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Triazole derivatives as potential antifungal agents: A structure-activity relationship (SAR) studies

Yuexiao Hu [a], Ziwei Liu [a], Gaofeng Zha [b], Sihui Long [a,*], M.B. Sridhara [c], Kothanahally S. Sharath Kumar [d], Kadalipura P. Rakesh [e,*]

[a] Key Laboratory for Green Chemical Process of Ministry of Education, Hubei Key Laboratory of Novel Reactor and Green Chemical Technology, School of Chemical Engineering and Pharmacy, Wuhan Institute of Technology, Wuhan, Hubei 430205, China
[b] Scientific Research Centre, The Seventh Affiliated Hospital, Sun Yat-Sen University, Shenzhan 518107, China
[c] Department of Chemistry, Rani Channamma University, Vidyasangama, Belagavi 591156, Karnataka, India
[d] DOS in Chemistry, Manasagangotri, University of Mysore, Mysuru 570006, India
[e] Department of Radiology, Biomedical Research Imaging Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

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ABSTRACT

Today's research is focused on developing new safe drugs of clinical importance. Nitrogen-containing heterocycles are abundant in the common of therapeutic scaffolds. Triazoles are heterocyclic compounds containing a five-membered ring of two carbon atoms and three nitrogen molecules. These structures have sparked enthusiasm for advancing new analogues with miscellaneous biological activities. The need for innovative antifungal drugs is an urgent issue in the current situation where the number of refractory suppressed patients is increasing. This review summarizes research leading to the innovation and progress of latest antifungal agents from a variety of resource during this time. This review primarily focuses on the in vitro and in vivo antifungal activity, design, and SAR of new antifungal agents.

1. Introduction

A day, there has been an increased demand for medicinally active compounds due to different types of biological complications. There is a need to create a competent and straightforward route to synthesize libraries of biologically active molecules [1–7]. Synthetic drug molecules for biological applications are the fundamental approach in the drug innovation progression. Last several years, various research laboratories in around the globe focused on the developing a novel reactions and reagents in the search for developing a medicinally effective analogs for drug innovation program [8–12]. Microorganisms are resistant to multi-drug approach in the worldwide due to structural modifications that have an exerted a massive threat to human health. To encounter this problem, there is an urgent need to produce novel drug molecules that can act against different types of microorganisms [13–15], which has been a huge assignment around the globe for medicinal chemistry scientists. Concerning this, modification of available clinical drugs by applying the structure-activity relationship (SAR) method to make use of new drugs with a outlook of dropping cross-resistance plays a crucial role [16,17].

Fungal infections are creating a massive risk for humanity during the past several years, particularly in immune-compromised individuals such as patients undergoing anticancer chemotherapy, those who have AIDS, and organ transplantation [18,19]. Fungal infections like *aspergillosis, candidosis*, and *cryptococcosis* are accountable for clinical infections in immune-compromised patients [20,21]. Several drug molecules are already in clinical use from different heterocyclic precursors to avoid these kinds of infections. The most commonly used triazole core moiety containing antifungal agents are itraconazole (ICZ), fluconazole (FCZ), posaconazole, and voriconazole (VCZ) [22–24]. Fig. 1 represents the some of antifungal drugs are available in the market.

Most important heterocyclic systems of the azole family is the triazole nucleus, a polynitrogen electron-rich heterocycle present in numerous biologically important precursors [25–28]. Triazole derivatives are very active components in the medicinal chemistry field due to the following properties: firm to metabolic degradation and equipped for framing hydrogen bonds. In this way, incorporating the triazole core is valuable to improve binding with bio-molecular targets, and increment the water dissolvability of target derivatives [29–31].

* Corresponding authors.
E-mail addresses: sihuilong@wit.edu.cn (S. Long), rakeshasg@gmail.com (K.P. Rakesh).

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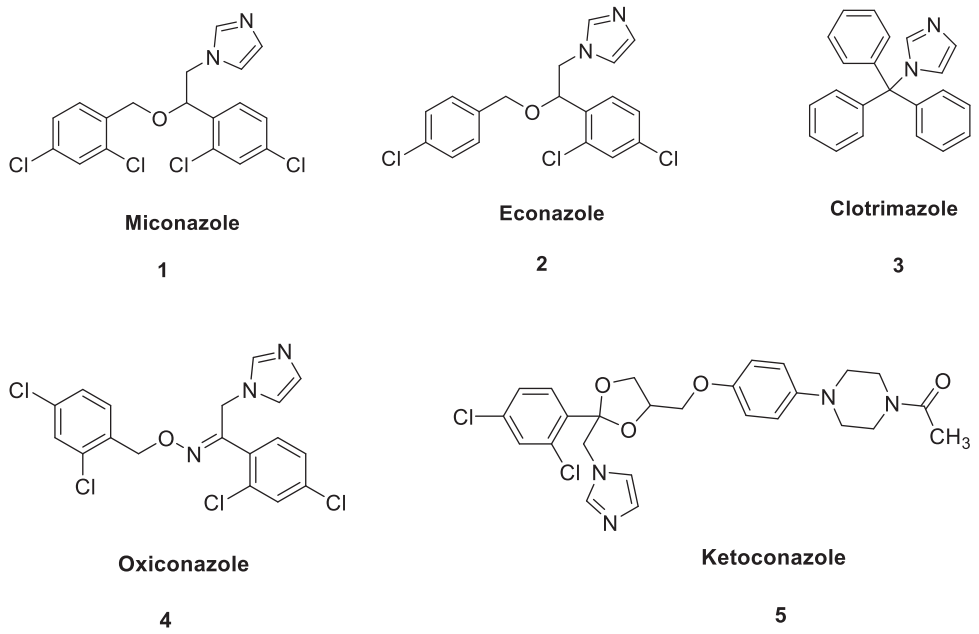


Fig. 1. Several antifungal drugs are commercially available in market.

Hence, triazole derivatives are vastly studied for their biological efficacy in different bioorganic medicinal chemistry fields to generate versatile antimicrobial agents like efinaconazole, itraconazole, and fluconazole terconazole, voriconazole, and posaconazole, etc. [32,33]. Fig. 2 represents the triazole-based antifungal drugs are available in the market.

Triazole nucleus showing excellent antifungal activities due to the considering the advantages like favourable pharmacokinetic characteristics, good safety profile and, diverse pharmacological properties [34–37] and also triazole ring responsible for the decrease in the toxicity level caused by some other heterocyclic system like imidazole ring result from its strong coordination influence with Fe^{2+} ion [38–40]. Regarding the likely triazole ring behavior, this review article presents SARs of the antifungal activity of triazole-based scaffolds against various fungal pathogens, including human and plant fungi. We hope that this short report will provide chemical biologists with detailed insights for further exploration of triazole-based derivatives for antifungal activity.

2. Triazole derivatives as showed potential antifungal activities

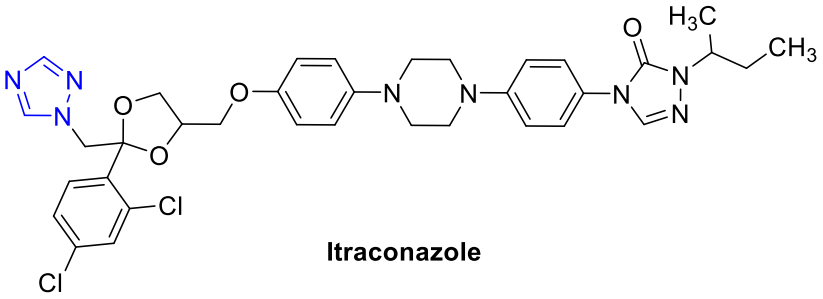
2.1. 1,2.4-Triazole analogs as full antifungal activities

Sahu and co-workers [41] have designed and developed a 1,2,4-triazole derived analogs **14a-e** (Fig. 3) and tested for in vitro antifungal efficacy in opposition to *A. niger* and *C. albicans* using serial plate dilution method. Some of the developed hybrids exhibited significant antifungal activities and results were expressed in Zone of Inhibition (ZoI) range from 6.25 to 25 mm, which were less active than standard compound **miconazole** (ZoI: 1.56 mm against both strains). An analog **14a** was found to be an excellent antifungal activity with ZoI of 12.5 and 6.25 mm in opposition to *C. albicans* and *A. niger*, respectively. SAR of **14a-e** revealed that -OCH_3 groups at R^1 and R^2 place and phenyl ring at Ar spot could favorably influence the antifungal activity. The replacement of the phenyl group with *p*-BrC_5H_4 at Ar position decreases the activity. Compound **14a** was further modified and developed as potent and safe antifungal agents shortly.

Potent 1,2,4-triazole-substituted heterocyclic scaffolds (Fig. 4) was developed and screened for antifungal and anti-inflammatory and anti-infective activity by Kucukguzel and colleagues [42]. All the designed analogs were tested against nineteen fungal strains using a disc-diffusion and microwell dilution method, and all the analogs exhibited moderate to high antifungal efficacy. Analog **15** (MIC: 15.25 μg/mL) was found to be an excellent antifungal agent against *the Trichophyton rubrum*, and compound **15** was considered to be next-generation antifungal against soon. The SAR of compound **16** (Fig. 4) exposed that -H and –Me groups at R spot in the 1,2,4-triazole ring could boost the antifungal efficacy against vegetable pathogens such as *Gibberlla nicotiancola*, *Pythium solani*, and *Gibberlla saubinetii* with EC_{50} in the range from 0.0038 to 0.1350 g/L. The replacement of –H and –Me groups with ethyl and *n*-propyl decreases the antifungal activity against tested pathogens. [43]. 1,2,4-triazole-bearing sulfonamides **17a-c** (Fig. 4), as shown as potential antifungal activities against various fungal pathogens using the micro-dilution method Zoumpoulakis et al. [44]. The SAR exposed that 1,2,4-triazole linked 3-thione acting as a critical role in attractive the antifungal activities and the different alkyl chain length substituents. Analog **17a** was found to be superior efficacy against tested three fungal pathogens, *A. flavus*, *T. viride* and *A. niger* with MIC of 0.01–0.25 μmol/mL, which were superior to the reference compound **ketoconazole** with MIC of 0.38–4.75 μmol/mL.

