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SUBSTITUTED-TRIAZOLES AND THEIR SCHIFF BASES AS ANTI-MICROBIAL AGENTS: A GENERAL REVIEW

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ABSTRACT

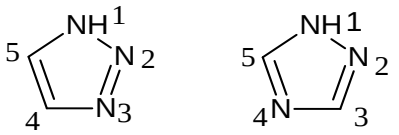
The global spread of drug resistance in bacteria requires new potent and safe antimicrobial agents. The Triazole derivatives possess divers biological activities such as antibacterial, antifungal, antiviral, anti-tubercular, anti-inflammatory, analgesic, antitumor, anticonvulsant and some other biological as well as chemical useful compounds. The biological profile of triazole moiety has attracted the attention of many researchers to explore its multiple potential against several biological activities. Compounds containing the 1, 2, 3-Triazole and 1, 2, 4-Triazole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. Triazole and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of various compounds with different types of biological activities. A large volume of research on triazole and their derivatives has been carried out, proving significant antibacterial activity of this heterocyclic core. There is a growing demand for the preparation of new antimicrobial agents due to the developing resistance towards conventional antibiotics. The 1,2,3-triazole moiety does not occur in nature, although the synthetic molecules that contain 1,2,3-triazole units show diverse biological activities. This article covers the information of some triazoles derivatives having antimicrobial activities. Thus, triazole acts as a promising medicinal agent and can be helpful to develop new triazole compounds that could have better efficacy and lesser toxicity.

Keywords: 1,2,4-Triazole. Biological activity. Schiff Base.

INTRODUCTION

Triazole nucleus is nowadays considered an important moiety in the design and synthesis of bioactive compounds that are associated with numerous biological activities [1] such as antibacterial, antifungal [2], anti-inflammatory [3], anticonvulsant [4], anti-HIV [5], anti-neoplastic, and anti-proliferative [6–13]. Additionally, there are review studies that indicate the fact that 1,2,4-triazoles occupy a distinctive place in the field of medicinal and pharmaceutical chemistry [14,15], as well as in industry [16]. Also, synthesis and complete characterization by both spectroscopic and thermal techniques were reported in literature for numerous derivatives bearing 1,2,4- triazole moieties [17–20].

Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, having a five membered ring of two carbon atoms and three nitrogen atoms. The two isomers are:



1,2,3-triazole 1,2,4-triazole

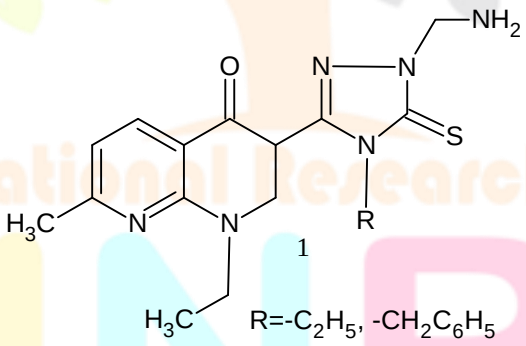
Fig 1: Different Isomers of Triazole.

The Triazole antifungal drugs include Fluconazole, Isavuconazole, Itraconazole, Voriconazole, Pramiconazole, and Posaconazole. The Triazole plant protection fungicides include Epoxiconazole, Triadimenol, Propiconazole, Metconazole, Cyproconazole, Tebuconazole, Flusilazole and Paclobutrazol. 1,2,3-Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called Triazole, which have a five-membered ring of two carbon atoms and three nitrogen atoms. Substituted Triazoles have received considerable attention during the last two decades as they are endowed with a variety of biological activities and have a wide range of therapeutic properties. Triazole heterocycle is a building block of great value in drug candidates and a large number of ring systems containing this heterocyclic core have been incorporated into a wide variety of therapeutically interesting drug compounds[21].

