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Review Article

Review on substituted 1, 2, 4-triazoles as potent antifungal and antibacterial agents

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ABSTRACT

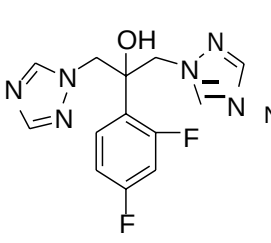
For the past two decades, modification of 1, 2, 4 triazole nucleus have made a tremendous significance in medicinal chemistry. 1, 2, 4 triazoles and their derivatives are found to have wide variety of pharmacological uses. From literature survey it is well known that triazole heterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Triazole is a synthetically versatile substrate used for the synthesis of a large variety of heterocyclic compounds, such as triazole fused with thiadiazole, oxadiazole and as a raw material for drug synthesis. Much work has been carried out on triazoles as potent anti fungal agents and many drugs with triazole nucleus having antifungal properties have come into the market (e.g. Fluconazole, Voriconazole, Itraconzole). This review represents the synthesized 1,2,4 triazole derivatives and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

Keywords: antibacterial; antifungal; Triazole; 1, 2, 4-triazole

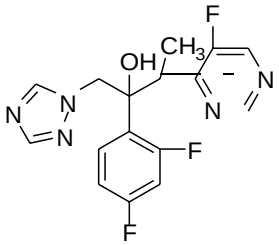
INTRODUCTION

Triazole- Biological Activity

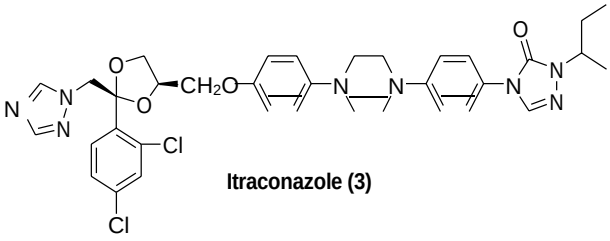
Systemic Bacterial and fungal infections are life-threatening and have become increasingly common in the immunocompromised hosts (Fridkin S. K & Jarvis W. R., et al. 1996) Triazoles are an important class of heterocyclic compounds which show various biological activities including antifungal (S.Eswaran et al., 2009), antimicrobial (T. Plech et al., 2011) anti-inflammatory (R. H. Udupi et al., 2007), antituberculosis (M. R. Shiradkar et al., 2007) antitumoral (H.K. NAIR *et al.*, 1997), anticancer (K. Sztanke et al., 2008), antibacterial (R.Ei-Sayed *et al.*, 2006), and antioxidant (I Khan *et al.*, 2010) activities. Triazole derivatives are increasingly explored for their InhA inhibitory activity (Christophe M. *et al.*, 2011) InhA is an essential enzyme in the FASH system involved in the synthesis of mycobacterial mycolic acids, usually inhibited by isoniazid. 1,2,4-triazole in general are being explored for their potential antiviral and antitumoral activity. 3-thiobenzyl-5-substituted-1,2,4-triazole derivatives were found to have a biphasic behavior, stimulating cell proliferation at low concentration and inhibiting it at higher ones (Romina *et al.*, 2011).



Fluconazole(1)



Voriconazole (2)



Itraconazole (3)

Antifungal activity

Currently, triazole drugs (fluconazole, itraconazole, voriconazole, and posaconazole) are the most frequently used antifungals in clinic.The triazoles function by action on fungal membrane by inhibiting the action of lanosterol 14α-demethylase, a cytochrome P-450 enzyme. However, resistance to azoles is emerging and may pose a serious health problem in the future. In addition, triazole drugs are often associated with hepatotoxicity and limited antifungal spectrum. Although amphotericin B, a polyene macrolide, remains the most

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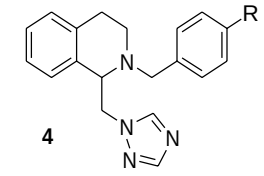
useful of the systemic antifungal drugs despite its toxicity. There is an evident need for accelerated development of new and more effective as well as less toxic antifungal agents, especially for treating systemic infections.

