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Review Article

1,2,4-TRIAZOLE: A REVIEW OF PHARMACOLOGICAL ACTIVITIES

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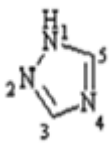
ABSTRACT

Different heterocyclic analogues were evaluated for their diverse biological activities. Out of them, the 1,2,4-triazole nucleus is an ubiquitous structural feature of many synthetic compounds with diversified therapeutic efficacy. A large volume of published literature over the last few decades precludes a comprehensive review. The triazole moiety seems to be very small but its broad biological profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. This article presents a comprehensive review on the pharmacological activities of some novel derivatives of the 1,2,4-triazole moiety.

Keywords: 1,2,3-triazole, 1,2,4-triazole, Heterocyclic Chemistry, Pharmacological activities

INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as in pharmaceuticals, herbicides, dyes, and many more compounds[1]. These heterocycles have great importance in drug discovery as the heteroatoms present in them make hydrogen bonds with the receptors present in the body and thus giving their significant pharmacological actions. Out of several heterocyclic compounds, those with Nitrogen atom in their structure give promising pharmacological activities**.** Triazole, also known as pyrrodiazole, is one of the classes of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions having molecular formula $C_2H_3N_3$. Two isomers of triazole are 1,2,4-triazole (1) and 1,2,3-triazole (2):



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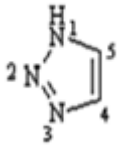


(2)

Tautomers of 1,2,4-triazoles

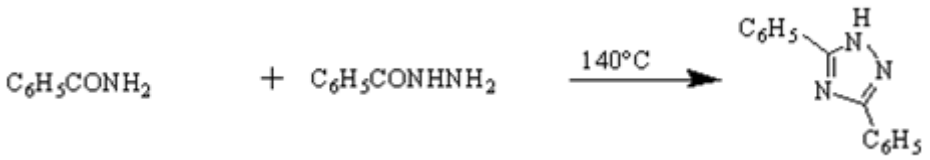
1,2,4-triazoles exists in two tautomeric forms. 1*H* and 4*H*-1,2,4-triazole is considered to be pharmacologically important nucleus[2].

(3) **(4)**

General methods of synthesis: Naming reactions

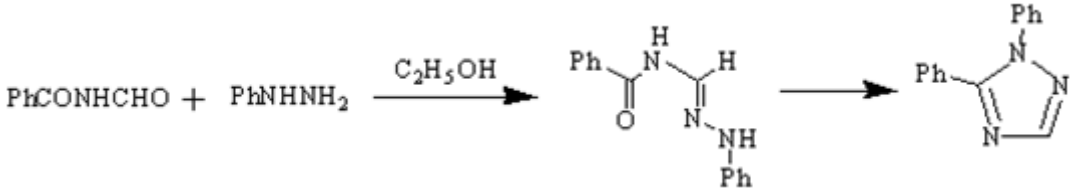
a) Pellizari Reaction

The synthesis of 1,2,4-triazole derivatives by the mixture of amide and acyl hydrazide is generally referred to as the Pellizzari reaction. It has been reported that heating the mixture of formamide and hydrazine hydrochloride with KOH yield of 1,2,4-triazole. For example benzamide and benzoyl hydrazide gave 3,5-diphenyl-1,2,4-triazole[3,4].



b) Einhorn- Brunner Reaction

The synthesis of 1,2,4-triazoles by condensation between hydrazines or mono substituted hydrazine and diacylamines in the presence of weak acid is known as the Einhorn–Brunner reaction. For example: *N*-formyl benzamide and phenyl hydrazine gave 1,5-diphenyl-1,2,4-triazole[3,4].

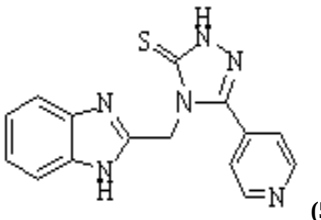


Pharmacological activities of 1,2,4-triazole derivatives

1,2,4-Triazole and its derivatives possess widely differing activities e.g. antibacterial[5-11], antifungal[12,13], anticancer[14-19], anti-tubercular[20-22], anti-inflammatory[23,24], analgesic[25], antiviral[26,27], anti-nociceptive[28-30], anticonvulsant[31-34], anti-corrosive[35], antihelmentic[36], antioxidant[37-41], urease & lipase inhibitors[42], hypoglycaemic[43], anti-migraine, anti-proliferative, sedative, diuretic, muscle relaxant and anti- HIV[44] etc.

Antibacterial and Antifungal activity

Barot *et al* synthesized a series of novel 1,2,4-triazole-5-thione derivatives of benzimidazole **(5)** and were evaluated for antibacterial and antifungal activities. Some of the synthesized compounds showed good antibacterial and antifungal activities with 2.0 and 2.5 μg/ml MIC, respectively. Stains used were *Bacillus cereus, Enterococcus faecalis, S. aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoni*a for the antibacterial activity and *Candida albicans, Aspergillus niger and Fusarium oxyspora* for the antifungal activity. Ofloxacin and Metronidazole were used as standard for antibacterial activity and Fluconazole was used as standard for antifungal activity[45].



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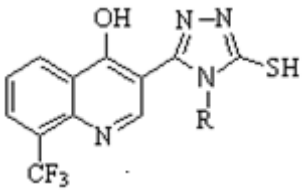
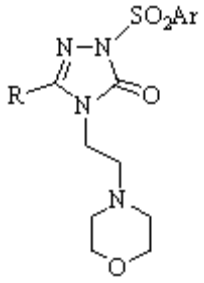


(6)

R- $-C_6H_5$; $-CH_2C_6H_4$; $-CH_2CH_2OCH_3$

Eswaran *et al* synthesized a new class of quinoline derivatives containing 1,2,4-triazole moiety and were evaluated for their *in vitro* antibacterial against *Escherichia coli*, *Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumoniae* and antifungal activities against *Aspergillus flavus, Aspergillus fumigatus, Penicillium marneffei and Trichophyton mentagrophytes*. Preliminary results indicated that most of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs ciprofloxacin & Ciclopirox olamine. The most effective compounds have exhibited activity at MIC of 6.25 mg/ml[46].

Sahin *et al* synthesized novel 1,2,4-triazole derivatives containing morpholine moiety **(7)** and screened for antimicrobial activity. The test microorganisms were *E. coli*, *E. aerogenes*, *Y. pseudotuberculosis*, *P. aeruginosa, S. aureus*, *E. faecalis*, *B. cereus*, *M. smegmatis*, *C. albicans*, *C. tropicalis*, *A. niger*, and *S. cerevisiae*. Ampicillin, Streptomycin, and Fluconazole were the standard drugs. Most of the compounds demonstrated very good antimicrobial activity comparable to the standard drugs[47].



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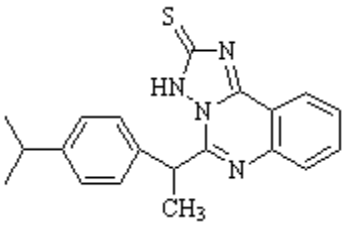


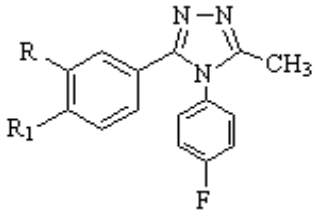
(8)

Ar- 4-Cl-C_6H_4; 4-Br-C_6H_4; 4-NO_2-C_6H_4
R- $-CH_2$; $-CH_2C_6H_5$

Abdulla *et al* synthesized derivatives of ibuprofen **(8)** by cyclization under various reaction conditions in a very good yield. The microbial inhibitory effect of the new agents has been assessed *in vitro* against *Staphylococcus aureous* (gram positive) and *Escherichia coli* (gram negative) using cup-plate method. Three compounds showed the highest antibacterial activities compared to other compounds and standard drugs[48].

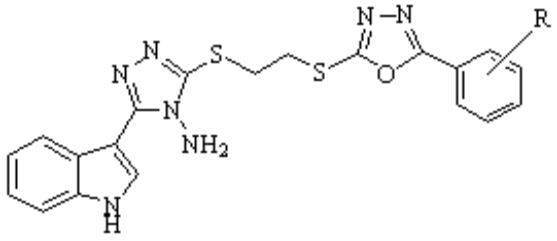
Desabatinna *et al* synthesized a new class of 1,2,4-triazole derivatives namely 3-(3,4-substituted-phenyl)-4-(4-fluorophenyl)-5-methyl-4*H*-1,2,4-triazoles **(9)** and screened for antimicrobial activity. The strains used for antibacterial activity were gram positive (*Staphylococcus aureus, Bacillus cereus) Escherichia coli* NCCS 265 and *Pseudomonas aeruginosa* & for antifungal activity were *Aspergillus niger* and *Candida albicans.*

The pharmacological properties of 1,2,4-triazoles were enhanced by introducing alkyl, alkoxy and halogen substituents. The minimum inhibitory concentration was evaluated by broth dilution method. The halogen substituted compounds were found to be better antimicrobial agents[49].



