, the new fungicidal hybrids of 5-flucytosine and fluconazole showed modest antifungal activity. Surprisingly, a hybrid of 3,4-dichlorobenzene can inhibit clinical-resistant strain C. albicans and the growth of C. albicans ATCC 90023 with MIC values of 0.02 and 0.008 mM, respectively. Compound 16e
inhibited *C. albicans* rapidly, whereas compound 16a lacked fungicidal activity due to the lack of substituents on the phenyl ring (ure 16) [99].

Xu et al. [100] described a series of novel triazole derivatives having γ-lactam that were screened for antifungal activity against six pathogenic fungi *in vitro*. Furthermore, the pyridyl- and phenyl-substituted compounds 17d and 17e showed moderate antimicrobial activity against *Cryptococcus neoformans* and *Candida* spp. (Figure 17).

Zhang et al. [101] reported the triazole sequence as a miconazole analogue with antifungal against five fungi. Among these compounds, 18b, 3,4-dichlorobenzyl had the highest activity. Furthermore, the antifungal activity of 3,4-dichlorobenzyl compound 18b (MIC = 0.5 μg/mL), 2,4-difluorobenzyl derivative 18c (MIC = 4 μg/mL), and 2-fluorobenzyl miconazole analogue 18e (MIC = 16 μg/mL) due to F or Cl may be significantly improved over nitro group compound 18d (nitrobenzyl). Surprisingly, substituted benzyl triazoles (MIC = 0.5–16 μg/mL) showed more potency than monosubstituted benzyl compounds (MIC = 0.5–32 μg/mL) (Figure 18).

The antifungal activity of a novel triazole-piperidine-oxadiazoleside group against clinically important fungal pathogens was investigated. Particularly, 19g (MIC = 0.031 μg/mL) and 20b (MIC = 0.016 μg/mL) showed high activity versus *Candida albicans* including fluconazole-resistant strains. Compounds 19c, 19d, 19h, 19n, and 20a had greater activity (MIC ≤ 0.125 μg/mL) than fluconazole.
Figure 2: Chemical structures of some bioactive 1,2,4-triazole-based marketed drugs.
| Drug/PubChem ID | Chemical name | Action of antifungal | Ref. |
|----------------|---------------|----------------------|-----|
| Itraconazole, CID: 55283 | 2-Butan-2-yl-4-[4-[(2R,4S)-2-(2,4-dichlorophenyl)-1,2,4-triazol-1-ylmethyl]dioxolan-4-yl]methoxy[phenyl]pirazin-1-yl[phenyl]-1,2,4-triazol-3-one | Treatment of onychomycosis and seborrheic dermatitis | [51–53] |
| Fluconazole, CID: 3365 | 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol | Effect on blastomycosis, cryptococcosis, candidiasis, coccidioidomycosis, histoplasmosis, dermatophytosis, and pityriasis versicolor | [54, 55] |
| Isavuconazole, CID: 6918485 | 4-[2-[(2R,3R)-3-(2,5-Difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl]benzonitrile | To treat invasive aspergillosis and invasive mucormycosis | [56, 57] |
| Efinaconazole, CID: 489181 | (2R,3R)-2-(2,4-Difluorophenyl)-3-(4-methylidenepiperidin-1-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol | The treatment of onychomycosis (nail fungal infection) | [58–60] |
| Posaconazole, CID: 468595 | 4-[4-[4-[4-[4-[(2R,3R,S,R)-3-(2,4-Difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy][phenyl]pirazin-1-yl]phenyl]-2-[[2(S,3S)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one | For the treatment of aspergillus and Candida and invasive fungal infections caused by the treatment of Scedosporium and fusarium species of pharyngeal candidiasis (OPC), including OPC retrofitting in the treatment of itraconazole and/or fluconazole | [61–66] |
| Voriconazole, CID: 71616 | (2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol | Treatment includes candidiasis, coccidioidomycosis, histoplasmosis, penicilliosis, aspergillosis, and infections by Scedosporium or Fusarium | [67–70] |
| Albacalone, CID: 208952 | 7-Chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one | Treatment of antiprotozoal agent | [71] |
| Ravuconazole, CID: 467825 | 4-[2-[(2R,3R)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]-1,3-thiazol-4-yl]benzonitrile | Limited activity against species of Scedosporium, fusarium, and zygomycetes | [72–74] |
| Propiconazole, CID: 43234 | 1-[2-(2,4-Dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl][methyl]-1,2,4-triazole | In terms of agriculture as a systemic fungicide grown in meadow plants for seeds and aesthetic value, sports, wheat, mushrooms, corn, wild rice, peanuts, almonds, sorghum, oats, pecans, apricots, peaches, nectarines, plums, and prunes are used | [75, 76] |
| Fosravuconazole, CID: 9807507 | [(2R,3R)-3-(4-Cyanophenyl)-1,3-thiazol-2-yl]-2-(2,4-difluorophenyl)-1-(1,2,4-triazol-1-yl)butan-2-yl][oxy]methyl dihydrogen phosphate | Treatment of onychomycosis, fungal nail infections, and treatment of eumycetoma | [31, 77] |
| Fosfluconazole, CID: 214356 | [(2R,3S)-2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4triazole-1-yl)propan-2-yl][oxy]phosphonic acid | Treatment and prevention of superficial and systemic fungal infections | [78] |
| Flusilazole, CID: 73675 | 1-[4-Bis(4-fluorophenyl)methylsilyl][methyl]-1H-1,2,4-triazole | Used to control fungal infections in a variety of fruit and vegetable products | [79–81] |
| Tefuconazole, CID: 86102 | (RS)-1-(4-Chlorophenyl)-4,4-dimethyl-3-(1H,1,2,4-triazol-1-ylmethyl)pentan-3-ol | Used in agriculture to treat pathogenic fungi of plants | [82] |
| Triadimefon, CID: 39385 | 1-(4-Chloroophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one | Used in agriculture to control various fungal diseases | [83] |
| Metconazole, CID: 86210 | 5-[(4-Chlorophenyl)methyl]-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol | To control a wide range of fungal infections including Alternaria, rust, fusarium, and Septoria | [84] |
| Paclobutrazol, CID: 158076 | (2RS,3RS)-1-(4-Chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-ol | Plant growth inhibitor, triazole fungicide, root growth, and drought stress resistance can be used as a chemical method to reduce the risk of habitat in cereal crops | [85] |
| Myclobutanil, CID: 6336 | 2-(4-Chlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)hexanenitrile | Used as a fungicide which is a steroid demethylation inhibitor, specially inhibiting ergosterol biosynthesis | [86, 87] |

