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1, 2, 4-Triazole Scafolds: Recent Advances and Pharmacological Applications

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KEYWORDS

Triazoles, 1,2,4-triazoles, Heterocycle compounds, Antifungal, Antimicrobial

A B S T R A C T

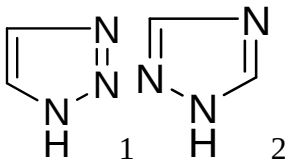
1,2,4-Triazole and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. The 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive, analgesic, anti-inflammatory, anti-tumor, anti-viral, urease inhibition and many other properties. Either as single heterocyclic derivatives or in fusion with the other cycles, these heterocycle is emerging as the most explored center to obtain clinically significant compounds. In present study we explore the method of preparation, some recent advances and biological activities of 1,2,4-triazoles which give an idea about this moiety as potent medicinal agent for new drug discovery.

Introduction

Now a day research for new drug discovery concentrated towards the development of safe therapeutic agents with clinical importance. In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. Azoles are important five membered heterocyclic rings containing at least one nitrogen atom like Isoxazole, Thiazole, Pyrazole and Triazole. 1,2,4 triazoles are one of the important moiety of medicinal agents which fulfill the requirements of new drug discovery. 1,2,4-Triazoles and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities including anti-microbial, sedative, anti-convulsant, anti-inflammatory and other properties, and consequently the synthesis of these heterocycles has received considerable attention in recent years. Some of the present day drugs such as Ribavirin (antiviral agent), Rizatriptan (antimigraine

agent), Alprazolam (anxiolytic agent), Fluconazole and Itraconazole (antifungal agents) are the best examples for potent molecules possessing triazole nucleus.

The heteroaromatic triazole ring system is composed of five atoms, two carbon and 3 nitrogen, which can be arranged in two combinations to give 1,2,3-triazole(1) or to give 1,2,4-triazole(2)



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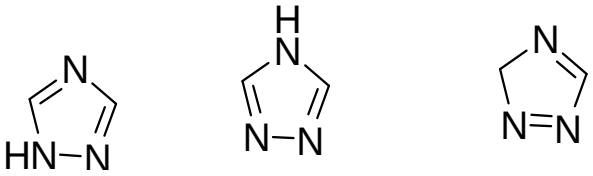
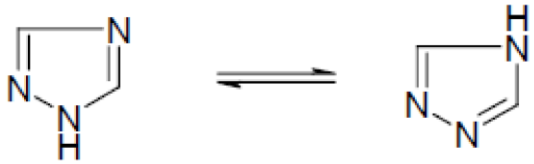
Although two NH and one CH_2 tautomeric forms are possible for 1,2,4-triazole, this structure is best represent as a positively charged hydrogen associated with the resonance stabilized triazole anion.



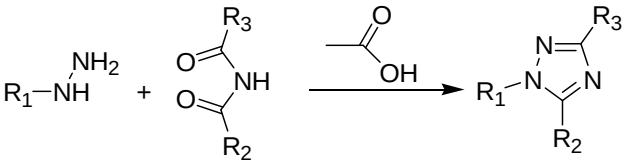
In other words 1,2,4-triazole refers to either one of a pair of isomeric chemical compounds with molecular formula C2H3N3, having a five-membered ring of two carbon atoms and three nitrogen atoms. 1,2,4-triazoles are exist in two forms i.e. 1*H* and 4*H*.



triazoles

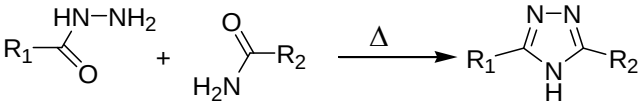
Preparation of 1,2,4-triazoles via the Einhorn–Brunner cyclization Reaction

The Einhorn–Brunner reaction occurs between an alkyl hydrazine and an imide. This cyclization reaction is catalyzed by an organic acid, such as acetic acid[1].



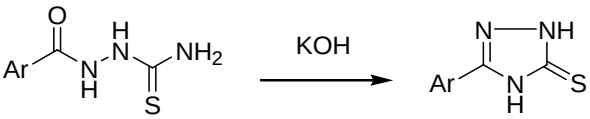
Preparation of 1,2,4-triazoles via the Pellizzari cyclization Reaction

In the Pellizzari reaction, an acyl hydrazide is condensed with an amide at high temperature[2].

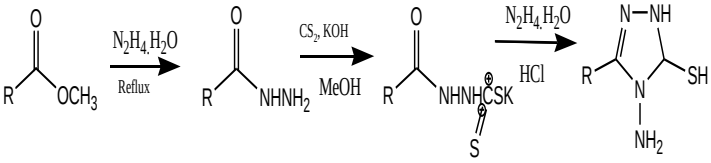


Prepration of 1,2,4-triazoles by 4-acylthiosemicarbazide

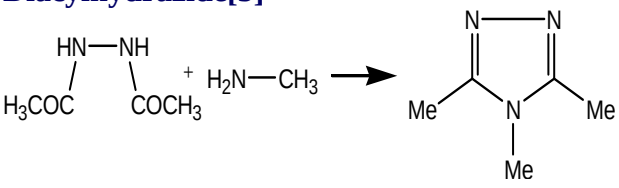
5-aryl-1,2,4-triazole-3-thiones, were obtained by the reaction of 4-acylthiosemicarbazide with KOH 10% under reflux, followed by the acidification with concentrated hydrochloric acid[3].



Prepration of 1,2,4-triazoles from Esters[4]



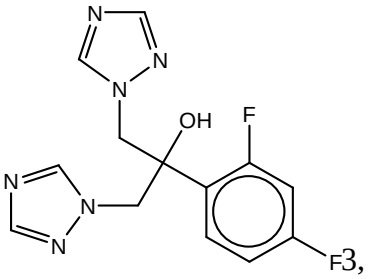
Prepration of 1,2,4-triazoles from Diacylhydrazide[5]



Antifungal Activity and Antimicrobial Activity

Antifungal activity exhibited by many potent antifungal agents is attributed to the presence of
triazole ring system. Major examples of triazole containing antifungal agents include

Fluconazole (3), **Voriconazole (4) and Itraconazole (5)**.



