Review Article

A Review on Synthesis and Biological Activity of 1,2,4-triazole Derivatives

Lala Ram Jat[1], Dr. Vandana Sharma[2], Richa Agarwal[3]
[1,3]Associate Professor, Biyani Institute of Pharmaceutical Sciences, Jaipur, India.
[2]Principal, Arya College of Pharmacy, Jaipur, India.
***Corresponding author's E-mail:** lalaramjat12@gmail.com

Received: 08-01-2023; **Revised:** 23-02-2023; **Accepted:** 28-02-2023; **Published on:** 15-03-2023.

ABSTRACT

Recently, various novel heterocyclic compounds and their derivatives have been synthesized and their biological functions have been studied. Even though the triazole moiety seems to be extremely small, many researchers are interested in this scaffold because of its biological profile and its various potential uses. Numerous pharmacological actions, including as antibacterial, antiviral, anticancer, anticonvulsant, and antifungal, are associated with the 1,2,4- triazole nucleus. This article provides an overview of 1,2,4-triazoles and their derivatives. A general synthetic approach is described along with a literature review of the steps involved in the preparation of 1,2,4-triazoles.

Keywords: Triazole, Heterocyclic chemistry, antifungal activity, anticonvulsant activity.

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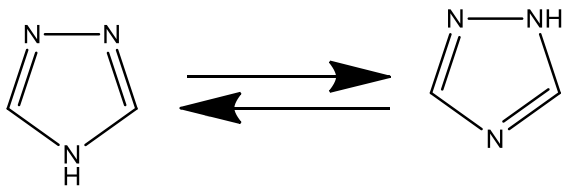
DOI: 10.47583/ijpsrr.2023.v79i01.016

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v79i01.016

INTRODUCTION

Triazoles are five-membered rings with the chemical formula $C_2H_3N_3$, which have two carbon & three nitrogen atoms. There may be an equilibrium between the *1H*-form and the *4H*-form of the 1, 2, 4-triazole ring (1a and 1b). The 1H tautomer is preferred over the 4H tautomer, according to computed energy differences between the azole tautomers.[1]



4H form 1a ⇌ *1H* form 1b

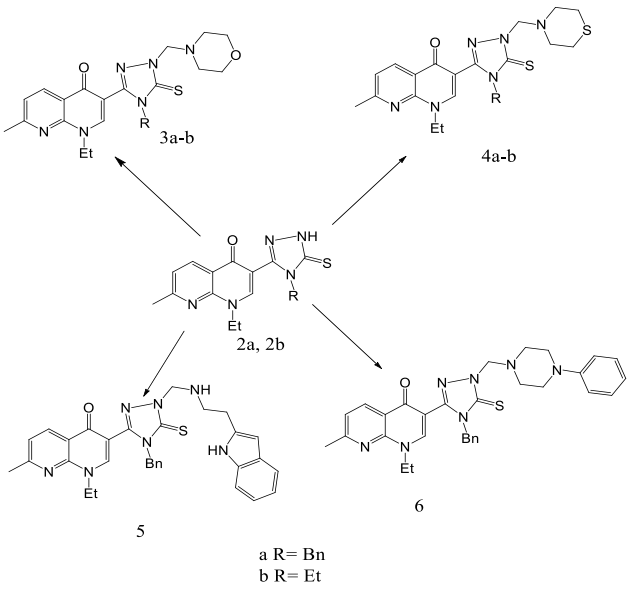
Figure 1: 1H-form and 4H-form of 1,2,4-triazole

Because of their versatility in synthesized processes and broad-spectrum bio-activity, 1,2,4-triazoles and their fused heterocyclic compounds have attracted considerable interest in recent years[2]. Numerous therapeutically significant drugs include the 1,2,4-triazole nucleus. Itraconazole, fluconazole, voriconazole, etizolam, triazolam, alprazolam and furacilin are examples of drug called to include 1,2,4-triazole rings. Other examples include ribavirin, hexaconazole, triadimefon, myclobutanil, rizatriptan, and fluotrimazole[3]. A unique class of heterocyclic chemicals called triazoles has a wide range of biological functions. For instance, information from earlier studies revealed that the 1,2,4-triazole moiety possesses various pharmacological activities, including antimicrobial[4], anti-bacterial[5], antifungal[6], anti-bacterial, antifungal[7], anticancer[8], antiviral[9], antitubercular[9,10], antimycotic activity[11], anticonvulsants[12], anti-inflammatory and analgesic[13], antinociceptive[14]. Triazoles are also used both before and after harvest to treat a number of mycosis of fruits, vegetables, legumes and grain crops[15-17].