**Table 1: Pharmacological properties and clinical implications of all marketing antifungal drugs.**
(MIC = 0.25 µg/mL). Additionally, the presence of pridinyl group (19a and 19l) 1,2,4-oxadiazole derivatives reduces antifungal activity. On the contrary, compound 19n with furan demonstrated better activity than compound 19b with substitutions on the phenyl ring that revealed distinct effects on antifungal activity. Furthermore, 4-methoxy (19f), 4-fluoro (19h), and 4-trifluoromethyl (19g) alterations demonstrated promising antifungal activity, with 19g showing the most activity against *C. albicans* (MIC = 0.031 µg/mL). Surprisingly, compound 19c exhibited significant fungicidal activity. In contrast, the antifungal activities of 4-ethyl (19k), 4-chloro (19j), and 4-nitro (19o) derivatives were decreased. On the other hand, fluorine-containing 1,2,4-oxadiazole derivatives such as 20f, 20i, and 20j demonstrated modest antifungal activity. Finally, the heterocyclic pyridinyl derivative 20a demonstrated the greatest activity (Figure 19) [102].

Mahmoudi et al. [103] evaluated some 1,2,4-triazole alcohols bearing *N*-(halobenzyl) piperazine carbodithioate scaffold as effective antifungal agent in *vitro* bioassays versus *C. albicans, C. glabrata, C. parapsilosis, C. krusei,* and *C. tropicalis* in which the best activity indicated *N*-(4-chlorobenzyl) derivative 21b with MIC values of 0.063–0.5 mg/mL, being several times more effective than fluconazole. Furthermore, the 3-chlorobenzyl compound 21a displayed a good activity toward both *albicans* and non-*albicans* species of *Candida*. Generally, according to MICs, 2, 4-difluorophenyl derivatives were more active than their dichlorophenyl compounds. In addition, SAR studies revealed that 2,4-difluorophenyl-carbinol was higher than the 2, 4-dichlorophenyl-carbinol scaffold. Moreover, assessment against fluconazole-resistant isolates showed that compound 21b was active against *C. albicans, C. krusei,* and *C. parapsilosis* isolates, with MIC values of 2 to 16 mg/mL (Figure 20).

Ciprofloxacin and itraconazole were employed to screen 1,2,4-triazole derivatives fused with novel benzene-ethanol which were assessed at concentrations ranging from 0.125 to 64 mg/mL. Furthermore, compounds 22a, 22g, and 22i showed much better growth inhibitory activity on *C. albicans* with MIC of 32 mg/mL (itraconazole was introduced as the standard drug MIC 1 mg/mL). Electronegativity, like substituent groups on the *para* and *ortho* positions of a benzene ring, can be effective in antifungal activity (Figure 21) [104].

A class of 1,2,4-triazole derivatives has been tested toward *Magnaporthe oryzae*. Aromatic ring structures revealed that the methyl group at position 1,4 of the phenyl ring 23b and the phenyl moiety at the *para* position of phenyl 23c reduced antifungal activity. When an electron-withdrawing fluorine atom entered this position (23e), the antifungal activity increased slightly. An electron-withdrawing group (tri fluoromethyl group) had a positive efficacy on increasing the antifungal activity of this synthetic series (comparison of antifungal activity 23b with 23f). The introduction of two chlorine atoms to the phenyl moiety...
Existence of 3 methylene units that compounds with methyl-, fluoro- and chloro-substituents, respectively, revealed maximum activity (MIC 0.06-0.25 μg/ml).

The antifungal activity as excellent (0.06-2 μg/mL), good (4-8 μg/mL), moderate (16-32 μg/mL), based on the MIC values.

Derivatives containing an alkylpiperazinyl linker showed strong in vitro antifungal activity.

Figure 5: Antifungal screening of novel hybrids of triazole derivatives.

Compound e(R1 = (p) OCH3-C6H4) also exhibited promising in vitro antifungal activity against some filamentous fungi such as Aspergillus fumigatus.

Figure 6: Chemical structure of novel azole antifungals containing a fused triazinone scaffold.

Fluorine-substituted showed more antifungal effect

Mono-fluorine, orto-CH3, para-CH3 on phenyl ring were improved the activity.

Increasing the number of fluorine atoms substituted on the phenyl ring could decrease the antifungal activity.

Figure 7: Chemical structure of novel triazole analogues featuring isoxazole moieties.
had a distinct effect on increasing antifungal activity. Compound 23g with the 2,4-dichlorophenyl analogue slightly increased the antifungal activity, while compound 23h with the 3,4-dichlorophenyl analogue notably reduced the antifungal activity. The mono chlorine substitution at position 4 of the phenyl ring (23i) reduced the antifungal activity of these synthesized derivatives. According to the preceding considerations, 23e demonstrated remarkable fungicidal activity in this synthetic series.

**Figure 8:** Novel triazole derivatives bearing alkylnyl side chains.

Para-substituted R groups had more antifungal activity rather than ortho and meta substituted R groups.

![Alkyne](image.png)

6b, 6c (MIC80 from 0.0156 mg/mL-0.5 mg/mL)

**Figure 9:** Benzylthio analogues of fluconazole.

The number of chlorin atom was effective in antifungal activities.

![Benzylthio](image.png)

Compounds b and e were active against fluconazole-resistant isolates of *Candida albicans* and *Candida parapsilosis* (MICs = 0.063-16 mg/mL).

**Figure 10:** The study of antifungal properties in new fluconazole derivatives.

Replacing one of the carbon atoms in the side-chain by an oxygen as in compound f has decreased the activity.

![Fluconazole Derivative](image.png)

4 of the phenyl ring (23i) reduced the antifungal activity of these synthesized derivatives. According to the preceding considerations, 23e demonstrated remarkable fungicidal activity in this synthetic series. The effect of the chlorine atom on the various positions of the phenoxy moiety (ring
Compound 9e was displayed the lowest activity against *C. albicans*.

Compound (b & d) showed better activity than other compounds against *A. niger*.

\[ a: R = 2-Cl; b: R = 4-Cl; c: R = 3F; d: R = 4-F; e: R = 4-NO_2 \]

**Figure 11:** Structure of azoles containing imidazole derivatives.

Compounds d, k, n, m and o revealed antifungal activities on the *Aspergillus fumigatus* strain (MIC80 range: 1-0.125 𝜇g/ml).

