Review Article

Structural significance of triazole derivatives for the management of various diseases

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ABSTRACT

The 1, 2, 4-triazole ring is an important heterocyclic ring having various synthetic uses. Triazole derivatives have been synthesized and published by various researchers as its important characteristic against various diseases. An emphasis has been given to structure–activity relationship, biological activity, and design strategy of various mono as well as polysubstituted triazoles to ensure the acceptance level of this heterocyclic ring in the field of medicinal chemistry. The derivative of this heterocyclic ring produced various biological activities such as anti-inflammatory, anticonvulsant, hypoglycemic, antitubercular, anxiolytic, antimicrobial, antitumor, and anticancer. The current review article focuses of pharmacological profile associated with 1,2,4-triazoles and mainly focuses on structural modification done for various targets along with brief description of targets.

Keywords: 1,2,4-triazoles, 1,2,3-triazoles, anti-inflammatory, anticonvulsant, hypoglycemic, antitubercular, anxiolytic, antimicrobial, antitumor, and anticancer

INTRODUCTION

1,2,4-Triazole is a five-membered, π-excessive, aromatic nitrogen heterocycle, comprised two carbon and three nitrogen atoms present at the 1, 2, and 4 positions of the ring. All the atoms in 1,2,4-triazoles are sp^2 hybridized and have 6π electrons delocalized over the ring, responsible for its aromatic character.[1-4] It is also known as s-triazole (symmetrical). 1,2,4-Triazole exists in two tautomeric forms known as 1H-1,2,4-triazole and 4H-1,2,4-triazole and it is very difficult to separate them due to their rapid interconversion. Recently, 1,2,4-triazole derivatives have been found by many researcher for their interesting application in different pharmacological activities such as anti-inflammatory,[5] anticonvulsant,[6] antibacterial.[7] and antitumor, against different cancer cell lines.[8] Furthermore, it was reported that triazole moiety showed free radical scavenging and antioxidative activity by inhibiting lipid peroxidation.[9]

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1,2,4-TRIAZOLES

This system was known as s-triazole (s-for symmetric). It is aromatic, like its structural isomer 1,2,3-triazole. Its ionization potential is 10.00 eV. Therefore, its HOMO is as low as that of 1,2,3-triazole. The dipole moment in the gas phase is 2.72 D and in dioxane 3.27 D.

Every C-carbon atom in 1,2,4-triazole is linked to two N-atoms. As a consequence, the C-atoms are π-deficient. MO calculations yield values up to 0.774 for the π-electron density in positions 3 and 5. The electron density on the N-atom is correspondingly high. 1,2,4-triazole forms colorless crystals, m.p. −121°C, bp 260°C. It is soluble in water.[1-3] Several 1,2,4-triazloes are known by trivial names, such as Azoman (4-cyclohexyl-3-ethyl-1,2,4-triazole), used to produce convulsions, and Amizol (3-amino-1,2,4-triazole), a herbicide.

PHARMACOLOGICAL PROFILE

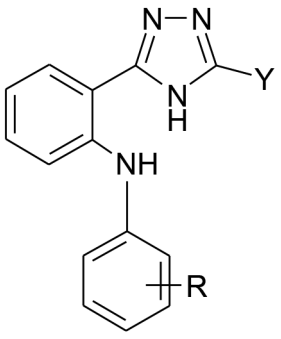
The 1,2,4-triazole scaffold is extremely versatile and has featured in a number of clinically used drugs. Out of which, only four 1,5-benzothiazepines are in therapeutic use for their coronary vasodilators, calcium antagonists (Diltiazem, Clentiazem) and as

antidepressant (e.g. Thiazesim and quetiapine fumarate) activities. The wide range of pharmacological profile shown by 1,5-benzothiazepine can be classified into the following categories.

1. Anti-inflammatory activity
2. Hypoglycemic activity
3. Anticonvulsant activity
4. Anti-tubercular activity
5. Anxiolytic and antidepressant activity
6. Antimicrobial activity
7. Anti-tumor and anticancer activity:
8. Other activities
    - Anabolic-catabolic activity and binding affinity to steroid receptors
    - Human rennin inhibitory activity
    - Non-peptide angiotensin II antagonists.
    - Selective antagonists of strychnine-induced convulsions and potential antispastic agents
    - Anti-HIV activity
    - Migraine.
    - Antithyroid activity
    - Openers of large-conductance Ca^{2+}-activated potassium (Maxi-K) channels
    - Insecticidal activity
    - Antiradical and antioxidant activity

Anti-inflammatory Activity

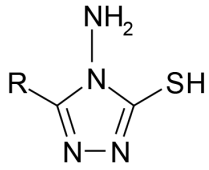
Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation particularly arthritis. NSAIDs reduce the inflammation and pain associated with arthritis by blocking metabolism of arachidonic acid by the enzyme cyclooxygenase (COX) and thereby the production of prostaglandins. On chronic use of NSAIDs, one of the prominent side effects is the formation of gastric ulcers. This adverse effect may be attenuated in the presence of an inhibitor of 5-lipoxygenase (5-LO). 1,2,4-triazoles found to possess anti-inflammatory properties by virtue of dual mechanism, that is, inhibit both CO and LO reducing the gastric ulcer formation.[10-12] Boschelli *et al.*[13] reported synthesis, *in vitro* inhibition of COX, and 5-LO activities of 1,2,4-triazoles analogs.



Y= OH, SH, NH_2, NHCN

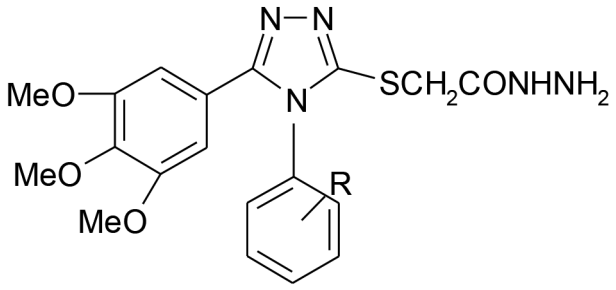
Major side effects of NSAIDs include dyspepsia, gastric ulceration, and nephrotoxicity.[14] It has been hypothesized that prostaglandins are cytoprotective, and therefore, the undesirable gastrointestinal side effects of NSAIDs are due to their ability to block prostaglandin synthesis.[15] In addition, there is evidence that suggests leukotrienes promote gastric ulceration.[16] On the basis of this information, we reasoned that a dual inhibitor of COX and 5-LO would provide anti-inflammatory agent with not only improved efficacy, but with fewer side effects.

George *et al.*[17] reported synthesis of some s-triazoles with potential analgesic and anti-inflammatory activities.

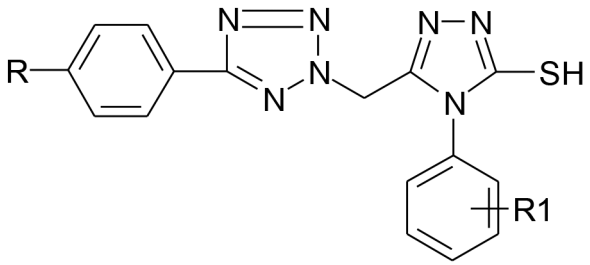


R= CH_3, C_2H_5, $(CH_2)_2CH_3$, CF_3, C_6H_5, CH_2OCH_3

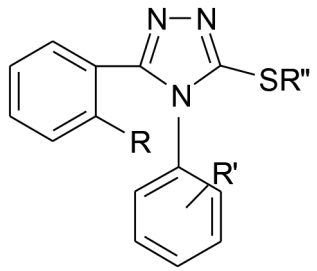
Some 5-(3,4,5-Trimethoxyphemyl)-4-substituted-aryl-3-hydrazino-carbonylmethylthio-4H-1,2,4-triazoles were synthesized for possible anti-inflammatory agents by Jaiswal *et al.*[18]



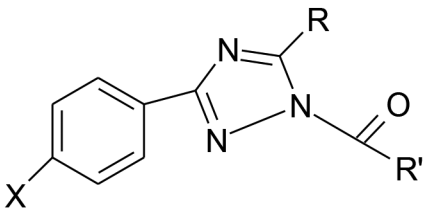
Kothari *et al.*[19] reported synthesis of some newer 5-(5-Aryl-2H-tetrazol-2-ylmethyl)-4-substituted-s-triazole-3-thiols as possible anti-inflammatory agents.



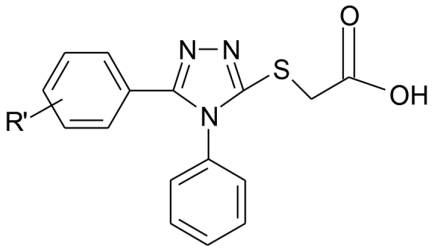
Tandon *et al.*[20] reported synthesis and anti-inflammatory activity of some new 3-(o-Substituted-phenyl)-4-substituted-phenyl-5-alkyl/alkenyl-mercapto-1H-1,2,4-triazoles.



Wade *et al.*[21] synthesized certain 1-acyl-3-phenyl-5-alkyltriazoles and evaluated them for anti-inflammatory activity using the mouse active Arthus reaction as the test system. Modification of the acyl group, 4-phenyl substituent, and alkyl group led to the selection of the most active member of this series, 1-acetyl-3-(4-chlorophenyl)-5-methyl-1,2,4-triazole, was the most active compound of the series.

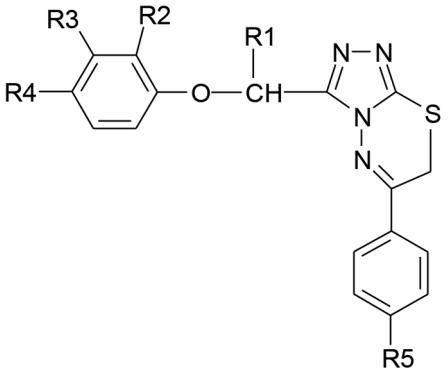


Maxwell *et al.*[22] reported [(4-phenyl-5-aryl-4H-1,2,4-triazol-3-yl) thio] acetic acids as anti-inflammatory agents.

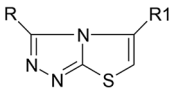


R= 4-OH, 3,4-di-OH, 3,4,5-tri-OH

Prasad *et al.*[23] reported the anti-inflammatory activity of a number of 3-aryloxyalkyl-6-aryl-7H-s-triazolo [3,4-b] [1,3,4] thiadiazines. They found that their effects were comparable to phenylbutazone.