BIOLOGICAL ACTIVITY

Antimicrobial Activity

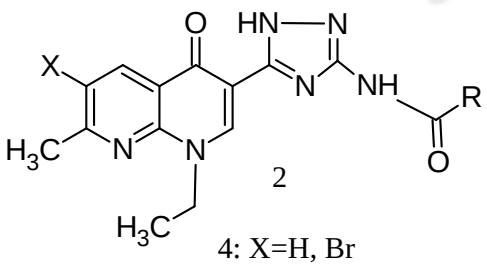
Ceylan et al. (2016) prepared Mannich bases bearing several biologically active amines (NH_2) and evaluated their antibacterial activity against *E. coli*, *Y. pseudotuberculosis*, *P.aeruginosa*, *S. aureus*, *E. faecalis*, *B. cereus*and*Mycobacterium smegmatis*. The results of the antimicrobial screening showed that compounds containing Norfloxacin, Ciprofloxacin or 7-aminocephalosporanic acid system showed excellent bacterial inhibition, especially against *Mycobacterium smegmatis*, with MIC values <1.9 µg/mL, which is better than that in the case of the standard drug, Streptomycin (MIC = 4µg/ml).



1

R=-C_2H_5, -$CH_2C_6H_5$

In 2018, Mohamed et al. prepared 3-(5-amino-(2*H*)-1,2,4-triazol-3-yl)- naphthyridinone derivatives (2) Results of antibacterial screening against a panel of bacteria revealed that both 3-(5-acylamino triazolyl) and 3-(5-Benzylidineamino triazolyl)-naphthyridones showed remarkable selectivity against 1,2,4-triazole analogues of nalidixic acid.



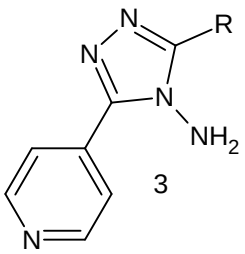
2

4: X=H, Br

R=(a) CH_2CL; (b) C_6H_5 ; (c) 4-ClC_6H_4

(d) 4-FC_6H_4 ; (e) 4-$CH_3OC_6H_4$

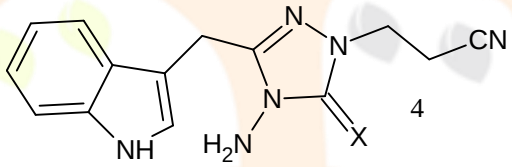
Muthal et al. (2010) synthesized 5-substituted-3-pyridin-4-yl-1,2,4-triazolesas antibacterial and anti-inflammatory agents. In vitro assay indicated that compound with 4-hydroxyphenyl moiety inhibited the growth of all bacteria (*B. subtilis, S. aureus, P. mirabilis* and *S. typhi*) to the extent comparable to levofloxacin (zones of inhibition of the compound 26–27 mm, compared to 28 mm for levofloxacin). *Proteus mirabilis* was most sensitive to all tested compounds. Additionally, the selected compounds showed moderate anti-inflammatory activity in a carrageenan-induced rat paw oedema model.



3

R=H; CH_3 ; CH_2SH ; 4-$NH_2C_6H_4$
2-HOC_6H_4 : 2-$NH_2C_6H_4$;
4-HOC_6H_4 ; 4-$CH_3C_6H_4$

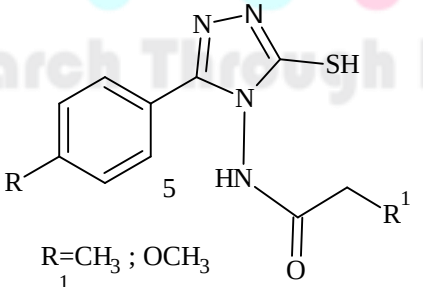
In 2013, Gadegoni et al. reported synthesis and antibacterial activity of 3-[4-amino-3(1*H*-indol-3-yl-methyl)-5-oxo(5-thioxo)-4,5-dihydro-1,2,4-triazol-1-yl]-propionitrilesand their 1,3,4-oxadiazole analogues. All compounds were subjected to invitro antimicrobial screening against *B. subtilis*, *S. aureus*, *M. luteus*, *P. vulgaris*, *S. typhimurium* and *E. coli*. Results revealed that triazoles were more potent than oxadiazole analogues, and the compound with thione-substituted triazole ring was equipotent with standard drug ampicillin against *B. subtilis*, *S. aureus* and *P. vulgaris* (MICs: 1.56, 1.56 and 6.25 µg/mL, respectively), while its 5-oxo analogue exhibited the strongest action against *E. coli* (MIC = 3.12 µg/mL). Additionally, all tested compounds exhibited considerable anti-inflammatory properties.



