IMPORTANT METHODS OF SYNTHESIS AND BIOLOGICAL SIGNIFICANCE OF 1, 2, 4-TRIAZOLE DERIVATIVES

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ABSTRACT

In the last few decades, several five membered heterocyclic compounds such as triazoles have been studied extensively owing to their interesting biological activities such as antimicrobial, antiviral, antitumor, anticonvulsant, antifungal etc. The five membered triazole ring exists in two isomeric forms i.e. 1, 2, 3-triazole and 1, 2, 4-triazole. The five membered 1, 2, 4-triazole ring exists in two tautomeric forms i.e. 1H-1, 2, 4-triazole, 4H-1, 2, 4-triazole collectively known as s-triazoles. The s-triazole derivatives possess extensive spectrum of biological activities such as antibacterial, antifungal, antitubercular, anxiolytic, anticonvulsant, anti-inflammatory, analgesic, anticancer, antioxidant activities. This diversity in the biological activity of 1,2,4-triazoles has attracted the attention of many researchers to explore this skeleton for its wide potential against several activities. This review contains various methods of synthesis of 1, 2, 4-triazole derivatives and their pharmacological activities.

Keywords: 1,2,4-Triazole, Methods of synthesis, Antibacterial, Antifungal, Anti-inflammatory, Anticancer, Anticonvulsant, Antioxidant, Antidepressant.

INTRODUCTION

Triazoles are the class of heterocyclic compounds which are under study since many a years. The five membered triazole ring exists in two isomeric forms i.e. 1, 2, 3-triazole and 1, 2, 4-triazole.
1,2,4-triazoles exists in two tautomeric forms. 1H and 4H-1,2,4-triazole is considered to be pharmacologically important nucleus.

Tautomers of 1,2,4-Triazole

Literature survey reveals that 1, 2, 4-triazole derivatives exhibit wide range of biological activities including antibacterial, antifungal, antitumour, anti-inflammatory, antitubercular, anti-convulsant, anticancer, antimalarial, antiviral, analgesic, antioxidant, antimalarial, and potassium channel activators.

Synthesis of 1, 2, 4-triazole and its derivatives

There are various methods for synthesis of 1, 2, 4-triazole are available in literature which involve conventional one pot, multi-components, microwave assisted, under free condition, regioselective. These methods can be summarized as below.

Scheme 1: C. Ainsworth and co-workers reported synthesis of 1, 2, 4-triazole (2) nucleus by the reaction of thiosemicarbazide (1) with formic acid forming 1-Formyl-3-thiosemicarbazide (2) as an intermediate. The reaction of 1-Formyl-3-thiosemicarbazide (16) with aqueous sodium hydroxide and hydrochloric acid yield 1,2,4-Triazole-3(5)-thiol (3) which on treatment with a mixture of water, concentrated nitric acid, and sodium nitrite finally produce 1,2,4-triazole (4) nucleus.
Scheme 2: S. Ueda, H. Nagasawa synthesized 1,2,4-triazole derivatives (5) by treatment of substituted amidine and benzonitrile in the presence of copper-catalyst under an atmosphere of air by sequential N-C and N-N bond-forming oxidative coupling reactions. Starting materials and the copper catalyst are readily available and inexpensive. A wide range of functional groups are tolerated.

\[
\text{Scheme 2: } \text{R. alkyl, Ph, } \text{NMe}_2
\]

Scheme 3: Pellizzar and co-workers reported synthesis of substituted 1, 2, 4-triazole (8) by the reaction of an amide (6) and a hydrazide (7).