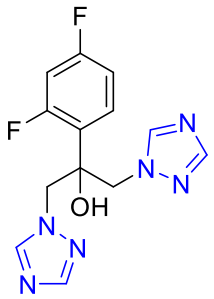
The SAR of compound **18a-d** (Fig. 4) showed that the incorporation of various natures of electronic properties of functional groups at R position taking place the benzene ring acting an imperative task in improved the antifungal activities against *G. zeae* and *P. sasakii* with percentage inhibition of 58.90% and 60.10%, respectively, which was superior to **hymexazol** (55.54% and 51.21% against *G. zeae* and *P. sasakii.* The substituents at the C-2 position on the phenyl ring could boost up the anti-*G. zeae* and anti-*P. sasakill* activity [45]. The –OH group at the C-2 (**18b**) position favorably impact on the antifungal activity.

Recently, Cheng et al. [46] reported synthetic antifungal action of 1,2,4-triazole-based scaffolds **19a-c** (Fig. 5). All the developed analogs showed moderate to high antifungal activities against *Sclerotinia sclerotiorum* and *Fusarium graminearum* with EC_{50} from 0.05 to > 50 μg/mL. Among them, **19a-c** showed potent antifungal activity against *G. graminis var. tritici* with $EC_{50\,s}$ of 0.01, 0.02, and 0.03 μg/mL, respectively, superior than **carbendazim** (EC_{50}: 0.21 μg/mL). Unfortunately, all three active compounds (**19a-c**) are inactive to the other two fungal strains *S. sclerotiorum*, and *F. graminearum.* The SAR revealed that R^1 and R^2 substituent's (alkoxy and ester carbonyl) could highly impact on the activity. The incorporation of more than one EWG's to aniline core, the antifungal action could be diminished. The lower EC_{50}



Itraconazole

6



Fluconazole

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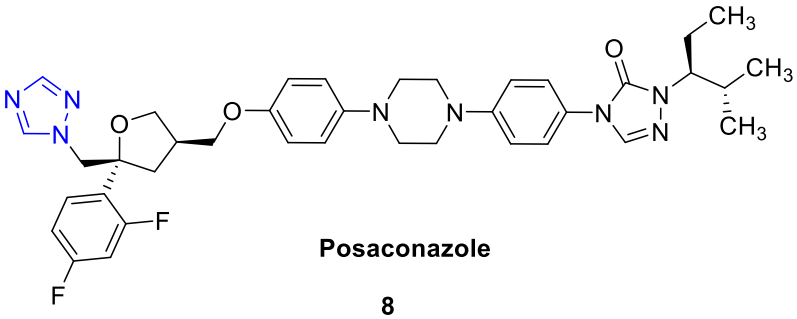

Posaconazole

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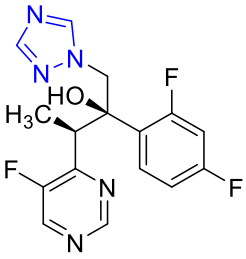
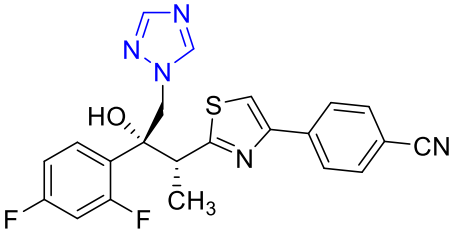


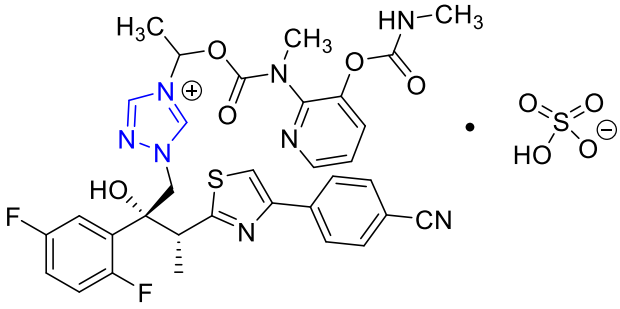
Voriconazole

9



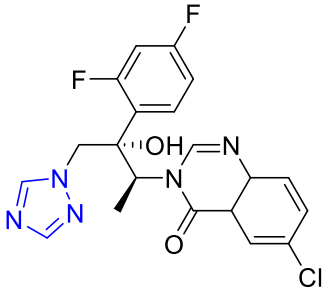
Ravuconazole

10



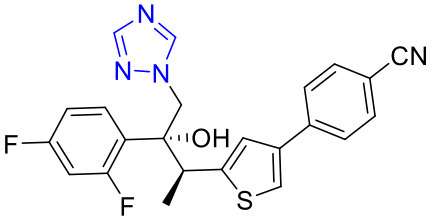
Isavuconazonium sulfate

11



Albaconazole

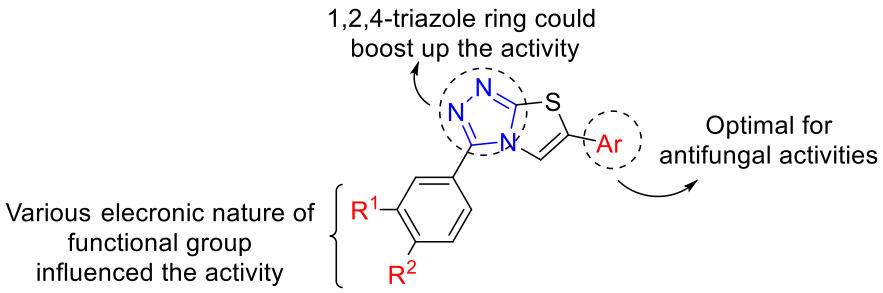
12



Ravuconazole

13

Fig. 2. Triazole-containing antifungal drugs are commercially available.



14a-e

Com. No	R^1	R^2	Ar	Antifungal activity (ZoI: mm)	
				C. albicans	*A. niger*
14a	$-OCH_3$	$-OCH_3$	C_6H_5	12.5	6.25
14b	$-OCH_3$	$-OC_2H_5$	C_6H_5	25	25
14c	$-OCH_3$	$-OCH_3$	$-CH_2C_6H_5$	12.5	25

Fig. 3. Antifungal activity of 1,2,4-triazole-based analogs.

suggested that compound **19a** could form into a good fungicide later on.

Synthesis of two series of 1,2,4-triazol-substituted-2-butanols comprised of triazole was done by Junqi Wu et al. [47] and tested for antifungal efficacy in opposition to **fluconazole** and **voriconazole** standard drugs. The results revealed 1,2,4-triazole containing compound **20** (Fig. 6) exhibited high antifungal potency with MIC of 0.03125 μg/mL against *C. albicans* SC5314 and MIC of 0.0156 μg/mL against *Cryptococcus neoformans*, superior than **fluconazole** (MIC: 1–2 μg/mL). SAR of compound **20** discovered that the presence of a morpholine ring could boost up the antifungal activities. Compound **20** was worth further assessment because of its magnificent antifungal movement toward multidrug-safe clinical isolates. Qian and co-workers [48] reported 4-pyridyl-1,2,4-triazole analogs (**21,** Fig. 6) as potent antifungal efficacy. SAR exposed that analogs bearing alicyclic and aliphatic side chains demonstrated promising antifungal activities. Among them, analogs **21a** (MIC: 0.125–2 μg/mL), and **21b** (MIC: 0.125–0.25 μg/mL) was most potential antifungal agents, superior to **fluconazole** (MIC of 0.5–2 μg/mL) and **racemic VT-1161** (MIC of 0.5–2 μg/mL). These discoveries recommended with the purpose of the novel 4-pyridyl-1,2,4-triazole structure was a valuable basic variety of the tetrazole for antifungal use.

Guzeldemirci and Kuçukbasmac [49] reported a 1,2,4-triazole containing imidazo[2,1-*b*]thiazoles (**22a-c;** Fig. 7) as a potential antifungal agent against six fungal pathogens. All prepared scaffolds exhibited significant antifungal activity with MICs ranging from 16 to 64 μg/mL, less active than the antifungal drug itraconazole. Analogues **22a-c** were isolated from the fungal pathogens *C. parapsilosis* ATCC 22019 and *C. albicans* ATCC 10231 and each have MICs of 16 μg/mL, but are less active than the antifungal **itraconazole**. SAR of **22c** showed that 4-$CH_3C_6H_4$ at the R position could enhance the antifungal activity, whereas substitution of 4-$CH_3C_6H_4$ with -CH_3- or CH_2 =CH=CH_2 groups decreased the antifungal activity. Further structural modification of analog **22c** was fit to potent antifungal agents in the future. The antifungal effect of 1,2,4-triazole-based scaffolds was developed by Tanaka and colleagues [50] against *C. albicans* TA using the paper disc technique. SAR of compound **23** (Fig. 7) showed that introduction of a tetrazole ring to analog **23** increased anti-*C. albicans* activity superior to **fluconazole** with MIC of 12.5 μg/mL (MIC: 100 μg/mL, *C. Albicans* TA. Rostom et al. [51] reported a triazole and tetrazole-based analog **24** (Fig. 7) as potent antifungal action in opposition to *C. albicans* with of 25 μg/mL, which was less effective than **clotrimazole** (MIC: 6.25 μG/mL) and **miconazole** (MIC: 6.25 μg/mL against *C. albicans*).