Their antifungal activity has a biological basis in the inhibition of ergosterol biosynthesis, which prevents the formation of fungal cell walls. They are steroid demethylation inhibitors as which also inhibit sterol 14 - demethylase. It is an inhibitor of chloroplast and mitochondrial function is 3-amino-1, 2, 4-triazole[18].

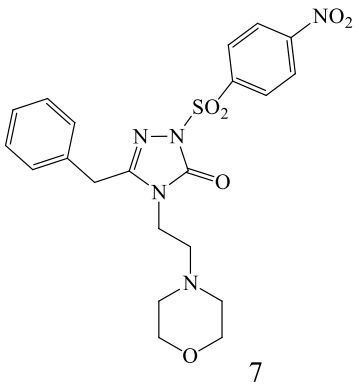
Synthesis of 1,2,4-triazole derivatives

Novel 1,2,4-triazole compounds with a nalidixic acid skeleton were synthesised using microwave assistance and traditional methods, according to S. Ceylan et al.[19]. It is generally recognised that by combining two biologically more active components into a single molecular framework, a more potent anti-bacterial molecule can be produced. This research aimed to modify the nalidixic acid skeleton by adding the 1,2,4-triazole moiety. The matching Mannich bases 3-6 comprising various pharmacophore groups were produced when compounds 2a and 2b interacted with a number of heterocyclic amine compounds in the presence of formaldehyde.



In accordance with the results of the antimicrobial screening, substances comprising norfloxacin, ciprofloxacin, or the 7-aminocephalosporanic acid system exhibit high antibacterial activity. Several compounds are more effective against M. smegmatis and E. coli than the common antibiotics ampicillin and streptomycin.

D. Sahin et. al.[20] synthesised derivatives of 1,2,4 triazoles with a morpholine nucleus. Compound 7 was the newly created compound that was most effective against the majority of the test bacteria.



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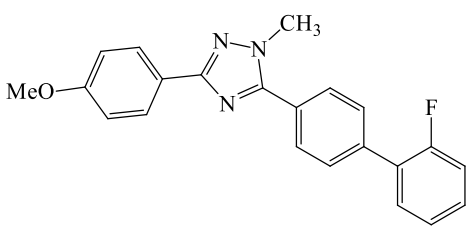
Some selected antibacterial activity of 1,2,4-triazole derivatives against common, environmental, and medicinal bacterial strains was assessed by Jacob H. J. et al.[21] The most effective of these 1,2,4-triazole compounds, compound 7, was shown to have activity against antibacteria comparable to penicillin G against B. cereus and more than penicillin G (the positive control) against P. aeruginosa.



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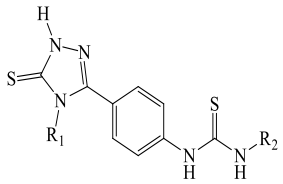
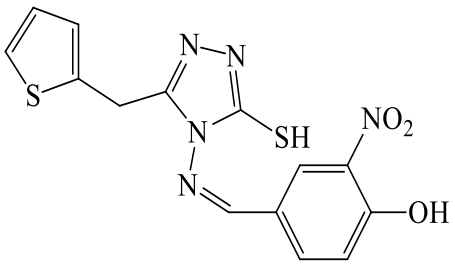
Mycobacterium fortuitum ATCC 6841, rapidly proliferating opportunistic pathogen, and Mycobacterium tuberculosis H37Rv were investigated for antimycobacterial action by Kucukguzel et al.[22] using certain 3-Thioxo/Alkylthio-1,2,4 triazoles that have substituted thiourea nucleus. Compounds 9 & 10-12 were discovered to have a MIC value against M. fortuitum ATCC 6841 that was identical to tobramycin's.



9 $R_1 = CH_3$ and $R_2 = C_6H_{11}$
10 $R_1 = CH_2CH{=}CH_2$ and $R_2 = CH_2CH{=}CH_2$
11 $R_1 = CH_2CH{=}CH_2$ and $R_2 = C_6H_5$
12 $R_1 = C_6H_{11}$ and $R_2 = CH_2CH{=}CH_2$

Ozdemir et al.[23] reported the BACTEC 460 radiometric system and BACTEC 12B medium, some novel 4-arylidenamino-4H-1,2,4-triazole-3-thiols were synthesised and their antitubercular action against Mycobacterium TB H37Rv (ATCC 27294) was evaluated. At 6.25 mg/mL with an 87% inhibition, compound 13 displayed an intriguing activity.