Scheme 4: G. M. Castanedo, and co-workers, provided a highly regioselective one-pot process which provides rapid access to highly diverse 1,3,5-trisubstituted 1,2,4-triazoles (11) from reaction of carboxylic acids (9) and primary amidines (10).
Scheme 5: D. V. Batchelor and co-workers\textsuperscript{23} reported synthesis of 3-N, N-Dialkylamino-1, 2, 4-triazole (14) from S-methylisothioureas (12) and acyl hydrazides (13) in presence of trifluoroacetaldehyde and tetrahydrofuran. 3-N, N-Dialkylamino-1, 2, 4-triazole (14) obtained in good yields. The reaction conditions are relatively mild and tolerate a broad range of functional groups.

\[
\begin{align*}
\text{R} & = \text{alkyl} \quad \text{R}' = \text{alkyl} \quad \text{R}'' = \text{alkyl, aryl} \quad \text{R}''' = \text{alkyl} \\
\end{align*}
\]

Scheme 6: L. Y. Wang and co-workers\textsuperscript{23} carried out an effective 1,3-dipolar cycloaddition for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole (17) derivatives by reaction of oximes (15) with hydrazonoyl hydrochlorides (16) using triethylamine as a base gave the desired 1,3,5-trisubstituted 1,2,4-triazoles (17) in good yields. The reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates.

Scheme 7: P. Yin and co-workers\textsuperscript{24} synthesized 1, 2, 4-triazole derivatives (20) by the reaction of substituted methyl N-cyanoarylimidate (18) and phenylhydrazine (19). N-cyanoarylimidate was prepared by mild, one-pot cyanoimidation of aldehydes using cyanamide as a nitrogen source and NBS as an oxidant and was achieved in high yields without the addition of a catalyst.
Scheme 8: E. Huntsman and co-workers\textsuperscript{25} synthesized substituted 1, 2, 4-triazolo [1, 5-a] pyridine (23) from 2-Aminopyridines (21) in good yields by cyclization of N-(pyrid-2-yl)formamidoximes (22) under mild reaction conditions with trifluoroacetic anhydride (TFAA) and tetrahydrofuran (THF).

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{H} \\
\text{21} & \quad \text{reflux, 3 h} & \quad \text{N} \quad \text{H} \\
\text{22} & \quad \text{MeO} & \quad \text{23} & \quad \text{MeO}
\end{align*}
\]

Scheme 9: S. Ueda and co-workers\textsuperscript{19} prepared 1, 2, 4-triazole derivatives (26) from the reaction of substituted pyridine-2-amine (24) and substituted nitrile (25). It is a copper-catalyzed reaction takes place in the presence of 1, 10-phenanthroline, zinc iodide and 1, 2-dichlorobenzene.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{H} \\
\text{24} & \quad \text{N=Ar} \\
\text{25} & \quad \text{5 mol-% CuBr} \\
\text{26} & \quad \text{5 mol-% 1,10-phenanthroline}
\end{align*}
\]

Scheme 10: Johannes Thiele and co-workers\textsuperscript{26} synthesized 4-Phenyl-1, 2, 4-triazole-3, 5-dione (PTAD) (33) an azodicarbonyl compound, first synthesized in 1894. PTAD is one of the strongest dienophiles and reacts rapidly with dienes in Diels-Alder reactions. The synthesis starts from diethyl carbonate (28) and hydrazine. The product (29) of this step is reacted with phenyl isocyanate and subsequently transformed to compound (31). Cyclization of compound (31) and subsequent oxidation of 4-Phenylurazol (32) formed with lead tetroxide in sulfuric acid yields PTAD (33).
Scheme 11: A. Reichelt and co-workers\(^{27}\) performed an efficient and convenient synthesis of [1,2,4]triazolo[4,3-\(a\)]pyridines(36) involving a palladium-catalyzed addition of hydrazides(34) to 2-chloropyridine,(35) which occurs chemoselectively at the terminal nitrogen atom of the hydrazide, followed by dehydration in acetic acid under microwave irradiation.

Scheme 12: Rahman Shah Zaib Saleem and co-workers\(^{28}\) synthesized 1, 2, 4-triazole derivative from substituted oxazolone (37) and azodicarboxylate (38) to yield 1, 2, 4-triazolines (39). Subsequent treatment of these 1, 2, 4-riazolines with NaOH gives corresponding triazoles (40).

