

Review Article

Recent advances in pharmacologically important 1,2,4-triazoles as promising antifungal agents against *Candida albicans*

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ABSTRACT

Candida infections are quite prevalent and constitute a significant etiological factor in the development of severe medical diseases attributed to fungal pathogens. This type of infection is particularly observed in individuals with compromised immune systems or those who are hospitalized. *Candida albicans* is well recognized as one of the most significant and widespread strain of candida, contributing to several nosocomial infections and posing a significant risk to individuals' lives. Furthermore, the growth of drug resistance has rendered many antifungal therapies useless, necessitating the urgent development of highly effective fungicidal drugs. The discipline of heterocyclic chemistry, specifically focusing on molecules featuring a 1,2,4-triazole scaffold, has emerged as a captivating area of research in recent times. The nucleus under consideration exhibits a wide range of biological activities, as documented in several scientific publications over the past thirty years. These studies have focused on the application of the 1,2,4-triazole nucleus in the creation of fungicidal drugs targeting *Candida albicans*. The present study aimed to introduce a comprehensive overview of numerous studies that have investigated the development of 1,2,4-triazole derivatives as powerful antifungal agents against *Candida albicans*. The elucidation of structure-activity relationships (SAR) serves as a valuable tool for contemporary medicinal chemists in the development and synthesis of novel target compounds containing the 1,2,4-triazole nucleus. This approach facilitates the development of effective treatments with desirable properties including selectivity, safety, and efficacy.

1. Introduction

In the realm of human health, invasive fungal infections (IFIs) induced by drug-resistant fungus are well recognized as a significant threat, often referred to as "hidden killers"[1]. Despite the existence of several antifungal medications, the death rate linked to (IFIs)

frequently surpasses 50%[2]. Based on estimations, a significant portion of overall mortality, ranging from 20% to 40%, can be linked to nosocomial infections resulting from *Candida albicans*[3, 4] which is the predominant fungal pathogen within the *Candida* genus and is responsible for the majority of invasive infections[5].

Candida albicans exists in a commensal relationship with the mouth cavity and gastrointestinal tract[6]. However, it is important to note that this fungus is also capable of causing severe infections in both mucosal and systemic regions, posing a significant threat to the affected individual's life[7]. According to reports, *Candida* ranks as the fourth-leading cause of bloodstream infections related to healthcare in the United States [8]. Therefore, it is imperative to foster the advancement of novel antifungal medications in order to mitigate the proliferation of resistance[9].

Azoles are a class of heterocyclic compounds that serve as privileged scaffolds in various domains [10, 11]. Their derivatives have shown promise as antifungal agents, primarily by impeding the synthesis of ergosterol, a key constituent of the fungal cell membrane [12, 13]. This inhibition is achieved through the suppression of the fungal cytochrome P450 enzyme, ultimately resulting in fungal apoptosis[14]. Moreover, azole based compounds possess various biological activity such as, anticonvulsants, antidepressants, antioxidants, anti-inflammatory agents, antibiotics, anti-fungal agents, antiviral agents, and so on [15].

Triazole compounds, including fluconazole, itraconazole, voriconazole[16], posaconazole, albaconazole, efinaconazole, ravuconazole, and isavuconazole, have garnered significant interest within the field of azole drugs [17]. This heightened attention can be attributed to their wider range of effectiveness, favorable pharmacokinetic properties, selectivity, and satisfactory safety profile [18]. Specifically, there has been considerable interest in the study of 1, 2, 4-triazole analogues in the context of their antifungal properties. The emergence of synthesized drug resistance against diverse fungal infections is a highly significant concern[19]. Consequently, the global priority lies in the synthesis and advancement of novel 1,2,4-triazoles that exhibit minimal toxicity[20].

This review primarily examines the most recent scholarly articles published between 2021 and 2023 that relate to the synthesis of novel 1,2,4-triazole compounds as antifungal agents. The objective is to investigate the structure-activity relationship (SAR) of these compounds in order to get a deeper understanding and facilitate the rational design of more potent 1,2,4-triazole antifungal candidates[21]. The aforementioned information, together with our interest in the development of effective antifungal medicines, including the 1,2,4-triazole moiety, has motivated us to present this study. It encompasses the latest advancements in the synthesis of novel antifungal

compounds using the 1,2,4-triazole scaffold, which have demonstrated significant potential in terms of their activity.

1.1. 1,2,4-Triazole derivatives with a Schiff base on one side of the chemical linkage:

In a recent study conducted by Janowska *et al.*, a novel set of triazole compounds was developed and synthesized. These compounds are derivatives of 1,2,4-triazole and possess the characteristics of Schiff bases. Specifically, they are generated from 4-amino-5-(3-fluorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione. The antifungal efficacy of the compounds under investigation is relatively low compared to Nystatin, which served as a positive control and exhibited a MIC and MBC range of 0.24-0.48 $\mu\text{g/mL}$. Compound 1d had weak action against *C. albicans*, having a 4-methoxyphenyl group and a (MIC) that reached 62.5 $\mu\text{g/mL}$. Compounds containing $-\text{CH}_3$ and $-\text{OCH}_3$ groups at positions two and three were synthesized to investigate the impact of substituent positioning on the aromatic ring on their antifungal properties. Among these compounds, 1l, bearing a 2-methoxyphenyl substituent, exhibited weak activity against *C. albicans*, with a (MIC) value of 125 $\mu\text{g/mL}$. This yeast strain exhibited little susceptibility to 1a, which included a 4-methylphenyl group, as evidenced by its (MIC) of 250 $\mu\text{g/mL}$. The determination of the minimal fungicidal concentration (MFC) was carried out for compounds exhibiting a (MIC) of less than or equal to 500 $\mu\text{g/mL}$ against yeasts. The presence of fungicidal activity was solely detected in the instance of 1k, specifically when a methoxy group was positioned in the m- position. This activity was observed toward *C. albicans*, with (MIC) of 500 $\mu\text{g/mL}$ and (MFC) of 1000 $\mu\text{g/mL}$ [22]. [Figure 1]

1.2. Alkynyl-methoxyl side chain 1,2,4 triazole analogs:

In their work, Fei Xie *et al.* conducted research on the design of novel antifungal drugs with enhanced efficacy, broader spectrum, and reduced toxicity. Their findings highlight the potential of triazole analogues in overcoming fungal resistance and improving the field of antifungal therapy. Compounds 2n, 2p, and 3c exhibited a wide range of antifungal efficacy against seven fungal species known to cause human pathogenic infections, as well as two isolates of fluconazole-resistant *C. albicans* and two isolates of multi-drug resistant *Candida auris*. In addition, the antifungal activity of 0.5 $\mu\text{g/mL}$ concentrations of compounds 2n, 2p, and 3c was shown to be superior to that of 2 $\mu\text{g/mL}$ of fluconazole in terms of reducing the growth of the tested fungal strains. However, compound 2n exhibited the highest level of activity by totally suppressing the proliferation of *C.*

albicans at a concentration of 16 µg/mL over a 24-hour period. Furthermore, it demonstrated an impact on biofilm development and effectively eradicated the fully developed biofilm at a concentration of 64 µg/mL.

Meanwhile, the majority of the target compounds exhibited potent inhibitory action against *C. albicans* SC5314, with (MICs) that vary from ≤0.125 to 0.5 µg/mL [23]. [Figures 2, 3]

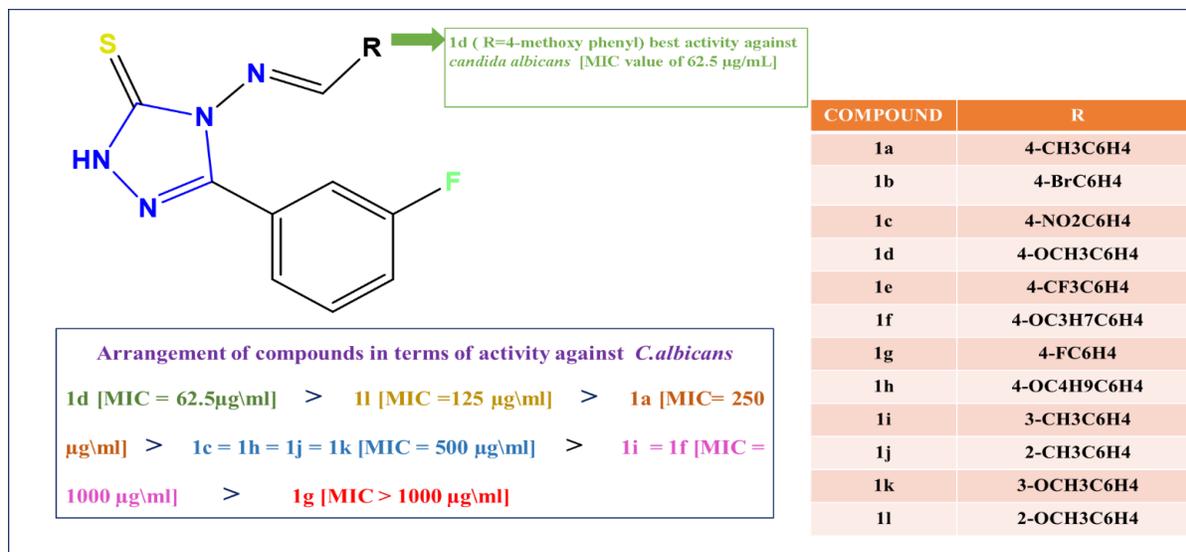


Figure 1: Chemical structures of New 1,2,4-Triazole derivatives with a Schiff base on one side of the chemical linkage.

1.3. 1,2,4-Triazole-3-thiones:

Within a set of eleven recently produced hybrid benzothiazolyl-triazole analogues, a compound denoted as 5-(benzothiazol-2-ylmethyl)-4-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione 4a has shown significant potential as an antifungal agent. Its (MIC) value against *Candida albicans* was found to be 0.39 µg/mL [24]. [Figure 4]

1.4. 1,2,4-Triazole containing benzoxyl phenyl isoxazole side chain:

A collection of 29 unique triazoles, distinguished by the presence of a benzyl oxyphenyl isoxazole side chain, were conceptualized and subsequently produced [25]. A significant proportion of the substances demonstrated notable efficacy in inhibiting fungal growth under controlled laboratory conditions.

Compounds 6a, 6h, and 7c exhibited significant antifungal activity, as evidenced by their (MIC) values ranging from less than 0.008 µg/mL to 1 µg/mL. Moreover, these compounds demonstrated notable inhibitory properties against the production of biofilms by *Candida albicans* SC5314. Moreover, compound 6a exhibited a moderate level of inhibition against human CYP1A2, but its inhibitory actions on CYP2D6 and CYP3A4 were found to

be restricted. These findings indicate a low likelihood of drug-drug interactions associated with this compound. Due to its notable efficacy in laboratory and in vivo studies, together with its favorable safety profile, compound 6a will be subjected to further examination as a promising antifungal agent. [Figures 5, 6].

1.5. 1,2,4-Triazole linked to Indolo[3,2-c]isoquinoline:

Basavarajaiah et al. reported the synthesis of newly developed 9-chloro-1-(4-substituted phenyl)-12H-indolo[2,3-c][1,2,4]triazolo[3,4-a]isoquinolines derivatives 9(a-h). Compounds 9b, and 9h have shown noteworthy antifungal efficacy. The results showed that compound 9h demonstrated the highest level of antifungal efficacy against all examined fungi, as indicated by its (MIC) of 3.125 µg/mL. Compound 9b exhibited antifungal activity against all tested fungi, manifesting (MIC) values of 6.25 µg/mL, which are comparable to the efficacy of the conventional pharmaceutical agent Itraconazole [26]. [Figure 7]

1.6. Quinoxaline linked 1,2,4-Triazole compounds:

Osmaniye et al. conducted the synthesis of 17 novel triazole derivative compounds. The researchers then proceeded to examine the antifungal properties of these

compounds on *Candida* strains using an in vitro methodology. The results reported that compound 10d exhibited significant antifungal activity against *Candida albicans*, as evidenced by its (MIC₉₀) value of 4 µg/mL. Upon examination of the molecular structure of the 10d

molecule, it becomes evident that the presence of the nitro substituent at the 4th position is noteworthy. The incorporation of this substituent into the molecular structure resulted in a substantial enhancement of the observed activity [27]. [Figures 8, 9]

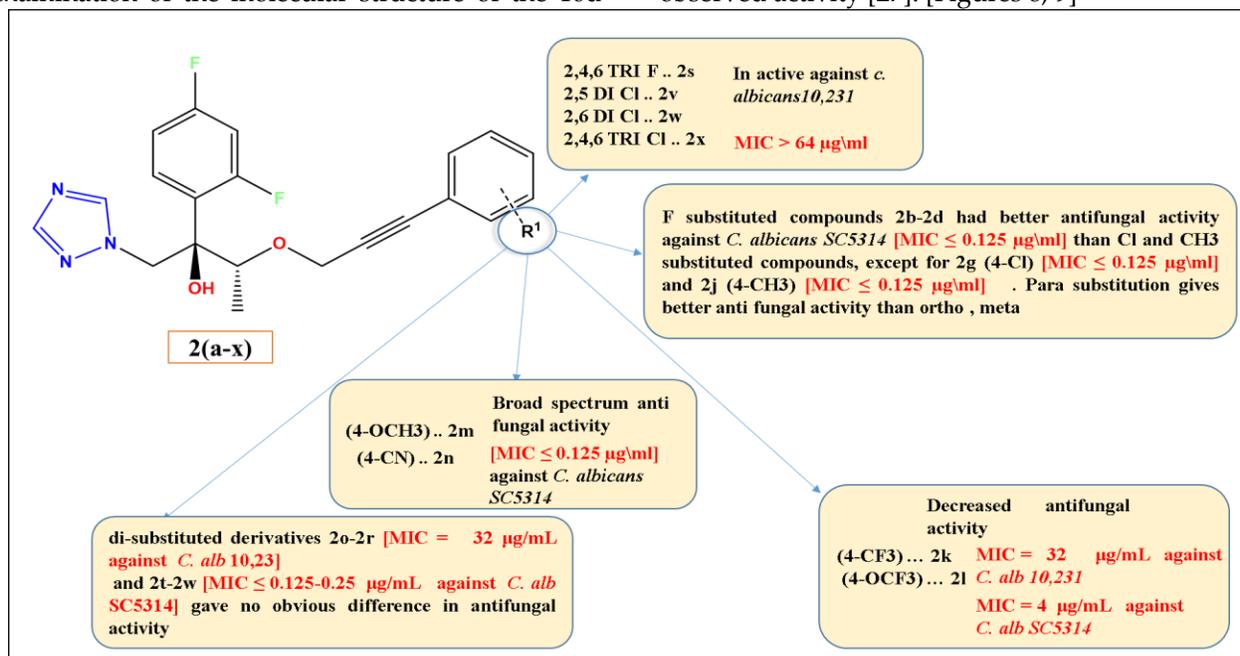


Figure 2: Structure-activity relationships study of targeted compounds 2a-x.