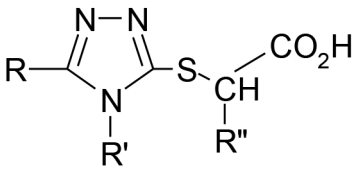
Pignatello *et al.* reported synthesis and evaluation of thiazolo-triazoles.[24]



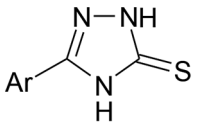
R= 3,4,5- $(OCH_3)_3$-C_6H_5

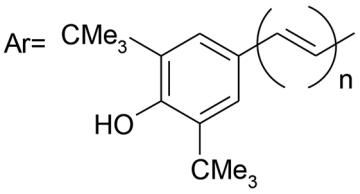
R_1= C_6H_5, C_6H_4-Cl(p), C_6H_4-Br (p), C_6H_4-CH_3(p), C_6H_4-C_6H_5(p),C_6H_4-NO_2(p)

Sung and Lee reported [(4,5-Disubstituted-4H-1,2,4-triazol-3-yl) thio] alkanoic acids and their analogs as anti-inflammatory agents.[25]

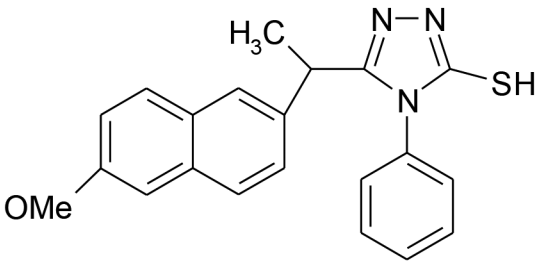


Mullican *et al.* reported design of 5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1,2,4-triazoles as orally active, non-ulcerogenic anti-inflammatory agents.[26]



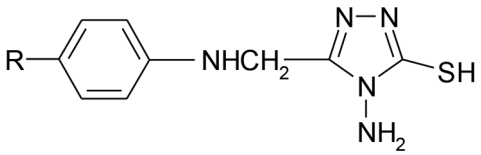


Alexander and Yuri reported the synthesis and anti-inflammatory activity of some novel-6-Methoxy-α-methyl-2-naphthalene acetic acid derivatives. It was interesting to note that one synthesized compound was found to be more potent (65.4%) than standard naproxen (60.8%).[27]

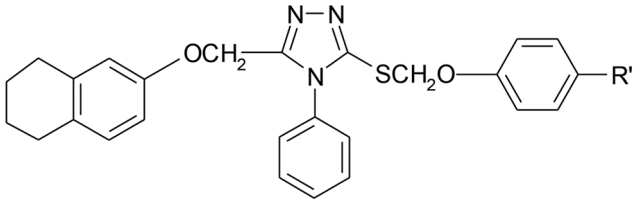


Anti-inflammatory activity of some new 3-substituted-4-amino-5-mercapto-4(H)-1,2,4-triazoles was reported by Talwar *et al.*[28]

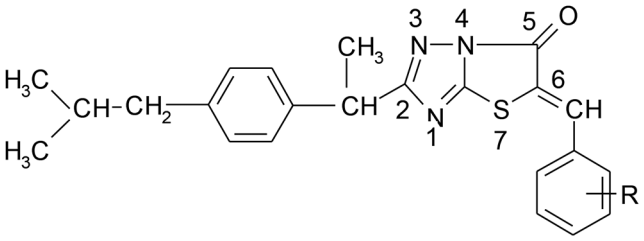
Turan-Zitouni *et al.* reported synthesis and analgesic activity of some triazoles.[29]



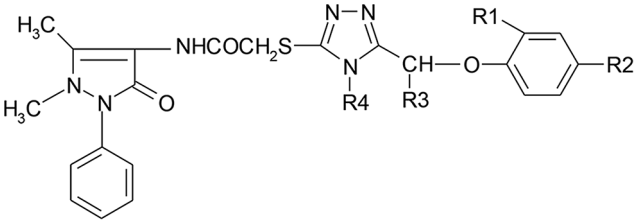
R= H, Cl, Br, CH_3, OCH_3, OC_2H_5



Tozkoparan *et al*. interested toward the chemical and pharmacological properties of thiazole[3,2-b]-1,2,4-triazoles, with the aim of obtaining the compounds with not only improved activity but also with reduced side effects, this triazole ring is combined with a nonsteroidal anti-inflammatory compound, ibuprofen to synthesize some new compounds.[30]

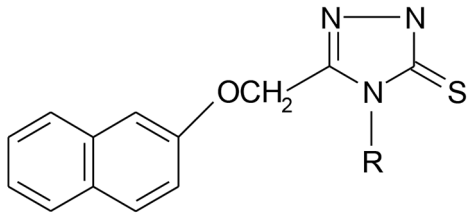


Turan-Zitouni *et al*. reported synthesis of some derivatives of triazoles with antipyrine and investigated their analgesic activity.[31]



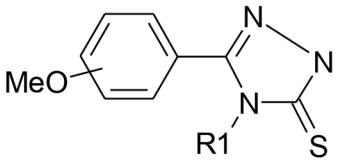
Labanauskas *et al*. synthesized and reported 3-(3,4-Dimethyloxyphen)-1H-1,2,4-triazole-5-thiones as anti-inflammatory agents.[32]

Prostaglandins (PGs) are well known to be mediators of inflammation, pain, and swelling.They are produced by the action of COX enzyme on arachidonic acid. COX is known to be the principal target of NSAIDs. NSAIDs might be accounted for by varying degrees of selectivity for COX-1 and COX-2. The potency and selectivity of NSAIDs appear to be directly related to their gastric, renal, and hepatotoxicity. A number of 1,2,4-triazole-3-thiones were synthesized and identified as potent anti-inflammatory compounds by Palaska *et al*.[33] These 1,2,4-triazoles-3-thiones were shown equipotent to naproxen, phenylbutazone, hydrocortisone, and other NSAIDs.



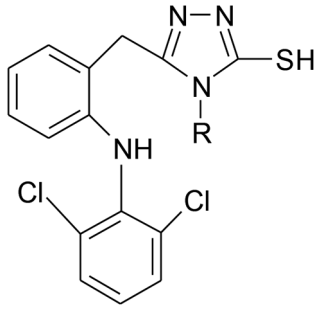
R= CH_3, C_2H_5, C_6H_5, C_3H_5

For search of anti-inflammatory agents, the series of S-alkylated derivatives 5-(2-,3- and 4-methoxyphenyl)-4-phenyl-4-H-1,2,4-triazole-3-thiol and 5-(2-,3- and 4 methoxyphenyl) -4H-1,2,4-triazole-3-thiol have been synthesized by Labanauskas *et al*.[34]

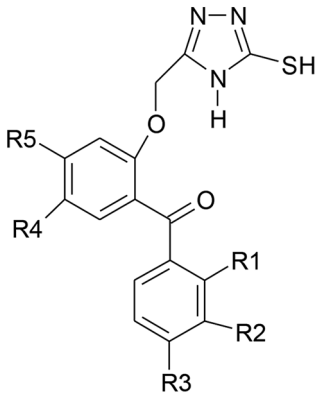


R_1= H, C_6H_5

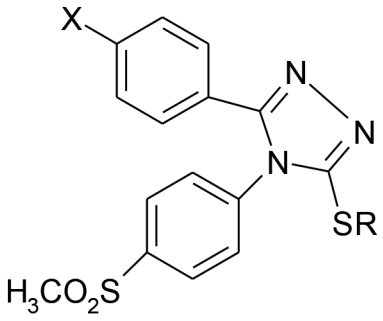
Amir *et al*.[35] reported novel triazole compounds in which they replaced the carboxylic acid group of diclofenac with 1,2,4-triazole nucleus, found appreciable anti-inflammatory activity in carrageenan-induced rat paw edema test.



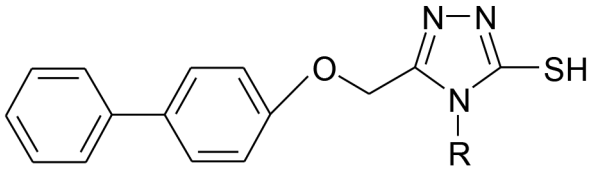
Khanum *et al*. reported synthesis of 3-(2-aroyloxy)methyl-5-mercapto-4H-1,2,4-triazole analogs for anti-inflammatory activities.[36]



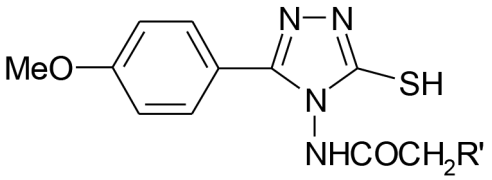
A new generation of anti-inflammatory drugs, celecoxib (Celebrex™) and etoricoxib (Arcoxia) is being prescribed to treat acute or chronic inflammation by providing symptomatic pain relief. A selective COX-2 inhibitor allows the desired synthesis of cytoprotective prostaglandins, in conjunction with a simultaneous inhibition of pro-inflammatory prostaglandin synthesis, thereby reducing dyspepsia and ulceration. Hence, to design novel selective COX-2 inhibitors, Navidpour *et al.*[37] reported design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4H-1,2,4-triazoles as selective COX-2 inhibitors.



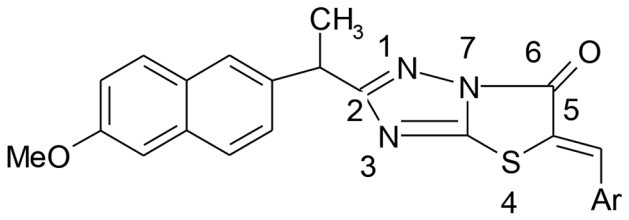
Some 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid were synthesized by Kumar *et al.*[38] and preliminary evaluation of these synthesized compounds was done.



Some 4-(substituted ethanoyl) amino-3-mercapto-5-(4-methoxy) phenyl 1,2,4-triazoles have been reported by Upmanyu *et al.*[39] for their anti-inflammatory and antinociceptive activity.

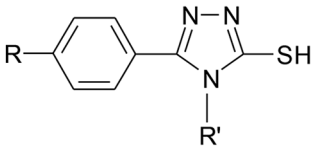


Deniz *et al.*[40] reported synthesis, biological evaluation, and molecular modeling studies of some novel thiazolo[3,2-b]-1,2,4-triazoles derived from naproxen with analgesic/anti-inflammatory properties.