Especially, compound k showed strong activity against all tested fungi.

**Figure 12:** Antifungal assessment of new triazole derivatives.

Nitrotriazole derivatives were favorable antifungal activity.

a-d and g, possessing nitrotriazole moiety, indicated maximum antifungal activity.

**Figure 13:** Fluconazole-derivatives bearing nitrotriazol or 2-(piperazine-1-yl) ethanol moieties.
B) such as 24a, 24b, and 24c can lead to an increase in antifungal activity. As a result, the fungicidal activity of the analogue without a chlorine substituent at ring B (24j) was the most effective against *M. oryzae* among these compounds (Figure 22) [105].

4.2. 1, 2, 4-Triazole Hybrids. Al-Wabli et al. [106] estimated the antifungal characteristics of a variety of novel indole-triazole compounds. The MIC value of compound 25f, which included N-phenyl and 3,4-dichlorobenzyl moieties, was 2 mg/mL against *Candida albicans*. In addition, the para
benzyl substituent exhibits antifungal activity. Also, MIC values for compounds 25b, 25c, 25d, 25e, 25f, and 25g having a phenyl moiety on the triazole ring are 250–500 μg/mL against *Bacillus subtilis*. Meanwhile, compounds 25o, 25p, and 25q with an *N*-cyclohexyl substituent showed moderate to good activity toward the tested *Candida albicans* strain (Figure 23).

The nortopsentin analogues containing 1,2,4-triazole demonstrated good antifungal activity. Compounds 26a, 26d, and 26f were more fungicidal toward *Cercospora*...
Figure 19: Structure-activity relationship between triazoles bearing piperdine-oxadiazoleside chains.

Two fluorine-containing compound (19c) showed excellent antifungal activity. The existence of pyridinyl group (19a and 19i) led to decrease of the antifungal activity. Substitutions on the phenyl group of 19a had various effects on the antifungal activity. 4-methoxy (19f), trifluoromethyl (19g), and fluoro (19h) substitutions displayed good antifungal activity. The 4-trifluoromethyl derivative 19g showed the best activity against C. albicans (MIC = 0.031 μg/mL).

20f, 20l, 20h with fluorine-containing showed moderate antifungal activity. 20b (MIC = 0.016 mg/mL) showed highly activity against Candida albicans counting fluconazole-resistant strains. The pyridinyl derivative 20a that is heterocyclic compound, displayed the most activity.
arachidicola" Hori than chlorothalonil and carbendazim (commercial fungicides). Compounds 26d and 26f indicated better actions against most of the fourteen plant pathogens (Figure 24) [107].

According to the study by Ahuja et al. [108], compound 27c has a lower ED50 value than the triazole fungicide propiconazole. Significantly, compound 27c showed the highest activity compared with other experimental fungi, with an ED50 value of 16 to 21 μg/mL, which is higher than the ED50 values of the standard commercial fungicides used (tilt: 20–25 μg/mL and carbendazim: 150–230 μg/mL) (Figure 25).

Microbiological studies revealed that benzimidazole-1,2,4-triazole hybrid compounds 28m, 28n, 28f, and 28g had good fungicidal activity (MIC50 values of 0.78 to 1.56 μg/mL) because of the presence of a fluoro or chloro substituent at the C-para position of phenyl, whereas compounds 28c, 28a, and 28b did not. Compounds 28d and 28e demonstrated adequate fungicidal activity (MIC50 values = 1.56–3.12 μg/mL). Compound 28l exhibited comparable antifungal activity with reference drugs fluconazole and ketoconazole. As a result, chloro or fluoro substitution at the C-5 position of benzimidazole is vital and could have had a significant influence on antifungal activity (Figure 26) [109].

The benzimidazole-triazole compounds showed moderate antifungal activity toward Candida krusei (ATCC 6258), Candida glabrata (ATCC 90030), Candida albicans (ATCC 24433), and Candida parapsilosis (ATCC 22019), with MIC50 values ranging from 12.5 to 0.78 mg/mL. The findings revealed that compound 3,4-dihydroxy has an influence on the activity (Figure 27) [110].

Novel tri-substituted 1,2,4-triazoles containing benzimidazole were tested for antifungal efficacy against three plant pathogenic fungus, and compounds 30e and 30g showed potent activity against Venturia nashicola. However, 30d and 30f indicated sufficient activity against Fusarium graminearum (Figure 28) [111].

Luo et al. [112] reported a new group of benzimidazole-derived triazoliums and naphthalimide triazoles that have been thoroughly tested for antifungal activities. Triazoliums 31g and 31f with 3-fluorobenzyl and 2-chlorobenzyl moiety demonstrated the highest antifungal activity (MIC = 2–19 mg/mL) against all tested fungal strains. However, 2,4-di-chlorobenzene triazolium 31h (MIC = 7–29 mg/mL) showed more efficacy than fluconazole (MIC = 7–230 mg/mL). Furthermore, bis (4-fluorobenzyl) triazolium 31b (MIC = 4–19 mg/mL) displayed high activity against all of the microorganisms tested except S. cerevisiae (Figure 28).

The antifungal efficacy of 1,2,4-triazoles having quinoline moiety against A. fumigatus and Candida albicans was highest owing to methoxy and chloro substituents. As a result, 32e, 32g, and 32m derivatives with methoxy and
Methyl group on the phenyl ring (b) and phenyl moiety at position 4 of phenyl ring (c) decreased antifungal activity. The 3, 4-dichlorophenyl analogue (h) and mono chlorine substitution at position 4 of the phenyl ring (i) significantly reduced the antifungal activity.

Electron-withdrawing fluorine atom (e) exhibited the most potent antifungal activity.

**Figure 22:** 1-(4-Phenoxymethyl-2-phenyl-[1, 3] dioxolan-2-ylmethyl)-1H-1,2,4-triazole derivatives.

Compound f including N-phenyl and 3, 4-dichlorobenzyl moieties illustrated MIC value of 2μg/ml against candida albicans.

**Figure 23:** Evaluation of the antifungal activity of new indole-1,2,4-triazole conjugates.
The presence of fluorine atom in meta-fluorobenzene ring 29d and ortho-trifluoromethyl compound 29f showed higher antifungal activities.

Figure 24: 1,2,4-Triazole derivatives containing nortopsentin.

Benzimidazole moiety

Fluoro or chloro substituent improve the activity

Fluorin atom enhance the activity

No difference between CH₃, C₂H₅

Figure 26: SAR outline of the benzimidazole-1,2,4-triazole hybrid compounds.
**Figure 27:** Structure of new benzimidazole-triazoles.