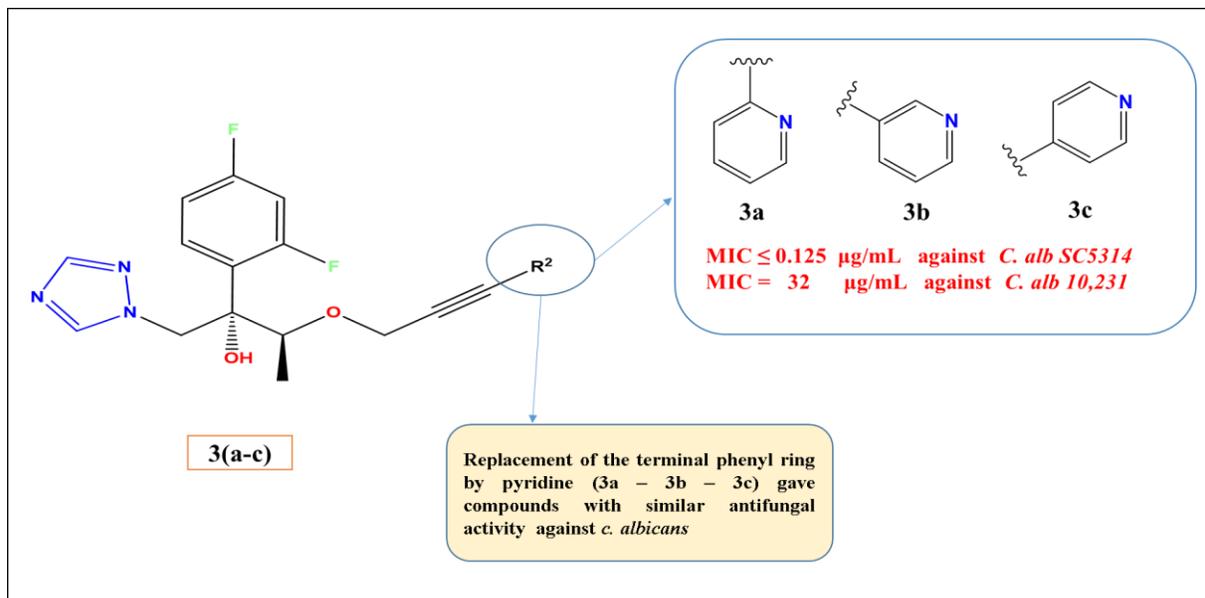


Figure 3: Structure-activity relationships study of targeted compounds 3a-c.

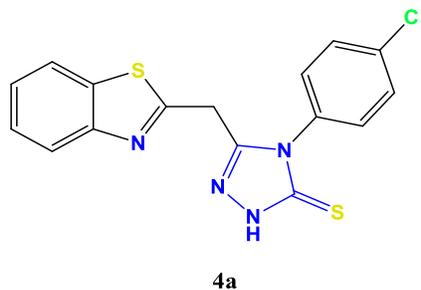


Figure 4: Chemical structure of new antifungal agent with 1,2,4-triazole-3-thione nucleus.

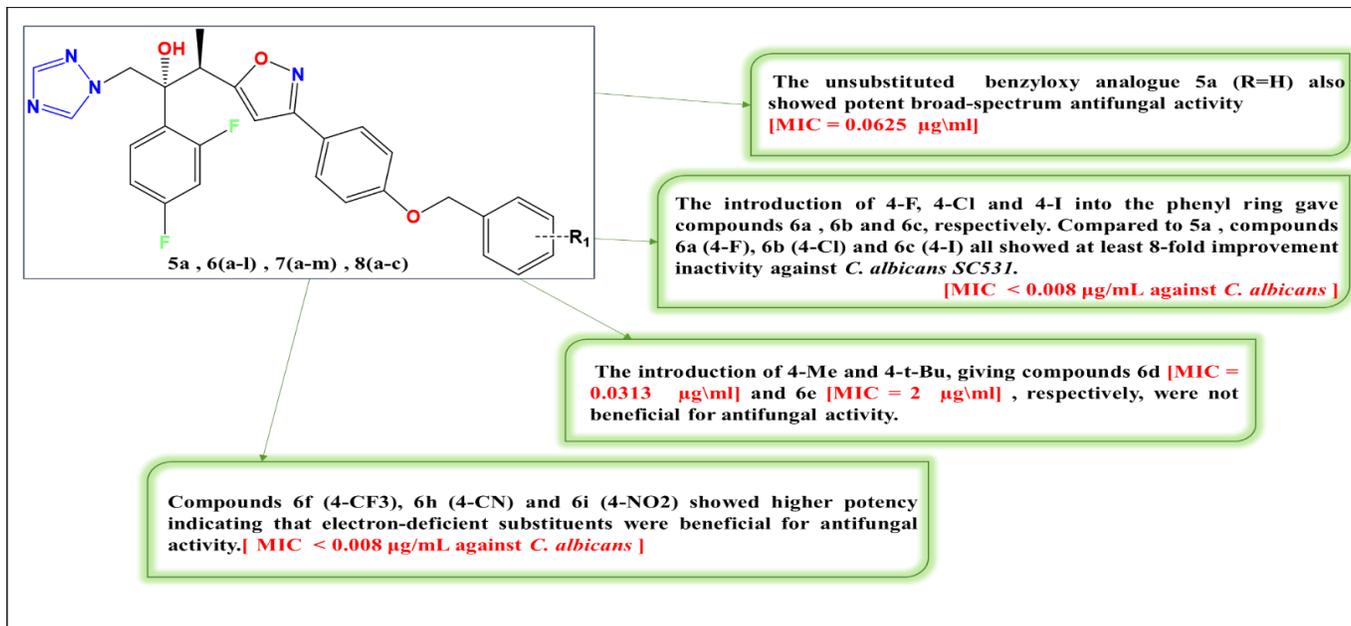


Figure 5: Chemical structure and SAR of triazoles containing benzyloxy phenyl isoxazole side chain

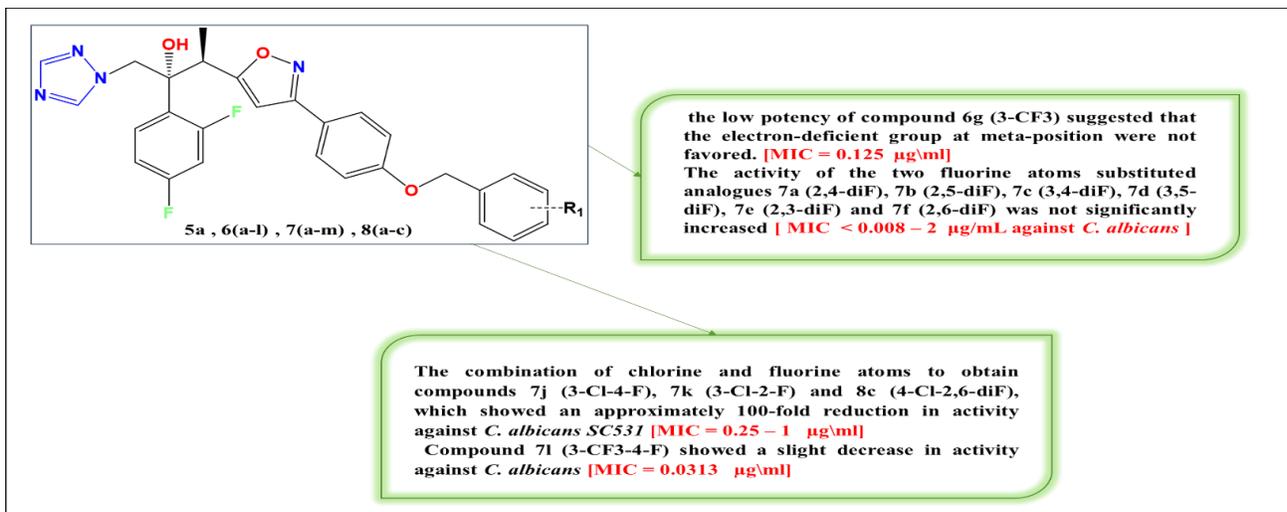


Figure 6: SAR of new antifungal triazoles.

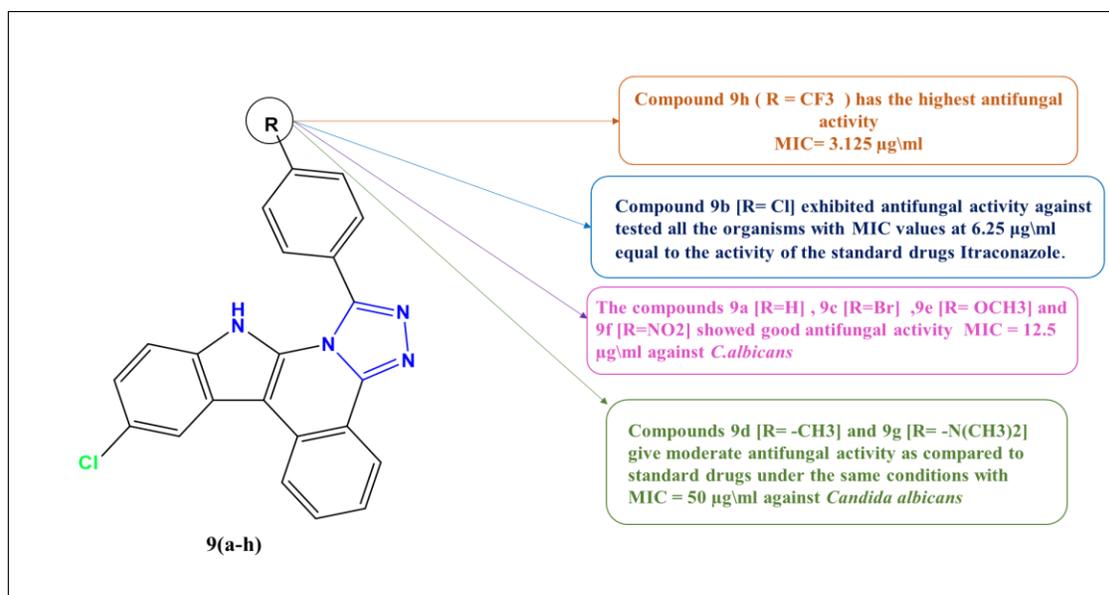


Figure 7: SAR of 1,2,4-Triazoles linked to Isoquinoline.

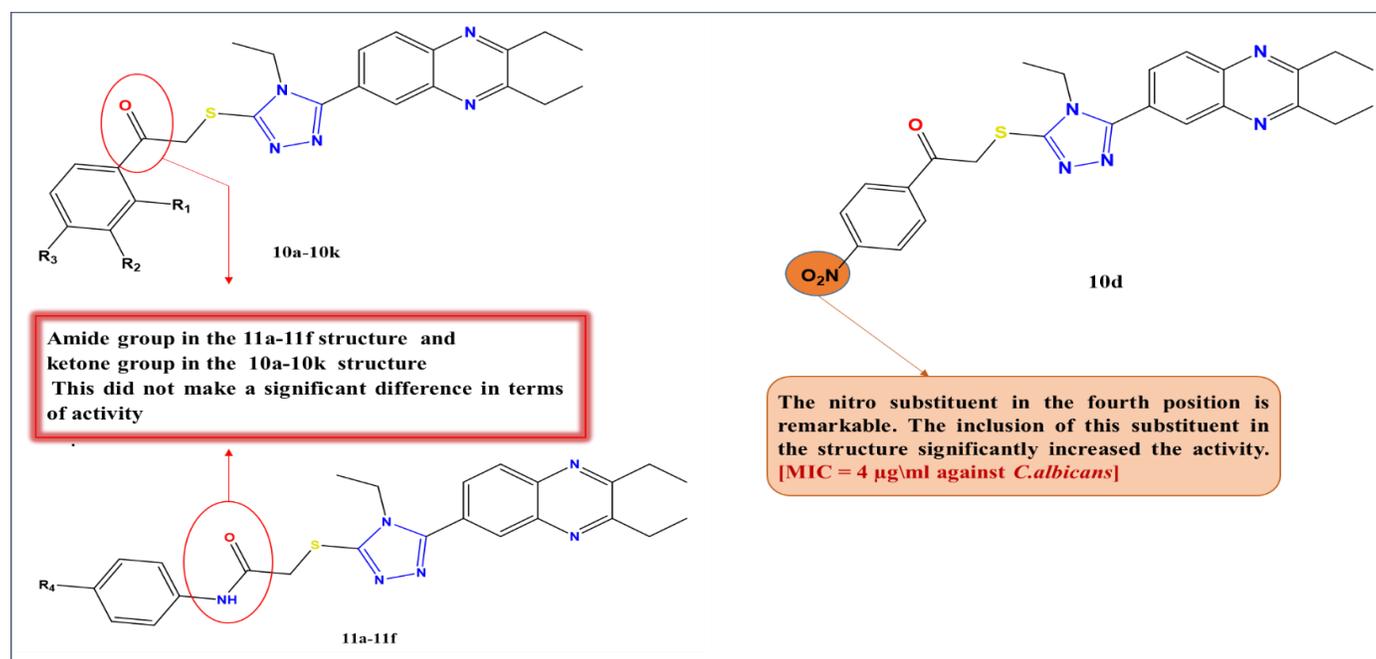


Figure 8: Structures and SAR of quinoxaline linked 1,2,4-triazole compounds.