Benzimidazolyl-triazole scaffolds (**25a–b**; Fig. 8) were tested *D. oryzae*, *F. vertcillioids*, *F. fujikuroi*, and *C. lunata* fungal pathogens by Ahuja and co-workers [52] and the antifungal results obtained showed less than promising efficacy with $ED_{50\,s}$ between 10 and 50 μg/mL. Introduction of 4-OMe at the C-4 position on phenyl ring **25a** (ED_{50}: 18 μg/mL against *C. lunata;* ED_{50}: 18 μg/mL against *F. fujikuroi*), and **25b** (ED_{50}: 10 μg/mL in opposition to *C. lunata;* ED_{50}: 12 μg/mL against *D. oryzae*) could increase the antifungal activity, superior to **Propiconazole** (ED_{50}: 21–25 μg/mL against *D. oryzae*, *C. lunata*, and *F. fujikuroi*). The MIC **26** of the triazole scaffold with alkynyl side chains (Fig. 8) showed in vitro activity against all pathogens tested, with MIC_{80} ranging from 0.0156 μg/mL to 0.5 μg/mL, superior to **fluconazole** and **ragconazole**. [53]. Among them, analogs **27a-b** (Fig. 8) had the most active antifungal activity against *C. glabrata* (MIC80: 0.03125 μg/mL), superior to **labronazole** (MIC_{80}: 0.125 μg/mL). Compounds **27a** and **27b** exhibited similar antifungal activity against *C. neoformans* (MIC_{80}: 0.0156 μg/mL). SAR showed that the CN and -Cl substituents at the C-4 position of the phenyl ring enhance the antifungal activity. The same research group's improved the SAR investigations of triazoles, and its a straight side chain made out of aryl rings is critical for their antifungal movement [54–57]. The SAR investigation indicating that the incorporation of various functional groups at R position plays a crucial role in enhancing antifungal activities against tested seven fungal strains [58]. The piperidine (**28a**, MIC: ≤0.125 μg/mL) and substituted phenyl piperazines (**28b**, MIC: ≤0.125 μg/mL) side chain could boost up the activity against *Cryptococcus neoformans* and *Candida glabrata*, superior to **Itraconazole** (MIC: 1 and 4 μg/mL against *C. neoformans* and *C. glabrata*), further detailed studies of these analogs [59] are worth for potent antifungal agents in future. The SAR of compound **29** (Fig. 8) revealed that incorporating a 3,4-dichloro functional group on the phenyl ring had influenced the highest antifungal efficacy against tested fungal strains. Analog **29** exhibited potential activity against *B. yeast*

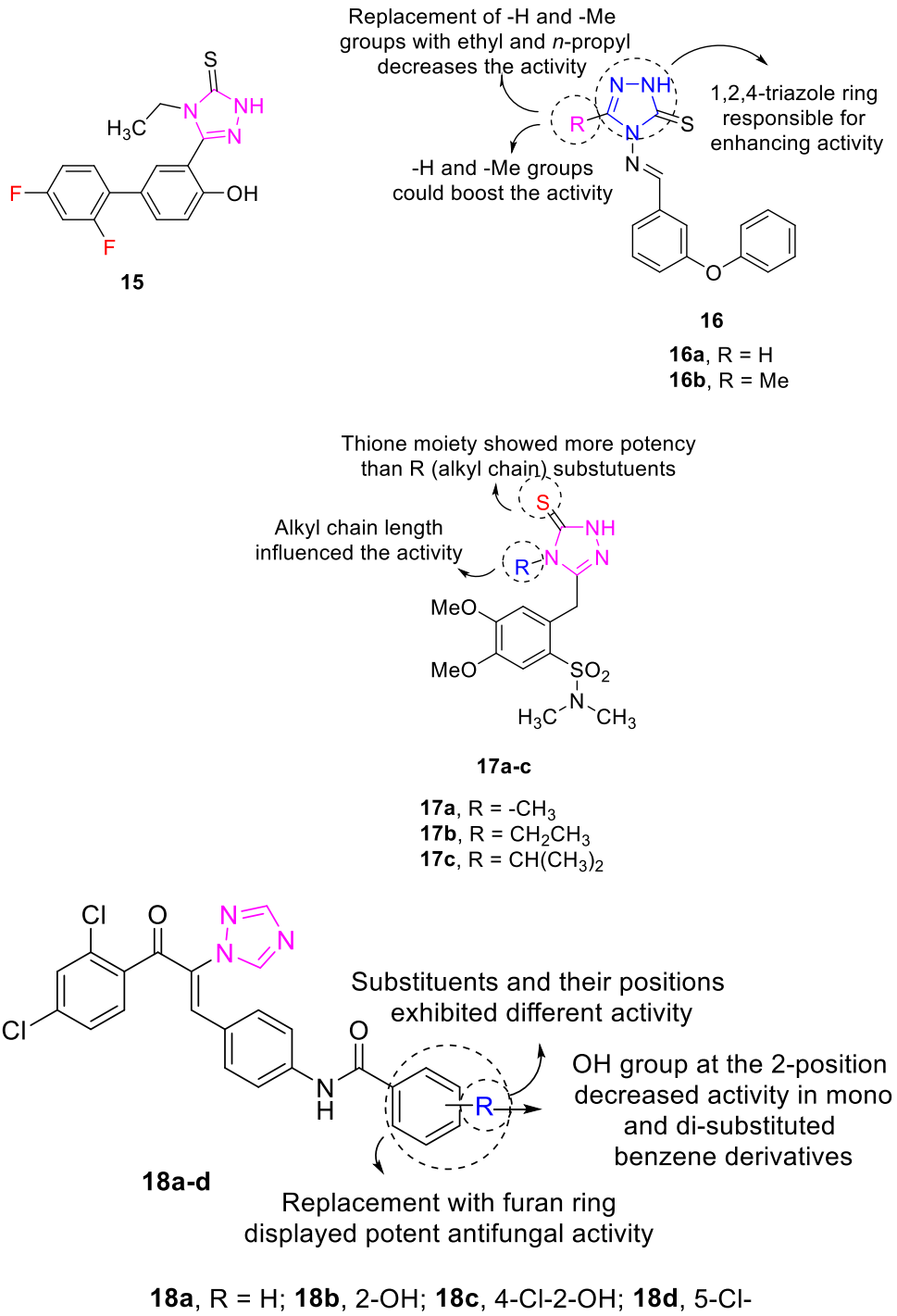
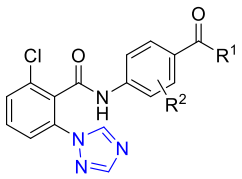


Fig. 4. Antifungal efficacy of 1,2,4-Triazole-based analogues.

with MIC: 0.5 μg/mL, superior to miconazole (MIC: 32 μg/mL) [60]. This uncovered 3,4-dichlorobenzyl triazole **29** could be filled in as a lead compound in improving more viable antifungal agents in the future.

Compared with the reference drug **fluconazole** with MIC_{80} of 0.25–2 μg/mL against *C. neoformans, C. albicans,* and *C. parapsilosis*, and, 1,2,4-triazole bearing hybrids **30a-e** (Fig. 9) (MIC_{80} range from 0.0312 to 1 μg/mL against *C. albicans*, *C. parapsilosis*, and *C. neoformans*) showed reasonable to superb antifungal activities by Xiaomeng He et al. [61]. Among them, compound **30c** possessed to highest antifungal efficacy against evaluated three fungal pathogens with MIC_{80}: 0.031 μg/mL against *C. albicans*, which was 8–12 folds more active than **fluconazole**, MIC_{80}: 0.5 μg/mL against *C. parapsilosis;* and MIC_{80}: 0.25 μg/mL against *C. neoformans*, strains respectively. SAR exposed that the 1,3,4-oxadiazole bearing EWG's at the C-4 position on the phenyl ring demonstrated highest activity than the parallel 1,2,4-oxadiazole hybrids. Analog **30c** was non-cytotoxicity against *Caenorhabditis elegans* at concentrations ranging from 1 μg/mL to 160 μg/mL. However, incorporation of 1,2,4- triazole analog could enrich the antifungal activities. In addition, molecular modeling studies revealed that the fluorophenyl group along with 1,2,4-triazole ring of **30c** formed hydrophobic interactions (Phe126, Ile131, and Tyr132) with the heme group in Fig. 10.

SAR uncovered that the combination of various types of functional groups at R position had highly influenced the antifungal activity



19a-c

Com. No	R^1	R^2	Antifungal activity (EC_{50}: μg/mL)		
			G. graminis var. tritici	*S. sclerotiorum*	*F. graminearum*
19a	O*i*-Pr	H	0.01	0.19	0.12
19b	O*t*-Bu	H	0.02	5.00	4.14
19c	O*t*-amyl	H	0.03	0.27	2.59
Carbendazim			0.21	0.17	0.65

Fig. 5. Antifungal activity of synthesized 1,2,4-triazole analogs.

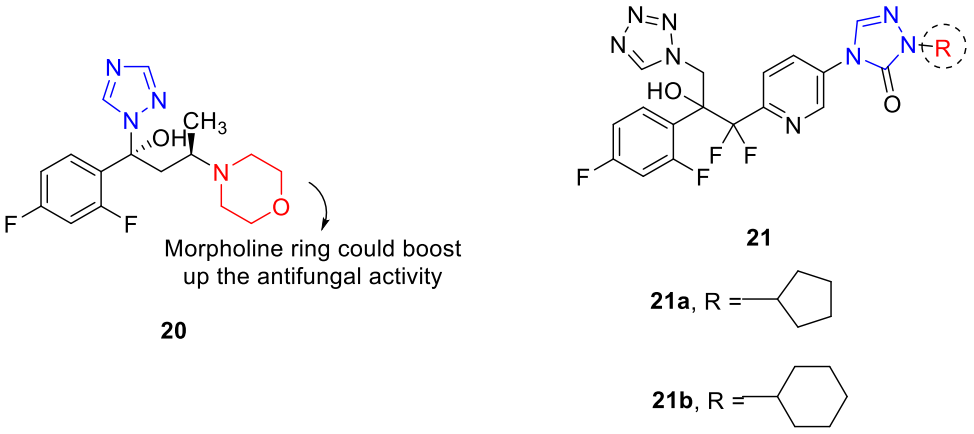


Fig. 6. 1,2,4-Triazole-based scaffolds exhibited potential antifungal agents.