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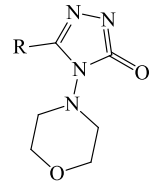
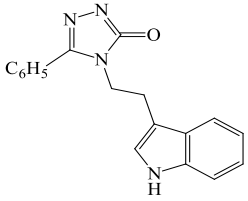
Demirbas, N., et al.[24] some new 1,2,4-Triazole compounds have been synthesized and their antimicrobial activities have been tested. While derivatives 15 and 16 demonstrated good antimicrobial activity against the test microorganisms, including E. aerogenes (En), S. aureus (Sa), E. faecalis (Ef), and B. careus, newly synthesised compounds 13 and 14 demonstrated moderate antimicrobial activity against E. coli (Ec) and K. pneumoniae (Kp) (Be). While compounds 17 and 18 showed good antibacterial activity against the examined pathogens.



13 R = $C_6H_4CH_2(P\text{-})$



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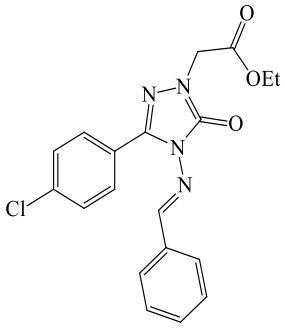

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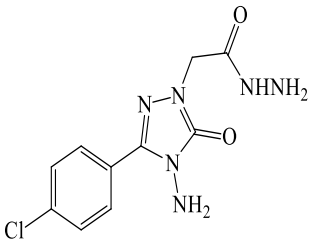

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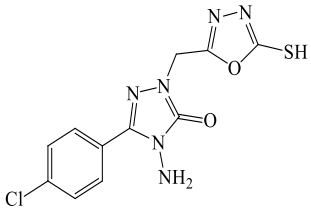

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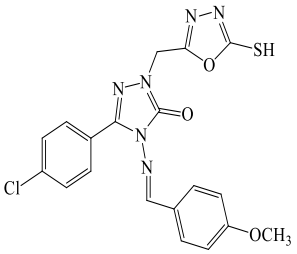
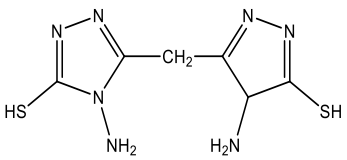


18

Abdulrasool M. M. et al.[25] developed a few heterocyclic derivatives with a 1,2,4-triazole moiety had their biological activities tested. The biological activity of compounds 19, 20, and 21 against the four-bacteria E. coli, K. pneumonia (gram negative), S. aureus, and E. faecalis was higher than that of amoxicillin and lower than that of ceftriaxone (gram positive). Fluconazole is outperformed by compounds 19, 21, and 22 in terms of biological activity as antifungal drugs against Candida albicans.



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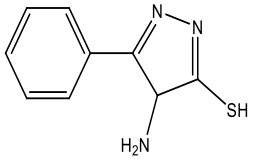

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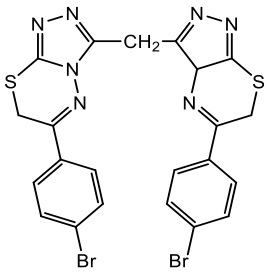

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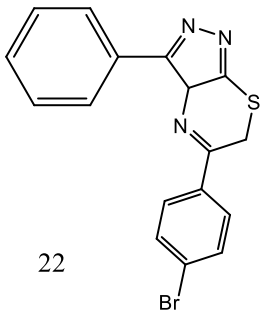
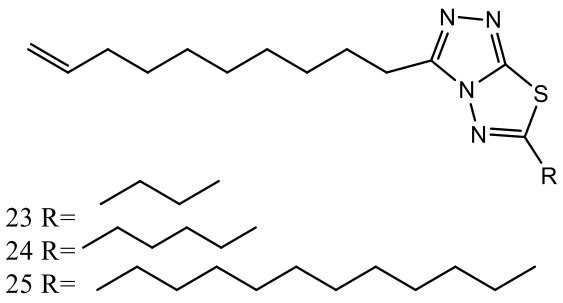


