Review Article

# TRIAZOLES: AS POTENTIAL BIOACTIVE AGENTS

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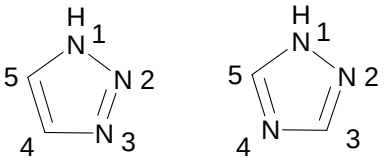
**ABSTRACT**

Triazoles and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities. This review article covers the latest information over active triazoles derivatives having different pharmacological action such as, antiviral, antibacterial, antifungal and antituberculosis. Thus triazole acts as a promising medicinal agent for the scientists working over this field. This review can be helpful to develop various more new compounds possessing triazoles moiety that could be better in terms of efficacy and lesser toxicity.

**Keywords:** Triazole, anticonvulsant, antimicrobial, antimalarial, anticancer.

## INTRODUCTION

Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, having a five-membered ring of two carbon atoms and three nitrogen atoms. The two isomers are:



1,2,3-triazole 1,2,4-triazole

The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole. The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol.

1,2,3-Triazole is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1,2,3-Triazole is a basic aromatic heterocycle.

Substituted 1,2,3-triazoles can be produced using the azide alkyne Huisgen cycloaddition in which an azide and an alkyne undergo a 1,3-dipolar cycloaddition reaction. It is a surprisingly stable structure compared to other organic compounds with three adjacent nitrogen atoms. However, flash vacuum pyrolysis at 500 °C leads to loss of molecular nitrogen ($N_2$) to produce aziridine. Certain triazoles are relatively easy to cleave due to so-called ring-chain tautomerism. One manifestation is found in the Dimroth rearrangement. 1,2,3-Triazole finds use in research as a building block for more complex chemical compounds, such as pharmaceutical drugs like tazobactam.

## BIOLOGICAL ACTIVITIES

### Anticonvulsant activity

Various 3-[4-(substituted phenyl) - 1, 3- thiazol -2-ylamino] -4-(substituted phenyl)-4,5- dihydro -1 *H* -1,2,4 - triazole -5- thiones(**1**) has been synthesised by clubbing thiazole and triazole moieties, keeping in view the structural requirement for the pharmacophore model for anticonvulsant activity[1]. Two compounds **1a** and **1b** showed significant anticonvulsant activity in both MES and subcutaneous pentylenetetrazole (sc PTZ) screen along with wide safety of margin with protective index (PI), median hypnotic dose (HD 50) and median lethal dose (LD 50) much higher than standard drugs.

Novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4] benzo diazepines **2** were prepared by treating 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione with various aromatic acid hydrazides. Compounds were tested for anticonvulsant activity. Four of the tested compounds exhibited excellent anticonvulsant activity in comparison with standard drug, diazepam[2].

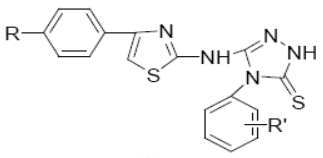
A new series of 4,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one **3** were synthesized to study the effect of cyclization of the semicarbazone moiety of aryl semicarbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant activity in four animal models of seizures, viz. 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. Eight compounds exhibited anticonvulsant activity in all the four animal models of seizure[3].

A series of novel 3-{[(substituted phenyl)methyl]thio}-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles **4** and several related Schiff's bases, 3-{[(substituted phenyl)-

methyl]thio}-4-alkyl/aryl-5-{[[(substituted phenyl/5-nitro-2-furyl)methylene]amino]-phenyl}-4*H*-1,2,4-triazoles **5** has been synthesized for evaluation of their biological properties[4]. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and neurotoxicity (NT) screens. A number of triazole derivatives, exhibited protection after intraperitoneal administration at the dose of 100 and 300 mg/kg in one or both models employed. Three compounds were subjected to oral MES screening in rats at 30 mg/kg and were observed to protect 50% of the animals employed in the experiment.

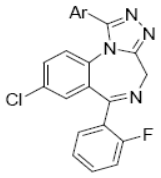
Analogues of 3-amino-7-(2,6-dichlorobenzyl)-6-methyltriazolo[4,3-b]pyridazine **6** PC25 containing amide or carboxylic acid function were synthesized and tested for anticonvulsant activity. The compounds having the imidazole ring substituted with an amide group have been found to be generally more active against maximal electroshock-induced seizures in mice ($ED_{50}$ = 37.5 mg/kg orally). Furthermore, maximum activity was generally associated with a 2,6-dichlorobenzyl substitution pattern. 3-Amido-7-(2,6-dichlorobenzyl)-6-methyltriazolo[4,3-b]pyridazine was also protective in the pentylenetetrazole-induced seizures test ($ED_{50}$ = 91.1 mg/kg orally) and blocked strychnine-induced tonic extensor seizures ($ED_{50}$ = 62.9 mg/kg orally). Moreover, calculated electrostatic isopotential maps of the whole active compounds were quite similar and, consequently, could be associated to optimum anticonvulsant activity [5].