4

(a) X=O; (b) X=S

Upmanyu et al. (2012) synthesized 4-(substituted acetylamino)-3-mercapto-5-(4-substituted phenyl)-1,2,4-triazole derivatives and tested them for their *in vitro* antibacterial activity against four bacterial strains (*S. aureus, B. subtilis, P. aeruginosa* and *E. coli*). The SAR analysis of the compounds indicated that 4-methoxy phenyl group is preferable at the 5-position of the triazole ring compared to 4-methyl group. Moreover, antimicrobial activity of the compounds was enhanced with an increase in the number of the carbon atom group (at the *C*-2 of acetamido group) at position *N*-4 of the triazole ring and decreased with branch chain substitution.

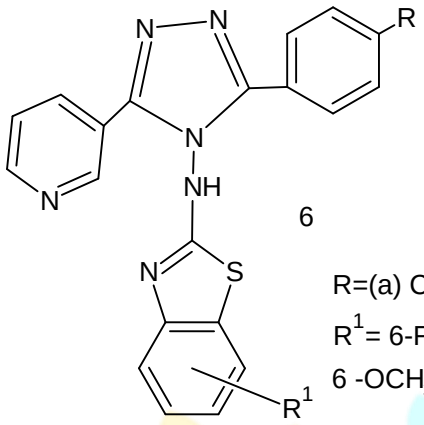


5

R=CH_3 ; OCH_3
R^1= -$N(C_2H_5)_2$; -$N(C_3H_7)_2$; $N(C_4H_9)_2$;
R^1= -$N(CH_3)C_4H_9$; -N(Isopropyl)$_2$

Patel et al. (2010,2013) designed3-(3-pyridyl)-5-(4-substituted phenyl)-4-[*N*(substituted1,3-benzothiazol-2-yl)amino]-4*H*-1,2,4-triazolederivativesas antituberculosis agents. Preliminary screening showed that among 4-methylphenyl derivatives, compounds containing 6-flouro and 6-methyl substituents at bezothiazole score exhibited activity against Gram-positive bacteria (*S.aureus*and *S. pyogenes*), which

was equal or even higher than in the case of ampicillin, used as a standard, while compound with 6-nitro substituent showed pronounced activity against Gram-negative bacteria (*E. coli* and *P. aeruginosa*), which was 4- to 8-fold higher than in the case of the standard drug. Moreover, 4-methylphenyland 4- chlorophenyl triazole with 4- chloro substituent on the benzothiazole ring showed potent antitubercular activity.