Compound	R1	R2	R3	R4
10a	H	H	CH3	
10b	H	H	OCH3	
10c	H	H	CN	
10d	H	H	NO2	
10e	H	H	F	
10f	H	H	Cl	
10g	H	H	Br	
10h	CH3	H	CH3	
10i	F	H	F	
10j	Cl	H	Cl	
10k	H	Cl	Cl	
11a				H
11b				CH3
11c				OCH3
11d				F
11e				Cl
11f				CF3

**Compounds 10j , 10k , 11c , 11d have moderate activity against *Candida albicans*.
[MIC = 32 µg/ml]**

**Compounds 10a , 10b , 10e , 10f , 10g , 10h , 10i , 11a , 11b , 11e , 11f have some activity against *C. albicans*
[MIC = 64 µg/ml]**

**Compound 10c has the lowest activity against *C. albicans*
[MIC = 128 µg/ml]**

Figure 9: Chemical structures of 1,2,4 triazole analogues and their SAR.

1.7. 1,2,4-Triazole-thiazolidin-4-one:

The successful synthesis of a group of [5-(substituted phenyl)-4H-1,2,4-triazol-4-yl]thiazolidin-4-ones compounds has been reported in the literature [4]. The produced compounds underwent in vitro testing to evaluate their effectiveness against fungal strains. Compounds that possess 2-Br, 4-Cl, 4-F, 4-OCH₃, and 4-CH₃, 2, 4-(CH₃)₂, and 4-NO₂ substituents have demonstrated excellent to good antifungal efficacy. The derivative containing a bromine atom at position 2 exhibited notable activity against *Candida albicans*, with (MIC) of 200 µg/mL. However, 1,2,4-triazole-linked thiazolidin-4-one compounds 12e and 12o, exhibiting (MFC) values of 250 µg/mL, representing two-fold superior activity compared to griseofulvin in inhibiting the growth of *Candida albicans*. Furthermore, compound 12b, at a concentration of 200 µg/mL, had the most pronounced antifungal activity against *C. albicans* compared to all other compounds tested. Additionally, compounds 12d, 12i, 12l, and 12m demonstrated (MFCs) of 500 µg/mL and comparable efficacy against *Candida albicans* when compared to the reference drug griseofulvin. While compounds 12n and 12o, with NO₂

group in the benzylidene phenyl moiety, demonstrated a modest level of antifungal activity. [Figure 10]

1.8. 1,2,4-Triazoles bearing a 5-benzoyl benzimidazol-2-ylthio side chain:

A novel class of triazole alcohol bearing 5-benzoylbenzimidazol-2-ylthio side chain has been synthesized and examined for their antifungal activity [28]. The design of these compounds involves combining the structural features of fluconazole, a commonly used triazole antifungal, with mebendazole, an anthelmintic drug known for its antifungal properties [8]. The key lead compounds (series A) were subjected to SAR analysis. This involved simplifying the 5-benzoylbenzimidazol-2-ylthio residue to either the benzimidazol-2-ylthio side chain (series B) or the benzothiazol-2-ylthio side chain (series C). Additionally, modifications were made to the halogen substituent on the phenethyl-triazole scaffold. In general, the series A compounds (13a–e), which encompass a 5-benzoyl benzimidazole scaffold, exhibited superior antifungal efficacy against *Candida* spp. in comparison to analogous compounds in series B and C. On the other hand, the 4-chloro derivative 13b exhibited superior outcomes, with (MICs) ranging from less than

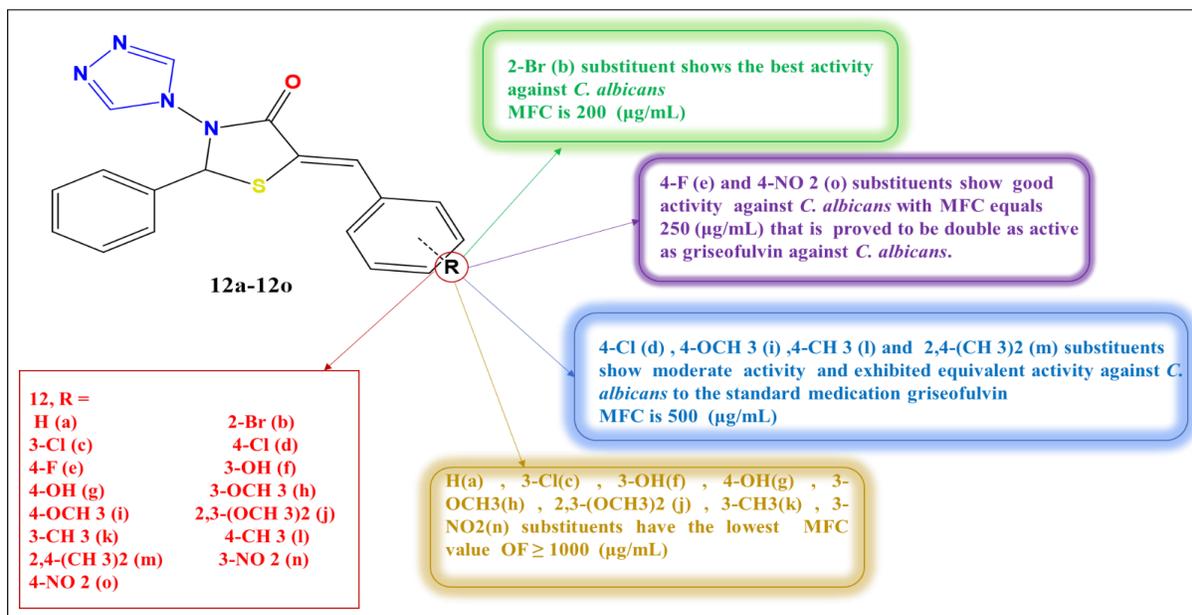


Figure 10: Structure–activity relationships of compounds 12a–12o: molecular framework and biological activities.

0.063 to 1 µg/mL. Even though the removal of the benzoyl group.

1.9. 1,2,4-Triazoles bearing a 5-benzoyl benzimidazol-2-ylthio side chain:

A novel class of triazole alcohol bearing 5-benzoylbenzimidazol-2-ylthio side chain has been synthesized and examined for their antifungal activity [28]. The design of these compounds involves combining the structural features of fluconazole, a commonly used triazole antifungal, with mebendazole, an anthelmintic drug known for its antifungal properties [8]. The key lead compounds (series A) were subjected to SAR analysis. This involved simplifying the 5-benzoylbenzimidazol-2-ylthio residue to either the benzimidazol-2-ylthio side chain (series B) or the benzothiazol-2-ylthio side chain (series C). Additionally, modifications were made to the halogen substituent on the phenethyl-triazole scaffold. In general, the series A compounds (13a–e), which encompass a 5-benzoyl benzimidazole scaffold, exhibited superior antifungal efficacy against *Candida* spp. in comparison to analogous compounds in series B and C. On the other hand, the 4-chloro derivative 13b exhibited superior outcomes, with (MICs) ranging from less than 0.063 to 1 µg/mL. Even though the removal of the benzoyl group from compound 13b had a detrimental impact on

its activity, the optimization of the phenethyl-triazole scaffold by the incorporation of a desirable halogen substituent led to the development of compound 14c, which exhibited comparable potency to that of 13b. The in vitro antifungal properties of compounds 13–15 was evaluated against various human pathogenic fungi. Most of the investigated compounds exhibited from excellent to moderate antifungal activity against *Candida albicans* species, with (MICs) ranging from less than 0.063 to 32 µg/mL. Generally, it was observed that series A, comprising compounds 13a–e with a 5-benzoylbenzimidazole scaffold, had superior antifungal activity compared to derivatives of benzimidazole and benzothiazole. This suggests that the general structure possesses inherent potential for antifungal activity. In general, the mono-halogenated compounds exhibited superior performance compared to their di-halogenated equivalents in many of the tested compounds. Consequently, the structure-activity relationship analysis revealed that the di-chlorophenyl derivatives exhibited greater potency compared to the di-fluorophenyl derivatives in all series. In a broader perspective, the biological findings indicate that the impact of a halogen substituent on the phenyl substructure is heavily dependent upon the specific side chain involved. [Figures 11, 12, 13, 14]

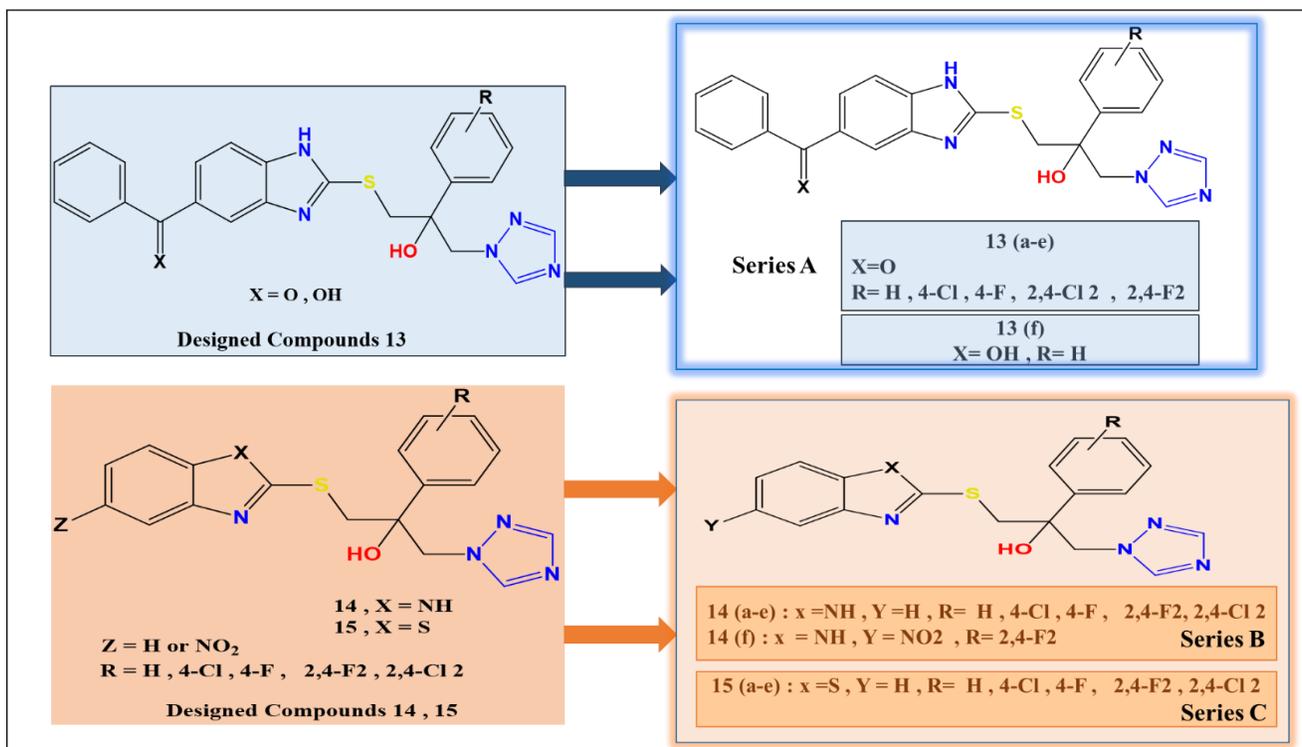


Figure 11: General structures of target compounds (series A-C)

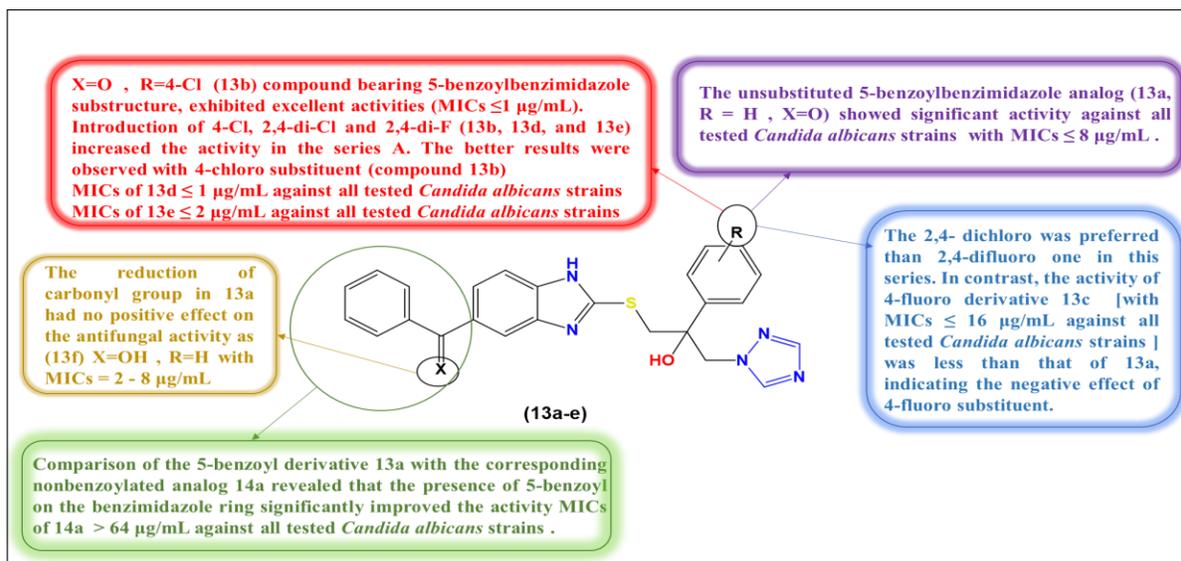


Figure 12: Relationship between series A chemicals' chemical structures and biological activities