Hypoglycemic Activity

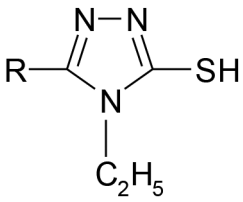
Mhasalkar *et al.* synthesized 4-Alkyl-5-aryl-4H-1,2,4-triazole-3-thiols as hypoglycemic agents.[41]



R=CH_3, C_2H_5, Cl, F, NO_2, NH_2 and SO_2NH_2

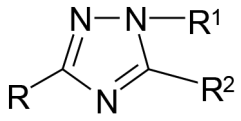
R'= CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_{11} and $CH_2CH_2OCH_3$

Mhasalkar *et al.* again studied substituted 4-H-1,2,4-triazoles for hypoglycemic activity.[42]

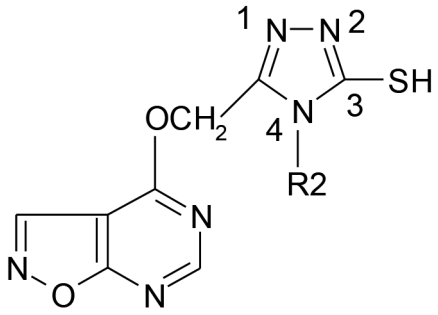


R= p-$H_2NSO_2C_6H_4$, P-ClC_6H_4

Synthesis of some 1,2,4-triazoles as potential hypoglycemic agents was reported by Blank *et al.*[43]

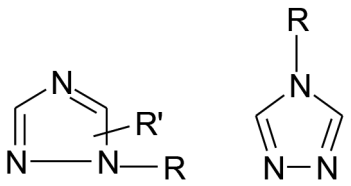


Agarwal *et al.* reported synthesis and pharmacological evaluation of some 3-mercapto-4-substituted Aryl/Alkyl-5-(3-Substituted Phenylisoxazolo [4,5-d] pyrimidin-4-yloxymethyl)-1,2,4-triazoles as hypoglycemic agents.[44]

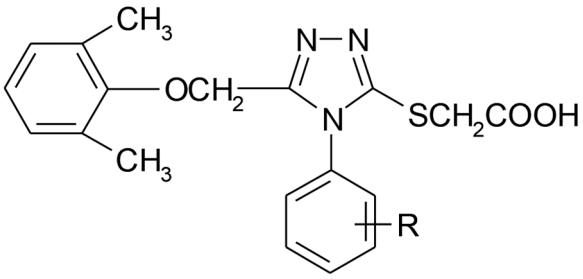


Anticonvulsant activity

Ainsworth *et al.* reported anticonvulsant activity of 1,2,4-triazoles.[45]

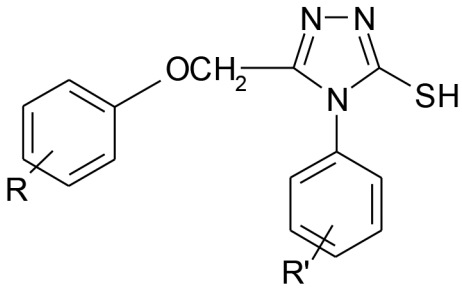


Design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4H-1,2,4-triazoles as Parmar *et al.* reported anticonvulsant activity and selective inhibition of NAD-dependent oxidations in rat brain homogenates by newer mercaptotriazoles as depicted below.[46]



R= H, o-CH_3, p-CH_3, o-OCH_3, p-CH_3, p-Cl

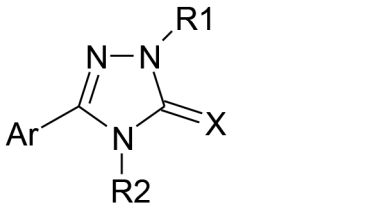
A series of some new substituted mercaptotriazoles and thiazolidones were studied for their monoamine oxidase inhibitory and anticonvulsant properties.[47]



R= o-OCH_3, p-OCH_3, p-NO_2

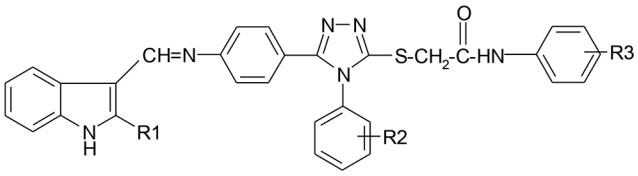
R'= H, p-CH_3, m-Cl, p-Cl

For anticonvulsant activities, some 2,4-Dihydro-3-H-1,2,4-triazol-3-ones were studied by Kane *et al.*[48]

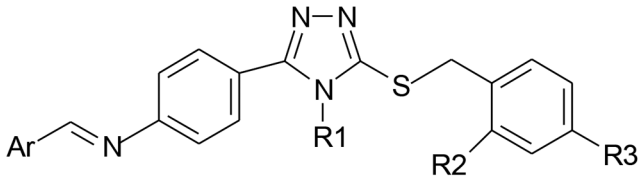


X=S, O

Shrimali *et al.* reported anticonvulsant activity of substituted indolyl-1,2,4-triazoles.[49]

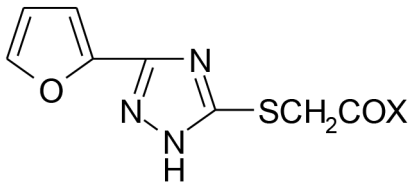


Kűćűkgůzel *et al.* reported anticonvulsant activities of some 3-(arylalkylthio)-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles. All compounds were evaluated for their anticonvulsant activity by maximal electroshock, subcutaneous pentylenetetrazole, and neurotoxicity screens.[50]

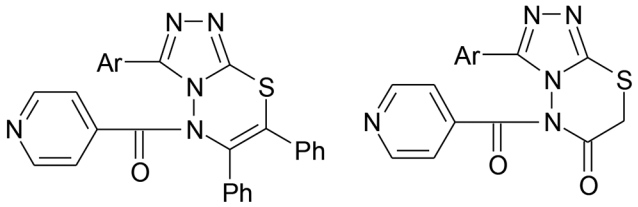


Antitubercular activity

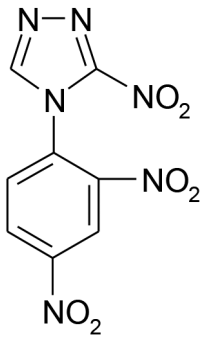
Mir and Siddiqui reported α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acethydrazide and related compounds as anti-tuberculosis agents.[51]



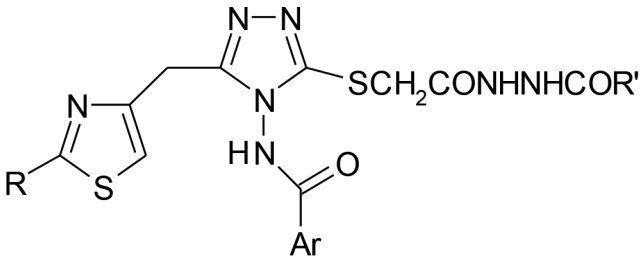
Antitubercular activities of some bridgehead nitrogen heterocycles (substituted 1,2,4-triazoles) were reported by Udupi *et al.*[52]



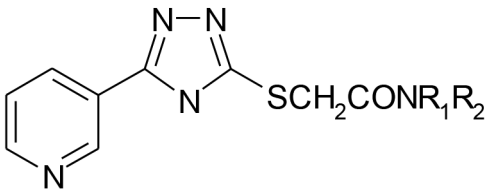
Walczak reported the antitubercular activity of some nitro-1,2,4-triazoles.[53]



Anti-mycobacterium tuberculosis agents of some new S-derivatives of clubbed triazolyl-thiazole were reported by Shiradkar *et al*.[54]

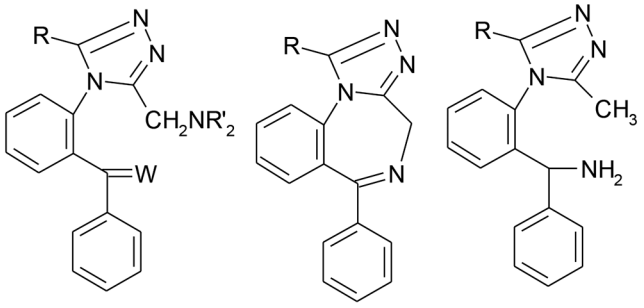


Twelve different 1,2,4-triazole analogs were synthesized by Mali *et al.* and these compounds were subjected to antifungal and antitubercular activities.[55]



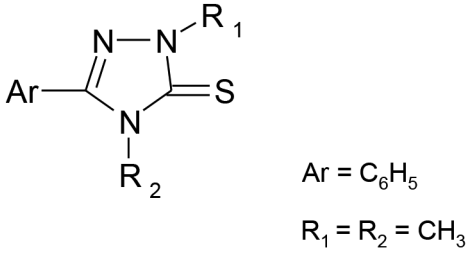
Anxiolytic and antidepressant activity

Gall *et al.* reported some novel anxiolytic agents derived from alpha.-amino-.alpha.-phenyl-o-tolyl-4H-triazoles.[56]

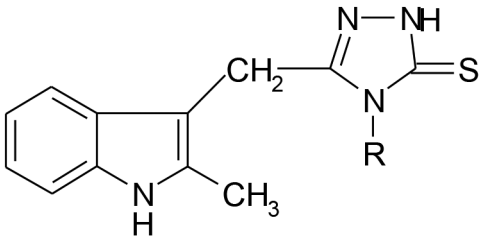


w=O,H

Kane *et al.* reported 2,4-Dihydro-3H-1,2,4-triazole-3-thiones as potential antidepressant agents.[57]

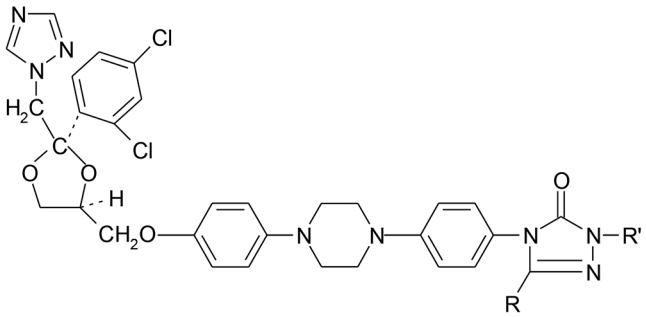


Varvaresou *et al.* reported the antidepressant evaluation of indole-containing derivatives of 1,3,4-thiadiazole and 1,2,4-triazole.[58]

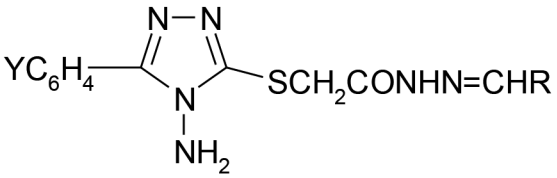


Antimicrobial activity

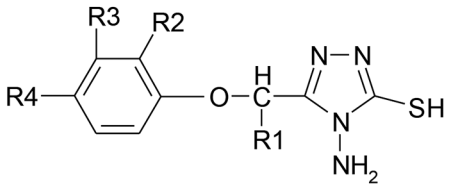
Suman *et al.* reported fungicidal activities of 3-Aryl/Aryloxymethyl-4-Aryl-5-Mercapto-1,2,4-triazoles and Bis-(3-Aryloxymethyl-4-Aryl-1,2,4-Triazol-5-yl) Methylene/Ethylene Disulfides.[59] Antifungal properties of a series of Novel Triazol-3-ones are reported by Heeres *et al*.[60,61]



Eweiss *et al.* reported synthesis and antimicrobial activity of some 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives.[62]

