1,2,4-Triazole as an Antimicrobial Scaffold

PARMINDER KAUR*, RAJWANT KAUR

University Institute of Pharma Sciences, Chandigarh University, Mohali-160101, India

Kaur, et al.: 1,2,4-Triazole as an Antimicrobial Scaffold

Abstract:
Microbiological evolution and bacterial resistance have hastened intensely over the last era. Nowadays, microbial infections have become a chief cause of morbidity and mortality. The requirement for novel antimicrobials has been more noteworthy than ever in the face of increasing resistance to the older ones. Over the most recent couple of decades, heterocyclic compounds have been concentrated broadly attributable to their intriguing pharmacological exercises. The most remarkable and well-known heterocyclic nucleus is triazole core, which exist in two isomeric structures: 1,2,3-triazole and 1,2,4-triazole. Out of which 1,2,4-triazole core is considered as a main fundamental component of many pharmacologically active agents such as antibacterial, antitubercular, antifungal, antiviral agents. It has been established as pharmacologically significant antimicrobial scaffolds due to its broad and potent activity. This fair diversity in the pharmacological activity has pulled in the consideration of numerous specialists to explore the wide potential of this skeleton. The current review abridges the literature dealing with antimicrobial activity of 1,2,4-triazole derivatives. Primer outcomes showed that the vast majority of the compounds exhibited generally excellent antimicrobial activity, tantamount to the first line standard drugs.

Keywords: Heterocyclic chemistry, 1,2,4-triazole, antibacterial, antifungal, antimycobacterial, antiviral

INTRODUCTION
In the recent decades, the frequency of microbial infection has expanded on startling levels world-wide over because of antimicrobial resistance. Microbial infections are an emerging issue in contemporary medicine and the utilization of antibiotics is regular over the world. On twenty nine April 2019, UN, international agencies and specialists discharged a groundbreaking report requesting prompt, coordinated and determined action to prevent a potentially disastrous drug-resistance catastrophe. Drug-resistant illnesses might cause ten million deaths annually by 2050 and damage to the economy as catastrophic. Antimicrobial resistance might force up to twenty four million individuals into outrageous poverty by 2030. Presently, a minimum of 700,000 individuals kick the bucket every year annually due to drug-resistant diseases. This report mirrors the profundity and extent of the response required to check its ascent and ensure a time of progress in wellbeing[1].

As bacteria is becoming resistant to antibiotics and a large figure of invading fungal species becoming resistant to currently prescribed antifungal drugs, there is extensive enthusiasm in the advancement of novel compounds with broad spectrum antimicrobial activity. The heterocyclic compounds assume a noteworthy job among organic compounds with biological activities.

Subsequently, there is a pressing requisite to augment new antimicrobial agents with broad spectrum activity against the resistant microorganisms. The present writing is supplemented with dynamic findings about the triazole heterocycles. It is recognized that the N-bridged

---

*Address for Correspondence:
Parminder Kaur
University Institute of Pharma Sciences, Chandigarh University, Mohali-160101, India
E-mail: hundalparminder275@gmail.com

Article History:
Received 30 March 2020
Revised 28 April 2020
Accepted 1 May 2020
J Pharm Res Ther 2020;01(02):62-70
heterocycles for example 1,2,4-triazoles discover applications in the arena of medicine, agriculture and industry[2].

**Heterocyclic chemistry:**

When heterocyclic compound alloxan (2,4,5,6-pyrimidinetetronate) was disengaged by Luigi Brugnatelli in 1818, the historical backdrop of heterocycles started its excursion. As a huge part of organic chemistry, it is representing about 33% of current publications. Genuinely, heterocyclic contributes to two third of organic compounds. When at least one atom replaces carbon atom in the ring system then the name assigned as a heterocyclic compound. Basic heteroatoms are nitrogen, oxygen and sulfur but heterocyclic molecules comprising other hetero atoms are likewise broadly recognized[3].

