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TRIAZOLE DERIVATIVES AND THEIR BIOLOGICAL POTENTIAL: A REVIEW

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Abstract
Azoles are nitrogen containing cyclic compounds with great importance in the field of pharmacology. Almost all azoles and their compounds shows various vital biological properties like antimalarial, anti-tubercular, anti-inflammatory, antibacterial, antileishmanial, antifungal, etc. so synthesis of azoles is now adays interested area for the researchers. Triazole is five membered, nitrogen containing aromatic cyclic system. To synthesize azoles different methods are used and they possess different therapeutics properties. This review contains structural development in triazole with their various biological activities.

Introduction

In the recent era number of heteroaromatic compounds are known and are used to treat fungal infections, among them azole molecule shows better antifungal property. Albaconazole, Fluconazole, Voriconazole, etc are commonly used antifungal moieties.Fluconazole is first synthetic antifungal agent which contains triazole and it is used in the treatment of systemic candida infections, fungal infections as Cryptococcal meningitis, oropharyngeal and esophageal candidiasis. It is also acts as cytochrome P450 (CYPs) enzyme inhibitor[1] in human, Vitamin d3 25-hydroxylase activity with protein. Voriconazole is also good antifungal agent and used to cure fungal infections. It also shows invasive candidiasis caused by any kind of candida, Scedosporium, Penicilliosis and Fusarium. Due to its easy metabolism by hepatic cytochrome P450, it interacts with many kinds of drugs .

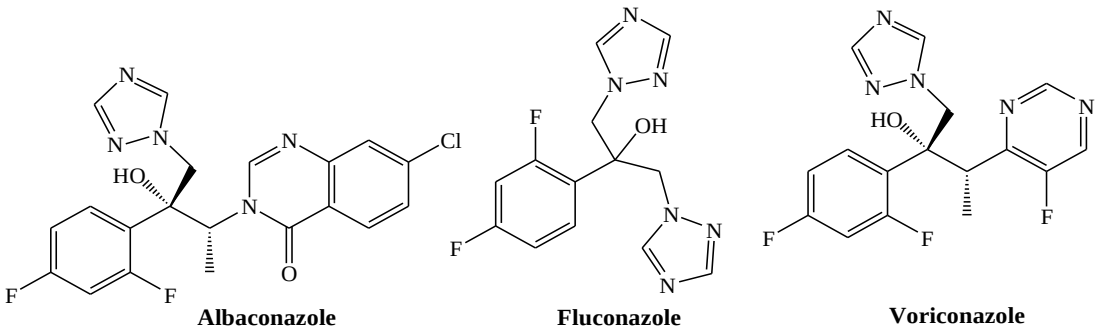
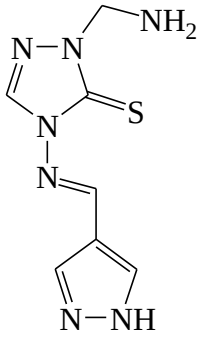


Figure 1: Common triazole containing antifungal agents

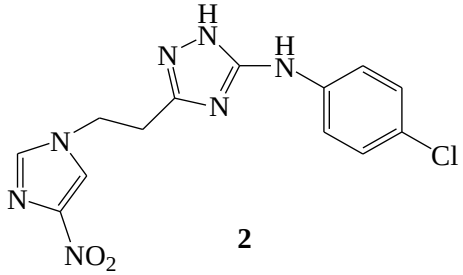
Along with antifungal activities triazole have broad spectrum of other biological activities like anti-tubercular[2], antitumor[3], anti-inflammatory[4], antimycobacterial[5], antiviral[6], antimalarial[7], antileishmanial[7], antioxidant[8], etc. Triazole motif attracts the most of the researchers due to their

importance in pharmacological field. Most of the chemist works on synthesis and biological evaluation of substituted heteroaromatic triazoles as antifungal agent. Isloor and co-workers[9] have synthesised new derivatives of triazole 4-[(3-substituted-1*H*-pyrazol-4-yl)methyleneamino]-5-substituted-2-[(4-methylpiperzine-1-yl)methyl]-2*H*-1,2,4-triazole-3(4*H*)-thiones (**1**) and evaluated for their antibacterial and antifungal activity. Some of the compounds from the series were found to show significant antifungal activity.