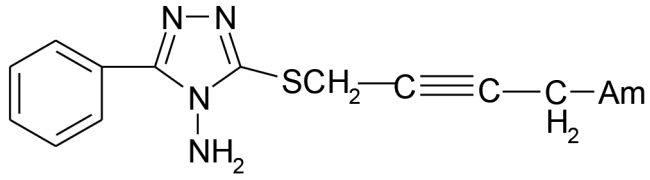


Prasad *et al.* synthesized 4-Amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazoles as antibacterial agents.[63]

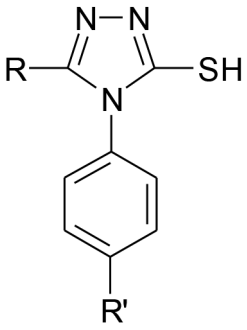


R_1= H, CH_3
R_2= H, CH_3, Cl
R_3= H
R_4= H, Cl

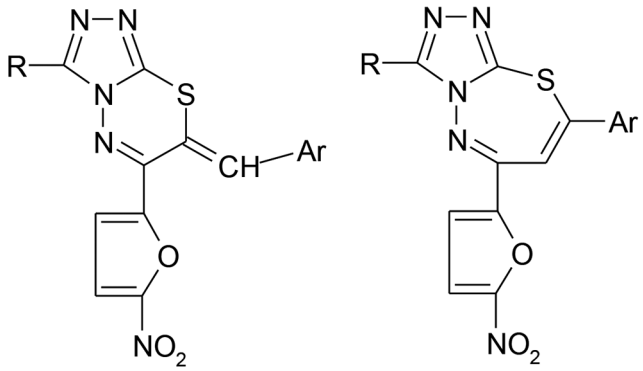
Synthesis and antimicrobial activities of 3-(4-tert-amino-2-butynyl) thio and alkyl/alkenylthio-4,5-disubstituted-4H-1,2,4-triazoles were reported by Muhi-Eldeen *et al*.[64]



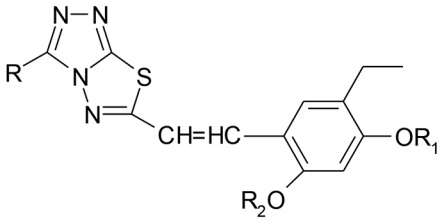
A series of 3,4-Disubstituted-5-mercapto-1,2,4-triazoles were synthesized by Mishra and Tiwari[65] for antifungal activities.



Holla *et al.* reported synthesis and antibacterial properties of some nitrofuryl triazolo [3,4-b]-1,3,4-thiadiazines.[66]

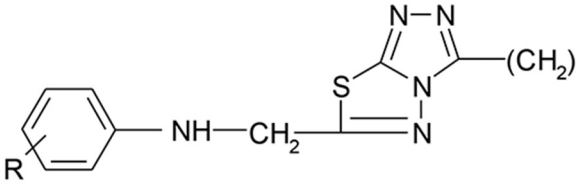


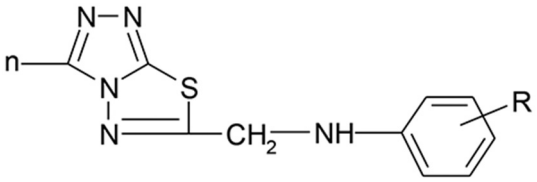
Gupta *et al*. reported reaction of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles with substituted cinnamic acids and determined the antimicrobial and anti-inflammatory activities of the compounds formed.[67]



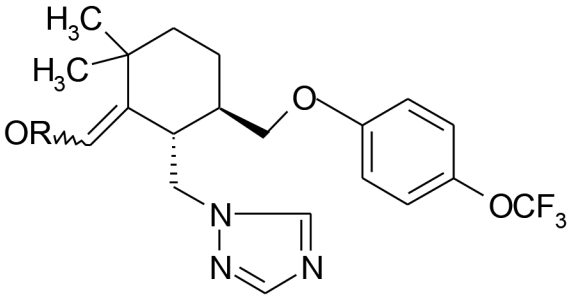
R=CH_3, C_2H_5, o-CH_3,o-OH, o-Cl, C_6H_5, p-Cl, p-OCH_3
R_1=R_2=CH_3, C_2H_5

Shivarama *et al.* studied some N-bridged heterocycles derived from bis-[4-amino-5-mercapto-1,2,4-triazol-3-yl]alkanes and showed their antibacterial activity.[68]



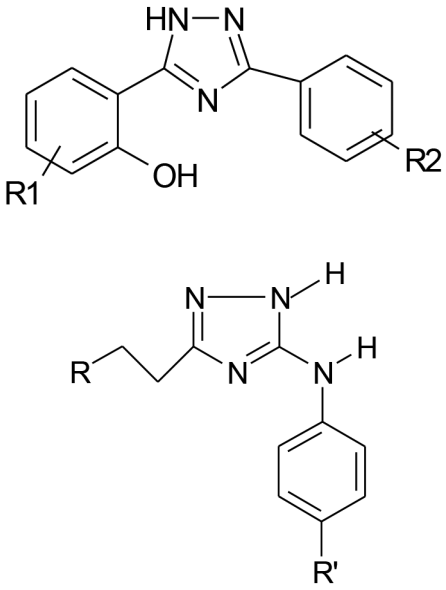


Tsukda *et al.* reported modeling, synthesis, and biological activity of novel antifungal agents with 1,2,4-triazole ring in them.[69]

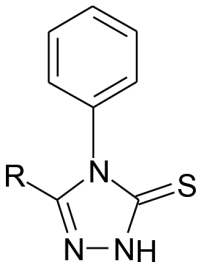


SAR studies of diaryl triazoles against bacterial two-component regulatory systems and their antibacterial activities were reported by Sui *et al*.[70]

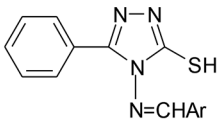
Udupi *et al.* synthesized some substituted 1,2,4-triazoles and evaluated their *in vitro* antibacterial activity.[71] Demirayak *et al.* synthesized and reported antimicrobial activities of some 3-arylamino-5-[2-(substituted 1-imidazolyl)ethyl]-1,2,4-triazole derivatives.[72]



Sangapure and Basawaraj reported antimicrobial activities of some triazoles and related compounds possessing benzofuran moiety.[73]

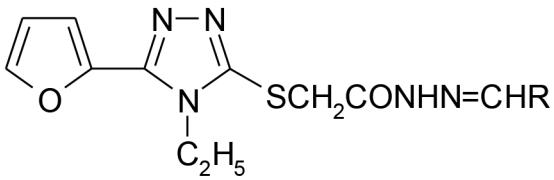


Rao *et al.* synthesized 11 compounds of the following types and reported their antimicrobial activity of compounds with a chloro, bromo, or a hydroxy group on the aromatic ring with azomethine linkage showed potent antibacterial activity and rest showed moderate activity.[74]



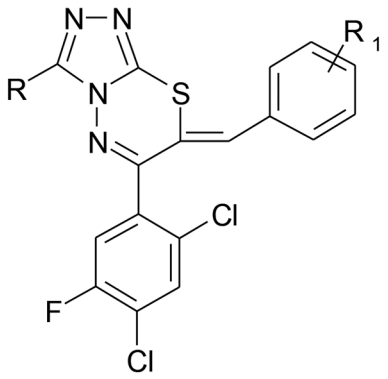
Ar= C_6H_5, o-$CH_3C_6H_4$, p-ClC_6H_4, o-$NO_2C_6H_4$, m-$NO_2C_6H_4$, o-OHC_6H_4

Ulusoy *et al.* reported antimicrobial activity of some 1,2,4-triazole-3-mercaptoacetic acid derivatives.[75]



R= OC_2H_5, $NHNH_2$,etc.

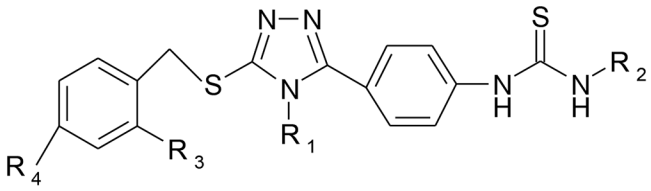
Shivarama-Holla *et al.* reported antibacterial and anticancer activities of some halogen-containing 1,2,4-triazolo-1,3,4-thiadiazines.[76]



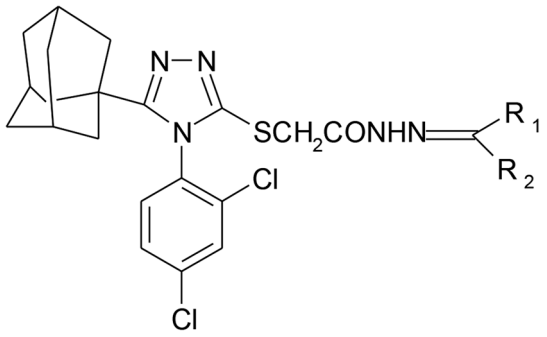
R= H, CH_3, C_2H_5, C_3H_7, C_6H_5, CH_3O-C_6H_4

R'=3,4-methylene-dioxy, 4-chloro, 3,4-dimethoxy

Küçükgüzel *et al.* reported some 3-Thioxo/Alkylthio-1,2,4-triazoles with a substituted thiourea moiety as possible antimycobacterial.[77]

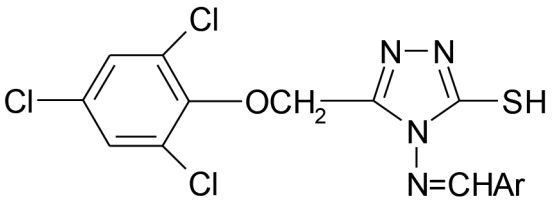


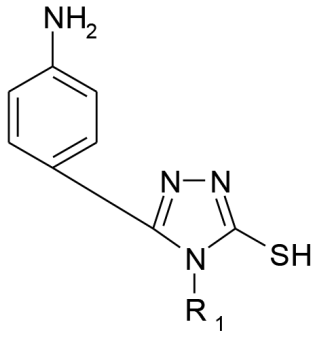
Papakonstantinou-Garoufalias *et al.* synthesized some novel 3-substituted derivatives of 4-(2,4-dichlorophenyl)-5-adamantyl-1-H-1,2,4-triazole as antimicrobial agents.[78]

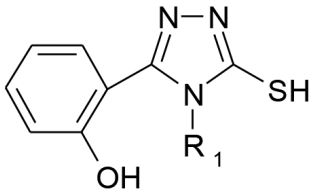


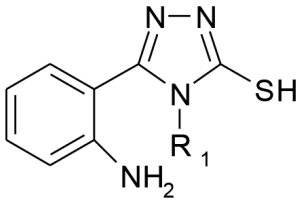
R_1= $(CH_2)_3$, $(CH_2)_4$, 1-indanyl, 9-fluorenyl

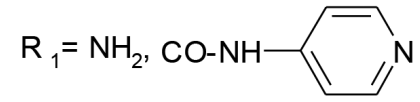
Patel *et al.* reported antibacterial activity of 1,2,4-triazoles against *Staphylococcus aureus, Salmonella typhi, Bacillus subtilis,* and *Escherichia coli*.[79]

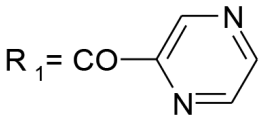






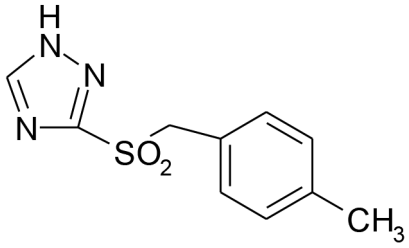




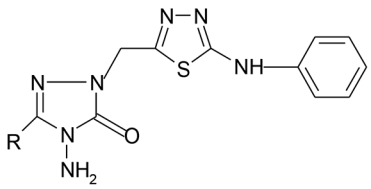


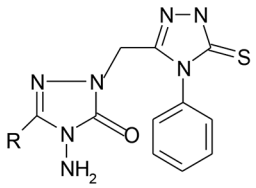
Ravi and Rajkannan reported antimicrobial activity of some new 1,2,4-triazoles.[80] All of them were highly active against bacterial cultures of *S. aureus*, *E. coli*, and fungal culture of *Candida albicans* at 500 μg/ml disc concentration.