5-membered N-heterocyclic compounds are significant structural fragments and considered as biologically active compounds. But the chemistry of 5-membered N-heterocyclic compounds, specifically tetrazole, triazoles, and their substituted derivatives are facing tremendous and ceaseless challenge. Triazole name was given to the carbon nitrogen ring framework by Bladin in 1885[4].

Pyrimidiazole, another name of triazole, comprises of a five membered ring with two double bonds, three nitrogen atoms and two carbon atoms at non-adjacent positions. Isomers of triazole are represented in fig. 1.

**Tautomers of 1,2,4-triazoles:**

Two tautomeric structures of 1,2,4-triazoles exists in nature i.e. 1H and 4H-1,2,4-triazole, which are considered as pharmacologically significant cores[5] (fig. 1).

**Pharmacological activities of 1,2,4- triazole derivatives:**

1,2,4-Triazoles and its derivatives have generally contrasting activities such as antibacterial[6-9], antifungal[10,11], anticancer[12-15], antitubercular[16,17], antiinflammatory[18,19], analgesic[20], antiviral[21,22], antinociceptive[23-25], anticonvulsant[26-29], anticorrosive[30], antihelmentic[31], antioxidant[32-36], urease and lipase inhibitors[37], hypoglycaemic[38], antiproliferative, diuretic, antimigaine, sedative, muscle relaxant and antiHIV[39], etc.

**ANTIMICROBIAL REVIEW**

**Antibacterial:**

1,2,4-triazole derivatives namely 3-(3,4-substituted-phenyl)-4-(4-fluorophenyl)-5-methyl-4H-1,2,4-triazoles synthesized and evaluated against Staphylococcus aureus, Bacillus cereus (Gram-positive) and Escherichia coli, Pseudomonas aeruginosa (Gram-negative) strains by broth dilution method for their antibacterial activities. Desabattinna VNK et al. found that the compounds in fig. 2 demonstrated very good antimicrobial activity when compared with Cefaclor. Structure-activity relationship study indicated that presentation of alkyl, alkoxy and halogen substituents enhanced activity[40]. Compounds containing Schiff and Mannich bases (morpholine) of 1,2,4-triazole synthesized and screened for antibacterial activity against Yersinia pseudotuberculosis, P. aeruginosa, Enterococcus faecalis, S. aureus, B. cereus, Mycobacterium smegmatis taking Ampicillin as standard. Unver et al. found that the Schiff base and the Mannich base in fig. 3 explored excellent activity. Carrying nitro substituent on the thiophene ring upgraded the activity[41]. Ghattas et al. screened Mannich-based triazole derivatives against B. cereus, P. aeruginosa and E. coli for antibacterial activity by agar diffusion method. Mannich base derivatives displayed...
excellent inhibition, especially compounds in fig. 4 showed the highest inhibitory effect against all types of bacteria excepting E. coli, which affected highly by chloromethyl substituted compound instead of morpholine and piperidine substitution. B. cereus and E. coli are excellently inhibited by sulfide containing compounds[42]. Derivatives of triazole derived Schiff base, ligand 2-[(1Z)-N-(1H-1,2,4-triazol-3-yl)-etanimidoyl]phenol coordinated with salts of transition metals viz. VO(IV), Cr(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) screened against several bacterial strains: E. coli, Salmonella typhi, B. subtilis, Klebsiella pneumonia, and S. aureus for antibacterial activity by the agar diffusion method taking ampicillin and streptomycin as reference drugs. Sumra et al. found that the complexes in fig. 5 demonstrated substantial antibacterial activity. Results revealed that triazole ligand displayed high activity[43]. 1-((5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-y1) methyl)-1,2,4-triazole-3-carboxylic acid derivatives evaluated for their antibacterial activity against E. coli by using serial broth dilution method. Brahmayya et al. concluded in SAR that compounds in fig. 6 are active on Gram-negative bacteria. These are substituted with 1,3,4-oxadiazole ring and most potent against the E. col[44]. A series of substituted pyrazolo triazolothiadiazines and triazole-3-thiones developed and assessed their antibacterial potency against S. aureus, Enterococcus faecalis, E. coli and P. aeruginosa by Nayak et al. The compounds in fig. 7 showed good antibacterial activity using the broth dilution method taking ciprofloxacin as a reference drug. SAR revealed that chloro, fluoro, di-methoxy, and di-hydroxy substituted derivatives displayed good activity over other derivatives. A thiadiazine ring-containing derivative with 4-chlorophenyl, 4-fluorophenyl, 3,4-dimethoxy phenyl substitutions displayed excellent activity[45]. Wang et al. synthesized oxime esters containing 1,2,4-triazole and their antibacterial activities against Xanthomonas axonopodis and X. oryzae were evaluated taking bismethiabazol as standard. All the compounds exhibited potent antibacterial inhibition. In particular, the compounds in fig. 8 exhibited remarkable antibacterial activity. SAR indicated that the compounds with the same substituents displayed improved activities against X. oryzae than X. axonopodis. Moreover, the contribution of 1,2,4-triazole fragments improved the antibacterial activities. Additionally, substitution of R2 Ph, 4-FPh and 4-CF3Ph groups enhanced inhibition against X oryzae[46]. Schiff bases of 1,2,4-triazoles screened for antibacterial activity against B. subtilis, S. aureus and E. coli comparable to chloramphenicol. Jin et al. indicated that the compound in fig. 9 exhibited excellent activities. The SAR manifested that of the triazole ring without substitution at 5th position is more active and introduction of 3-phenoxy phenyl group improved the antibacterial activity. It was also specified that triazole ring, S atom and benzene ring made a major impact on the activity[47].