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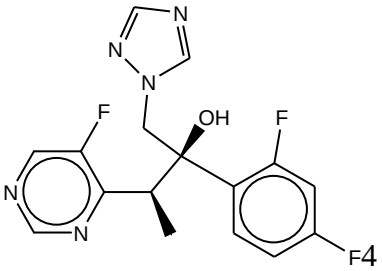

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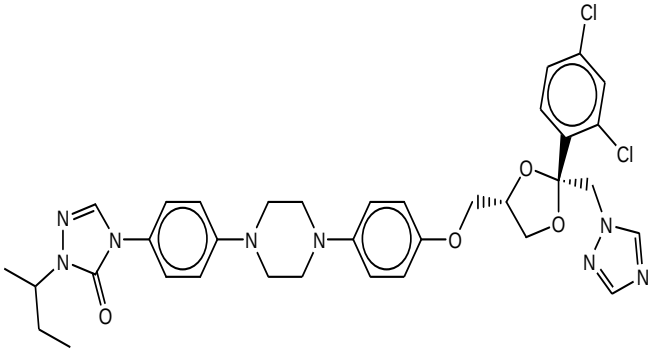

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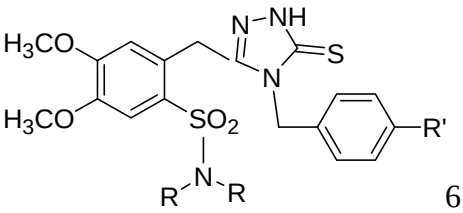
Iraj Rahavi Ezabadi *et al* [6] synthesized a series of 10 new 5-[2-(substituted sulfamoyl)-4,5-dimethoxy-benzyl]-4aryl-s-triazole-3-thiones(6) and evaluated for in vitro antifungal and antibacterial activity. All compounds tested showed significant antifungal activity against all the micromycetes, compared to the commercial fungicide bifonazole.

Jianming Xu *et al* [7] designed and synthesized based a series of novel 1,2,4-triazole derivatives with a 4-(4-substitutedphenyl) piperazine side chain on the structure of lanosterol 14a-demethylase (CYP51). Their antifungal activities against eight human pathogenic fungi were evaluated in vitro and resulted that all tested compounds (7) were found to be more potent against *Candida albicans* than control drug fluconazole.



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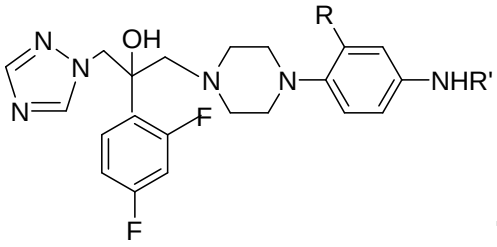
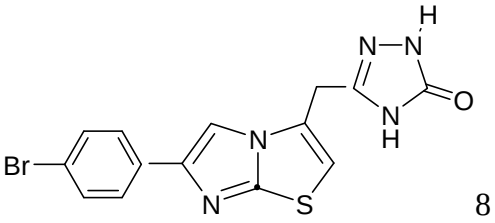


7

Nuray Ulusoy Guzeldemirci *et al* [8] synthesized a series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones (8) starting from 6-(4-bromophenyl)imidazo [2,1-b]thiazole-3-acetic acid hydrazide. All compounds were tested for antibacterial and antifungal activities and resulted that these are potent antimicrobial agents.

Xiaoyun Chai *et al* [9]synthesized a series of 1-(1H-1,2,4-triazole-1-yl)-2-(2,4 difluoro-phenyl) -3-substituted benzylamino-2-propanols (9) as analogs of fluconazole and evaluated as antifungal agents. Results of preliminary antifungal tests against eight

human pathogenic fungi in vitro showed that all the title compounds exhibited excellent activities with broad spectrum.



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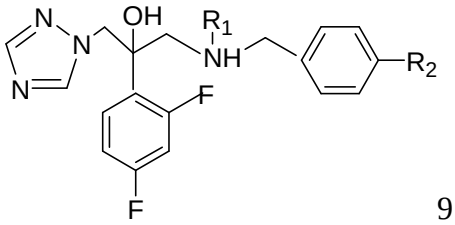
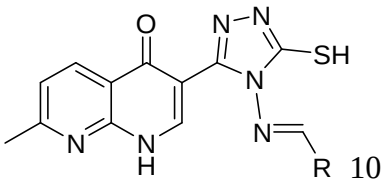


9

Nisha Aggarwal *et al* [10] synthesized Novel nalidixic acid based 1,2,4-triazole (10) derivatives were synthesized and all these compounds were screened for antimicrobial activity against five bacteria and two pathogenic fungi. Most of these compounds showed better antimicrobial activity than the parent compound 4-amino-5- mercapto-1,2,4-triazole.

Sumesh Eswaran *et al* [11] synthesized A new class of quinoline derivatives containing 1,2,4-triazole moiety (11) from derivatives of 4-hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide most of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs.

Seref Demirayak *et al*[12]synthesized some 3-arylamino-5-[2-(substituted imidazol-1-yl or benzimidazol-1-yl)ethyl]-1,2,4-triazole (12) derivatives by reacting 3-(substituted imidazol-1-yl)propionyl hydrazides, with *S*-methyl-*N*%-arylisothiouronium iodide salts. Antimicrobial activities of the compounds were observed against *Staphylococcus aureus*, *Micrococcus luteus, Escherichia coli* B, *Pseudomonas aeroginosa* and the fungi *Candida albicans* and *Candida glabrata* by using the tube dilution technique.



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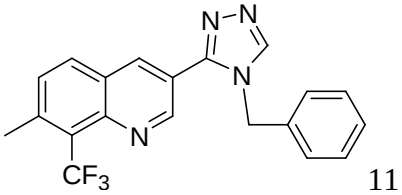

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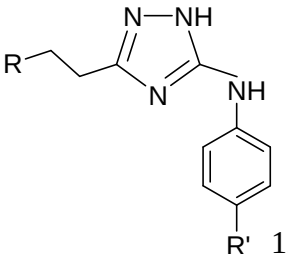
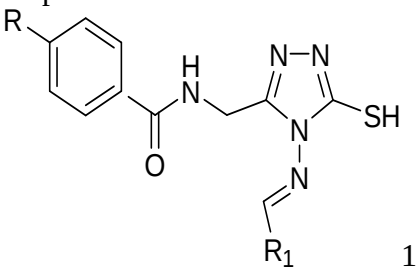


12

Yatin J. Mange *et al* [13] synthesized a series of new Schiff bases (13) by the condensationof N-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-4-substituted-benzamides all these compounds showed antimicrobial activity.