A series of 4-(4-alkoxylphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives **7,8** was synthesized as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 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. For explanation of the possible mechanism of action, it was tested in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test[6].



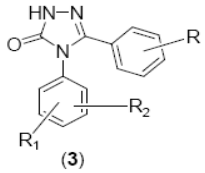
(**1**)

(**1a**); R=Cl,R'=4-$OCH_3$
(**1b**); R=Br,R'=2-$CH_3$



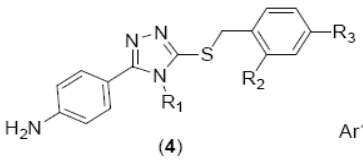
(**2**)

Ar = Pyridin-4-yl, 4-$NO_2$-1H-indol-2-yl, 6-$OCH_3$-2-naphthyl 4-$FC_6H_4$, 2-Br-5-$OCH_3C_6H_3$, Pyridin-3-yl

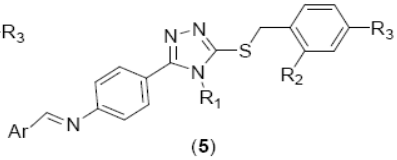


(**3**)

R = H, $NO_2$, $NH_2$, $CH_3$, OH
$R_1$ = H, 2-$CH_3$;
$R_2$ = 4-$CH_3$, 5-$CH_3$, 6-$CH_3$, 4-F

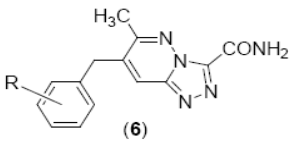


(**4**)



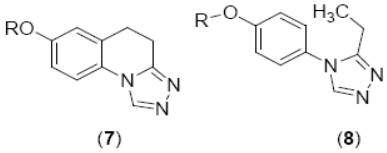
(**5**)

$R_1$ = H, $CH_3$, $R_2$ = $R_3$ = H, halo, alkyl, Ar = phenyl, cyclohexyl, pyridyl



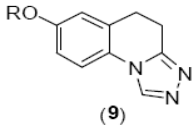
(**6**)

R = H, 2,6-Cl



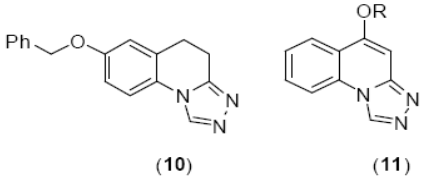
(**7**) (**8**)

R = $CH_2C_6H_5$, $CH_2C_6H_5$(*p*-F), $CH_2C_6H_5$ (*p*-$CH_3$)



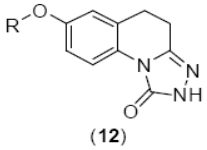
(**9**)

R = *n*-$C_2H_5$, *n*-$C_3H_7$, $CH_2C_6H_5$



(**10**) (**11**)

R = $CH_3$, $C_2H_5$, $C_3H_7$, $C_4H_9$, $CH_2Ph$, $CH_2Ph$(4-F)



(**12**)

R = $C_4H_9$, $C_5H_{11}$, $C_6H_{13}$, $C_7H_{15}$

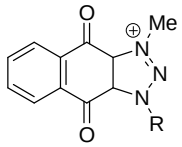
A series of 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline derivatives **9** was synthesized using 6-hydroxy-3,4-dihydro-1*H*-quinolin-2-one as a starting material[7]. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test) and the subcutaneous (sc) pentylenetetrazol test (scMet test), and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES and scMet tests show that 7-(4-fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline was found to be the most potent with $ED_{50}$ value of 11.8 and 6.7 mg/kg and protective index (PI = $TD_{50}/ED_{50}$) value of 4.6 and 8.1 respectively.

A series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives **10**, **11** were synthesized using 4-hydroxyquinolin-2(1*H*)-one as the starting material. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES) and their neurotoxicities were measured by the rotarod test. The results of these tests demonstrated that 5-hexyloxy-[1,2,4]triazolo[4,3-a]quinoline was the most potent anticonvulsant, with median effective dose ($ED_{50}$) of 19.0 mg/kg and protective index (PI = $TD_{50}/ED_{50}$) values of 5.8 in the MES test. Compound 5-benzyloxy-[1,2,4]triazolo[4,3-a]quinoline, exhibited a little weaker activity than previous compound in controlling the seizure induced by MES test at the dose of 22.8 mg/kg, but it possessed lower neurotoxicity with PI value of 12.0, which was safer than marketed drug carbamazepine. To explain the possible mechanism of anticonvulsant activity, the compounds were tested in pentylenetetrazole test, isoniazid test, thiosemicarbazide test; 3-mercaptopropionic acid and strychnine test [8].

