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SYNTHESIS AND BIOLOGICAL SIGNIFICANCES OF 1, 2, 4-TRIAZOLE AND ITS DERIVATIVES: A REVIEW

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Keywords:

Triazole, Heterocyclic, Antifungal, Anticancer Activity, Anti-Inflammatory Activity, Antiviral, Anticonvulsant Activity

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ABSTRACT: In the last few decades, to synthesize the different new heterocyclic compounds along their derivatives which were evaluated for their biological activities as antimicrobial, antiviral, antitumor, anticonvulsant, antifungal, the triazole moiety seems to be very small but in the biological profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. In this review we provides a brief response of the medicinal chemistry of 1, 2, 4-triazole and its derivatives. A literature survey of procedures for the preparation of 1, 2, 4-triazole and 1, 2, 3-triazoles is presented by generalized synthetic method.

INTRODUCTION: Triazoles are the class of heterocyclic compounds [1] which are under study since many a years. 1, 2, 4-Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms azole ring are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus display versatile biological activities.

In recent years, the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance.

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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**. 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 [2], low toxicity and good Pharmacokinetic and Pharmacodynamic profiles. Its diversity in showing the pharmacological activities is mind blowingly identified well by the medicinal chemists as;

(1) (2)

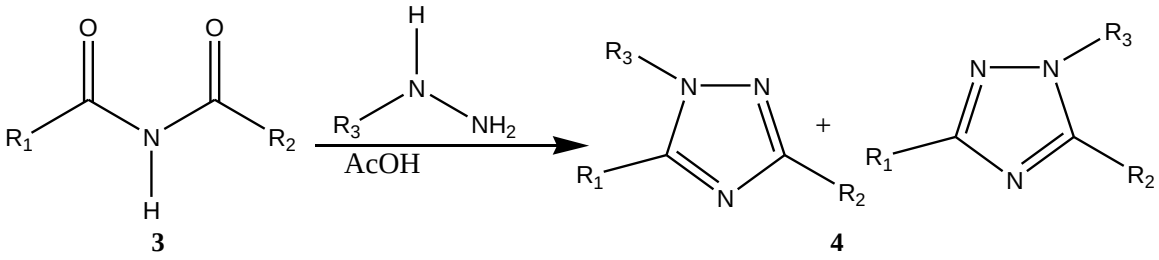
1, 2, 3-TRIAZOLE **1, 2, 4-TRIAZOLE**

FIGURE 1: TRIAZOLES

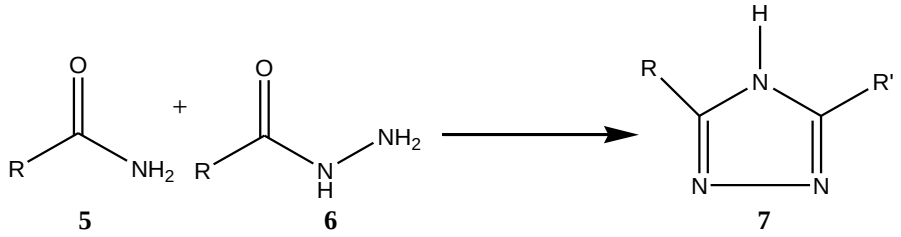
Pyrimidines [3], D-manno-pentitol-1-yl-1, 2, 4-triazoles [4], benzotriazoles [5], indoles [6], quinolones [7], triazolo thymidines [8], are in record. Literature survey reveals that 1, 2, 4-triazole derivatives exhibit wide range of biological activities including antibacterial [9-11] antifungal [12-13] antitumour [14], anti-inflammatory [15], antitubercular [16], anti-convulsant [17], anticancer [18], antimalarial [19], antiviral [20], analgesic [21] and antimigrain [22].

Synthesis of 1, 2, 4-triazole backbone: 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.

Einhorn-Brunner [23-26] reported synthesis of a mixture of isomeric 1, 2, 4-triazoles (4) from the reaction of imides (3) with alkyl hydrazines in presence of acyl hydroxide (**Scheme 1**). Pellizzari [27] reported synthesis of substituted 1, 2, 4-triazole (7) by the reaction of an amide (5) and a hydrazide (6) (**Scheme 2**).

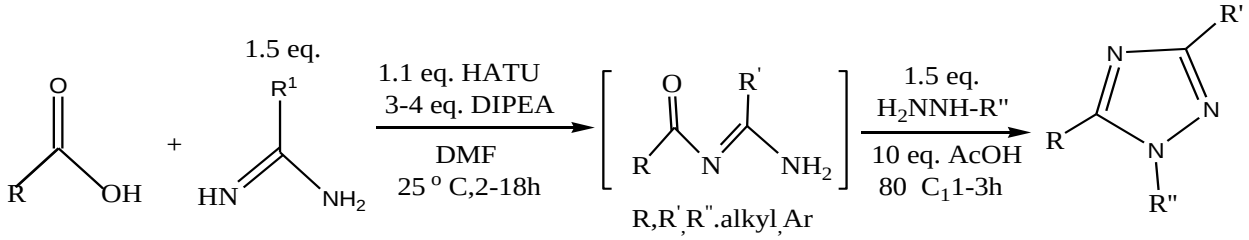


SCHEME 1: Synthesis of a mixture of isomeric 1, 2, 4-triazoles using imides with alkylhydrazines in presence of acyl hydroxide



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

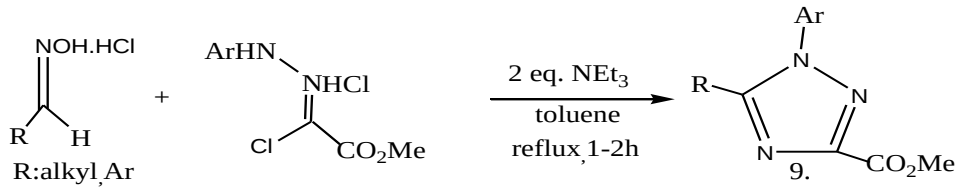
G.M. Castanedo *et al*, [28] have synthesized a highly regioselective one-pot process provides rapid access to highly diverse 1, 3, 5-trisubstituted 1, 2, 4-triazoles (8) from reaction of carboxylic acids, primary amidines, and monosubstituted hydrazines.