After the advent of triazole as medicinal agents much work has been reported about triazole derivatives with wide range of biological activity. (L.T. LIU *et al.*, 1996) has reported a series of novel 1,2,3,4-tetra hydroisoquinoline derived azoles as antifungal agents which might function as inhibitors of cytochrome P-450 dependent lanosterol 14α-demethylase. *In vitro* tests showed that some of these compounds (4) effectively inhibit the growth of several strains of yeasts as well as molds. Several sulfur-containing triazoles were synthesized and studies (Miyauchi *et al., 1995)* were carried out for their structure-activity relationships as potential antifungal agents. The SAR gave some important points like the pentylthio, heptylthio or nonylthio substituted triazole and the introduction of hydroxyl group (5) at the end of their alkyl chain increased the activity against both candidiasis and aspergillosis.



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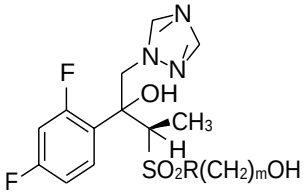
R= H,4-Cl, 4-F, 2,4 Cl_2 ,2,4-F_2



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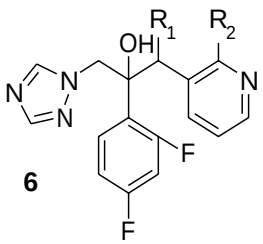
Similar fluorine containing triazole derivatives were reported by (R.P. Dickinson *et al.*, 1996). The replacement of a triazole ring of fluconazole with 4-pyridinyl moiety and pyrimidinyl moiety and α-methyl group resulted in an increase in activity against Aspergillus fumigates. The pyridinyl(6) and pyrimidinyl (7) analogues of triazole were thus found to have a broad range of activity against fungal pathogens including A. fumigatus and Candida krusei. Both sulphur and fluorine containing triazole derivatives as 5-hydroxypentylthio (8) and 7-hydroxyheptylthio (9) (Hiroshi et. al., 1985) were found to be the better active antifungal molecules, with the introduction of hydrophilic group in alkyl chains increasing their antifungal activity. An attempt to make carboxylic acid derivatives from (9) resulted in complete loss of activity. However a different strategy to incorporate amide derivative of triazoles (T. Uchida *et al.*, 2009) resulted in excellent in vitro activity against Candida, Cryptococcus and Aspergillus species.



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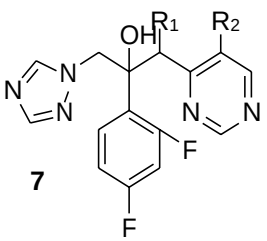

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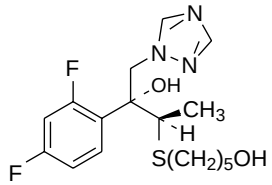

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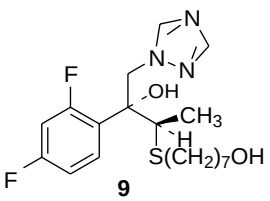

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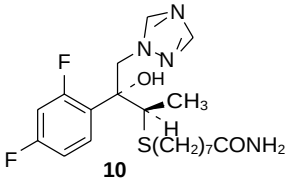

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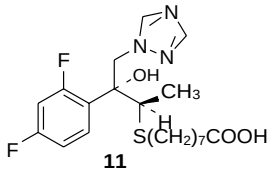