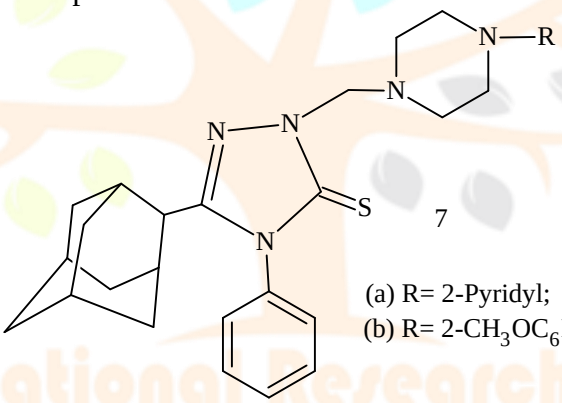


6

R=(a) CH_3; (b) NO_2; (c) Cl

R^1= 6-F; 6-Br; 6-Cl; 6-NO_2; 6-CH_3; 6 -OCH_3; 4-CH_3; 4-NO_2; 4-Cl; 5,6-diCl

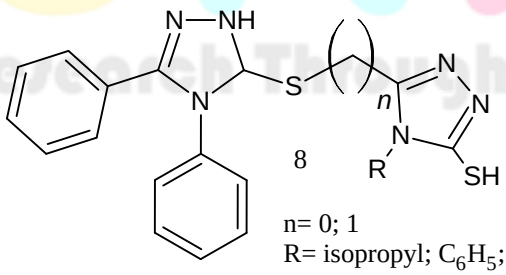
Al-Abdullah et al. (2014) synthesized Mannich bases of 5-(1-adamantyl)-4- substituted1,2,4-triazol-3-thioneand screened their antibacterial activity panel of bacterial strains (*S. aureus*; *B. subtilis*; *M. luteus*; *E. coli*; *P. aeruginosa*). Among the tested compounds, 5-(1-adamantyl)-4-phenyl-2-[4-(pyrid-2-yl)-piperazine-1-ylmethyl]- 1,2,4-Triazoline-3-thione and its 2-methoxyphenyl piperazine analogue showed excellent antibacterial activity with growth inhibition zones > 19 mm against all of the tested microorganisms, and were found to be more active than Ampicillin and Gentamicin.



7

(a) R= 2-Pyridyl;
(b) R= 2-$CH_3OC_6H_4$

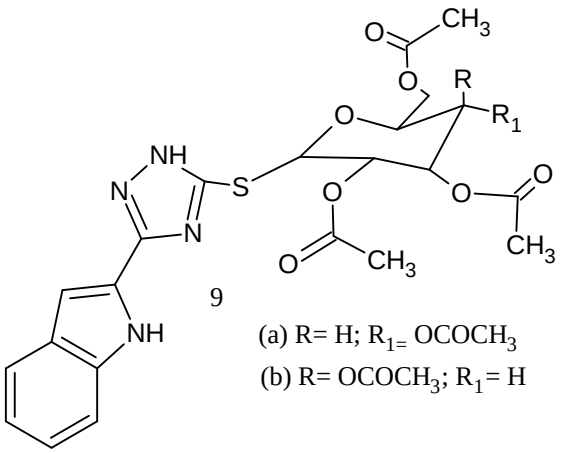
Singh et al. (2013) synthesized asymmetric bis-1,2,4-Triazoles and determined their invitro antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*. Among the tested compounds, a series with S-methyl linker (*n* = 1),in particular 5-[(4,5-diphenyl-4*H*-1,2,4-triazol-3-ylthio)methyl]-4-phenyl(4-flfluorophenyl)-4*H*-1,2,4triazole-3-thioles,were observed to be most potent against all bacterial strains.



8

n= 0; 1
R= isopropyl; C_6H_5; 4-ClC_6H_4
4-FC_6H_4; 4-$CH_3OC_6H_4$; 4-$C_2H_5OC_6H_4$

El Ashry et al. (2013) evaluated *S*-glycosides and *S*, *N*-diglycosides of 1,2-dihydro-5-(1*H*indol-2-yl)-1,2,4-triazole-3-thione for antibacterial activity against two human pathogenic microbes. The obtained data revealed that *Bacillus subtilis* was far more sensitive to the newly obtained compounds than *Pseudomonas aeruginosa*, and S-glycosylated 1,2,4-Triazoles showed the same antibacterial effect in comparison with the standard drug, Chloramphenicol.

