EXPLORING POTENTIAL OF 1, 2, 4-TRIAZOLE: A BRIEF REVIEW

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Summary: Triazole, a heterocyclic nucleus has attracted a wide attention of the medicinal chemist in search for the new therapeutic molecules. Out of its two possible isomers, 1, 2, 4-triazole is (wonder nucleus) which posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. This review provides a brief summary of the medicinal chemistry of 1, 2, 4-triazole system and highlights some examples of 1, 2, 4-triazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 1, 2, 4-triazole is presented in sections by generalized synthetic methods.

Key words: 1, 2, 4-Triazole, Heterocyclic, Antifungal .

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1. Introduction

The search for new agent is one of the most challenging tasks to the medicinal chemist. The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications, such as propellants, explosives, pyrotechnics and especially chemotherapy. In recent years, the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. The derivatization of Triazole is considered to be based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen atom yields triazole analogue. There are two possible isomers of triazole **(1, 2)** depending on the position of nitrogen atom in the ring and are numbered as shown

in **Fig. 1.**

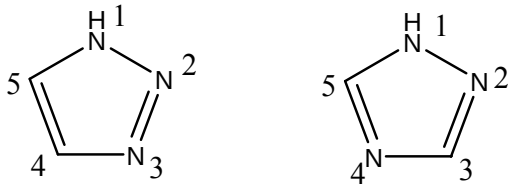


Fig. 1

Out of the two triazoles, 1, 2, 4- triazole have drawn great attention to medicinal chemists from two decades due to its wide variety of activity,[1] low toxicity and good Pharmacokinetic and Pharmacodynamic profiles. Literature survey reveals that 1, 2, 4-triazole derivatives exhibit wide range of biological activities including Antibacterial[2-4], Antifungal[5,6], Antitumour[7], Anti-inflammatory[8], Antitubercular[9], Hypoglycaemic[10,11], Antidepressant[12], Anticonvulsant[13], Anticancer[14], Antimalarial[15], Antiviral[16], Anti-proliferative[17], Analgesic[18] and antimigrain[19].

1, 2, 4-Triazole

2.1 Physical Properties:

1, 2, 4-triazole derivatives usually exist in solid forms. 3, 4, 5-substituted 1, 2, 4-triazole derivatives melt with thermolysis at high temperature when heated at 316^0C for 30 minutes. [20] 1, 2, 4-Triazole derivatives are readily soluble in polar solvents and only slightly soluble in nonpolar solvents, however, the solubility in non-polar solvents can be increased by substitution on the nitrogen atom.

2.2 Chemistry of 1, 2, 4-triazole

The first studies of 1, 2, 4-triazoles were concerned with structural isomerism[21]. Modern instrumental and theoretical methods achieved much success in dealing with tautomeric problems, the complexity of which is one of the enduring charms of the chemistry of 1, 2, 4-triazoles. Example of tautomerisation is shown by 3-Phenyl-1H-1, 2, 4-triazol-5-amine with 5-phenyl- 1H-1,2,4-triazol-3-amine.[22] Due to annular tautomerism in 1,2,4-triazole ring, there is a theoretical possibility of three tautomeric forms, namely 3-phenyl-1,2,4-triazol-5-amine (3), 5-phenyl-1,2,4-triazol-3-amine (4), and 5-phenyl-4H-1,2,4-triazol-3-amine (5). (**Fig2)**. Usually, tautomerizable 1,2,4-triazoles with nonequivalent substituents at positions 3 and 5 crystallize as a tautomer bearing at position 5 substituent with relatively more pronounced electron donor

properties. Considering significant difference in electronic properties of phenyl and amino group, the crystal would be assembled from the molecules of tautomer (3) analogously to the reported 3-pyridin-2-yl-1, 2, 4-triazol-5-amine. Two tautomers, viz. 3-phenyl-1, 2, 4-triazol-5-amine (3) and 5-phenyl-1, 2, 4-triazol-3-amine (4) are crystallized together in equal amounts. This is the first example of existence in crystal of unequally 3, 5-disubstituted tautomerizable 1, 2, 4-triazole tautomeric form with electron donor group located at position 3. The geometry of the tautomer (3) molecule is essentially planar. **(Fig.3)**. Amino group is involved in π-electron delocalization with the 1, 2, 4-triazole nucleus. It is almost planar with small deviation 0.06 (2) Å of the nitrogen atom from the C8/H4A/H4B plane. The length of the C8—N4 bond is 1.337 (3) Å. The π-electron delocalization of the amino group of (4) with the 1, 2, 4-triazole nucleus is significantly lower. The nitrogen atom (N8) of the amino group adopts a pyramidal configuration with 0.21 (2) Å deviation of the nitrogen atom from the C16/H8A/H8B plane. The C16—N8 bond [1.372 (3) Å] is also longer. The phenyl ring of (3) makes a small dihedral angle of 2.3 (2)° with the mean plane of the 1,2,4-triazole ring. The molecule of tautomer (4) loses this planarity. The mean planes of the phenyl and 1, 2, 4-triazole rings of (4) form a dihedral angle of 30.8 (2)°. The molecules are linked into a two-dimensional network parallel to the (100) by N—H···N hydrogen bonds. **(Fig.4)**.

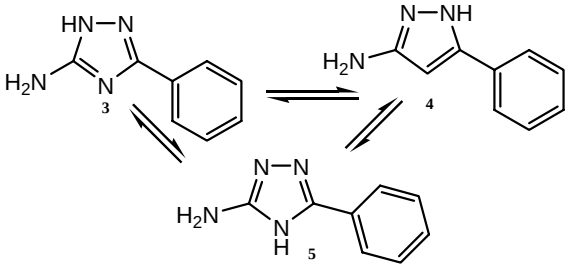


Fig.2: showing tautomeric form by substituted 1, 2, 4-triazole

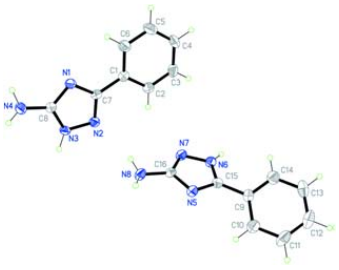


Fig.3: Showing the planar geometry of the tautomer I molecule

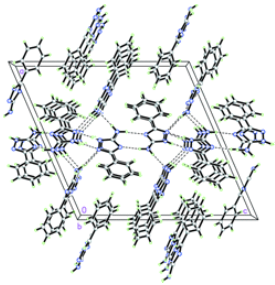


Fig.4: Molecules are linked into a two-dimensional network

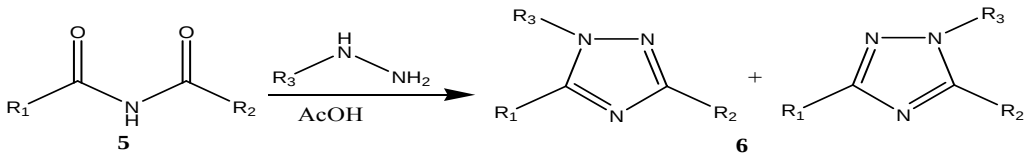
1, 2, 4-Triazole derivatives undergoes mannich reaction (Mannich reaction is a 3-component condensation reaction involving an active hydrogen containing compound, formaldehyde, and a secondary amine. The aminomethylation of aromatic substrates by the Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds [23]) formed Schiff base. Amino group at position 4 of 1, 2, 4-triazole derivative undergoes reaction with 4-methoxybenzaldehyde [24] eliminate water molecule with the formation of Schiff base. The compounds having Schiff base structure may exist as E/Z geometrical isomers about the –

N=CH- double bond. The compounds containing imine bond are present in higher percentage in dimethyl-d_6 sulfoxide solution in the form of geometrical E isomer about –N=CH- double bond. The Z isomer can be stabilized in less polar solvents by an intramolecular hydrogen bond. 1, 2, 4-triazole and 4, 5-dihydro-1H triazol-5-one rings -1, 2, 4- have weak acidic properties, so some 1, 2, 4-triazole and 4, 5-dihydro-1H derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents such as acetonitrile, isopropyl alcohol and N, N-dimethylformamide, and the half-neutralization potential values and the corresponding p K_a values of the compounds were determined [25].

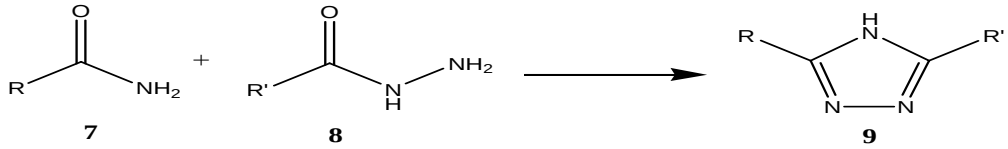
2.3 Syntheses of 1, 2, 4-triazole backbone

Several methods for synthesis of 1, 2, 4-triazole are available in literature which involve conventional one pot, multicomponents, microwave assisted, under free condition, regioselective, and by sonificationmethod. These methods can be summarized in to following points:-

Einhorn-Brunner [26-29] reported synthesis of a mixture of isomeric 1, 2, 4-triazoles (6) from the reaction of imides (5) with alkyl hydrazines in presence of acyl hydroxide **(Scheme 1)**. Pellizzari [30] reported synthesis of substituted 1, 2, 4-triazole (9) by the reaction of an amide (7) and a hydrazide (8) **(Scheme 2)**.