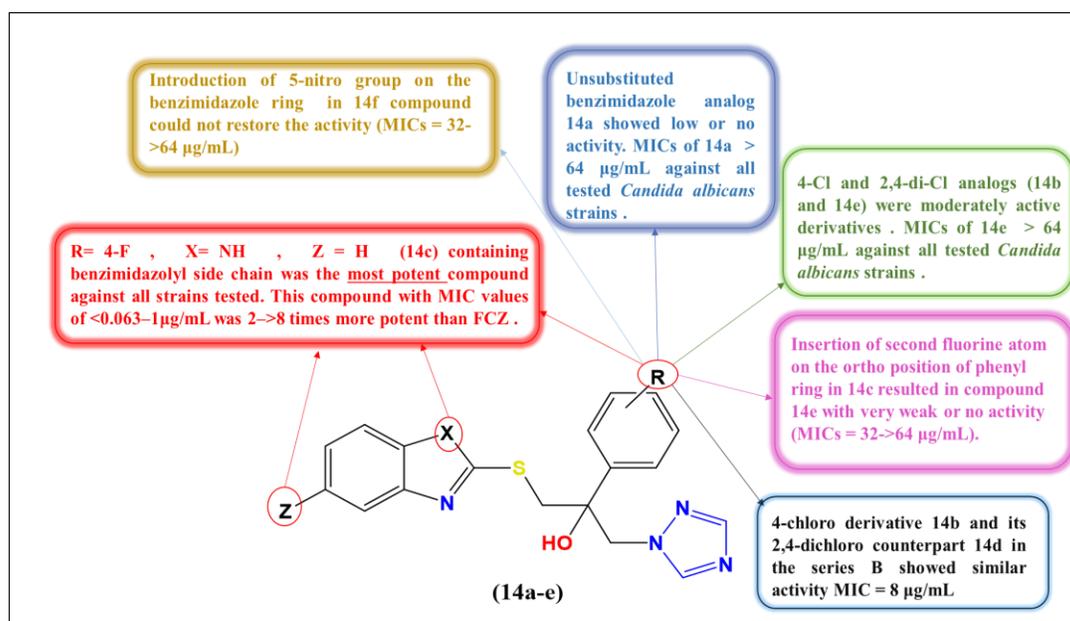


Figure 13: Relationship between series B chemicals' chemical structures and biological activities.

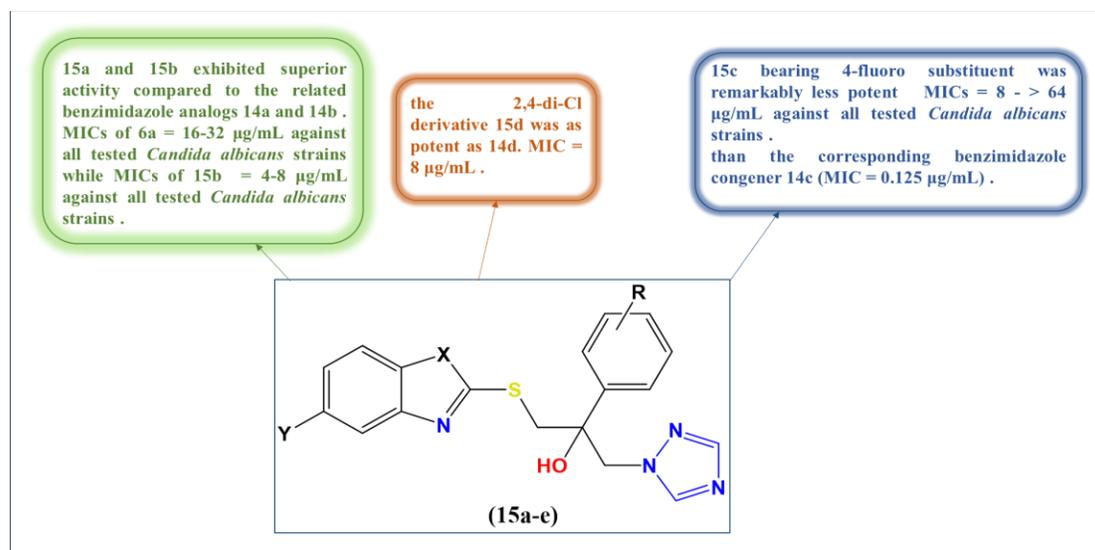


Figure 14: Relationship between series C chemicals' chemical structures and biological activities

1.10. 1,2,4-Triazoles linked to ketone:

Sadeghian et al. developed and synthesized a novel set of 1,2,4-triazole analogues (16a-i) and examined their antifungal efficacy against various strains of yeast, specifically those belonging to the *Candida* species. Compounds 16g and 16h exhibited enhanced potency against yeast strains, including both fluconazole-resistant and fluconazole-sensitive clinical strains, as evidenced by their lower (MIC) values of 0.5 µg/mL compared to that of the control drug fluconazole. In general, the second series of the targeted compounds, specifically the 1, 3, 3 triphenyl propane 1-one compounds, had more favorable

effects compared to that of the first series, 1, 3 diphenyl propane 1-one derivatives. Meanwhile, compounds 16g and 16h, which included F and Cl substitutions at the para position of the benzoyl ring, exhibited the most significant antifungal activity among all the yeast strains tested. Their MIC values were measured at 0.5 µg/mL, indicating a higher potency compared to the standard drug fluconazole. Additionally, it was observed that compounds 16c and 16d exhibited a moderate inhibitory impact on isolates resistant to fluconazole, as evidenced by their (MIC) values ranging from 1-32 µg/mL [4]. [Figures 15, 16]

1.11. 1,2,4-Triazole linked to methyl Carbazole:

O. Merzouki et al. have successfully synthesized three distinct chemical compounds. The inclusion of triazole in the 17c compound enhances its efficacy against the targeted strains in comparison to 17a (dimethyl pyrazole) and 17b (pyrazole) [29]. [Figure 17]

1.12. 1,2,4-Triazole linked to quinazolinone [quinazolinone-azole hybrids]:

The antifungal efficacy of ten newly synthesized quinazolin-4(3H)-one derivatives was investigated [30]. Compounds 18(a-d), 19(a-d), and 20(a,b) resulted from the nucleophilic substitution process of 2-(chloromethyl)-3-(4-chlorophenyl) quinazolin-4(3H)-one and either 1,3,4-oxadiazole or 1,2,4-triazole. However, the results indicated that compound 19b was the most effective among the tested compounds. [Figure18]

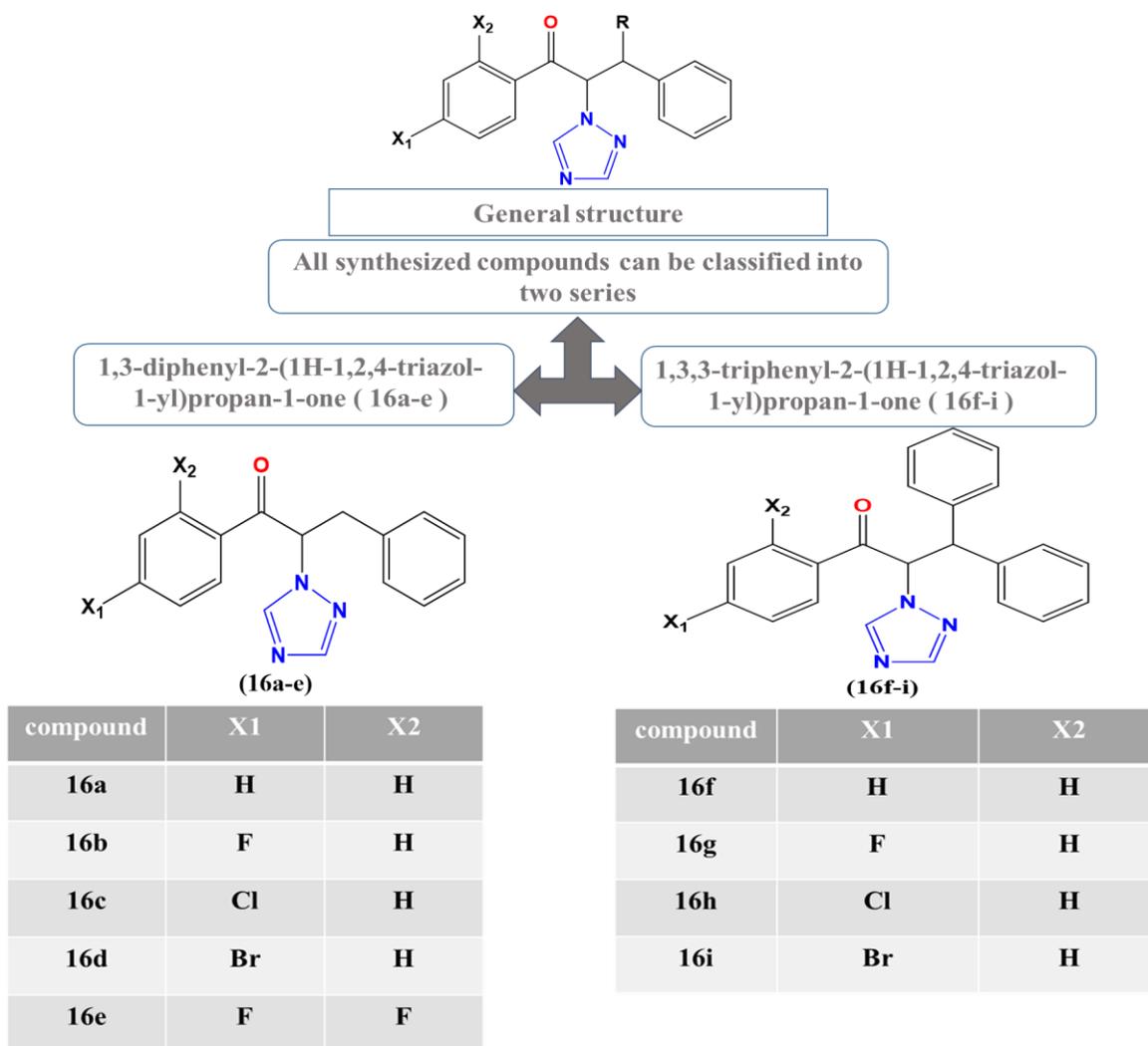


Figure 15: Design of new 1,2,4-triazole derivatives 7a-i.

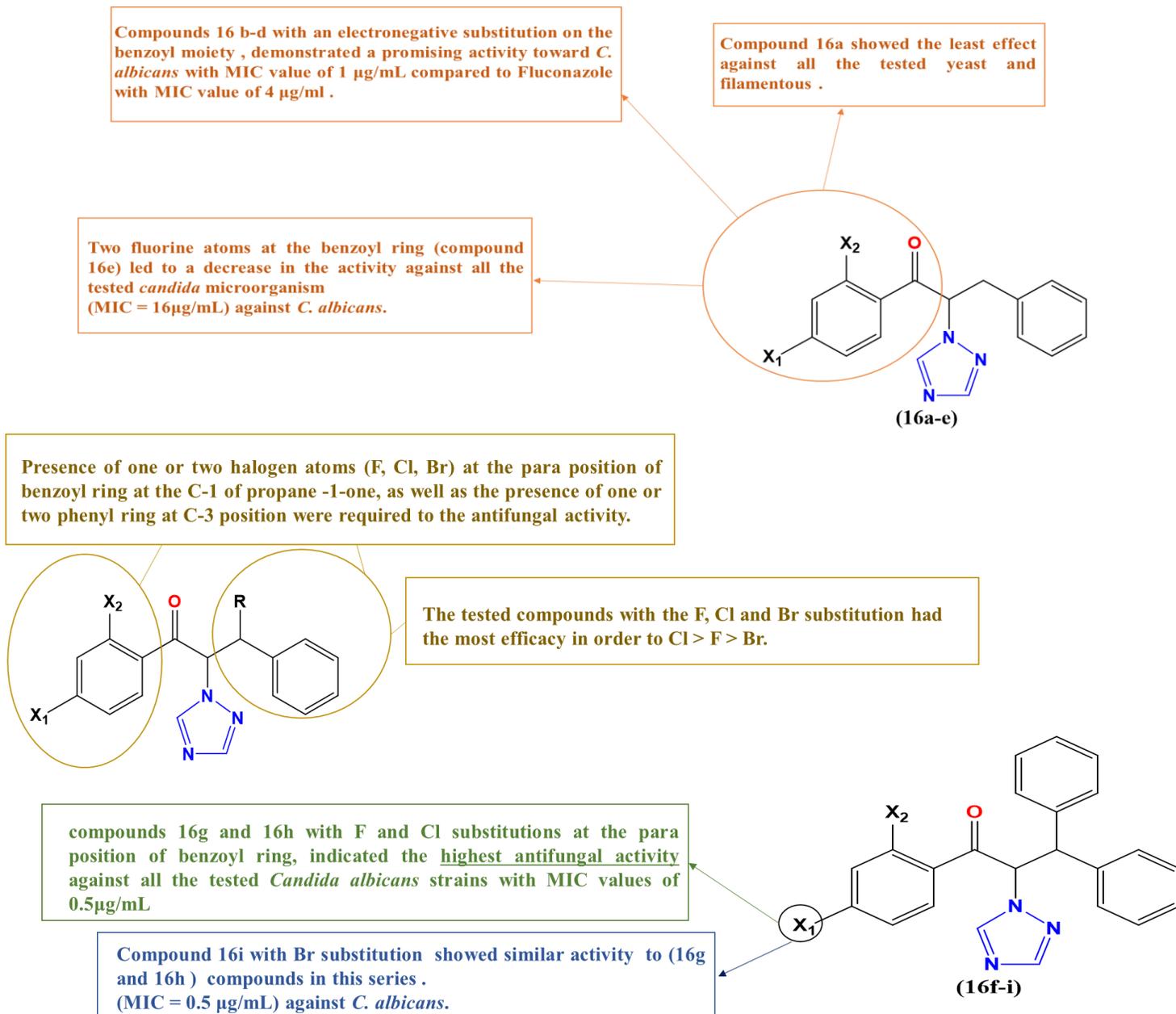


Figure 16: Structure activity relationship of new 1,2,4 triazoles.