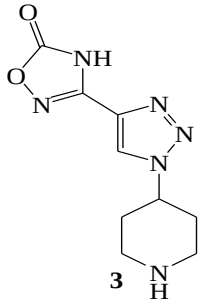
1

Demirayak and co-workers[10] reported the synthesis of 3-arylamino-5-[2-(substituted imidazole-1-yl or benzimidazol-1-yl) ethyl]-1,2,4-triazole compounds (**2**), furthermore they were screened for antifungal activity against the strains Candida glabrata and Candida albicans. Some of the compounds may consider as potential antifungal agents.



2

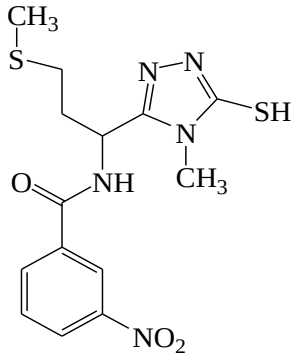
Sangshetti and co-workers[11] have synthesised 1,2,4 oxadiazole containing 1,2,3 triazole derivatives (**3**) and screened them for antifungal activities. One of the compound is excellent antifungal agent against *Aspergillus flavus* (MIC value 10 mg/ml), *Candida albicans* (MIC value 20 mg/ml) as well as against *Aspergillus niger* (MIC value 12.5 mg/ml) and *Fusarium oxysporum* (MIC value 25mg/ml). The other compound also shows good potency against *Aspergillus niger* (MIC value 10mg/ml) and *Candida albicans* (MIC value 20 mg/ml).



3

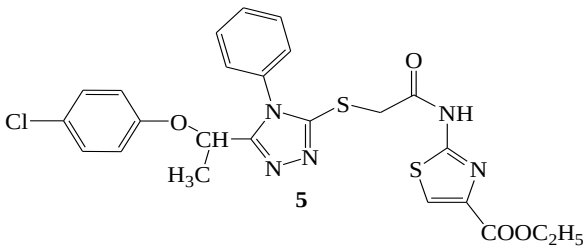
Pintilie and co-workers[12] synthesised 1,2,4-triazole compounds having a D,L-methionine moiety (**4**) and evaluated them for antimicrobial activity using the strains Staphylococcus aureus ATCC 25923, Bacillus cereus ATCC 10987,

Bacillus antracis ATCC 8705, Escherichia coli ATCC 25922 and Sarcina lutea ATCC 9341. Some of the synthesised compounds show excellent activities against Bacillus cereus and Bacillus antracis.



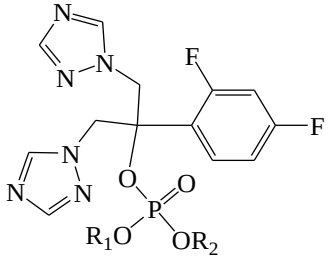
4

Zitouni and co-workers[13] have synthesised 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[*N*-(2-thiazolyl)acetamido]thio-4-*H*-1,2,4-triazole derivatives (**5)** and evaluated them for antimicrobial activities against *Candida glabrata*, *Candida albicans* (two strains), *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Among the synthesised compounds some of them showed excellent antifungal activities .