Nasser S. A. M. Khalil [14]studied that Glucosidation of some 4-amino- and 4-arylideneamino-5-(pyridin-3-yl)-2,4-dihydro-[1,2,4]-triazole-3-thiones (14) with 2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl bromide followed by chromatographic separation gave the corresponding N- and S-b-D-glucosides. Antimicrobial screening of 14 selected compounds resulted in their activity against *Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum, Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis,* and *Escherichia coli.*

Krzysztof Sztanke *et al* [15] synthesized 7-(4-methylphenyl)-3-methylthio-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazole (15) by the alkylation of the respective 7-(4-methylphenyl)-2,5,6,7-tetrahydroimidazo [2,1-c] [1,2,4] triazol-3 (H)-thione with methyl iodide. Compoundwas found to be equipotent to chloramphenicol in vitro, whereas showed superior activity (MIC) to ampicillin.



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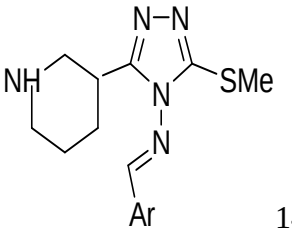

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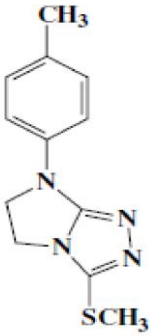

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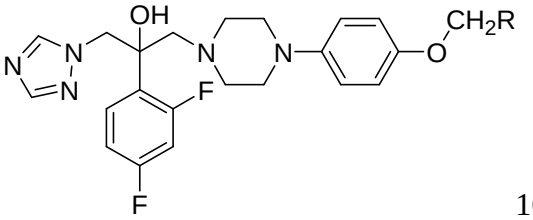
Qiu Qin He *et al*[16]synthesized novel triazole compounds (16) based on the active site of Aspergillus fumigatus lanosterol 14a-demethylase (AF-CYP51). The results showed that all the target compounds exhibited excellent activities with broad spectrum; compounds showed comparable activities against *A. fumigatus* to the control drug itraconazole.

Xiaoyun Chai *et al*[17] synthesized a series of 1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols (17) and evaluated as antifungal agents. The MIC80 values indicate that the compounds showed higher antifungal activities against *Candida albicans*.



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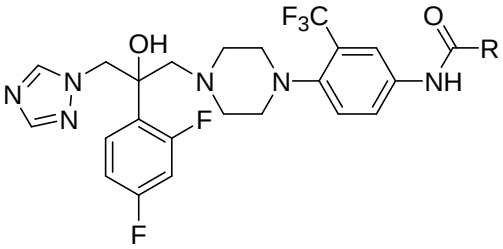


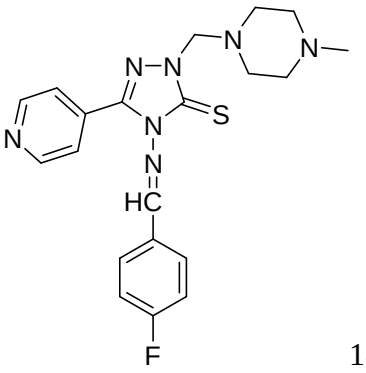
17

Hacer Bayrak *et al*[18] synthesized 4-amino-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (18). All newly synthesized compounds were screened for their antimicrobial activity. The antimicrobial activity study revealed that all the compounds screened showed good or moderate activity.

Haythem A. Saadeh *et al* [19] synthesized 1,2,4-triazole-3-thiol metronidazole derivatives (19) The antiparasitic activity of the compounds against Entamoeba histolytica and Giardia intestinalis was investigated. The antibacterial and antifungal activity of the compounds, assessed as minimal inhibitory concentration, was also investigated.

Zafer Asım Kaplancıkl *et al*[20] synthesized new 1,2,4-triazole and 1,2,4-triazolo[3,4-b][1,3,4] thiadiazine derivatives (20) were synthesized as novel antimicrobial agents. Their antimicrobial activities against *Micrococcus luteus, Bacillus cereus, Proteus vulgaris, Salmonella typhimurium, Staphylococcus aureus, Escherichia coli,*

Candida albicans and *Candida glabrata* were investigated and significant activity was obtained.



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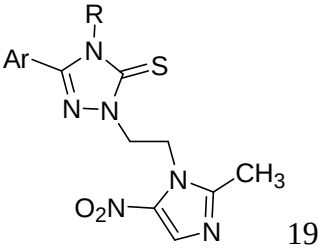

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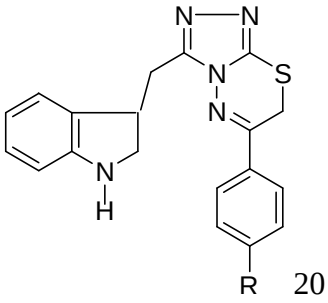
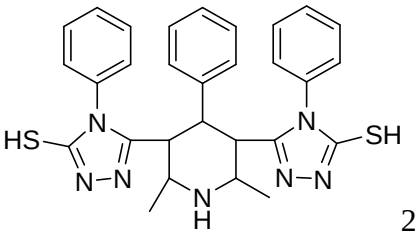


20

Kudari *et al*[21]synthesized certain Bis-1,3,4-oxadiazoles, Bis- 1,3,4-thiadiazoles, Bis-1,2,4-triazoles (21), and Bis-N-amino 1,2,4- triazoles and screened them for anti-microbial activity.

Shigare *et al*[22]synthesized certain dihydro-pyridino triazoles (22) and thidiazoles and screened them for anti-microbial activity.