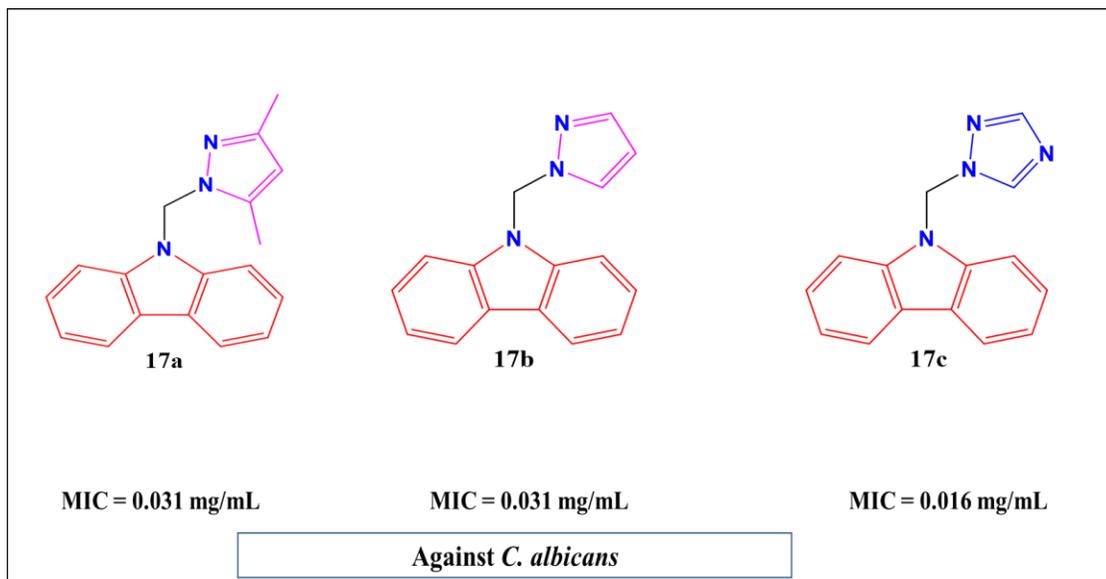


Figure 17: General structures and comparison of MICs of new compounds.

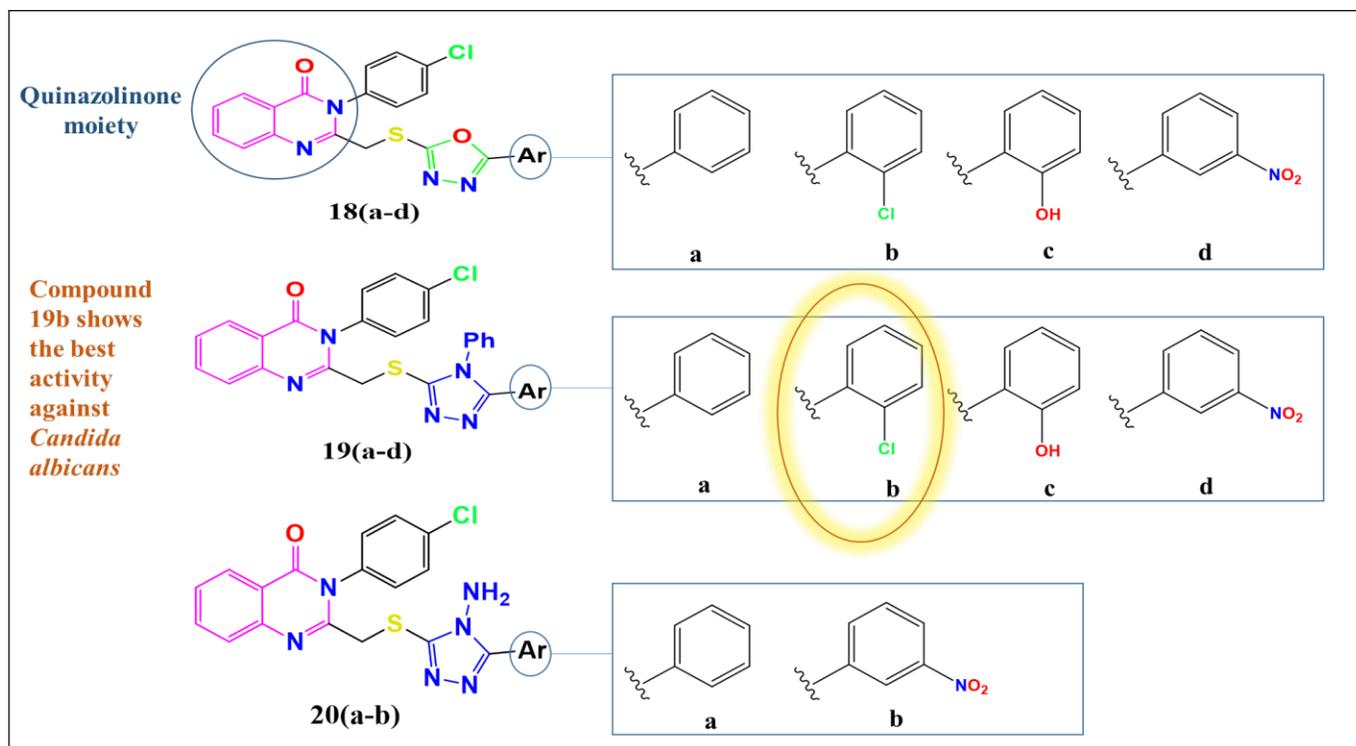


Figure 18: Chemical structures of quinazolinone-azole hybrids.

1.13.

1.14. Fluconazole-like compounds bearing 4-nitrotriazole and/ or piperazine ethanol moieties:

The antifungal characteristics of various newly synthesized triazole derivatives were examined by Emami et al. in both in vivo and in vitro environments,

specifically focusing on their efficacy against a systemic infection caused by *C. albicans*. The effectiveness of derivatives was assessed in mice treated with cyclophosphamide to induce suppression of the immune system. The antifungal properties of the produced

compounds were then compared to fluconazole. Compounds 22b and 23b had the most notable effectiveness, as evidenced by their (MIC) values ranging from 0.5 to 1 $\mu\text{g/mL}$, when tested against the *C. albicans* pathogen. The presence of electronegative substituents, such as chlorine (Cl) and fluorine (F), at the phenyl ring is essential for the manifestation of antifungal activities, as

demonstrated by the structure-activity relationship (SAR). Moreover, in the instance of compounds 23a – 23e (a molecule resembling fluconazole with piperazine ethanol groups), it was observed that compounds possessing two electronegative substitutions exhibited the most favorable action [8]. [Figure 19, 20]

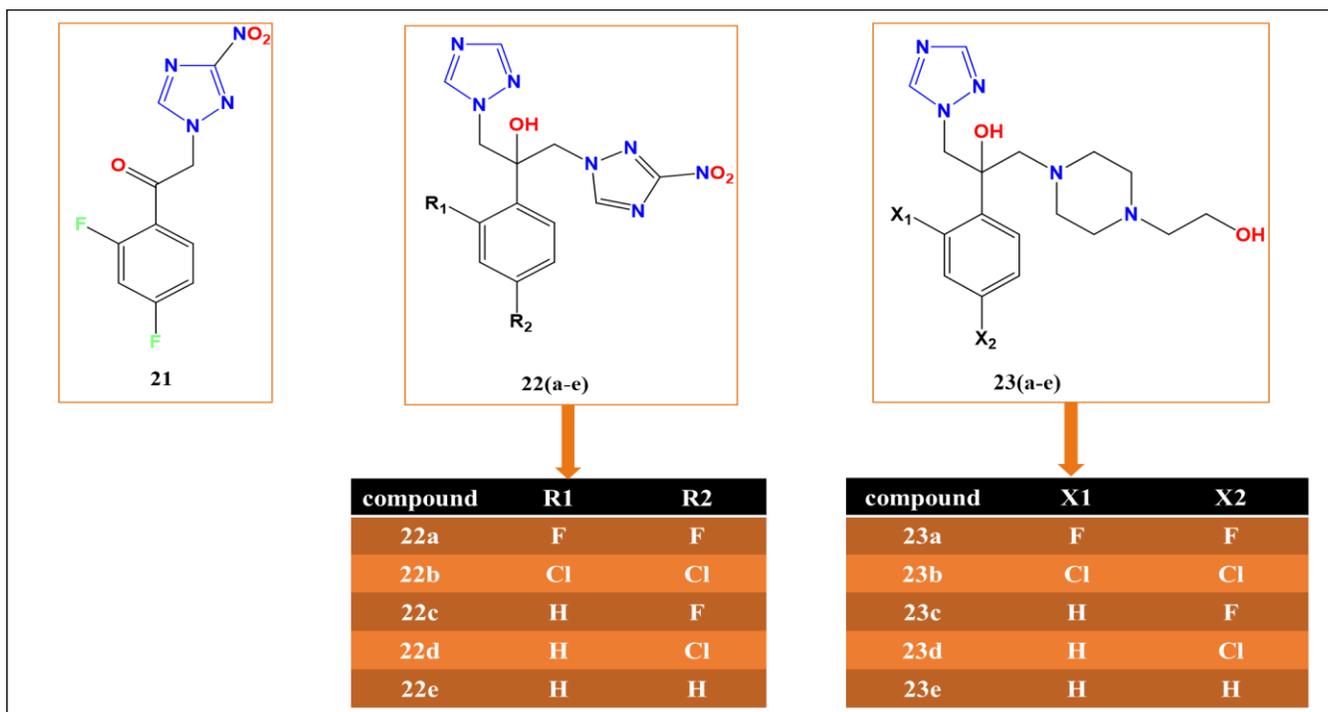


Figure 19: The chemical structures of the substances under study.

1.15. 1,2,4-Triazole linked to quinazolinone [quinazolinone-azole hybrids]:

The antifungal efficacy of ten newly synthesized quinazolin-4(3H)-one derivatives was investigated [30]. Compounds 18(a-d), 19(a-d), and 20(a,b) resulted from the nucleophilic substitution process of 2-(chloromethyl)-3-(4-chlorophenyl) quinazolin-4(3H)-one and either 1,3,4-oxadiazole or 1,2,4-triazole. However, the results indicated that compound 19b was the most effective among the tested compounds. [Figure18]

1.16. 1,2,4 triazole derivatives with selenium-containing hydrophobic side chains:

Meng-bi Guo et al. developed and produced a collection of innovative 1,2,4-triazole derivatives with hydrophobic side chains containing selenium. These derivatives were designed by taking into consideration the molecular makeup of lanosterol 14-demethylase (CYP51). The in vitro evaluation of their antifungal activity against several

pathogenic fungal species was conducted by testing the minimal inhibitory doses. The target compounds 24(a-j), 25(a-h) displayed a wide range of antifungal properties that were highly efficient against the strains tested. Mechanistic investigations revealed that these target compounds exhibited inhibitory activity against fungal CYP51. On the same context, the tested compounds demonstrated minimal cytotoxicity against mammalian cell lines. Furthermore, the docking outcomes revealed that the investigated compounds exhibited a superior binding pattern to *Candida albicans* CYP51 compared to fluconazole, particularly within the confined hydrophobic gap [31]. [Figure 21]

1.16. 1,2,4-triazoles including substituted 1,2,3-triazole-methoxyl side chains.:

The lead compound 26 underwent structural alterations in order to maximize its properties, resulting in the development of novel triazole derivatives 27(a-q),28(a-

l),29(a-c) [32]. Most of the target compounds displayed noteworthy in vitro antifungal activities against *Candida albicans*, with (MIC) value of 0.125 $\mu\text{g/mL}$ or lower. Specifically, compounds 27b and 28a exhibited inhibitory impacts on filamentation in a strain of *C. albicans* that is resistant to azole drugs. Most of the target compounds demonstrated from excellent to moderate inhibitory action against *C. albicans* 10231, apart from *C. albicans* 911. In contrast to FCZ and RCZ, compounds 28a, 28c, 28g, 28h, 28i, 28l, 29a, 29b, and 29c exhibited comparable efficacy against *C. albicans* 911, but compounds 27a–27q demonstrated much lower activity. Moreover, compounds 28b, 28d, 28e, 28f, and 28k had no activity against the tested strains. Compound 27b exhibited diminished antifungal efficacy over *C. albicans* 911 in comparison to the lead compound 26. Conversely, compound 28a showed enhanced and somewhat superior activity

compared to the lead compound against the tested fungi. [Figures 22, 23, 24]

1.17. Complexes of Ni (II) with 1,2,4-Triazoles:

A group of nickel (II) complexes (31a-31b-31c) comprising Schiff bases (30a-30b-30c) derived from the reaction between 1,2,4-triazole compound and *o*-, *m*-, and *p*- nitro benzaldehyde were synthesized, with chemical formula of $[\text{Ni}(\text{L})_2(\text{H}_2\text{O})_2]$ [33]. The antifungal properties of both Schiff bases as well as Ni (II) complexes were evaluated through a screening process against *Candida albicans*. The findings of the study indicated that the metal complexes displayed notably higher antimicrobial activities compared to their corresponding ligands when tested against the tested species. Moreover, the ligand exhibited little activity against *Candida albicans* while, Ni (II) complexes exhibited a moderate level of activity. [Figure 25]