8

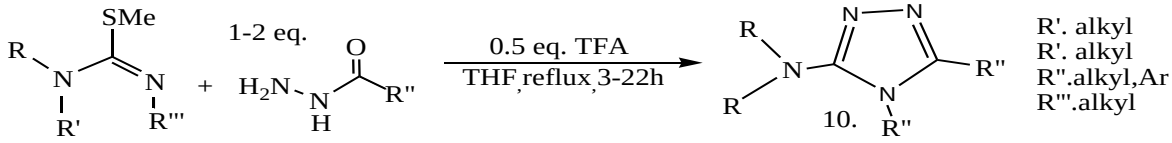
SCHEME 3

L.Y. Wang *et al*, [29] have synthesized an effective 1, 3-dipolar cycloaddition for the synthesis of 1, 3, 5-trisubstituted 1, 2, 4-triazole derivatives (9) by reaction of oximes with hydrazonoyl hydrochlorides using triethylamine as a base gave the desired 1, 3, 5-trisubstituted 1, 2, 4-triazoles in good yields. The reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates.



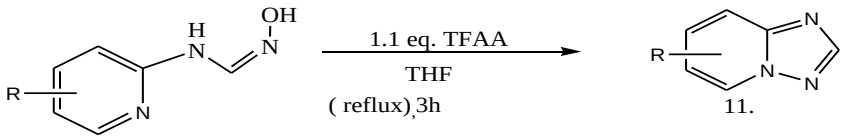
SCHEME 4

D.V. Batchelor *et al*, [30] have synthesized 3-*N*, *N*-Dialkylamino-1, 2, 4-triazoles (10) can be prepared from *S*-methylisothioureas and acyl hydrazides in good yields. The reaction conditions are relatively mild and tolerate a broad range of functional groups.



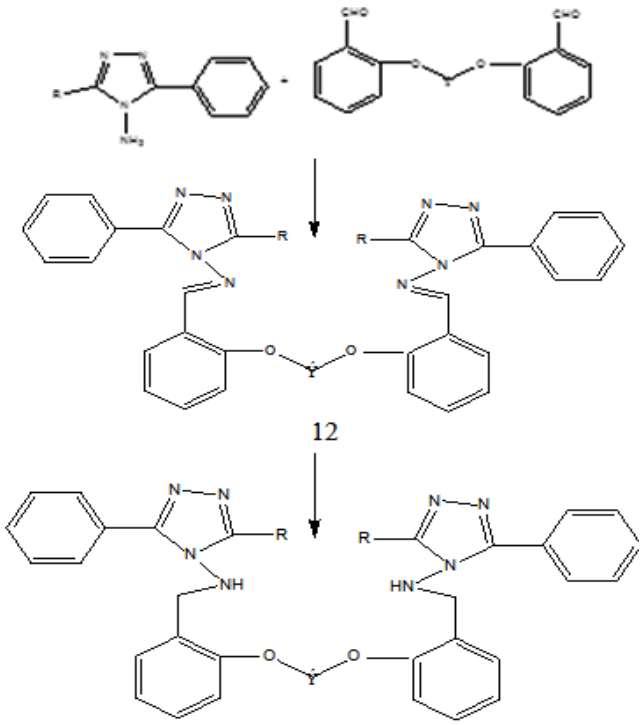
SCHEME 5

E. Huntsman *et al*, [31] have synthesized [1, 2, 4] Triazolo[1, 5-*a*]pyridines (11) have been prepared in good yields from 2-aminopyridines by cyclization of *N*-(pyrid-2-yl) formamidoximes under mild reaction conditions with trifluoroacetic anhydride.



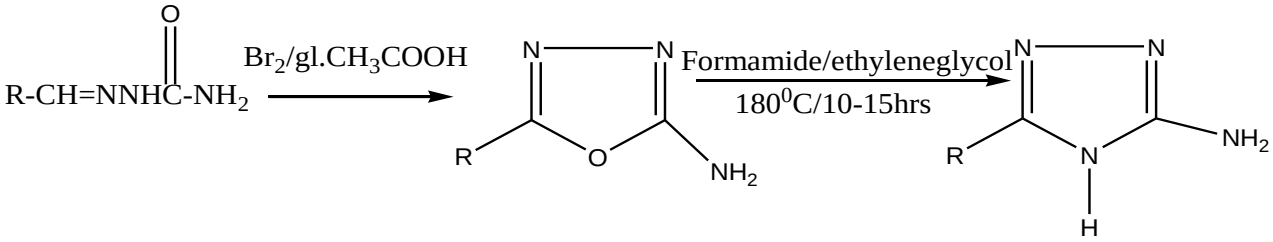
SCHEME 6

Olcay Bekircan et al [32] have synthesized new bis-1, 2, 4-Triazole derivatives by the reaction of 3-Aryl-5-phenyl-4-amino-4H-1, 2, 4-triazoles and bis-aldehydes 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. Compounds (12) 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 (13)



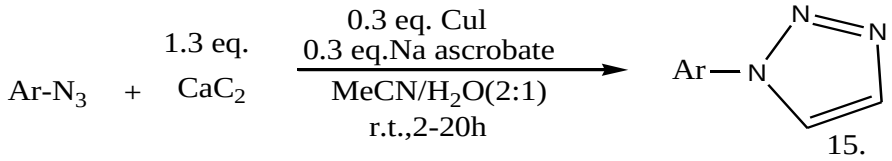
SCHEME 7

V. Ram *et al*, [33] have synthesized (14) triazole derivatives as below;



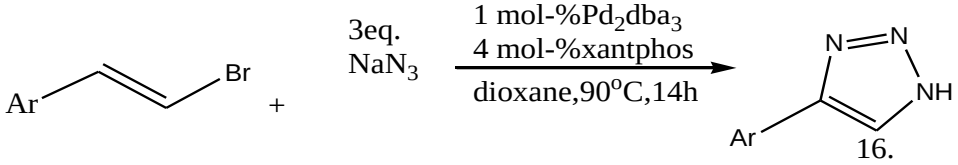
14

Y. Jiang *et al*, [34] have synthesized 1-monosubstituted aryl 1, 2, 3-triazoles (15) was prepared in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1, 3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H_2O mixture.