**Figure 28:** Tri-substituted 1,2,4-triazoles containing benzimidazole moiety.

**Figure 29:** Structure-activity relationships between benzimidazole-derived naphthalimide triazoles.
Methoxy and chlorin groups could be effective on antifungal activity for example: e, g, m. The MIC values of the tested compounds a, b, c, n, and 1 are higher than 1.5 μg/mL.

- **e**: (MIC = 0.40 mg/mL) C. albicans
- **g**: (MIC = 0.20 mg/mL) C. albicans
- **m**: (MIC = 0.20 mg/mL) C. albicans

**Figure 30**: 1,2,4-Triazole hybrids of 2-(aryloxy) quinolones.

Existence Cl on the aromatic ring has improved the antifungal activity in comparison to OCH₃, CH₃. Quinoline moiety

**Figure 31**: Antifungal activity evaluation of quinolone-triazole derivatives.

Amongst these compounds, c and h indicate noticeable the activity

**Figure 32**: Quinazoline thioether-1,2,4-triazolo [4,3-a] pyridine derivatives.
chloro substituents had the highest enhanced activity (Figure 30) [113].

D’Souza et al. [114] investigated the fungicidal of new quinoline-triazoles. Compounds 33b and 34b with chlorine substituents on the aromatic ring demonstrated more antifungal activity than (33e, 33f, 34e, and 34f) that included OCH₃ and CH₃ (Figure 31).

Fan et al. [115] investigated the antifungal activity of 1,2,4-triazolo-[4,3-a]pyridine-containing quinazoline thioether derivatives at 50 mg/mL. Except for compound 35c against the fungi Verticillium dahlia and Fusarium oxysporum (inhibition rates of 65.4 and 52.5%, respectively), all of these compounds failed to demonstrate apparent fungicidal activity (≥45%) against the case fungi, with compound 35h against the pathogen V. dahliae (46.8%) (Figure 32).

Most of the 2-phenoxy-benzo[g][1,2,4]triazolo[1,5-a]quinazine derivatives indicated in vitro antifungal activity against ten fungal strains except C. neoformans. Nevertheless, 37a and 37b exhibited activity only against A. niger and A. fumigatus. Compounds 37c, 37d, 37e, 37f, and 38b revealed excellent fungicidal activities against A. fumigatus (MIC = 0.98–1.95 μg/mL), and 37g showed the ability to produce amphotericin B (MIC = 0.49 μg/mL). In contrast, 38b had stronger inhibition with respect to the reference drug toward S. racemosus (MIC = 0.49 μg/mL) and 37e confirmed similar activities to amphotericin B (MIC = 0.98 μg/mL). In addition, compounds 37c-37e, 38a, and 38b showed the highest activity versus G. candidum (MIC = 0.49–0.98 μg/mL) as compared with amphotericin B (MIC = 1.95 μg/mL) (Figure 34) [117].

El-Attar et al. [118] investigated the antifungal activities of 1,2,4-triazolos [4,3-a]-quinazoline derivatives with various substituted pyrazole moieties at position 4. When compared with the reference clotrimazole (MIC = 12.5 μg/mL), compound 39 demonstrated reasonable growth inhibition (MIC = 25 μg/mL) against C. Albicans. Compounds 39, 41a, and 41b inhibited only weakly (MIC = 50 μg/mL) growth against the same organism. Clotrimazole activity against the fungus A. fumigatus was reduced by one-quarter in studies 39 and 42. Regarding the activity against R. oryzae, compounds 39, 40, 41a-c, and 42 showed weak growth inhibition (MIC = 25 μg/mL) when compared with the reference clotrimazole (MIC = 6.25 μg/mL) (Figure 35).

Yang and Bao [119] demonstrated that 1,2,4-triazole derivatives (43a-43k) containing N-(substituted phenyl) acetamide and the quinazolinylipiperidinyl moiety group did not exhibit remarkable inhibition activity against phytopathogenic fungi such as Phytophthora infestans, Verticillium dahliae, and Gibberella zeae) at 50 mg/mL. save compounds 43e and 43k that showed modest inhibitory activity against the fungus G. zeae (Figure 36).

Sompalle et al. [120] investigated the antifungal activity of a class of 1,2,4-triazole-quinazolinethiones (44a-l) against Aspergillus niger (A. niger) and Aspergillus flavus (A. flavus) in combination with the commonly used antifungal drug flucconazole (Figure 37).

All triazole derivatives with N-alkylated groups were tested for fungicidal activity toward Candida albicans and Aspergillus flavus and anthelmintic activity against Pherecima posthuma, and the compound containing group CH₃ at the ortho position of the phenyl ring showed good inhibition with the inhibition zone 24.17 ± 0.32 and 15.02 ± 0.41 mm against A. flavus and C. albicans in comparison with a standard antifungal drug, Nystatin, while the antifungal activity of the other structures was lower (Figure 38) [121].

Jin et al. [122] investigated the fungicidal activity of novel compounds containing 1,2,4-triazole with different substituted groups toward Gibberella nicotianacola, Pythium solani, Gibberella saubinetii, and Fusarium oxysporum Esp. niveum in vitro. Compound 46 had good activity against the case fungus, indicating that 1,2,4-triazole-imidazole can contribute to antifungal properties. Methyl at position Q increased the activity, the activity order is 47>46, and compound 47 demonstrated a remarkable antifungal activity. As a result, positions P and Q may have an impact on the activity at the same time (Figure 39).

1,2,4-Triazole derivatives with a pyrimidine moiety were evaluated for fungicidal activity, with compounds 50c and 50d showing the best antifungal activity against Phomopsis sp. that was even better than pyrimethanil (32.1 mg/mL). Compound 50d, on the other hand, had higher activity against B. cinerea and B. dothidea with 55.1 and 40.1 mg/mL, respectively, when compared with Pyrimethanil (57.6 and 62.8 mg/mL) (Figure 40) [123].

Antifungal evaluation [1, 2, 4] of triazole [5,1-b] quinazolin-8(4H) one scaffolds (51a-n) in vitro exhibited that compounds 51e and 51i display higher activity than standard drug griseofulvin (MIC 500 mg/mL) against C. albicans. Surprisingly, the substitution at the C-6 carbon of the final moiety and para-substituted phenyl ring was responsible for variable biological results, while the triazole with nonsubstituted or diversely para-substituted (Cl, OCH₃, and NO₂) phenyl core or heterocyclic nucleus showed the best properties. In addition, the compounds having OCH₃ group substitution (compound 51f) effectively showed poor inhibition toward A. clavatus and A. niger inhibited the S. aeruginosa, P. aeruginosa, and S. pneumonia strains, although the derivative with the electron-withdrawing group such as NO₂ (compound 51i) efficiently inhibited the E. coli bacterial strain as well as was found potent toward the C. albicans strain. Finally, compound bearing heteroaryl substitution (compound 51l) led to the improvement in the activity against the E. coli strain (Figure 41) [124].