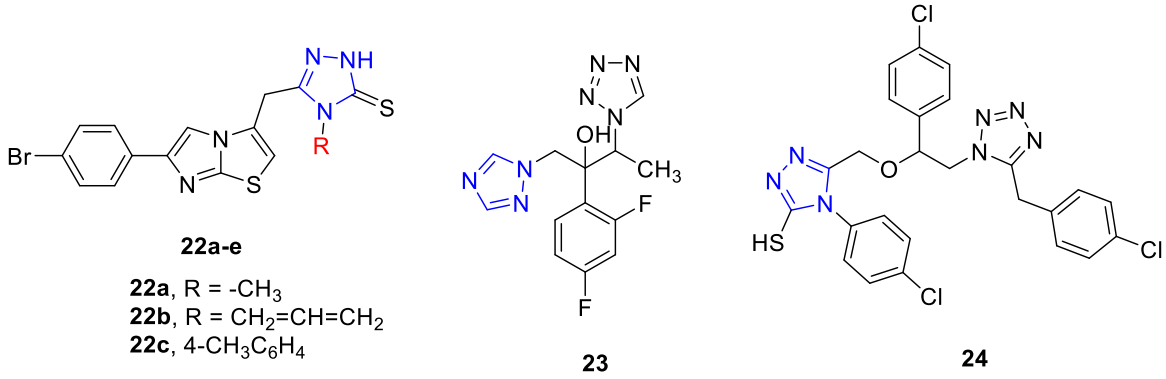


Fig. 7. Antifungal activities of 1,2,4-triazole based derivatives (**22–24**).

against *Aspergillus fumigates* strain with MIC_{80} of 0.5–2 μg/mL, which were equivalent to or high efficacy than **itraconazole** (MIC_{80}: 2 μg/mL against *A. fumigates*) [62]. The incorporation of $–CH_3$, and-CH_2CHCH_2 functional groups with the 1,2,4-triazole ring, plays a crucial role in antifungal activity. Compounds **31a-c** (Fig. 11) exhibited excellent anti-*A. fumigates* with MIC_{80} of 0.5–2 0.5–2 μg/mL. Among them, analog **31b** is considered potent antifungal agents in the future, and the mode of action of **31b** is still not explored. In medicinal chemistry, the indole ring plays a very important role in enhancing the various biological properties. Guillon et al. [63], continuous to research on indole-based 1, 2,4-triazole analogs as exhibited potent antifungal efficacy. Analog **32** (Fig. 11) was found to obtain as potent antifungal agents with MIC80 of 3 ng/mL, compounds bearing an *N*-Boc group on the indole ring, and –F atom enhanced the antifungal efficacy against other compounds.

The SAR elucidation of compounds **33a-d** (Fig. 11) exposed the introduction of various electronic natures of functional groups responsible for improving the antifungal activities against tested eight fungal pathogens [64]. The 3,4-diCH_3, 4-CN, and 4-NO_2 on the phenyl ring exhibited powerful antifungal efficacy against *C. albicans* (**33a-d**, MIC: ≤0.125 μg/mL) and *Candida parapsilosis* (MIC: ≤0.125 μg/mL against

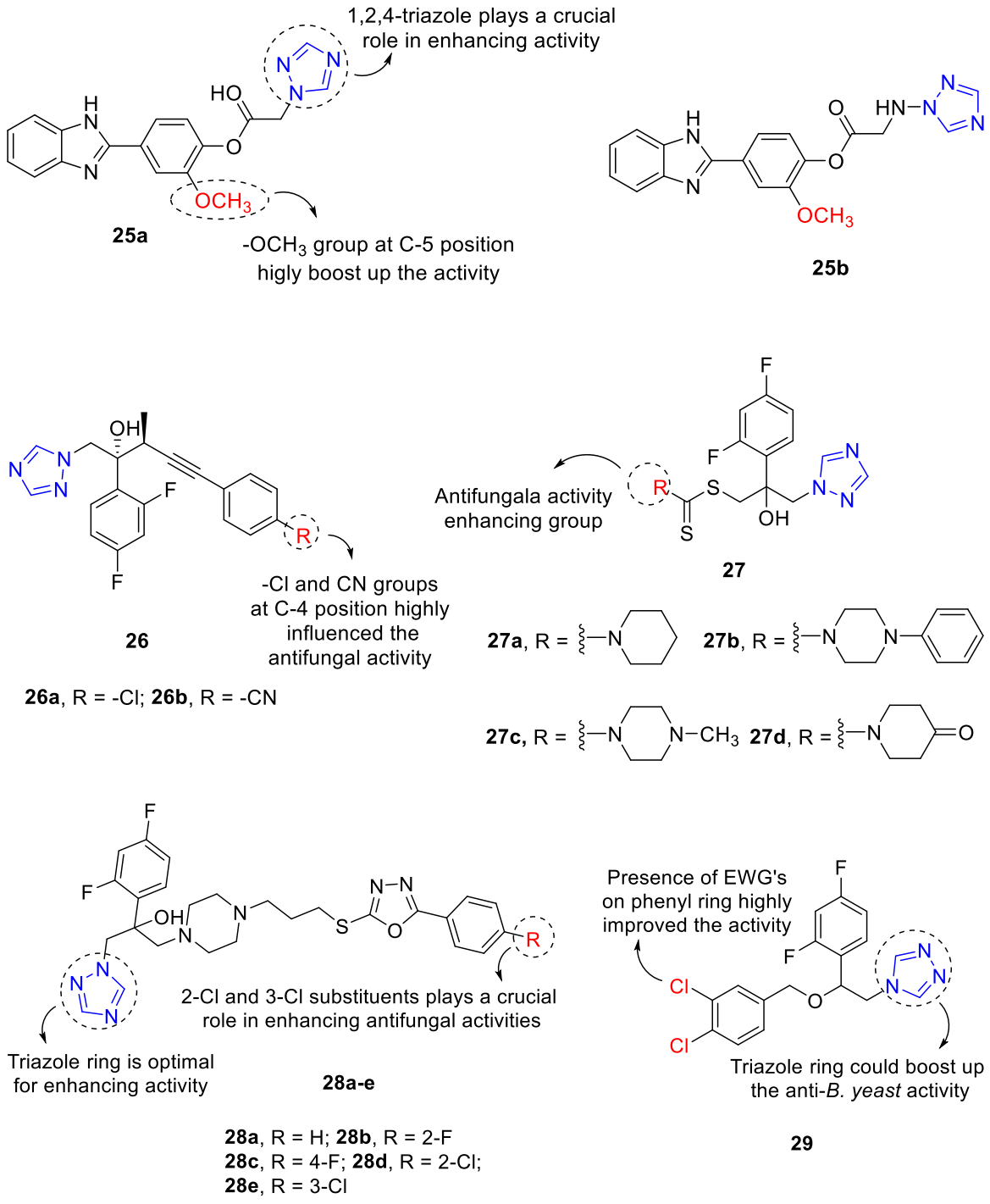
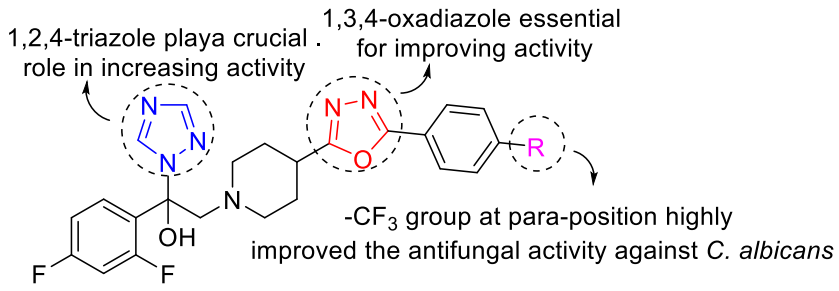


Fig. 8. 1,2,4-Triazole-based scaffolds (**25–29**) as showed potential antifungal activities.

analogs **33a** and **33d;** MIC: 0.5 μg/mL against analogs **33b** and **33c),** which were highly active than **fluconazole** (MIC: 1 μg/mL, against *C. parapsilosis* and *C.albicans*). Among them, compounds **33a** and **33b** exhibited highly potent than other compounds **33c** and **33d** due to the strong hydrophobic groups at R position on the phenyl ring. Further evolution of compounds **33a** and **33b** emerged as strong antifungal agents in soon.

A series of triazole hybrids **34a-e** (Fig. 12) were developed and evaluated in vitro antifungal efficacy against eight human fungal pathogens by Shichong Yu and co-workers [65]. All the reported analogs exhibited moderate to good antifungal activities with MIC_{80} in the range of 0.0625–25 μg/mL. Some of the analogs were highly active than **fluconazole** (MIC_{80}: 0.5 μg/mL). The incorporation of –Cl, -F, -NO_2, and –Br groups at R position on the benzene ring could boost the antifungal activities. Among them, 3-NO_2 (**34b**, MIC_{80}: 0.0156 μg/mL against *C. albicans* SC5314; <0.125 μg/mL against *C. albicans* YO109; and 0.0625 μg/mL against *Candida tropicalis*), which was superior to **fluconazole** (MIC_{80}: 0.5 μg/mL). The activity order of 3-NO_2 > 4-CN > 3-F > 4-Cl = 4-Br.

Tetrahydroprotoberberine (THPB) was a superb basic option with enormous biological applications [66–68]. Expanded misuse is coordinated towards THPBs for their remedial worth. Duan and colleagues [69] revealed THPB bearing triazoles as powerful antifungal agents. The reasonable length of an alkyl chain appeared to be the hexyl chain: the



30a-e

Com. No	R	Antifungal activity (MIC_{80}: μg/mL)		
		C. albicans	*C. parapsilosis*	*C. neoformans*
30a	-H	0.125	0.5	0.25
30b	-OMe	0.031	0.5	0.25
30c	$-CF_3$	0.031	0.5	0.25
30d	-F	0.063	0.5	0.125
30e	$-NO_2$	0.25	2	1
Fluconazole		0.25	2	0.25

Fig. 9. Triazole-based derivatives exhibited potential antifungal activities.