Scheme 13: Y. Xu and co-workers\(^{29}\) synthesized a series of new oxamide-derived amidine reagents in excellent yield with minimal purification necessary. A subsequent reaction of these reagents with various hydrazine hydrochloride salts efficiently generated 1,5-disubstituted-1,2,4-triazole compounds in good yields. Both aromatic and aliphatic hydrazines react readily with the amidine reagents under very mild reaction conditions.
Scheme 14: B. Wong, and co-workers synthesized 1,5-Disubstituted 3-Amino-1H-1,2,4-triazoles (46) from 1,3,4-Oxadiazolium Hexafluorophosphates (45). Hexafluorophosphoric acid promotes the formation of 1,3,4-oxadiazolium hexafluorophosphate salts (45) from N'-acyl-N-aryloyl-N-arylhydrazides or N'-acyl-N-aryl-N-arylhydrazides (44) under mild conditions. A subsequent reaction with cyanamide in propan-2-ol in the presence of triethylamine generates 1,5-disubstituted 3-amino-1H-1,2,4-triazoles in good yields.

Scheme 15: K. Mogilaiah and co-workers synthesized 9-aryl-6-(3-fluorophenyl)-1, 2, 4-triazolo[4,3-a][1,8] naphthyridines (48) from arylaldehyde 3-(3-fluorophenyl)-1,8-naphthyridin-2-ylhydrazones (47) using FeCl3·6H2O under solvent free conditions by microwave irradiation method.

Scheme 16: Olcay Bekircan and co-workers synthesized new bis-1, 2, 4-Triazole derivatives by the reaction of 3-Aryl-5-phenyl-4-amino-4H-1, 2, 4-triazoles (49) and bis-aldehydes (50) \( \{Y = (CH_2)_2; (CH_2)_3\} \) to yield 1,2/1,3-bis[o-(N-methylidenamino-3-aryl-5-phenyl-4H-1,2,4-triazole-4-yl)phenoxy]ethane/propane derivatives (51). Compounds (51) were reduced with NaBH4 to afford the corresponding 1, 2/1, 3-bis [o-(N-methylamino-3-aryl-5-phenyl-4H-1,2, 4-triazole-4-yl)phenoxy]ethane/propane derivatives (52).
BIOLOGICAL SIGNIFICANCES

The 1, 2, 4-triazole nucleus has been incorporated into a wide variety of therapeutically important agents. Ribavirin (antiviral)\(^{33}\), Rizatriptan ( antimigraine)\(^{34}\), Vorozole, Letrozole and Anastrozole (antitumor)\(^{35}\) Posaconazole, Fluconazole and Itraconazole (antifungal)\(^{36}-^{37}\) are some common examples of drugs containing 1, 2, 4-triazole moiety. A number of biological activities such as antibacterial, antifungal\(^{38}-^{39}\) anti-inflammatory, analgesic\(^{40}\) anticonvulsant\(^{41}\), anticancer\(^{42}-^{43}\) antitumor\(^{44}-^{45}\), antiviral\(^{46}\), antileishmanial\(^{47}\), potassium channel activators\(^{17}\), antiplatelet\(^{48}\) and anti-oxidant\(^{15}\) have been associated with N-substituted triazole attached with different hetrocyclic nuclei. It has been noticed continuously over the years that interesting biological activities are associated with triazole derivatives.

Antibacterial activity

V. Ram\(^{49}\) have synthesized triazole substituted triazolo-pyrimidine derivatives (53) and found to possess antibacterial activity. \(\{ R= \text{pyridyl} \}\)

Sahar MI Badr and Rasha M Barwa\(^{50}\) synthesized new series of fused 1,2,4-triazoles (54,55) such as, 6-(aryl)-3-(5-nitrofuran-2-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, 6-(alkyl/aryl amino)-3-(5-nitrofuran-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles and 6-(4-substituted phenyl)-3-(5-nitrofuran-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines have been synthesized via the reaction of 4-amino-5-(5-nitrofuran-2-yl)-4H-1,2,4-triazole-3-thiol 3 with various reagents such as hetero aromatic aldehydes, alkyl/aryl isothiocyanates and 4-substituted phenacyl bromides, respectively. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies. The newly synthesized triazole derivatives have been investigated for their in vitro antibacterial activity. Most of the tested compounds showed interesting antibacterial activity against Staphylococcus aureus.
Ying Jun Li and co-workers\textsuperscript{51} demonstrated a synthesis of novel series of 3,6-disubstituted 1,2,4-triazolo [3,4- b]-1,3,4-thiadiazoles (56) and evaluated for their antibacterial activity. Some compounds showed excellent antibacterial activity.