To further investigate anticonvulsant activity of quinoline derivatives, a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1(2*H*)-one derivatives **12** was synthesized starting from 7-hydroxyl-3,4-dihydro-2(1*H*)-quinoline [9]. In initial (phase I) screening and quantitative (phase II) evaluation, compound 7-benzyloxyl-4,5-dihydro-[1,2,4]thiazolo[4,3-a]quinoline-1(2*H*)-one was among the most active and also has the lowest toxicity. In the anti-MES potency test, it showed median effective dose ($ED_{50}$) of 12.3 mg/kg, median toxicity dose ($TD_{50}$) of 547.5 mg/kg, and the protective index (PI) of 44.5, which is much greater than PI of the prototype drugs phenytoin, phenobarbital, carbamazepin, and valproate. It was chosen for further evaluation. In phase III pharmacological test, the compound had median hypnotic dose ($HD_{50}$) and median lethal dose ($LD_{50}$) of 1204 mg/kg and >3000 mg/kg, respectively, thus demonstrating much greater margin of safety compared to prototype drugs. It also showed significant oral activity against MES-induced seizures and low oral neurotoxicity in mice in phase IV pharmacological test. Possible structure–activity relationship was discussed.

**Antimicrobial activity**

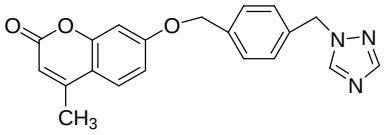
A novel class of cationic anthraquinone analogs **13** has been synthesized [10].Among these compounds synthesized **13a** showed high potency (MIC<1ug/ml) and selectivity against gram positive pathogens including methicillin resistant staphylococus aureus (MRSA), while modest activity against gram negative bacteria. Compound **13b** and **13c** exhibit broad antibacterial activity including MRSA and vancomycin- resistant Enterococcus faecalis (VRE), which is comparable to other commercially available cationic antiseptic chemicals.



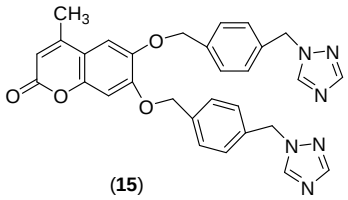
(**13**)

(**13a**); R= $-CH_2(CH_2)_6CH_3$
(**13b**); R= $-CH_2(CH_2)_{10}CH_3$
(**13c**); R= $-CH_2(CH_2)_{14}CH_3$

A series of new coumarin based 1,2,4 triazol derivatives has been synthesized and evaluated for antimicrobial activities in vitro against Gram-positive bacteria (Staphylococcus aureus, MRSA, Bacillus substilis and micrococcus luteus), four Gram-negative bacteria (Escherichia coli, Proteus vulgaris, Salmonella typhi and Shigella dysenteriae) as well as fungi( Candida albicans, Sacchoromyces cerevisiae and Aspergillus fumigatus) by two fold serial dilution techniques. Compounds **14** and **15** displayed stronger antibacterial and antifungal efficacy [11].



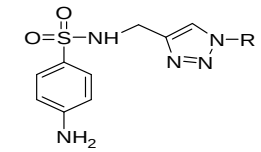
(**14**)



(**15**)

A series of novel sulphanilamide derived 1,2,3 triazol compounds(**16**) has been synthesized and screened in vitro for their antibacterial and antifungal activities [12]. Compounds 4-amino-*N*-((1-dodecyl-1*H*-1,2,3-trizol-4-yl) methyl) benzenesulfonamide **16a**, 4 amino-N-((1-(2,4-dichlorobenzyl)-1*H*-1,2,3 triazol-4-yl) methyl)-4-aminobenzenesulfonamide **16b** and 4-amino-*N*-((1-(2,4-diflurobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl) benzenesulfonamide **16c** were found to be most potent compounds against all the tested strain except Candida albicans and Candida mycoderma.

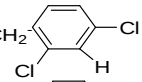
Bay synthesized six new series of *N,N* bis ( 1,2,4 triazol-1-yl methyl) amines and evaluated for their antifungal activity against the budding yeast Saccharomyces cerevisiae and antibacterial activity against Escherichia coli. Compounds 2,6-bis (bis( 1*H*-1,2,4-triazol-1-yl) methyl) amino) hexanoic acid **17** and *N,N* (bis ((1*H*-1,2,4-triazol-1-yl) methyl) - 2 methyl propane-amine **18** showed strong antifungal and antibacterial activity[13].