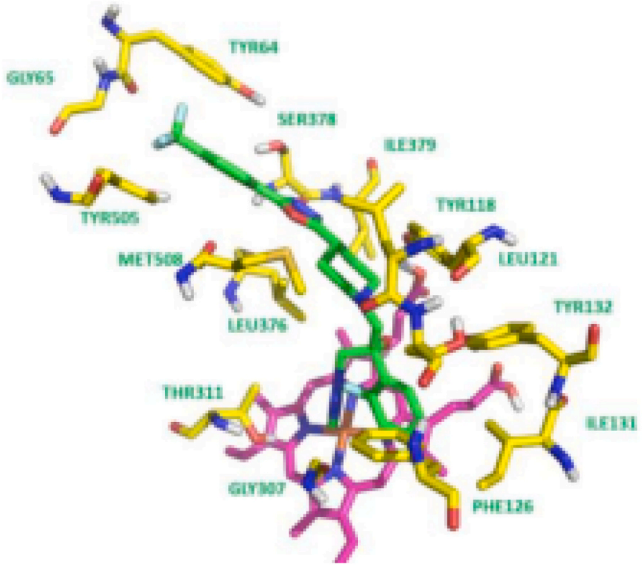


Fig. 10. The hydrogen bonding of **30c** in the active site of CACYP51.

hexyl derivative **35** (Fig. 13) applied the best antifungal viability with MIC values between 2 and 32 μg/mL against all the tried fungal growths, better than other alkyl scaffolds with a shorter or longer chain length. SAR found that the emergence of 1,2,4-triazole-based-1,3-disulfonamides and proper alteration of the *N*-alkyl-benzylamine groups aid in antifungal effects. A hybrid with a cyclopropyl substituent at N of benzylamine was positive for antifungal activity [70]. The EC_{50} ranged from 0.69 to 23.99 mg/L, superior to other cycloalkyl substituents. Notably, compound **36** (Fig. 13) had an EC_{50} of 0.69 mg/L, comparable to that of amisulbromine. Bioassay outcome indicated that phenyl substitution could have a significant impact on antifungal efficacy.

1,2,4-Triazole-based analog **37** (Fig. 13), as exhibited as potential antifungal efficacy against tested five fungal pathogens by Zhang and colleagues [71]. Analog **37** was superior to miconazole (MIC: 4–256 μg/mL) against all five pathogens *A. flavus*, *C. albicans*, *C. utilis*, brewer's yeast, and *C. mycoderma* with MICs ranging from 0.5 to 8 μg/mL. SAR indicates that the existence of -Cl groups at the C-2 and C-4 positions of the phenyl ring affects the antifungal movement, making 37 act as a potential antifungal agent in the near future. 1,2,4-Triazole-based derivatives **38a-b** (Fig. 13) showed potential antifungal efficacy against five human pathogenic fungi developed by Hashemi et al. [72]. SAR investigation showed that the existence of -OH group at the C-4 position of the phenyl ring reduced the antifungal efficacy. Introduction of a -Cl group to the phenyl ring can enhance activity over **fluconazole**. Analogs **38a** and **38b** showed good antifungal efficacy with MIC of 0.25 μg/mL each in opposition to *C. glabrata* strain. In addition, both 40 and 41 active compounds are non-cytotoxicity against tested the human hepatoma HepG2 cell line.

2.2. 1,2.3-Triazole analogs as potent antifungal activities

Ramírez-Villalva and colleagues [73] designed and prepared 1,2,3-triazole-based hybrids (**39a–e**; Fig. 14) and used the microdilution M38-A method to isolate several fungal pathogens. All the reported analogs exhibited reasonable to outstanding antifungal action with MIC of 0.12–8 μg/mL against *C. albicans*, *C. glabrata, and C. parapsilosis,* but significantly less active than antifungal reference drug **Itraconazole** (MIC: 0.03–1 μg/mL). Hybrids **39a-c** exposed very good activity against *C. glabrata* fungal strains with MIC of 0.012–0.25 μg/mL, but the same analogs showed low antifungal activity *C. albicans* strain. SAR revealed that incorporating different substituents at the R^1 and R^2 positions of the 1,2,3-triazole ring positively impacted the antifungal action.

The 1,2,3-triazole bearing carboxamide derivatives (**40;** Fig. 15)

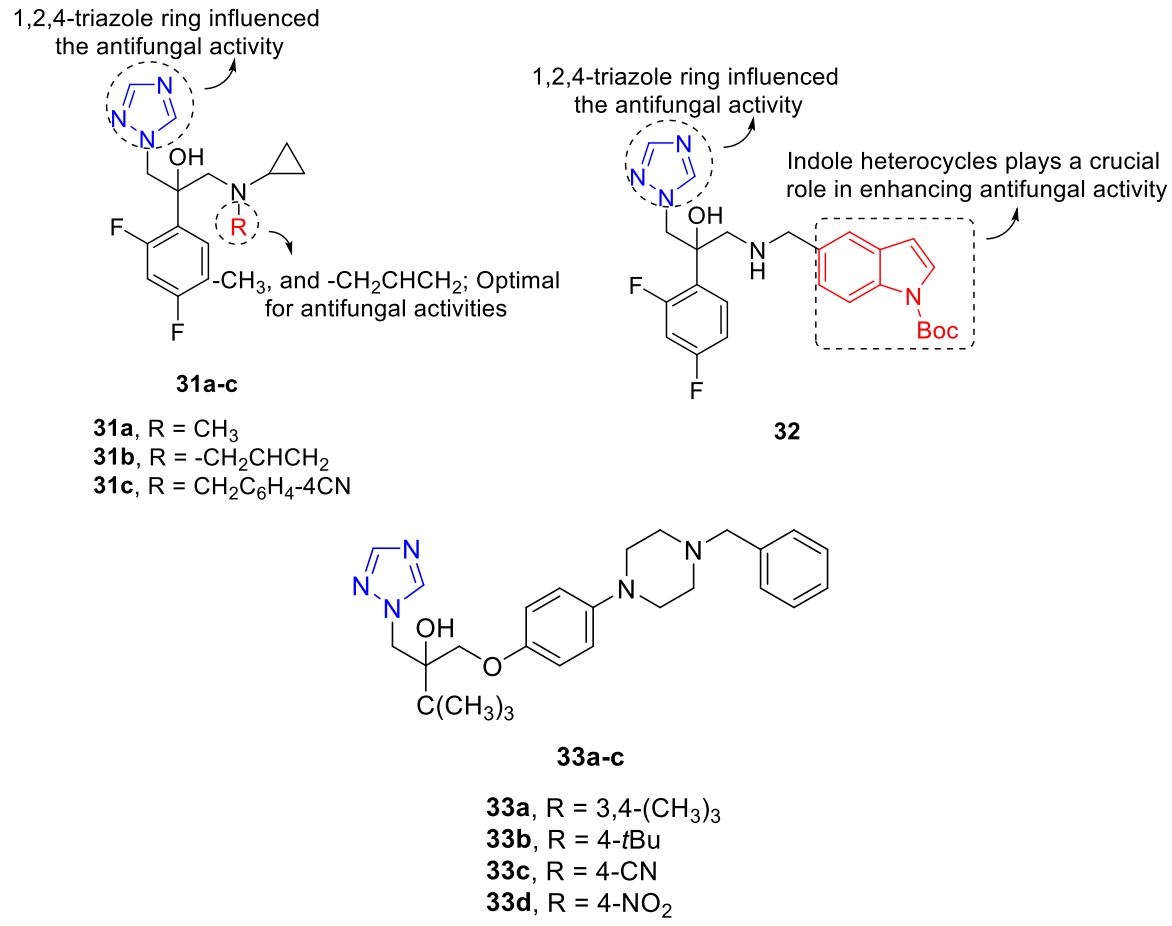
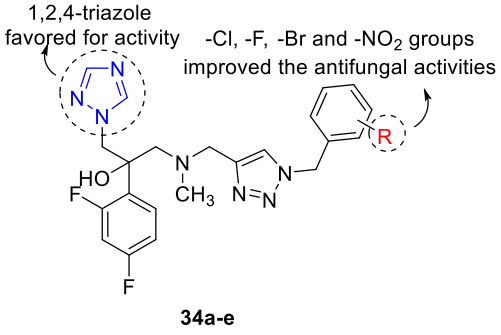


Fig. 11. 1,2,4-Triazole-based analogs as displayed excellent antifungal activities.



Com. No	R	Antifungal activity (MIC80: μg/mL)		
		C. alb SC5314	*C. albYO109*	*C. tropicalis*
34a	3-F	0.25	0.25	16
34b	3-NO_2	0.0156	<0.0125	0.0625
34c	4-CN	0.0625	<0.0125	0.0625
34d	4-Cl	0.25	<0.0125	4
34e	4-Br	0.25	<0.0125	4
Fluconazole		0.5	0.5	2

Fig. 12. Triazole hybrid exhibited potential antifungal activities.