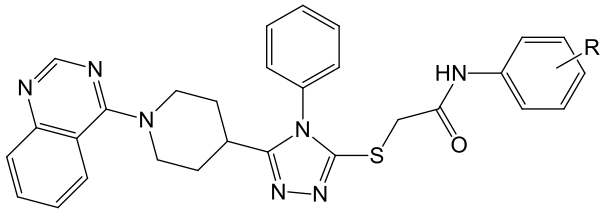
22

R. C. R. Jala et. al.[26] were prepared analogues of the 3,6-dialkyl-[1,2,4] triazolo-[3,4-b][1,3,4]-thiadiazole were tested for their antineoplastic and antimicrobial properties. The chemicals 23, 24, and 25 derivatives were shown to have positive antibacterial activity against the strains that were tested. While majority of the substances examined have cytotoxic action, with IC50 values ranging from 13.67 to 18.62 M, compounds 24 and 25 demonstrated substantial activity against SKOV3 and MCF-7 cell lines.



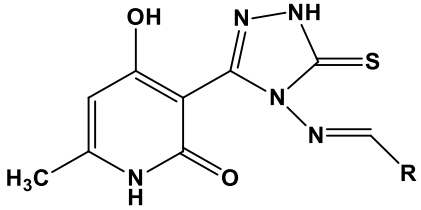
23 R=
24 R=
25 R=

New 1,2,4-triazole derivatives with quinazolinylpiperidinyl nucleus and the N-(substituted phenyl)-acetamide group were synthesised by X. P. Bao et al.[27] X. oryzae pv. oryzae (Xoo), a phytopathogenic bacterium, was demonstrated to have good to exceptional antibacterial activity against several of the target chemicals according to the bioassay results. When compared to the widely used bactericide Bismerthiazol (85.6 g mL-1), compounds 26, 27, 28, 29, and 30 showed EC50 values of 34.5-47.5 g mL-1.



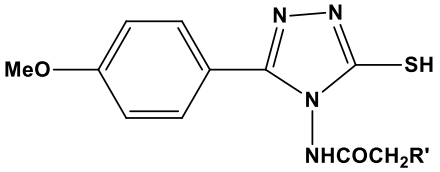
26 R= 2,4-di-F, 27 R= 3-F 28 R= 2-NO_2
29 R= 3- $COCH_3$ 30 R= 3-NO_2

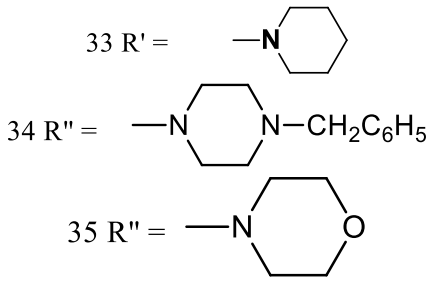
F.Y. Pan et.al.[28] new 3-[(4-hydroxy-6-methly-2(1H)-pyridinones)-3-yl] synthesised thione-containing -4-substituted (1H)-1,2,4-triazoles. When their in vitro anticancer activities were tested using the SRB and MTT procedures, the compounds 31 and 32 displayed greater activity than other compounds.



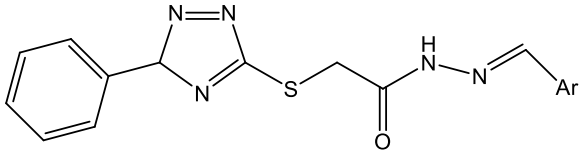
31 R= 2-OH-3,5-$(Br)_2$-C_6H_2 32 R= 2-OH-3,5-$(Cl)_2$-C_6H_2

4-(substituted ethanoyl) amino-3-mercapto-5-(4-methoxy) phenyl-1,2,4-triazoles have been studied for their anti-inflammatory and antinociceptive activities by N. Upmanyu et al.[29]. The most synthesised of these chemicals, 33, 34, and 35, have been shown to have the strongest anti-inflammatory activity. The most potent active derivative of these substances 35 showed promise antinociceptive efficacy.