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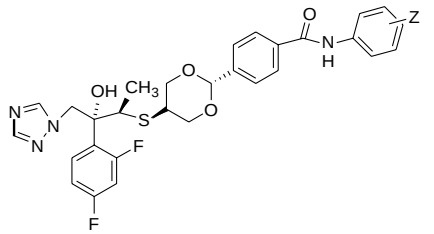
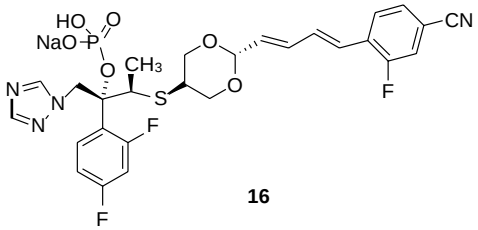
Compounds with a halogen atom at the C4 position on the benzene ring (12, 13, and 14) showed good MICs. Compound 15, in which a cyano group was introduced to the C4 position on the benzene ring, showed the best MICs of all the compounds, particularly against C. albicans. Triazole phosphoryl ester (16) derivatives similar to the above series containing sulphur linkage were synthesized by (Yoshiko Kagoshima *et al.*, 2009) as potential antifungal agents and as injectable prodrugs. The compound showed very good water solubility solubility (> 30 mg.ml) and was converted to 17 as the active drug. 16 is reported as a broad spectrum antifungal spectrum agent covering Aspergillus spp, fluconazole-resistant candida species and has a good safety profile including low drug-drug interaction. The water solubility of 17 was low for parentral formulation and hence the prodrug 16 resolves this issue. Similar to this series the Triazole derivatives having sulphur linkage when replaced by ether linkage as reported by (P. Liu *et al.*, 2008) retained their antifungal activities with some compounds showing antifungal activity higher than voriconazole against Candida albicans.



Z= 4-F = **12,**Z= 4-Cl= **13,** Z= 4-Br= **14,** Z= 4-CN= **15**



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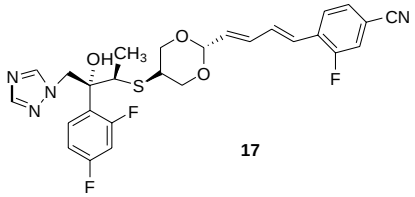

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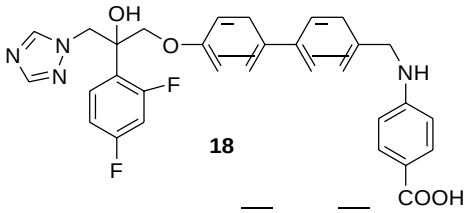
These analogs showed improvement in vitro antifungal activities especially against Candida species. This research has led to the discovery of compounds (18, 19, and 20) for further optimizations.



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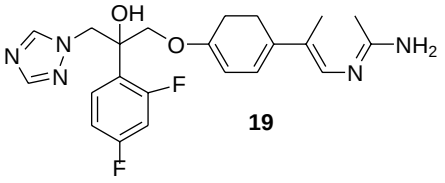

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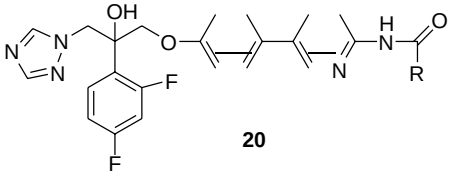
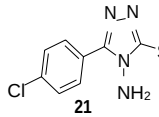


20

R= 4-($ClCH_2$)C_6H_4

Further work on sulphur containing triazole derivatives as antifungal agents were reported by (X. Collin *et al.*, 2003) as 3-mercapto-1, 2, 4- mono/ di-substituted triazoles. Many of these derivatives exhibit high activity against Candida albicans and Candida tropicalis. It showed that introduction of a chlorine atom in the para position (21) and incorporation of a methylene chain between the phenyl and the 1,2,4-triazole cycle (22) increased the antifungal activity from 30 to 50% on the yeasts species, affording the most efficient compounds of the series. On the other side keeping the aromatic group constant on the tetrazolyl carbon 5 (phenyl group) and alkylation of the thiol function by a methyl cyano group (23) led to an increase (1 mm) of the diameter of inhibition on each yeast compared to that of 1. Enhancement of the alkyl chain (24) and introduction of a phenyl group (25) between cyano group and sulfur atom did not increase the antifungal activity.