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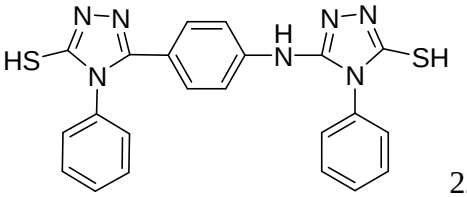

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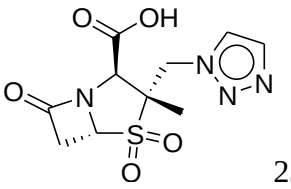
Anticoulvensant Activity and Antipsycotic Activity

The clinically useful derivatives of 1,2,3-triazole includes Tazobactam (23) which is used in combination with β-lactam antibiotics as antibacterial and Rufinamide (24) an anticonvulsant.



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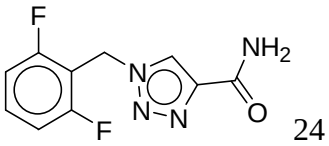


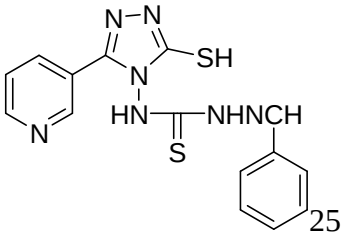
24

Aniket *et al*[23] 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 anticonvulsantactivity by Maximum Electroshock (MES) method and found that total recovery time and time for hind limb extension recovery for compound (25) was less than the standard (Phenytoin).

Jing Chen *et al*[24] synthesized 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazoles from the condensation of Dimethoxy-N,N-dimethyl methanaminel, propionohydrazide and p-aminophenol Theanticonvulsant activities of the synthesized compound were evaluated by the maximal electroshock test and their neurotoxicity was evaluated by the rotarod neurotoxicity test and result showed

that compound (26) produced significant antagonism activity against seizures induced by pentylenetetrazole, 3-mercaptopropionic acid, thiosemicarbazide and Isoniazid, suggested that the compound 3r might have effects on GABAergic neurotransmission and activate glutamate decarboxylase (GAD) or inhibit (GABA)–a-oxoglutarateamino transferase (GABA-T) in the brain.

M. Shalini *et al*[25] synthesized some substituted diphenyl-1,2,4-triazole-3-ones by the condensation of substituted benzoyl chlorides and substituted phenyl semicarbazides.The anticonvulsant activity of these compound were screened by using four animal models of seizure which include, maximal electroshock seizure, subcutaneous pentylenetetrazole, subcutaneous strychnine, and subcutaneous picrotoxin induced seizure threshold tests. Neurotoxicity screening was done by Rotarod test to detect the motor deficit in mice., Behavioral depression was measured by evaluating the locomotor activity of the animal using actophotometer, CNS depression was studied by Porsolt's swim pool test. Results show that compound (27) exhibited anticonvulsant activity in all the four animal models of seizure.



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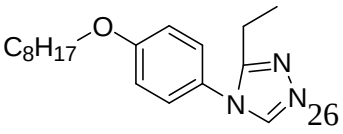

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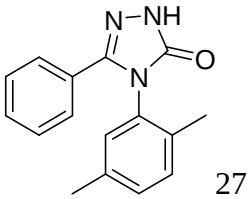
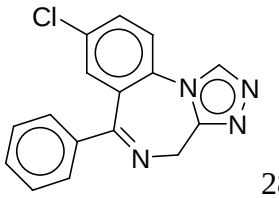


27

The triazole ring has been fused at 1,2-position of 1,4-benzodiazepines to give Estrazolam (28)andTriazolam (R=CH3, X=Cl,Y=Cl) the potent hypnotic agents and Alprazolam (R= CH3, X= Cl, Y= H) (29) a potent antipsychotic agent.



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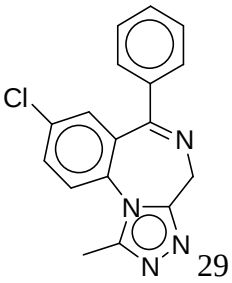

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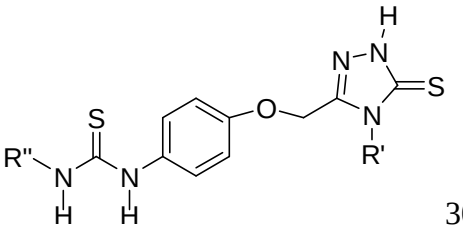
Antitumor / Anticancer Activity

K. Subrahmanya Bhat *et al* [26] synthesized a series of 3-(2,4-dichloro-5-fluorophenyl)-6-(substituted phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (30) . Among the compounds tested for their antitumor activity three compounds exhibited in vitro antitumor activity with moderate to excellent growth inhibition against a panel of sixty cancer cell lines of leukemia, non-small cell lung cancer, melanoma, ovarian cancer, prostate and breast cancer.

M. A. Kaldrikyan *et al* [27] synthesized a series of 3-benzofuryl-4-phenyl(allyl)-5-mercapto-1,2,4-triazoles (31) by cyclization of the corresponding substituted thiosemicarbazides of benzofuran-2-

carboxylic acid. The antitumor activity of the synthesized compounds was tested and found that some of them have potent antitumor activity.



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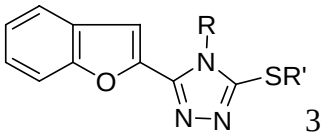


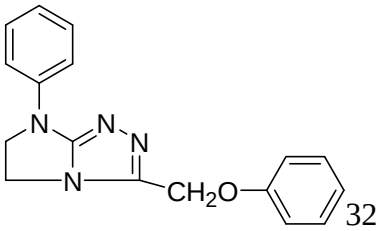
31

Krzysztof Sztanke *et al* [28] synthesized derivatives of 3-Unsubstituted and 3-substituted-7-aryl-5H-6,7-dihydroimidazo [2,1-c][1,2,4]triazoles (32). Compounds were evaluated for their cytotoxic activity against three cancer cell lines: human Caucasian colon adenocarcinoma cell line e LS180 (ECACC 87021202), human uterus carcinoma cell line e SiHa (ECACC 85060701) and human breast carcinoma cell line e T47D (ECACC 85102201). These showed potent antitumor activity.

Anelia Ts. Mavrova *et al* [29] synthesized novel derivatives of 4,5-substituted-1,2,4-triazole-thiones (33) and evaluated for their cytotoxicity. The biological study indicated that compounds 4-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3- thione and 4-amino-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2, 4-dihydro-3H-1,2,4-triazole-3-thione possessed high cytotoxicity in vitro against thymocytes.

