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Original Article

A Brief Review on Antitubercular Activity of Pharmacological Active Some Triazole Analogues

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ABSTRACT

Triazole is a five member heterocyclic nucleus has attracted a wide consideration in exploration for the new remedial agents. This nucleus acts very important role in biological fields for various biologically active molecules. The chemistry of triazole compounds has expected considerable interest due to their synthetic and effective biological properties likes analgesic, antinflammatory, antioxidant, analeptic, sedatives, antianxiety, antimicrobials, anticonvulsant, anticancer, and other biological activities. There are various known drugs in market containing the triazole moiety likes voriconazole, triazolam, fluconazole, intraconazole, furacylin, alprazolam, etizolam etc. This review supplied a concise outline on triazole compounds as an antitubercular molecule. Because present antitubercular drugs are more toxic and multiple drug therapy is required. So it is significant to find out the triazole analogues with excellent antitubercular activity.

Keywords: Antitubercular agents, Triazole derivatives, Pharmacological activities.

INTRODUCTION

Nitrogen enclosing heterocyclic compounds has been draw growing attention because of their usefulness in various types of applications. Due to the search for innovative biological active compounds is one of the most demanding tasks to the researchers. The nitrogen containing heterocyclic compounds have been attracted to numerous chemical scientists. The triazole moiety is one of the most significant five member heterocycle compound which is a quality of natural and synthetic compounds. Triazole and its various derivatives have a extensive range of purposes. They are principally surrounded by the type of compounds used such as antimicrobial, antifungal, antiviral, anti-inflammatory, analgesic, antiepileptic,

antihypertensive, antimalarial, antioxidants, antihistaminic, antianxiety, antidepressant, and antitubercular agents etc[1-5]. Triazole derivatives are also used as optical corrosion inhibitors, brightening agents, and as additives with a variety of other purposes. Various pigments and dye stuffs have this heterocyclic nucleus. The significances of triazole derivatives have good position in the field heterocyclic chemistry, due to its various types of biological activities. This nitrogen containing heterocyclic compounds are found in abundance in most of the medicinal compounds. The triazole has established substantial awareness due to their synthetic and effective biological significance. There are two probable isomers of triazole depending on the location of nitrogen atom in the moiety[6-12]. Triazole derivatives have drawn huge attention to chemists due to its broad diversity of activities, low toxicity and high-quality pharmacokinetic and pharmacodynamic outlines.

Chemistry

Triazole is also recognized as pyrrodiazole. It is an organic heterocyclic compounds having a five membered di-unsaturated ring structure. It composed of three nitrogen atoms and two carbon atoms at non-adjacent positions in their ring structure. The simplest structure of the triazole family is triazole itself. Triazole is a crystalline solid, white to pale yellow colour, weakly basic compound, characteristic odour. It is soluble in water and alcohol and melting point (MP) 120°C and boiling point (BP) at 260°C. It occur as a pair of chemically isomeric compounds 1, 2, 3-triazole (1) and 1, 2, 4-triazole (2) with molecular weight of 69.06 and molecular formula $C_2H_3N_3$[12-15].

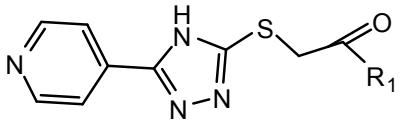

1, 2, 4 triazole 1, 2, 3 triazole

Pharmacological actions

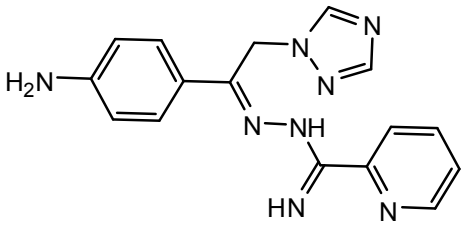
The triazole compounds are versatile and have been characteristics in various clinically used drugs. The most appropriate studies have exposed that triazole derivatives have extensive spectrum pharmacological behaviors such as antimicrobial, anti-inflammatory, analgesic, anti convulsant, antimalarial, antiviral, antiproliferative, anticancer and various other pharmacological activities[15-20]. Nowadays research is concentrated towards the introduction of new and safe therapeutic agents for clinical importance. The achievement of imidazole moiety as an essential moiety of various medicinal agents guided to introduction of the triazole compounds. The triazole compounds are said to be the isosters of imidazole compounds in which the carbon atom of imidazole is isosterically substituted by nitrogen atom.