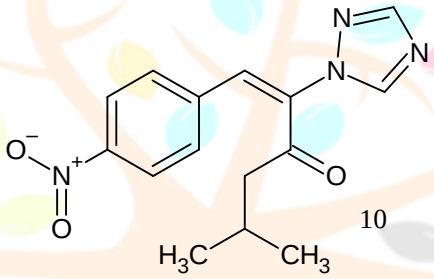


9

(a) R= H; $R_{1=}$ $OCOCH_3$

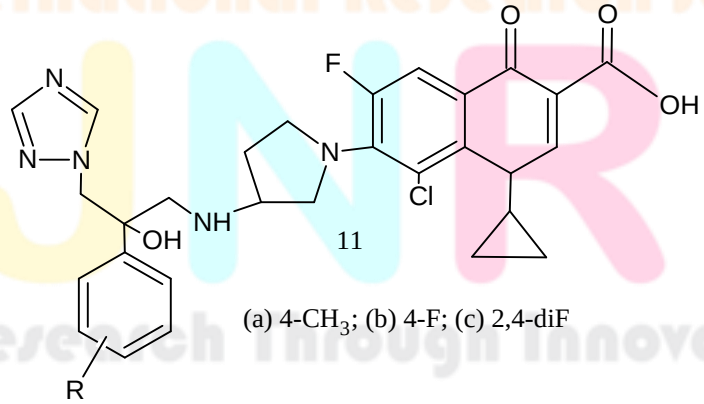
(b) R= $OCOCH_3$; R_1= H

In 2020, Stingaci et al. synthesized vinyl-1,2,4-Triazole derivatives as antimicrobial agents. Synthesized compound exhibited excellent activity against all bacterial species (*B. subtilis*, *P. fluorescens*, *E. amylovora*, *E. carotovora*, *X. campestris*) with MIC and MBC ranging from 0.0002 to 0.0033 mm, which were comparable to Ampicillin and Chloramphenicol.



10

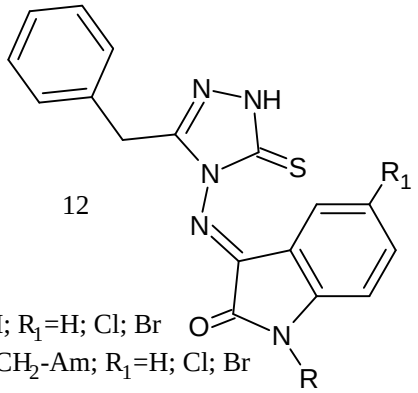
In 2012, Wang et al. synthesized a series of clinafloxacin-triazole hybridsand tested their activity against a panel of bacterial strains (*S. aureus*, *B. subtilis*, *M. luteus*, *E. coli*, *S. dysenteriae*, *P.aeruginosa*, *B. proteus*). Additionally, the research was also based on methicillin-resistant strain of *S.aureus*. Most of 1,2,4-triazole derivatives of clinafloxacin displayed high inhibitory efficacy towards both Gram-positive and Gram-negative bacteria with MIC values ranging from 0.25 to 32 µg/ml.



11

(a) 4-CH_3; (b) 4-F; (c) 2,4-diF

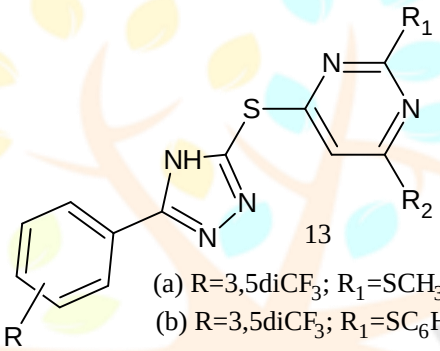
Murthy et al. (2012) evaluated a series of Schiff and Mannich bases of isatin derivatives of 4-amino-5 benzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione for their antibacterial activities against *S. aures*, *B. subtilis*, *P. aeruginosa*, and *E. coli*. The SAR indicated thatcompounds with chloro and bromo groups at the *C*-5 position of isatin exhibited broadspectrum antibacterial activity with the inhibition zone of 20–27 mm, comparable to ciprofloxacin (inhibition zone of 25–30 mm). In general, antimicrobial activity of Mannich bases (2)was less than that of Schiff bases (1).



12

(1) R=H; R_1=H; Cl; Br
(2) R=-CH_2-Am; R_1=H; Cl; Br

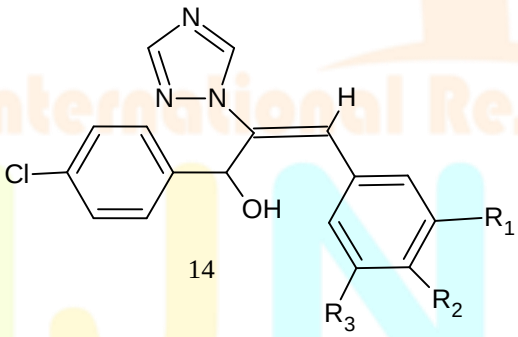
Cui et al. (2016) designed a series of 1,2,4-triazole-pyrimidine derivatives linked by sulfurcompound (13), and then carried out extensive in vitro and in silico studies of theirantimicrobial activity. Preliminary screening against two representative strains (*S. aureus* and *E. coli*) revealed two most potent compounds with 2-methyl- or 2-phenylthio moieties at the 2-position of the pyrimidine ring (4a–b).