(9)

R- H; Cl; F; Br; OCH_3; CH_3; NO_2
R_1- H; Cl; F; Br; OCH_3; CH_3

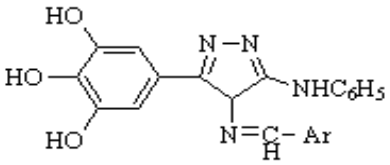


(10)

R- H; 4-OCH_3; 2,4-CH_3; 2-CH_3**;** 2-OCH_2CH_3

Shi *et al* synthesized thirteen novel indole derivatives **(10)**. The minimum inhibitory concentration (MIC) values ranged from 2-8 mg/ml. Amoxicillin was used as the standard reference drug. The minimum inhibitory concentration (MIC) values ranged from 2–8 mg/mL. Determination of MIC and half-maximal inhibitory concentration (IC_{50}) of the active compounds suggested that amino-containing derivative showed maximum activity against most of the strains tested, with MIC of 8 mg/ml for *E. coli*, 8 mg/mL for *B. subtilis*, 16 mg/mL for *P. aeruginosa* and 2 mg/mL for *S. aureus*[50].

Mandal *et al* synthesized triazole derivatives of gallic acid **(11)** and subjected to evaluation of antibacterial and antifungal activity. The bacterial screening indicated that two test compounds showed moderately activity against all the tested bacterial strains *Bacillus subtilus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia* using Ciprofloxacin (10 µg/ml) as standard drug. The remaining compounds were found to be less active. Antifungal screening revealed that the test compounds showed moderate activity against *Aspergillus niger* when compared with Ketoconazole. The MIC was 43 µg/ml[51].



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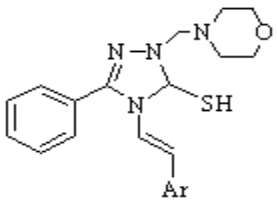
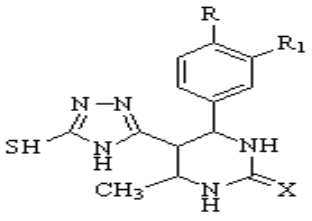


(12)

Ar- 3-OH-C_6H_4; 4-OH-C_6H_4; 3-NO_2-C_6H_4;
Ar- 4-Cl-C_6H_4; 4-CH_3-C_6H_4; 3,4,5-$(OCH_3)_3$-C_6H_2 4-NO_2-C_6H_4; -C_6H_2 -(3,4,5-OCH_3)$_3$

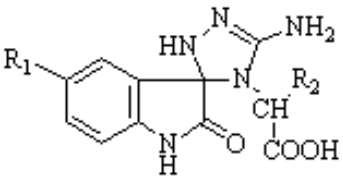
Gupta *et al* afforded a series of 4-(4- substituted benzylideneamino)-2-(morpholinomethyl). 5(substituted phenyl)-2*H*-1,2,4-triazole-4(4*H*)thione **(12)** by the reaction of corresponding Schiff base with formaldehyde and morpholine with the formation of iminium ion. The investigation of antifungal screening data revealed that five compounds are more potent than fluconazole (standard antifungal drug) for *A. niger with* MIC value 64 µg/ml. Some synthesized compounds are equipotent as fluconazole against *C. albican* with MIC value of 32 µg/ml. The good activity is attributed to the presence of electronegative group, 4-chloro and 2,4-dichloro groups at aryl moiety attached to 5th position of triazole nucleus[52].

B. Andrews *et al* synthesized a series of pyrimidine bearing 1,2,4-triazole **(13)** and evaluated for antifungal activity. Most of the compounds shown promising antifungal activity when compared with the standard drug Amphotericin-B. All these compounds were screened for antifungal activity by *Candida albicans, Penicillium sps. and Aspergillus niger.* Amphotericin-B was used as standard drug. Most of the synthesized compounds showed moderate to good inhibition at 10 µg/ml concentration. However the activity was less compared to the standard drugs[53].



(13)

R- H; Cl; OH; $N(CH_3)_2$ X- O; S
R_2- CH_3; C_3H_7S; $C_4H_5N_2$; C_9H_8N; C_4H_9



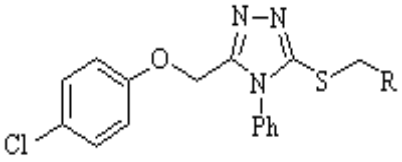
(14)

R_1- Cl; NO_2; H

R_1- H; NO_2

Sachdeva *et al* afforded the formation of spiro indole-triazoles **(14)** and were screened for antibacterial activity against grampositive bacteria *Bacillus licheniformis*, *Staphylococcus aureus* and *Micrococcus luteus* and Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*. Antifungal activity was performed at concentration 500 ppm and 250 ppm against *Aspergillus niger*, *Penicillum* sp. *fusarium oxysporum*, *Alternaria brassicicola*, *Chaetomium orium* and *Lycopodium* sp. The reference standards used were streptomycin and erythromycin. One compound showed excellent activity against bacteria *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Micrococcus luteus* at 500 ppm concentration[54].

Min *et al* synthesized a series of novel thioether derivatives containing 1,2,4-triazole moiety **(15)** from 4-chlorophenol and ethyl 2-chloroacetate as starting materials by multi-step reactions under microwave irradiation and screened for antifungal activity against *Pythium ultimum*, *Phytophthora infestans*, *Corynespora cassiicola*, *Botrytis cinerea* and *Rhizoctonia solani*. Chlorothalonil, Procymidone, Validamycin and Dimethomorph were taken as standard drugs. Four compounds displayed excellent inhibition for the fungal *Corynespora cassiicola* at a concentration of 100 μg/ml[55].

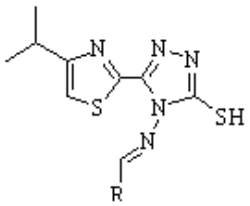


(15)

R- C_3H_7; C_6H_5; 4-Cl-C_6H_5; 4-Br-C_6H_5Br

Anti-tubercular activity

Kumar *et al* synthesized a series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole **(16)** & were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis H37Rv* strain by using broth dilution assay method which indicated that two compounds at MIC 4 μg/ml exhibited two fold enhanced potency than parent compound and the results indicated that some of them exhibited promising activities at MIC 16-16.5 μg/ml and they deserve more consideration as potential anti-tubercular agents when compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with standard isoniazid[56].



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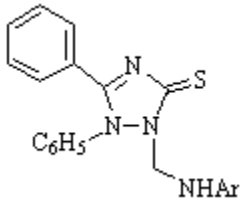
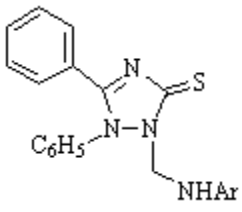


(17)

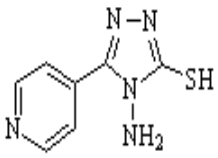
R- 4-CH_3-C_6H_4; 4-Br-C_6H_4; 2-OHC_6H_4; Ar- 4-NO_2-C_6H_4; 4-CH_3-C_6H_4; 4-F-C_6H_4; 2-Cl-C_6H_4; 4-$OCH_3C_6H_4$; 2,4-$(OCH_3)_2$-C_6H_4 3-Cl-C_6H_4

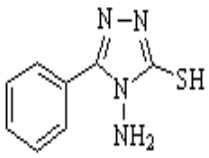
Godhani *et al* synthesized a series of 2-((arylamino)methyl)-5-(3-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole-3-thione **(17)** and screened for antitubercular activity against *Mycobacterium tuberculosis H37Rv* strain by using LJ slope method. Four compounds shown good anti-tubercular activity at 250 μg/ml concentration compared to standard drug Isoniazid. The activity depends upon electronegative nature of substituent groups[57].

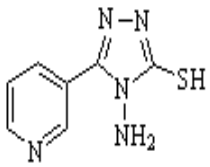


(17)

Ar- 4-NO_2-C_6H_4; 4-CH_3-C_6H_4; 4-F-C_6H_4; 3-Cl-C_6H_4



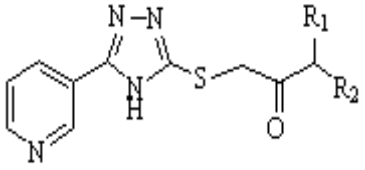




(18-20)

Afreen *et al* afforded the synthesis of 4-amino-5-(aryl)-4*H*-1,2,4-triazole-3-thiol **(18-20)** and evaluated for antitubercular activity against *M. tuberculosis* using non-toxic method Microplate Almar Blue Assay (MABA). The compound-III showed highest activity [12.5 μg/ml MIC value] followed by Compound I [25 μg/ml MIC value] and Compound II [50 μg/ml MIC value]. The result showed that introduction of the triazole ring in pyridine-3-carboxylic acid possess anti-TB activity, but it is less than that of standard drugs Streptomycin and Pyrazinamide[58].