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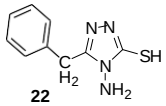

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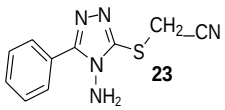

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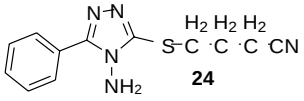

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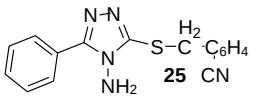
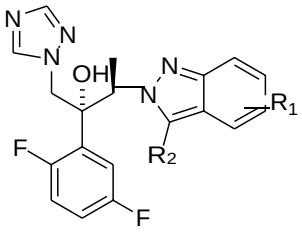


25

A novel water soluble prodrug of triazole derivative (RO0098557) was synthesized (J. Ohwada *et al.*, 2003), which is converted to the active molecule RO0094815 (26). The prodrug showed good activity against both systemic candidiasis and pulmonary aspergillosis in rat by both intravenous administration and oral administration. The prodrug is therefore a promising drug for treatment of systemic fungal infections through parenteral and oral administration. Indazole triazole derivatives like (2R, 3R)-2-(2, 4-difluorophenyl)-3-(substituted indazol-1-yl)-1-(1H-1, 2, 4- triazol-1-yl) butan-2-ol were found to have good antifungal activity as reported by (Joon Seok Park et al., 2007).



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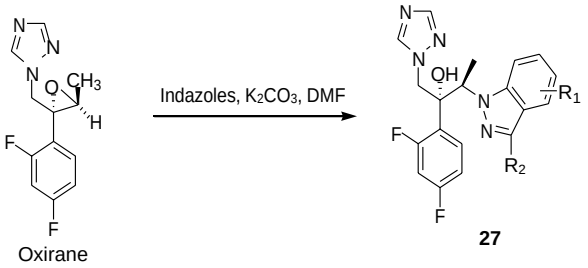
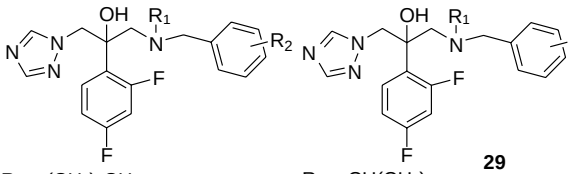


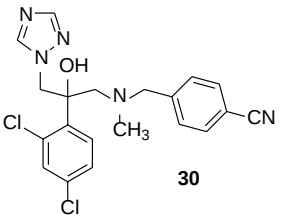
Oxirane

27

Among them the halogen substituents were found to have better activity against Candida and Aspergillus species. The compounds were also potent on oral administration against Candida Albicans in infected mice. Also the compounds contain phenyl groups like 27 were devoid of antifungal activity. The target compounds were synthesized by reaction of oxirane with various indazoles in the presence of K_2CO_3 and DMF. (Xiaoyun Chai *et al., 2009*) synthesized some antifungal triazole derivatives based on the results of computational docking on the active site of CYP51, by altering the structure of fluconazole. The synthesis of potential molecules involved the conversion of triazolo oxirane derivatives to 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-di fluorophenyl)-3-substituted benzylamino-2-propanols. Micro-broth dilution method was used for determine the minimum inhibitory concentrations of the compounds against Candida Albicans and Cryptococcus neoformans with fluconazole, itraconazole, ketoconazole, voriconazole, amphotericin B and terbinafine were chosen as the positive control. The compounds 28 and 29 showed excellent antifungal activities against the fungi except against Aspergillus fumigatus. The study also indicates that substituted benzyl side chain linked to the triazole pharmacophore increases the antifungal activity. Several triazole derivatives were reported by (F. Giraud *et al.*, 2009) by replacement of fluorine with chlorine atom resulting in the synthesis of 1-(N-benzylamino)-2-phenyl-3-(1H-1,2,4-triazol-1-yl)propan-2-ols retaining the antifungal activity. The most active compound (30) was docked into a home-made 3D model of the targeted enzyme confirming the importance of Tyr118, His377, and Ser378 residues in its binding mode.