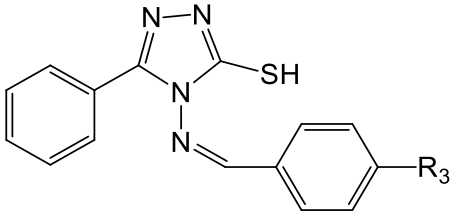


Dharmesh S. Dayama et. al.[30] synthesised some novel 1,2,4-triazole derivatives and evaluated for biological activity. Compounds 36 and 37 demonstrated the greatest antibacterial activity when compared to the other derivatives against all bacterial species, with a MIC of 200 g/ml. Compound 37 was discovered to be the most effective antifungal medication against C. albicans and A. niger.



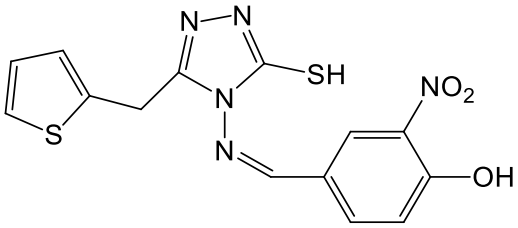
36 Ar = p-Cl-C_6H_5 37 Ar = OCH_3-C_6H_5

Sumitra Chanda et al.[31] created novel triazole compounds and tested their efficacy against microorganisms. The 1,4-Dioxan extraction of compounds 38 and 39 shown antibacterial activity against K. pneumoniae.



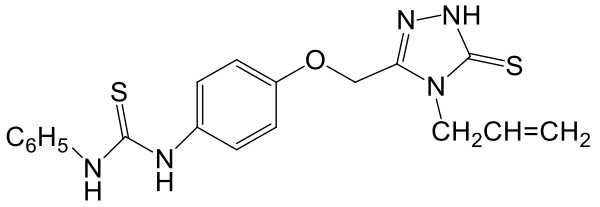
38 R_3 = 4-OCH_3 39 R_3 = 4-F

A. Ozdemir et al.[32] synthesised a few BACTEC 460 radiometric system and BACTEC 12B medium were used to assess the antituberculer activity of 4-arylidenamino-4H-1,2,4-triazole-3-thiol derivatives against Mycobacterium TB H37Rv (ATCC 27294). At 6.25 mg/mL, compound 40 shown an intriguing activity with an 87% inhibition.



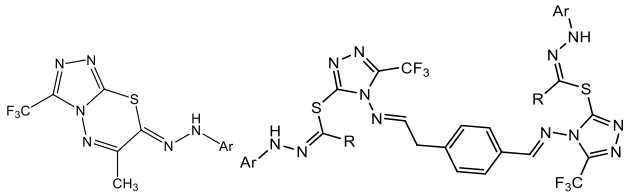
40

Kucukguzel et al.[33] developed new derivatives of thiourea from 5-[(4- aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and examined them for their effectiveness as antiviral/anti-HIV and anti-tuberculosis drugs. The most active derivative in this series is compound 41, which has a selectivity index of 5 and a MIC value of 16 mg/ml against Coxsackie virus B4. This drug was also effective against the Varicella-zoster virus, with an EC50 value of 9.9 mg/ml (TK VZV, OKA strain). The most effective chemical, compound 41, inhibited M. tuberculosis H37Rv by 79%.



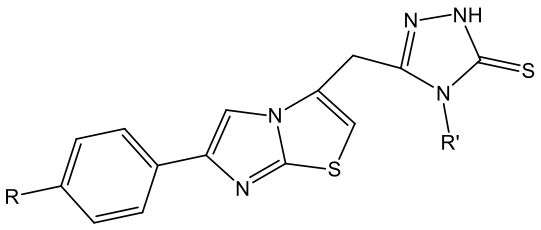
41

Farghaly et al.[34] synthesized a sequence of 1,2,4-triazolo-7-arylazo-5H-3-(trifluoromethyl)-6-methyl-[3,4-b] -1,3,4-thiadiazines. The results of testing some of the products for their anti-cancer potential are encouraging and show that compounds 42 and 43 are the most potent inhibitors of HEPG-2, while 42 and 44 are effective against HCT cell lines.