Novel 4,5-diphenyl-1H-imidazol-1-yl-1H-1,2,4-triazole derivatives screened for their antibacterial activities...
against *E. coli*, *P. aeruginosa* (Gram-negative) and *B. subtilis*, *Micrococcus luteus* (Gram-positive) bacteria taking ciprofloxacin and tetracycline used as the positive controls. The derivatives in fig. 10 showed potential antibacterial activities. Dastmard et al. revealed in SAR that the compounds with heterocyclic moieties viz. imidazole and triazole and substituted aromatic rings demonstrated good antibacterial activity\(^{[49]}\), Alyahyaoy et al. synthesized 1,2,4-triazole-3-thiol derivatives and antibacterial effect was assessed against certain types of Gram-positive and negative bacteria taking amoxicillin and ceftriaxone as standard drug. The SAR indicated that the triazole-3-thiol moiety produced antibacterial activity against certain types of bacteria according to side chain group (beside thiol). The compounds with side alkyl chain (S-R) ethyl and butyl did not exhibit any biological activity. The triazoles containing ester and hydrazide group as in fig. 11 displayed promising activity\(^{[50]}\). Novel analogues of 1,2,4-triazole clubbed with pyridine synthesized by Mahajan et al. When screened for antibacterial activities against *S. aureus*, *B. subtilis* (Gram-positive) and *P. aeruginosa*, *E. coli* (Gram-negative) strains by broth dilution method utilizing ciprofloxacin as a standard drug, the compound in fig. 12 exhibited comparable activity. SAR revealed that di-thiol substituted derivatives were the most active from the series\(^{[50]}\). Binuclear nitrosyl iron complex \([Fe_2(SR)_2(NO)_4]\) (R is 5-phenyl-1H1,2,4-triazole-3-thiol) screened against *E. coli* (Gram-negative) and *Micrococcus luteus* (Gram-positive) strains for antibacterial activities by Sanina et al. Double-series dilution method utilized and compared with kanamycin, ceftriaxone and streptomycin. The complex in fig. 13 showed higher inhibition against *M. luteus*. It was concluded that mercapto-1,2,4-triazole series containing sulfur hold promise for the strategy of new nitrosyl iron complexes with potent antibacterial activity\(^{[51]}\).