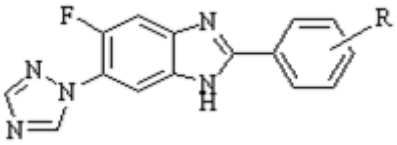
Somani *et al* designed a reaction of 3-(3'-pyridyl)-1,2,4-triazole-5-thiol with N-substituted-α-chloroacetanilides which yielded corresponding 5-(*N*-substituted carboxamidomethylthio)-3-(3'-pyridyl)-1,2,4-triazoles **(21)**. These compounds were subjected to *in-vitro* anti-tubercular activity against Mycobacterium tuberculosis H37 Rv at the concentration of 50 μg/ml using Microplate Alamar Blue Assay method. Six compounds exhibited excellent activity when compared to the standard drug Rifampicin[59].



(21)

R_1- H; morpholinyl
R_2- 4-NO_2-C_6H_4; 4-OCH_3-C_6H_4; 4-Br-C_6H_4; 3-Cl-C_6H_4; *n*-butylamine

Nandha *et al* synthesized a series of 1,2,4-triazole substituted fluoro benzimidazoles with phenyl and benzyl group at 2nd position **(22,23)** and screened for antitubercular activity against against M. tuberculosis H37Rv using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA) with Isoniazid as a standard. 1,2,4-triazole substituted fluoro benzimidazoles with 2-benzyl and 4-$N(CH_3)_2$ substituted 2-phenyl/2-phenyl-1-benzyl counterpart were found to be the most active of all the compounds at MIC 16.5 µg/ml. The SAR studies indicated thatb1,2,4-triazole ring, the fluoro benzimidazole scaffolds are important pharmacophores for antitubercular activity[60].



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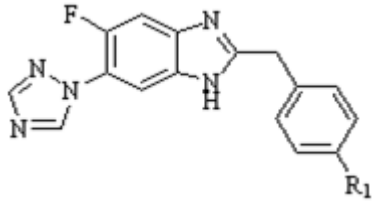
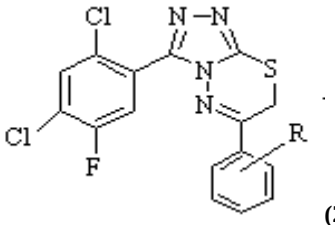


(23)

R- H; Cl; 4-$N(CH_3)_2$; 4-OCH_3; R_1- H; 4-Cl

Anticancer activity

Bhat *et al* synthesized a series of 3-(2,4-dichloro-5-fluorophenyl)-6-(substituted phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines **(24)** by the cyclization of 3-(2,4-dichloro-5-fluorophenyl)-1,2,4-triazol-5-thiol with substituted phenacyl bromides and evaluated 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. One compound showed promising antiproliferative activity with GI_{50} values in the range of 1.06-25.4 µM[61].



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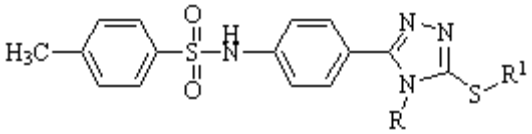
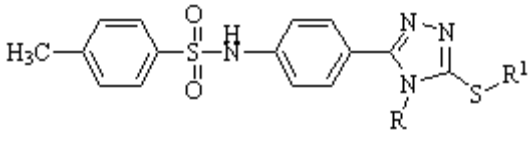


(25)

R- H; 4-Cl; 4-Br; 4-CH_3; 4-OCH_3
R- C_6H_5; 4-OCH_3-C_6H_4; 4-Br-C_6H_4; -CH_2-C_6H_5
R^1- 4-CH_3-C_6H_4-$NHCOCH_2$-; 2-CH_3-C_6H_4-$NHCOCH_2$-; 4-OCH_3-C_6H_4-$NHCOCH_2$-; 4-Cl-C_6H_4-$NHCOCH_2$-

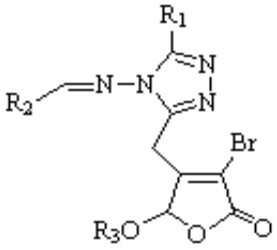
Fattah *et al* synthesized 2-[4-Substitued-5-(4-tosylamino)phenyl-4H-1,2,4-triazol-3ylthio]N-substituted acetamides **(25)** starting from 4-tosylamino benzohydrazide and investigated their cytotoxic activity against breast carcinoma (MCF7) and colon carcinoma (HCT116) cell lines. The cytotoxic activity showed that two compounds have high activity against the two cell lines in range of 3-11 µg/ml. The standard drug used was Doxorubicin[62].



(25)

R- C_6H_5; 4-OCH_3-C_6H_4; 4-Br-C_6H_4; -CH_2-C_6H_5
R^1- C_2H_5; 4-CH_3-C_6H_4-$NHCOCH_2$-; 2-CH_3-C_6H_4-$NHCOCH_2$-; 4-OCH_3-C_6H_4-$NHCOCH_2$-; 4-Cl-C_6H_4-$NHCOCH_2$-

Li *et al* reported the synthesis of a new series of hybrid 1,2,4-triazole Schiff bases bearing γ-substituted butenolide **(26)** prepared via tandem Michael addition-elimination reaction of γ-substituted butenolides with 5-substituted 1,2,4-triazole Schiff bases under phase-transfer catalysis conditions. The synthesized compounds were evaluated for their *in vitro* anticancer activities against cervical cancer cell lines (HeLa) using the MTT assay. All the compounds displayed good inhibition activities on HeLa cell lines. One compound exhibited the best inhibitory activity with an IC_{50} of 1.8 µM[63].



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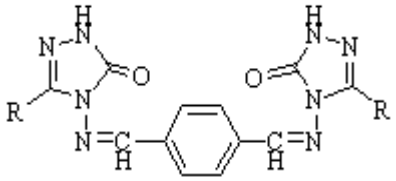
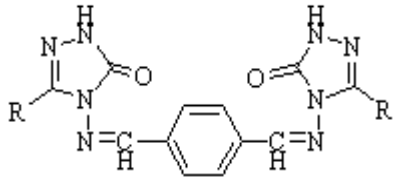


(27)

R_1- CH_3; C_6H_5; 4-OCH_3-C_6H_4; 4-OHC_6H_4; -CH_2-C_6H_5 R- CH_3; CH_2CH_3; $CH_2CH_2CH_3$;
R_2- 4-NO_2-C_6H_4; 4-OH-C_6H_4; 4-OCH_3-C_6H_4; 4-Cl-C_6H_4 $CH_2C_6H_5$; C_6H_5; 4-Cl-$CH_2C_6H_5$
R_3- 1-menthyl; bornyl

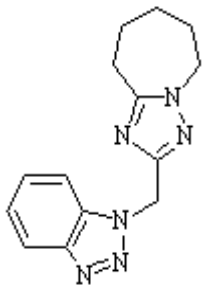
Ikizler *et al* afforded the synthesis of *N,N'*-bis(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4 yl)-1,4-xylenediimines **(27)** and were screened for antitumour activity using 60 cell lines derived from human solid tumours (lung, colon, melanoma, renal, ovarian, CNS, prostate, breast and leukemia). The compounds with benzyl and chloro substituted benzyl showed weak cytostatic activity[64].



(27)

R- CH_3; CH_2CH_3; $CH_2CH_2CH_3$; $CH_2C_6H_5$; C_6H_5; 4-Cl-$CH_2C_6H_5$

Alsoud *et al* supported the synthesis of new substituted 1,2,4-triazole derivatives **(28-30)** and six compounds screened for antitumour activity *in vitro* against a panel consisting of 60 human tumor cell lines (leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancers). Three compounds showed remarkable activity against leukemia, ovarian, renal and lung cancers (with GI_{50} of 0.70 μM, 0.07 μM against leukemia, 0.02 μM against ovarian and 0.60 μM against renal and lung cancers)[65].



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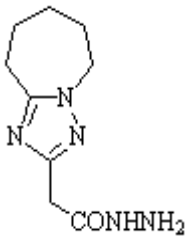

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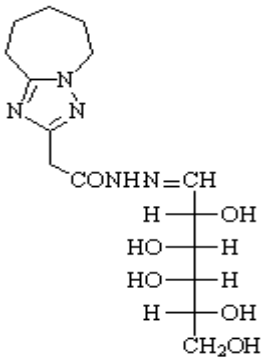
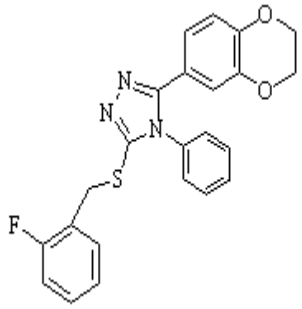


(30)

Hou *et al* synthesized a series of 1,2,4-triazole derivatives containing 1,4-benzodioxan **(31)** and their biological activities were evaluated as potential MetAP2 inhibitors. Fluoro-substituted compound showed the most potent biological activity against HEPG2 cancer cell line (IC_{50}= 0.81 μM for HEPG2 and IC_{50}= 0.93 μM for MetAP2), which was comparable to the positive control TNP-470. Analysis of the most potent compound's binding conformation demonstrated that it was stabilized by hydrogen bonding interaction with ARG 337[66].