42 Ar = 4-$OCH_3C_6H_4$ 43 Ar = 4-$COCH_3C_6H_4$ 44 Ar = COOEt/ Ph

N. U. Guzeldemirci et al.[35] synthesised various hydrazinecarbothioamide 1,2,4-triazole derivatives and assessed their antifungal and antibacterial properties. They were tested against Trichophyton mentagrophytes var. erinacei NCPF 375, Microsporum gypseum NCPF 580, and T. tonsurans NCPF 245. They were also tested against S. aureus ATCC 29213, P. aeruginosa ATCC 27853, E. coli ATCC 25922, C. albican ATCC 10231, C. parapsilosis ATCC 22019, C. 45, 46, 49 and 50 exhibited highest antibacterial activity. Especially 45, 46, 47, 48, 50 exhibited the highest fungicidal activity against tested fungi.

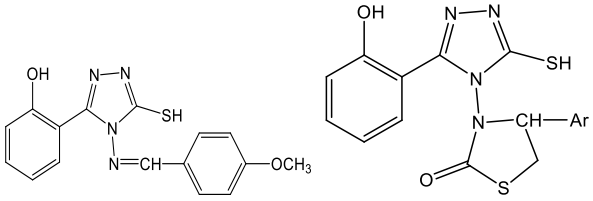


45 R = H, R'= C_3H_7 46 R = H, R'= C_6H_5 47 R = 4-ClC_6H_4

48 R= Cl, R' = C_3H_7 49 R= Cl, R' = Allyl 50 R = Cl, R' = C_6H_5

Pattan et al[36] produced a number of new 2- (4-substituted) 5 -mercapto-4H-1,2,4-triazol-3-yl)phenol and three-(3- (2-hydroxyphenyl) -5-mercapto-4H-1,2,4-triazol-4-yl) derivatives of thiazolidin-4-one with a 2 substitution. The synthesised compounds were tested for their ability to inhibit the growth of Aspergillus niger and Candida albicans as well as E. coli and S. aureus using the cup and plate agar diffusion method. Inhibition was powerfully

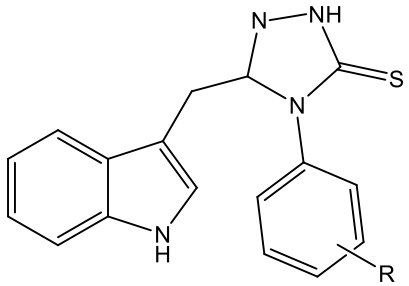
displayed by compounds 51, 52, and 53 against all bacterial and fungal species.



51 52

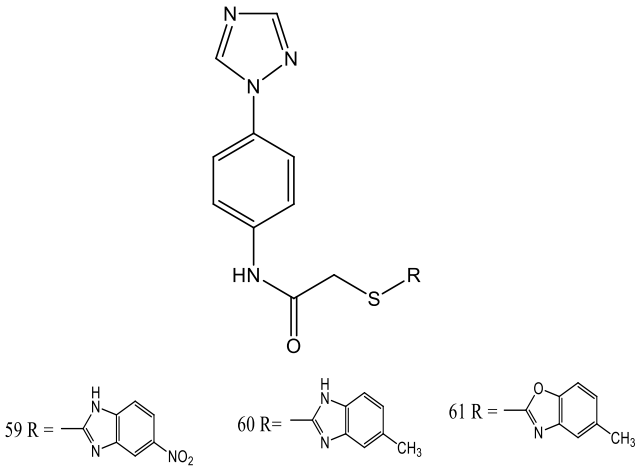
Ar = $3OCH_3$, $4\text{-}OHC_6H_3$ 53 Ar = $-OC_4H_3$

N. Siddiqui et al.[37] investigated a number of derivatives of the compound 5-(1H-indol-3-yl) methyl-4-(substituted aryl)-2,4-dihydro-3H-1,2,4-triazole-3-thione. All newly created compounds were tested for their anticonvulsant efficacy in the MES model and contrasted with the standard medications carbamazepine and sodium phenytoin. The following derivatives 55 and 58 showed approximate MES activity to phenytoin and carbamazepine after 0.5 h. Compounds 54, 56 and 57 showed lower neurotoxicity than phenytoin.

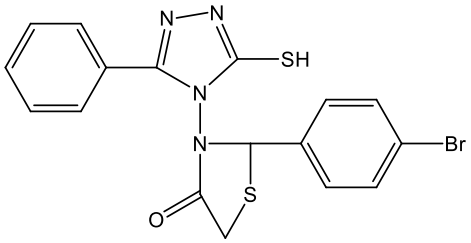


54 R = H, 55 R= 2-Cl, 56 R= $2\text{-}OCH_3$, 57 R= $4\text{-}OCH_3$, 58 R= $2\text{-}CH_3$

Yusuf Ozkay et al.[38] were synthesized to investigate the anticandidal and anticholinesterase properties of novel triazole compounds. Four distinct fungi strains were tested for anti-candidal activity. The anticandidal activity of compounds 59, 60, and 61 against Candida albicans (ATCC 90030) and Candida glabrata was modest (ATCC 10231).