Klimeŝovà *et al.* reported antimycobacterial activity of 1,2,4-triazole 3-benzylsulfanyl derivatives.[81]

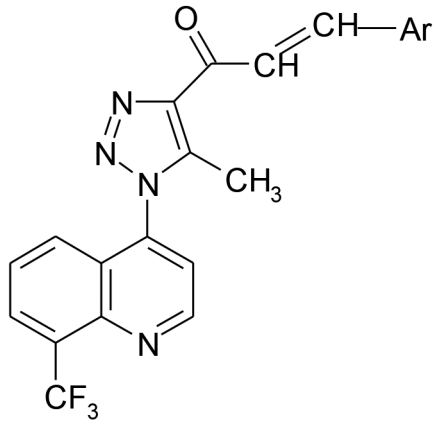


Demirbas *et al.* reported antimicrobial activities of some new 1-(5-phenylamino-[1,3,4] thiadiazol-2-yl)methyl-5-oxo-[1,2,4]-triazoles and 1-(4-phenyl-5-thioxo-[1,2,4]-triazol-3-yl)methyl-5-oxo-[1,2,4]triazoles.[82]

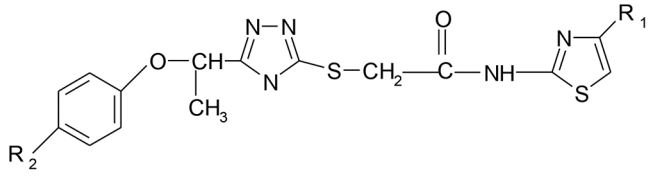




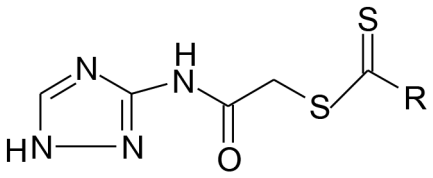
A series of some substituted 1,2,3-triazoles were synthesized by Holla *et al.* as antimicrobial agents.[83]



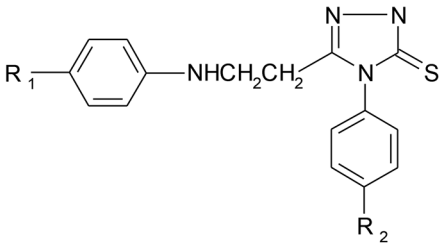
Turan-Zitouni *et al.* reported synthesis of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazoles.[84] These compounds were reported to be active against *S. aureus, E. coli,* and *Pseudomonas aeruginosa*. They also reported antifungal activity against *C. albicans* and *Candida glabrata*.



Ozkirimli *et al.* synthesized 10 new triazolyl-N,N-Dialkyldithiocarbamates for screening against *Microsporum canis, Microsporum gypseum,* and *Trichophyton rubrum*.[85] These were found to possess moderate to fairly good antifungal activity.



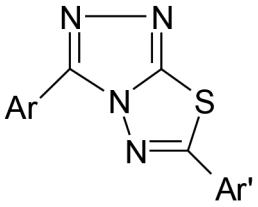
Some new 3-(p-substituted anilinoethyl)-4-(p-substituted phenyl)-5-thioxo-1,2,4-triazoles synthesized by Siddiqui *et al.* showed antifungal activity against *C. albicans* and *Aspergillus niger*.[86]



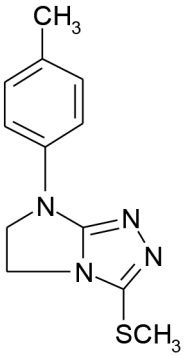
R_1= H,OCH_3, Br, Cl,

R_2= H,CH_3, Br, Cl

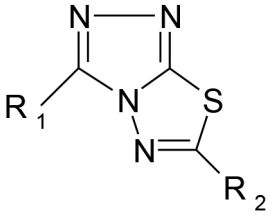
Mathew *et al.* reported synthesis, antimicrobial, and anti-inflammatory activity of some substituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles.[87]



Sztanke *et al.* reported synthesis of imidazo[2,1-c][1,2,4]triazole aryl derivative containing the methylthio group as possible antibacterial agents.[88]



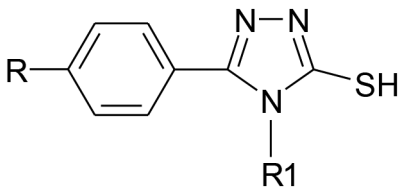
Swamy *et al.* reported the antimicrobial activities of condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazoles.[89]



Holla *et al.* synthesized some new fluorine containing triazolothiadiazines and as depicted below and tested their antibacterial activities against *E. coli, S. aureus, P. aeruginosa,* and *B. subtilis*, and antifungal activities against *C. albicans*. Their anticancer activities were also reported.[90]

El-sayed *et al.* reported synthesis, antibacterial, and surface activity of 1,2,4-triazole derivatives.[91]

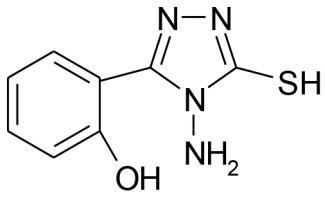
Baluja *et al.* reported a facile synthesis and antimicrobial activity of some 4-aryl triazoles.[92]



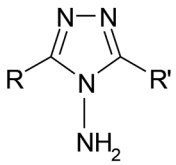
R= -OCH_3

R_1= Aryl

Synthesis and antibacterial activity of some 1,2,4-triazole derivatives of salicylic acid and its synthetic intermediates were reported by Khiati *et al.*[93]

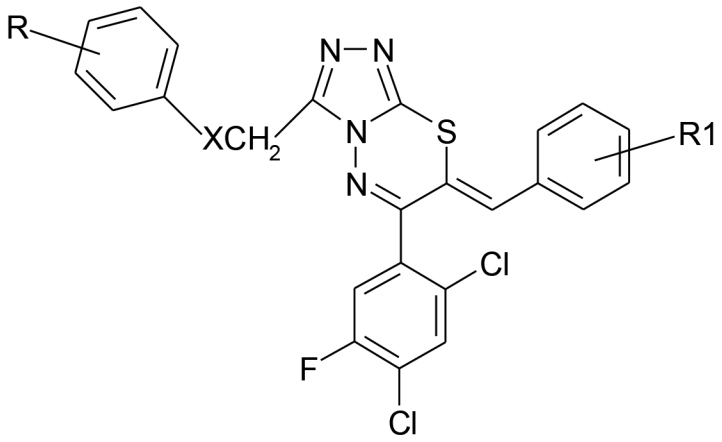


Serdar *et al.* synthesized some novel 3,5-diaryl-1,2,4-triazole derivatives and investigated their antimicrobial activity.[94]

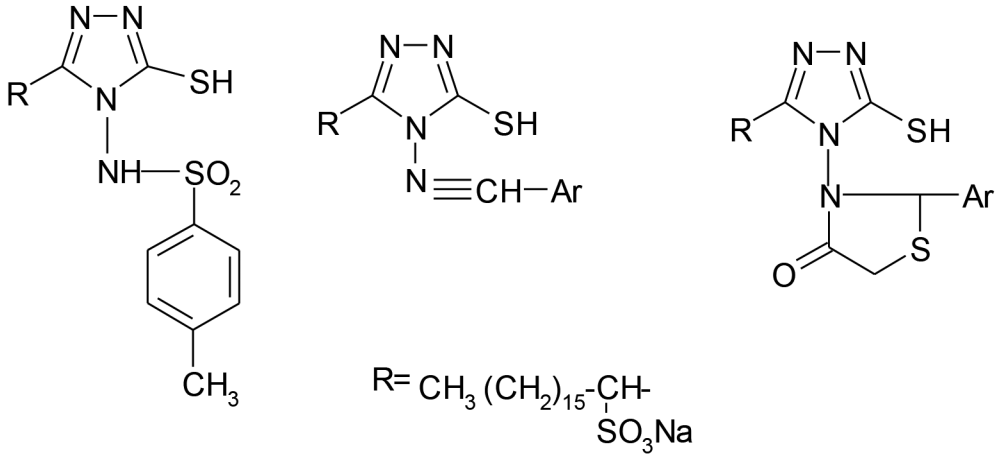


R= CH_3, C_6H_5OH(P-), $C_6H_4CH_3$ (P-), C_6H_4N(P-), -C_6H_5

R'= -C_6H_5, -CH_3

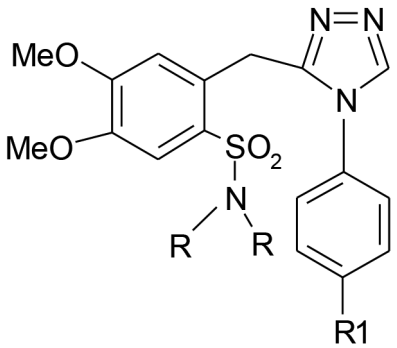


R= 2-Cl;4-Cl;3- CH_3, 2,4 -Cl2, 3-F

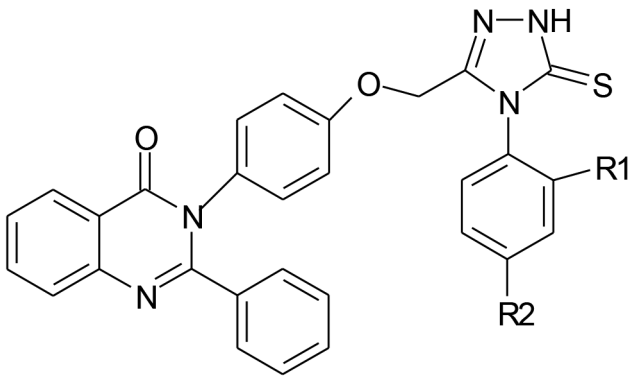


R= $CH_3(CH_2)_{15}$-CH-
SO_3Na

Ezabadi *et al*.[95] reported some sulphonamides-1,2,4-triazole derivatives as antifungal and antibacterial agents.