**Antifungal:**

Pyrimidine bearing 1,2,4-triazole derivatives evaluated for antifungal activity against *Candida albicans*, *Penicillium* sp. and *Aspergillus niger* by agar well disk diffusion method taking Amphotericin-B as reference drug. Andrews et al. found the compounds in fig. 14 showed moderate to good inhibition but less than standard drug\(^{[52]}\). Min et al. evaluated antifungal activity of thioether derivatives of 1,2,4-triazole moiety against *Pythium ultimum* Trow, *Phytophthora infestans* (Mont.) de Bary, *Corynespora cassiicola*, *Botrytis cinerea* and *Rhizoctonia solani* by potted plant test method taking controls viz. chlorothalonil, dimethomorph, zhongshengmycin, procymidone, and validamycin. The compounds in fig. 15 with butyl, benzyl, 4-chlorophenoxy and 3-chlorobenzyl substitution
exhibited good efficacy against *Pythium ultimum* Trow. The compounds with 4-chlorobenzyl, 4-bromobenzyl and 2-chlorobenzyl displayed excellent inhibition of fungal *Corynespora cassiicola*.[53] Derivatives of 4-aryl-5-(1-phenyl-5-methyl-1,2,3-triazol-4-yl)-1,2,4-triazole-3-thiones evaluated for antifungal activity applying the agar diffusion method. Chu *et al.* indicated that the compounds in fig. 16 exhibited moderate inhibition against cucumber grey mold, rape sclerotium, and wheat gibberella, early blight of tomato, apple black rot and cotton damping-off. Moreover, the inhibiting effects of compounds with two 1,2,4-triazole moieties are higher than compounds with one,[54] 1,2,4-triazol derivatives containing an amide moiety evaluated for antifungal activities against the pathogenic fungi of kiwifruit soft rot disease by the poison plate technique taking Pyrimethanil as reference drug. The compounds in fig. 17 possessed good antifungal activities according to Wu *et al.* They revealed that the compounds substituted with 4-hydroxy phenyl, 4-pyridine and benzyl groups displayed effective inhibition of *Botrytis cinerea*. Meanwhile, ethyl substituted compound highly affect *Phompsis* sp. SAR revealed that the smaller alkyl substituent groups enhance the activities against *B. cinerea* and *B. dothidea*. In addition, the antifungal activities were better when R was 4-pyridine instead of 2-pyridine.[55] Appna *et al.* screened 1,2,4-triazole fused pyrido[2,3-d]pyrimidine derivatives against several Candida strains for determining the antifungal activity taking miconazole as a control drug. The compounds in fig. 18 exhibited promising antifungal activity. The presence of fluoro, trifluoromethyl, bromo and nitro groups on phenyl and furyl rings in pyrido[2,3-d]pyrimidine upheld antifungal activity.[56] Xu *et al.* evaluated 1,2,4-triazoles with a 4-(4-substitutedphenyl)piperazine side chain against eight human pathogenic fungi utilizing fluconazole and voriconazole as control drugs. Nearly all tested compounds, especially in fig. 19, were more effective against *C. albicans*. SAR manifested that the introduction of aliphatic side chain with a proper length instead of aromatic analogues increased the activity.[57] Pyrimidine moiety containing derivatives of 1,2,4-triazole evaluated for their fungicidal against *Phompsis* sp., *B. dothidea* and *B. cinerea* utilizing pyrimethanil as standard drug. Some of the compounds exhibited moderate to good fungicidal activities. Wu *et al.* found compounds with 2,4-dichlorobenzyl and 3,4-dichlorobenzyl substitutions in fig. 20 displayed excellent antifungal activity against *Phompsis* sp. Meanwhile, compound with 3,4-dichlorobenzyl group showed better fungicidal activities against *B. dothidea* and *B. cinerea*.[58] Borthakur *et al.* found derivatives shown in fig. 21, namely, [1,2,4]triazolo[1,5-alpyrimidin-6-one as excellent inhibitors of *Rhizoctonia solani* and *Trichoderma* sp. strains when compared with carbendazim. SAR indicated that the compounds with chloro and methoxy substitutions were more active against *Rhizoctonia* sp. while the compounds with dimethyl amine substituent inhibited *Trichochoderma* sp. effectively.[59] Li *et al.* revealed five derivatives of *N*-