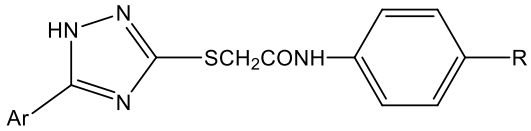


F. Hassan et. al.[39] were synthesized a number of triazole derivatives were created using cyclization reactions, and the anti-oxidant activity of these derivatives was assessed using the stable free radical 1,1-diphenyl-2-picryl-hydrazyl DPPH. In comparison to conventional ascorbic acid, which had an IC50 value of 5.84 g/ml, compound 62 was the most effective at all concentrations.



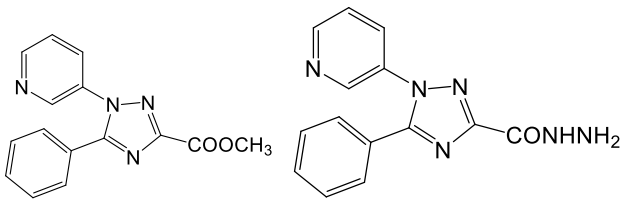
62

No. of N-Phenyl-2-(5-aryl-1H-[1, 2, 4] triazol-3-ylsulfanyl)-acetamides were synthesized by Radhika Chelamalla et al.[40]. Using a mouse tail suspension test, the newly synthesised compounds' antidepressant efficacy was assessed. Compounds 63 and 64 were the most active of the series.



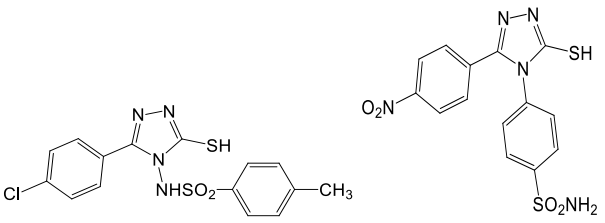
63 Ar = 4-OH Phenyl, R = H64 Ar = 23-OH Phenyl, R = H

S. M. Rabea et al.[41] were developed a number of derivatives of 5-phenyl-1-(3-pyridyl)-1H-1,2,4-triazole-3-carboxylic acid. At two dose levels, 5 and 10 mg/kg, compound 65 and compound 66 showed promising outcomes and were discovered to be equally potent as or more potent than indomethacin and celecoxib as standard medications. They also have no action that causes ulcers.



65 66

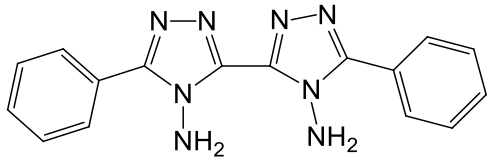
A series of 1,2,4-triazole derivatives have been synthesized by Pal et al.[42] The results revealed that compounds 67 and 68 exhibited good anti-bacterial action as compared with reference drug Ofloxacin.



67 68

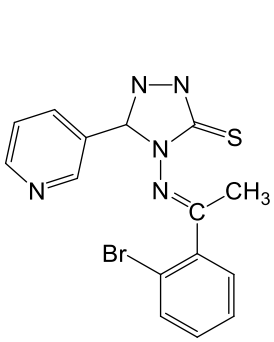
5,5'-diphenyl-4H- 4'H-3,3'-bi-1,2,4-triazole-4,4'- diamine was synthesized into a number of triazole derivatives by

Molkere et al.[43]. Compound 69 showed a maximum anti-inflammatory and antifungal activity.

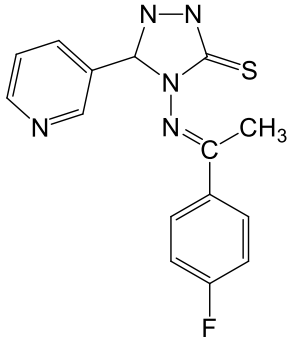


69

Sabiya Praveen et al.[44] a number of substituted 1,2,4-triazole compounds were synthesised, and their anticonvulsant and antibacterial effects were assessed using the MES model and the Cup-plate method. Significant antibacterial and anticonvulsant efficacy against E. coli was demonstrated by compounds 70 and 71.