All 1,2,4-triazole having amine derivatives were evaluated and shown to be effective in inhibiting fungal pathogens with MIC values ranging from 1 to 256 μg/mL. They were proposed as the potential antifungal agents that synthesized under optimized conditions as 3(5)-substituted 1,2,4-triazol-5(3)-amine 52. As starting materials, however, several
heteroaryl hydrazides and aryls were used as starting materials (Figure 42) [125].

Appna et al. [126] described the fungicidal activity of novel 1,2,4-triazole fused pyrido [2,3-d] pyrimidine derivatives (53a-d and 54a-c) against different Candida strains. The antifungal activities of the synthesized compounds 53d, 54b, and 54c were shown. SAR investigations revealed that trifluoromethyl, fluoro, bromo, and nitro groups on the furyl and phenyl rings of pyrido [2,3-d] pyrimidine could increase antifungal activity. Compounds (53d, 54b, and 54c) 4-fluoro-2-chlorophenyl triazole and 2-furyl substituent in pyrido [2,3-d] pyrimidine exhibited the best activity. As well, 4-nitrophenyl triazole in combination with 2-furyl pyrido [2,3-d] pyrimidine (54b) exhibited the same activity. The antifungal effects of 2-chloro-4-fluoro phenyl triazole with 2-phenyl pyrido [2,3-d] pyrimidine (53d) were favorable (Figure 43).

A new series of 1,2,4-triazole derivatives were synthesized by Singh et al. The antifungal characteristics of the compounds showed that most of them could effectively inhibit the growth of the tested fungal strains. However, none of them were superior to the reference drug fluconazole. Compound 55l had the most potent antifungal activity against both fungi. 55l revealed comparable activity (A. niger: MIC = 11.7 μM; C. albicans: MIC = 10.9 μM) with the reference fluconazole (A. niger: MIC = 9.4 μM; Candida albicans: MIC = 10.2 μM). Apart from that, antifungals 55f (A. niger: MIC = 15.6 μM; C. albicans: MIC = 14.1 μM) and 55a (A. niger: MIC = 28.1 μM; C. albicans: MIC = 18.8 μM) were found to be potent (Figure 44) [127].

Jin et al. [128] investigated the antifungal effects of a variety of 4-amino-5-substituent 1,2,4-triazole-3-thione Schiff bases toward Pythium solani, Gibberella nicotiancola, Gibberella saubinetti, and Fusarium oxysporum f.sp. niveum. Compounds 56a and 56b showed antifungal activity In general, all the compounds displayed favorable antifungal activity against Gloeosporium fructigenum.

Figure 33: 1,2,4-Triazole containing quinazolin derivatives.

Figure 34: Chemical structure of 2-phenoxy-benzo-triazole quinazoline derivatives.
Zhang et al. [129] displayed a new class of piperazine-containing 3-(furan-2-yl)-1,2,4-triazole important in vitro fungicidal activity toward a variety of plant fungi. In particular, compounds 58a, 58b, 58c, 58d, 58e, 58f, 58g, and 58h showed triadimefon against a variety of test fungi. Compounds 58g, 58f, and 58h having \( R_1 = \text{C}_3\text{F}_3 \) performed better than others (\( R_1 = \text{F} \) or Cl). In comparison, the SARs of the compounds revealed 2-positions of the para position of substituted benzylideneamino and ortho position of phenyl-piperazine, where a large group would be favorable for higher fungicidal activity. Finally, compounds with an EWG at the benzyl ring position or an electron-donating group at the 2,4-position of the benzene ring, such as 58b and 58a, demonstrated higher activity (Figure 46).

Trialkylamine compounds having a triazole moiety were evaluated in vitro for antifungal activity against six phytopathogenic fungi at 50 mg/mL (Magnaporthe grisea, Curvularia lunata, Alternaria solani, Fusarium solani, A. alternata, and F. graminearum). Compounds 59k (3-F), 59m (3,4-diCl), and 59n (4-Br) had good activity toward

**Figure 35:** Antifungal study on pyrazol-1,2,4-triazol-quinoxalines.

Compounds 39, 41a, and 41b exhibited weak growth inhibition (MIC = 50 μg/ml) against the same organism.

**Figure 36:** 1,2,4-Triazole derivatives containing the quinazolinylpiperidinyl moiety.
A. solani with EC50 values of 2.88, 8.20, and 1.92 mg/mL, respectively. Furthermore, compounds 59c (4-Cl), 59f (3,4-diCl), and 59d (2-Br) showed good antifungal activity against F. graminearum with EC50 values of 11.60, 5.14, and 16.24 mg/mL, respectively. Also, electron-donating groups 59o (Me) or 59p (OMe) considerably reduced the activity. In contrast, the presence of halogen atoms such as 59k (3-F), 59c (4-Cl), (3,4-diCl), and 59n (4-Br) might increase the activity (Figure 47) [130].

1,2,4-Triazole-pyridine products with hydrazone scaffold (compounds 60a-60h) were tested in vivo at 100 mg/mL against Stemphylium lycopersici (Enjoji) Yamamoto (SL) and Fusarium oxysporum sp. Cucumebrium (FO). Compound 60d as well as compounds having electron-donating groups at the 4-position of benzene such as 60e (p-N(CH$_3$)$_2$), 60b (p-F), 60f (p-CF$_3$), and 60g (p-CH$_3$) demonstrated strong antifungal activities. As a result, the furan ring-substitution exhibited more activity against SL and FO than the aryl or alkyl groups. Furthermore, both poly- and single-substituted benzene compounds showed excellent activity against FO (Figure 48) [131].

Remarkable antifungal activity of a number of new 1,2,4-triazole derivatives against different strains of Aspergillus fumigatus, Candida albicans, and Candida crocus has been reported in comparison with those of commercial fungicides ketoconazole and itraconazole. All of the derivatives investigated, the dichloro urea analogue and bromo substituted triazole, stand out as the most favorable compounds. The most potent compounds against A. fumigatus were 64l, 61b, 61a, and 61c, with MIC values ranging from 0.114 to
Compound 46 showed best antifungal activity, which showed methyl at position Q and 4-imidazol-benzyl at position P can keep the antifungal activity.