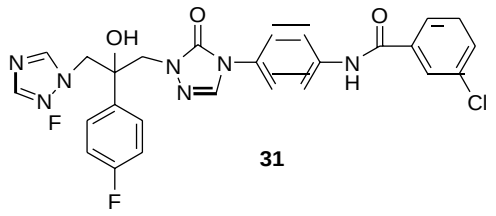


R_1= -$(CH_2)_2CH_3$ **28** R_1= -$CH(CH_3)_2$ **29**
R_2= H, R_2= H,



30

Y. Jiang *et al.,* 2011 has reported the synthesis of several other fluconazole analogs that were screened for eight human pathogenic fungi. In vitro antifungal activity assay indicated that most of these compounds showed higher antifungal activities against C. albicans than the reference drug fluconazole and amphotericin B. Compounds 31 and 32 possessed excellent activities against C. albicans, C. tropicalis and C. parasilosis, Flexible molecular docking was also used to analyze the structure–activity relationships (SARs) of the target compounds. The designed compounds interact with CACYP51 through hydrophobic, van der Waals and hydrogen-bonding interactions. The replacement of triazole moieties in fluconazole by 2H-1,4-benzothiazin-3(4H)-one or 2H-1,4-benzoxazin-3(4H)-one moiety (H. B. Borate *et al.,* 2010) resulted in few new chemical entities that were screened against various fungi and it was observed that the compounds 33 and 34 are potent inhibitors of Candida strains. The structure activity studies revealed that the compounds containing benzothiazinone moiety are more active than those containing benzoxazinone.



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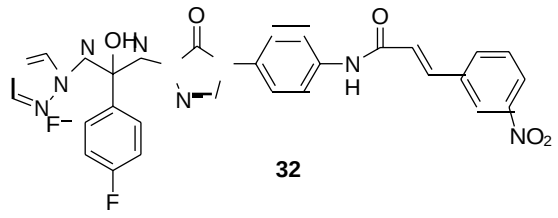
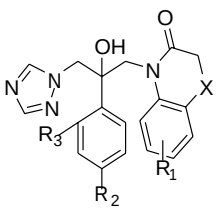


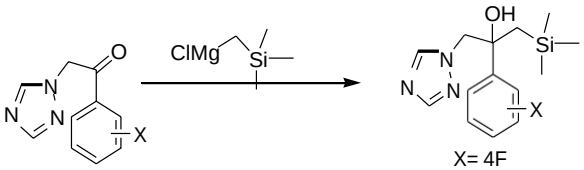
32

In the benzothiazinone series, replacement of fluorine by hydrogen reduces the activity (compound nos 34 v/s 38 and 36 v/s 39). The same is true for benzoxazinone series (compound no 41 v/s 45). In the benzothiazinone series, halogen substituent at C7 position is tolerated with slight decrease in activity (compound no 33 v/s 34 or 35) while substituents like methoxy or methyl decrease the activity considerably (compound no 33 v/s 36 or 37). In case of benzoxazinone series, no substituent at C6 is tolerated and all compounds having substituents like Cl, Br, NO2 or Ac lost the activity (compound no 40 v/s 41, 42, 43 or 44).



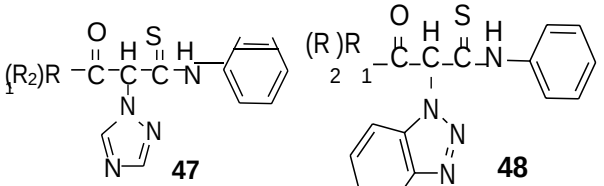
COMPOUND	STRUCTURE
33	X=S, R_1= H, R_2=R_3= F
34	X=S, R_1= 7-Cl, R_2=R_3= F
35	X=S, R_1= 7-Br, R_2=R_3= F
35	X=S, R_1= 7-OMe, R_2=R_3= F
36	X=S, R_1= 7-Me, R_2=R_3= F
37	X=S, R_1= 7-Cl, R_2=F, R_3= H
38	X=S, R_1= 7-OMe, R_2=F, R_3= H
39	X=O, R_1= H, R_2=R_3= F
40	X=O, R_1= 6-Cl, R_2=R_3= F
41	X=O, R_1= 6-Br, R_2=R_3= F
42	X=O, R_1= 6-NO_2, R_2=R_3= F
43	X=O, R_1= 6-Ac, R_2=R_3= F
44	X=O, R_1= 6-Cl, R_2= Br ,R_3= H