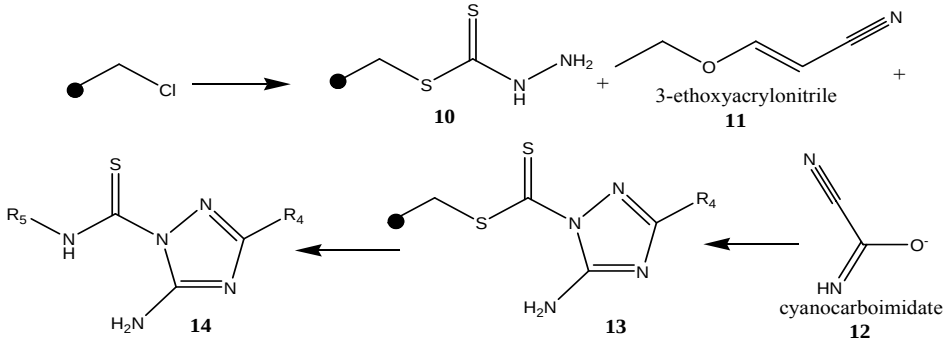
Scheme 1: Synthesis of a mixture of isomeric 1, 2, 4-triazoles using imides with alkyl hydrazines in presence of acyl hydroxide



Scheme 2: Synthesis of a substituted 1, 2, 4-triazole from amide and a hydrazide

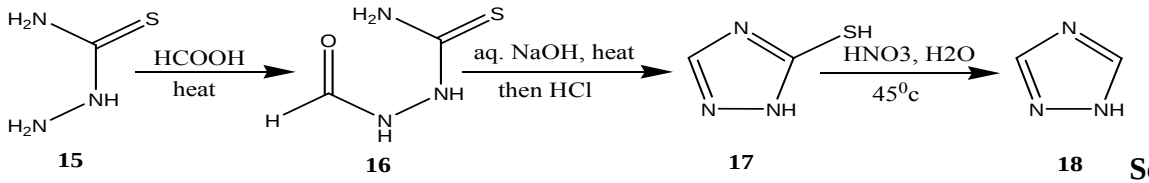
Jong Yeon Hwang et al [31] reported Solid-Phase synthesis of 5-Amino-1-(Substituted Thiocarbamoyl)1, 2, 4-Triazole via Dithiocarbazate (10) Linker based on the cyclization of polymer-bound dithiocarbazate (10) **(Scheme 3)** with various electrophiles, such as 3-ethoxyacrylonitriles (11) and cyanocarboimidates (12). The polymer-bound dithiocarbazate (10), produced by nucleophilic reaction with carbon disulfide and Fmoc-hydrazine on the Merrifield

resin, served as the key intermediate for subsequent heterocycle diversification. Further nucleophilic substitution on these polymer-bound 5-amino-1-dithiocarboxy1, 2, 4-triazoles (13) with various amines under thermal cleavage condition produced the desired 5-amino-1-(substituted thiocarbamoyl) 1, 2, 4-triazoles (14). The progress of reactions could be monitored as polymer-bound intermediates by ATR-FTIR spectroscopy on single bead. The final compounds, obtained in good four-step overall yields and high purities upon cleavage from the resins, were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.



Scheme 3: Solid-phase synthesis of a 5-amino-1-(substituted thiocarbamoyl)1,2,4-triazole

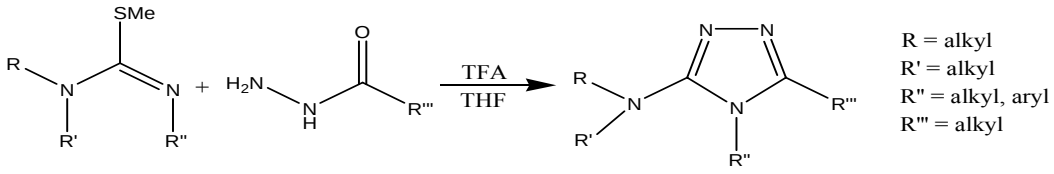
C. Ainsworth **[32]** reported synthesis of 1, 2, 4-triazole (18) nucleus by the reaction of thiosemicarbazide (15) with formic acid **(Scheme 4)** forming 1-Formyl-3-thiosemicarbazide (16) as an intermediate. The reaction of 1-Formyl-3-thiosemicarbazide (16) with aqueous sodium hydroxide and hydrochloric acid yield 1,2,4-Triazole-3(5)-thiol (17) which on treatment with a mixture of water, concentrated nitric acid, and sodium nitrite finally produce 1,2,4-triazole (18) nucleus. Modifications of this procedure for the preparation of 1, 2, 4-triazole have been used to prepared 3-aryl-1, 2, 4-triazoles **[33]** and 3-alkyl-1, 2, 4-triazoles **[34]**.



Scheme 4: Synthesis of 1, 2, 4-triazole from the reaction of thiosemicarbazide (15) and formic acid

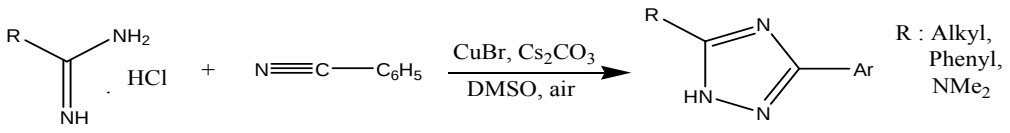
D. V. Batchelor et al **[35]** reported synthesis of 3-N, N-Dialkylamino-1, 2, 4-triazole (21) from S-methylisothioureas (19) and acyl hydrazides (20) **(Scheme 5)** in presence of trifluoro-acetaldehyde and tetrahydrofuran. 3-N, N-Dialkylamino-1, 2, 4-triazole (21) obtained in good

yields. The reaction conditions are relatively mild and tolerate a broad range of functional groups. S. Ueda et al [36] synthesized 1, 2, 4-triazole derivatives (24) by treatment of substituted amidine (22) and benzonitrile (23) **(Scheme 6)**. It is a copper-catalyzed reaction takes place in presence of cesium carbonate, dimethylsulphoxide and under an atmosphere of air provides 1, 2, 4-triazole derivatives (24) 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.



19 **20** **21**

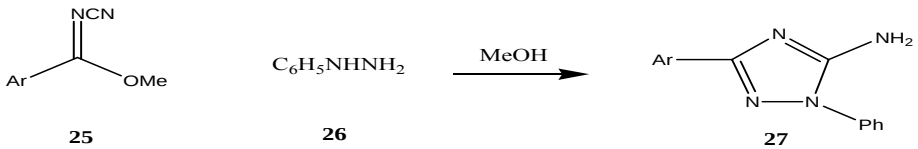
Scheme 5: Synthesis of 3-N, N-Dialkylamino-1, 2, 4-triazole (21) from trifluoroacetaldehyde and tetrahydrofuran



22 **23** **24**

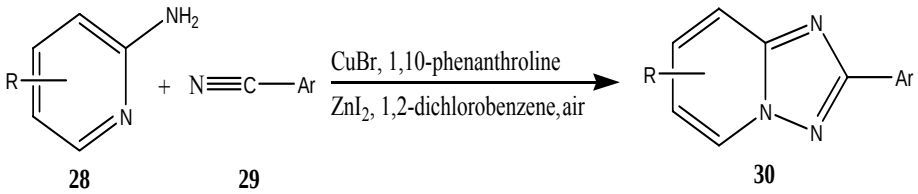
Scheme 6: Synthesis of 1, 2, 4-triazole derivatives (24) from substituted amidine (22) and benzonitrile (23)

P. Yin et al [37] synthesized 1, 2, 4-triazole derivatives (27) by the reaction of substituted methyl N-cyanoarylimidate (25) and phenylhydrazine (26) **(Scheme7)**. A mild, one-pot cyanoimidation of aldehydes using cyanamide as a nitrogen source and NBS as an oxidant was achieved in high yields without the addition of a catalyst. S. Ueda et al [36] prepared 1, 2, 4-triazole derivatives (30) from the reaction of substituted pyridine-2-amine (28) and substituted nitrile (29). **(Scheme8)**. It is a copper-catalyzed reaction takes place in the presence of 1, 10-phenanthroline, zinc iodide and 1, 2-dichlorobenzene.



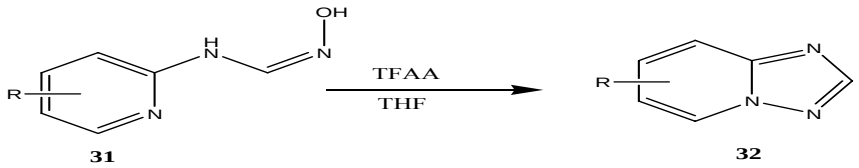
25 **26** **27**

Scheme7: Synthesis of 1, 2, 4-triazole derivatives (27) by cyclization



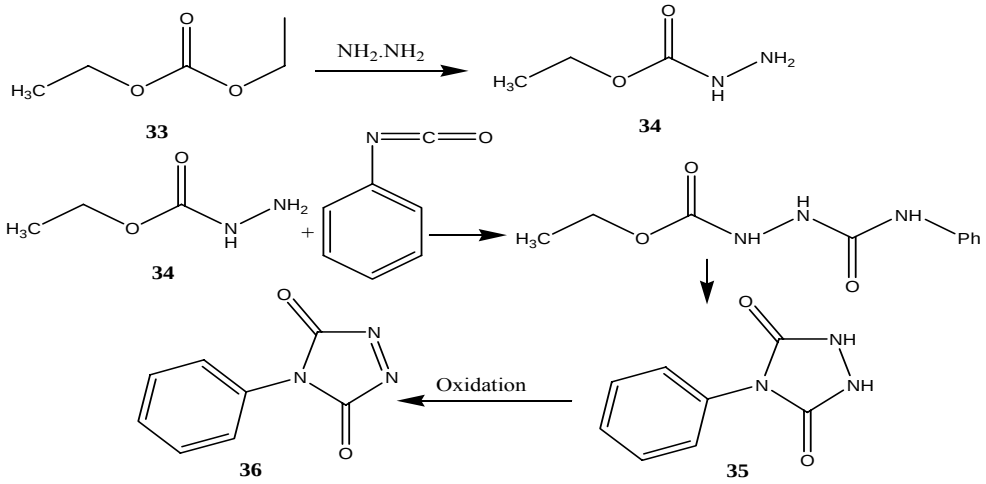
Scheme8: Synthesis of 1, 2, 4-triazole derivatives (30) from substituted pyridine-2-amine (28) and substituted nitrile (29)

E. Huntsman et al [38] synthesized substituted 1, 2, 4-triazolo [1, 5-a] pyridine (32) from 2-aminopyridines **(Scheme 9)** in good yields by cyclization of N-(pyrid-2-yl)formamidoximes (31) under mild reaction conditions with trifluoroacetic anhydride (TFAA) and tetrahydrofuran (THF).