13

(a) R=3,5diCF_3; R_1=SCH_3;R_2=Cl
(b) R=3,5diCF_3; R_1=SC_6H_5;R_2=Cl

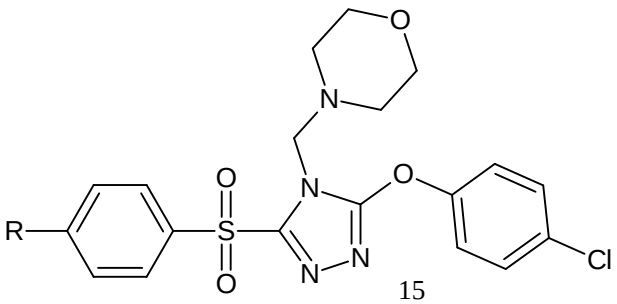
Uchil et al.[22] have been synthesized and used (substituted-(+) α-(4-chlorophenyl)-β- (phenylmethylene)-1H-1,2,4-triazole-1-ethanols) compound (14) as bacteriostatic agent.



14

a: R_1=R_3=H; R_2=Cl
b: R_1=Br; R_2=R_3=H
c: R_1=R_2=R_3=OCH_3
d: R_1=R_3=H; R_2=SCH_3
e: R_1=OC_6H_5; R_2=R_3=H
f: R_1=OCH_3; R_2=OH; R_3=H
g: R_1=R_3=H; R_2=OH
h: R_1=R_2=OCH_2O; R_3=H
i: R_1=R_3=H; R_2=$N(CH_3)_2$

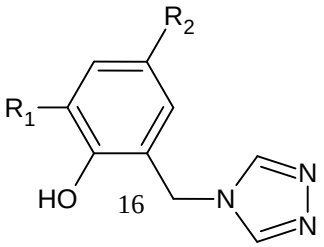
Narayana Rao et al. [23], have been synthesized and characterized a new 1,2,4-triazole derivatives. Also, they have been evaluated the biological activity 4- [(3-(4- substituted-phenoxymethyl)-5-benzylsulfonyl)-1,2,4 triazole- 4-yl) methyl]-morpholine compound (15) and All the title compounds showed good antibacterial and antifungal activities.



15

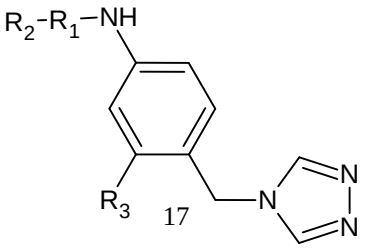
a: R=H
b: R=CH_3
c: R=OCH_3
d: R=NO_2
e: R=Cl
f: R=Br
g: R=F

El-Zemity et al.[24] have been synthesized and evaluated the Bactericidal Potential of (1H-1,2,4-triazol-1-ylmethyl)phenols (16), N,N-dialkyl Anilines (17), and N-alkyl Anilines (18).



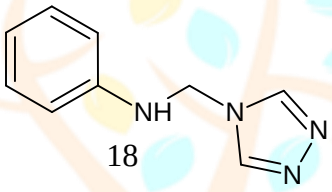
16

a:R_1=R_2=H
b: R_1=CH_3; R_2=H
c: R_1=H; R_2=CH_3
d: R_1=i-C_4H_9; R_2=H
e: R_1=t-C_4H_9; R_2=CH_3
f: R_1=s-C_4H_9; R_2=CH_3