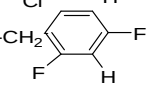
(**16**)

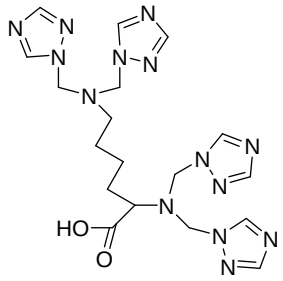
(**16a**); -$(CH_2)_{11}CH_3$

(**16b**);-$CH_2$-

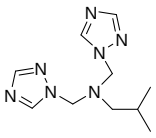


(**16c**); -$CH_2$-

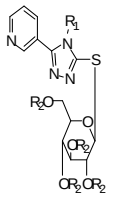




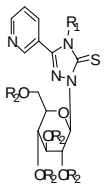
(**17**)



(**18**)



(**19**)



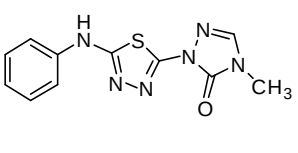
(**20**)

$R_1$=H, $NH_2$, $C_6H_5CH$=N, 4-$CH_3C_6H_4CH$=N, 4-$CH_3OC_6H_4CH$=N, 4-$ClC_6H_4CH$=N

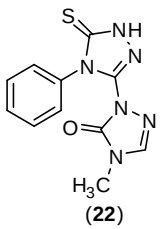
$R_2$=$COCH_3$, H

Glucosidation of some 4-amino- and 4-arylideneamino-5-(pyridin-3-yl)-2,4-dihydro-[1,2,4]-triazole-3-thiones with 2,3,4,6-tetra-*O*-acetyl-α-d-glucopyranosyl bromide **19, 20** has been performed followed by chromatographic separation that gave the corresponding *N*- and *S*-β-d-glucosides[14]. The structure of these two regiosiomers was established chemically and spectroscopically. Deaminations as well as deacetylation of some selected nucleosides have been achieved. Antimicrobial screening of 14 selected compounds resulted in their activity against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli*.

Some newer 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazoles **21** and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo- [1,2,4]triazole derivatives **22** were synthesized and reported [15]. All the synthesized compounds were tested for their antimicrobial properties. Eight compounds have shown antimicrobial activity against one or more microorganism, but no antifungal activity has been observed against yeast like fungi. Also inhibitory effect on mycelial growth by three compounds had been observed.

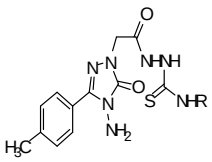


(**21**)

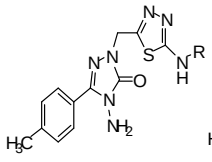


(**22**)

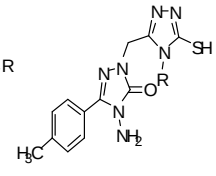
Synthesis of some newer 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazoles **23-25** has been reported [16]. The newly synthesized compounds were well characterized by elemental analyses, IR, $^1$H NMR, $^{13}$C NMR and mass spectral studies. They were also screened for their microbial activities. The antimicrobial activity study revealed that some of them showed good activity against a variety of microorganisms.



(**23**)



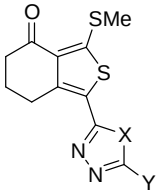
(**24**)



(**25**)

R=4-$FC_6H_4$, $C_6H_5$, 4-$OCH_3C_6H_4$

A series of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)ones **26** were synthesized and tested to demonstrate *in vitro* antimicrobial activity. Some of these compounds exhibited a good activity against *Staphylococcus aureus*, *S. epidermidis* and *Bacillus subtilis* [17].

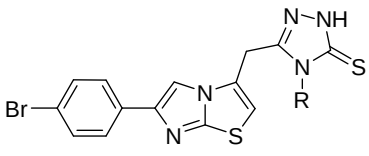


X = NR, S

Y = $NH_2$, NHR, SH, SMe

(**26**)

A series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl-3*H*-1,2,4-triazole-3-thiones **27** was synthesized starting from 6-(4-bromophenyl)imidazo[2,1-b]thiazole-3-acetic acid hydrazide[18] .All compounds were tested for antibacterial and antifungal activities. The antimicrobial activities of the compounds were assessed by the microbroth dilution technique. The compounds were also evaluated for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv (ATCC 27294). The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.