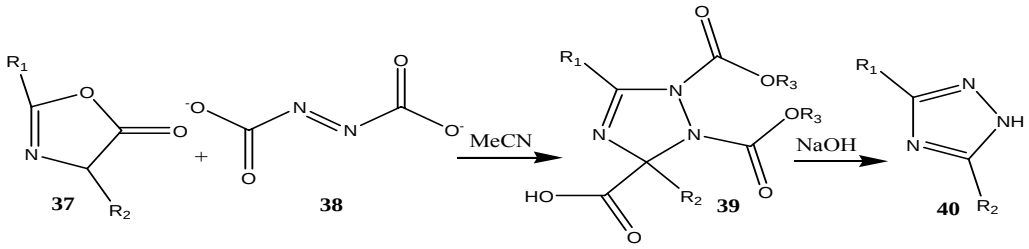


Scheme9: Synthesis of substituted 1, 2, 4-triazolo [1, 5-a] pyridine (32)

Johannes Thiele et al [39] synthesized 4-Phenyl-1, 2, 4-triazole-3, 5-dione (PTAD) **(Scheme10)**, an azodicarbonyl compound, first synthesized in 1894. PTAD is one of the strongest dienophiles and reacts rapidly with dienes in Diels-Alder reactions. [40] The synthesis starts from diethyl carbonate (33) and hydrazine. The product (34) of this step is reacted with phenyl isocyanate and subsequently transformed to the 4-Phenylurazol (35). Cyclization and subsequent oxidation of 4-Phenylurazol with lead tetroxide in sulfuric acid yields PTAD (36). Rahman Shah Zaib Saleem et al [41] 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-triazolines with NaOH provides efficient access to the corresponding triazoles (40) **(Scheme11)**.

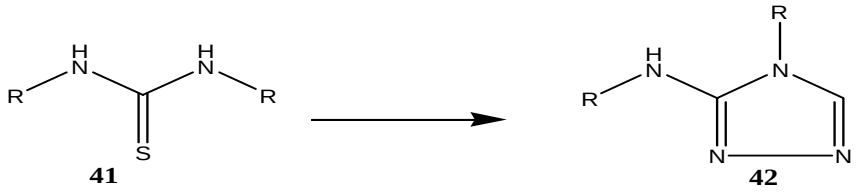


Scheme10: Preparation of 4-Phenyl-1, 2, 4-triazole-3, 5-dione (36) from diethyl carbonate (33) by cyclization and oxidation

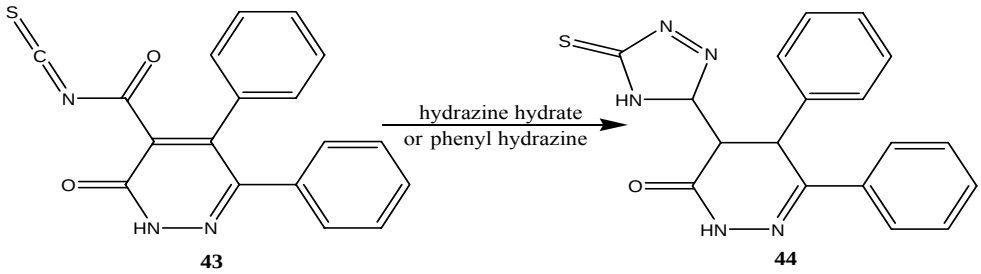


Scheme 11: Synthesis of substituted 1, 2, 4-triazole (40) from substituted oxazolone (37) and azodicarboxylate (38)

Amarnath Natarajan [42] and his co-workers prepared disubstituted 4H-[1, 2, 4] triazole-3-yl-amines (42) as urea mimetics from the corresponding 1, 3-disubstituted thioureas (41) **(Scheme 12)**. The reaction proceeds through the formation of a carbodiimide, followed by a sequential addition−dehydration with acyl hydrazides. 1, 3-Branched dialkylthioureas result in the formation of the corresponding ureas. The electronic and steric effects of the substitution on the phenyl rings of the 1, 3-diarylthioureas play an important role in the formation of the intermediary carbodiimde and the direction of the subsequent ring closure of the N-acyl hydrazide adduct. Hemdan and his co-workers [43] synthesized 1, 2, 4-triazole derivative (44) in a one pot-reaction by the reaction of 3-Oxo-5, 6-diphenyl-2, 3-dihydropyridazine-4-carbonyl isothiocyanate (43) with hydrazine hydrate, or phenyl hydrazine **(Scheme13)**.

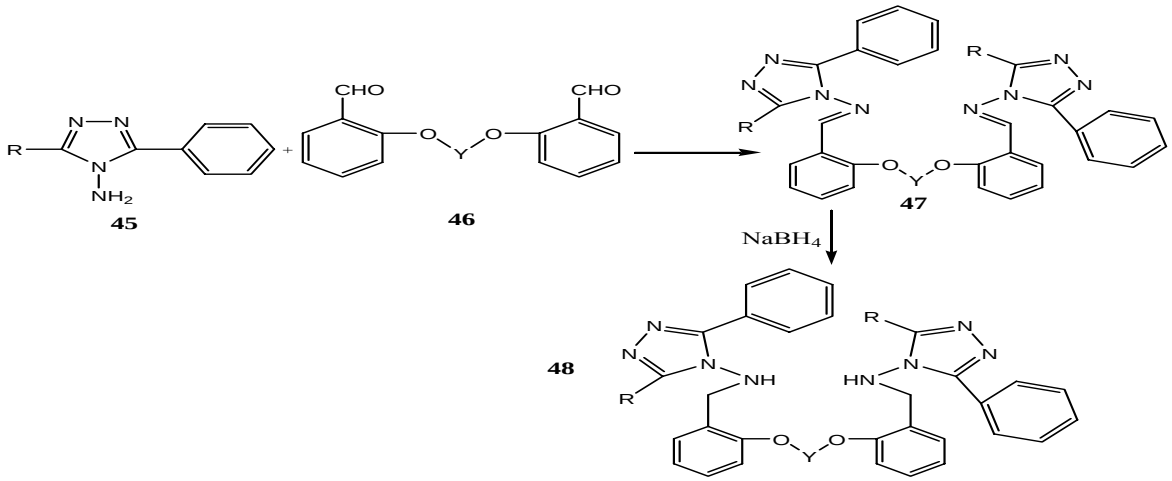


Scheme 12: Synthesis of substituted 1, 2, 4-triazole (42) from 1, 3-disubstituted thioureas (41)

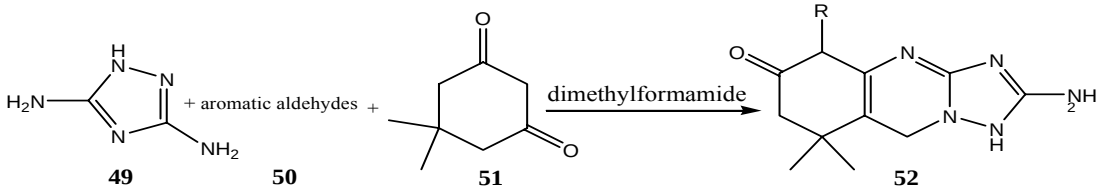


Scheme13: Synthesis of 1, 2, 4-triazole derivative (44) from 3-Oxo-5, 6-diphenyl-2, 3-dihydropyridazine-4-carbonyl isothiocyanate (43)

Olcay Bekircan et al [44] synthesized new bis-1, 2, 4-Triazole derivatives (If two triazole units are linked by carbon atoms, then they form bis-triazole) by the reaction of 3-Aryl-5-phenyl-4-amino-4H-1, 2, 4-triazoles (45) and bis-aldehydes (46) 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 (47). Compounds (47) 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 (48) **(Scheme14)**. V. V. Lipson et al [45] synthesized 1, 2, 4-Triazole derivatives by multi-component reactions involving 3, 5-diamino-1, 2, 4-triazole (49) with aromatic aldehydes (50) and dimedone (51) in dimethylformamide gives 2-amino-5-aryl-8, 8-dimethyl-5,6,7,8,9,10-hexahydro[1,2,4-triazolo][3,2-b]quinazolin-6-ones (52) **(Scheme15)**.