5

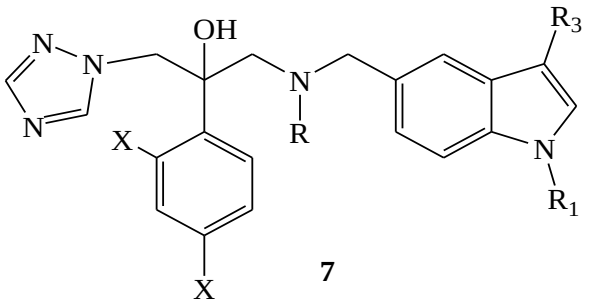
Nguyen and co-workers[14] have synthesised triazole having carbohydrate phosphate esters (**6**) and evaluated for in vitro antifungal activity against *A. niger*, *C. albicans* and *Cryptococcus neoformans*. All the synthesised triazole derivatives were less active while diester and triester derivatives were stronger against *A. niger* and *C. albicans*. The compound which having the substituent as R_1 = C_2H_4CN, R_2 = nCH_2 = $CH–C_9H_{18}$ which shows good activity as well as if R_1 =CH_3 it also shows better activity with MIC values 258-1628 mg/ml.



6

Remi and co-workers[15] have synthesised substituted derivatives of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols (**7**) and screened them for antifungal activity against *A. fumigatus* and *C. albicans*. Compound with R = H, R_1 =

Boc, X = F showed moderate antifungal activities against the used strains with MIC values 3.8 to 33.0 mg/ml.



7

Chandrika and co-workers[16] have reported the synthesis of alkylated piperazines (**8**) and studied their cytotoxicity against mammalian cells, hemolytic activity against murine erythrocytes. All the synthesised compounds were tested for antifungal activity and most of them showed better activity with MIC values against Aspergillus and non-albicans Candida strains

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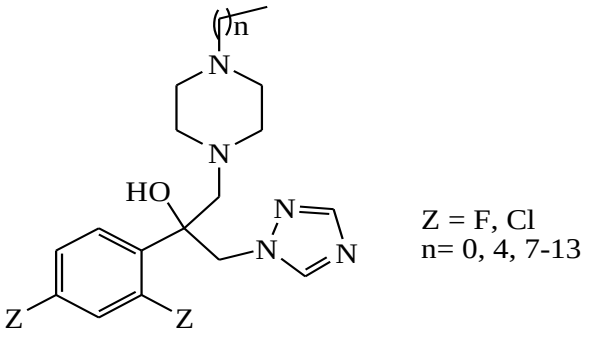

Z = F, Cl
n= 0, 4, 7-13

8

Jiang and co-workers[17] have synthesised the piperidine containing triazole (**9**) derivatives and tested them for antifungal activity. Many compounds showed excellent antifungal activity against a variety of clinically important fungal pathogens (*Trichophyton rubrum*, *Aspergillus fumigatus*, *Candida glabrata*, *Cryptococcus neoformans*, *Candida parapsilosis* and *Candida albicans*). Some of the synthesised compounds were highly active fungal inhibitors

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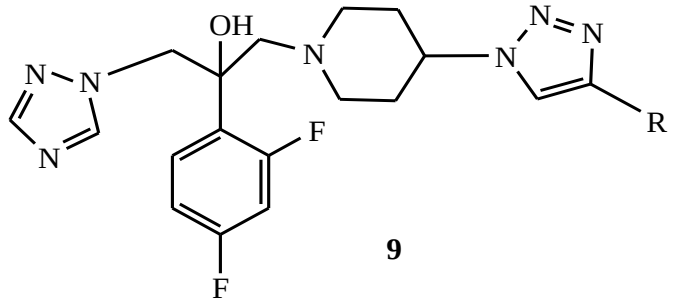
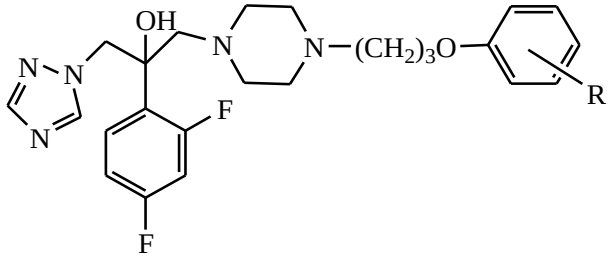


9

Che and co-workers[18] have reported the synthesis of a series of substituted phenoxypropyl piperazine (**10**) and evaluated for antifungal activity. In vitro evaluation of newly synthesised molecules showed moderate to good activity. Most of the compounds showed highest activity against *Candida parapsilosis* and *Candida albicans*. Some of the compounds show more potency than standard itraconazole and fluconazole with the MIC values 0.06–