Vikrant S. Palekar and co-workers\textsuperscript{52} had reported synthesis of 1,4-bis(6-(substituted phenyl)-[1,2,4]-triazolo[3,4- b]-1,3,4-thiadiazoles and 4-bis(substituted phenyl)-4-thiazolidinone derivatives (57) and screened for their antibacterial activity. Several compounds showed potential antibacterial activity\textsuperscript{3}.

Gabriela Laura Almajan and co-workers\textsuperscript{53} reported synthesis of 3-[4-(4-X-phenylsulfonyl) phenyl]-6-(substitutedphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (58) and evaluated for their antibacterial activity. Some of compounds possessed good activity.
Stefania-Felicia Barbuceanu and co-workers\textsuperscript{54} had reported synthesis of 2-[(4-(4-X-phenylsulfonyl) phenyl) -6-(4-Y-phenyl)[1,3]thiazolo[3,2-b][1,2,4]triazoles (59) and screened for their antibacterial activity.

Tomasz Plech\textsuperscript{55}, demonstrated synthesis of 5-(3-chlorophenyl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones (60) and evaluated for their antibacterial activity. Some of the compounds showed good activity.

Nuray Ulusoy and co-workers\textsuperscript{56} established a synthesis of new N-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides (61) and tested for antimicrobial activity. One Compound showed anti-bacterial activity against some bacteria.
Antifungal Activity: Yan Zou and co-workers\textsuperscript{57} synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols (62) which are analogues of fluconazole, via Cu(I)-catalyzed azide-alkyne cycloaddition on the basis of computational docking experiments to the active site of the cytochrome P450 14a-demethylase (CYP51). The in vitro antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi. one of the Compound showed the best antifungal activities.

Monika Gupta and co-workers\textsuperscript{58} reported synthesis of 1- substituted-8-aryl-3-alkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines (63). The title compounds were screened for their antifungal activity.

Katica Colanceska-Ragenovic and co-workers\textsuperscript{59} synthesized a few 4-allyl/amino-5-aryl-1, 2, 4-triazoles(64,65) and tested for antibacterial and antifungal effects against Escherichia coli, Bacillus subtilis, Salmonella enteritidis, Staphylococcus aureus, Aspergillus niger and Candida albicans.
Qing Jie Zhao and co-workers\textsuperscript{60} reported a synthesis of 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-(Ncyclopropyl-N-substituted-amino)-2-propanol (66) derivatives and screened for their antifungal activity. Some of the title compounds had higher antifungal activity and broader antifungal spectrum than fluconazol.

P. Zoumpoulakis and co-workers\textsuperscript{61}, prepared a variety of 5-[2-(N-dimethylsulfamoyl)-4,5-dimethoxy-benzyl]-4-alkyl-s-triazole-3-thiones/3-ones (67) and screened for their antifungal activity.

Xiaoyun Chai and co-workers\textsuperscript{62} synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols (68) and evaluated for their antifungal activity. Some of the compounds showed excellent antifungal activity.
Nizamuddin and co-workers\textsuperscript{63} reported the synthesis of 2- Aryl/aryloxy methyl-1,3,4-oxa/thiadiazolo[4,5-b]1,2,4- triazolo[5,4-c]thiazolo-spiro-7-cyclohexanes (69) and investigated as fungicidal agents.

Qing-Yan Sun and co-workers\textsuperscript{64} prepared various 1,2,4-triazol-1-yl)- 2-(2,4-difluorophenyl)-3-[(4-substituted phenyl)- piperazin-1-yl)-propan-2-ols (70) and investigated for their antifungal potency.