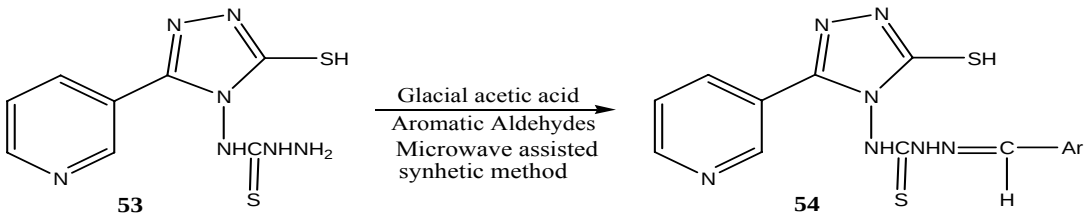


Scheme14: Preparation of bis-1, 2, 4-Triazole Derivatives (48)

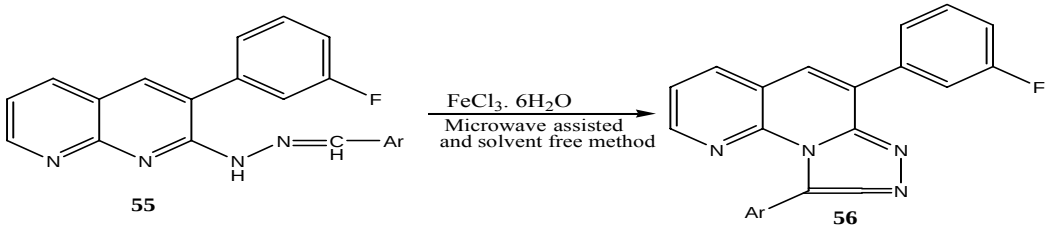


Scheme15: Synthesis of 1, 2, 4-triazole derivatives (52) by multicomponent reactions

Aniket Kshirsagar et al [46] synthesized thiosemicarbazones (54) by microwave assisted method by the reaction of 5- mercapto-3-(3'-pyridyl)-4H-1,2,4- triazole-4-ylthiosemicarbazide (53) in glacial acetic acid reacted with various aromatic aldehydes in microwave oven for 40 minutes. **(Scheme16)**. K. Mogilaiah et al [47] synthesized 9-aryl-6-(3-fluorophenyl)-1, 2, 4-triazolo[4,3-a][1,8]naphthyridines(56) from arylaldehyde3-(3-fluorophenyl)-1,8-naphthyridin-2-ylhydrazones (55) using $FeCl_3$. $6H_2O$ under solvent free conditions by microwave irradiation method **(Scheme17)**.

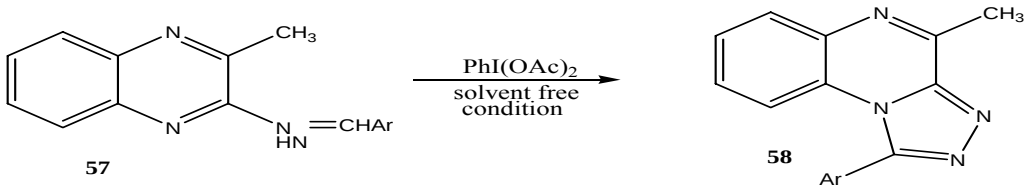


Scheme16: Synthesis of substituted thiosemicarbazones by microwave assisted method



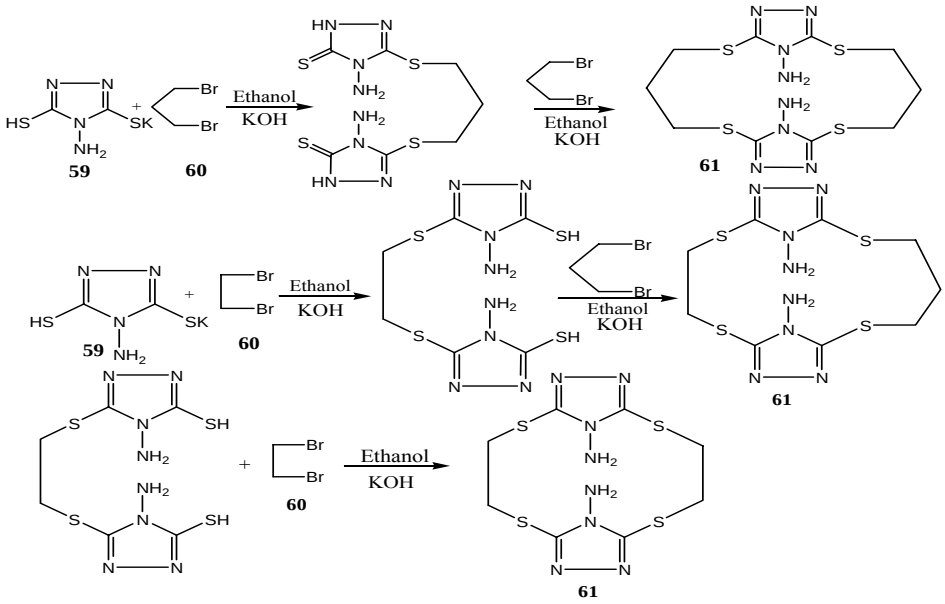
Scheme17: Synthesis of substituted 1, 2, 4-triazolo [4, 3-a][1,8]naphthyridines (56).

Dalip Kumar et al [48] synthesized 1-aryl-4-methyl-1, 2, 4-triazolo [4, 3-a]quinoxalines (58) from arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazones (57) under solvent-free conditions using iodobenzene diacetate **(Scheme18)**.



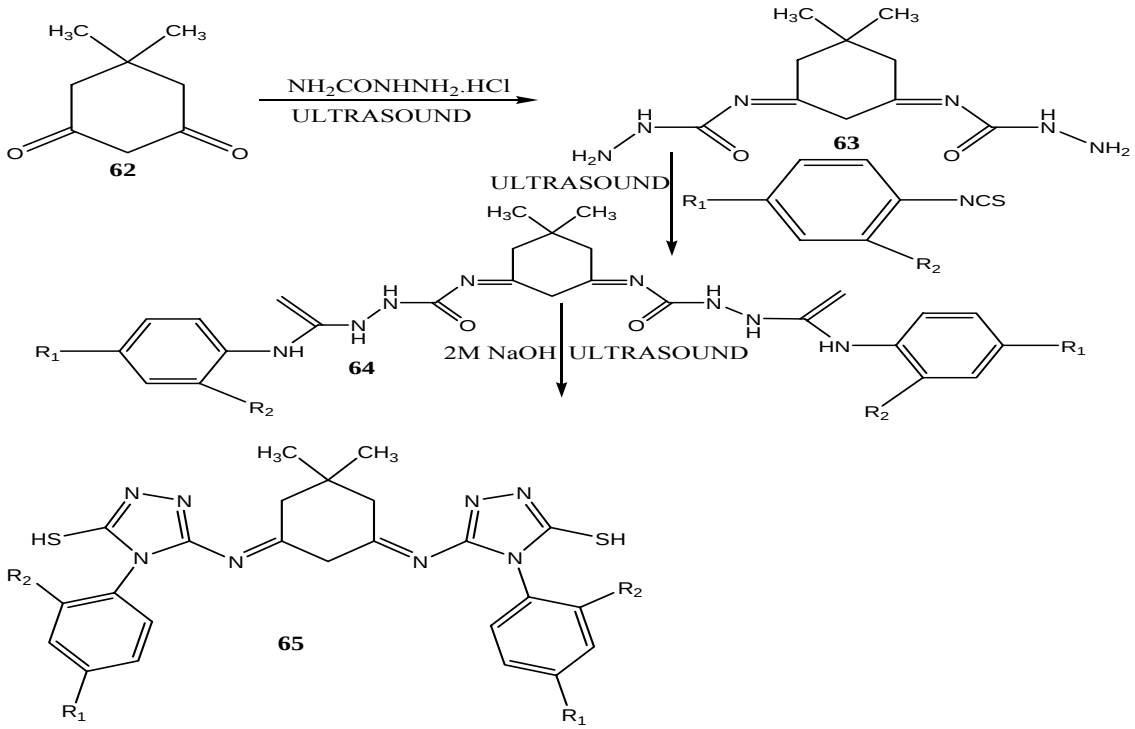
Scheme18: Synthesis of substituted 1, 2, 4-triazole (58) under solvent-free conditions

Madhukar S. Chande et al [49] synthesized macrocycles containing 4-Amino-1,2,4-Triazoles by regioselective method by the reaction of 4-amino-3,5-dimercapto-1,2,4-triazole (59), with appropriate 1,□-dibromo alkanes (60) followed by further alkylation with 1,□-dibromo alkanes to afford the desired substituted triazolophanes (61) **(Scheme19)**.



Scheme19: Synthesis of substituted triazolophanes (61) by regioselective method

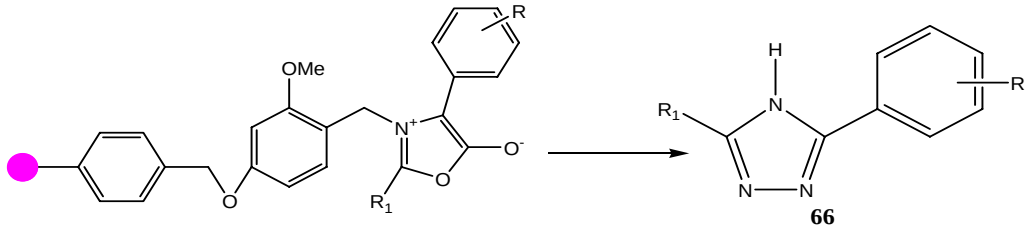
Vijay V. Dabholkar et al [50] synthesized Bis-1, 2, 4-Triazole derivatives by sonification method involving reaction between 5, 5-Dimethylcyclohexane-1,3-dione (62) with semicarbazide to yield its acid hydrazide (63), which on further reaction under ultrasound condition with aryl isothiocyanates gave 1,3-bis-imino-[1-(carboxy)-4-substituted phenylthiosemicarbazide]-5,5-dimethylcyclohexane (64). This compound in basic medium gave 1, 3-bis-imino-[4-(substituted) phenyl-5-mercapto-1, 2, 4-triazol-3-yl-]-5, 5-dimethylcyclohexane (65) **(Scheme20)**.