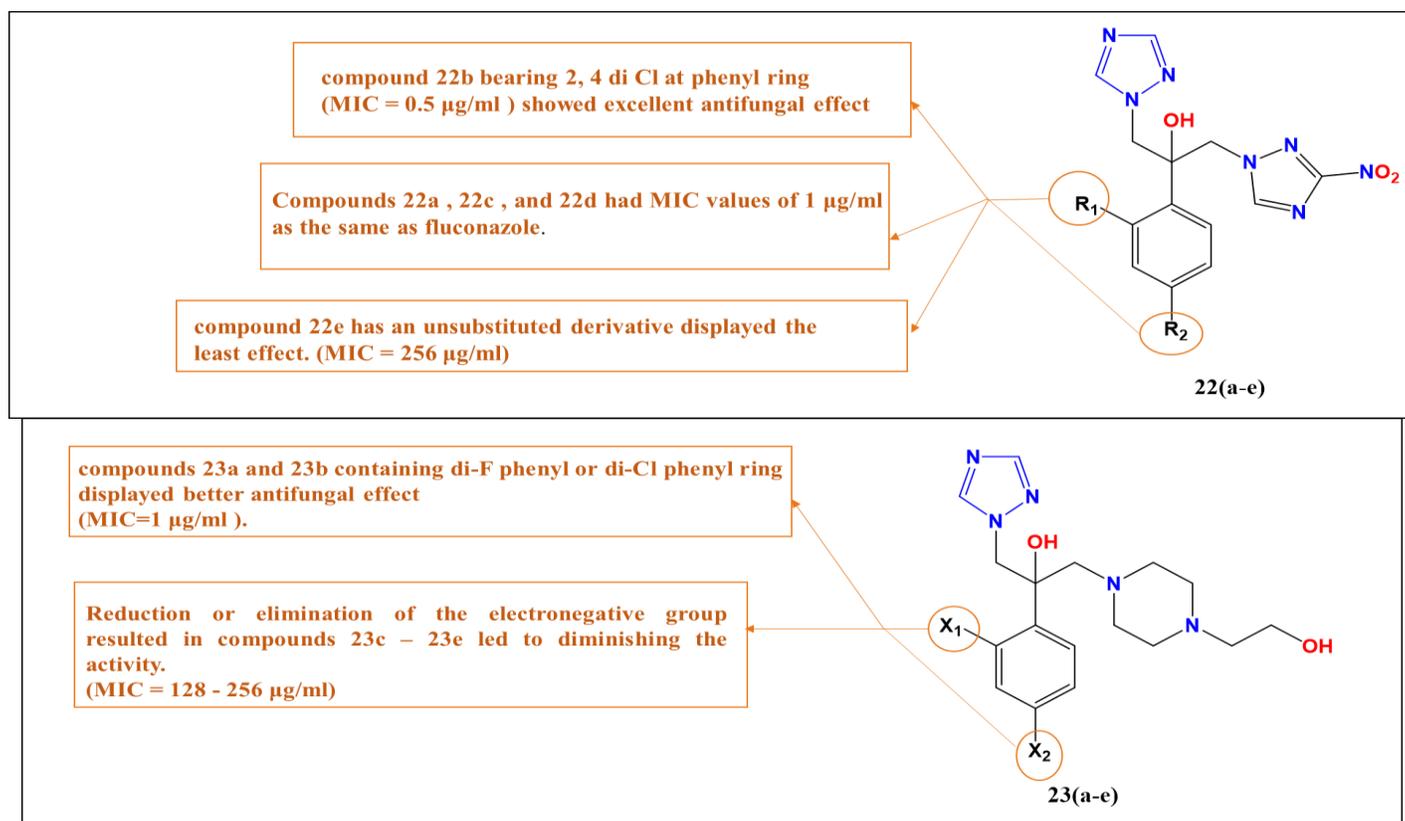


Figure 20: The SAR and chemical structures of the substances under study

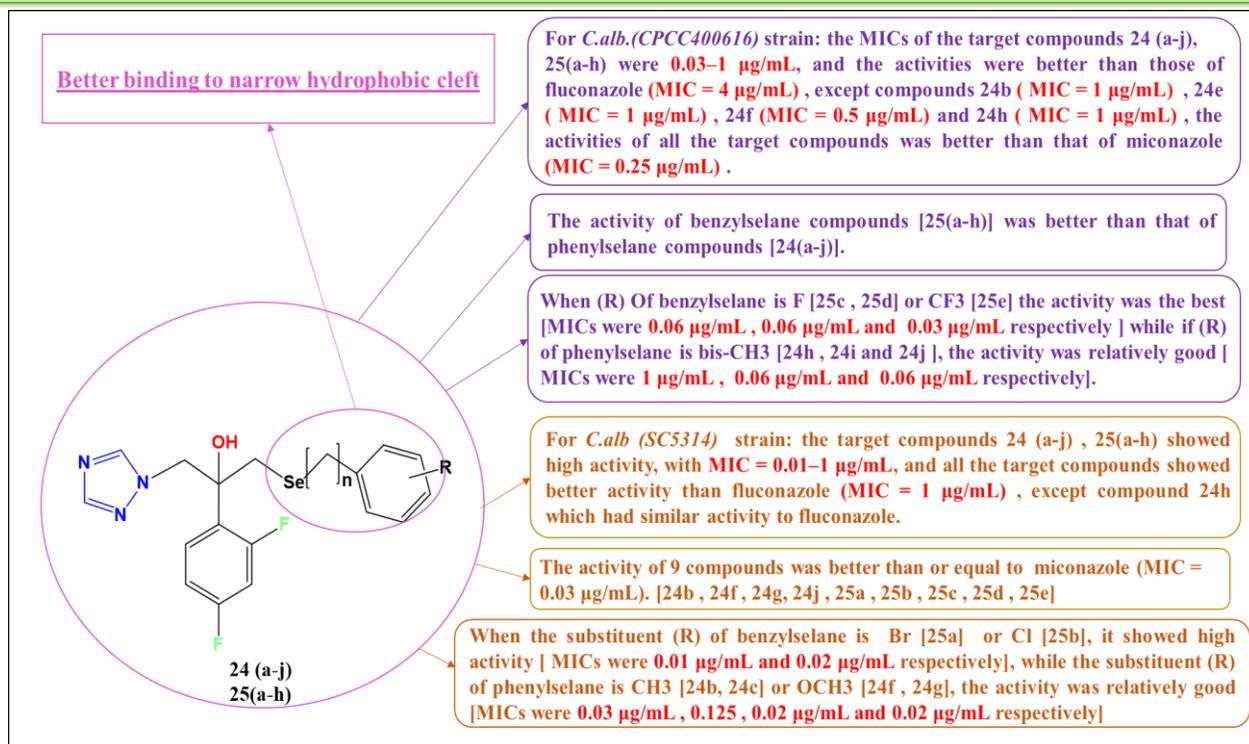
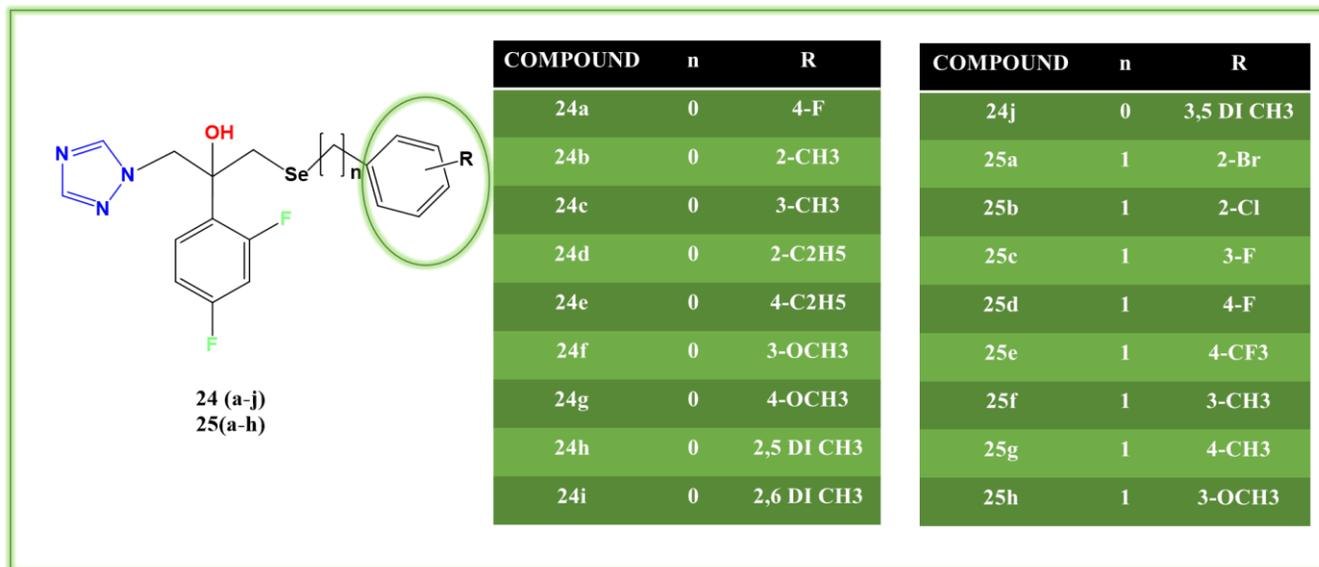


Figure 21: The basic structures of target compounds and the impact of various substituents on their action

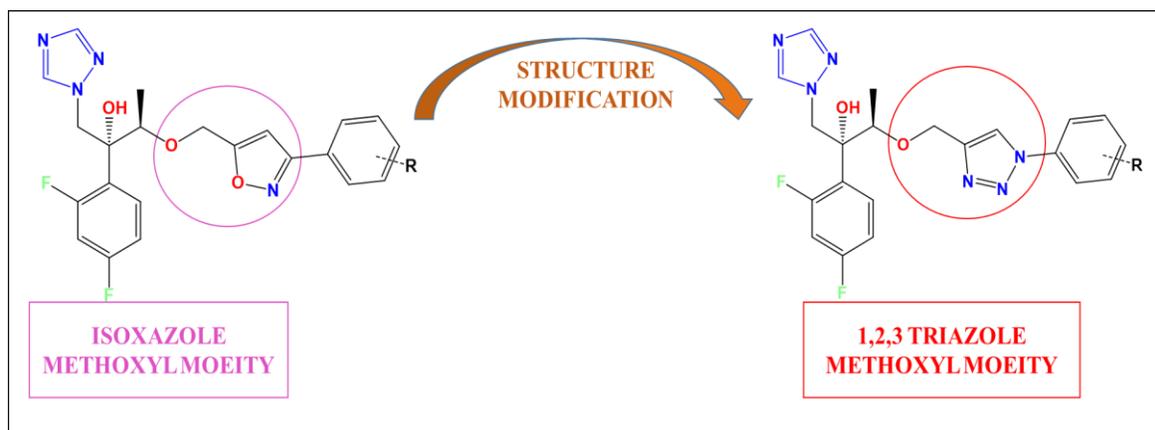


Figure 22: Design strategy of novel triazoles.

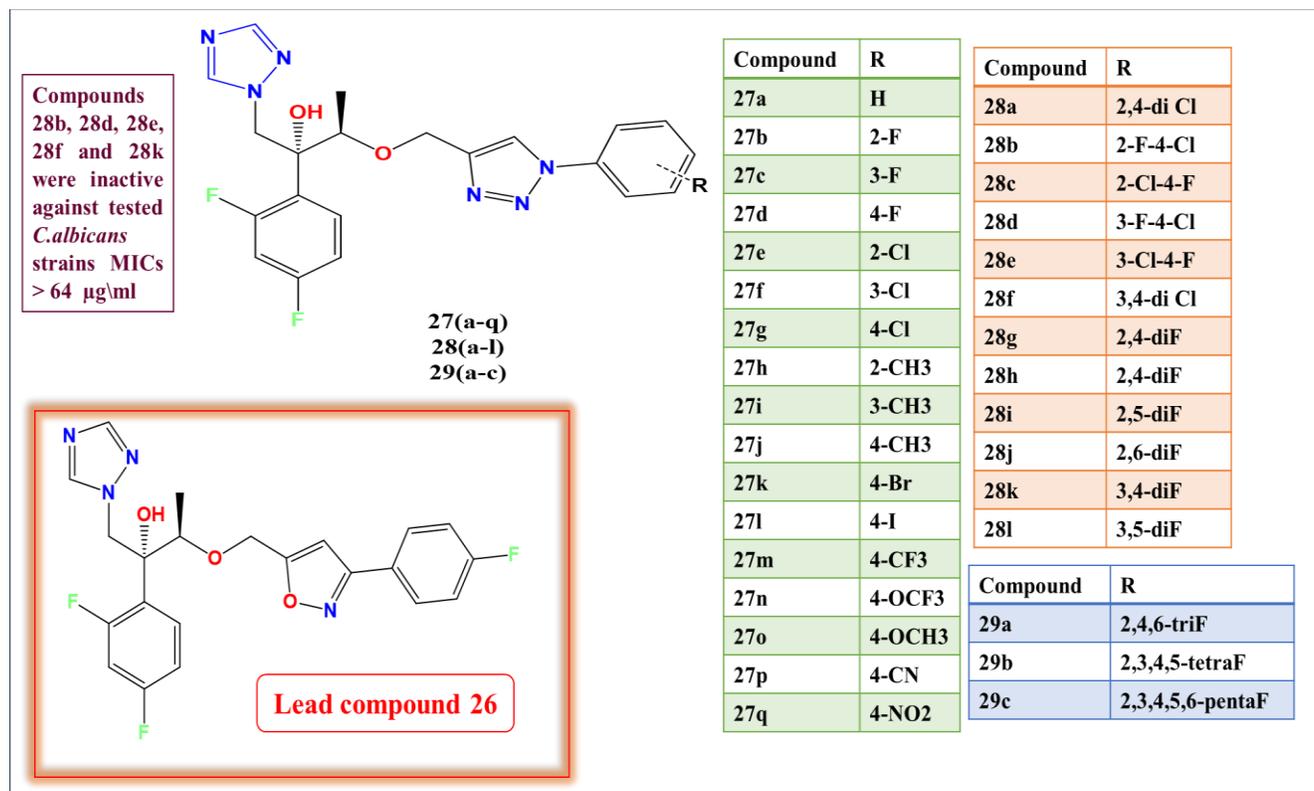


Figure 23: The molecular structures of recently synthesized triazole molecules.