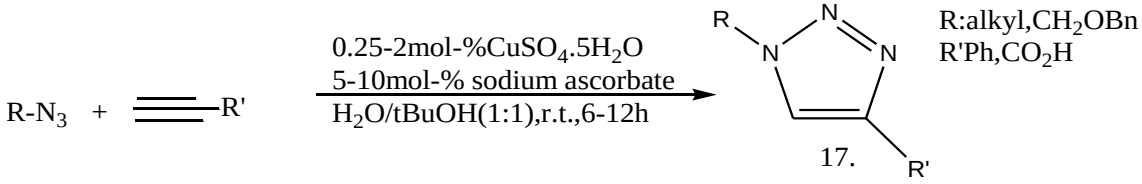
15.

J. Barluenga *et al*, [35] have synthesized (16) a Pd-catalyzed synthesis of 1*H*-triazoles from alkenyl halides and sodium azide represents a completely new reactivity pattern in the context of Pd chemistry.



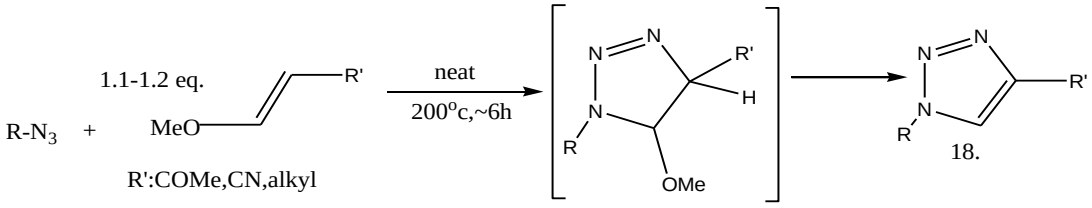
16.

F. Himo *et al*, [36] have synthesized, Cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to (17) 1, 4-disubstituted 1, 2, 3-triazoles and 3, 4-disubstituted isoxazoles, respectively.



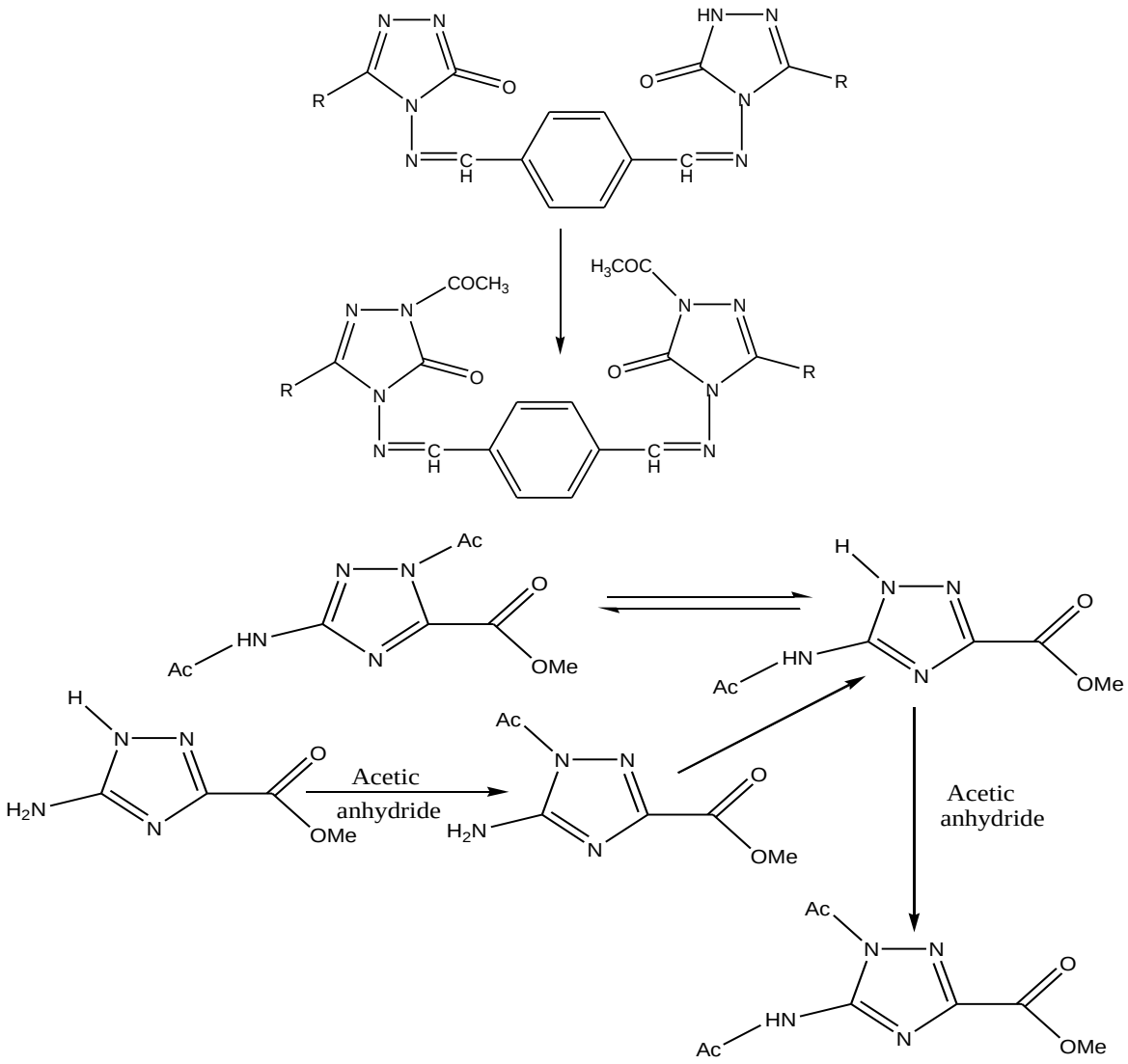
17.

D. R. Rogue *et al*, [37] have synthesized 1, 2, 3-Triazoles (18), were prepared in good to modest yields by cycloaddition of alkyl azides onto enol ethers under solvent-less conditions. The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable. The 1, 2, 3-triazole products bear functionality that may be readily derivatized.



18.