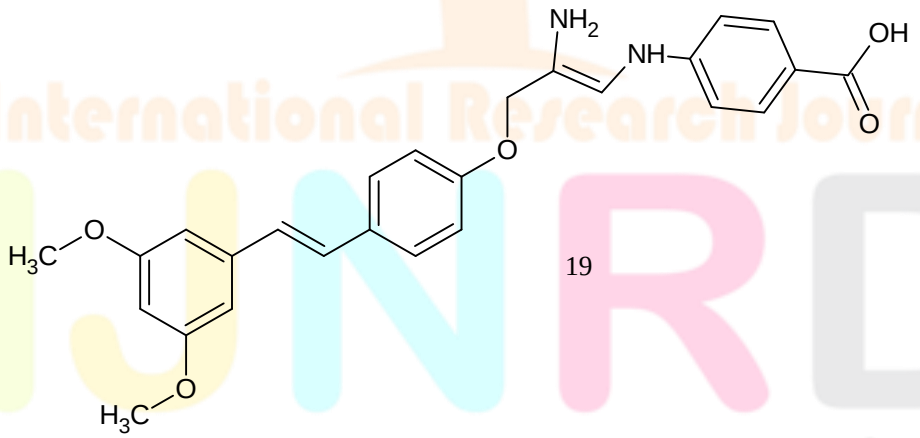
17

a: R_1=R_2=R_3=H
b: R_1=CH_3; R_2=R_3=H
c: R_1=C_2H_5; R_2=R_3=H
d: R_1=C_2H_5; R_2=H; R_3=CH_3
e: CH_3CH_3H
f: R_1=R_2=R_3=CH_3



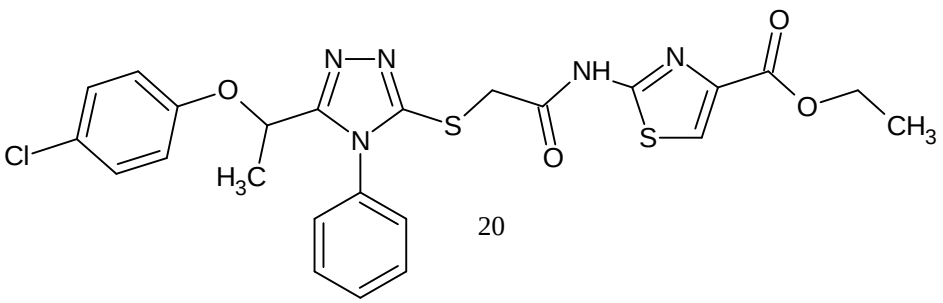
18

Tang et al. synthesized the triazolyl-pterostilbene derivatives, and their antimicrobial activity was evaluated. Among all the compounds, compound (19) showed the most potent antimicrobial activity with MIC values of 1.2–2.4 μg/mL and MBC values of 19.5–39 μg/mL. On the other hand, structural activity analysis showed introduction of the phenyl group as a spacer on compound (4) exhibited significant antimicrobial activity[25].



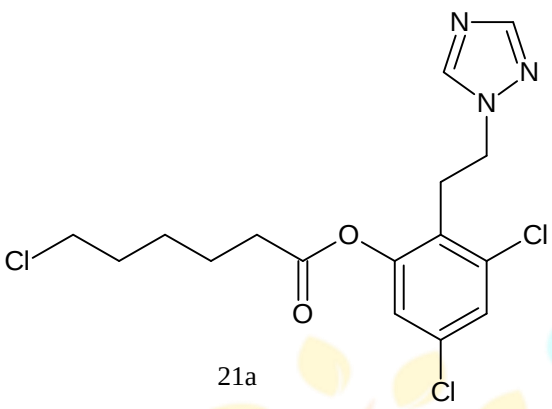
19

Turan-Zitouni et al. synthesized 4-phenyl-cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole analogues and tested theirantimicrobial activity.Among thesesynthesized compounds, only compound(20) showed excellent antifungal activity [26].

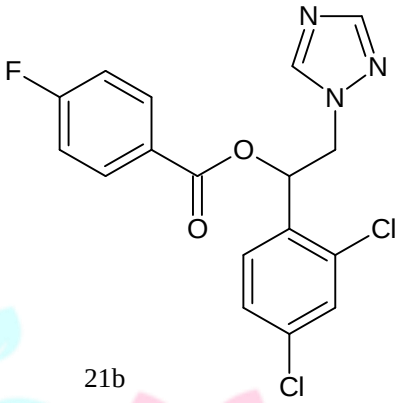


20

Han et al. reported a new series of triazole derivatives containing different ester skeletons and evaluated as antifungal agents. The antifungal activity was investigated by utilizing the microdilution broth method. In all the synthesized compounds, compounds (21a) and (21b) showed the most significant activity against four important fungal pathogens (MIC80 = 2–8 μg/mL). Molecular docking studied revealed the target compounds interact with CYP51 mostly by Van der Waals and hydrophobic interactions [27].