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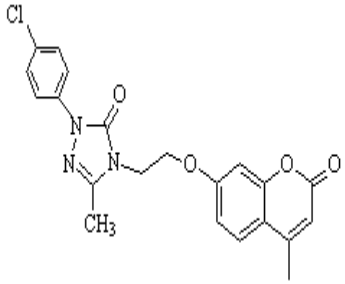

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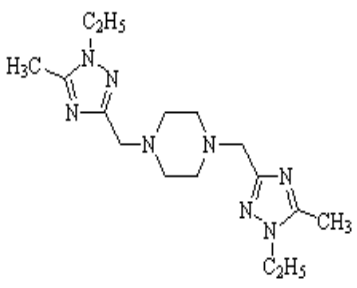


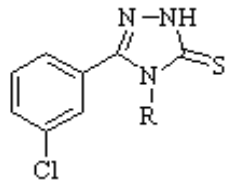
(33)

Kattimani *et al* synthesized a series of novel 1,2,4-triazol-3-one appended to different heterocyclic/aryl moieties **(32)** and was studied *for in vitro* anti-cancerous action against NCI-60 Human Tumor Cell Lines. A compound comprising 1,2,4-triazolin-3-one appended to 4- methylcoumarin ring has shown potent and broad anticancer activity against various cell lines at a single high dose (10^{-5} M) concentration. It has also exhibited marked anticancer activity even at micro molar (µM) concentration against Leukemia, Non-Small Cell Lung Cancer, Renal Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer and Breast Cancer cell panels[67].

Alsoud *et al* synthesized bis-N,N′-trisubstituted 1,2,4-triazolo-piperazine derivatives **(33)** and assayed *in vitro* against a panel consisting of 60 human tumor cell lines, derived from nine cancers types (leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers). Based on the requirement for cell line screening set by NCI is that the percent growth of tumor cells (PG%) is 30% or less, in at least one of the cell lines, it was concluded that all the compounds are inactive since did not approach this value except the given below compound which showed a PG% of 39% in the CCRF-CEM (leukemia) cells at a concentration of 10^{-4}. Substitution of piperazine moiety with bis-1,4-(disubstituted-1,2,4-triazole) residues can play an important role in increasing antitumor activity[68].

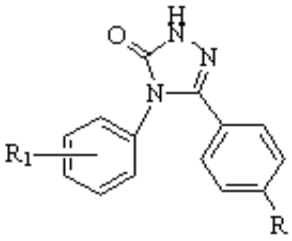
Anticonvulsant activity

Plech *et al* synthesized 4-alkyl-5-(3-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(34)** in two step reaction and screened for anticonvulsant activity using maximal electroshock-induced seizure (MES) test. The compounds having no alkyl substituent and with long alkyl chains at N-4 position of the 1,2,4-triazole ring lacked the protective anticonvulsant effect due to the inability to cross the blood brain barrier (BBB). Compounds with alkyl fragment in position 4 of the 1,2,4-triazole nucleus resulted into rapid onset and long lasting effects at the dose of 300 mg/Kg in mice when compared to the standard drug Valproate[69].



(34)

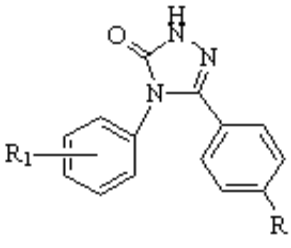
R- C_2H_5, C_4H_9; C_5H_{11}; C_6H_{13}; C_7H_{15}; C_9H_{19}



(35)

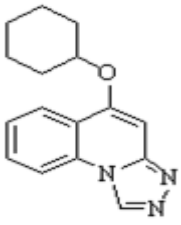
R- H; OH; NO_2; NH_2; CH_3 R_1- H, 2-CH_3

Shalini *et al* supported the synthesis of a new series of 4,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one **(35)** to study the effect of cyclization of the semicarbazone moiety of aryl semicarbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant activity in four animal models of seizures, viz. maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)-induced seizure threshold tests. The compounds were also evaluated for neurotoxicity. Most of the compounds exhibited anticonvulsant activity in all the four animal models of seizure at the dose of 100 mg/Kg. However, some of them cause neurotoxicity. Phenytoin and Carbamazepine were used as standard drugs[70].



(35)

R- H; OH; NO_2; NH_2; CH_3 R_1- H, 2-CH_3



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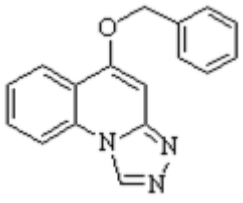
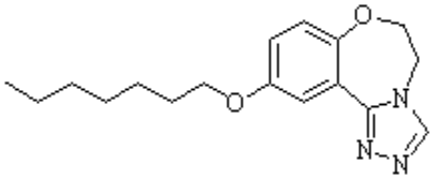


(37)

Gou *et al* synthesized a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives **(36,37)** and evaluated anticonvulsant activity by MES test. The neurotoxicities were measured using rotarod test. The results of these tests confirmed that compound 5-hexyloxy[1,2,4]triazolo [4,3-a]quinoline was the most potent anticonvulsant compound with ED_{50} value of 19.0 mg/kg. The compound 5-benzyloxy-[1,2,4]triazolo[4,3-a]quinoline exhibited a little weaker anticonvulsant activity at the dose of 22.8 mg/Kg, but it possessed lesser neurotoxicity with the PI value of 12.0, which was safer than marketed drug carbamazepine (PI = 6.4)[71].

Deng *et al* synthesized compound 10-heptyloxy-5,6-dihydro-triazolo[4,3-d]benzo[f][1,4] oxazepine **(38)** which showed better anticonvulsant activity and higher safety (ED_{50}= 6.9 mg/Kg) than marketed drugs carbamazepine (ED_{50}= 9.5 mg/Kg) and phenytoin (ED_{50}= 11.8 mg/Kg). The neurotoxicity value of 65.7mg/Kg were observed which results higher PI value of 9.5 compared to Carbamazepine and Phenytoin (PI= 6.4 and 6.9 respectively)[72].



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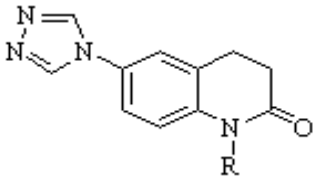
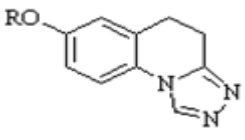


(39)

R- *n*-CH_3; *n*-C_2H_5; *n*-C_3H_8; *n*-C_5H_{11}; *n*-C_6H_{13}

Deng *et al* synthesized a series of 1-substituted-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydro quinolin-2(1*H*)-ones derivatives **(39)** and screened for anticonvulsant activities. Two compounds showed moderate levels of anticonvulsant activity in MES test and protected 100% of the animals at a dose of 100 mg/Kg. Both the compounds do not showed any neurotoxicity in the rotarod test at a dose of 100 mg/Kg. The compound bearing n-pentyl and hexyl chain respectively showed greatest anticonvulsant activities indicating that these compounds possessed the optimum level of lipophilicity form the congeners to act on the central nervous system[73].

Chen *et al* synthesized a series of 4-(4-alkoxylphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives **(40,41)** as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolones and evaluated for anticonvulsant activities by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). 3-ethyl-4-(4-octyloxyphenyl)-4*H*-1,2,4-triazole was found to be the most potent with ED_{50} value of 8.3 mg/Kg and protective index ($PI=TD_{50}/ED_{50}$) value of 5.5, but compound 3-ethyl-4-(4-octyloxyphenyl)-4*H*-1,2,4-triazole, exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin. 4-alkoxyl-3-ethyl-4*H*-1,2,4-triazoles, the open-chain analogues of 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolines, exhibited remarkable anticonvulsant activity and lower neurotoxicity[74].



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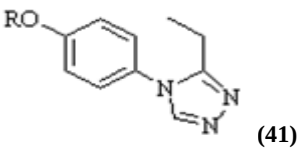
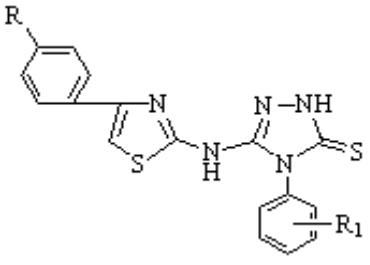


(41)

R- $-CH_2C_6H_5$; $-CH_2C_6H_4$(4-F); $-CH_2C_6H_4$(4-Cl); $-CH_2C_6H_4$(4-OCH_3); $-C_2H_5$; -*n*-C_7H_{15}; -*n*-C_8H_{17}

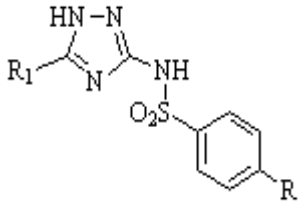
Siddiqui *et al* afforded the synthesis of various 3-[4-(substitutedphenyl)-1,3-thiazol-2-ylamino]-4-(substitutedphenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones **(42)** and screened for anticonvulsant activity by maximal electroshock seizure (MES) and subcutaneous pentylene-tetrazole (scPTZ). Two compounds showed significant activity in both the screens with ED_{50} values 23.9 mg/Kg and 13.4 mg/Kg respectively in MES test and 178.6 mg/Kg and 81.6 mg/Kg respectively in scPTZ test. The compounds displayed a wide margin of safety with median lethal dose (LD_{50}) much higher than the standard drugs Phenytoin, Ethosuximide, Phenobarbital[75].