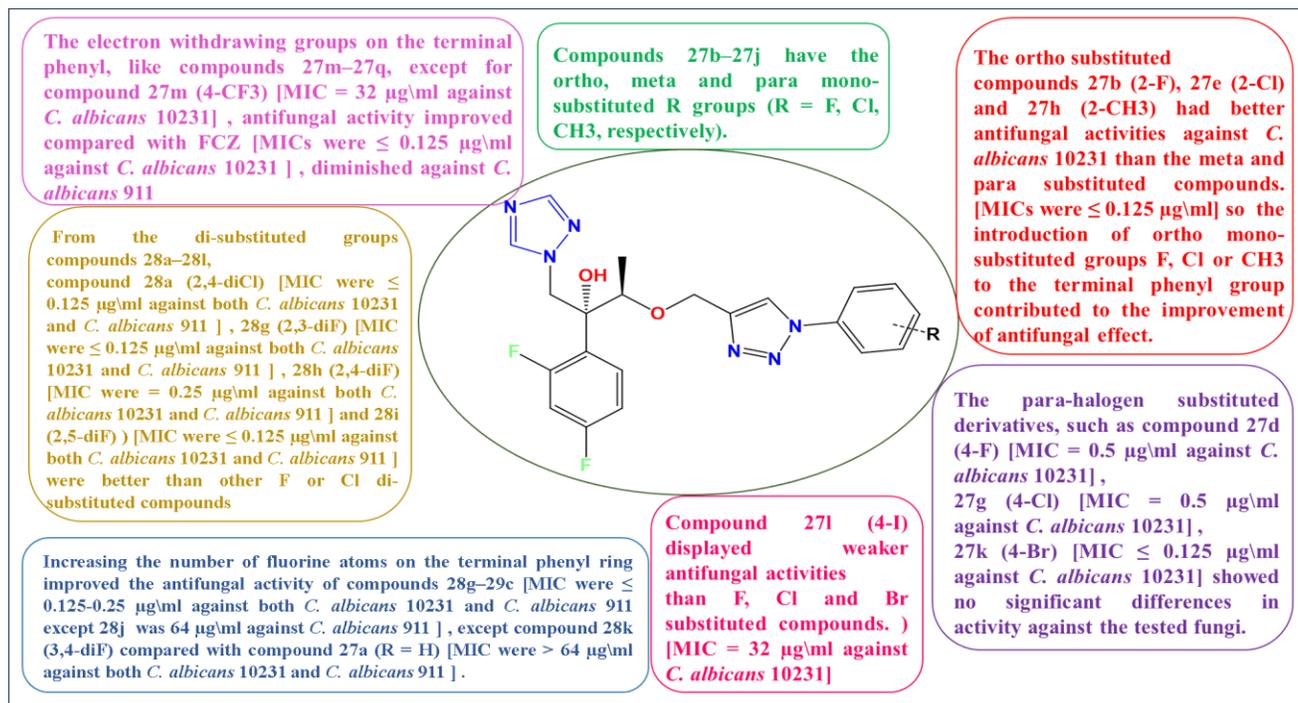


Figure 24: New triazole compounds: molecular structure and SAR

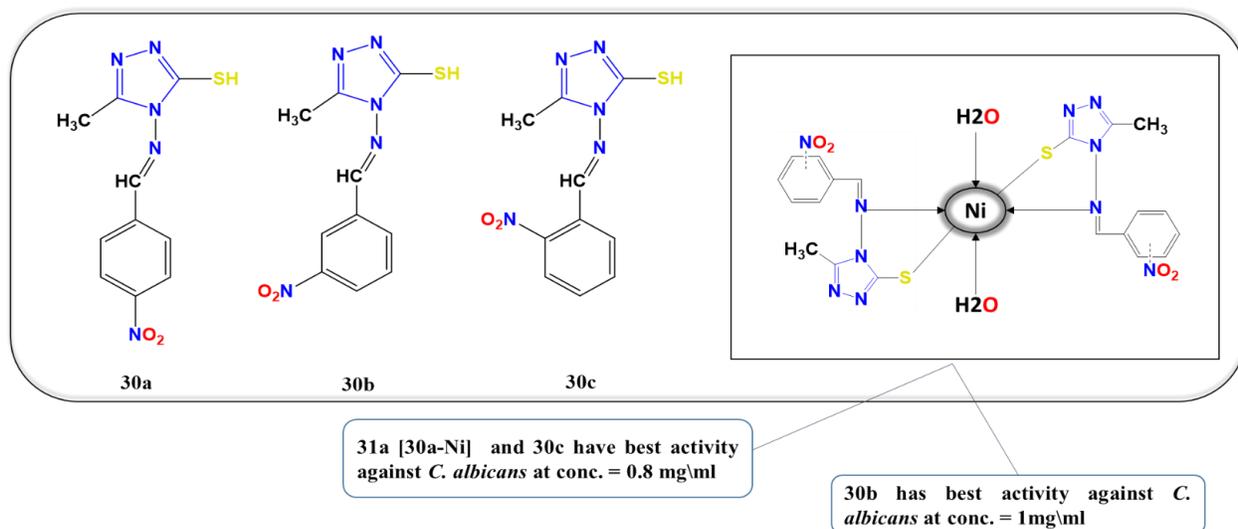


Figure 25: Triazole-derived Schiff base ligands and their structures (30a–c) and their respective metal complexes (31a–c).

1.18. Ethers substituted with 1,2,4-triazoles:

A number of benzyl and alkyl ethers, substituted with phenyl, furyl, and 1H-1,2,4-triazole groups, were developed [34]. These compounds had been subsequently assessed for their antifungal properties against *Candida albicans*. Compound 34f exhibits superior effectiveness with (MIC) value of 12.5 µg/ml. However, it is important to note that despite its efficacy, compound 34f remains

less potent than fluconazole, which possesses a MIC of 0.78 µg/ml. Several compounds (34c, 34d, 32b, 33b, 36a, 35c, 35e, 35h, and 35i) derived from the series of benzyl and alkyl ethers substituted with furyl groups exhibited considerable antifungal activity against *C. albicans*, as evidenced by their (MIC) values of 25 and 50 µg/mL. [Figures 26, 27, 28, 29]

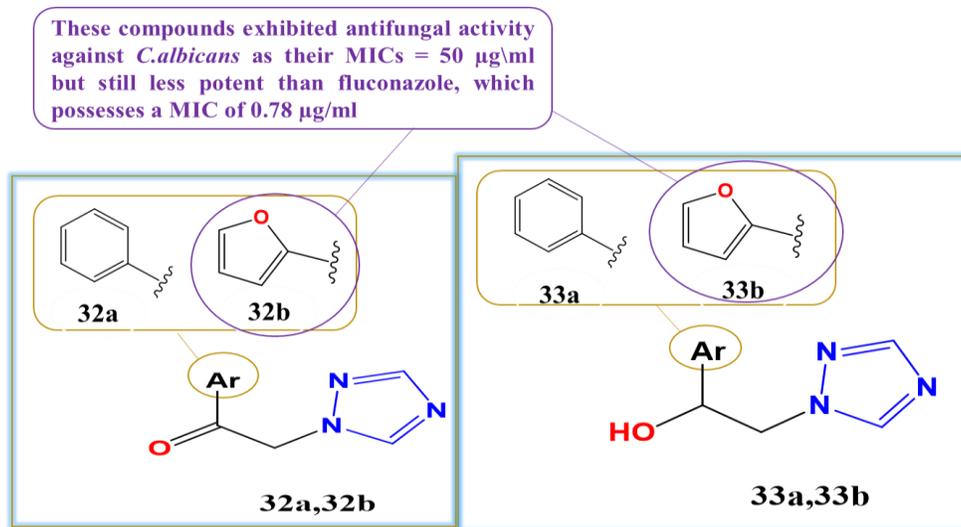


Figure 26: Activity against *C. albicans* and molecular structure of 1H-1,2,4-triazole derivatives

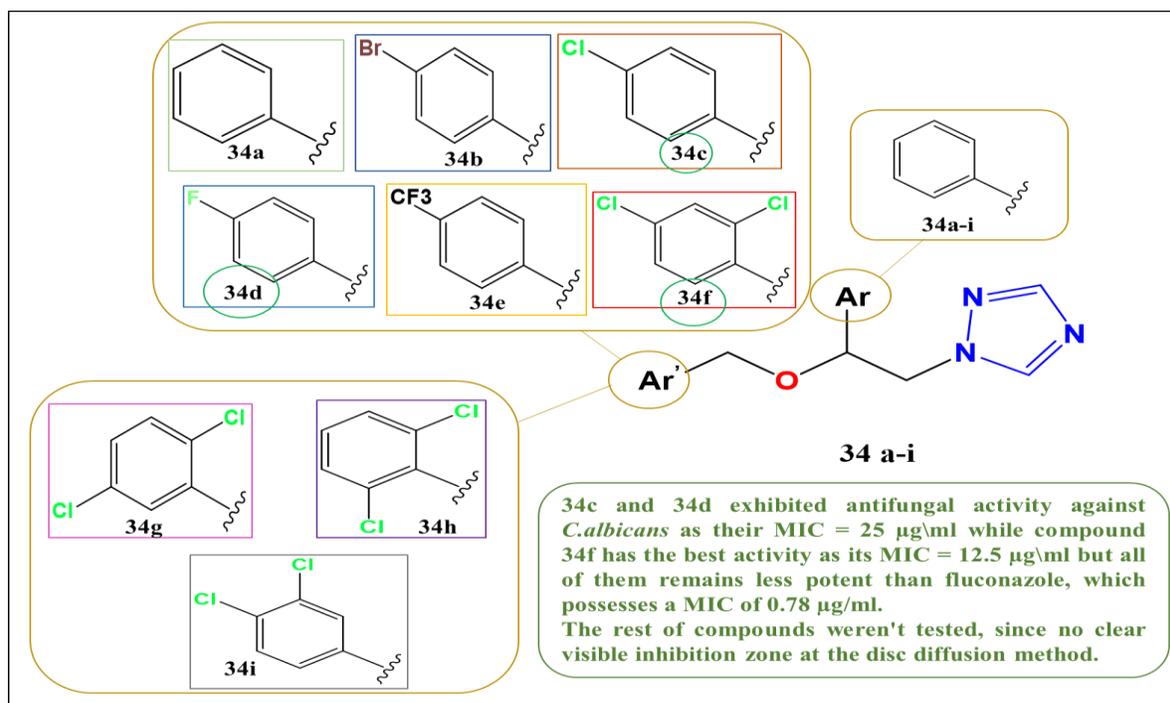


Figure 27: The molecular structure and activity of derivatives of 1,2,4-triazoles against *Candida albicans*

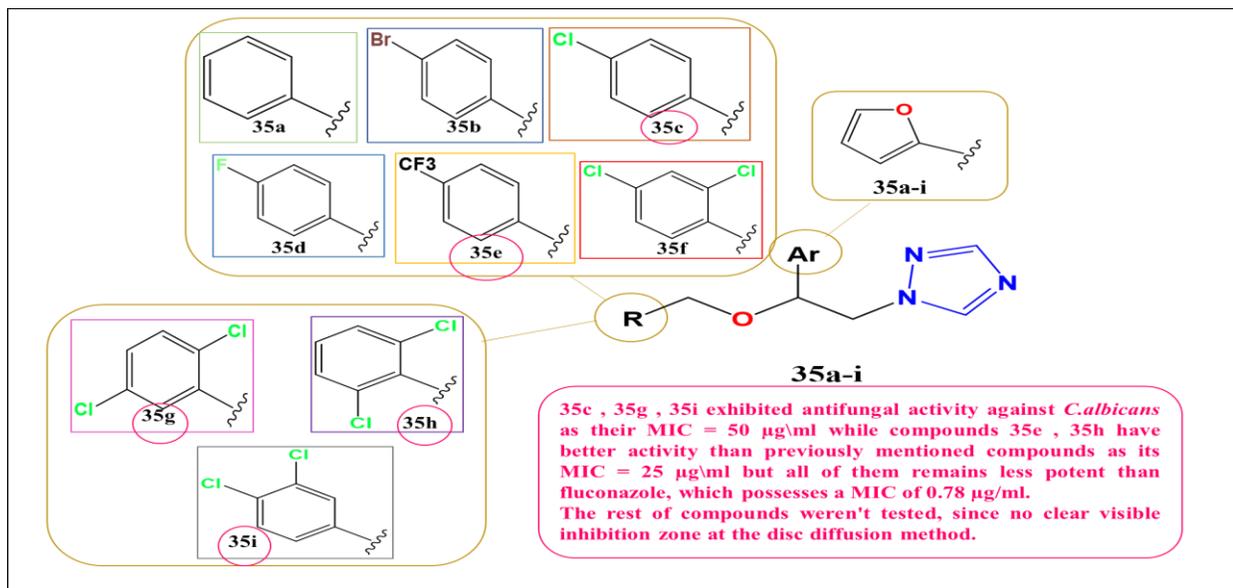


Figure 28: Structure and activity against *C. albicans* of 1H-1,2,4-triazole derivatives

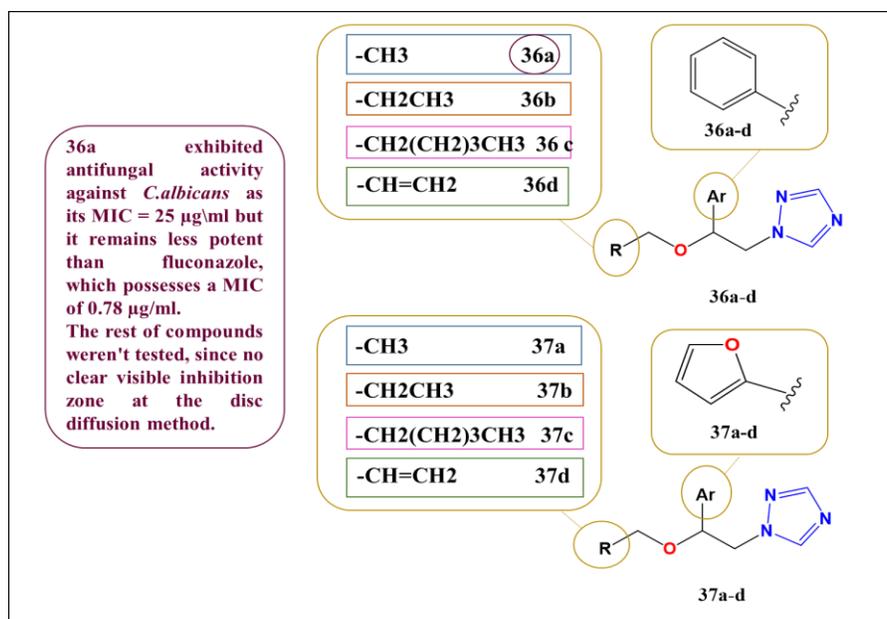


Figure 29: Activity against *C. albicans* and molecular structures of 1H-1,2,4-triazole derivatives

1.19. 1,2,4 triazole linked to benzimidazole:

A group of benzimidazole-1,2,4-triazole analogues (38a–l) has been developed by Güzel et al. The present study involved the evaluation of the in vitro antifungal properties of new compounds against *Candida albicans* and other species of *Candida*. The antifungal activity of all produced compounds (38a–38l) was found to be equivalent to that of reference medicines, as evidenced by their MIC₅₀ values ranging from 0.97–1.95 µg/mL.