Mitscher L.A and co-workers\textsuperscript{65} reported a novel 2-substituted-5-[isopropylthiazole] clubbed 1, 2, 4-triazole were synthesized as potent antifungal agent. The activity was shown by the compound (71), named 3-(4-Isopropylthiazol-2-yl)- 6-(4-nitrophenyl)-[1, 2, 4]triazolo[ 3, 4-b][1, 3, 4]thiadiazole
Anti-inflammatory activity: Ashraf M. and co-workers\textsuperscript{66} synthesized a series of ethyl 5-(un)substituted benzamido-1H-1,2,4-triazole-3-acetate from the amino guanidine bicarbonate and malonic acid and screened them for anti-inflammatory activity by carageenan-induced rat paw edema test and ulcerogenic effect.

Compound (72) showed higher anti-inflammatory activity than the 5-acylamino derivatives,

Birsen Tozkoparan and co-workers\textsuperscript{67} reported a series of 3-(methyl/ethyl sulfonyl) -5-aryl-1,2,4-triazole from 5-aryl-3- mercapto-1,2,4-triazole (73) and screened them for their anti-inflammatory and analgesic activity. Results shows that compounds having an alkylsulfone derivative were greater active than those of alkylthio group

J. Gowda and co-workers\textsuperscript{68} prepared 4-{{[1-substituted aminomethyl-4-benzylideneamino-5-sulfanyl-4,5- dihydro-1H-1,2,4-triazol-3-yl)methyl]-2H-1,4-benzothiazin-3(4H)-one} and derivatives. The compounds (74) were evaluated for their anti-inflammatory activity.
Mario Di Braccio and co-workers\textsuperscript{69} prepared 5-(alkylamino)-N-N-diethyl[1,2,4]triazolo[4,3-a][1,8]napthyridine carboxamide and its derivatives (75) and screened for their anti-inflammatory activity.

R.K. Mali and co-workers\textsuperscript{70} synthesized 5-(N-substituted carboxamidomethylthio)-3-(3'-pyridyl) - 1, 2, 4-triazole derivatives (76). Anti-fungal activity was carried out against C. albicans and A. niger at the concentrations of 50 and 100 µg/mL using Fluconazole as the standard.

Mari Sithambaram Karthikeyan and co-workers\textsuperscript{71} prepared series of 2-(2,4-dichloro-5-fluorophenyl)-6-(4-substituted phenyl)-1,3-thiazolo[3,2-b]-1,2,4-triazole and evaluated for their anti-inflammatory activity. Some compounds (77) exhibited excellent anti-inflammatory activity.
Xian-Yu Sun and co-workers\cite{72}, synthesized several new 6-alkoxy (phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives (78) and screened for their anti-inflammatory activity. Compounds (6-(2-chlorophenoxy) [1,2,4]triazolo[3,4-a]phthalazine-3-amine) and (6-(4-aminophenoxy)-[1,2,4] triazolo[3,4-a]phthalazine-3-amine) exhibited the highest anti-inflammatory activity.

Mihaela Moise and co-workers\cite{73} synthesized 4-substituted-5-[1-(p-nitrobenzoylamino)-2-phenyl-ethyl]-3-thio-1,2,4-triazole and evaluated for their anti-inflammatory activity. Compound (79) established an appreciable anti-inflammatory activity that is comparable with that of other nonsteroidal anti-inflammatory agents.

**Analgesic activity:** P. K. Goyal and co-workers\cite{74} reported a synthesis of 3-substituted-4-(3-disubstituted-1-triazenyl)-4H-1,2,4-triazol-5-thiol (80) and these compounds were evaluated for their analgesic activity. Some of the compounds showed excellent analgesic activity.
Umut Salgin-Goksen and co-workers\textsuperscript{75}, synthesized 5-methyl-3-((4-alkyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)benzo[d]oxazol-2(3H)-one (81) and evaluated for their analgesic activity.

Anees A. Siddiqui and co-workers\textsuperscript{76} synthesized some 4- {{1-(aryl)methylidene}-amino}-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole derivatives (82) starting from isonicotinic acid hydrazide, ethanol, potassium hydroxide and carbon disulphide and screened for analgesic, antipyretic activities.