Methyl at position Q can improve the antifungal activity

**Figure 39:** Chemical structure of novel 1,2,4-triazole derivatives.

**Pyrimidine moiety**

**Compounds 50c and 50d were favorable antifungal activity**

50d displayed better fungicidal activities against *B.cinerea* and *B.dothidea* with (EC50) values 55.1 and 40.1 mg/mL.

**Figure 40:** The structure of triazole derivatives with a pyrimidine moiety.

**Quinazoline**

**Compound containing heteroaryl substitution (compound l) effectively increased activity against E.coli strain.**

**Compounds 51e and 51i display better activity than standard drug griseofulvin (MIC 500 mg/mL against *C. albicans*)**

**Compound having OCH3 group substitution (compound f) effectively**

**Compounds show poor inhibition against *A.niger* and *A.clavatus* para-substituted phenyl ring and the substitution at the C-6 carbon of the final moiety are responsible for varying the biological results**

The compound with electron withdrawing group like NO2 (compound 51i) efficiently inhibited the *E.coli* bacterial strain and also found active against *C.albicans* fungi strain.

**Figure 41:** [1, 2, 4] Triazolo [5,1-b] quinazolin-8(4H) derivatives.
All compounds were effective at inhibiting fungal pathogens with MIC values 1 to 256 $\mu$g/mL.

Figure 42: Study of 1,2,4-triazole derivatives.

Compounds 53d, 54b and 54c showed excellent activity against all the fungal strains at the MIC value of 3.9 $\mu$g/mL except for C. albicans MTCC 7315, C. parapsilosis MTCC 1744, which is equal to the standard miconazole. The order of activity is found to be 53d<54b = 54c.

The existence of fluoro, trifluoromethyl, bromo and nitro group on phenyl and furyl in pyrido (2, 3-d) pyrimidine was significant to increase antifungal activity.

2-Furyl substituent in pyrido (2, 3-d) pyrimidine (compound 54c) showed excellent antifungal activity.

Figure 43: Chemical structure of new 4-hydrazone functionalized/1,2,4-triazole fused pyrido [2,3-d] pyrimidine derivatives.

Compound f (A. niger: MIC = 15.6 $\mu$M; C. albicans: MIC = 14.1 $\mu$M) and compound a (A. niger: MIC = 28.1 $\mu$M; C. albicans: MIC = 18.8 $\mu$M) were also found to be potent antifungal.

Compound 551 exhibited most potent antifungal activities against both fungus.

Figure 44: Antifungal evaluation of novel bioactive 1,2,4-triazoles.

Compounds 56c, 56d, and 57a showed good antifungal activity against four pathogens.

Derivative 56a indicated better effective against gibberella nicotiancola and gibberella saubinetii than triadimefon.

Figure 45: Chemical structure of new 1,2,4-triazole Schiff base derivatives.
Compounds containing an electron-donating group at the 2- or 4-position of the benzene ring or an electron-withdrawing group at the position of the benzyl rings, such as 58a and 58b, exhibited higher activity.

Compounds f, g, and h bearing CF3 were more favorable rather than others containing F, Cl groups.

Figure 46: Study of the structure of new piperazine-bearing 3-(furan-2-yl)-1, 2, 4-triazole.

Electron-donating substituents like Me (59o) or OMe (59p) significantly decreased the activity. Halogen atoms could increase the activity like 2, 4-diCl, 3, 4-diCl whilst OMe group decreased the activities.

Compounds containing the para position of substituted benzylideneamino and ortho position of phenylpiperazine where, a bulky group would be favorable for higher antifungal activity.

Figure 48: (SAR) analysis of 1,2,4-triazolo-pyridine derivatives containing hydrazone moiety.
0.230 μmol/mL. Instead, amide analogues such as 62f can influence the activity, with the amide moiety 62f having higher activity than less bulky triazoles such as 65o and 65p. Furthermore, compound 63h with the sulfonamide substitution is responsible for the activity reduction. Compounds 64l and 61b have the highest activity, being several times more potent than ketoconazole. Conversely, these derivatives were less active than itraconazole (Figure 49) [132].

Dincel et al. [133] screened a group of novel hydrazine-carbothioamide (66), 4-thiazolidinone (67), and 1,2,4-triazole-3-thione (68) for the fungicidal properties against C. parapsilosis ATCC 22019, C. Albicans ATCC 10231, M. gypseum NCPF580, C. krusei ATCC 6258, T. tonsurans NCPF245, and T. mentagrophytes var. echinacea. Generally, 1,2,4-triazole-3-thiones and 4-thiazolidinones showed better fungicidal activity rather than thiosemicarbazide derivatives. As a result, the 3-allyl substitution of 4-thiazolidinones is critical for their antifungal activity. Compounds 67d (R=CH₂CH=CH₂), 68c (R=C₃H₇), and 68d (R=CH₂CH=CH₂) had the highest fungicidal activity against S. aureus (MIC = 32 μg/mL). Also, 68c (R=C₃H₇) and 68d (R=CH₂CH=CH₂) showed the greatest activity against E. coli (MIC = 32 μg/mL). In addition, 68d (R=CH₂CH=CH₂) showed the greatest activity towards P. aeruginosa (MIC = 32 μg/mL) (Figure 50).

Cheng et al. [134] investigated the fungicidal activity of new groups of 1,2,4-triazole benzoyl aryl amines. The findings revealed a clear relationship between the structure and training in these compounds as well. The electron-withdrawing group oi-pr(isopropyl) at the para position has a favorable impact on high activity, and the preferred groups were alkoxy carbonyls. This compound indicated the most effective fungicidal activities with EC50 values of 0.12, 0.19, and 0.01 mg/mL against S. sclerotiorum, F. graminicola, and G. graminis var. tritici, respectively. Alkoxy carbonyl of these ester carbonyls revealed the highest activities (69a-b and 69c-g). In contrast, no significant increase in the activity was observed when more than one electron-withdrawing group was added to aniline. For instance, if the second electron-withdrawing groups such as CF₃ or Cl were added to the meta position of aniline, the activity against G. graminis var. tritici would be reduced (69e and 69f) (Figure 51).