Rebecca Hluhanich *et al*, and Ilkay kucukguzel *et al*, summarized acetylation reactions**:** N, N'- bis(3-alkyl-4, 5-dihydro-1, 2, 4-triazol-5-on-4-yl)-1, 4-xylenediimines 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-4-yl)-1,4-xylenediimines **[62],** methyl 5-amino-1H-[1, 2, 4] triazole-3-carboxylate undergoes acetylation in presence of acetic anhydride (AC_2O) to form two isomeric diacetylated products **[63].**



19

BIOLOGICAL SIGNIFICANCES:

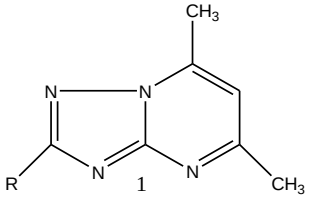
Antibacterial activity:

Antibacterial: Bacteria are the simplest and smallest unicellular organisms found individually or in clusters. The multitude of highly effective and relatively non-toxic drugs available for the treatment of bacterial infections has provided tough competition for the medicinal chemist, attempting synthesis of new antibacterial agents. The medicinal chemistry is towards its advancement, many antibiotics are now chemically modified from original compounds present naturally e.g. beta lactams [38] and named as amino glycosides and a lot more are synthetically derived as sulfonamides [39], the quinolones and the oxazolidinones.

They are classified in two types based on their mode of action as bactericidal agents and bacteriostatic agent [40]. Among various triazole derivatives, base and sugar modified nucleoside derivatives reflect a potent anti-microbial activity resulting in its application in the chemotherapy of cancer and viral infection.

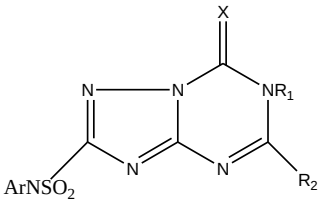
The inhibitory effect of N-glucosides (1), (3) and those of S-glucosides (2) are manipulated by changing the position of substituent on aromatic ring.

V. Ram *et al*, [41] have synthesized triazole substituted triazolo-pyrimidine derivatives and found antibacterial activity. In compound (1), R= pyridyl



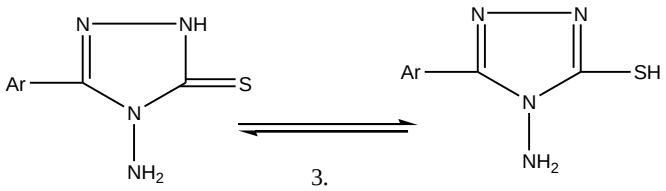
1

Westerman *et al*, [42] have prepared 6, 7-dihydro-1, 3, 4-triazolo[1, 5-a]-1, 3, 5-triazin-2-Sulfonamides (2) and found them as agents with herbicidal and plant growth regulting activity. In compound 2, Ar=(un) / substituted Ph, naphthyl, pyridyl; R=H, acyl, alkyl,phenyl-alkyl,(un) substituted carbonyl etc.R_1,R_2= phenyl; X=O,S.



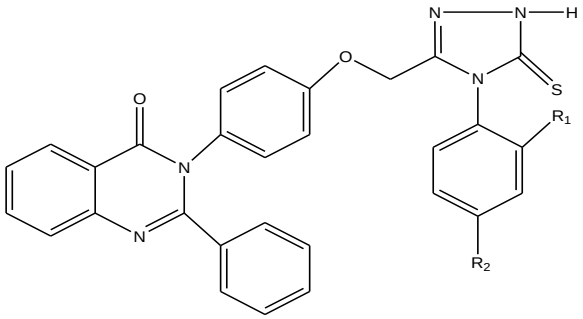
(2)

Katica Colanceska-Ragenovic *et al*, [43] synthesized a few 4-allyl/amino-5-aryl-1, 2, 4-triazoles (3) and tested for antibacterial and antifungal effects against *Escherichia coli, Bacillus subtilis, Salmonella enteritidis, Staphylococcus aureus, Aspergillus niger* and *Candida albicans*.



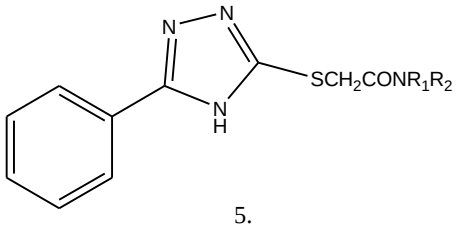
3.

Freddy H. Havaldar *et al*, [44] have 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 (4) and were evaluated *in vitro* for their antibacterial activity.



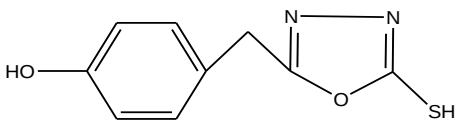
4

R.K. Mali *et al***,** [45] have synthesized 5-(N-substituted carboxamidomethylthio)–3-(3'-pyridyl) - 1, 2, 4-triazole derivatives and were evaluated in for their antibacterial activity.

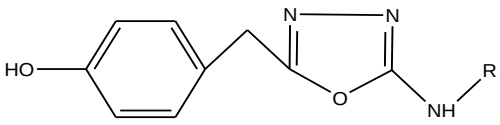


5.

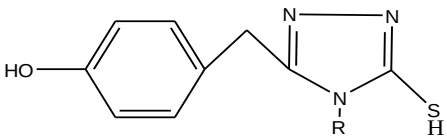
Anti-inflammatory Activity: Mohammad *et al*, [46] synthesized a series of 1, 3, 4-oxadiazole [6a-6b] and 1, 2, 4-triazole [6c] derivatives of 4-hydroxyphenyl acetic acid and evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method. The compounds, which showed good anti-inflammatory activity, were screened for their ulcerogenic and lipid peroxidation activities.



(6a)

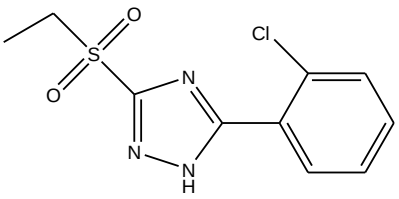


(6b)



(6c)

Birsen Tozkoparan *et al***,** [47] synthesized triazoles (7-8) showed anti-inflammatory activity.