(42)

R- H; Cl; Br; NO_2

R_1- H; 2-CH_3; 4-CH_3; 2-OCH_3; 4-OCH_3

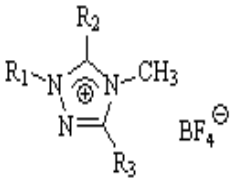


(43)

R- H; F; Cl; Br; CH_3 R_1- H; CH_3; CF_3

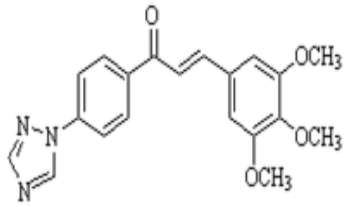
Boechat *et al* synthesized 1*H*-1,2,4-triazol-3-yl benzenesulfonamide derivatives and screened for antimalarial activity by using a model of the active site of *P. falciparum* DHPS, constructed *in silico* from the crystal structure of *Escherichia coli* DHPS. Ligand-enzyme docking simulations were performed with MolDock. Compounds with CF_3 groups on 5th position of the triazole ring, showed stronger interaction with enzyme. The non-substituted triazole analogs exhibited the weakest intermolecular interactions with the enzyme. The halogenated compounds presented better docking scores than Sulfalene and Sulfadoxine[76].

Vlahakis *et al* synthesized triazolium salts **(44)** and evaluated as Plasmodium inhibitors. Many of triazolium salts were highly potent with active concentrations in the nanomolar range in Plasmodium falciparum cultures, and specific to Plasmodium with highly favorable therapeutic ratios. An electron-deficient core was required so that the compound may thereby interact with a negatively charged moiety on the parasite merozoite[77].



(44)

R_1- $-CH_2C_6H_5$; 4-Br-$CH_2C_6H_5$
R_2- H; C_6H_5; R_3- C_6H_5



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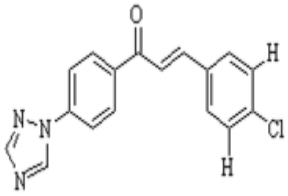
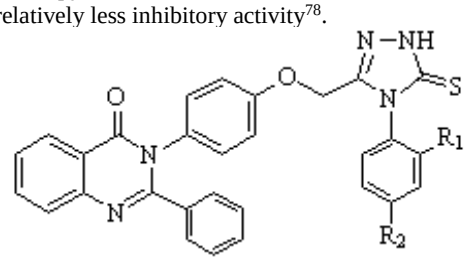


(46)

Mishra *et al* synthesized novel 1,3-diaryl propenone derivatives **(45,46)** and evaluated for their anti-malarial activity *in vitro* against *Plasmodium falciparum.* Chalcone derivatives were prepared via Claisen-Schmidt condensation. The compounds showed antiplasmodial IC_{50} activity ranged between 1.5 and 12.3 μg/ml. The chloro substituted derivatives were found to be the most effective in inhibiting the growth of *P. falciparum* while pyrrole and benzotriazole substituted chalcones showed relatively less inhibitory activity[78].

Havaldar *et al* synthesized 3-{4-[4-(substitutedphenyl)-4*H*-[1,2,4]triazol-3-yl-methoxy]-phenyl}-2-phenyl-3*H*-quinazolin-4-ones **(47)** and were evaluated for the sensitivity of Chloroquine-resistant *P. falciparum* malarial parasite *in vitro* by using triturated hypoxanthine incorporation assay. The 4-fluoro substituted derivative was found to be most active against *P. falciparum* strains and its IC_{50} value was 1.2M[79].

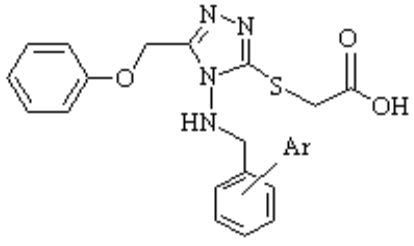


(47)

R_1- H; F; R_2- H; F; NO_2

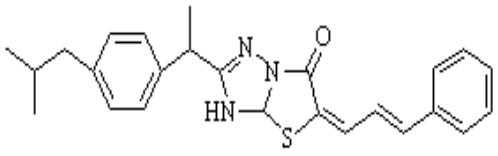
Analgesic and Anti-inflammatory activity

Hunashal *et al* synthesized 2-[4-(substitutedbenzylideneamino)-5-(substitutedphenoxy methyl)-4*H*-1,2,4-triazol-3-yl-thio]acetic acid derivatives **(48)** and were evaluated for *in vivo* anti-inflammatory and analgesic activities. Among the series some compounds showed significant anti-inflammatory activity with P< 0.001 (62-64% edema inhibition) as compared to the standard drug Diclofenac (67.0%). Two compounds also exhibited significant analgesic activity with P< 0.001 (55.9% and 54.9% protection) and less ulcerogenic activity as compared with standard drug aspirin (57.8%)[80].



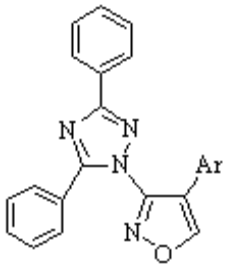
(48)

Ar- 4-CH_3; 4-NO_2; 4-OCH_3; 2-OH; 4-Cl; 2,4-Cl



(52)

Khanage *et al* synthesized some 1,2,4-triazole heterocycles clubbed with pyrazole, tetrazole, isoxazole, pyrimidine **(49,50,51)** and screened for *in vivo* analgesic activity by using acetic acid induced writhing test and Hot plate method. Ibuprofen (10 mg/Kg) and Pentazocine (10 mg/Kg) were taken as standard drugs for writhing test and hot plate method repectively. Chloro, nitro and methoxy, hydroxy and bromo substituted derivatives showed excellent analgesic activity at the dose of 25-100 mg/Kg and dimethylamino, furan and phenyl substituted derivatives showed moderate analgesic activity in both of the methods[81].



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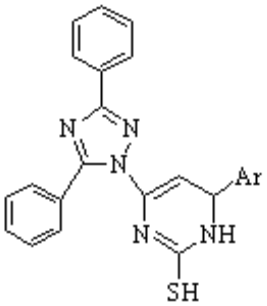

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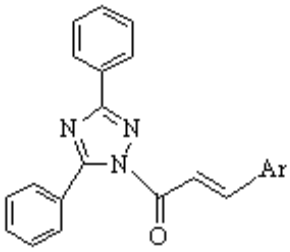
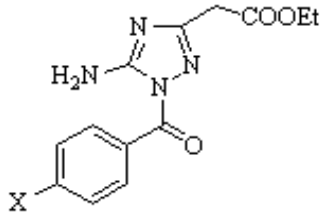


(51)

Ar- 4-Cl-C_6H_5; 4-Br-C_6H_5; 4-OH-C_6H_5; 4-OCH_3-C_6H_5; -NO_2-C_6H_5; 4-$N(CH_3)_2$-C_6H_5

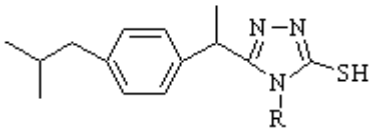
Baran *et al* synthesized thiazolo[3,2-b]-1,2,4-triazole-5(6*H*)-one substituted with ibuprofen **(52)** and evaluated for analgesic and anti-inflammatory activities *in vivo* in mice by using Carrageenan-induced paw edema test, tail flick test and hot plate methods with Ibuprofen (50 mg/Kg)and Oxycodone (100 mg/Kg) as standard drugs . The ulcerogenic risks of the compounds were also determined. None of the compounds represent a risk for developing stomach injury as much as observed in the reference drugs. The compounds carrying a 3-phenyl-2-propenylidene, (biphenyl-4-yl)methylidene and (1-methylpyrrol-2-yl)methylidene at the 6th position of the fused ring were evaluated as potential analgesic/anti-inflammatory agents without a gastro- intestinal side effect[82].

Abdel-Megeed *et al* synthesized different acylated 1,2,4-triazole-3-acetate derivatives **(53)** and were evaluated for their anti-inflammatory activites as well as gastric ulcerogenic effects and acute toxicity by using carageenan-induced rat paw edema , molecular modeling and acute toxicity methods. Results showed that 1-acylated-5-amino-1,2,4-triazole-3-acetates showed higher anti-inflammatory activity with low gastric ulcerogenicity compared with indomethacin. Tested compounds exhibited significant ($P < 0.05$) inhibition against carrageenan-induced rat paw edema at 10 mg/Kg dose. Compounds substituted with chloro, bromo and nitro were found to be more potent than indomethacin[83].