The evaluation indicated that all 1,2,4-triazole derivatives had fungicidal activity, with MIC values ranging from 0.02 to 0.52 mM, which was better than bifonazole (MIC values of 0.32–0.64 mM) and ketoconazole (MIC values of 0.28–1.88 mM). Compound 70c, having a MIC value of 0.02–0.04 mM, exhibited the best antifungal activity rather than compound 70a (Figure 52) [135].

Wu et al. [136] evaluated the fungicidal activity of a novel series of 1,2,4-triazole derivatives containing an amide moiety. Compounds 71a, 71d, 71e, and 71f had the highest antifungal activity against Botrytis cinerea. Meanwhile, compound 71b, when R was CH₃, exhibited better antifungal property against Phomopsis sp., compared with that of pyrimethanil. SAR studies revealed that 4-pyridine in the R substituent group and the smaller alkyl substituent groups (H or CH₃) could have a favorable influence on the activity, such as 71a>71b>71c. Meanwhile, when R = OH is added to the 4-positions of phenyl and substituted phenyl, the action against Phomopsis sp., B. dothidea, and B. cinerea rises in the sequence 71d>71g>71k. Furthermore, when R = 4-pyridine, the antifungal activities of the corresponding compound 71h against Phomopsis sp., B. dothidea, and B.
Hydrazinecarbothioamide (66), 4-thiazolidineone (67), and 1,2,4-triazole-3-thione (68) were screened for antifungal activity against *C. albicans* ATCC 10231, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *M. gypseum* NCPF80, *T. mentagrophytes* var. *erinacei*, *T. tonsurans* NCPF245.

**Figure 50:** Structure of hydrazinecarbothioamides, 4-thiazolidinones, and 1,2,4-triazole-3-thiones.

1, 2, 4-triazole-3-thione derivatives and 4-thiazolidinone showed higher antifungal activity rather than thiosemicarbazide derivatives.

**Figure 51:** The structure of 1,2,4-triazole benzoyl arylamine compounds.

Compound 70c with MIC at 0.02-0.04 mM exhibited the best antifungal activity rather than compound 70a.

**Figure 52:** New vinyl-1, 2, 4-triazole analogues.
cinerea were higher than those of compound 71e (R = 2-pyridine) (Figure 53).

Yurttaş and Cantırk [137] investigated triazole-oxadiazole compounds against C. krusei, C. glabrata, C. albicans, and C. parapsilosis and found that triazole-oxadiazole derivatives 72e and, particularly, 73i had the highest activity against C. glabrata and C. albicans (MIC90 = 62.5 mg/mL). The oxadiazole rings of these derivatives differ due to the benzothiazole and phenyl rings linked to the acetamide molecule. Meanwhile, compounds 72e (R = NO2) and compound 73e (R = F) were found to have the highest activity (Figure 54).

Li et al. [138] reported a group of N-phenylacetamide containing 1,2,4-triazole derivatives (74a-f) that were screened in vitro for antifungal assessment, and specific compounds, such as 74b-f derivatives, inhibited the growth of the tested fungus. Among all synthesized compounds, 74a exhibited no antifungal activity. Moreover, mono-substituted halogen substituents in the benzene ring, in either the ortho or the para position, displayed antifungal activity (Figure 55).

The antifungal properties of the synthesized 1,2,4-triazole-3-yl-mercapto derivatives toward two Candida albicans strains (C. albicans ATCC 10231 and C. albicans ATCC 18804) and one non-Candida albicans strain (C. krusei ATCC 6258) were evaluated. Its antifungal activity was shown by the presence of a halogenated aryl substituent linked to the 3-mercapto group. Compounds 75d, 75f, and 75g had smaller MIC values than the other 1,2,4-triazolyl-thioethers, indicating that the 1,2,4-triazole-3-yl-mercapto derivatives with a 4-Cl-phenyl component had more excellent antifungal activity against the Candida krusei ATCC 6258 strain. In this series, compound 75d in this series has the lowest MIC value (Figure 56) [139].

Antifungal activities of new myrtenal derivatives containing 1,2,4-triazole were tested against Physalospora piricola, Fusarium oxysporum f.sp. cucumerinum, Cercospora arachidicola, Alternaria solani, and Gibberella zeae at...
Among these compounds, 76a (R = Et), 76c (R = i-Pr), and 76e (R = o-NO2 Bn) had the most significant antifungal activity against P. piricola. Among these derivatives, 76a (R = Et), 76c (R = i-Pr), and 76e (R = o-NO2 Bn) indicated the highest antifungal activity against P. piricola (Figure 57) [140].

Cheng et al. [141] evaluated a series of 4,5-disubstituted-3-S-(β-D-acetyl glycosyl)-1,2,4-triazoles for their antifungal activities in which compounds revealed reasonable activities at the concentration of 50 μg/mL. Particularly, compounds 77c, 77g, 77n, and 77p displayed 60–68.6% inhibitory rates against B. cinerea and 77c, 77d, 77g, 77m, 77n, and 77p derivatives exhibited 63.6%–78.8% inhibitory rates against S. sclerotiorum, with the antifungal activity of R2 = ethyl being lower than those of the other compounds against S. sclerotiorum. In other words, compounds containing a galactosyl moiety, such as compound 77n, demonstrated highly favorable antifungal action, whereas compounds with a glucosyl moiety showed comparably weak antifungal activity (Figure 58).

Bitla et al. [142] synthesized and screened bis(1,2,3 and 1,2,4)-triazole derivatives for antifungal activity, and compounds 78a, 78d, 78f, and 78i had the highest activity. It is remarked that bromo and chloro substitutes at meta and para positions of the aryl ring were highly important. Compound 78f indicated superior activity against S. aureus MTCC 96 (MIC 3.9 ± 0.05 μg/ml) (Figure 59).

Beyzaei et al. [143] synthesized and tested a new class of 1,2,4-triazole-3-thiones in glycerol/potassium carbonate and assessed them for antifungal activity. Significant inhibitory
special effects were detected notably against fungal infections. *Fusarium oxysporum* and *Aspergillus fumigatus* were inhibited with all of them. The most excellent antifungal activities indicated triazole 79c that contains R=4-nitro-phenyl has the highest antifungal activity as well as the high-affinity binding to the receptor. Hydrogen bonds between the N-1 azole ring and some amino acid residues in the target enzyme interact predominantly. These findings might aid in the development of antifungal drugs (Figure 60).

Some studies have been conducted on the fungicidal activities of the novel 1,2,4-triazole derivatives. Compounds 80a-d (Figure 61) in particular showed high antifungal activity. The relationship between biological activity and structure revealed that compounds with the sulfur atom exclusively in the thiol form exhibited activity. Furthermore, compounds 80a and 80c, at a concentration of 1000 mm, inhibit the growth of *C. albicans* by 35–40%, respectively [144].