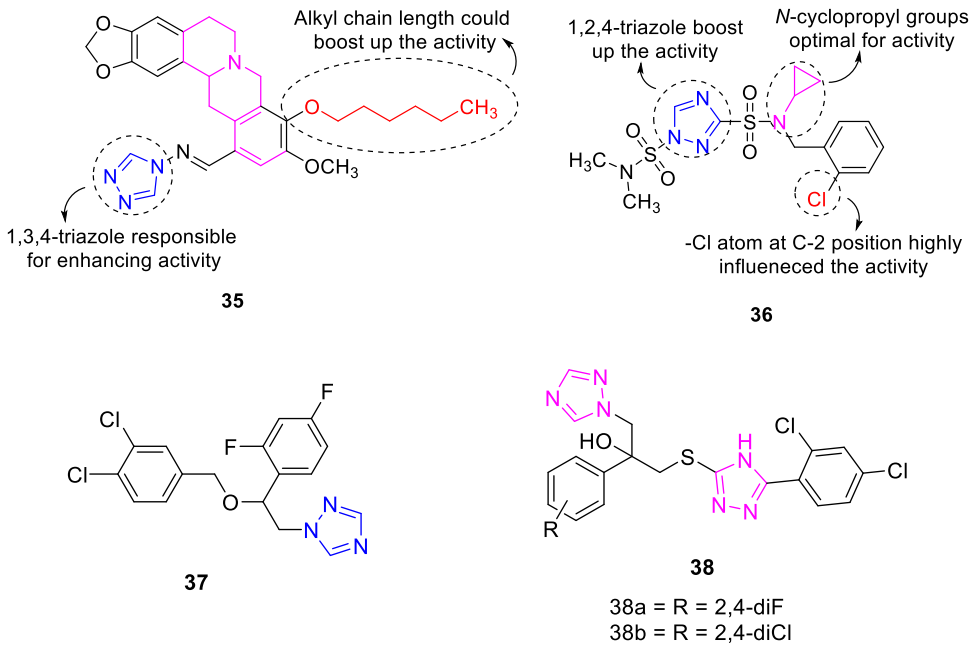
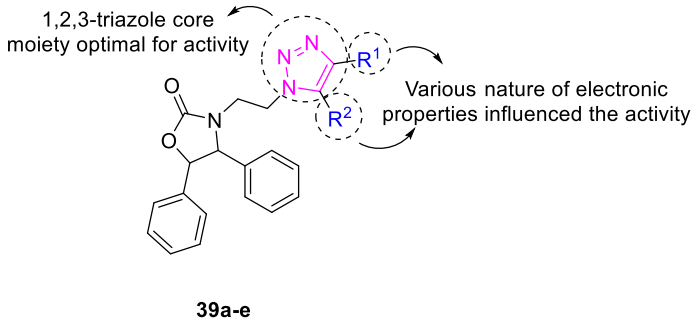


Fig. 13. 1,2,4-Triazole-based derivatives (35–38) exhibited good antifungal efficacy.



Com. No	R^1	R^2	Antifungal activity (MIC: μg/mL)		
			C. albicans	*C. glabrata*	*C. parapsilosis*
39a	2-NO_2-Ph	SO_4-*p*-Tol	8	0.12	0.5
39b	pentyl	SO_2-Ph	8	0.25	8
39c	-CN	Ph	8	0.12	8
39d	CH3	COCH3	8	2	4
39e	Ph	SO_2-*p*-Tol	8	1	8
Itraconazole.			**0.03**	**1**	**0.06**

Fig. 14. 1,2,3-Triazole-based derivative showed potent antifungal activity.

demonstrated excellent antifungal activities against *Botrytis cinerea, Gaeumannomyces graminsis, Rhizoctonia cereals, and S. sclerotiorum* with an EC_{50} of of 8.75, 5.30, 1.67, and 1.08 μg/mL, respectively, superior to reference drug **boscalid** [74]. In addition, analog **40** was chosen for further in vivo studies on cole leaves' protective activity by *S. sclerotiorum* against RSR. SAR of analogue **40** showed that incorporation of a strong -Cl group into the phenyl ring can enhance its antifungal action in opposition to the screened fungal strains. A SAR study of the 1,2,3-triazole-based hybrid **41** (Fig. 15) confirms that the incorporation of the -Cl group at the C-4 position of the phenyl ring has a significant impact on the antifungal activity against the two fungi *R. solani* (EC_{50}: 6.1 μg/mL) and *B. cinerea* (EC_{50}: 5.4 μg/mL). A significant proportion of them were less active than the reference drug **carbendazim** (EC_{50}: 1.8 μg/mL against *R. solani*) [75]. Kamble and co-workers [76] have developed potential antifungal agents **42** (Fig. 15), all the developed scaffolds exhibited moderate to superior antifungal efficacy with ZoI in the range of 11–18 mm at 25 μg/mL, against *A. niger*, *Aspergillus flavus*, C. albicans, and *A. fumigatus*, but less active compared to **fluconazole** (ZoI: 19–22 mm at 20 μg/mL). SAR of analog **43** (Fig. 15) revealed that the quinazolinone heterocycles play a

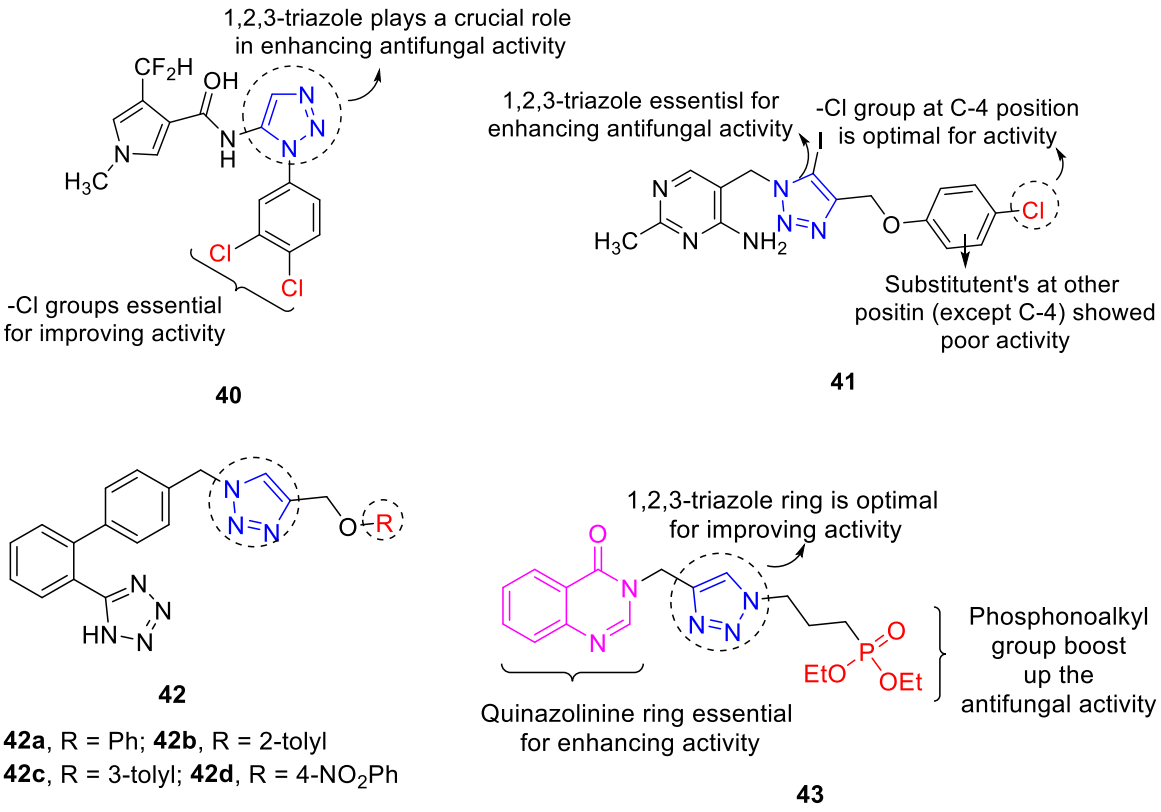


Fig. 15. Potential antifungal activities of 1,2,3-triazole-basedderivatives (40–43).

vital role in enhancing antifungal efficacy against *A. brasiliensis* and *C. albicans* and with a MIC of 1.25 μg/mL. [77].

The 1,2,3-triazole piperidine-based derivatives **44a** and **44b** (Fig. 16) showed high activity against *C. neoformans* and *C. albicans*, with MICs ranging from 0.125 μg/mL to 0.0125 μg/mL was superior to **fluconazole** (MIC: 1–2 μg/mL) and **itraconazole** (MIC: 1–2 μg/mL) [78]. SAR found that the introduction of cyclopropyl, ethyl, and propyl groups on the 1,2,3-triazole ring reduced efficacy. C-4 acetyl (**44a**) and C-4 trifluoromethoxy group (**44b**) showed good anti-*C. albicans* with MICs of 0.0625 and 0.0125 μg/mL, respectively. Piperazine-based triazoles **45a-b** (Fig. 16) was developed to fight several fungal pathogens *F. gramillarium* and *F. oxysporum*. SAR revealed that main chain **45a**, containing her EWG in the phenyl ring, is responsible for the enhanced antifungal activity. Analog **45b** exhibits high antifungal activity against *F. gramillarium* and *F. oxysporum* with MICs $>$ 64 μg/mL [79]. Very recently, Reddyrajula and Dalimba [80] have designed and synthesized zolpidem analogs **46a-b** (Fig. 16) and tested for antifungal efficacy against *A. flavus*, *A. niger* and *C. albicans*, and by using the disc diffusion method. Reported scaffolds were shown reasonable to excellent antifungal efficacy at different concentration level (25–75 μg/mL). The SAR exposed that 3-carboxamide zolpidem analogs were showed superior antifungal activities than 2-carboxamide zolpidem analogs. The nature of electronic properties on the phenyl ring could positively influence the antifungal activity. Analog **46a** exhibited superior activity with Zone of Inhibition (ZoI) of 30 mm at 75 μg/mL concentration against *A. niger*, which was better than reference drug fluconazole (ZoI: 26 mm at 75 75 μg/mL concentration). Compound **46a** also showed potent activity against *A. niger* with ZoI: 28 mm at 75 75 μg/mL concentration. In addition, potent compounds **46a** and **46b** led non-cytotoxicity against Vero cell lines (Monkey kidney) with IC_{50} of 309.8 and 262.1 μg/mL, respectively. The 1,2,3-triazole ring intertwined with pyridine/pyrimidine was planned and screened for their in vitro antifungal movement. Compound **47** (Fig. 16) demonstrated great antifungal action against *F. recini* with MIC of 25 μg/mL [81].