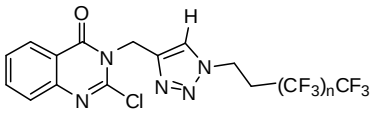


(**27**)

R = $CH_3$, $C_2H_5$, $C_3H_7$, $C_4H_9$, $CH_2$=$CHCH_2$, $C_6H_5$

Formation of *N*- and *O*-propargylated quinazoline derivatives 2, 3 from quinazol-4-ones **28** was theoretically predicted by optimizations at B3LYP/6-31G* level, analyzed kinetically and thermodynamically[19]. Theoretical predictions are validated by experiment to observe the trends and found deviation. Thus, the compound was propargylated in basic media to obtain two compounds in definite proportions. Each compound was further subjected to [3:2] cycloaddition using perfluoroalkyl azides through Click reaction under Sharpless conditions, and obtained a series of novel perfluoroalkyl-1*H*, 1,2,3-triazol-4-yl substituted quinazolines. All the compounds

were screened for antimicrobial activity and identified potential compounds.

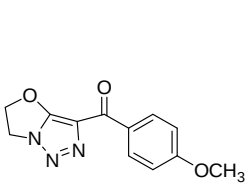


(**28**)

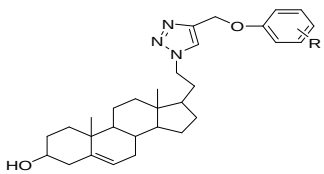
**Anticancer activity**

Synthesis of a series of heterocycle-fused 1,2,3 triazoles by 1, 3 -dipolar cycloaddition of heterocyclic ketene aminals or *N, O*-acetals with sodium azide and polyhalo isopthalonitriles has been carried out and evaluated in vitro against a panel of human tumour cell lines [20].Compound 4-Methoxy-phenyl substituted 1,3, -oxazoheterocycle fused 1,2,3 triazole **29** was found to be most potent derivative against A 431 and K 562 human tumor cell lines.

Synthesis of 21- triazolyl derivatives of pregnenolone **30** has been performed with transformation of pregnenolone acetate which is used as starting material, using 'click chemistry' approach[21]. Compound **30a** showed most active anticancer activity when screened for their anticancer activity against seven human cancer cell lines.

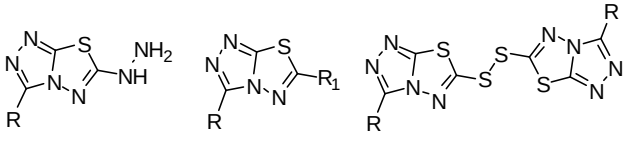


(**29**)



(**30**)
(**30a**); R= p-$OCH_3$

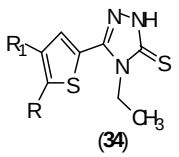
A new series of 3,6-disubstituted triazolo[3,4-b]thiadiazole derivatives **31-33** has been synthesized by simple, high yielding routes [22].The newly synthesized compounds were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines by the National Cancer Institute (NCI) and some of them demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at $10^{-5}$ M level and in some cases at $10^{-7}$ M concentrations. In this assay, the anti-tumor activity of the newly synthesized compounds could not be interpreted in terms of tyrosine kinase inactivation but more likely as a relatively broad specificity for the ATP-binding domain of other kinases. The pharmacological mechanism of action for these intriguing compounds has not, as yet, been successful.



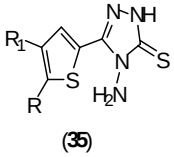
(**31**) (**32**) (**33**)

R = $R_1$ = H, halo, alkyl, phenyl

Novel derivatives of 4,5-substituted-1,2,4-triazole-thiones **34-35** was synthesized and evaluated for their cytotoxicity [23].The biological study indicated that compounds 4-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione, *N*-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazol-2-amine, 4-amino-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and 4-amino-5-(5-phenylthien-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione possessed high cytotoxicity *in vitro* against thymocytes. The corresponding $IC_{50}$ values were 0.46 µM, $5.2 \times 10^{-6}$ µM, 0.012 µM and $1.0 \times 10^{-6}$ µM. Most toxic compound against lymphocytes was having $IC_{50}$ = 0.012 µM. The tested compounds showed a general stimulation effect on B-cells' response.



(**34**)



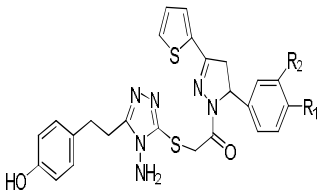
(**35**)

R = $R_1$ = F, Cl, $NO_2$, OH, $CH_3$, $OCH_3$

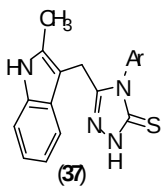
**Antidepressant activity**

Some triazole-pyrazoline derivatives **36** have been synthesized and screened using both modified forced swimming and tail suspension test. Rota- rod test was also performed for the examination of probable neurological deficits due to the test compounds [24].Among the series compound **36a**, **36b** were more effective than the reference drugs fluoxetine with respect to antidepressant activity.