Antitubercular activity

Tuberculosis (TB) is an infection disease and caused by a Gram positive bacteria called *Mycobacterium tuberculosis*. The *M. tuberculosis* frequently attacks the lungs, but they can also harm other parts of the body[21]. Some 1, 2, 4-triazole analogues (1) were reported as anti-TB agents[22]. The N`-[1-aryl-2-(1H-imidazol-1-yl and 1H-1, 2, 4-triazol-1-yl)-ethylidisne]-pyridine-2 carbo -xamidrazone derivatives (2) and evaluated their anti-TB activity[23].

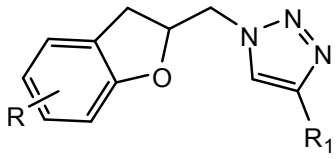


1R_1= -4-Chlorophenyl, 4-Nitrophenyl, 3-Nitophenyl, 2, 6-Dichlorophenyl, 2, 6-Dimethylphenyl.

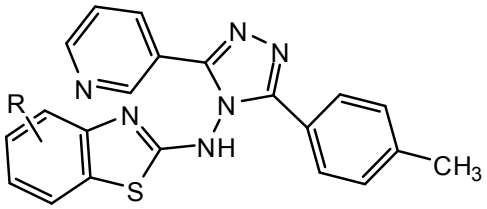


2 R = H, C_6H_5

Different 1, 4-Disubstituted-1, 2, 3-triazoles (3) has been developed and screened for anti-TB activity against *M. tuberculosis* H37Rv and exhibited anti-TB activities with MIC ranging from 12.5 to 3.12 ug/ml[24]. Newly 1, 2, 4 triazoles analogs has been synthesized and carried in vitro anti-TB activity against *M. tuberculosis* H37Rv strain. Compound 3-(3-pyridyl)-5-(4-methylphenyl)-4-(*N*-4-chloro-1, 3-benzo thiazol-2-amino)-4*H*-1, 2, 4 triazole (4) was exhibited improved antitubercular activity than reference drug rifampicin[25].

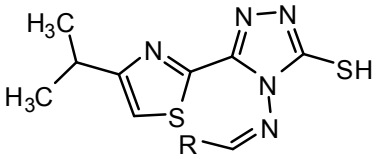


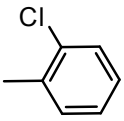
3 R= -4CHO, -2,5-Di-CH_3; R_1= -$(CH_2)_4CH_3$, -C_6H_5, -CH_2OH.



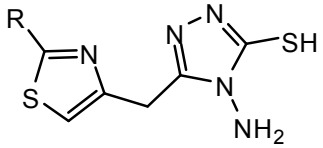
4 R= -4Cl

A series of 2-substituted-5-[isopropyl thiazole] clubbed 1, 2, 4-triazole and 1, 3, 4-oxadiazole were evaluated for their anti-TB activity against *M. tuberculosis* H37Rv strain by broth dilution assay method, compound 4-(2-chlorobenzylidene amino)-5-(4-isopropylthiazol-2-yl)-4*H*-1, 2, 4-triazole-3-thiol (5) were exhibited considerable anti-TB activity[26]. A series of *N*-{4-[(4-amino-5-sulfanyl-4*H*-1, 2, 4-triazol-3-yl)methyl]-1, 3-thiazol-2-yl}-2-substituted-amides (6) were also exhibited[27] preliminary *in vitro* antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhus* and were also evaluated as anti-TB activity against *M. tuberculosis* H37 Rv strain by broth micro dilution assay method. The antibacterial statistics of the tested compounds showed that most of the synthesized compounds were showed better antibacterial activity against different bacteria strains and compared to reference drugs. The *in vitro* anti-TB activity also reported that the tested compounds against *M. tuberculosis* strain H37 Rv showed moderate to better activity. The thiazolyl-triazole derivatives (7) were investigated of their anti-TB and antimicrobial activities[28]. Various compounds have shown promising anti-tubercular activity while others were inactive.