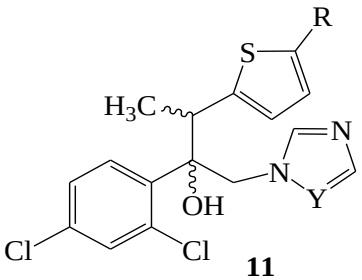
0.016 mg/ml, against *C. neoformans* is 0.06 mg/ml and against *A. fumigatus* in the range of 1–2 mg /ml. Compounds also show good activity against *dermatophytes*. Among all the synthesised compounds 12i show excellent activity against *C. neoformans* is 0.06 mg/ml, and is comparable with voriconazole.



12a: R = 4-CH_3
12b: R = 3-CH_3
12c: R = 2-CH_3
12d: R = 3-Br
12e: R = 4-F
12f: R = 2-Cl
12g: R = 4-Br
12h: R = 4-NO_2
12i: R = 4-$C(CH_3)_3$
12j: R = 4-Cl
12k: R = 2-Br
12l: R = 2-NO_2
12n: R = 3-NO_2

10

Chevreuil and his co-workers[19] have synthesised a series of 2-aryl-1-azolyl-3-thienylbutan-2-ols (**11**) then screened for their antifungal activity against both strains of *C. glabrata* and two other major human pathogenic fungi, *C. albicans* and *Aspergillus fumigatus*. The synthesised compounds showed better activity, as well as good potency against the petite mutant, from that it is observed that they may overcome the increased expression of the efflux pumps basically observed in clinical yeast isolates resistant to current azoles.

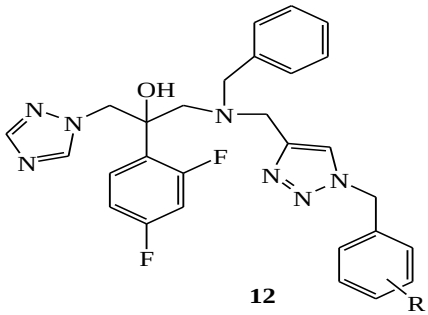


R= H/Cl

Y= N/CH

11

Xu and co-workers[20] was synthesised a series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols (**12**) and tested for in vitro antifungal activity against eight fungi strain (*C. albicans* 14053, *C. albicans* 20352, *Candida glabrata*, *Candida parapsilosis*, *Cryptococcus neoformans*, *Trichophyton rubrum*, *Aspergillus fumigatus* and *Microsporum gypseum*). Most of the compounds were active towards all fungi to some extent, except C. glabrata and A. fumigatus. Halo-substituted compounds showed promising activities than remaining compounds

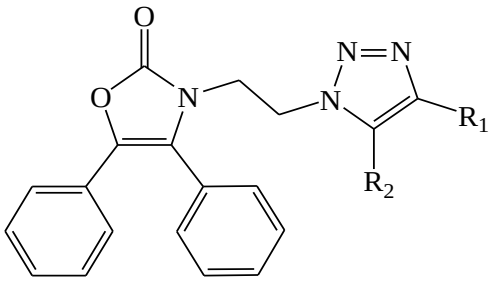


1a: R= 2-F
1b: R= 3-F
1c: R=4-F
1d: R=2-Cl
1e: R=3-Cl
1f: R=4-Cl
1g: R=2-Br
1h: R= 3-Br
1i: R= 4-Br
1j: R= 2-CH_3
1k: R= 2-CH_3
1l: R= 2-CH_3
1m: R= 2-CN
1n: R= 3-CN
1o: R= 4-CN
1p: R= 2-NO_2
1q: R= 3-NO_2
1r: R= 4-NO_2

12

Ramirez-Villalva and co-workers[21] have synthesised 1,2,3-triazole-4,5-diphenyloxazol-2-one (**13**) containing series of compounds. Some of the synthesised compounds showed excellent antifungal activities against the strains *M. hiemalis*, *C. glabrata* and *T. cutaneum*, while some of the

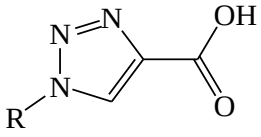
compounds are inactive against *C. utilis*, *C. krusei*, *C. albicans*, *C. tropicalis*, *A. fumigatus*, *C. parapsilosis* and *R. oryzae*.