3-[(2-Methyl-1*H*-3-indolyl) methyl]-4-aryl-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones **37** and their respective *N*-{5-[(2-methyl-1*H*-3-indolyl) methyl]-1,3,4-thiadiazol-2-yl}-*N*-arylamines have been prepared [25]. The antidepressant profile of the compounds was studied on mice with respect to that of the analogous 3-(1*H*-1-indolylmethyl)-4-aryl-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones and the respective *N*-15{(2-methyl-1*H*-3-indolyl)methyl]-1,3,4-thiadiazol-2-yl}-*N*-arylamines, the synthesis and antimicrobial potency of which have been reported. Behavioral effects, induced by the members of both series, in conjunction with their activity in some specific tests (forced swim, pentetrazole convulsions) on mice, showed that these derivatives cross the blood-brain barrier and could develop an antidepressant activity comparable to that of imipramine. Blood-brain barrier penetration is also supported by the lipophilicity data obtained for all analogs.



(**36**)
(**36a**); $R_1$=H,$R_2$=H
(**36b**); $R_1$=Cl,$R_2$=H

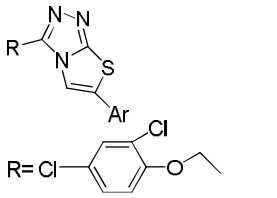


(**37**)

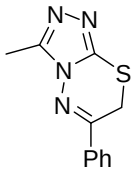
Ar = phenyl, chlorophenyl, bromophenyl, tolyl

**Anti-inflammatory activity**

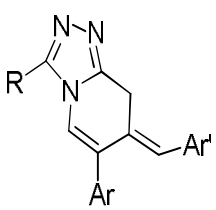
Synthesis of a series of 3 - (2,4 - dichlorophenoxy) methyl )-1,2,4 -triazolo (thiadiazoles and thiadiazines) and screened for their anti-inflammatory activity [26].Among the synthesized compound, 3 -(( 2, 4 - dichlorophenoxy) methyl) -6-(4- methoxyphenyl)- [1,2,4] triozolo [3,4-b] (1,3,4) thiadiazole **38**, 3,6 -Bis ((2,4-dichlorophenoxy) methyl) - [1,2,4] triazolo [3,4-b]-[1,3,4] thiadiazole **39**, 3-((2,4-Dichlorophenoxy) methyl)-6-phenyl-7*H* - [1,2,4] triazole [3,4-b] [1,3,4] thiadiazine **40** and 3-((2,4-Dichlorophenoxy methyl) -7-((3-benzofuran-2-yl) -1-phenyl-1*H*-pyrazol-4-yl) methylene)-6-(benznofuran-3-yl) -7*H*-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine **41**, showed potent anti inflammatory activity.



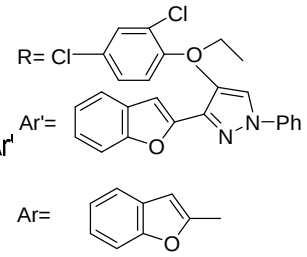

Ar; (**38**)= 4-$OCH_3C_6H_4$
(**39**)= 2,4 dichlorophenoxy



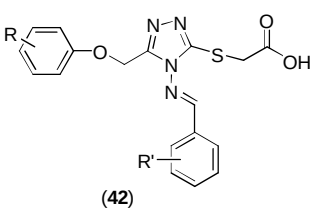

(**40**)




(**41**)

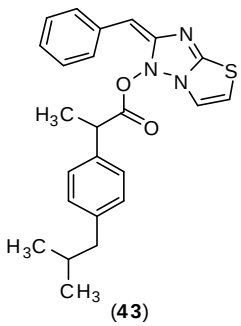



New series of 2-[4-(substituted benzylideneamino)-5-(substituted phenoxymethyl)-4*H*-1,2,4-triazole -3- ylthio] Acetic acid derivatives **42** has been synthesized and were evaluated in vivo anti inflammatory activities [27].Among the series 2-[4-(2,4-dichlorobenzylidenemino) -5-phenoxymethyl)-4*H*- 1,2,4 triazole-3-yl thio] acetic acid **42a**, 2-[4-(4-dichlorobenzylideneamino)-5-phenoxy methyl) -4*H*-1,2,4 triazole-3-yl thio] acetic acid **42b**, 2-[4-(2,4-dichlorobenzylideneamino) -5-[(2,4-dichlorophenoxy) methyl]-4*H*-1,2,4-triazole-3-ylthio] acetic acid **42c** and 2-[5-[(2,4-dichlorophenoxy)methyl)]-4-(4-chlorobenzylidene amino)-4*H*-1,2,4-triazole-3yl thio]acetic acid **42d** showed significant anti inflammatory activity.