Yaseen A. Al-Soud *et al*[30] synthesize 2-[H-Benzotriazole-1-yl(methylene)]-6,7,8,9-tetrahydro- 5H-[1,2,4] triazolo[1,5-a] azepine and other derivatives which are examined and showed that these derivatives has antitumor activity.

Datar, P. *et al* [31] synthesizedsome imidazolidinyl-triazolidin-5-thione derivatives (34). These derivatives were reported to possess weak antimicrobial activity against *S. aureus, S. typhi*and *C. albicans*. The anticancer study indicates that these compounds possess 100% cytotoxicityagainst Dalton's lymphoma cell lines and Ehrlich ascites carcinoma cell lines.



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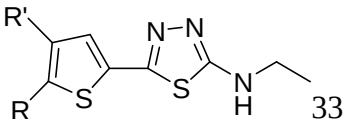

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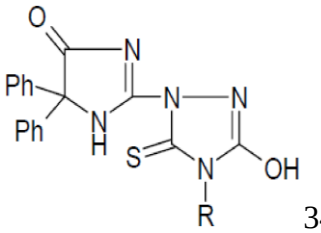


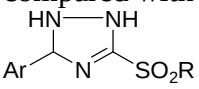
34

Anti-inflammatory Activity

Birsen Tozkoparan *et al*[32] prepared a series of 5-aryl-3-alkylthio-1,2,4-triazoles (35) and corresponding sulfones, these compounds showing better significant analgesic–antiinflammatory activity with minimum ulcerogenic risk.

Latifeh Navidpour *et al*[33]designed and synthesized a new type of 4,5-diaryl-4H-1,2,4-triazole, possessing C-3 thio and alkylthio (SH, SMe or SEt) substituents (36), these compounds were evaluated as selective cyclooxygenase-2 (COX-2) inhibitors with in vivo anti-inflammatory activity.

Ashraf M. Abdel-Megeed *et al* [34] synthesized 1-acylated-5-amino-1,2,4-triazole-3-acetates and their derivatives (37) which showed higher anti-inflammatory activity than the corresponding 5-acylamino derivatives in carageenan-induced rat paw edema test with low gastric ulcerogenicity compared with indomethacin.



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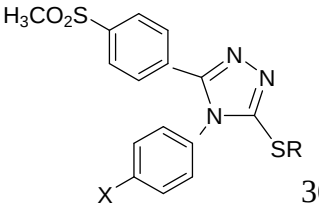

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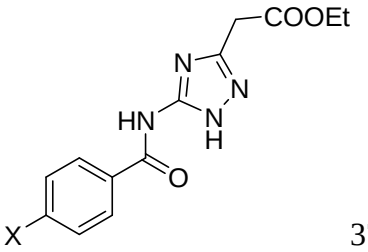
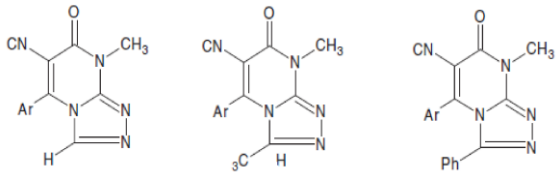


37

Chetan M. Bhalgat *et al* [35] carried out the synthesis of novel dihydropyrimidine carbonitrile, its dimethylated adduct, and hydrazine derivative of and its triazole fused derivatives (38). Further the novel derivatives were investigated for their in vitro antioxidant and anti-inflammatory activity. The results revealed that some of the tested compounds showed potent antioxidant and anti-inflammatory activity.

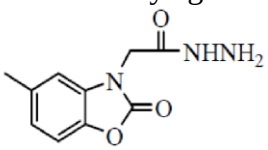


38

Umut *et al* [36] reported a series of 1acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones from the reaction of 5-methyl-2-hydroxyaniline and urea and evaluated anti-inflammatory, analgesic activity. The newly synthesized compounds were tested for their analgesic and anti-inflammatory activities. tested compounds (39) possessed considerably high amount of analgesic activity and high anti-inflammatory activity.

Peter, C. *et al*[37] reported anti-inflammatory activity of 1-acyl-3-p-substituted-phenyl-5-
alkyl-triazole (40) . Modification of the acyl group, p-substituted phenyl and alkyl group led to the selection of the most active member of the series, 1-acetyl-3-(p-chlorophenyl)-5-methyl-1,2,4-triazole, for further evaluation as a novel non-acidic anti-inflammatory agent.

Stenberg V. *et al*[38] prepared and evaluate the anti-inflammatory activity of [(4-phenyl-5-aryl-4H-1,2, 4-triazole-3-yl) -thio]-acetic acid derivatives (41). The hydroxyl substituted derivatives compounds were effective as *in vitro* scavengers of peroxide but were not effective as *in vivo* anti-inflammatory agents.



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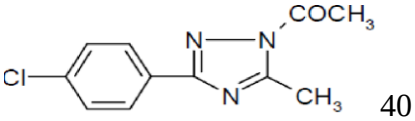

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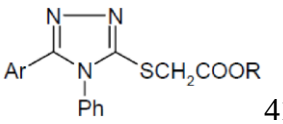


41

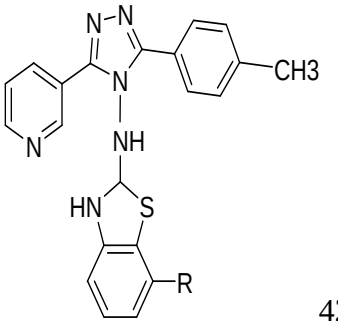
Anti tubercular Activity

Navin B. Patel *et al* [39] synthesized a series of 3-(3-pyridyl)-5-(4-methylphenyl)-4-(N-

substituted-1,3-benzothiazol-2-amino)-4H-1,2,4- Triazole (42) and also observed that these are promising antimicrobials have proved to be better antitubercular. Some Compound showed better antitubercular activity compared to rifampicin.