Scheme20: Synthesis of substituted 1, 2, 4-triazole by sonification method

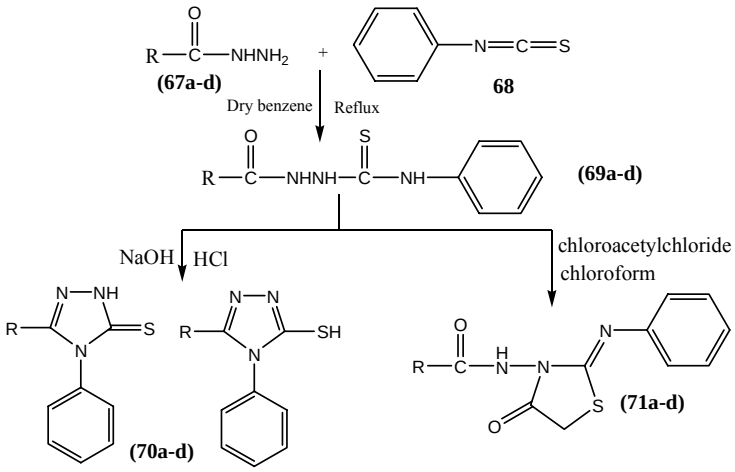
Jari Yli-Kauhaluoma et al [51] developed 3, 5-disubstituted 1, 2, 4-triazoles on polymeric supports. The synthetic process utilizes immobilized mesoionic 1, 3-oxazolium-5-olates as key intermediates in the 1, 3-dipolar cycloaddition reaction. The initial step in the synthesis involves reductive alkylation of phenylglycine methyl esters with Ameba resin. The resulting immobilized amino acid esters were subsequently acylated with a variety of carboxylic acid chlorides and subjected to hydrolysis with 15% KOH to yield the polymer-bound carboxylic acids. Finally, the cycloaddition between diethyl diazocarboxylate or 4-phenyl-4H-1, 2, 4-triazoline-3, 5-dione and the polymer-bound 1, 3-oxazolium-5-olates generated from the corresponding carboxylic acids afforded the polymer-bound 3, 5-disubstituted 1, 2, 4-triazoles (66) **(Scheme21)**. Cleavage from

the polymeric support using trifluoroacetic acid gave the desired 3, 5-disubstituted 1, 2, 4-triazoles with excellent yield and high purity.



Scheme21

Abdul Rauf et al [52] synthesized a series of (Z)-5-(alk-9/8-en-1-yl)-4-phenyl-1,2,4-triazole-3-thiones, (Z)-5-(8/11-hydroxy alk-11/8-en-1-yl)-4-phenyl-1,2,4-triazole-3-thiones, (Z)-N-[2-(phenylimino)-3-yl]-alk-9-enamide-4-thiazolidinone and (Z)-9/12-hydroxy-N-[2-(phenylimino)-3-yl]alk-12/9-enamide-4-thiazolidinone derivatives from different fatty acids and hydrazides. These compounds have been tested for their antibacterial activity against Escherchia coli, Enterobacter aerogenes, Staphylococcus aureus and Salmonella typhi by cup-plate method.



Compound	R
67a-71a	H_E, $CH_2=CH(CH_2)_8$, H_Z
67b-71b	$CH_3(CH_2)_7CH_2=CH_3(CH_3)_7$
67c-71c	$CH_3(CH_2)_5CH(OH)CH_2CH_2=C(CH_2)_7$
67d-71d	$CH_3(CH_2)_4CH=CH(CH_2)_2CH(OH)(CH2)_7$

Scheme22

2.4 Spectral study

Ultra violet spectra

The ultraviolet absorption spectra of a series of 2, 4-dihydro-4-(2-phenylethyl)-5- (isomeric pyridyl)-3H-1, 2, 4-triazole-3-thiones containing isomeric pyridine in the 1, 2, 4-triazole nucleus have been observed. 2 and 4-pyridyl isomer shows three distinct absorption maxima at 203.1-208.0 nm, 253.9-257.6 nm and 303.0-312.6 nm, while in case of 3-pyridyl-1,2,4-triazole derivative, only two absorption maxima were observed, at 205.3 nm and 257.1 nm. These absorption bands are assigned to the n→ π* and π→ π*transition associated with the molecules[53].

Infrared Spectra (IR)

The IR spectra of 1, 2, 4-triazoles are helpful in determining the structure of compounds. The absorption band of C=O of the carboxyl group of 3-carboxychromone appeared at 1750 cm^{-1}, which is higher than 1734 cm^{-1} of 2-carboxychromone [54]. The characteristic absorption band of C=O in pyrone appeared at 1620-1670 cm^{-1}, and the IR spectra displayed a broad band at 3000 $cm^{-1}$for CONH, CSNH functional groups, and a band at 1700 cm^{-1}(C=O of CONH) or 1310 cm^{-1} (C=S).

NMR spectra

Both ^{1}H and ^{13}C NMR are important so as to confirm the structure of the derivatives and are also useful in regioselective synthesis of isomers [49]. Due to the propylenic linkage ^{1}H-NMR of triazolophane structure (shown in structure no. of 61 scheme 19) in DMSO–d_6 showed a quintet at δ 2.1 and a triplet at δ 3.1, it also showed a singlet at δ 5.6 due to two-NH_2 groups, which conclusively proved a high symmetry of triazolophane structure. The two sharp singlets at δ 5.5 & 5.9 in ^{1}H-NMR spectrum of triazolophane structure could be due to close proximity of N and N' amino groups respectively in triazolophane ring The rest of the molecule showed only a sharp singlet at δ 3.4 due to four S-CH_2 protons exhibiting the high symmetry of triazolophane ring. The electron-acceptor substituent at position in compound affect chemical shift [55]. Another example is illustrated by NMR spectra of ciprofloxacin analogue as shown in **Fig. 5** below. The presence of -N-CH_2-N- [56] peak at 4.8 ppm confirmed its formation. The Schiff bases were confirmed by the presence of -N=CH- at 10.3 ppm at ^{1}H NMR spectra.

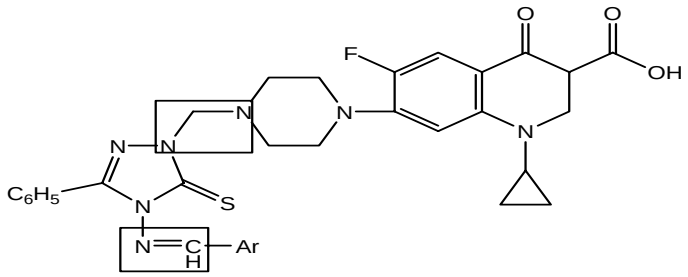


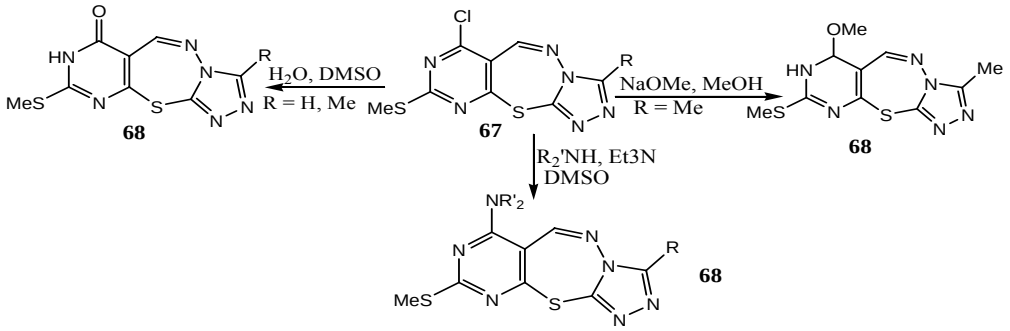
Fig. 5

Mass Spectra

The molecular ion peaks in the mass spectra of 3-amino-5-dimethylamino-1, 2, 4-triazole and 3-azido-5-dimethylamino-l, 2, 4-triazole have been assigned . Five major peaks in the mass spectrum of 3-amino-5-dimethylamino-1, 2, 4-triazole occurs. The extent to which these fragmentations account for the peaks in the mass spectra depends on the substituents of the 1, 2, 4-triazoles. Metastable peaks for compounds in which the methyl group is separated from the triazole nucleus by a sulfur atom have been observed in the mass spectrum of 3-methylthlo-
1, 2, 4-triazole and the daughter ion of the process in which CHS is lost is regarded as protonated 1, 2, 4-triazole[57]. Mass spectra of the 3-azido-5-dilnethylamino-l, 2, 4-triazole are characterized by a strong peak corresponding to the molecular ion and the base peak which together account for 28 to 48% of the total ionization at 70 e V.