(**42**)

(**42a**); R=H,R'= 2,4Cl
(**42b**); R=H,R'= 4-Cl
(**42c**); R=2,4-Cl,R'= 2-OH
(**42d**); R=2,4-Cl,R'= 4-Cl



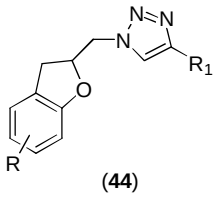

(**43**)

Synthesis of 3-[1-(4-(2-methylpropyl)phenyl)ethyl]-1,2,4-triazole-5-thione **43** has been carried out and its condensed derivatives 6-benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6*H*)-ones were described [28]The structures of the compounds were elucidated by spectral and elemental analysis. In the pharmacological studies, anti-inflammatory activities of these compounds have been screened. Among the compounds examined, the two compounds possessed the most prominent and consistent activity. In gastric ulceration studies the synthesized compounds were generally found to be safe at a 200 mg/kg dose level.

**Antimycobacterial activity**

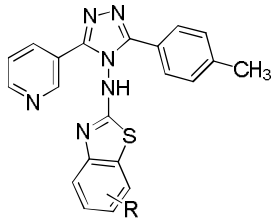
Different 1,4-Disubstituted -1,2,3-triazoles **44** has been developed and screened for antitubercular activity against Mycobacterium tuberculosis H37Rv and exihibited antitubercular activities with MIC ranging from 12.5 to 3.12 ug/ml.[29].

Newly 1,2,4 triazoles analogs has been synthesized and carried in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv strain[30].Compound 3-(3-pyridyl)-5-(4-methylphenyl)-4-(*N*-4-chloro-1,3-benzo thiazol-2-amino)-4*H*-1,2,4 triazole **45** showed better antitubercular activity compound to rifampicin.



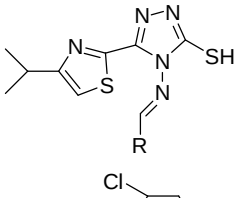

(**44**)

R= -4CHO, -2,5-Di-Me
$R_1$= $-(CH_2)_4CH_3$, $-C_6H_5$, $-CH_2OH$




(**45**);R= 4-Cl

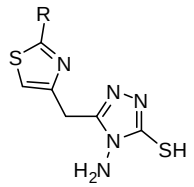
A series of 2-substituted -5-[isopropylthiazole] clubbed 1,2,4 triazole and 1,3,4-oxadiazole has been reported and evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method, compound 4-(2-chlorobenzylidene amino)-5-(4-isopropylthiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **46** exhibit significant antitubercular activity[31].







(**46**); R=

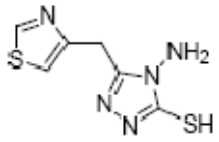



R = H, $CH_3$, $NH_2$, $NHCH_3$
(**47**)

A series of *N*-{4-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted-amides **47** were synthesized in good yields and characterized by IR, $^1$H NMR, mass spectral and elemental analyses[32]. The compounds were evaluated for their preliminary *in vitro* antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhosa* and then were screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}$ Rv strain

by broth micro dilution assay method. The antibacterial data of the tested compounds indicated that most of the synthesized compounds showed better activity against bacteria compared to reference drugs. The *in vitro* antitubercular activity reports of tested compounds against *M. tuberculosis* strain $H_{37}$ Rv showed moderate to better activity.

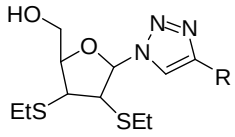
Synthesis of thiazolyl- triazole derivatives **48**, starting from ethyl acetoacetate, by microwave organic reaction enhancement method (MORE) and results of investigations of their antimycobacterial and antimicrobial activities has been reported [33].Many compounds have shown promising activity while others were inactive.



(48)

**Antiviral activity**

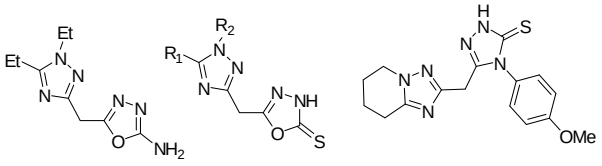
A series of novel 2',3'-dideoxy-2',3'-di-ethanethioribonucleosides has been reported which is modified into a triazole ring **49** and evaluated for their antitumour activity. Nucleosides with a triazole ring **49a**, **49b**, **49c** shared significantly improved activity towards broad range of tumour cell lines[34].