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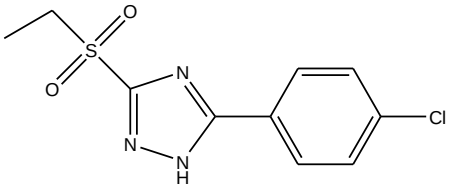
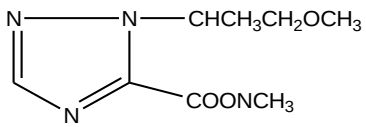


8

Abbas *et al* [48] synthesized substituted (9-10). Triazoles showed anti-inflammatory activity.



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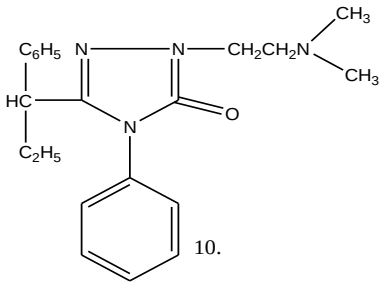
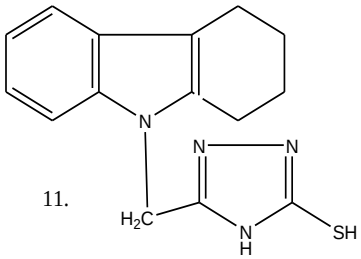


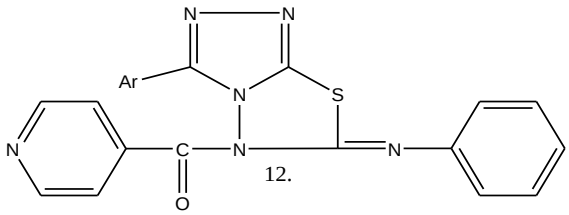
10.

Radhakrishana T.R. *et al,* [49] synthesized triazoles (11).showed anti-inflammatory activity.



11.

R.H.Udupi *et al,* [50] synthesized triazoles derivative (12).showed anti-inflammatory activity.

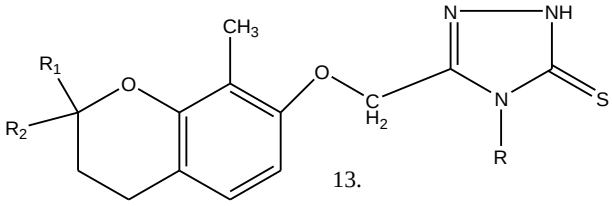


12.

Ar=Phenyl

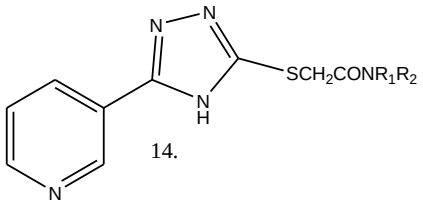
Antifungal activity: Antifungals are the class of drugs that are used to eradicate fungal infections from the human body. Fungi are heterotropic microorganisms that are distinguished from algae by lack of photosynthetic ability. Fungi include both yeast and moulds. The former are spherical, oval and mucosid colonies in agar medium and the latter consists of elongated cells that usually reproduce by budding and forming branches of cells.

Ahluwalia *et al,* [51] have synthesized (13). 5-(3', 4'-dihydro-2', 2', 8'-trimethyl-2'H-1'-benzopyran-7-yloxymethyl)-4-phenyl-1, 3, 4-triazole-3(4H)-thiol (III) which shows significant antifungal activity. R=C_6H_5, mcl-C_6H_4, pcl-C_6H_4,m-or pCH_3- C_6H_4, pCH_3O- C_6H_4.R_1=CH_3, C_6H_5,R_2=H,CH_3.



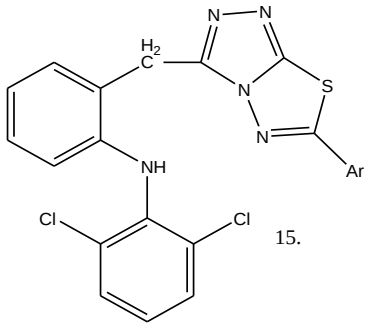
13.

R.K. Mali *et al,* [52] synthesized 5-(N-substituted carboxamidomethylthio)–3-(3'-pyridyl) - 1, 2, 4-triazole (90) derivatives (14). 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.



14.

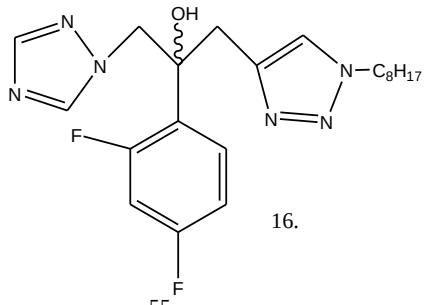
K. Ilango *et al,* [53] synthesized a new series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles. The compounds (15) were screened for antifungal activity against *Candida albicans* and *Aspergillus niger* using Ketoconazole as standard.



15.

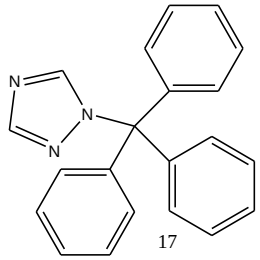
Nilkanth G. Aher *et al,* [54] Candida fungal pathogens were impinged by the new triazole derivatives **(16),** analogous to the fluconazole both by *in vivo* and *in vitro*. The easily accessible molecules, 1, 4-disubstituted-1, 2, 3-triazole compounds with long alkyl chains displayed a good antifungal activity.

It was more potent than the standard drugs namely ketoconazole, amphoterecin B and fluconazole. The enantiomers are still under process as they are supposed to have more potent activity than the racemic compounds.



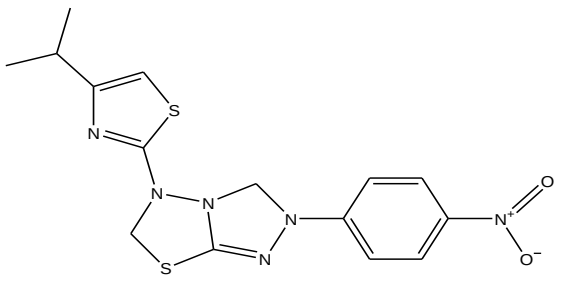
16.