![Fig. 16: 4-aryl-5-(1-phenyl-5-methyl-1,2,3-triazol-4-yl)-1,2,4-triazol-3-thiones](image)

![Fig. 17: 1,2,4-triazol derivatives containing an amide moiety](image)

![Fig. 18: 1,2,4-triazole fused pyrido[2,3-d]pyrimidine derivatives](image)

![Fig. 19: 1,2,4-triazole derivatives with a 4-(4-substitutedphenyl) piperazine](image)

![Fig. 20: 1,2,4-triazole derivatives containing a pyrimidine moiety](image)

![Fig. 21: Derivatives of [1,2,4]triazolo[1,5-alpyrimidin-6-one](image)
phenylacetamide bearing 1,2,4-triazole especially in fig. 22 as potent inhibitors of fungus C. albicans when compared with itraconazole. SAR revealed that mono halogen substituted benzene ring displayed potent inhibition without signifying its position[60].

Antimycobacterial:
A series of substituted isopropylthiazole clubbed with 1,2,4-triazole synthesized and assessed for their antitubercular activity against M. tuberculosis H37Rv strain by broth dilution assay method utilizing isoniazid as reference drug. Kumar et al. indicated that many compounds shown in fig. 23 displayed moderate to excellent inhibition. SAR revealed that the compounds with 2-chlorophenyl and 3-phenylallyl substitution exhibited enhanced potency than parent compound[61]. Tehrani et al. evaluated 4-amino-1,2,4-triazole-5-thione analogues for their antimycobacterial activity against M. bovis BCG by broth dilution assay method utilizing ethambutol as reference drug. They indicated that the compounds in fig. 24 were the most active ones. SAR revealed that compound with CH$_3$ group as the most potent derivatives[62]. Novel 1,2,4-triazole derivatives based on econazole moiety evaluated against M. tuberculosis H37Rv and multi-drug resistant (MDR) strains of Mycobacterium for antitubercular activity by Microplate Alamar Blue assay technique utilizing econazole as reference drug. Kumar et al. revealed that functional groups at para position of the phenyl ring (no matter electron donating or withdrawing nature) attached to the 1,2,4-triazole ring enhance the activity of compounds as represented in fig. 25. Compounds substituted with chlorine fluorine in the phenyl ring are tolerable in comparison to fluorine substituted analogs. The presence of pyrazine moiety is also favorable for anti-tubercular activity[63]. 3-aryl-5-(alkylthio)-1H-1,2,4-triazoles screened against M. tuberculosis H37Ra strain and M. bovis BCG for antimycobacterial potency taking rifampicin as the reference drug. Rode et al. revealed that the presence of a nitro group on the aromatic ring and S-alkyl substitution have shown excellent activity. The position and nature of the electron withdrawing substitution chiefly influenced the activity, considering the results for the active compounds in fig. 26. Compounds bearing C4 chain lengths displayed highest inhibitory potencies[64]. Seelam et al. found fused pyrazolo thiazolo-1,2,4-triazole derivatives especially in fig. 27 as the potent inhibitor of M. tuberculosis H37Rv strains when compared with Streptomycin by the agar micro dilution method. The compounds bearing electron withdrawing groups (Cl, NO$_2$, Br) displayed excellent inhibition[65]. Novel derivatives of 1,2,4-triazole-5-thione evaluated for antimycobacterial potential by resazurin microtiter assay using M. tuberculosis H37Rv strain. Vora et al. found the compounds in fig. 28 potent and identified

![Fig. 22: N-phenylacetamide bearing 1,2,4-triazole derivatives](image1)

![Fig. 23: Substituted isopropylthiazole clubbed with 1,2,4-triazole](image2)

![Fig. 24: 4-Amino-1,2,4-triazole-5-thione analogues](image3)

![Fig. 25: 1,2,4-Triazole derivatives based on econazole moiety](image4)

![Fig. 26: 3-Aryl-5-(alkylthio)-1H-1,2,4-triazoles](image5)

![Fig. 27: Fused pyrazolo thiazolo-1,2,4-triazole derivatives](image6)

![Fig. 28: derivatives of 1,2,4-triazole-5-thione](image7)
compound bearing p-tolyl substitution as hit with Mtb H37Rv. SAR indicated that the electron donating methyl group present at 4th position prompts positive inductive effect which appears vital for carbonyl group activation which can form more stable hydrogen bond network[66].