(**49**)

(**49a**); -$C_6H_5$
(**49b**); -4F$C_6H_4$
(**49c**); -4OMe$C_6H_4$

A series of 1,5-dialkyl-1,2,4-triazole derivatives **50-52** of acetic acid alkylidene hydrazides, the acid, 1,5-dialkyl-3-(5-mercapto-4-*N*-aryl-1*H*-[1,2,4]-triazol-3-ylmethylene)-1*H*-[1,2,4] triazoles, their 1,3,4-oxadiazole analogues, as well as the 1,2,4-triazoloindoles were prepared [35]. The *Z/E* conformations of some acetic acid alkylidene derivatives were studied by NMR spectroscopy. Most of the target compounds were evaluated in a series of human cancer cell in cultures and none had shown activity except one which exhibited remarkable activity against nine cancer types. No *in vitro* antiviral activity against HIV-1, HIV-2, HSV-1, HSV-2, SV, CV-B4, RSV, P3V, RV, SinV, PTV had been found for all the synthesized compounds.



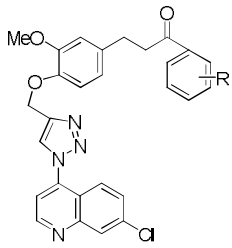
(**50**) (**51**) (**52**)

$R_1$ = H, Cl, $CH_3$; $R_2$ = H, $CH_3$, $C_2H_5$

**Antimalarial activity**

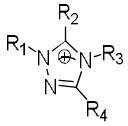
A series of triazole- linked chalcone and dienone hybrid compounds **53** has been synthesized and evaluated for in vitro antimalarial activity[36].Several chalcone-chloroquinoline hybrid compound were found to be active, with compound 3-{4-[1-( 7-chloro-quinoline-4- yl) 1*H*-[1,2,3] triazol-4-yl methoxy]-3-methoxy phenyl} -1-(2,4-dimethoxyphenyl)-propenone **53a**, the most active against D10, Dd2 and W2 strains of plasmodium falciparum.

Synthesis of a series of triazolium salts **54** has been carried out and found to be highly potent with active conc. in the nanomolar range in plasmodium falciparum cultures. It is hypothesized as electron deficient cores that are essential to interact with negatively charged moiety on the parasites merozoite which determine both the potency and selectivity of the compound [37].



(53)

(**53a**); R= 2'4'-dione

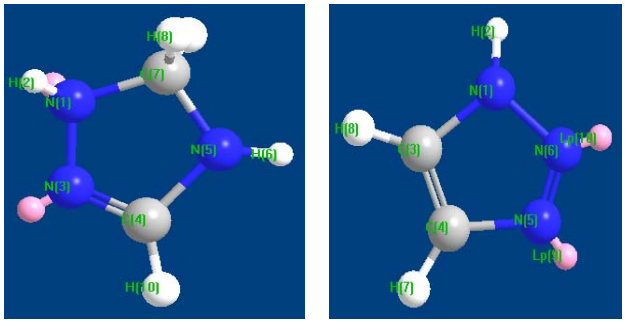


(**54**)

$R_1$= -$C_6H_5$, 4-Br$C_6H_5CH_3$, -$C_6H_5CH_2COCH_3$, -$C_6H_5CH_2CH_2COCH_3$
$R_2$= -$CH_3$, -$C_6H_5$ , -H
$R_3$= -$C_6H_5$, -$CH_3$,
$R_4$= -$SCH_3$, -$C_6H_5$

## THREE-DIMENSIONAL STRUCTURE ANALYSIS

The three dimensional structure of Triazoles was studied by using the software Chem 3D-Ultra 8.0. The 3D diagram of the Triazole was drawn at 50% probability and it is shown in Fig. 1



**1, 2, 4-Triazole** **1, 2, 3-Triazole**

**Figure 1:** 3D- diagram (50% probability) by Chem 3D-Ultra 8.0 of Triazoles showing Atom-numbering scheme

## CURRENT ASPECTS OF TRIAZOLES

There are number of triazoles derivatives reported in this review possessing different biological activity comparable to clinically synthetic compounds. Excellent anticonvulsant activity is shown by 3-[4-(substituted phenyl)-1,3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-thione and 8 chloro-6-(2-fluorophenyl)1-(aryl)-4*H*-[1,2,4]triazolo[4,3-

a][1,4]benzodiazepine comparable to standard drug. Substituted coumarin 1, 2, 4 triazol and sulphanilamide derived 1,2,3 triazol compounds displayed stronger antibacterial action. Potent anticancer activity was demonstrated by heterocycle fused 1,2,3 triazole and 3,6-disubstituted triazolo[3,4-b]thiadiazole derivatives. Compounds having pharmacophore such as methyl, methoxy, chloro, cyno, chloro, fluoro, and bromo groups have exhibited best anticonvulsants, anti-inflammatory, anticancer, antitubercular and antimicrobial activity. From the above discussions it may be concluded that the modifications in triazole moiety displayed valuable biological activities and these modifications can be utilized to develop potentially active agents for future investigations.

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