Silicon containing triazoles derivatives also has good fungicidal effect (Flusilazole). (H. Itoh *et al.,* 2002) has reported a novel and efficient method to synthesize silicon-containing triazolyl derivatives from (1,2,4-triazol-1-yl) acetophenones (45) with Grignard reagents in the presence of magnesium bromide diethyl etherate. The obtained silicon-containing azole derivatives (45) were proved to show maximum activity against rice sheath blight by submerged application. QSAR studies of eighteen triazoles derivatives were reported by (Qing- Li Wei *et al.,* 2006) for their potential antifungal activity. It was found that the carbonyl group and changes in the functional groups, attached to the carbonyl group had a major impact on the antifungal activity.

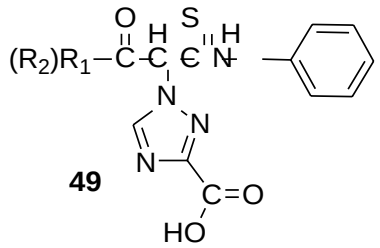


X= 4F **45** **46** X= 4F

Hence the carbonyl group may be considered important for retaining the activity as revealed from the higher electrostatic charges around the carbonyl carbon. (47, 48, 49).

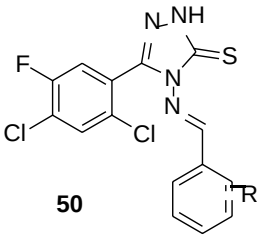


47 **48**



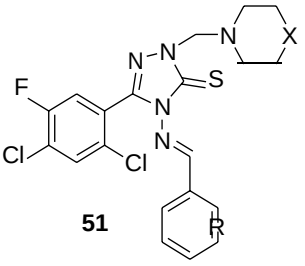
49

Dichlorofluorophenyl triazoles bearing Schiff bases with p-methoxyphenyl substituents (50) (M. S. Karthikeyan *et al*., 2006) showed good antibacterial and antifungal activity. Similarly dichlorofluorophenyl triazoles bearing Mannich bases compounds containing N-methyl piperazinyl(51) moiety showed good antibacterial activity against all strains comparable with that of flucanozole as standard drug.