(53)

X- H; Cl; Br; OCH_3; NO_2

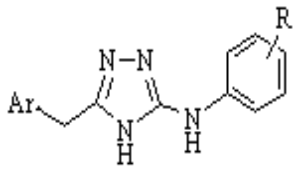


(54)

R- -$CH_2CH_2CH_3$; 4-Cl-C_6H_4; 4-F-C_6H_4; 2-$CH_3C_6H_4$; 2-OCH_3-C_6H_4

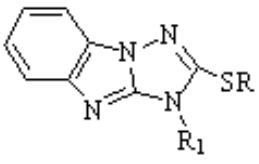
Amir *et al* synthesized 5-[2-(4-*i*-butylphenyl)ethyl]-4-alkyl/aryl-3-mercapto-1,2,4(*H*)-triazole derivatives **(54)** and screened for their anti-inflammatory activity by the carrageenan induced rat paw edema method, analgesic, ulcerogenic and lipid peroxidation activities Some compounds showed 50 to 86% inhibition, whereas the standard drug ibuprofen showed 92% inhibition at the same oral dose of 70 mg/Kg. Five compounds showed more than 80% anti-inflammatory activity with a significant reduction in ulcerogenic activity compared to ibuprofen through the severity index 0.5 to 0.8, *vs*. ibuprofen 1.8[84].

Metwally *et al* afforded the synthesis of 3-arylamino-5-(1-substituted-ethyl)-4*H*-1,2,4-triazoles **(55)** and screened for anti-inflammatory activity with less side-effects by using carrageenan rat paw edema test using Ibuprofen as a reference substance. Hydrocortisone was additionally used as a second reference standard representing steroidal anti-inflammatory agents. The obtained pharmacological results revealed that the compounds substituted with electron-withdrawing groups like halogens were more potent than Ibuprofen which were further evaluated for their ulcerogenic potential in rats and showed a better GI safety profile (0-33.3% ulceration) compared to Indomethacin[85].



(55)

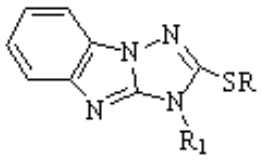
R- 3-Cl; 4-Cl; 4-Br; 4-F; 4-CH_3; 4-OCH_3
Ar- 4-isobutylphenyl; 2-fluorobiphenyl; 6-methoxynaphthyl



(56)

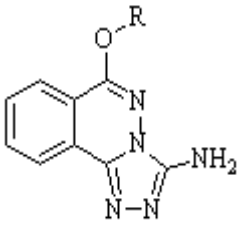
R- H; -CH_3; -C_2H_5; *n*-C_3H_7; *i*-C_3H_7; -$CH_2C_6H_5$
R_1- H; -$COCH_3$; -COC_6H_5; 4-Cl-C_6H_4CO; 4-$CH_3C_6H_4SO_2$

Mohamed *et al* synthesized 1-acyl-2-alkylthio-1,2,4-triazolobenzimidazoles **(56)** and screened for analgesic activity by hot plate method and for anti-inflammatory activity by using carrageenan induced rat paw edema method. Nine compounds were tested for their anti-inflammatory and analgesic effects, most of these compounds showed potent and significant results compared to indomethacin at the dose of 10 mg/Kg. Moreover, ulcerogenicity and the median lethal dose (LD_{50}) of the most active compound was found to be 275 mg/Kg (*i.p.*) in mice[86].



(56)

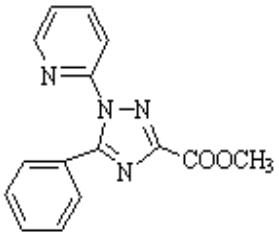
R- H; -CH_3; -C_2H_5; *n*-C_3H_7; *i*-C_3H_7; -$CH_2C_6H_5$
R_1- H; -$COCH_3$; -COC_6H_5; 4-Cl-C_6H_4CO; 4-$CH_3C_6H_4SO_2$



(60)

R- 2-Cl-C_6H_4; 2-Cl-C_6H_4; 4-Cl-C_6H_4; 4-F-C_6H_4; 2-CH_3-C_6H_4; 4-OCH_3-C_6H_4; 4-NH_2-C_6H_4

Rabea *et al* synthesized 5-phenyl-1-(3-pyridyl)-1*H*-1,2,4-triazole-3-carboxylic acid derivatives **(57,58,59)** and evaluated for anti-inflammatory activity carrageenan-induced rat paw edema in albino rats using Indomethacin and Celecoxib as reference drugs at two dose levels of 5 and 10 mg/Kg. Most of the tested compounds showed significant ($P < 0.05$) inhibition against carrageenan-induced edema in rats ranged from 45.6–94.5%, whereas standard drug Indomethacin showed an activity of 78.4% after 3 h. Higher activity was obtained by *p*-bromo-phenyl (82.6%). This means that the aryl substitution on amide nitrogen or N4 of thiosemicarbazide is very important for the activity[87].



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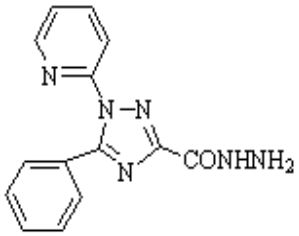

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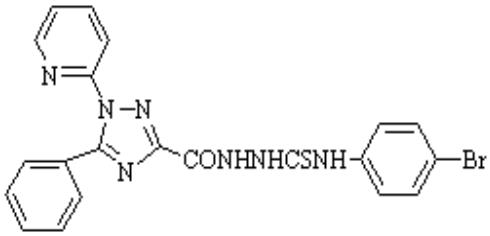
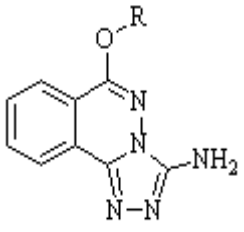


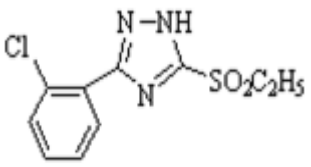
(59)

Sun *et al* synthesized several new 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives **(60)** and screened for anti-inflammatory activity by an *in vivo* inhibition assay by monitoring xylene-induced ear edema in mice using Ibuprofen as standard drug at the dose of 100 mg/Kg. The study showed that the compounds (6-(2-chlorophenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine) and (6-(4-aminophenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine) exhibited the highest anti-inflammatory activity (81% and 83% inhibition) which were slightly more potent than the reference drug Ibuprofen (61%)[88].



(60)

R- 2-Cl-C_6H_4; 2-Cl-C_6H_4; 4-Cl-C_6H_4; 4-F-C_6H_4; 2-CH_3-C_6H_4; 4-OCH_3-C_6H_4; 4-NH_2-C_6H_4



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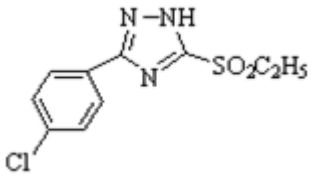
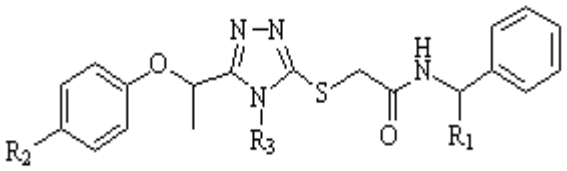


(62)

Tozkoparan *et al* synthesized a series of 5-aryl-3-alkylthio-1,2,4-triazoles **(61,62)** and corresponding sulfones and screened for the better analgesic & anti-inflammatory activity with minimum ulcerogenic risk by using PBQ-induced writhing test & carrageenan induced hind paw edema model in mice respectively. Compounds with 2-chlorophenyl and 4-chlorophenyl exhibited the highest analgesic and anti-inflammatory activity, with percentage inhibition values 37.9%, 40.2%, respectively, at 50 mg/Kg dose level. In contrast to reference compound Acetyl Salicylic Acid and Indomethacin, these compounds did not induce gastric lesions[89].

Zitouni *et al* synthesized 4-aryl/alkyl-5-(1-phenoxyethyl)-3-[*N*-(substituted)acetamido]thio-4*H*-1,2,4-triazole derivatives **(63)** and evaluated their anti-inflammatory activity by using carrageenan induced rat paw oedema method with the standard drug Indomethacin. The four compounds exhibited maximum inhibition values of 70.5%, 73.1%, 73.8%, 72.1% while the standard drug indomethacin showed an inhibition of 67.3%. The SAR observations showed that the substitution on the phenoxy moiety has an interesting role on the activity. The unsubstituted phenoxy and *p*-Cl-substituted phenoxy derivatives are the more active than the *p*-methyl derivatives[90].

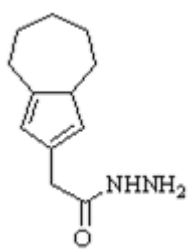


(63)

R_1- CH_3; C_6H_5 R_2- H; Cl; CH_3 R_3- C_6H_5; C_6H_{11}

Antiviral activity

Al-Soud *et al* synthesized a series of 1,5-dialkyl-3-(5-mercapto-4-*N*-aryl-1*H*-[1,2,4]-triazol-3-ylmethylene)-1*H*-[1,2,4] triazoles **(64,65,66)** and were evaluated for *in vitro* antiviral activity against HIV-1, HIV-2, HSV-1, HSV-2, SV, CV-B4, RSV, P3V, RV, SinV, PTV. Only one compound showed activity against HIV-1 and HIV-2 at >0.48, and 0.436 µg/ml, respectively. One more compound exhibited activity against Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus at16 µg/ml, with SI< 1.0 but revealed no selective activity against the mentioned viruses as well. Delviridine was used as a standard drug[91].