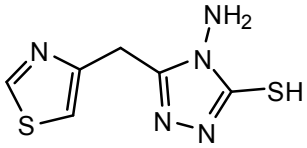




5 R=

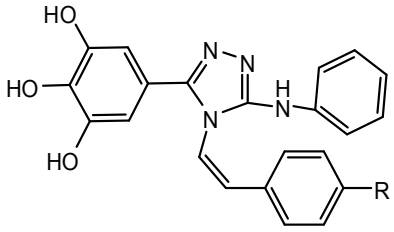


6 R = H, CH3, NH2, NHCH3

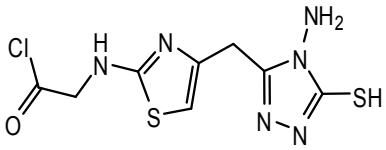


7

Various derivatives of substituted 1, 2, 4-triazol-(3-yl) benzene-1, 2, 3-triol derivative (8) and screened them for anti-tubercular activity. It was found that compounds 8a and b possess comparable activity with that of standard drug Rifampicin against M. tuberculosis. The remaining compounds were found less active than reference drug[29]. The thiazolyl-triazole analogues (9) were developing new molecules with enhanced effectiveness for treating M. tuberculosis H37Rv strain infections and with decreased drug resistance. They also investigated them for their anti-TB activities. Numerous compounds have shown promising activity against Mtb. The 1, 2, 4-triazole substitutes are showing antitubercular effects such as α-[5-(2-furyl)-1, 2, 4-triazoles-3ylthio] acehydrazide (10) and other related compounds were also showing anti-tubercular activities. Mannich-bases of substituted triazoles are also exhibited good antibacterial activities[30].



8a R= NO_2; 8b R=OH



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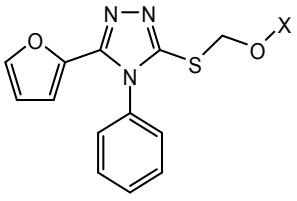

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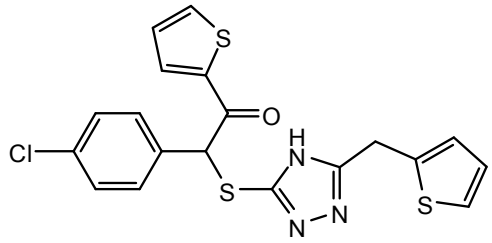
Some 3-alkylsulphanyl-1, 2, 4-triazole derivatives **(**11**)** and evaluated them for anti-TB activity. Antitubercular effects of the compounds was evaluated against *M. tuberculosis* H27Rv at 6.25 µg/mL and the evaluated compounds exhibited significant inhibition ranging from 58-84 %[31]. A series of quinoline derivatives possessing triazolo **(**12**)** ureido and thioureido substituents and evaluated their anti-TB properties. Three compounds inhibited *M. tuberculosis* H37Rv up to 96%, 98% and 94% respectively, at concentration of 6.25µg/ml. the minimum inhibitory concentration (MIC) value is 3.125µg/ml was observed for two of the tested compounds while for one compound was found to be MIC value 6.25 µg /ml[32].