R_1= 2-NO_2-Ph, R_2= SO_2-4-Tol
R_1= pentyl, R_2 = SO_2-Ph
R_1= Ph, R_2= CN

13

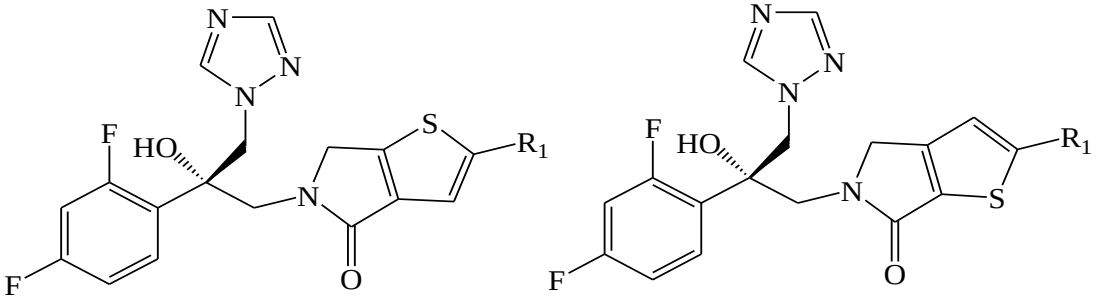
Fu and co-workers[22] in their recent investigation, synthesise the series of 1-alkyl-1*H*-1,2,3-triazole-4-carboxylic acid with linear alkyl chain (**14**). The 1,2,3-triazoles with C8 and C10 linear alkyl chains shows inhibition of *C. albicans* cell growth as well as the C10 alkyl chain compound, 1-decyl-1*H*-1,2,3-triazole-4-carboxylic acid showed the best activity for *C. albicans* with 90% inhibition, germ tube germination and inhibition of hyphal growth in *C. albicans*.



R= $(CH_2)_9CH_3$

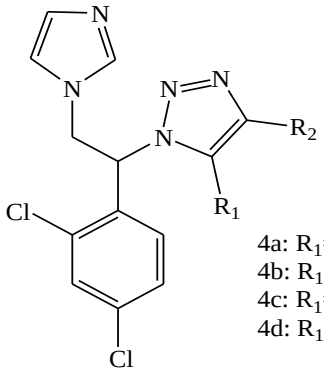
14

Cao and co-workers[23] have synthesised 5,6-dihydro-4*H*-thieno[2,3-c]pyrrol-4-one ring or a 4,5-dihydro-6*H*-thieno[2,3-c]pyrrol-6-one ring compounds (**15**). These synthesised derivatives were potent against Candida strains, including *C. glabrata*, *C. albicans* and *C. parapsilosis*. These compounds also show excellent activity against *C. neoformans* as well as *A. fumigatus*.

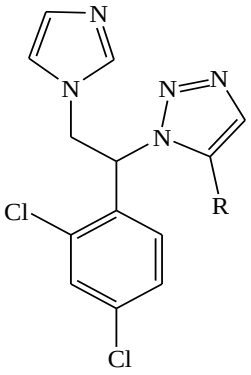


15

Gonzalez-Calderon and co-workers[24] have been synthesised series of 1,4,5-tri and 1,5-disubstituted triazole scaffold (**16**) by 1,3-dipolar cycloaddition of azide-enolate. The antifungal bioactive assay of these compounds was evaluated against fungi species *Mucor hiemalis* (ATCC-8690), *Trichosporon cutaneum* (ATCC-28592), *Aspergillus fumigatus* (ATCC-16907), *Rhizopus oryzae* (ATCC-10329) as well as candida species (three). This biological studies shows that some of the synthesised compounds showed good to excellent activity.