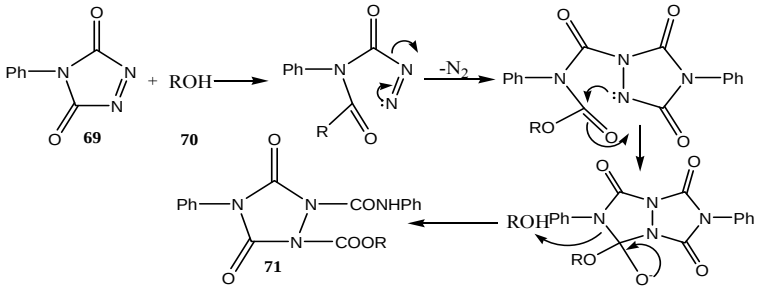
2.5 Reactivity of the 1, 2, 4-triazoles:

(A) Nucleophilic substitution and rearrangement reaction: The 1, 2, 4-triazole ring is rather susceptible to attack by strong neucleophile. Thus the parent compound is stable to acids but is readily cleaved by bases. Nucleophilic substitution of 7-chloro-9-methylthio-3-substitutedpyrimido[5,4-f][1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazepines (67) with water, sodium methoxide and amines occurs with the formation of the corresponding 3,7-disubstituted 9-methylthiopyrimido[5,4-f][1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazepines (68) [58], **(Scheme22)**.

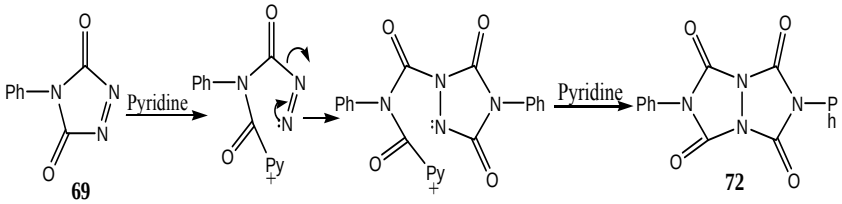


Scheme22:Reaction of 7-chloro-9-methylthio-3-substitutedpyrimido[5,4-f][1,2,4]triazolo [3,4-b]-[1,3,4]thiadiazepines (67) with various nucleophiles

Compound 4-phenyl-4H-1, 2, 4-triazole-3, 5-dione undergoes nucleophilic reactions and subsequent rearrangement in presence of alcohols and primary and secondary amines [59]. 4-phenyl-4H-1, 2, 4-triazole-3, 5-dione (69) react with alcohols (70) to give 1-substituted-3,5-dioxo-4-phenyl-2-(phenylcarbamoyl)-1,2,4-triazolidine (71). **(Scheme23)**. The yields of **(71)** are seen to be good to excellent for the oxidation of primary alcohols; aldehydes were not detected. From benzyl alcohol and both secondary aliphatic alcohols, yields of **(71)** were low, benzaldehyde or the ketone being the major product. 4-Phenyl-4H-1, 2, 4-triazole-3, 5-dione (69) react with pyridine or alternatively triethylamine to give 2,6-diphenyl-[1,2,4]triazolo[1,2-a][1,2,4]triazole-1,3,5,7(2H,6H)-tetraone (72) **(Scheme24)**, first obtained by Stolle [60].



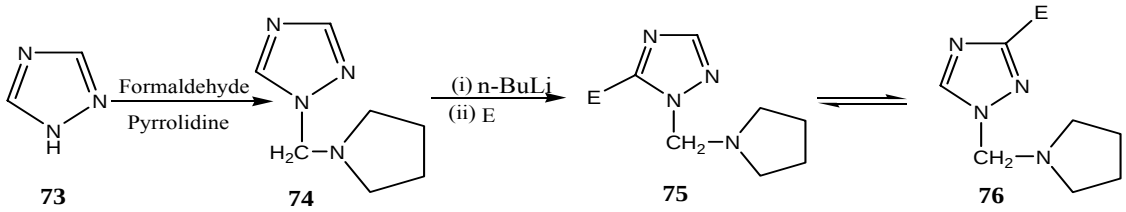
Scheme23: Reaction of 4-phenyl-4H-1, 2, 4-triazole-3, 5-dione (69) with alcohols (70)



Scheme24: Reaction of 4-phenyl-4H-1, 2, 4-triazole-3, 5-dione (69) with amines

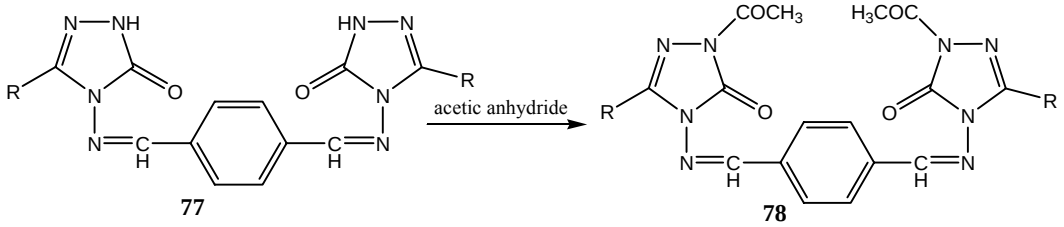
(B) Electrophilic substitution reaction: Electrophilic substitution usually occur at 5-postion on 1, 2, 4-triazole nucleus. For the synthesis of 3(5)-substituted-1, 2, 4-triazoles, first of all, the N-

substituted-1, 2, 4-triazole (74) is formed by mannich reaction by reacting 1, 2, 4-triazole nucleus (73) with formaldehyde and pyrrolidine and then it allow to lithiation by reacting with n-butyllithium [61]. Need for preparing N-substituted-1, 2, 4-triazole occurs because lithiation always occurs in presence of N-substituted-1, 2, 4-triazole because N-substituted-1, 2, 4-triazole is able for the lithiation (N-unsubstituted trazoles can't be lithiated as they form unreactive N-anions). For preparing 5(3)-substituted-1, 2, 4-triazoles (75 and 76), compound (74) react with electrophiles. **(Scheme25)**. The lithiation surely results in the formation of compound (75), but subsequent isomerization favours structurally more stable compound (76) because of its less steric hinderance.

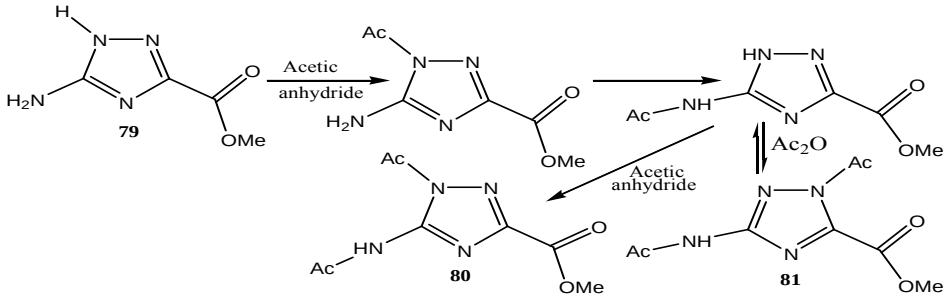


Scheme25: Reaction of N-substituted-1, 2, 4-triazole (74) with n-butyllithium and electrophiles

(C) Acetylation reactions: N, N'- bis(3-alkyl-4,5-dihydro-1,2,4-triazol-5-on-4yl)-1,4-xylenediimines (77) undergoes acetylation reaction in presence of acetic anhydride to form N, N'- bis(1-acetyl-3-alkyl-4,5-dihydro-1,2,4-triazol-5-on-4yl)-1,4-xylenediimines [62] (78), **(Scheme26)**. Methyl 5-amino-1H-[1, 2, 4] triazole-3-carboxylate (79) undergoes acetylation in presence of acetic anhydride (Ac_2O) to form two isomeric diacetylated products [63] (80) and (81), **(Scheme27)**.

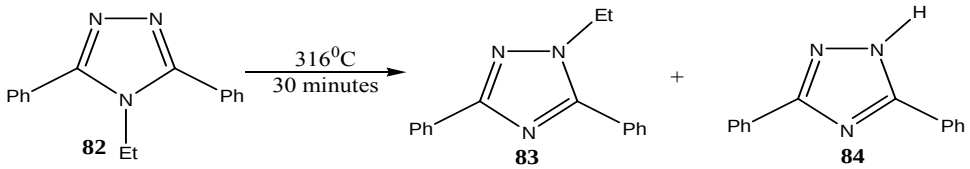


Scheme26: Reaction of 1, 2, 4-triazole derivative with acetic anhydride



Scheme27: Reaction of methyl 5-amino-1H-[1, 2, 4] triazole-3-carboxylate (79)

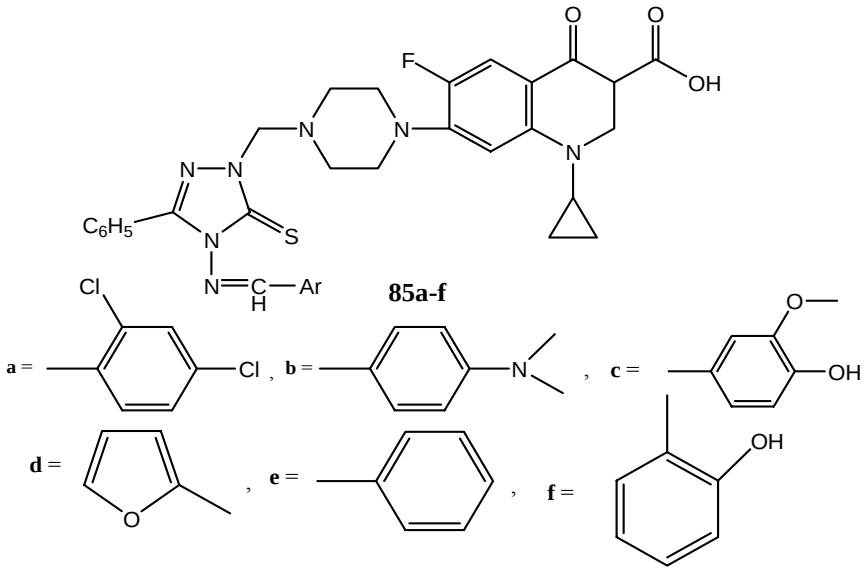
3, 4, 5-substituted-1, 2, 4-triazole (82) undergo thermolysis when heated at higher temperature of 316^0C for 30 minutes and rearranged to yield 1, 3, 5-substituted 1, 2, 4-triazole (83) together with elimination of small amount of 3, 5-substituted-1H-1, 2, 4-triazole derivative [20] (84), **(Scheme28)**.