SAR studies of nitrofuran-triazole congeners **48a-f** (Fig. 17) showed that the introduction of the 1,2,3-triazole moiety significantly affected their in vitro antifungal activity against several tested fungal strains. Of these, some of the compounds were more active than the reference drug, **miconazole**. Incorporation of electron-withdrawing groups at the C-2, C-3, C-4, and C-5 positions of the phenyl ring affected the highest antifungal activity. Compound **48d** bearing two-Cl groups at C-2 and C-3 position on the phenyl ring showed excellent antifungal efficacy with the MFC ranging between 7.8 and 31.2 μg/mL [82]. Among them, **48d** led MFC: 3.9 μg/mL, against *C. parapsilosis* MTCC 1744, displayed the same efficacy as miconazole (MFC: 7.8 μg/mL). Cytotoxicity results revealed that **48d** was non-cytotoxicity against the MRC5 cell line with IC_{50} of 142.8 ± 0.26 μg/mL. Moreover, compound **48d** could be considered as a promising antifungal candidate for the near future.

Attractive pharmacological properties of 1,2,3-triazole-based scaffolds **49a-e** (Fig. 17) were synthesized by Z.C. Dai and co-workers [83] and screened antifungal efficacy against four fungal pathogens. Compounds **49a-e** showed a different range of antifungal activities depending on the aromatic ring's electronic nature on 1,2,3-triazole moiety. The SAR of compound **49a-e** exposed that the presence of more the number of electron-withdrawing atoms like –F, -NO_2, -Cl and –Br on the phenyl ring could boost up the antifungal activities against tested fungal pathogens *R. solani*, *S. sclerotiorum* and *P. capsici*, which is evident with 2-Cl at R^1 and 4-F at R^2 in compound **49d.** The EDG's –OCH3 at R^1 and –H at R^2 position showed inferior activity against *S. sclerotiorum* and *P. capsici* with EC_{50}: $>$ 25 μg/mL each fungal strain.

The SAR of the triazole moiety (**50a-d;** Fig. 18) significantly affected potency, in the order 3-CN>H> 4-NO_2 > -Br; modification at the R position of the phenyl ring appears to be beneficial for antifungal activity, whereas the C-3 or C-4 positions were detrimental to activity. Replacing -Br and -NO_2 with electron-donating groups on the benzene ring further reduced the antifungal activity. Compounds **50a** (MIC_{80}: 0.0039 μg/mL), **50b** and **50c** (MIC_{80}: 0.0156 μg/mL) exhibited excellent activity against *C. albicans* Y0109, which were superior to **fluconazole**

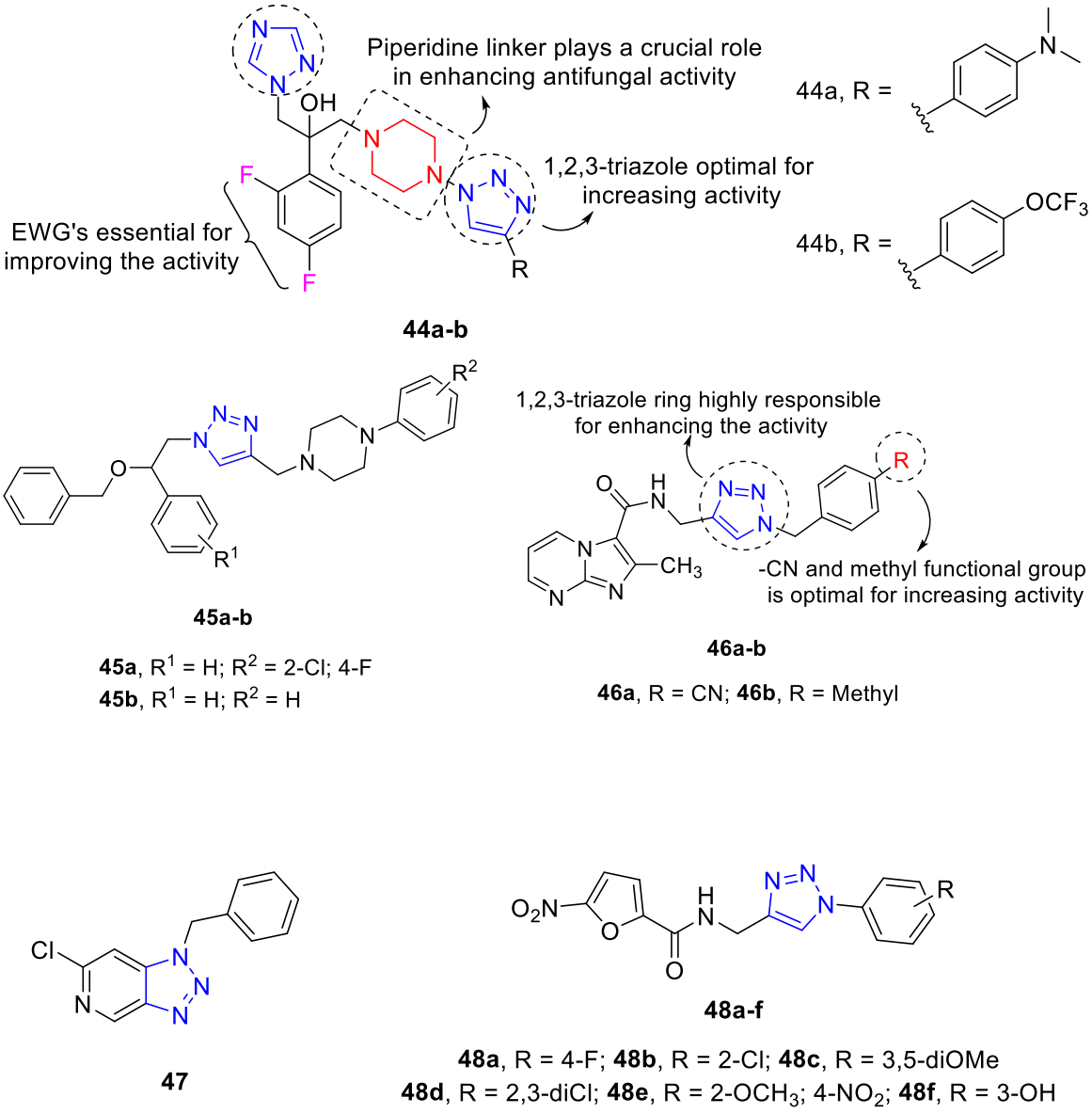


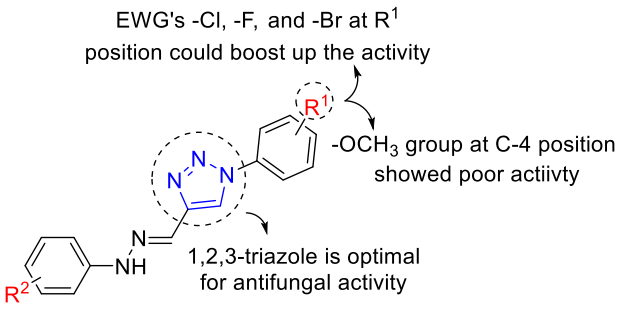
Fig. 16. 1,2,3-Triazole-based analogs (44–48) showed potent antifungal activities.

(MIC_{80}: 0.5 μg/mL against tested fungal strains). The most active hybrid **50a** has potential as a novel antimicrobial agent [84].

A new class of active antifungal agents of **51a–c** (Fig. 19) was described by Ramirez-Villalva and colleagues [85]. SAR of hybrids **51a-c** disclosed that -CN or *p*-NO_2Ph group at the C-5 position of the triazole ring plays a vital role in exerting antifungal activity; triazole at R^1 and R^2 position were most favorable to the activity, while -CN at R^1 position and –Ph at R^2 position could improve the antifungal activity. Compounds **51a**, **51b**, and **51c** exhibited superior activity against *C. glabrata* (MICs of 0.12, 0.25, and 0.12 μg/mL, respectively), superior to **itraconazole** (MIC: 1 μg/mL).

The SAR studies of 1,2,3-Triazolyl chalcone derivatives **52a-e** Fig. 20) suggested that 2-Cl-Phenyl and pyridyl groups at Ar position influenced the antifungal potency greatly. In contrast, phenyl and 4-OH-phenyl groups at Ar position showed reasonable to weak activities in opposition to *C. albicans*, *A. flavus*, and *C. keratinophilum* with ZoI of 7–22 mm [86]. The –Cl and –F phenyl were gainful to the antifungal action, while 4-methoxy phenyl ring diminished the movement contrasted and the unsubstituted analog. Among them, analog **52a** and **52b** exhibited good antifungal activities against *C. albicans* with ZoI: 18 mm each, but slightly less active than reference drug **Fluconazole** (ZoI: 22 mm against *C. albicans*), making it a lead for further optimization. All the reported potent compounds **52a** and **52b** showed less-cytotoxicity against tested line lines MDA-MB-231, MCF-7, VERO, and MCF-10A.