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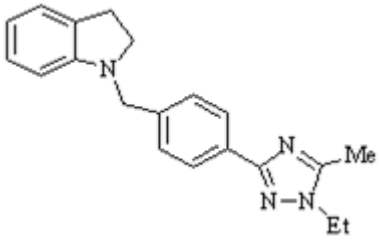

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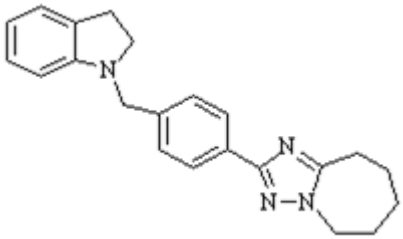
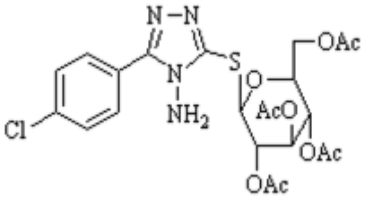


(66)

Barbary *et al* synthesized some new 4-amino-1,2,4-triazole derivatives **(67,68)** and screened for antiviral activity against HIV-1 was performed in MT4 cell cultures infected with either wild-type HIV-1 (strain IIIB) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)-resistant HIV-1 and HBV. None of the tested compounds showed any significant antiviral activity at 100 μM against HIV-1. Only three compounds showed a moderate activity against HBV at 40-63 μM[92].



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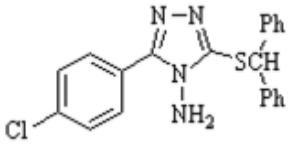

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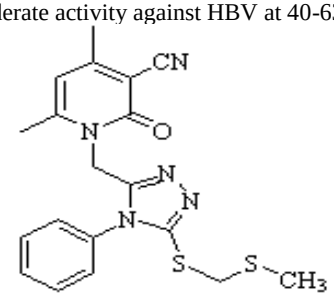
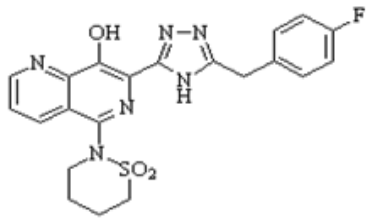


(69)

Essawy *et al* synthesized some new 1,2,4-triazol-2-yl-2-pyridinone derivatives **(69)** and evaluated for the antiviral activity against hepatitis B virus (HBV). The drug lamivudine which is a potent selective inhibitor of HBV replication has been used as a standard positive control. Three componds were active against HBV having selectivity index of 2500.0. Five compounds showed moderate inhibition with moderate cytotoxicity while the other tested compounds exhibited less activity against HBV. It was revealed that the substitution of the oxygen atom in the acyclonucleoside analogue by a sulfur atom (given below) increases the viral inhibition.[93]

Johns *et al* synthesized a series of HIV-1 integrase inhibitors containing a novel metal binding motif consisting of the 8-hydroxy-1,6-naphthyridine core and triazole **(70)**. The synthesized compounds were subjected to antiviral activity. A preliminary examination of C5 substitution showed significant improvements in antiviral activity[94].



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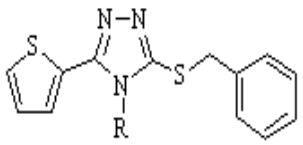


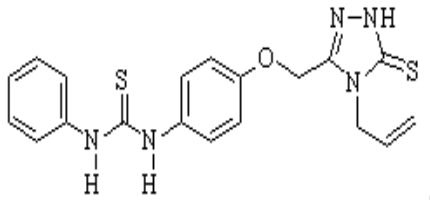
(71)

R- -CH_3; -C_6H_5; -CH_2-$CH_2C_6H_5$; -CH_2-C_6H_5; -CH_2-C_6H_4(4-OCH_3); -CH_2-C_6H_4(4-Cl)

Kirschberg *et al* synthesized a series of 3,4,5-trisubstituted 1,2,4-4*H* triazole derivatives **(71)** and investigated for HIV-1 reverse transcriptase inhibition. An X-ray structure with HIV-1 RT secured the binding mode and allowed the key interactions with the enzyme to be identified. The 4-benzyl derivate was the only one that displayed anti-HIV activity. Shortening or lengthening the distance of the phenyl ring from the core or

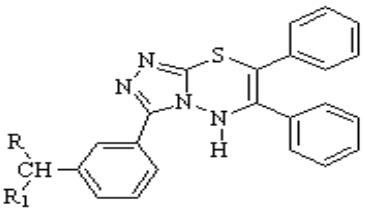
removing it altogether led to dramatic loss of activity, as did the introduction of chlorine or methoxy substituents[95].

Kucukguzel *et al* afforded the synthesis of 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **(72)** and screened for *in vitro* antiviral activity 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. Only one compound (given below) was the most active derivative in this series which showed moderate protection against Coxsackie virus B4 with an MIC value of 16 μg/ml and a selectivity index of 5. This compound was also active against thymidine kinase positive Varicella-Zoster virus (TKþ VZV, OKA strain) with an EC_{50} value of 9.9 μg/ml[96].



(72)

R- phthalimido, phthalimidomethyl, 2-phenyl -3-methyl-quinazolin(3*H*)4-one, nicotinamido

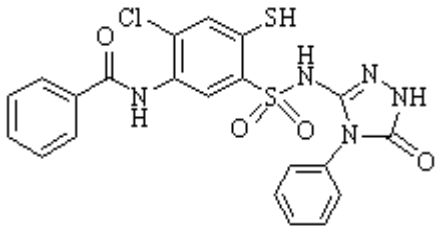


(73)

R_1- H, C_6H_5

Pandey *et al* synthesized derivatives were evaluated for their antiviral activity against two animal viruses, namely, *Japanese encephalitis virus* (JEV) strain and *herpes simplex virus-1* (HSV-1) strain. A compound having R=H and R_1= 2-phenyl-3-methylquinazolin(3*H*)4-one, displayed moderate anti-JEV activity while the other three compounds containing phthalimido, phthalimidomethyl, and nicotinamido substituents **(73)**, respectively, were found insignificantly active at the same dose level. It was predicted that a larger substituent like 2-phenyl-3-methyl-quinazolin(3*H*)4-one is mainly responsible for exerting anti-JEV activity. The activity percentage ranged from 10 to 23%[97].

Pomarnacka *et al* synthesized a series of 4-chloro-2-mercapto-N-(4,5-dihydro-5-oxo-4-phenyl-1*H*-1,2,4-triazol-3-yl)benzenesulfonamide derivatives **(74)** and evaluated for their *in vitro* antiviral activity against T-4 lymphocytes (CEM-SS cell line) uninfected or infected with HIV-1. The compound given below (R_1-NHCOPh, R_2-H) displayed moderate activity (IC_{50}>200 μM, EC_{50}=28.8 μM, TI_{50}>6.94)[98].



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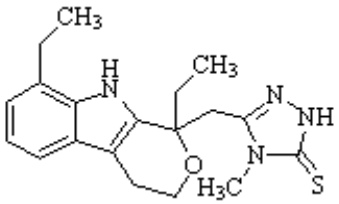
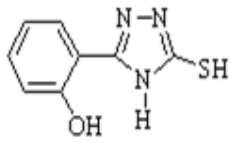


(75)

Suzgun *et al* synthesized a novel series of new etodolac 1,2,4-triazoles derivatives **(75)** and investigated for their antiviral activity against HCV NS5B polymerase. One compound 4a was found to be the most active with IC_{50} value of 14.8 μM. Etodolac, the parent molecule, included in this investigation for comparison, yielded ~10% inhibition of NS5B polymerase, while its derivatives displayed~5.0-80.0% inhibition of NS5B polymerase activity. All 11 etodolac 4-thiazolidinones proved to be weak NS5B polymerase inhibitors with ~50% anti-NS5B activity[99].

Antioxidant activity

Cetin *et al* synthesized a series of 1,2,4-triazole derivative compounds substituted with groups of phenol and pyridine **(76)** in high yields and screened against several antioxidant activity parameters such as DPPH, ABTS, metal-chelating, reducing power and the total antioxidant activity. The compounds showed better than expected antioxidant activity between the studied biological activity parameters. Among these, compound (2-(5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol) had a high total antioxidant activity potential with value of 232.12±6.89mmol/ml. Also showed fairly good ABTS cation radical and DPPH radical scavenging activity with values of IC_{50}=4.59±4.19 and IC_{50}= 7.12±2.32 μg/ml respectively[100].



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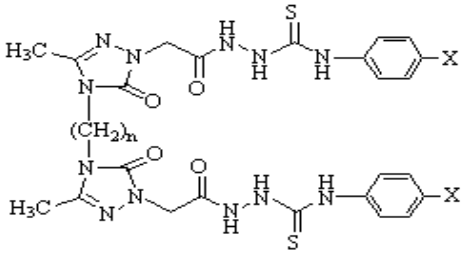
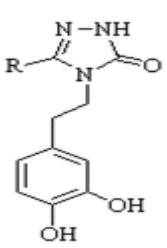


(77)

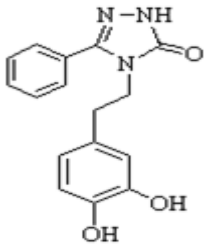
X- Cl; Br; CH_3 n- 4, 6

Dugdu *et al* synthesized N-(substitutedphenyl)-2-(2-(4-(4-(1-(2-(2-(4-fluorophenylcarbamo thioyl) hydrazinyl)-2-oxoethyl)-3-methyl-5-oxo-1*H*-1,2,4-triazole-4(5*H*)-yl)alkyl)-3-methyl-5-oxo-4,5-dihydro-1,2,4-triazole-1-yl)acetyl)hydrazinecarbothioamides **(77)** and screened for anti-oxidant activity by DPPH radical scavenging method. Sample concentration providing 50% inhibition (IC_{50}) was calculated form the graph plotted inhibition percentage against extract concentration. Butylated Hydroxyl Toluene (BHT) was used as positive control. Some compounds were found to possess good antioxidant properties[101].