Recent Advancement in the Therapeutic Potential of 1, 2, 4-Triazole derivatives:

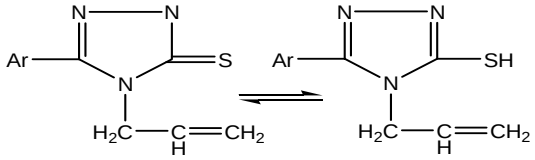
Antimicrobial activity

S. Jubie et al [56] have synthesized some novel ciprofloxacin analogues (85) as antimicrobial agents. Ciprofloxacin have been incorporated to the new series of Schiff bases of 1, 2, 4- triazole via Mannich reaction. The new compounds have been evaluated in vitro for their antimicrobial activity against B. subtilis, K. pneumoniae, and P. aeruginosa at 10µg/ml concentration. All the compounds showed in vitro gram positive and gram negative activity generally comparable or superior to that of reference ciprofloxacin.

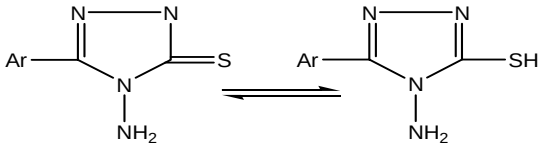


Antibacterial- Antifungal activities

Katica Colanceska-Ragenovic et al [64] synthesized a few 4-allyl/amino-5-aryl-1, 2, 4-triazoles (86/87) and tested for antibacterial and antifungal effects against Escherichia coli, Bacillus subtilis, Salmonella enteritidis, Staphylococcus aureus, Aspergillus niger and Candida albicans.



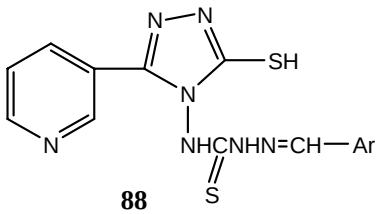
86



87

Antibacterial-Antifungal-Anticonvulsant activities

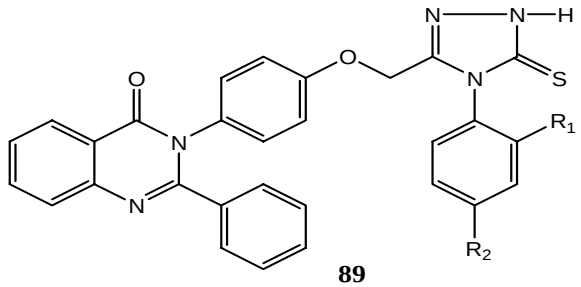
Aniket Kshirsagar et al [46] synthesized schiff's bases of 5-mercapto-3-(3-pyridyl)-4H-1, 2, 4-triazole-4-yl-thiosemicarbazide (88) by microwave assisted method. The synthesized compounds have been evaluated in vitro for their Antibacterial-Antifungal-Anticonvulsant activities.



88

Antibacterial-Antifungal-Antimalarial activities

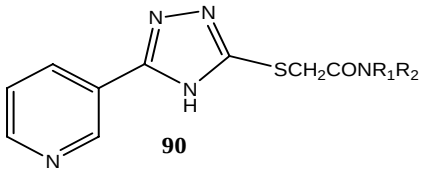
Freddy H. Havaldar et al [65] synthesized 3-[4-(4-substituted phenyl-5-thioxo-4, 5-dihydro-1H-1, 2, 4 triazol-3-ylmethoxy)-phenyl]-2-phenyl-3H-quinazolin-4-one (89). The synthesized compounds were evaluated in vitro for their antibacterial activity against Staphylococcus aureus, Escherichia coli and Bacillus subtilis by the ditch-plate technique using concentrations of 50 µg/mL. The compounds synthesized were screened for their antifungal activity against Aspergillus niger, Candida albicans and Cryptococcus neoformans by paper-disc diffusion method at concentrations of 50 µg/mL. The chloroquine-resistant Plasmodium falciparum malarial parasite was cultured in vitro and the sensitivity of parasite to the newly synthesized compounds was evaluated using the tritiated hypoxanthine incorporation assay.



89

Antifungal-Antitubercular activities

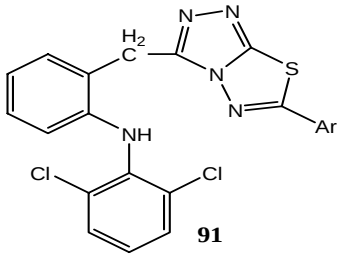
R.K. Mali et al [66] synthesized 5-(N-substituted carboxamidomethylthio)–3-(3'-pyridyl) - 1, 2, 4-triazole (90) derivatives. Anti-fungal activity was carried out against C. albicans and A. niger at the concentrations of 50 and 100 µg/mL using Fluconazole as the standard and in-vitro anti-tubercular activity was done at 50 µg/mL against Mycobacterium tuberculosis H_{37} Rv.



90

Antifungal-Antioxidant activities

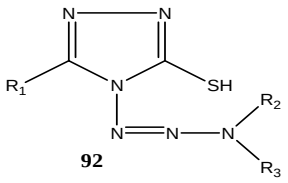
K. Ilango et al [67] synthesized a new series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles. The compounds (91) were screened for antifungal activity against Candida albicans and Aspergillus niger using Ketoconazole as standard and antioxidant activity by DPPH and Nitric oxide methods using Ascorbic acid as standard.



91

Anti-inflammatory Activity

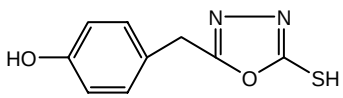
Pradeep K. Goyal et al [68] synthesized some new derivatives of 3-substituted-4H-1, 2, 4-triazoles (92). All the synthesized compounds were evaluated for anti-inflammatory activities and acute toxicity. Most of the compounds showed potent and significant results compared to standard Ibuprofen.



92

Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
92a	CH_3	H	C_6H_5	92f	C_6H_5	H	C_6H_5
92b	CH_3	H	C_6H_4-NO_2-p	92g	C_6H_5	H	C_6H_4-NO_2-p
92c	CH_3	H	C_6H_4-CH_3-o	92h	C_6H_5	H	C_6H_4-CH_3-o
92d	CH_3	H	C_6H_4-OCH_3-p	92i	C_6H_5	H	C_6H_4-OCH_3-p
92e	CH_3	C_6H_5	C_6H_5	92j	C_6H_5	C_6H_5	C_6H_5

Mohammad et al [69] synthesized a series of 1, 3, 4-oxadiazole [93 and 94] and 1, 2, 4-triazole [95] derivatives of 4-hydroxyphenyl acetic acid and evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method. The compounds, which showed good anti-inflammatory activity, were screened for their ulcerogenic and lipid peroxidation activities.



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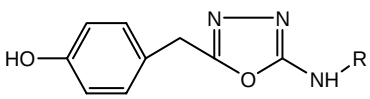
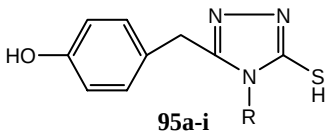


94a-i

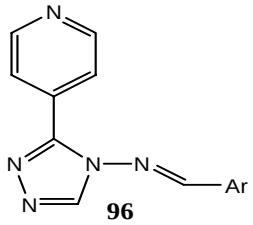


95a-i

94a	**Phenyl**	**94f**	**2-Methylphenyl**	**95a**	**Phenyl**	**95f**	**2-Methylphenyl**
94b	**2-Chlorophenyl**	**94g**	**4-Methylphenyl**	**95b**	**2-Chlorophenyl**	**95g**	**4-Methylphenyl**
94c	**4-Chlorophenyl**	**94h**	**4-Methoxyphenyl**	**95c**	**4-Chlorophenyl**	**95h**	**4-Methoxyphenyl**
94d	**4-Bromophenyl**	**94i**	**n-Butyl**	**95d**	**4-Bromophenyl**	**95i**	**n-Butyl**
94e	**4-Fluorophenyl**			**95e**	**4-Fluorophenyl**		

Analgesic-Antipyretic activities

Anees A. Siddiqui et al [70] synthesized some 4- [{1-(aryl)methylidene}-amino]-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole derivatives (96) starting from isonicotinic acid hydrazide, ethanol, potassium hydroxide and carbon disulphide and screened for analgesic, antipyretic activities. Analgesic activity evaluated by tail-flick method in rats at a dose of 25mg/kg and antipyretic activity was evaluated using Brewer's yeast-induced pyrexia in rats. Fever was induced by subcutaneously administered 20 ml/kg of 20% aqueous suspension of Brewer's yeast in normal saline, below the nape of the neck and rectal temperature was recorded with a clinical thermometer. Aspirin (300 mg/kg) was used as a standard drug for comparing the antipyretic action of compounds.