Particularly, compounds 38b, 38i, and 38j exhibited the highest efficacy within the series, as indicated by their (MIC) value of 0.97 µg/mL. The efficacy of these compounds was seen to be twice that of the reference medicine voriconazole and fourfold that of fluconazole. Within this group, compounds 38a, 38c, 38d, 38e, 38f, 38g, 38h, 38k, and 38l exhibited comparable activity to voriconazole, with a twofold increase in effectiveness compared to fluconazole. The utilization of molecular

docking techniques has yielded a potential binding configuration for compounds 38b, 38i, and 38j within the

active site of the 14-demethylase enzyme[35]. [Figures 30, 31]

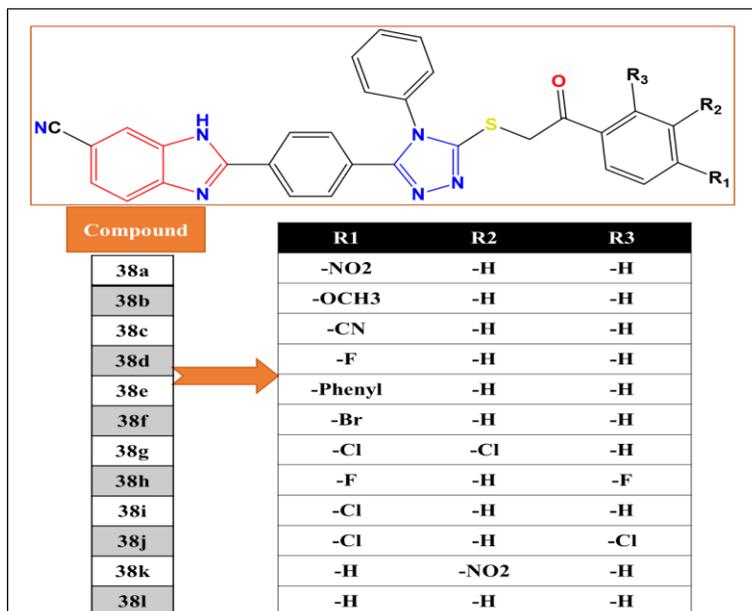


Figure 30: Molecular structures of new triazole antifungal agents.

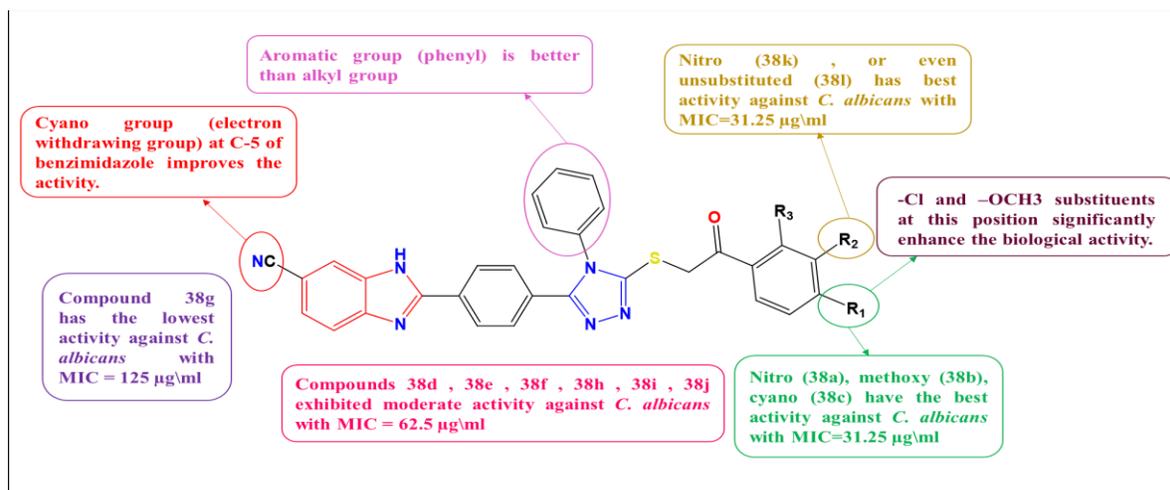


Figure 31: SAR of new 1,2,4 triazole linked to benzimidazole.

1.20. 1,2,4 triazole derivatives from Deferasirox:

Yiping Hu and colleagues have successfully developed and synthesized 1,2,4-triazole Deferasirox analogues [14]. These derivatives, denoted as 39a-i and 40a-g, were obtained using a method of ring opening using phenyl hydrazine or its substitutes in combination with imines. However, compounds 40c and 40e exhibited notable antifungal efficacy against *Candida*

albicans, with a (MIC) value ranging from 0.5 to 2.0 µg/mL. [Figures 32, 33]

1.21. Miconazole based 1,2,4 triazoles:

The synthesis of novel 1,2,4-triazoles was achieved through the utilization of eugenol and dihydroeugenol as starting materials then developed and afterwards evaluated for their antifungal properties [36]. It was hypothesized that the antifungal activity may be

improved by replacing the alcohol's hydroxyl group for a *p*-chlorobenzyl or *p*-chlorobenzoyl group. This hypothesis assumed that a ring containing a halogen might occupy the entrance cavity of the CYP51 enzyme and thereby contribute to its activity. However, contrary to expectations, these compounds were found to be inactive against *Candida* species even at the highest concentrations tested. [Figure 34]

Conclusion: The above study has demonstrated that the 1,2,4-triazole core is widely acknowledged as a favored nucleus and holds great importance as a scaffold within the field of medical research. It has been found to possess notable biological activities, particularly in terms of its anti-fungal properties. The

present study has highlighted compounds containing 1,2,4-triazole derivatives targeting *Candida albicans*, along with an examination of their structure-activity relationship. This review aims to aid medicinal scientists in the process of designing, developing, and synthesizing medicinally significant drugs that utilize the 1,2,4 triazole nucleus to tackle fungal infections produced by *Candida albicans*.

Ethical consideration: All of the participants in this study gave their informed permission.

Conflicts of Interest: No conflicts of interest are disclosed by the authors.

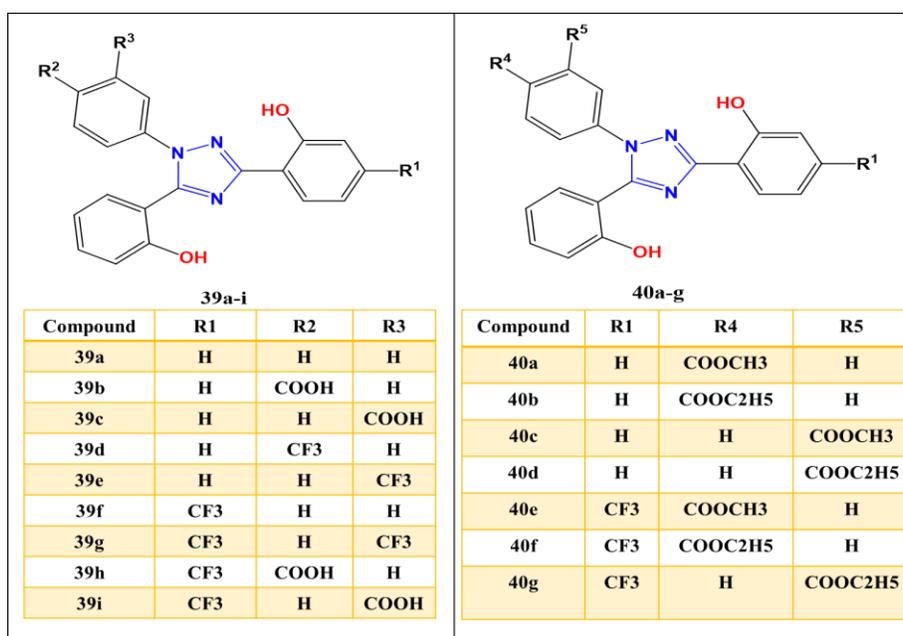


Figure 32: 1,2,4-Triazoles from Deferasirox with antifungal effects.

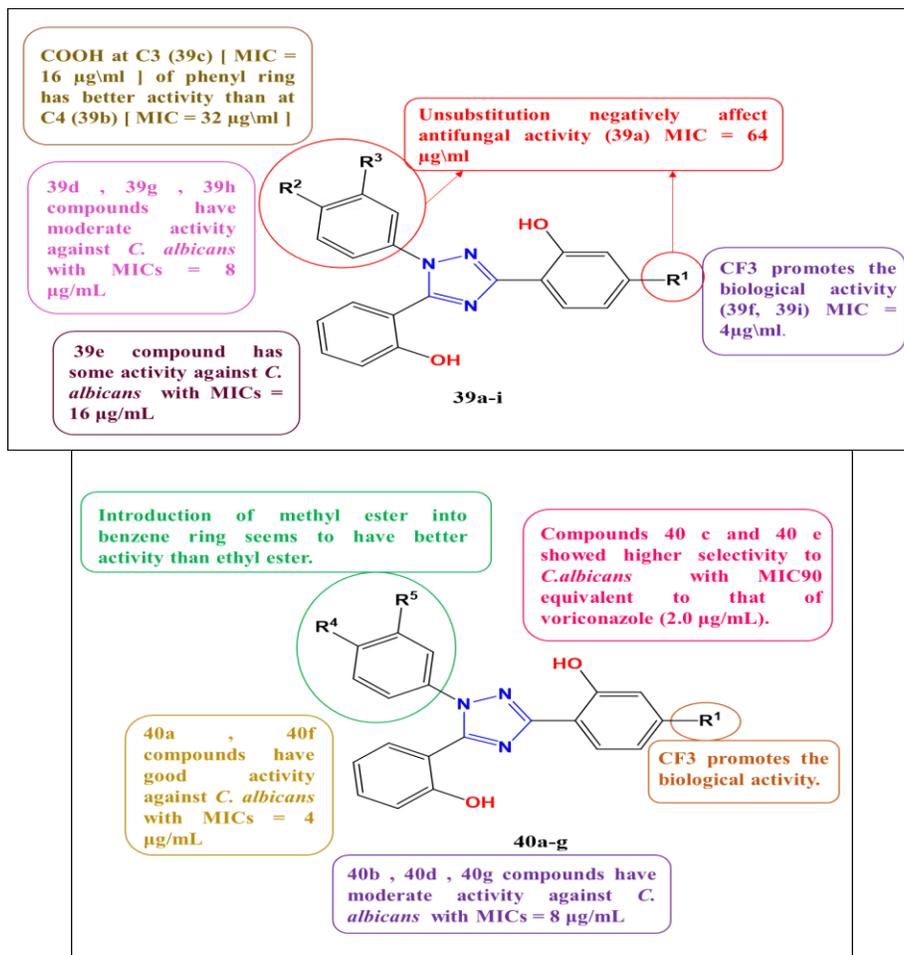


Figure 33: 1,2,4-Triazole derivatives from Deferasirox with antifungal action and their SAR.

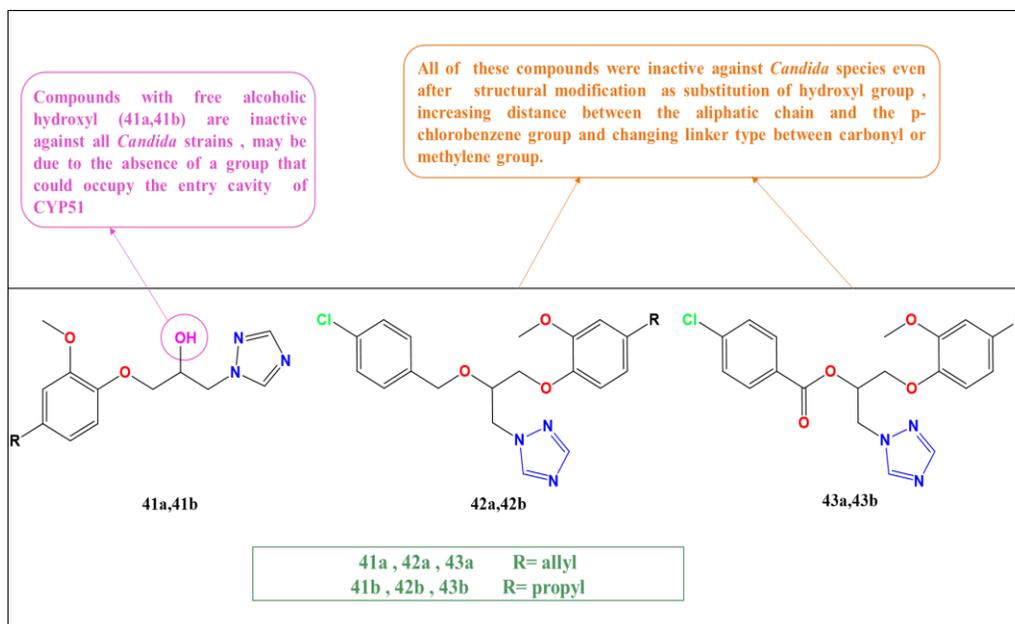


Figure 34: Chemical structure of Miconazole based 1,2,4 triazoles.

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