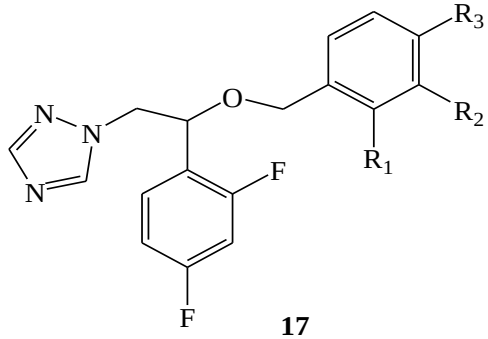
4a: R_1=CH_3, R_2 = $COCH_3$
4b: R_1= Ph, R_2 = COPh
4c: R_1= Ph, R_2= CN
4d: R_1= $CH_3(CH_2)_4$-, R_2= SO_2Ph



7a: R= cyclohexyl
7b: R= $CH_3(CH_2)_3C(CH_3)_2$-
7c: R= p-(CH_3S)phenyl

16

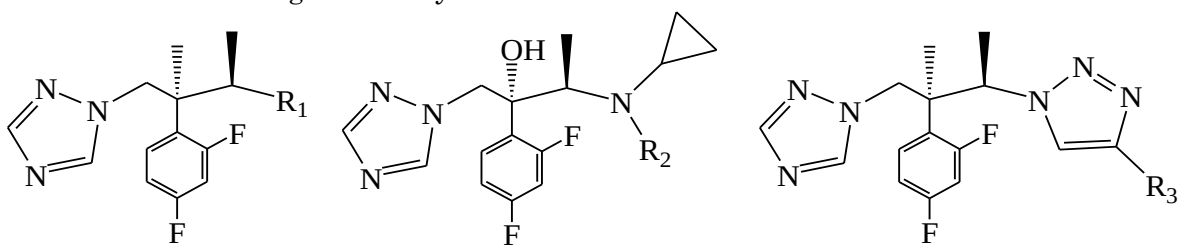
Zhang and co-workers[25] have synthesised a series of triazole (**17**) derivative which on antifungal screening shows excellent to good range of activities than reference drugs fluconazole and miconazole. The compound 3,4-dichlorobenzyl derivative (5b) showed excellent activity against fungal strains (*C. mycoderma*, *Beer yeast*, *A. flavus*, *C. utilis* and *C. albicans*).



a. R_1= Cl, R_2= H, R_3= Cl
b. R_1= H, R_2= Cl, R_3= Cl
c. R_1= F, R_2= H, R_3= F
d. R_1= H, R_2= H, R_3= NO_2
e. R_1= F, R_2= H, R_3= H
f. R_1= Cl, R_2= H, R_3= H
g. R_1= H, R_2= Cl, R_3= H
h. R_1= H, R_2= H, R_3= Cl

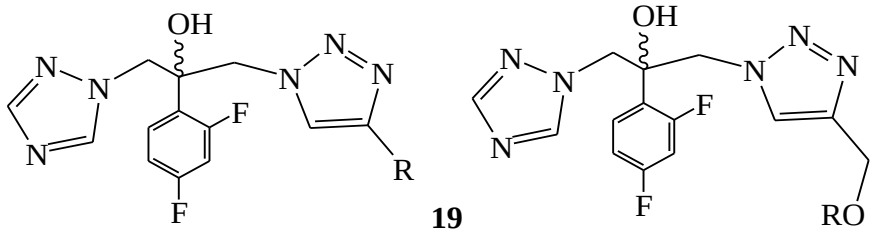
17

Wu and co-workers[26] have designed and synthesised series of voriconazole analogues, (2R,3R)-1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(*N*-substituted)-2-butanols (**18**) and screened them for antifungal activity. Some of the synthesised compounds showed better activities as compared to fluconazole while some of the compounds showed significant activity against *Aspergillus fumigatus*.