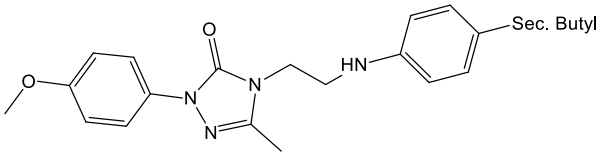


70

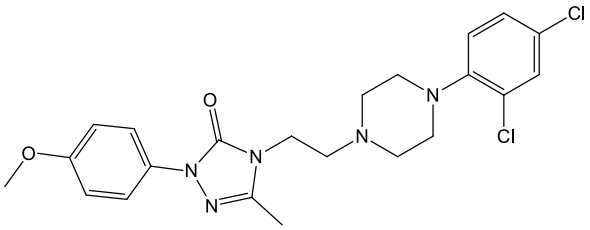


71

B. S. Patil et al.[45] have been prepared a series of some novel [1,2,4]-triazole derivatives. The anti-microbial activity of the recently synthesised compounds was estimated. Compound 72 demonstrated the most efficacy against S. aureus and E. coli, whereas compound 73 demonstrated the greatest activity against P. aeruginosa among all the derivatives.

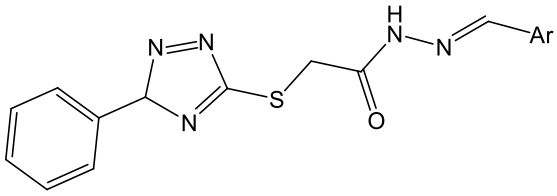


72



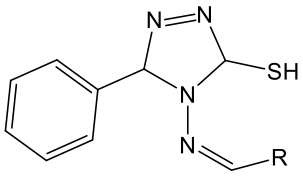
73

Dharmesh S. Dayama et al.[46] Synthesised and evaluated biological activity of some novel 1,2,4 triazole derivatives. With a MIC of 200 g/ml, compounds 74 and 75 showed the best antibacterial activity when compared to the other compounds against all bacterial species. The most efficient antifungal drug against Candida albicans and Aspergilus niger was compound 75.



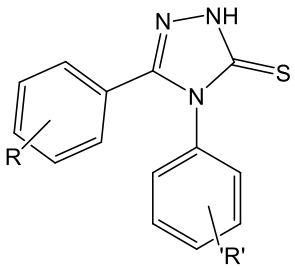
74 Ar = p-ClC_6H_5 75 Ar = p-$OCH_3C_6H_5$

Singh et al.[47] were designed and synthesised new bioactive 1,2,4-triazoles and screened for antitubercular and antimicrobial activity. While compounds 76, 77, and 78 were found to be more effective than isoniazid against clinical isolates of S, H, R, and E resistant M. tuberculosis, compound 77 and compound 78 had superior antitubercular activity than the reference isoniazid against M. tuberculosis H37Rv strain. In comparison to ampicillin, compound 76 showed greater antibacterial activity against B. subtilis. The most effective antifungal activity in the series, comparable to that of regular fluconazole, was demonstrated by compound 78.



76 R = 4-FC_6H_4 77 R = 4-$CH_3C_6H_4$ 78 R = -CH=CHC_6H_5

I. Khan et al.[48] were reported some new 1,2,4-triazole and 1,3,4-thiadiazole compounds. Newly synthesized derivatives were evaluated for their urease inhibition and antioxidant activities. Compound 79 and 80 exhibited potent urease inhibitory activities.



79 R = 3-NO_2 R’ = 2,4-diCH_3 80 R = H R’ = 2,4-diCH_3

Z. Li et al.[49] was reported a number of modified D-glucopyranosyl residues were added to a variety of substituted-phenyl-1,2,4-triazol-3-thione analogues, and their antiproliferative properties were assessed. Against human MCF-7 and Bel-7402 cancerous cell lines, analogues 1 and 5 shown antineoplastic activity.

CONCLUSION

Due to their versatility in synthetic processes and broad-spectrum bioactivity, 1, 2, 4-triazoles and their fused heterocyclic compounds have attracted considerable interest in recent years. The various biological functions of 1,2,4-triazole derivatives are discussed in this review along with the structures of several compounds that have particularly strong biological activities.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.