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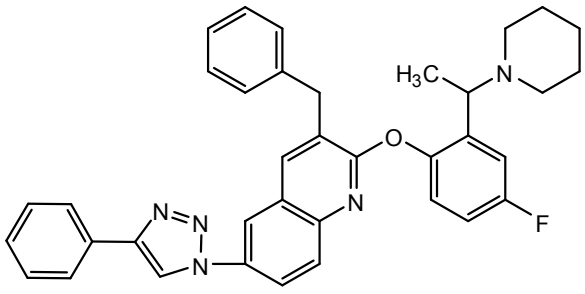

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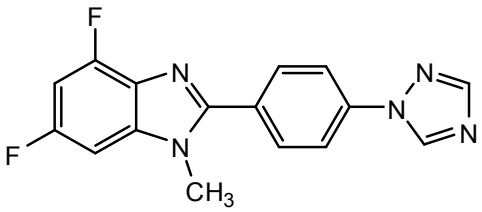
A series of 2-[4-(1*H*-[1, 2, 4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1*H*benzo[d] imidazole derivatives **(**13**)** for their preliminary *in-vitro* antibacterial activity against *P. aeruginosa*, *E. coli*, *S. aureus*, and *S. typhus* and then these compounds were screened for their anti-TB activity against *M. tuberculosis* H37Rv strain. The antibacterial

data suggested that the analogues with electronegative substituents emerged as the most promising antimicrobials. A few of the selected analogues are under further evaluation for secondary anti-TB screening, as they have shown better activity when compared to rifampin[33].



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DISCUSSION

Triazole ring can be used as an attractive pharmacophore to produce innovative functional drug molecules, providing a convenient and efficient pathway to build up a variety of bioactive and useful molecules. The triazole ring is also an important isostere of imidazole, oxazole, pyrazole, thiazole, amide moiety in designing various types of new drug molecules. A large number of triazole derivatives have been extensively prepared and investigated for their biological activities, which is one of the most active areas in the researches and developments of new drugs[34-38]. Triazole nucleus have been included into a ample array of therapeutically attractive drug applicants including anti-inflammatory, anticancer, antimicrobial, anti fungal, central nervous system (CNS) stimulants, sedatives, antianxiety, antidepressant, antiviral, and other related biological activities. Particularly, triazole compounds as antifungal drugs have been playing a quite important role in the treatment of fungous infection. Triazole analouges with strong pharmacological activities, low toxicities or adverse effects, less drug resistances, high bioavailability, good pharmacokinetics and drug-targeting, diversity of drug administration, broad spectrum, better curative effect have been frequently becoming clinical drugs or candidates for the management of diverse types of diseases[39-42]. All these showed extensive potential of triazole-based compounds as therapeutic agents.

CONCLUSION

Triazole analogues have paying attention in the fields of chemical, medicine and agrochemical research area, due to it's exclusively structures and chemical properties. Triazole and its analogues belong to a class of remarkably active compounds having different types of pharmacological properties. Triazole compounds have finalized much significance as they have also been explored for their diverse biological activities. Different new and potent compounds will prepared to explore more effective and potent molecule by substitution of different atoms or groups on triazole ring with different pharmacological activities.

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Table 1. Physical properties of 1, 2, 3-triazole and 1, 2, 4-triazole

S. No.	1, 2, 3-triazole ring moiety	1, 2, 4-triazole moiety
1	Molecular formula-$C_2H_3N_3$	Molecular formula-$C_2H_3N_3$
2	Molar mass 69.0654	Molar mass-69.0654
3	Boiling point 203°C	Boiling point-260
4	Melting point 23-25°C	Melting point-120-121°C
5	Density 1.192 g/cm^{-3}	Density - 1.394 g/cm^{-3}
6	Appearance colourless liquid	Appearance white solid
7	Solubility in water very soluble	Solubility in water very soluble
8	Alkalinity (p*K*b) 9.4	Alkalinity (p*K*b) 10.3
9	Acidity (p*K*a) 1.2	Acidity (p*K*a) 2.2
10	Vapour Pressure 0.4 mmhg (at 25°C)	Vapour Pressure 0.02 mmhg (at 25°C)