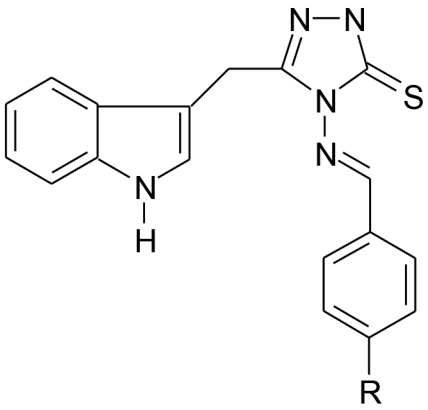


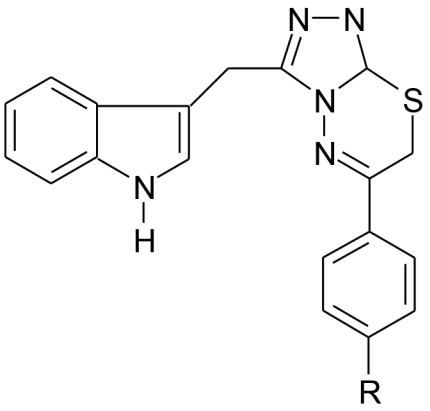
Havalda *et al*.[96] reported synthesis of 1,2,4-triazole derivatives and their biological activity.



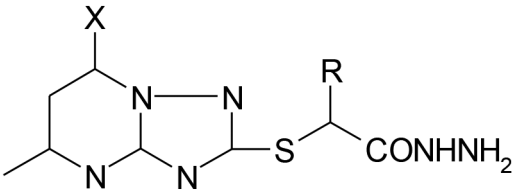
Kaplancikli *et al*.[97] reported some new triazole and triazolothiadiazine derivatives as possible antimicrobial agents.

Synthesis, antifungal activity, and CoMFA analysis of novel 1,2,4-triazolo [1,5-a] pyrimidine derivatives were reported by Chen *et al*.[98]



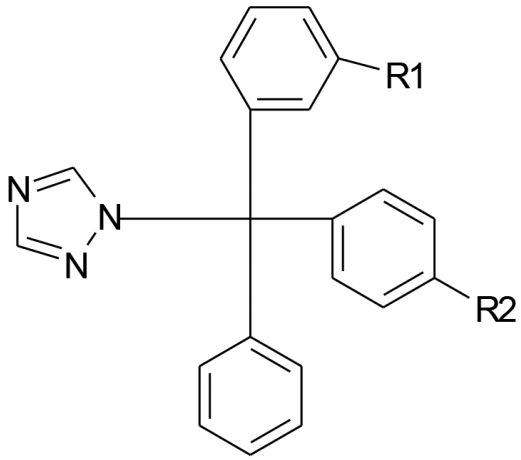


R= H, Cl, CH_3, NO_2, $N(CH_3)_2$

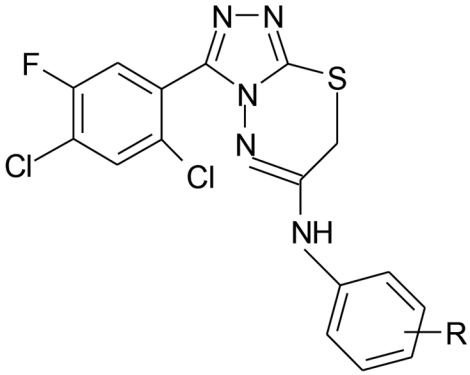


R= X= H, CH_3

Rezaei *et al.*[99] reported design, synthesis, and antifungal activity of some triazole and benzotriazole derivatives.

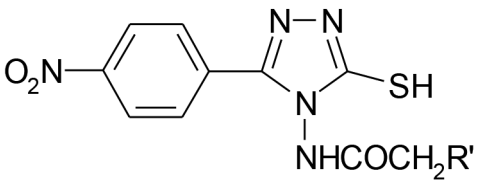


Karthikeyan *et al.*[100] reported synthesis and antimicrobial studies of novel dichlorofluorophenyl containing aminotriazolothiadiazines.



R= 4- CH_3 ,4-Cl, 4-OMe ,4-OC_2H_5 ,4-F, 2,3-Cl_2

Upmanyu *et al.*[101] reported synthesis and antimicrobial evaluation of some novel 1,2,4-triazole derivatives.

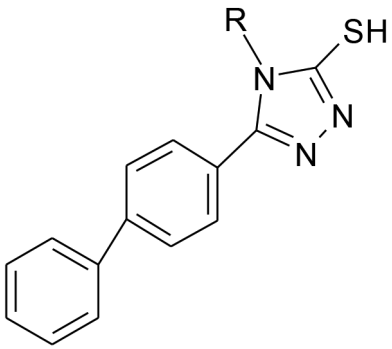


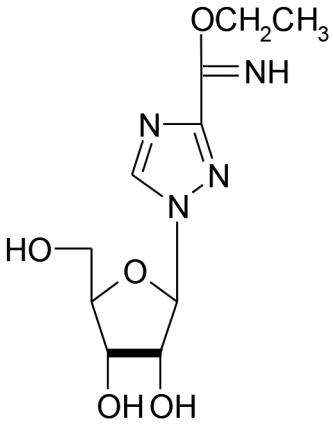
Rakesh *et al.*[102] reported synthesis, characterization, and biological evaluation of novel 1,2,4-triazole derivatives as potent antibacterial and anti-inflammatory agents.

Antitumor and anticancer activity

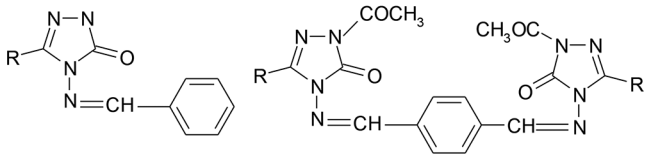
Methyl 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxidimidate and ethyl 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxidimidate were

synthesized and tested for antitumor and antiviral activity by Kini *et al.*[103] Both the compounds exhibited significant activity *in vivo* against murine leukemia L1210.

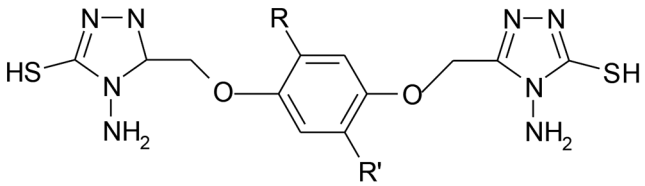




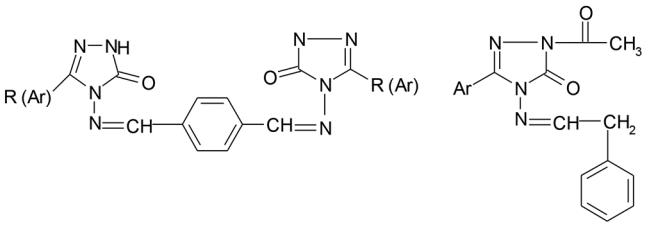
Ikizler *et al.*[104] reported 13 new derivatives of 1,2,4-triazoles. Three of these compounds were screened for their antitumor activities using cell lines derived from human solid tumors.



Holla *et al.*[105] reported new bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents.



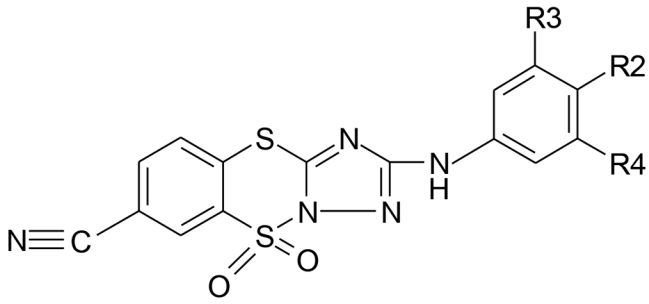
Demirbas *et al.*[106] reported synthesis of 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro-1H-1,2,4-triazol-5-ones and 3-alkyl-4-alkylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones as antitumor agents.



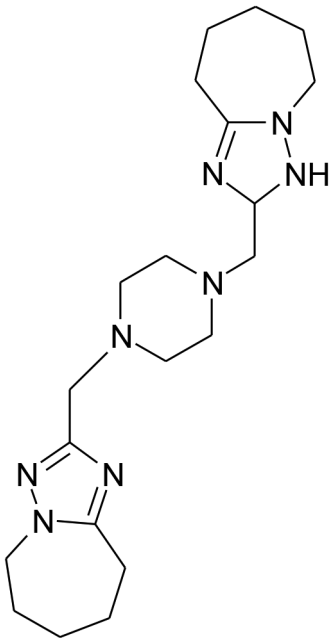
Al-Soud *et al.*[107] reported synthesis and properties of new substituted 1,2,4-triazoles and showed them as potential antitumor agents.

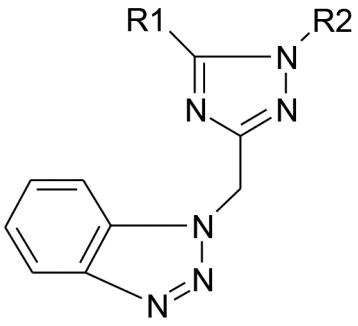
Holla *et al.*[108] synthesized some Mannich bases derived from 1,2,4-triazoles and characterized them and reported their anticancer activity.

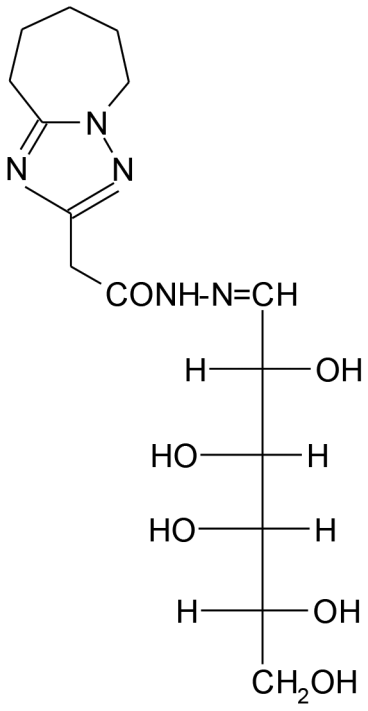
Pomarnacka and Gdaniec[109] reported synthesis and anticancer activity of 2-amino-8-chloro-5,5-dioxo[1,2,4]triazolo[2,3-b][1,4,2] benzodithiazine derivatives.