Xiaoyun Chai, *et al*, [55] *fumigatus* was impinged by nearly all type of synthesized compounds and showed broad spectrum activity. The compound **(17)** showed 128 times more activity against *Candida albicans*.



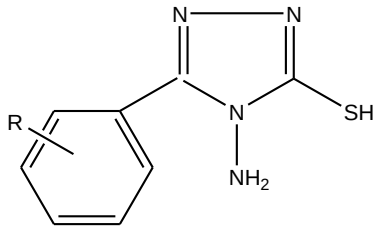
17

Mitscher LA *et al*, [56] 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 (**18),** named 3-(4-Isopropylthiazol-2-yl)-6-(4-nitrophenyl)-[1, 2, 4]triazolo[3, 4-b][1, 3, 4]thiadiazole.



18

Todoulou O.G *et al*, [57 and 58-60] have evaluated the compounds (19-22) as below and found antifungal activity.



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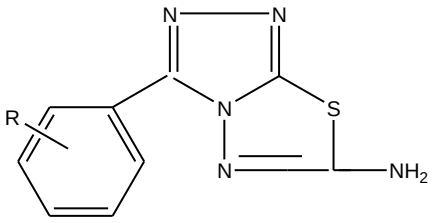

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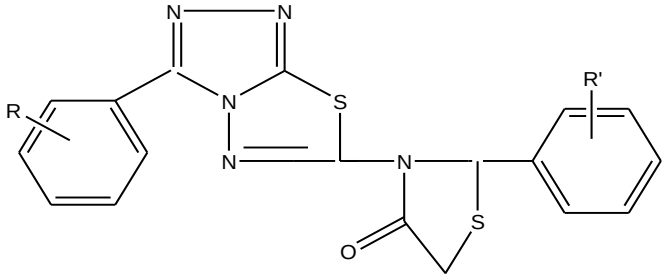

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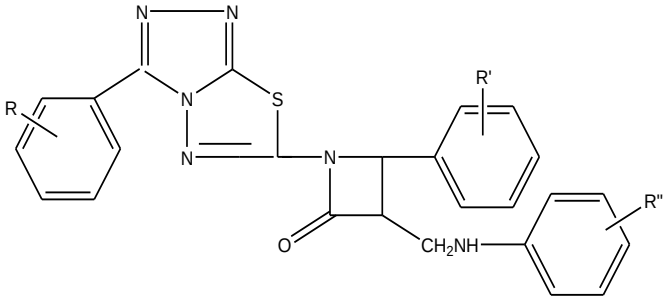
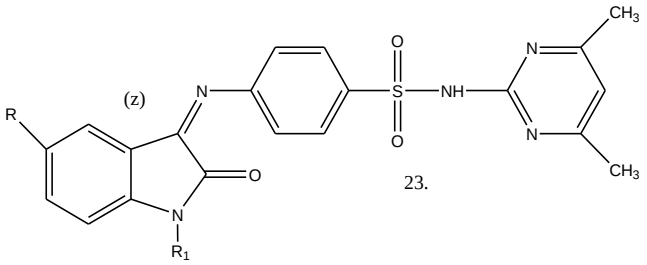


22

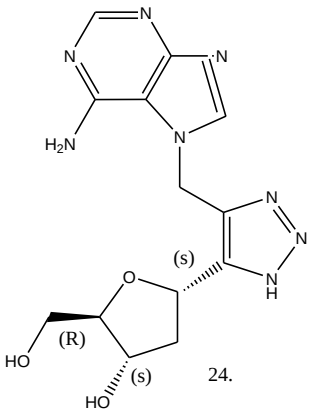
Antiviral activity: HIV (retrovirus) is a virus resulting in the slow depletion of immune system of the affected human beings resulting in opportunistic infections.

Some new compounds were synthesized by P. Selvam *et al*, [61] 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 (**23)** were prepared and they were found active against replication of HIV-1 and HIV-2 in MT-4 cells.



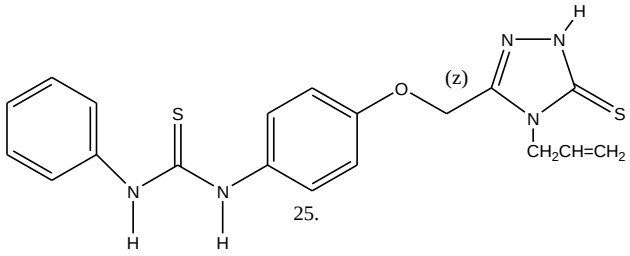
23.

Rebecca Hluhanich *et al*, [62] synthesized Various derivatives of trisubstituted triazoles (**24)** were prepared as inhibitors of reverse transcriptase and the two derivatives with difference in thio group position were found out to be most active compounds .



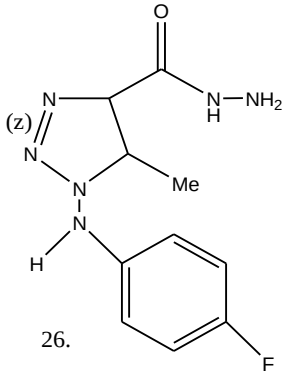
24.

Ilkaykucukguzel *et al*, [63] prepared as the novel thiourea derivatives obtained from 5-[(4-amino phenoxy)methyl]- 4-alkyl/aryl-2, 4-dihydro-3H-1, 2, 4 triazole-3- thiones (25) which proved to be having a good activity against cox sacie virus B4, also active against the thymidine kinase positive *Varicella zoster* Virus.



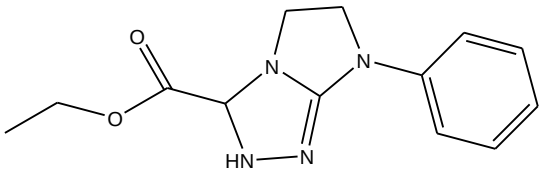
25.

Alessandro K. *et al*, [64] prepared (26) N-amino-1, 2, 3-triazole and evaluated for Antiviral activity against cantalago virus.



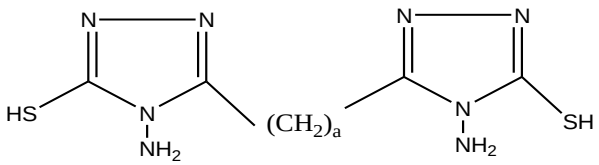
26.