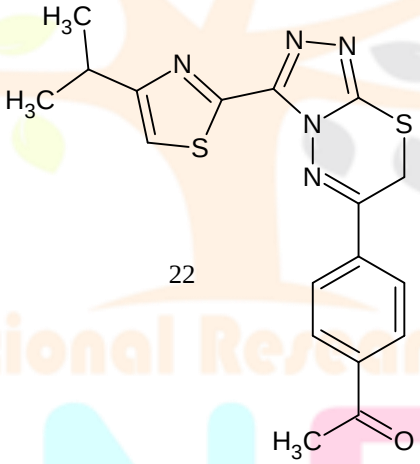


21a



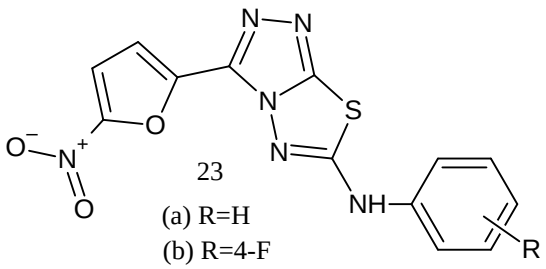
21b

Kumar et al. (2010) developed a new series of isopropylthiazole-derived 1,2,4-triazole moiety fused with 1,3,4-dihydrothiadiazole, 1,3,4-thiadiazole and 1,3,4-thiadiazine, and tested them as antibacterial agents. Antimicrobial study revealed that 1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazinecompound (22)demonstrated excellent activity against all tested Gram-positive and Gram-negative pathogens.



22

Badr et al. (2011)studied a series of fused 1,2,4-triazoles compound 14 starting from 4-amino-5-(5-nitrofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol. Antimicrobial activity against two bacterial strains, namely*S. aureus*and *E. coli*, was determined as the minimum inhibitory concentration (MIC) and theminimum bactericidal concentration (MBC). Compounds,3-(5-nitrofuran-2-yl)-*N*-aryl-1,2,4triazolo[3,4-*b*][1,3,4]thiadiazol-6-amines (23a–c) inhibited the growth of *S. aureus*in a concentration of 25 μg/mL, which was equivalent to that of standard ampicillin[28].

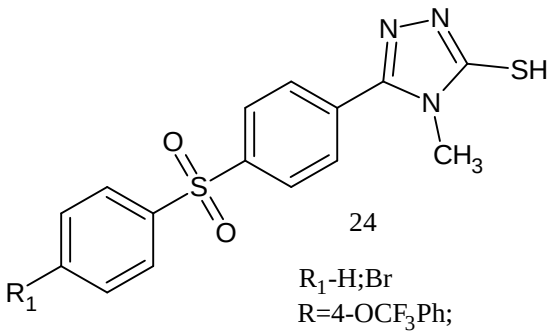


23

(a) R=H
(b) R=4-F
(c) R=4-C_2H_5

Barbuceanu et al. reported the synthesis and antibacterial activity of mercapto-1,2,4-triazoles bearing diphenylsulfonecompound (24) against S.aureus, B. cereus, E. coli, Enterobacter cloacae, Acinetobacter

baumannii and P. aeruginosa [29]. Among them, one of the compounds having bromo diphenylsulfone moiety at position-3 and 3,4,5-trimethoxyphenyl fragment at the nitrogen atom N-4 of triazole ring,exhibited the strongest action against B. cereus (MIC: 8 mg/mL).



24

R_1-H;Br
R=4-OCF_3Ph;
3,4,5-$(OCF_3)_3$Ph

CONCLUSION

This review article highlights research work of many researchers reported in literature for antimicrobial activity on Substituted triazole compounds. Triazole analogues have paying attention in the fields of chemical, medicine and agrochemical research area, due to its exclusive structures and chemical properties.

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