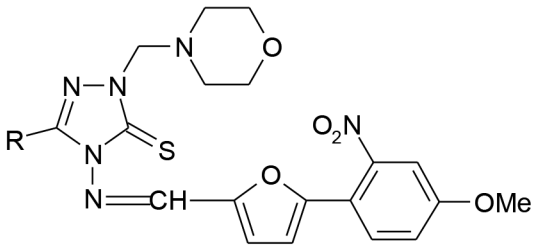


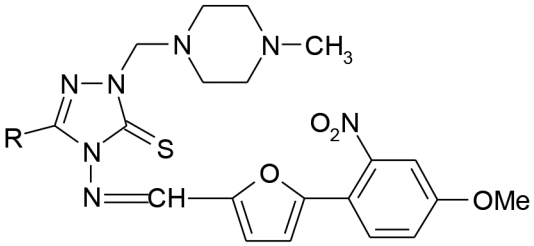
Al-Soud and Masoudi[110] reported antitumor activity and DNA affinity of bis-N,N'-trisubstituted 1,2,4-triazolo-piperazines.



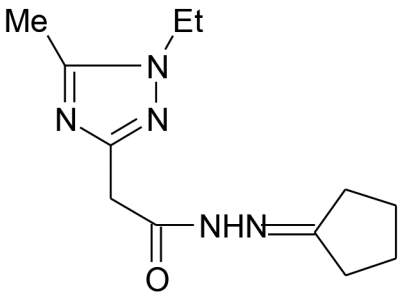








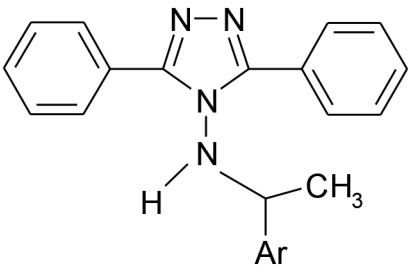
Al-soud *et al.*[111] reported synthesis, antitumor, and antiviral properties of some 1,2,4-triazole derivatives.



Bekircan and Gümrükçüoğlu[112] reported synthesis of some 3,5-diphenyl-4H-1,2,4-triazole derivatives as antitumor agents.

Victoriya *et al.* reported docking studies and biological evaluation of anticancer activity of new 1,2,4 triazole (4H) derivatives.[113]

Georgiyants *et al.*[114] reported anticancer activity of new 1,2,4-triazole (4H) derivatives.

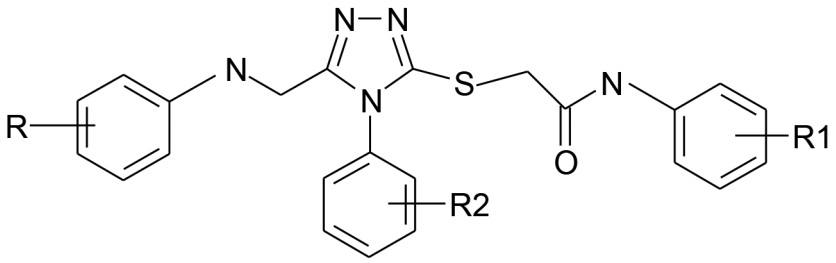


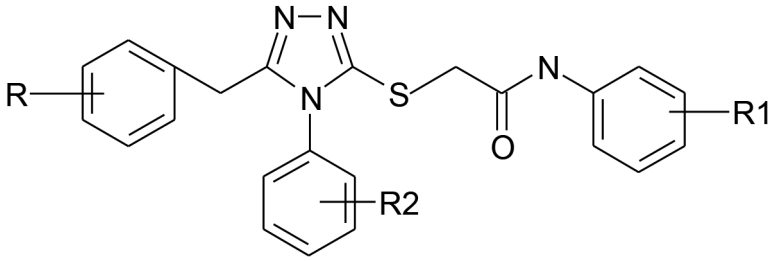
Ar= Phenyl, 4- OMe Phenyl, 4- NO_2 Phenyl

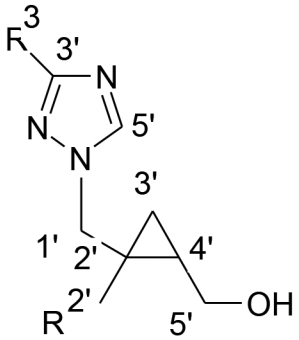
Benci *et al.*[115] reported synthesis of some novel 1,2,4-triazole and purine acyclic cyclopropane nucleoside analog and evaluated them for antiviral and cytostatic activity.

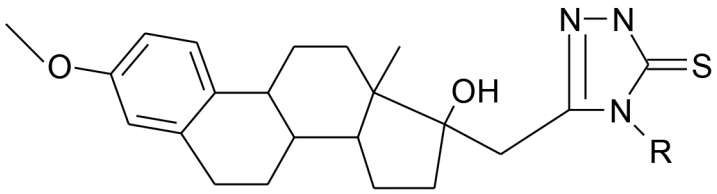
Other activities

Omar and Aboul Wafa[116] reported synthesis of estradiol-17α-triazolines and tested *in vitro* for anabolic-catabolic activity and binding affinity to steroid receptors.









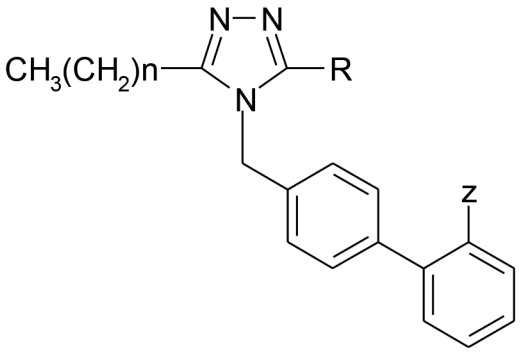
R= C_6H_5, p-$H_3CC_6H_5$, p-$H_3COC_6H_5$, p-ClC_6H_5, p-BrC_6H_5, p-FC_6H_5

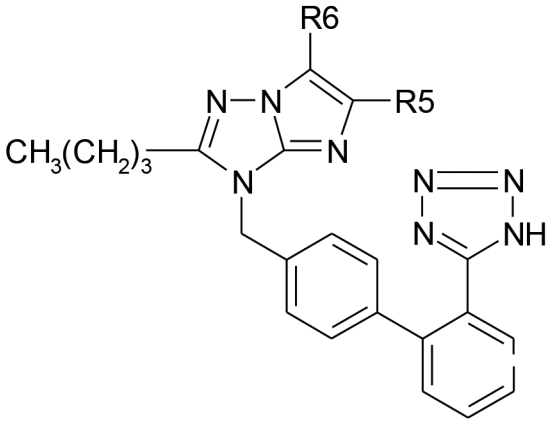
Witkowski *et al.*[117] reported design, synthesis, and broad-spectrum antiviral activity of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide and related nucleosides.

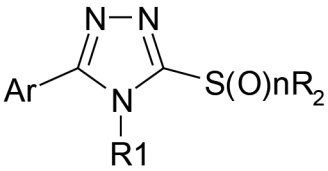
Bradbury and Rivett[118] synthesized two series of 1,2,4-triazolo-[4,3-a] pyrazine derivatives with human rennin inhibitory activity which incorporates the transition-state mimetics (3S,4S)- and (3R,4S)-5-cyclohexyl-3,4-diaminopentanoic acid ((S)- and (R)-CDAPA), and (4-S)-4-amino-5-cyclohexyl-2,2-difluoro-3-oxopentanoic acid (ACDFOPA).

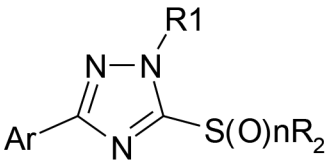
Ashton *et al.*[119] synthesized a series of 3,4,5-trisubstituted 4H-1,2,4-triazoles and related series of 3H-imidazo[1,2-b][1,2,4]Triazoles and evaluated them *in vitro* and *in vivo* as non-peptide angiotensin II antagonists.

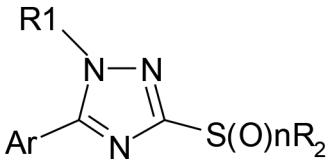
Kane *et al.*[120] reported 5-Aryl-3-(alkylamino)-4H-1,2,4-triazoles as selective antagonists of strychnine-induced convulsions and potential antispastic agents. The most potent antagonist of strychnine-induced convulsions was 5-(2-Fluorophen)-4-methyl; 1,3-(methylthio)-4H -1,2,4-triazole, while the most selective antagonist was 5-(3-fluoro phenyl)-4-methyl)-3-(methyl sulfonyl) 4H-1,2,4-triazole.