Sidhu and Kukreja [145] reported new compounds based on lead hybridization of 1,2,4-triazoles with fluorinated benzothiazol-2-yl that were tested for fungicidal activity against *P. striiformis, D. oryzae*, and *U. hordei* in contrast with conventional fungicides. Furthermore, derivatives 81b.
and 81c are active against most of the experimental fungi. Compounds 81a and 81e caused the antifungal potential of EC50 0.23 and 0.19 mmoles/L, respectively, against *P. striiformis* that was compared to the standard fungicide (EC50 value 0.10 of mmoles/L). Compound 81a has the greatest EC50 value (0.17 mmoles/L) against *U. hordei* when compared to Vitavax (EC50 value 0.09 mmoles/L) (Figure 62).

Shingare et al. [146] presented a new series of pyrazole bearing triazolo-thiadiazole derivatives (82a-l) which were evaluated to have antifungal activity versus *A. Niger,* *C. H N N S R1 R2*

Figure 60: Antifungal study on 4,5-substituted 1,2,4-triazole-3-thiones.

Compounds containing the sulfur atom only in the thiol form showed antifungal property

Figure 61: Derivatives of 1,2,4-triazole with a thiomethyl bridge.

Benzothiazole

Figure 62: Series of new fluorinated benzothiazol-2-yl-1,2,4-triazoles.
Fluoro substitution at para-position of phenyl ring (82) increased antifungal activities.

**Figure 63:** Chemical structures of pyrazole bearing triazolo-thiadiazole derivatives.

82
- a: R = 4-OCH3-Ph
- b: R = 2-OCH3-Ph
- c: R = 2, 4-di-OCH3-Ph
- d: R = 2-Cl-Ph
- j: R = 4-F-Ph
- k: R = 4-pyridinyl

**Figure 64:** The study of the chemical structure of triazole based heterocycles.

83a: Ar = 4-Cl-Ph, R = 4-OCH3-Ph
83b: Ar = 4-Cl-Ph, R = 4-OCH3-Ph
83c: Ar = 2, 4-di-Cl-Ph, R = 4-OCH3
83d: Ar = 4-CH3-Ph, R = Ph
83e: Ar = 4-OCH3-Ph, R = 4-NO2-Ph

83d compound (MIC = 90 µg/mL) against A. flavus.
83i compound (MIC = 110 µg/mL) against A. flavus.

84a compound had the best antifungal activity with (MIC = 70 µg/mL) against A. flavus.
84c compound (MIC = 85 µg/mL) against A. flavus.

84a: Ar = 4-OCH3-Ph, Ar’ = 4-Br-Ph
84b: Ar = Ph, Ar’ = 4-Br-Ph
84c: Ar = 4-Cl-Ph, Ar’ = 4-Br-Ph
84d: Ar = 2, 4-di-Cl-Ph, Ar’ = 4-Br-Ph

**Figure 65:** 1,2,4-Triazole analogues having oxime ether and phenoxy pyridinyl moiety.

85
85a: R2 = H, R3 = 2-Cl
85b: R2 = H, R3 = 2-Br
85c: R2 = H, R3 = 2-t-But
85d: R2 = H, R3 = 4-CF3
85e: R2 = H, R3 = 3-Cl
85f: R2 = H, R3 = 4-NO2
85g: R2 = H, R3 = 4-Cl

Electron-withdrawing group at 2-position on the phenyl ring were favorable the activity
Halogen group could have good antifungal affect especially Cl, on the phenyl ring
a bulky 2-tert-butyl group on phenylring were unfavorable
CF3,NO2 groups effect could impove the activity
The antifungal activity of 1,2,4-triazolo containing thiadiazoles (83a-e) and 1,2,4-triazol-3-ylthio-N-aryl) acetamides (84a-d) was evaluated. Compound 84a had good antifungal activity toward A. flavus with a MIC value of 70 μg/mL compared with standard fluconazole; derivatives 83d, 83a, 84c, and 84a demonstrated moderate activity (Figure 63) [147].

Bai et al. [148] assessed several novel 1,2,4-triazole analogues for antifungal activity against eight phytopathogens and found that the majority of them exhibited acceptable to outstanding fungicidal characteristics. Almost all of the compounds demonstrated moderate to excellent fungicidal activity toward the tested phytopathogens. In general, the fungicidal activity of methyl oxime ether group 85 (R1 = methyl) was significantly greater than benzyl oxime ether group 86 (R1 = benzyl). It is clear that electron-drawing groups at the 2-position of the phenyl ring, such as 85b, 85d, 86b were more helpful for fungicidal activity. Because of the halogen substituent effect, compounds 85b, 85d, 85g, 85k, and 86b demonstrated significantly higher inhibitory activities against fungal pathogens than other compounds, with the chlorine atom playing a more significant role in improving fungicidal activity in each position of the benzene ring.

Furthermore, the prevention rates of compounds 85d, 86e, and 85f against all of the fungi examined were meager. It is shown that for benzyl oxime ether series 85, a bulky 2-tert-butyl group on the benzene substituent was not best for the activity. Compound 85d (2-Cl-4-Br) containing two mixed halogen atoms showed broad-spectrum fungicidal activity, with EC50 values of 1.59, 0.46, 0.27, and 11.39 mg/L against four fungal pathogens (Figure 65).

5. Conclusion

A privileged structure in medicinal and organic chemistry is 1,2,4-triazole-hybrids having a broad spectrum of antifungal activity. The 1,2,4-triazole nucleus and its derivatives are essential scaffolds in the discovery and development of drugs that have a multitude of biological activities. An acceptable reason for its broad biological profile is a small and stable cyclic ring structure wherein the nitrogen atoms can act both as hydrogen bond donor and as acceptors at the active site of the receptor. The pentacyclic triazole ring processes plasticity for the synthesis of a number of derivatives due to of its multifold binding sites. This potent scaffold will act as a lead molecule in drug synthesis in the future. The various methods for the regioselective synthesis of 1,2,4-triazole-scaffold will be a great tool in medicinal chemistry in the future. The most challenging problem in fungal therapy is antifungal resistance, which may be progressed by drug target overexpression. This review is focused to summarizing recent research on 1,2,4-triazole-hybrids as fungicidal agents over the last decade. It will aid researchers and medicinal chemists in the discovery and the synthesis of new antifungal compounds with 1,2,4-triazole-moiety.
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