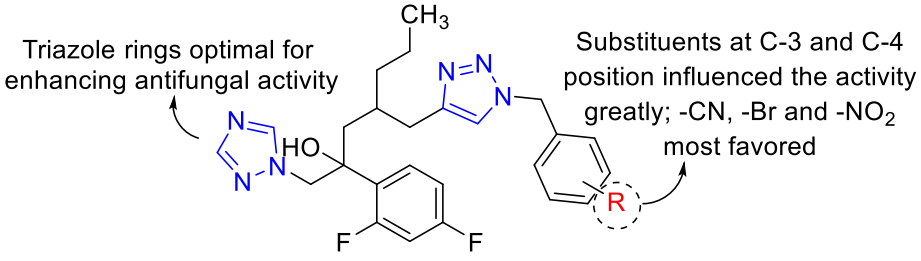
Target compound **53** exhibited high antifungal activity against *C. albicans* and *A. niger* with MICs of 0.32–0.63 μg/mL [87]. By substituting 1,2,3-triazole for 1,2,4-triazole and attaching valuable substituents with different electronic properties to the triazole ring, the triazole scaffold has significantly extended synthetic and biological possibilities. Capabilities were added [88–90]. The MIC values of **54a-b** (Fig. 21) showed excellent antifungal activity against all fungal strains tested, with MIC_{90} ranging from 4 to 16 μg/mL. In contrast, some of the compounds showed moderate loading with MIC_{90} ranging from 64 to 128 μg/mL [91]. SAR suggested that the two -Cl substituents at the C-2 and C-4 positions of the phenyl A ring strongly affected the activity. -Cl- to -F- groups on the phenyl B ring slightly reduced antifungal activity. Analog **54a** (MIC_{90}: 4–16 μg/mL) was the most active against all fungi tested and was comparable to fluconazole (MIC_{90}: 2–32 μg/mL). In addition, two potent antifungal agents **54a** and **54b** were tested for MFC against *C. albicans* ATCC 24433, *C. albicans* ATCC 10231, and *C. glabrata*



49a-e

Com. No	R^1	R^2	Antifungal activity (EC_{50}: μg/mL)		
			R. solani	*S. sclerotiorum*	*P. capsici*
49a	H	H	3.01±0.11	>25	>25
49b	4-OMe	H	49.13±0.79	>25	>25
49c	2-Cl	4-Cl	0.65±0.03	4.47±0.21	4.75±0.24
49d	2-Cl	4-F	0.18±0.02	2.28±0.01	1.85±0.02
49e	2-F	4-Br	0.80±0.02	>25	>25
Carbendazim			1.42±0.02	0.15±0.03	---

Fig. 17. Antifungal activity of reported 1,2,3-triazole derivatives.



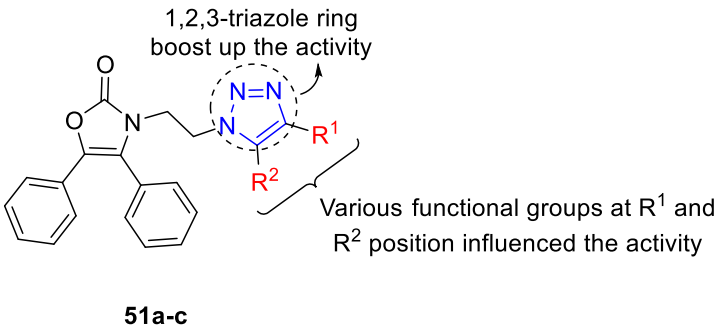
50a-d

Com. No	R	Antifungal activity (MIC8O: μg/mL)	
		C. albicans Y0109	*C. albicans* SC5314
50a	3-CN	0.0039	0.25
50b	-H	0.0156	<0.125
50c	NO_2	0.0156	0.25
50d	4-Br	0.0625	0.5
Fluconazole		0.5	0.5

Fig. 18. 1,2,3-Triazole-based scaffolds as exhibited potential antifungal efficacy.

NCYC 388 and showed MFC values between 16 and 32 μg/mL, hybrids of these triazoles are potential antifungal agents.

Antifungal efficacy of 1,2,3-triazole-based moieties **55a-b** (Fig. 21) was reported by Kaushik et al. [92]. Analogs **55a** and **55b** showed promising antifungal activity against *C. albicans* with MICs of 1.53 and 1.38 μg/mL, except *A. niger*. The introduction of halogen substituents at the positions had a positive impact on the antifungal activity. It may be an ideal starting point for synthesizing new antifungal drugs in the near future. The utilization of 1,2,3-triazole moieties in the state-of-the-art design of antifungal agents has opened the possibility of synthesizing new antifungal specialists containing 1,2,3-triazole pharmacophores [93–95]. In 2017, Dhavale and colleagues [96] had planned and developed a novel class of intense morpholine-intertwined 1,2,3-triazole **56a-b** (Fig. 21) as shown brilliant antifungal movement against *C. albicans*. Also, analogs **56a** (MIC: 0.85 μM) and **56b** (MIC: 0.025 μM) indicated a more strong antifungal movement against *C. albicans* than

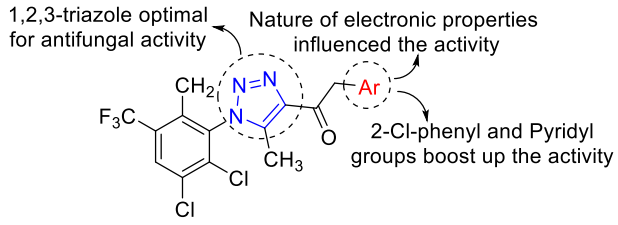


51a-c

Com. No	R^1	R^2	Antifungal activity against *C. glabrata* (MIC: μg/mL)
51a	SO_2-*p*-Tol	*m*-NO_2Ph	0.12
51b	SO2Ph	Pentyl	0.25
51c	-CN	Ph	0.12
Itraconazole	--	--	1

Fig. 19. Antifungal activity of 1,2,3-triazole derivative showed good potency against tested fungal pathogens.

tested fungal pathogens.



52a-e

Com. No	Ar	Antifungal activity (ZoI: mm)		Cytotoxicity
		A. Flavus	*C. Albicans*	MCF-7
52a	2-Cl-Phenyl	**12±0.2**	**18±0.3**	**78.3±0.4**
52b	Pyridyl	**12±0.3**	**18±0.2**	**91.5±0.2**
52c	Phenyl	06±0.2	08±0.2	>100
52d	4-OH-Phenyl	08±0.3	12±0.3	74.8±0.2
52e	4-F-Phenyl	11±0.2	10±0.4	6.4±0.4
Fluconazole	--	**14±0.3**	**22±0.2**	**---**
Doxorubicin	--	**---**	**---**	**1.1±0.1**

Fig. 20. 1,2,3-triazole derivative showed good potency against tested fungal pathogens.

the antifungal reference drug **amphotericin b** (MIC: 1.25 μM). In this manner, the integrated spiroiminosugars may open another period of expected fanciful drugs in comorbidity treatments.

3. Conclusion

With the rise of new fungal pathogens, new antifungal drug advances have become the clinical basis and have recently driven the gifts of various researchers around the world. We acknowledge that triazole-based lead frameworks with low and high selectivity are further improved. The improved SAR may prepare for additional research and breeding of new triazole scaffolds with improved potency to overcome resistance. It is our hope that this report will provide a thoughtful summary of the latest chemical discoveries spanning more than a decade and serve as a call to action for current and emerging researchers interested in helping fight fungal diseases.

Declaration of Competing Interest

we have not submitted the same manuscript to any other journals elsewhere.

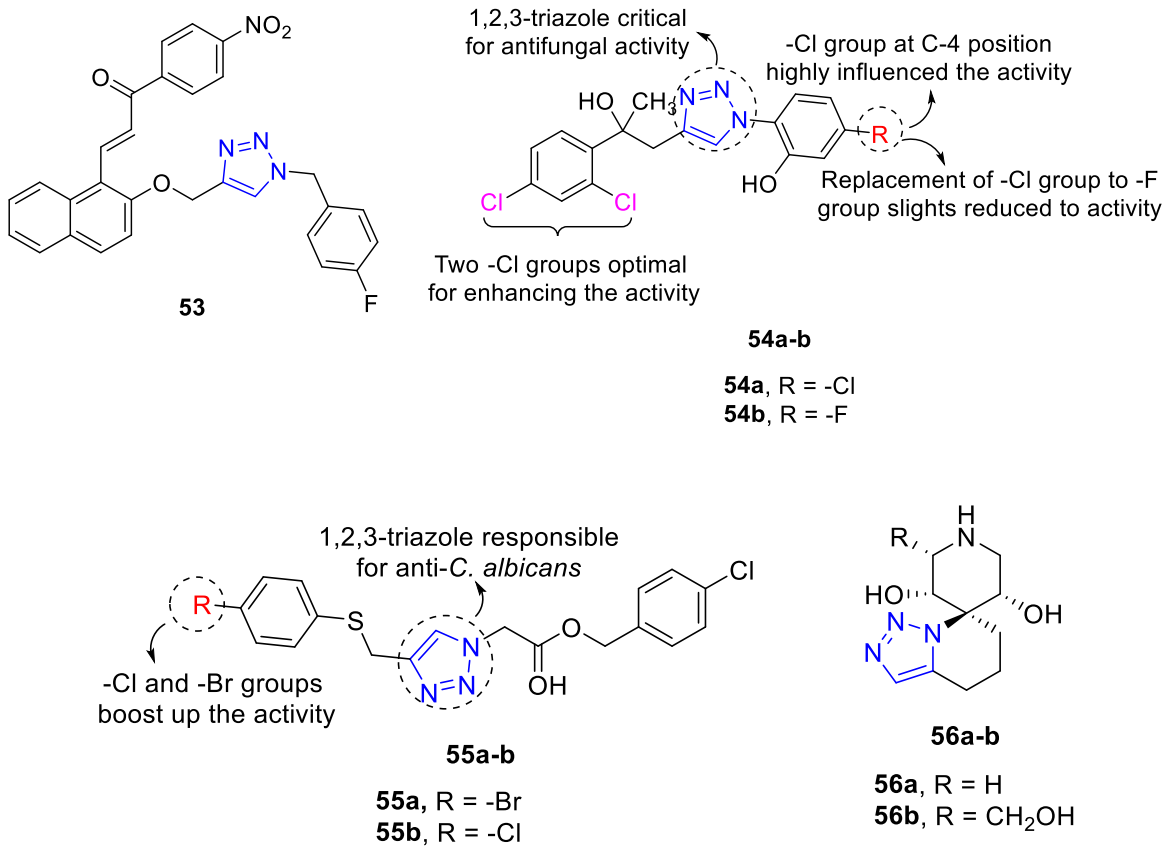


Fig. 21. 1,2,3-Triazole-based derivatives (**53–56**) exhibited potent antifungal activities against tested fungal strains.

Data Availability

No data was used for the research described in the article.

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