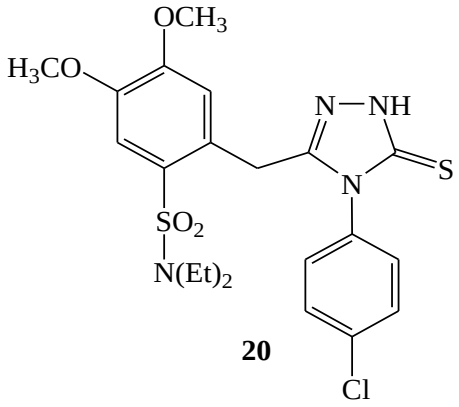
18

Aher and co-workers[27] have synthesised potent antifungal agent containing 1,2,3-triazole (**19**) motif. All the synthesised compounds were tested for in vitro antifungal activity against Candida fungal pathogens then on further structural modifications these compounds were screened in vivo against *Candida albicans*.



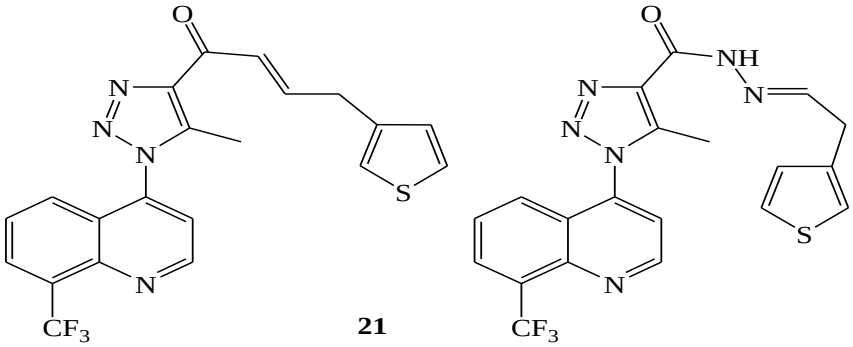
19

Ezabadi and co-workers[28] synthesised new series of 5-[2-(substituted sulfamoyl)-4,5-dimethoxybenzyl]-4-aryl-1,2,4-triazole-3-thiones (**20**) and screened for antifungal activity (In vitro) against *Aspergillus versicolor*, *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus ochraceus*, *Penicillium funiculosum* and *Trichoderma viride*. The 1,2,4-triazole molecule containing chloro functionality shows higher activity as compared to others .



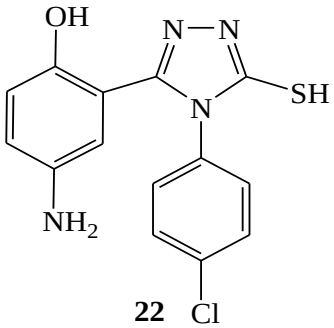
20

Holla and co-workers[29] synthesized triazole scaffold (**21**) and screened for antifungal activity against the fungal strain *Candida albicans*. Among the synthesised triazole derivatives below compounds 1-(1-(8-trifluoromethylquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-yl)-4-(thiophen-3-yl)but-2-en-1-one and 1-(8-trifluoromethylquinolin-4-yl)-*N*-(2-(thiophen-3-yl)ethylidene)-1*H*-1,2,3-triazole-4-carbohydrazide showed better antifungal activity.



21

Hussain and co-workers[30] have synthesised amino substituted 1,2,4-triazole derivatives (**22**) and screened them for antifungal activity against *Aspergillus niger*. Chloro substituted triazole compound shows 25 µg/ml minimum inhibitory concentration (MIC) against the strain species .



22

Conclusions and Future Prospects

Triazole is a vital class of five membered heterocyclic compound having nitrogen atoms. Due to potent biological activities associated with triazole containing derivatives, it becomes important pharmacophore in the medicinal field. In present review we have focused on various triazole and their derivatives along with their broad spectrum of activities. The information provided in this article can be useful for researchers for getting an idea about structural modifications to discover potent lead components which is useful in medicinal field.

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