Ilkay Kuc¸ukguzel *et al*[40] synthesized a series of novel 5-[(4-aminophenoxy)-methyl] -4-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones and several related thioureas, N-alkyl/aryl-N0-{4-[(4-alkyl/aryl-5-thioxo- 4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy]phenyl}thioureas (43) and evaluated for antiviral potency. compounds were evaluated in vitro against HIV-1 (IIIB) and HIV-2 (ROD) strains in MT-4 cells, as well as other selected viruses such as HSV-1, HSV-2, Coxsackie virus B4, Sindbis virus and Varicella-zoster virus using HeLa, Vero, HEL and E6SM cell cultures, and anti-tuberculosis activity against Mycobacterium tuberculosis H37Rv. Some of them were found very potent.

Alagarsamy, V. *et al*[41] synthesized some novel 1,4-disubstituted-1,2,4-triazolo [4,3-a]- quinazolin-5(4*H*)-ones (44) and screened for anti HIV and antimicrobial activity. Their study indicates that the synthesized compounds do not exhibit significant anti-HIV activity while the synthesized derivatives possess good activity against *M. tuberculosis, C. albicans* and *A. niger.*



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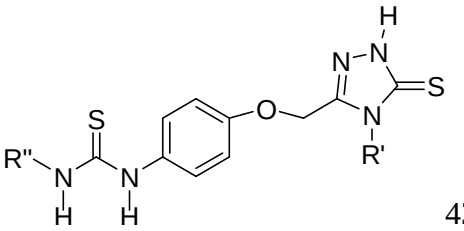

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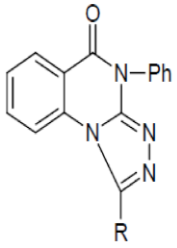
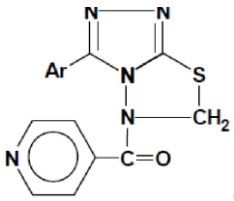


44

Shingare *et al*[42]synthesized certain 1,4-benzothiazinyl thiosemicarbazides, triazoles (45), oxadiazoles, and thiadiazoles and screened them for anti-tubercular activity.

S.D. Joshi *et al*[43] synthesized a novel series of some derived 5-substituted-4-amino-1,2,4-triazolin-3-thione (46) . Compounds were evaluated for their preliminary in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria and compounds were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. Some compounds showed very good antibacterial and antitubercular activities.

Udupi *et al*[44]carried out their studies on antitubercular agents. They synthesized 4-pyridoyl-3-substitued-1, 2,4-triazolo (3,4-b) (1,3,4)-thiadiazolidines (47) , and exhibiting significant anti-tubercular activity. They also reported the anti-inflammatory activity for some of the compounds synthesized.



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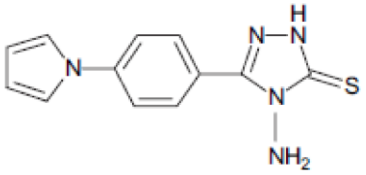

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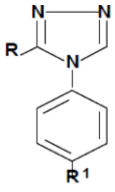
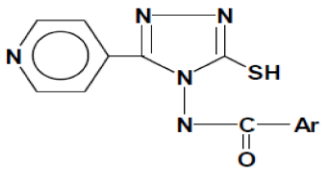


47

Udupi *et al*[45]carried out the synthesis and biological activity of 3-pyridyl-4-[N-substituted phenyl carboxamido]-5-mercapto-1,2,4- triazoles (48) and screened them for anti-bacterial, anti-fungal and anti-tubercular activity.

Nuray Ulusoy Gu zeldemirci *et al*[46] synthesized a series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4- triazole-3-thiones (49) . Compounds were also evaluated for antituberculosis activity against Mycobacterium tuberculosis H37Rv (ATCC 27294). The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.



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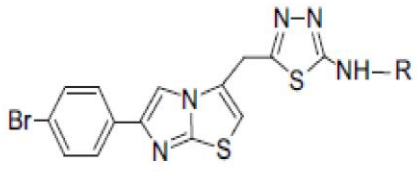


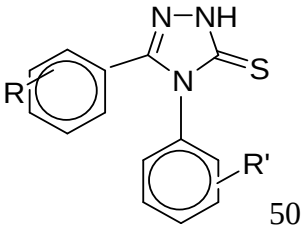
49

Urease Inhibition

Imtiaz Khan *et al*[47] synthesized new series of 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones (50) and 2,5-disubstituted-1,3,4-thiadiazoles by dehydrative cyclization of hydrazinecarbothioamide derivatives, compounds were screened for their antioxidant and urease inhibition activities. 4-(2,3-dimethylphenyl)-5-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione exhibited potent urease inhibitory activities.

Monazza *et al*[48] reported 5-aryl-4-(1-phenylpropyl)-2H-1,2,4-triazole-3(4H)-thiones from
aryl carboxylic acids as a potent inhibitor of Jack bean urease. Compound (51) was found to be more potent than the standard, with the IC50 values of 7.8 ± 0.2 compared to standard thiourea with IC50= 21.0 ± 0.1 μM).

Mahmood-ul-Hassan Khan *et al*[49]synthesized a series of 4-amino-5-aryl-3H-1,2,4-triazole-3-thiones (52) by reaction of aryl hydrazideswith CS2 and hydrazine hydrate and their urease inhibition activity was evaluated usingjack bean urease. All but one of the synthesized compoundswere active, and two of them were found to be more potentthan the standard, with 50% inhibition concentration (IC50)values of 17.5 ± 0.52 and 4.3 ± 0.169 lM, respectively(standard IC50 = 21.0 ± 0.11 lM). Tentative statementsregarding the role of different functional groups in bindingto the enzyme active site are also presented.



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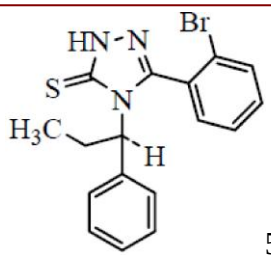

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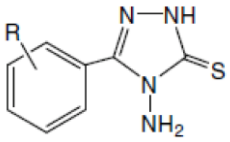
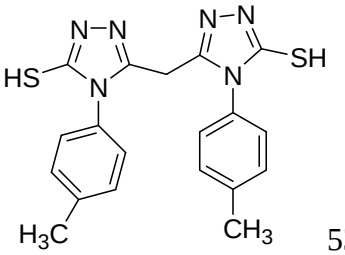


52

Antioxidant Activity

Rohini *et al* [50] synthesized bis-triazole derivatives, 5, 5/-methylene bis [4-substituted phenyl/alkyl -4H-1, 2, 4-triazole-3-thiol] screened for their antioxidant by DPPH method and anti-inflammatory activities by carrageenin induced paw oedema method. One of the compound (53) was found to have potent antioxidant and anti-inflammatory activity.