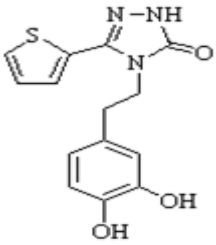
Unver *et al* synthesized 4-(3,4-dihydroxyphenethyl)-5-methyl-2*H*-1,2,4-triazol-3(4H)-one derivatives **(78,79,80)** and evaluated their antioxidant activity by DPPH method taking butylated hydroxytoluene (BHT) as a positive control. Compound concentrations providing 50% inhibition (IC_{50}) were calculated from a graph plotted as inhibition percentage against compound concentration[102].



(79)



(80)

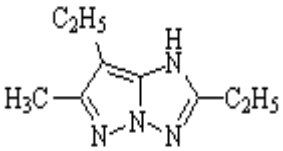


(81)

R- -CH_3; -C_2H_5; -C_3H_7

Antihypertensive activity

Okazaki *et al* afforded the synthesis of alkyl-substituted pyrazolo[1,5-b][1,2,4]triazole derivatives **(82)** and screened for their angiotensin II receptor antagonistic activity. Some compounds inhibited the angiotensin II-induced pressor response in rats after oral administration in the *in vivo* tests. These compounds also produced a dose-dependent decrease in blood pressure when administered orally to conscious furosemide-treated dogs, having a longer duration of action as compared to DuP753 suggesting them to be useful agents for the treatment of angiotensin II-dependent disease, such as hypertension[103].



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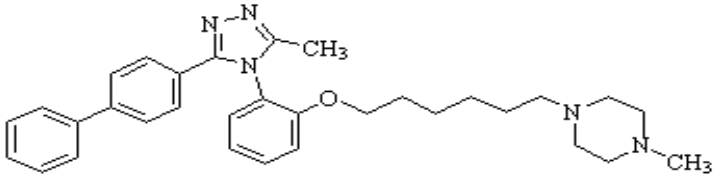
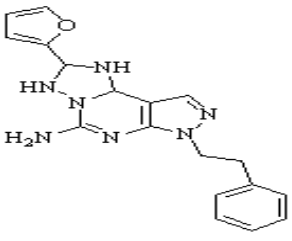


(83)

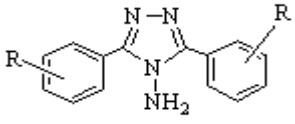
Kakefuda *et al* synthesized and evaluated a series of 5-(4-biphenyl)-3-methyl-4-phenyl-1,2,4-triazole derivatives **(83)** as selective antagonists for human vasopressin V-1A receptor. The compounds were examined for their affinity to the cloned human V-1A receptor hV-1A and selectivity versus the cloned human V-2 receptor h-V2. One particular compound, 5-(4-biphenyl)-3-methyl-4-[2-[6-(4-methyl-1-piperazinyl)hexyloxy]phenyl]-1,2,4-triazole showed potent affinity to hV-1A and high selectivity with a 1700-fold selectivity versus h-V2, it also showed antagonist activities toward an arginine vasopressin-induced increase in diastolic blood pressure after intravenous or oral administration and long-lasting oral activity[104].

Antiparkinsonian activity

Ongini *et al* synthesized aseries of non-xanthine heterocycles **(84)** starting from the non-selective adenosine antagonist triazoloquinazoline and evaluated for its anti-bacterial activity. Thus, replacement of the phenyl ring with a heterocyclic ring, led to a series of interesting compounds whose prototype, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine became a reference A2A receptor antagonist. The relevance of the A2A receptors in the central nervous system, made this class of adenosine receptor blockers of interest for treatment of neurodegenerative disorders such as Parkinson′s disease[105].



(84)



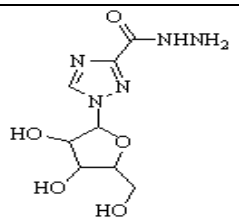
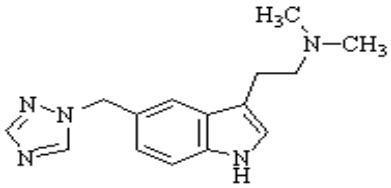
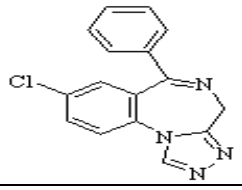
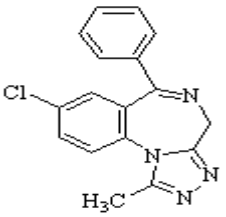
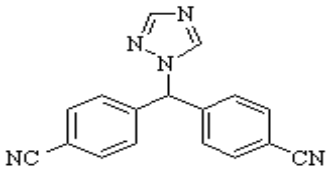
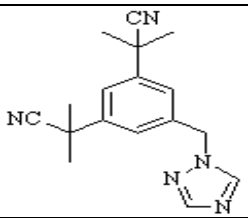
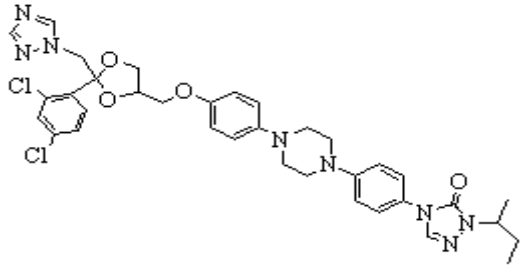
(85)

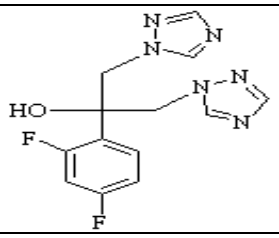
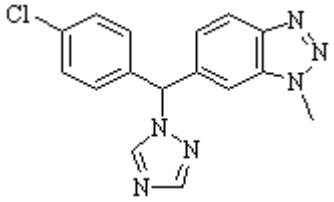
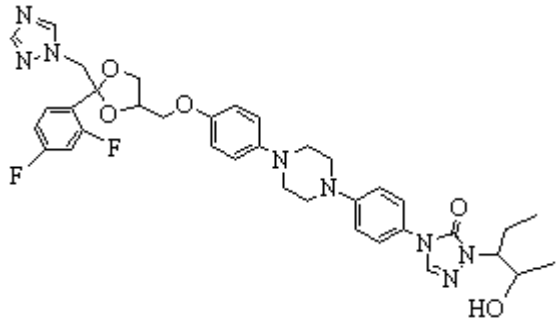
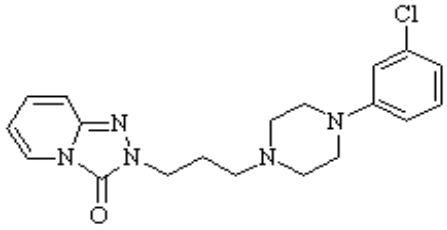
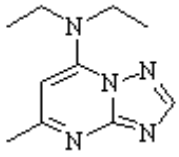
R- -H; 4-Cl; 3-NH_2; 3-NO_2; 4-NO_2; 4-CH_3

Inhibitors of mammalian cathepsin B and cathepsin H

Raghav *et al* synthesized some triazole derivatives **(85)** and evaluated as protease inhibitors and inhibitory studies were done on cathepsin B and cathepsin H. The compounds, found inhibitory to endogenous proteolysis in liver homogenate at pH 5.0, were further studied for determination of inhibition type and Ki values on purified cathepsin B and cathepsin H. 3-(30-nitrophenyl)-5-(30-nitrophenyl)-4-amino-1,2,4-triazoles, 3-(40-chlorophenyl)-5-(40-chlorophenyl)-4-amino-1,2,4-triazoles,3-(30-aminophenyl)-5-(30-aminophen-yl)-4-amino-1,2,4-triazoles exerted the maximum inhibitory effect [106].

Clinically used 1,2,4-triazole containing drugs

S. No.	Drug	Chemical Structure	Pharmacological activity
1.	Ribavirin		Antiviral
2.	Rizatriptan		Anti-migraine
3.	Estazolam		Anxiolytic, Sedative, Hypnotic
4.	Alprazolam		Anxiolytic, Tranquillizer
5.	Letrozole		Breast cancer
6.	Anastrozole		Breast cancer
7.	Itraconazole		Antifungal

8.	Fluconazole		Antifungal
9..	Vorozole		Aromatase inhibitor
10.	Posaconazole		Antifungal
11.	Trazodone		Antidepressant
12.	Trapidil		Vasodilator, Antiplatelet drug, Antihypertensive

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