A.M. Vijesh and co-workers\textsuperscript{77}, demonstrated synthesis of 4-{{[(E)-{4-[aryl]-1Hpyrazol-3-yl}methylidene] amino}-5-(substituted)-4H-1,2,4-triazole-3-thiol derivatives (83) and these compound screened for their analgesic and antimicrobial activity.
Anticonvulsant activity: Aniket and co-workers\textsuperscript{78} designed and synthesized the substituted N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone from nicotinic acid and evaluated them for anticonvulsant activity by Maximum Electroshock (MES) method and found that total recovery time and time for hind limb extension recovery for compound (84) was less than the standard (Phenytoin).

Li-Jun Guo and co-workers\textsuperscript{79}, reported synthesis of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives (85) and evaluated for anticonvulsant activity. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES) and the compound 5-hexyloxy-[1,2,4]triazolo[4,3-a]quinoline was the most potent anticonvulsant agent.

Hong Guang Jin and co-workers\textsuperscript{80} reported the synthesis of 7-alkoxy-4, 5- dihydro[1, 2, 4]triazolo[4, 3- a]quinoline1(2H)-ones (86) and investigated for anticonvulsant activity and neurotoxicity.
S. Moreau and co-workers\textsuperscript{81} reported the synthesis of 3- amino-7- (2, 6-dichlorobenzyl)-6-methyl triazolo[4, 3-b]pyridine derivatives (87) of amide and carboxylic acid and investigated for their anticonvulsant potency.

Nadeem Siddiqui and co-workers\textsuperscript{82} prepared a various 3-[4-(substituted phenyl)-1,3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thiones (88) and screened for their anticonvulsant activity. Two compounds showed significant anticonvulsant activity.

S. Botros and co-workers\textsuperscript{83} reported a synthesis of 3-[(4-Alkyl/aryl-5-sulphanyl-4H-1,2,4-triazol-3-yl) methyl]-5,5 diphenyl imidazolidine-2,4-dione derivatives (89) and evaluated for their anticonvulsant activity. Some of the compounds displayed promising anticonvulsant effect.
Sudhir N. Sambrekar and co-workers\textsuperscript{84}, synthesized various 3-substituted-4-Amino-5-Mercapto-4(H)-1, 2, 4-triazole derivatives (90) and evaluated for their anticonvulsant activity by Maximum electro seizures (MES) and Minimum electro threshold seizures (METS) methods.

\begin{center}
\includegraphics[width=0.5\textwidth]{90.png}
\end{center}

Dayanand Kadadevar and co-workers\textsuperscript{85} synthesized N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamo] acetamide derivatives (91) and tested for anticonvulsant activity by MES method.

\begin{center}
\includegraphics[width=0.5\textwidth]{91.png}
\end{center}

Tomasz Plech and co-workers\textsuperscript{86}, designed and synthesized 5-(3-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (92) and screened for anticonvulsant activity. Some of the compounds showed excellent activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{92.png}
\end{center}

Ali Almasirad and co-workers\textsuperscript{87}, synthesized series of 5-[2- (phenylthio)phenyl]-1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives (93) and evaluated for their anticonvulsant activity. Some of compounds had potent activity as compared to Diazepam.
Antitubercular activity

G.V. Suresh Kumar and co-workers synthesized some new 4-(substituted benzylideneamino)-5-(4-isopropyl thiazol-2-yl)-2-substituted-2H-1,2,4-triazole-3(4H)-thione and 3-(4-isopropylthiazol-2-yl)-5-thioxo-1H-(1,2,4-triazol-4(5H)-yl) substituted benzamides and 3-(4-isopropylthiazol-2-yl)-5-thioxo-1H-(1,2,4-triazol-4(5H)-yl) substituted benzamides (94) and evaluated for their antitubercular activity. Some of the compounds exhibited good antitubercular activity when compared with first line drug such as isoniazid.

Navin B. Patel and co-workers synthesized series of 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-substituted-1,3-benzothiazol-2-amino)-4H-1,2,4-triazole (95) and screened for their antimicrobial and antitubercular activity. One of the compounds showed better antitubercular activity compared to rifampicin.

Anticancer activity: H. Mujagic and co-workers synthesized Compound 1-(6, 7, 8, 9-Tetrahydro-5H-[1, 2, 4]-triazolo[1, 5-a]-azepine-2-yl)benzyl]indole (96), was prepared
and evaluated for anticancer activity against human tumour cell lines derived from nine cancer cell lines. The anticancer activity was moderate or weak in comparison to other lead series of compounds namely vincristine and vinblastine.