Yuksek, H. *et al*[51] some 4-benzyl-idenamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives (54) and investigated for antioxidant property. Their study indicatesthat the compounds with phenyl substitute group possess good antioxidant property.



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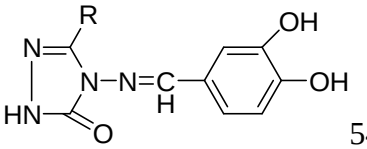
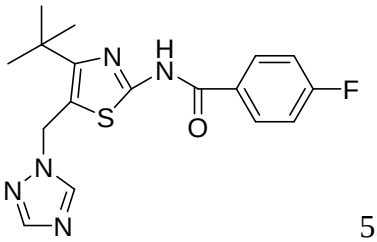


54

Plant Growth Activity

Xue Qin *et al*[52]presented a series of N-(5-((1H-1,2,4-triazol-1-yl)methyl)-4-tertbutyl thiazol- 2-yl)-4-carboxamide derivatives (55) and evaluated plant-growth regulatory activity by using cucumber cotyledon rhizogenesis method , The studies suggested that the presence of fluorine atom at position 2, 3, 4 of phenyl ring are crucial for exhibited plant-growth regulatory activities and the substitution with chlorine atom at both 2- position and 4-position of benzene ring caused a decrease of the activity while the presence of a strong electron-withdrawing group such as nitro-group led to decrease in activity.compound having fluorine atom at 4th position connected to the phenyl ring produced exellent plant-growth regulatory activity.

Jianbing Liu *et al*[53] synthesized some new 1H-1,2,4-triazole derivatives (56) containing ferrocenyl moiety in various yields by the condensation of ferrocenecarboxaldehyde with 1-(1H-1,2,4 triazol-1-yl)-3-aryl-2-one in toluene. Their results of bioassay showed that some title compounds exhibited some degree of antifungal and plant growth regulatory activities.



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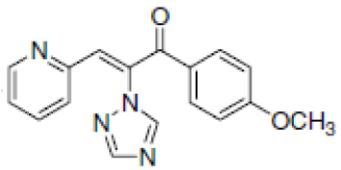
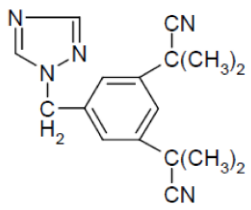


56

Antiestrogens

Some derivatives of 1*H*-1,2,4- triazole are also found to be useful as potent antiestrogens, major examples of which are Anastrozole (57), vorozole (58) and letrozole (59).



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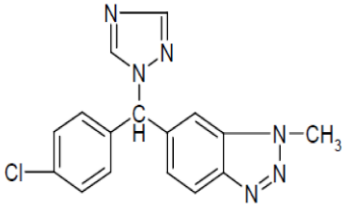

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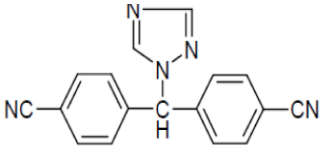
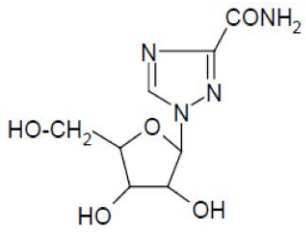


59

Other Biological Activites of Triazoles

Ribavirin (60) an antiviral agent, Israpafant (61) an antiasthmatic, Lotrifen (62) an Abortifacient.



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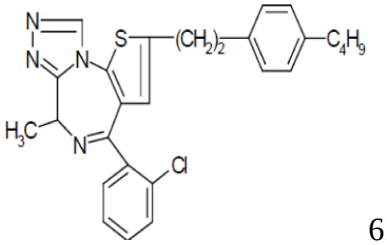

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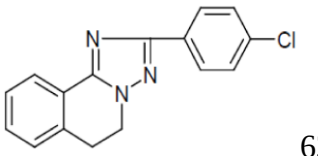
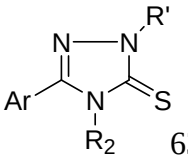


62

John M. Kane *et al*[54]synthesized a series of 5-aryl-2,4-dihydro-3H-1,2,4-triazol-3-thiones(63) and evaluated their antidepressant activity. Members of this series were found to possess potentantide pressant property.

Xin Yong *et al* [55] prepare a series of 4-Amino-5-furyl-2-yl-4H-1, 2, 4-triazole-3-thiolderivatives and assayed for their Endothelin (ET) Receptor Antagonists by using the cell culture solution of the rat heart ventricle muscle membranes. Compound (64) represented a new leading compound of ET receptor antagonist which exhibited high inhibition of 71.93%.



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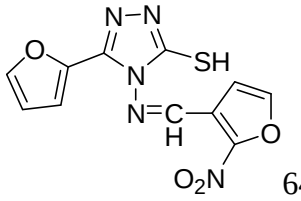
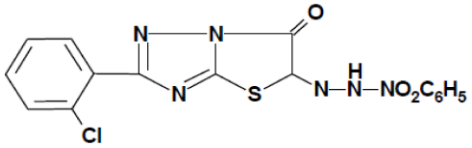


64

Sen *et al*[56]synthesized 2-o-chlorophenyl-5-oxo-5,6 dihydro- 4H thiazolo [2,3-b] 1,3,4-triazoles (65) and screened them for anti-filarial activity.

Mohan *et al*[57]synthesized certain thiazolo [3,2-b]-s-triazoles and isomeric thiazolo[2,3-c]-s-triazoles (66) and screened them for anti-microbial and diuretic activity.