Krzysztof Sztanke *et al*, [65] reported synthesis of (27). ethyl 1-(7-phenyl-2H-3, 5, 6, 7- tetrahydro-imidazo [2, 1-c] [1, 2, 4]triazol-3-yl)formate 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 adenovirus5 (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. Ethyl 1-(7-phenyl-2H-3,5,6,7-tetrahydroimidazo[2,1-c][1,2,4]triazol-3-yl)formate



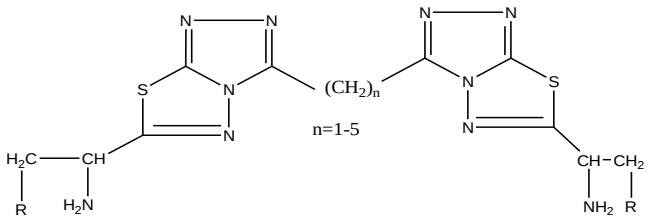
27.

Anticancer activity: Mohammad Al-Amin *et al*, [66] synthesized a series of bis–[4-N-amino-5-mercapto-1, 2, 4-triazol-3-yl] alkanes and and bis–[1, 2, 4-triazolo[3, 4-b] - 1, 3, 4-thiadiazol-4-yl] alkanes derivatives (28).

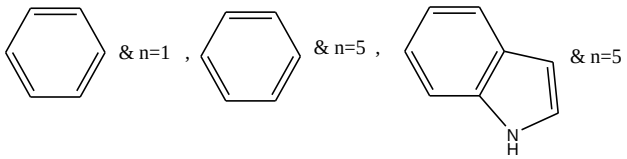


n=1-5

(28)



(29)



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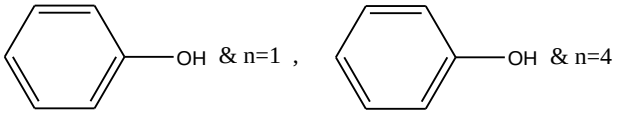
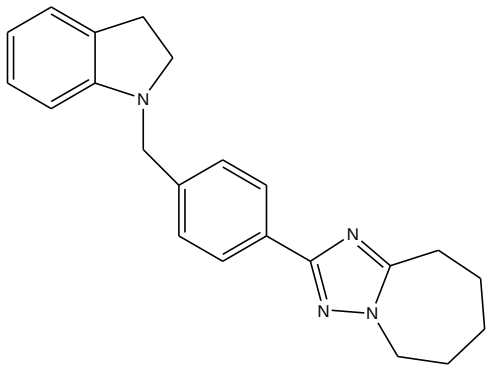


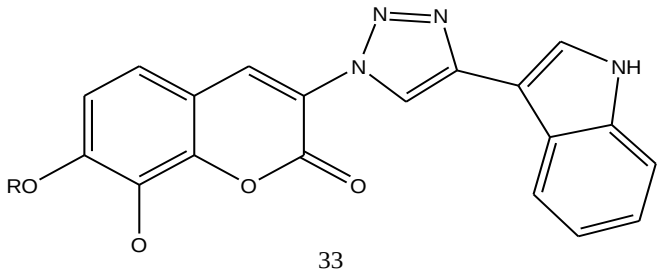
(31)

H. Mujagic *et al*, [67] synthesized Compound 1-(6, 7, 8, 9-Tetrahydro-5H-[1, 2, 4]-triazolo[1, 5,-a]-azepine-2-yl)benzyl]indole (32**),** 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.



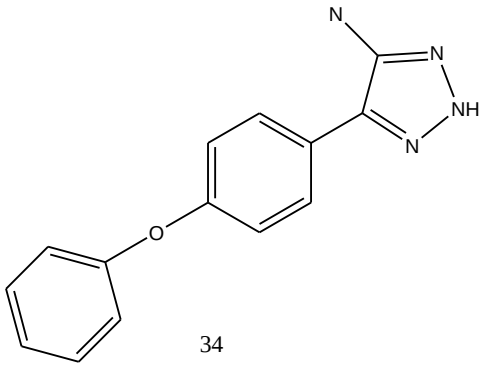
32

Laura B. Peterson *et al*, [68] synthesized triazole analogues (**33)** where triazole moiety is analogy to amide moiety of natural products. The SAR suggest that the sterically demanded side chains consisting of biaryl, indole or homologated aryl groups showed better activity than substituted aryl compounds



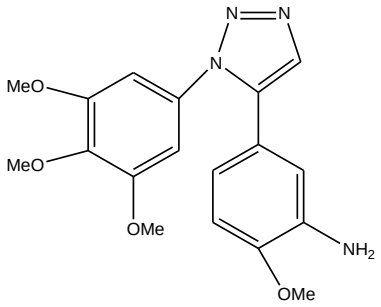
33

Zhi-Yi Cheng *et al*, 69 synthesized 4-aryl-5-cyano-2H-1, 2, 3-triazole were synthesized and found to have HER2 tyrosine kinase inhibitors. The lipophilicity of the substituting groups in (**34)** is the main bioactivities which is rational by the IC_{50} value. 4 Phenyl position on the triazole is the best substituting position for inhibitory activity.



34

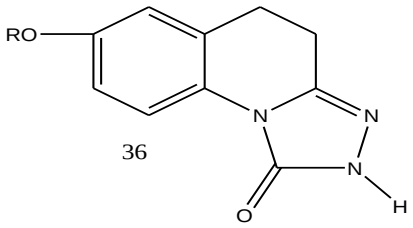
Kristin Odlo *et al*, [70] synthesized a compound named 2-methoxy-5-(1-(3, 4, 5-trimethoxyphenyl)-1H-1, 2, 3-triazol-5-yl) aniline showed potent cytotoxic activity. Molecular modelling supported that the activity of (**35)** was most likely due to binding site of α, β-tubulin in the β subunit. They were represented as cis restricted analogue of combresatin.



35

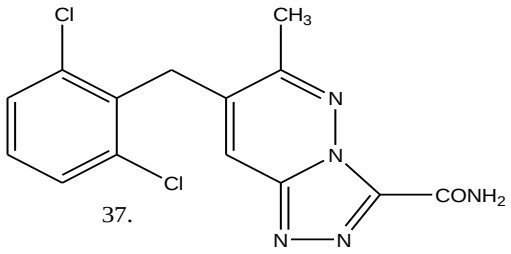
Anticonvulsant agents: Seizures initiate by the rapid and excessive firing of neurons and is controlled by the class of drugs called Anticonvulsant.