Antiviral:
Myricetin derivatives containing a 1,2,4-triazole Schiff base screened against tobacco mosaic virus for antiviral activity taking Myricetin, Ribavirin and Ningnanmycin as reference drugs. Chen et al. revealed that majority of compounds displayed excellent activity. SAR indicated that the compounds substituted with Ph, 3,4-di-CH3-Ph, 3,4-di-CH3O-Ph and 2-thiophene displayed curative and defensive activities. The compound with 3,4-di-CH3O-Ph in fig. 29, displayed better passivation activity[67]. Chiral triazole derivatives prepared and screened for antiviral activities against EV71 and CVB3 in cell-based assays taking ribavirin as control. Cao et al. indicated that some of these chiral derivatives displayed excellent antiviral activities against EV71. SAR revealed that the compounds with S-configuration as in fig. 30 were the most potential molecules[68]. 1,2,4-triazoloindoles derivatives evaluated for their antiHIV activity using IIIB strain for HIV-1 and the ROD strain for HIV-2. Al-Soud et al. found that none of these compounds inhibited HIV-1 or HIV-2 replication in comparison to the antiviral agent Delviridine[69]. Pandey et al. found 5-(3-aralkylamido/imidoalkyl)phenyl]-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazines, especially in fig. 31 as potent inhibitor of Japanese encephalitis virus and herpes simplex virus-1. Compound having R= H and R'= 2-phenyl-3-methylquinazolin(3H) 4-one showed moderate anti-JEV activity while the other compounds containing nicotinamido phthalimido and phthalimidomethyl substituents were found insignificantly active. SAR predicted that a larger substituent like 2-phenyl-3-methyl-quinazolin(3H)4-one is favorable for anti-JEV activity[70].

Conclusion:
Triazole is an exclusive moiety which is accountable for numerous pharmacological activities. Out of the two triazoles, 1,2,4-triazole have drained pronounced consideration due to its broad spectrum activities, little toxicities and great pharmacokinetic and pharmacodynamic profiles. This article featured research efforts of numerous researchers stated in literature for various antimicrobial activities on synthesized triazole compounds. 1,2,4-triazole containing ring framework have been incorporated into a varied therapeutically interesting drug candidates including antibacterial, antimycobacterial, antifungal, antiviral agents. To overwhelm the rapid development of drug resistance, new agents should preferably have precise chemical features that evidently vary from those of existing agents. To assess additional activities of triazole for many diseases, whose treatments are difficult, more investigations must be carried out furthermore.

REFERENCES
8. Guzeldemirci NU, Kucukbasmaci O. Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles.
22. Ilango K, Valentina P. Synthesis and biological activities of novel 1,2,4-triazolo-[3, 4-b]-1,3,4-thiadiazoles. Der Pharm Chem 2010;2(2):16-22.
38. Bekircan O, Menteş E, Ucker S. Synthesis of some new 1,2,4-triazole derivatives starting from 3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4H-1,2,4-triazol with anti-lipase and anti-urease activities. Archiv Der Pharm 2014;347:387–397.


54. Chu CH, Hui XP, Zhang Y, Zhang ZY, Li ZC, Liao RA. Synthesis and antifungal activities of 6-([4-Aryl-4-(1-phenyl-5-methyl-1,2,3-triazol-4-yl)]-1,2,4-triazol-3-thio)-6-(1H-1,2,4-triazol-1-yl)acetophenones. J Chin Chem Soc 2001;48(1):121–125.


70. Pandey VK, Tusi Z, Tusi S, Joshi M. Synthesis and biological evaluation of some novel 5-{[3-arylalkyl amido/iminodialkyl] phenyl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines as antiviral agents. ISRN Org Chem 2012; 1