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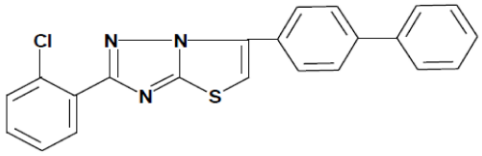
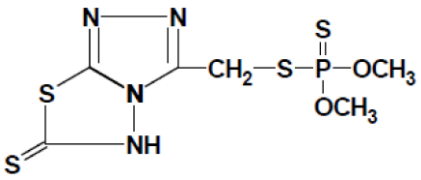


66

Chande *et al* [58] synthesized organophosphorus compounds containing substituted s-triazole and fused ring heterocycles (67) screened them for insecticidal activity.

Kudari *et al*[59]carried out the synthesis of 1,8-Bis (4-amino-5-mercapto-1,2,4-triazol-3-yl) octanes and the derivatives (68a, 68b) . Some of the bis-triazoles have shown anti-HIV, anti-cancer particularly prostrate cancer and anti-fertility activity.

Dae-Kee Kim *et al*[60]synthesized, and performed biological evaluation of novel 2-pyridinyl- [1,2,4]triazoles (69) as inhibitors of transforming growth factor*b*1 type 1 receptor.



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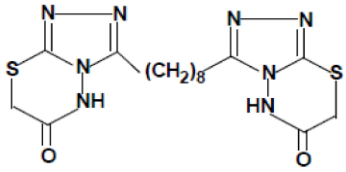
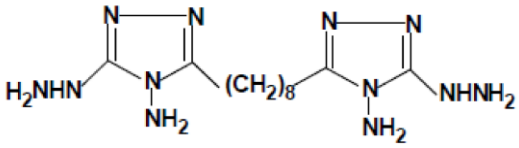


68a



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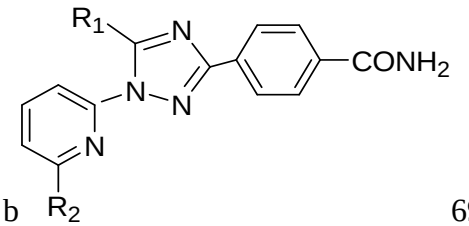
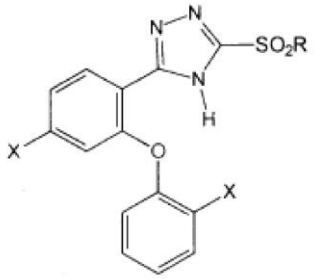


b 69

Tahmineh Akbarzadeh *et al*[61] synthesized a series of new 5-substituted analogues of 4H-3-(2-phenoxy)phenyl-1,2,4-triazole (70) and its chlorinated derivatives. Conformational analysis and superimposition of energy minima conformers of the compounds on estazolam, a known benzodiazepine receptor agonist, revealed that the main proposed benzodiazepine pharmacophores were well matched. Rotarod and pentylenetetrazole-induced lethal convulsion tests showed that the introduction of an amino group in position 5 of 1,2,4-triazole ring especially in chlorinated derivatives had the best effect which was comparable with diazepam.

Mahmoud Balba *et al*[62] investigated in vivo and in vitro effects of 4,5-Diphenyl-1,2,4-triazole-3-thiol (71) and 5-(2-Hydroxyphenyl)-4-phenyl-1,2,4-triazole-3-thiol (72) on a-glucosidase and a-amylase. 4,5-Diphenyl-1,2,4-triazole-3-thione showed a reversible inhibition of the competitive and non-competitive types, with Ki value of 10_5 M magnitude, for a-glucosidase and a-amylase. On the other hand, 5-(o-hydroxyphenyl)-4-phenyl-1,2,4-triazole-3-thione did not display an inhibitory effect towards a-amylase but showed a potent inhibition of the competitive type for hepatic a-glucosidase with 10_5 M magnitude of Ki value.



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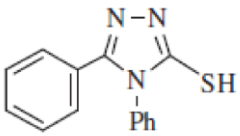

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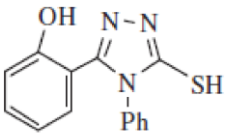
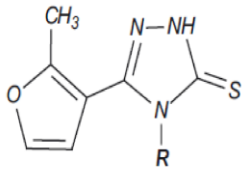


72

Agata Siwek *et al*[63] studied and investigated that by the reaction of 2-methyl-furan-3-carboxylic acid hydrazide with isothiocyanates, 1-[(2-methyl-furan-3-yl)carbonyl]-4-substituted thiosemicarbazides were obtained. Further cyclization with 2% NaOH led to the formation of 3-(2-methyl-furan-3-yl)-4-substituted- Δ2-1,2,4-triazoline-5-thiones (73) . The pharmacological effects on the central nervous system in mice were investigated. Strong antinociceptive properties of the investigated derivatives were observed in a wide range of doses.

Anees A. Siddiqui *et al*[64] synthesized a number of 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3- yl)-4,5-dihydropyridazin-3(2H)-one derivatives by a sequence of reactions starting from respective aryl hydrocarbons. The final compounds (74) were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. The compounds showed appreciable antihypertensive activity comparable with that of standard hydralazine and propranolol.

Xiaohu Ouyang *et al*[65] studied a novel triazole-containing chemical series (75) was shown to inhibit tubulin polymerization and cause cell cycle arrest inA431 cancer cells with EC50 values in the single digit nanomolar range. Binding experiments demonstrated that representative active compounds of this class compete with colchicine for its binding site on tubulin



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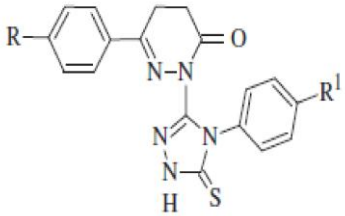
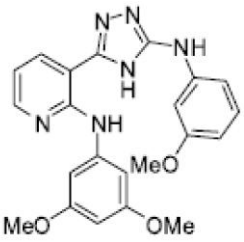


74



75

Conclusion

After a detail study of recent research and advances of 1,2,4-triazoles and its derivatives we can say that this heterocyclic azole moietycan be consider as the very important and potent moiety in new drug discovery. 1,2,4-triazoles can be consider with different biological activities such as antimicrobial, antipshycotic, antifungal, antitubercular, antiviral, anticancer, urease inhibitor, antihypertensive, plant growth regulator, abortifacient, antinoceceptive, anti-inflammatory, anticoulvensent etc.

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