50

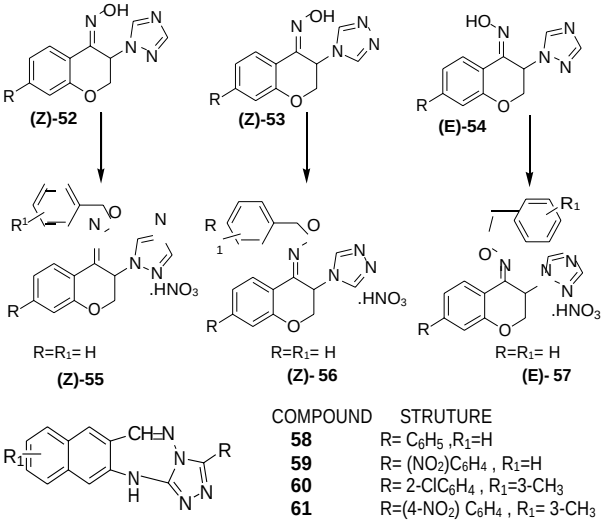
R=4-N(CH₃)₂,4-Cl



51

R=4-N(CH₃)₂,4-Cl
X= O,N-CH₃,CH₂

Several triazole oxime derivatives(S Emami *et al.*, 2004) were also found to have good antifungal activity. The 1, 2, 4-triazolylchromanone oxime ethers tested for in vitro antifungal activity were found to have high activity against Candida albicans, Saccharomyces cerevisiae, Aspergillus niger and Microsporum gypseum. The 1,2,4-triazolylchromanone oxime ethers (55), (56) and (57) were prepared by reacting oximes (E)-52, (Z)-53 and (Z)-54 with substituted benzyl halides in DMF, in the presence of NaH at room temperature or K_2CO_3 at 50°C. Two stereo selective synthetic pathways were used to obtain the (E)- or (Z)-stereoisomer of oximes (E)-52, (Z)-53 and (Z)-54. Comparison between MICS of the synthesized (E)- and (Z)-isomers against M. gypseum revealed equal activity except (Z)-55 and (E)-57. In the latter, (E)-57 (MIC¼2 lg/mL) was eight times more active than (Z)-55 (MIC¼16 lg/mL). In terms of structure–activity relationship, as expected the 1, 2, 4-triazol-1-yl derivatives (57) showed more potent antifungal activity than 1, 2, 4-triazol-4-yl derivatives 7(56). Triazole triazepines derivatives(Monika Gupta., 2011) also presented good antifungal activity especially against Aspergillus niger species. 9-substituted-3-aryl-5H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4] triazepines were synthesized from 5-aryl-3,4-diamino-1,2,4-triazoles and 2-chloro-3-formyl quinolines in ionic liquid as solvent, under microwave heating as well as using oil-bath heating at 80°C. The screening data indicate that the compounds 58, 59, 60 and 61 show excellent activity against Aspergillus niger 1000 µg concentration and Pencillium notatum species at 500 µg as well as 1000 µg concentrations whereas, these compounds show good to moderate activity against Aspergillus flavus and Rhizopus species at both the concentrations. Moreover, ionic liquid is found to be recyclable for at least three consecutive runs that makes the process cost-effective and economic and leads to the area of Green chemistry as recyclability is one of the most important features of Green Chemistry.



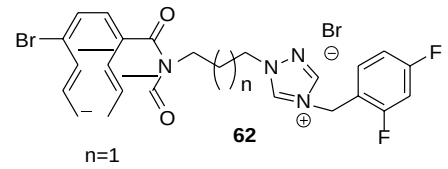
(Z)-52 **(Z)-53** **(E)-54**

R=R₁= H **(Z)-55** R=R₁= H **(Z)- 56** R=R₁= H **(E)- 57**

COMPOUND	STRUTURE
58	R= C_6H_5 ,R_1=H
59	R= $(NO_2)C_6H_4$, R_1=H
60	R= 2-ClC_6H_4 , R_1=3-CH_3
61	R=(4-NO_2) C_6H_4 , R_1= 3-CH_3

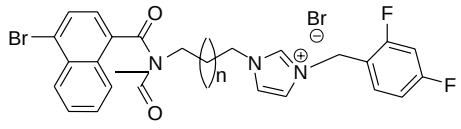
Triazole derivatives with both antibacterial and antifungal activity

Some novel naphthalimide-derived azoles (Y.-Y. Zhang & C.-H. Zhou., 2011) bridged by flexible alkyl chains were found to have good antibacterial activity when evaluated for their antibacterial and antifungal activity in vitro against eight bacteria and two fungi by two fold serial dilution technique. Most synthesized compounds exhibited good antimicrobial potency with low MIC values ranging from 1 to 16 µg/ mL. Noticeably, naphthalimide triazolium (62) and imidazoliums (63-64) displayed even better antibacterial and antifungal activities against some tested strains than the reference drugs Orbifloxacin, Chloromycin and Fluconazole, respectively.



62

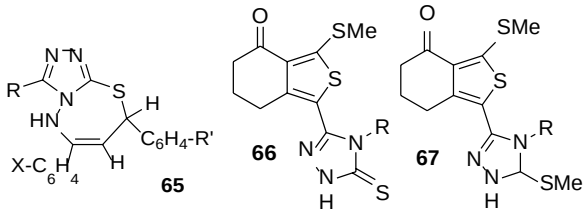
n=1



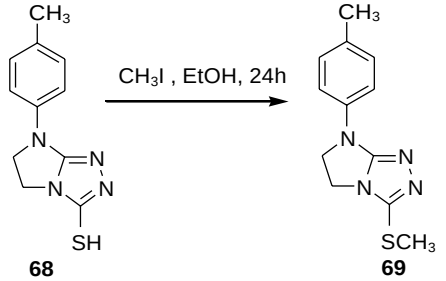
COMPOUND	STRUCTURE
63	**n=1**
64	**n=2**