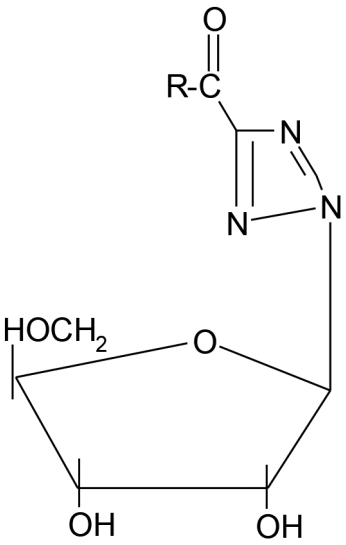


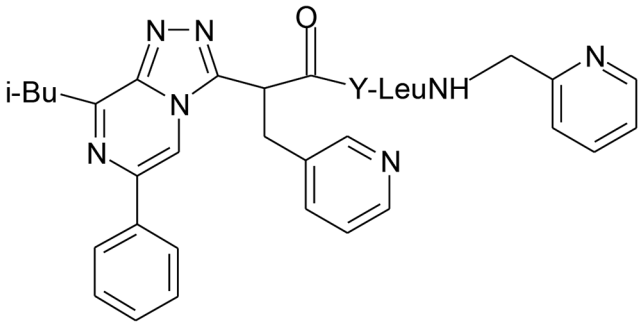




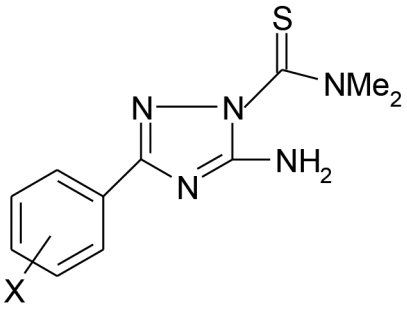




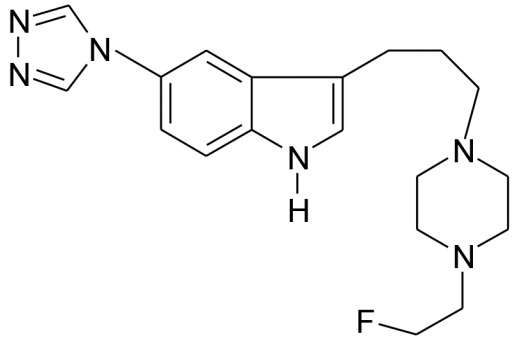


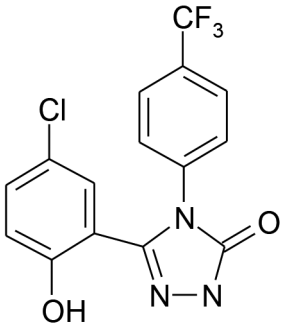
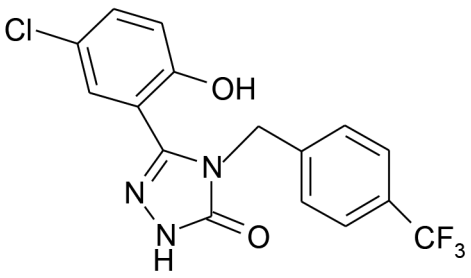
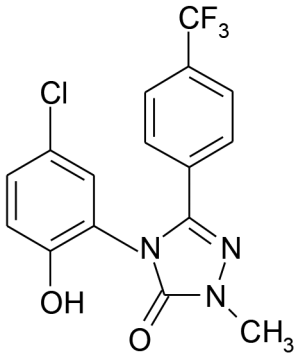
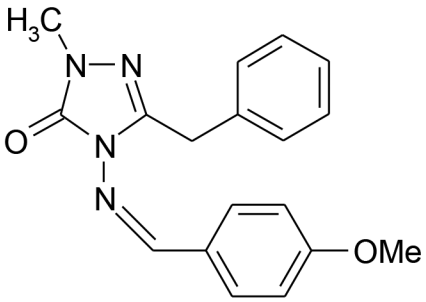
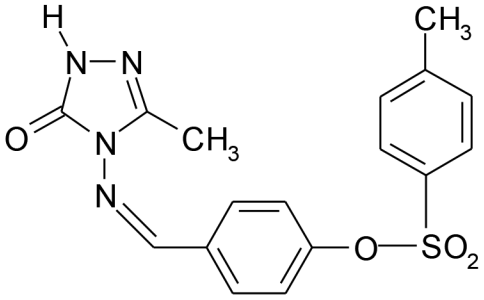


Naito *et al.*[121] reported synthesis and pharmacological activity of triazole derivatives inhibiting eosinophilia. To develop novel antiasthmatic agents based on a new mechanism of action, a series of 3-substituted 5-amino-1-[(methylamino) (thiocarbonyl)]-1,2,4-triazole derivatives were synthesized and evaluated in a model in which eosinophilia was induced in the airway through intravenous(iv) injection of Sephadex particles on days 0, 2, and 5.

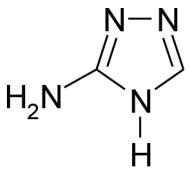


Mark *et al.*[122] reported 1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]-4-(2-(3-fluorophen)ethyl) piperazine as a potential candidate in the treatment of migraine.



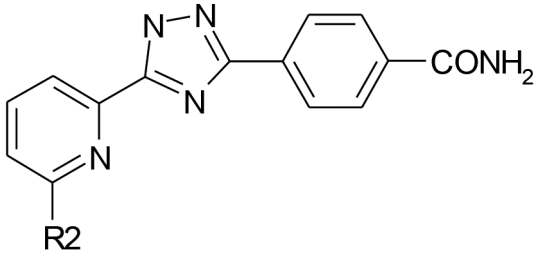
Demirayak *et al.*[123] reported the synthesis and antithyroid activity of 3-amino1,2,4-triazole. In rat 3-Amino-1,2,4-triazole proved to be fairly potent antithyroid agent which inhibits the formation of organically bound iodine but does not affect the iodine trap.



Romine *et al.*[124] reported 4,5-Diphenyltriazol-3-ones: Openers of large-conductance Ca^{2+}-activated potassium (Maxi-K) channels. A series of diphenyl-substituted heterocycles were synthesized and evaluated by electro-physiological techniques as openers of the cloned mammalian large-conductance, Ca^{2+}-activated potassium (maxi-K) channel. The series was designed from deannulation of known benzimidazolone maxi-K opener NS-004. The triazolone ring system was the most studied wherein 4,5-diphenyltriazol-3-ones was identified as the optimal maxi-K channel opener.

Bing *et al.*[125] synthesized and screened insecticidal activity of 2-tert-Butyl-4-chloro 5[(3-(substituted)-1H-1,2,4-triazol-5yl) thio] pyridazin-3H-2-one derivatives. Insecticidal activity of all the compounds was screened by leaf dip method. Antiradical and antioxidant activity of 1,2,4-triazole derivatives was reported *in vitro* by Hyder *et al.*[126]

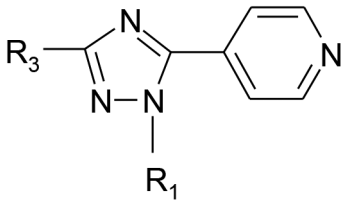
Kim *et al.*[127] reported design, synthesis, and biological evaluation of novel-2-pyridinyl-[1,2,4-] triazoles as inhibitors of transforming growth factor β_1 type 1 receptor.



Jin *et al.*[128] reported plant growth regulating effect of some fused triazole derivatives.

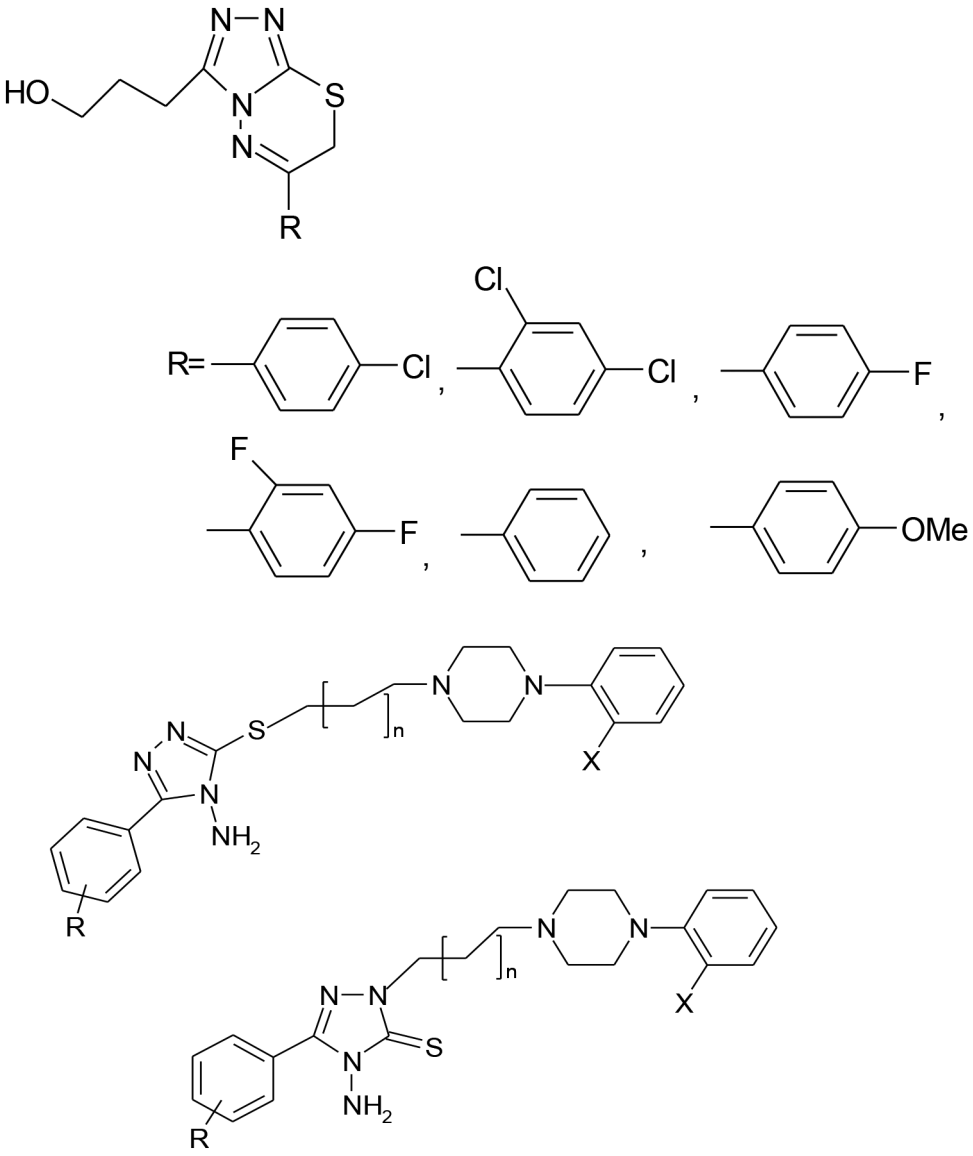
[1,2,4]-triazole derivatives as 5-HT_{1A} serotonin receptors ligands were reported by Sarva *et al.*[129]

Baldwin *et al.*[130] reported some 1,2,4-triazoles as new classes of xanthine oxidase inhibitors.



Akerblom and Cambell reported[131] nitrofuryltriazole derivatives as potential urinary tract antibacterial agents.

Yadagiri *et al.* reported synthesis and evaluation of benzosuberone embedded with 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole moieties as new potential antiproliferative agents.[132]

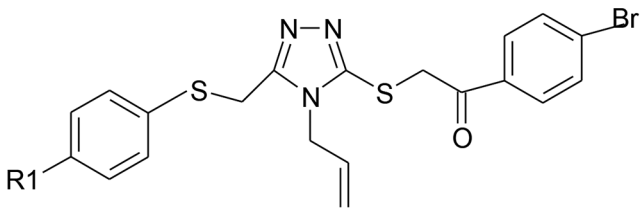


R= H, 2-Cl, 4-CH_3O, 3-CH_3O, 4-CH_3, 4-Cl, 4-Br, 4-n-C_3H_7O

X= CH_3O, NO_2

n= 0,1

Georgiyants *et al.* reported synthesis, docking studies, and biological evaluation of anti-ulcer activity of 4-allyl-5-(4-R1)-Phenylthiomethyl-1,2,4-triazole-3-ylmercaptoacetic acid derivatives.[133]



CONCLUSION

Triazoles have attracted considerable attention in the field of medicine and agrochemical research as well as in materials science, due to their unique structures and properties. Triazole and its derivatives belong to a class of exceptionally active compounds possessing many pharmacological properties. In this review, various activities related to triazole derivatives have been described which their structural perspectives. Literature data published previously have been included in the study to help the reader to find information appropriate for the chemistry of triazoles. The review may be helpful for the development of potential inhibitors.

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