Ya-Ping Hou and co-workers\textsuperscript{91} had reported synthesis of 3- substituted (benzylthio)-5- 2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)-4-phenyl-4H-1,2,4-triazole (97) and screened for antitumor activity. One of the compound possessed significant antitumor activity against HEPG2 cancer cell line.

K. Subrahmanya Bhat and co-workers\textsuperscript{92} synthesized a series of 3-(2,4-dichloro-5-fluorophenyl)-6-(substituted phenyl) -1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (98) and evaluated for their antitumor activity. Some of the compounds exhibited in vitro antitumor activity with moderate to excellent growth inhibition against a panel of sixty cancer cell lines.
Olcay Bekircan and co-workers\textsuperscript{93}, reported synthesis of various 4-arylmethylenamino-4H-1,2,4-triazoles (99) and screened for their anticancer activity. Some of compounds exhibited remarkable anticancer activity in 60 human cancer cell lines.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{99}
\caption{4-arylmethylenamino-4H-1,2,4-triazoles (99)}
\end{figure}

**Antioxidant activity**

Diwedi Rohini and co-workers\textsuperscript{94} synthesized several 5,5'- methylene bis (4-substituted phenyl /alkyl)-4H-1,2,4-triazole-3-thiol (100) and investigated for their antioxidant activities.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{100}
\caption{5,5'-methylene bis (4-substituted phenyl /alkyl)-4H-1,2,4-triazole-3-thiol (100)}
\end{figure}

Canan Kus and co-workers\textsuperscript{95}, reported a synthesis of 5-[(2-(substitutedphenyl)-1H-benzimidazol-1-yl) methyl-4-methyl-2H-1,2,4-triazole-3(4H)-thiones (101) and tested for antioxidant properties by using various in vitro systems.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{101}
\caption{5-[(2-(substitutedphenyl)-1H-benzimidazol-1-yl) methyl-4-methyl-2H-1,2,4-triazole-3(4H)-thiones (101)}
\end{figure}

**Antiviral activity:** P. Selvam and co-workers\textsuperscript{96} synthesized some new compounds and evaluated for the anti-HIV activity. 4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-N (4, 6- dimethyl -2-pyrimidinyl) -benzene sulphonamide and its derivatives (102) were prepared and they were found active against replication of HIV-1 and HIV-2 in MT-4 cells.
Ilkaykucukguzel and co-workers\textsuperscript{97}, synthesized the novel thiourea derivatives obtained from 5-[(4-amino phenoxy)methyl]-4-alkyl/aryl-2, 4-dihydro-3H-1, 2, 4 triazole-3-thiones (103) which proved to be having a good activity against cox sacie virus B4, also active against the thymidine kinase positive Varicella zoster Virus.

Harish Kumar and co-workers\textsuperscript{98} had reported a synthesis of diazotied 5-phenyl-4-amino-3-mercaptop-1,2,4-triazole derivatives (104,105) and screened for their antiviral activity.

\textbf{Antidepressant activity}

Zafer Asim Kaplancikli and co-workers\textsuperscript{99} synthesized 1-[[4-amino-3-[2-(4-hydroxyphenyl)ethyl]-4H-1,2,4-triazol-5-yl]thioacetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline (106) and investigate their potential antidepressant activities.
CONCLUSIONS

This article, has summarized the various methods of synthesis of 1,2,4-triazole derivatives and their biological activity. The various synthetic methods discussed here may serve as a support for the planning of new molecules containing the 1,2,4-triazole moiety. Moreover the various pharmacological activities discussed here proves biological importance of 1,2,4-triazole moiety. So it can be seen from the literature review that 1,2,4-triazole ring containing heterocyclic system has wide medicinal applications. We hope that in the future many new biological profiles will be added to it and more investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are challenging in the field of medical sciences. Thus by studying all the derivatives showing variety of activities can say that 1, 2, 4-triazole ring have been explored in past years and is still used for future development of new drugs against many more pathological conditions.

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