(M.Kidwai *et al.*, 2001) synthesized some novel 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazepines as potent antimicrobial agents by microwave assisted solid support method. The reaction involved the treatment of substituted 2-mercapto-1-amino triazoles with substituted chalcones on basic alumina that are accelerated by exposure to microwaves. The reaction time has been brought down form hours to seconds with improved yield as compared to conventional heating method. The synthesized compounds screened for their in vitro antibacterial activity (Bacillus subtilis, Pseudomonas aerogenasa, Klebsilla aerogenes and Brodettla bronchiseptica) by cup-plate agar diffusion method. Various synthesized compounds were most potent and compa-

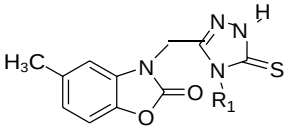
rable to activities of norfloxacin. And antifungal activity (*A.niger* and *A.flavis*) by the paper disc diffusion method. The compound (65) showed the best antifungal activity. Several thiophene linked triazole derivative (S. Tehranchian *et al.*, 2005) were also found to have moderate activity against Gram positive strains. The preliminary results of antimicrobial activities indicated that some of the compounds exhibited a moderate to good activity against, however none of the compounds exerted a significant effect against the Gram negative strains or fungi. Presence of bulky group of n-butyl or p-nitrophenyl at 4-position of 1, 2, 4-triazole in compounds (66) and (67) produced active compounds against Gram positive strains. Although, S-methylation of 1, 2, 4-triazole - 3- thiones 4c, e resulted in broader activity. Similarly imidazo-triazole derivatives reported by (K. Sztanke *et al.*, 2006) were found to good antimicrobial activity.



The 7-(4-methylphenyl) -3-methylthio-5H- 6,7-di hydroimidazo [2,1-c][1,2,4]triazole (70) was obtained in good yield (78%) from the respective 7-(4-methylphenyl)-2,5,6,7-tetrahydroimidazo-[2,1-c][1,2,4] triazol-3(H)-thione (68) by alkylation with methyl iodide. Eight compounds tested in the present study were found to have highly significant antibacterial activities against the microorganisms but no antifungal activities. All examined compounds were also inactive against moulds and yeast-like fungi. Screened 7-(4-methylphenyl)-3-methylthio-5H-6,7-di hydroimidazo [2,1-c] [1,2,4]triazole (69) was strongly active against S. aureus ATCC 25923, with MIC results at 31.7 µM. (U Salgin Goksen *et al.*, 2007) reported the synthesis of various substituted triazole and thiadiazole derivatives. Most compounds exhibited high analgesic-anti-inflammatory activity. The various triazole and thiadiazole derivatives were prepared from starting material 5-Methyl-2-benzoxazolinone.



The treatment of 5-Methyl-2-benzoxazolinone with ethyl chloroacetate in K_2CO_3/Acetone gave the N-alkylated product. The corresponding acid hydrazide and thiosemicarbazide derivatives has prepared by treatment with hydrazine hydrate and with various alkyl/ aryl isothiocyanate respectively. Finally thiosemicarbazides underwent smooth cyclization through dehydration to afford various triazole derivatives (70-73).



COMPOUND	STRUCTURE
70	R_1= CH_3
71	R_1= C_2H_5
72	R_1= C_3H_7
73	R_1= C_6H_5

CONCLUSION

The 1,2,4- triazole nucleus has recently been incorporated in to a wide variety of therapeutically interest drugs including H_1/H_2 histamine receptor blockers, cholinesterase active agents, CNS stimulants anti-anxiety agents and sedative, it is also observed that the presence of amide linkage (CONH), thiadiazole, oxadiazole plays an important role imparting antifungal and tubercular activity to the triazole molecules. Also dihalo-substituted benzene is an important and essential part along with triazole nucleus in imparting the antifungal activity. In certain cases the presence of the bulky side chain increases the antibactereial activity especially against gram positive bacteria. The survey of the literature reveals that triazole is a versatile lead molecule for designing antifungal agents. Further we can conclude that many other derivatives of triazole can be synthesized which will be expected to show potent pharmacological activities.

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