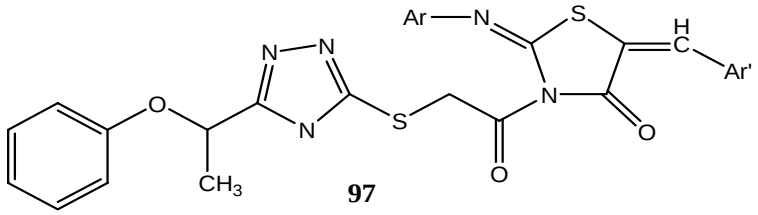


96

Ar = -C_6H_4-4Cl (93a), -C_6H_5-4N $(CH_3)_2$ (93b), -C_6H_5-3NO2 (93c), -C_6H_5-3OH (93d), -C_6H_5-4OCH_3 (93e), -C_6H_5-3Cl (93f)

Anticonvulsant activity

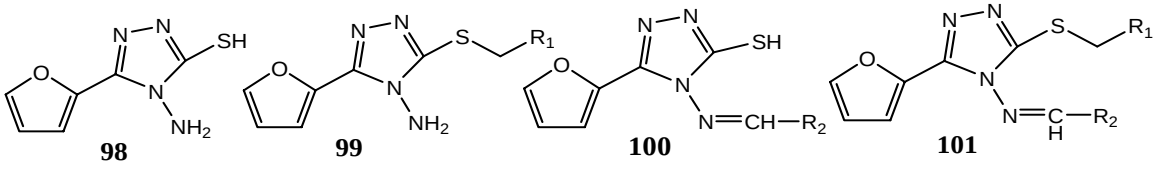
Number of articles were found for the anticonvulsant potential of 1, 2, 4-triazole where substitution on 2, 3, 5 positions were done. Recently anticonvulsant activity of clubbed Thiazolidinone-barbituric acid and Thiazolidinone-triazole derivatives have been reported **[71]**. 3-(2-chloroacetyl)-2-arylimino-5-[(Z)-arylmethylidene]-1, 3-thiazolan-4-ones on treatment with 5-(1-phenoxyethyl)-4H-1, 2, 4-triazole-3-thiol in identical conditions provided a set of bulkier derivatives which have also shown the anticonvulsant potential (97).



97

Vasoconstriction activity

Endothelin (ET), as a peptides family secreted from endothelial cell, plays a very important physiological role in vasoconstraction, and receptor antagonists attract much attention in search for novel therapeutics for the various cardiovascular diseases (CVDs). Xin Yong Liu et al [72] synthesized a series of novel 3-alkylthio-4-arylideneamino-5-(2-furyl)-1, 2, 4-triazole (98-101) derivatives. ET receptor competitive binding assay showed that some compounds exhibited high selective as potent ET-1 receptor antagonist.

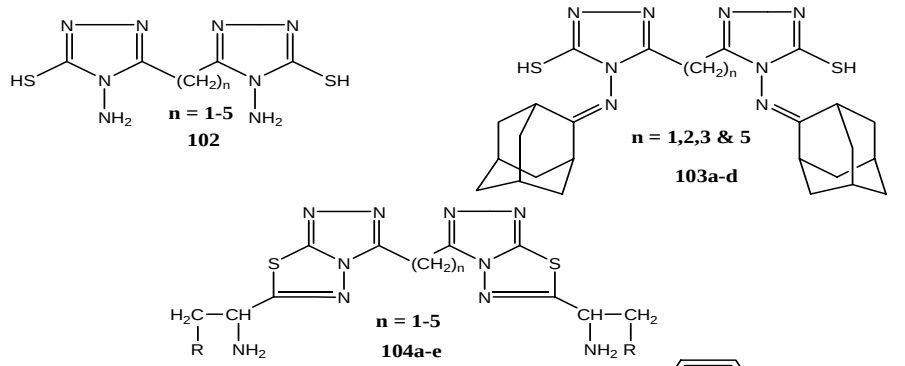


98 **99** **100** **101**

				R_1	**R_2**
99a	R_1= phenyl	**100a**	R_2=2-nitrofuryl	**101a** phenyl	2-nitrofuryl
99b	R_1=3-methoxylphenyl	**100b**	R_2=3,5-dimethylphenyl	**101b** 3-methoxyphenyl	2-nitrofuryl
99c	R_1=4-cyanophenyl			**101c** 4-cynophenyl	2-nitrofuryl
99d	R_1=ethoxylcarbonyl			**101d** dethoxycarbonyl	2-nitrofuryl
				101e phenyl	3,4-dimethoxylphenyl
				101f ethoxylcarbonyl	3,4-dimethoxylphenyl

Anticancer activity

Mohammad Al-Amin et al [73] synthesized a series of bis–[4-N-amino-5-mercapto-1, 2, 4-triazol-3-yl] alkanes (102) and their Schiff bases with 2-adamanta-none (103) and bis–[1, 2, 4-triazolo [3, 4-b] - 1, 3, 4-thiadiazol-4-yl] alkanes (104) derivatives. The cytotoxicity study of these newly synthesized compounds against brine shrimp lethality test performed.



n = 1-5
102

n = 1,2,3 & 5
103a-d

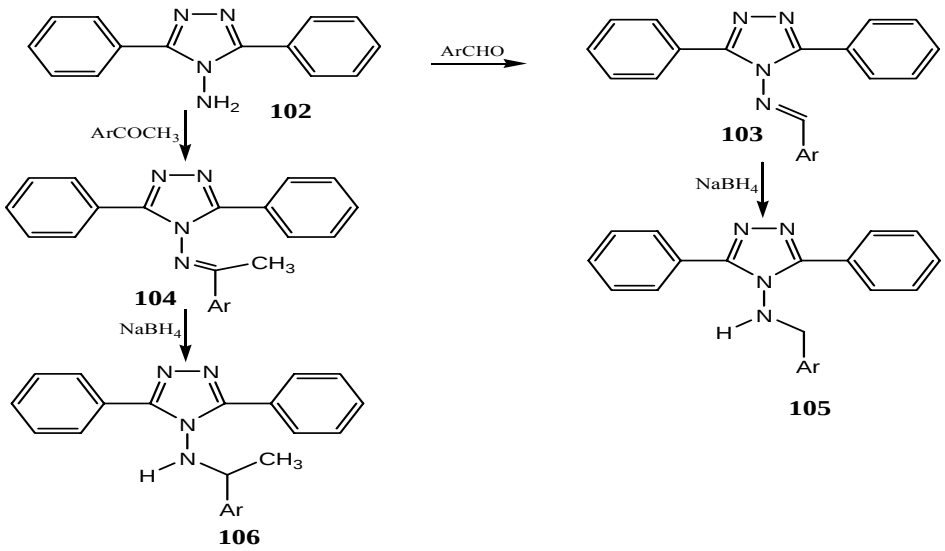
n = 1-5
104a-e

104a = & n = 1 , **104b** = & n = 5 , **104c** = & n = 5

104d = & n = 1 , **104e** = & n = 4

Anti-tumor activity

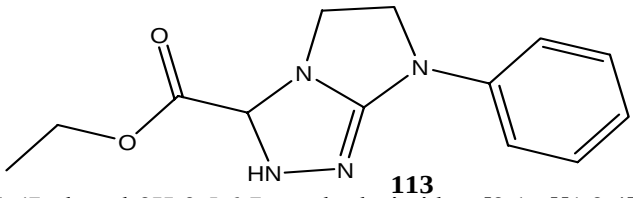
Several articles devoted to the synthesis and biological activity of 4-arylideneamino-4, 5-dihydro-1H-1, 2, 4-triazol-5-ones have been published recently [74]. Due to their structural features, the 4-arylideneamino-4H-1, 2, 4-triazoles are important as potentially bioactive agents [75]. **Olcay Bekircan et al** [76] synthesized a series of 4-arylideneamino-4H-1, 2, 4-triazoles (103) and 4-(1-aryl)ethylidene-4H-1, 2, 4-triazoles (104) by the treatment of 4-amino-1, 2, 4-triazole with certain aldehydes and ketones. Compounds 103 and 104 have been reduced with $NaBH_4$ to yield corresponding 4-arylmethylamino-4H-1, 2, 4-triazoles (105) and 4-(1-aryl) ethylamino-4H-1, 2, 4-triazoles (106). Compound 102 was obtained from the reaction of ethylbenzoate benzoylhydrazone with hydrazine using the published method [77]. In general, the reduction of an imine type compound can be possible [78-83]. Compounds have been screened on three human tumor cell lines, breast cancer (MCF7), non small cell lung cancer (NCI-H460), and CNS cancer (SF-268) at the National Cancer Institute, USA. The compounds are found to exhibit low anti-proliferative activity in the anticancer tests.



Antiviral activity

Krzysztof Sztanke et al [84] reported synthesis of ethyl 1-(7-phenyl-2H-3, 5, 6, 7-tetrahydroimidazo [2, 1-c] [1, 2, 4]triazol-3-yl)formate [113]. The influence of the ethyl 1-(7-phenyl-2H-3, 5, 6, 7- tetrahydro-imidazo[2,1-c][1,2,4]triazol-3-yl)formate on human adenovirus 5 (Ad-5) and human enterovirus (Echo-9) replication has been investigated. For this compound,

the activity against the selected DNA (Ad-5) and RNA (Echo-9) viruses and the cytotoxicity towards normal GMK (Green Monkey Kidney) cells were determined.



113

Ethyl 1-(7-phenyl-2H-3,5,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazol-3-yl)formate

Miscellaneous Uses

1, 2, 4-Triazole find used as analytical reagents for determination of boron [85], antimony [86] and cobalt [87], other triazoles find many synthetic uses as halogenating agents [88] or as activating polymeric reagents [89].

CONCLUSION

The synthesis of 1, 2, 4-triazole heterocycles that have been reported to present date illustrates different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel chemical derivatives. In general, 1, 2, 4-triazole derivatives are prepared by appropriate rearrangements, ring opening and substitution reaction. The literature reveals that 4-triazole has diverse biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers.

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