Hong Guang Jin *et al*, [71] reported the synthesis of 7-alkoxy-4, 5- dihydro[1, 2, 4]triazolo[4, 3-a]quinoline1(2*H*)-ones (36) and investigated for anticonvulsant activity and neurotoxicity



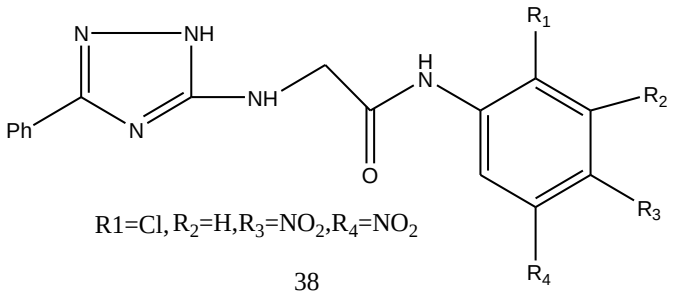
36

S. Moreau *et al,* [72] reported the synthesis of 3-amino-7- (2, 6-dichlorobenzyl)-6-methyl triazolo[4, 3-b]pyridine derivatives (37) of amide and carboxylic acid and investigated for their anticonvulsant potency



37.

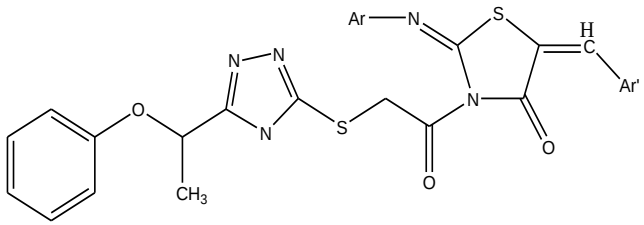
Dayanand Kadadevar *et al,* [73] reported the synthesis and evaluation of N-(substituted phenyl)-2-[5-phenyl-2*H*-1, 2, 4-triazol-3-yl-amino]acetamide (38) for their anticonvulsant activity



R1=Cl, R_2=H,R_3=NO_2,R_4=NO_2

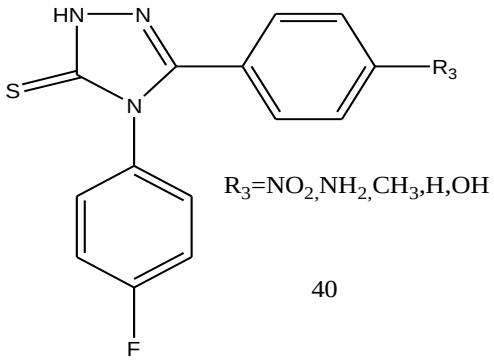
38

Liu Xin *et al,* [74] recently anticonvulsant activity of clubbed Thiazolidinone-barbituric acid and Thiazolidinone-triazole derivatives have been reported (39).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.



39

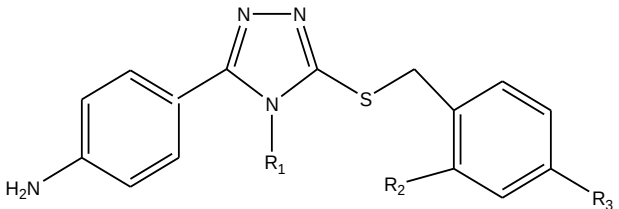
M. Shalini *et al,* [75] synthesized and anticonvulsant activity of 4,5-diphenyl-2H-1,2,4- triazole was carried out on four animal models of seizures namely , viz. Maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)- induced seizure threshold tests. The various substituted compounds (40**)** showed the anticonvulsant activity



R_3=NO_2,NH_2,CH_3,H,OH

40

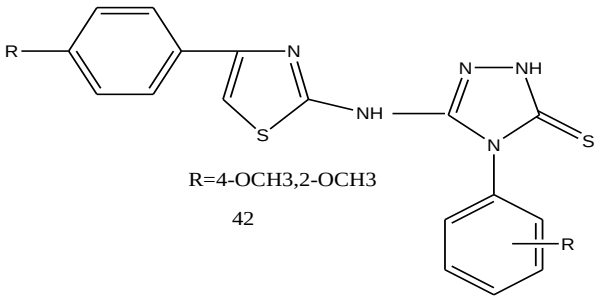
Ilkay Kucukguzel *et al,* [76] synthesized a Novel series of 3-{[(substituted phenyl) methyl] thio} -4-alkyl/aryl-5-(4-aminophenyl)- 4H-1, 2, 4-triazoles (**41),** was synthesized which were similarly evaluated by the above said technique and the two active compounds were evaluated and was concluded that the alkyl substitution or primary amino group were essential for the compound to show an activity.



R_1=CH_3,CH_2,$CH=CH_2$

R_2=H,R_3=H 41

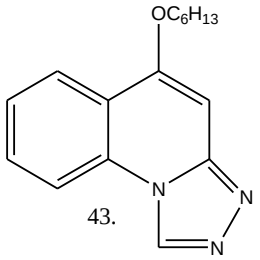
Nadeem Siddiqui *et al,* [77] synthesized a new class of drug (**42)** incorporating triazoles to thiazoles 3-[4-(substituted phenyl)-1, 3-thiazol -2- ylamino] -4-(substituted phenyl)-4, 5-dihydro-1H-1, 2, 4-triazole-5-thiones were synthesized and found to have anticonvulsant activity which was designed as keeping in view the structural requirement of pharmacophore model. The figures of Protective index (PI), Median Hypnotic Dose (HD_{50}), and Median lethal dose were higher than the standard drugs.



R=4-OCH3,2-OCH3

42

Li-Jun Guo *et al*, [78] synthesized 5-hexyloxy-[1, 2, 4] triazolo [4, 3-a] quinoline (**43)** and evaluated, found potent anticonvulsive in nature with low level of neurotoxicity. All the possible mechanism of anticonvulsive activity was done in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test**.**



43.

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