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1, 2, 4-TRIAZOLES: AS BIOLOGICALLY IMPORTANT AGENTS

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Keywords:
1, 2, 4-triazole derivatives, Antimicrobial, Anticonvulsant, Anticancer Activities

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ABSTRACT

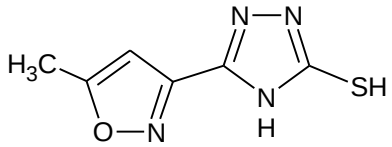
The chemistry of heterocyclic compounds containing five membered 1, 2, 4-triazole nucleus has been an intresting field of study for past few decades. The five membered 1, 2, 4-triazole ring exists in two tautomeric forms i.e., 1*H*-1, 2, 4-triazole, 4*H*-1, 2, 4-triazole collectively known as s-triazoles. The s-triazole derivatives possess extensive spectrum of biological activities such as antibacterial, antifungal, antitubercular, anxiolytic, anticonvulsant, anti-inflammatory, analgesic, anticancer, antioxidant activities. The present review provides a broad view of pharmacological activity of compounds bearing 1, 2, 4-triazole nucleus. It can be useful for medicinal chemists to design and develop novel compounds consisting 1, 2, 4-triazole nucleus to get better agents in terms of efficacy and safety.

INTRODUCTION: The 1, 2, 4-triazole is a five membered heterocyclic compound containing two carbons and three nitrogens with a molecular formula of $C_2H_3N_3$. It exists in two tautomeric forms. 1*H* and 4*H*-1, 2, 4-triazole is considered to be pharmacologically important nucleus.

The literature review shows that 1, 2, 4-triazole possess wide spectrum of biological activities. In particular compounds having 1, 2, 4-triazole nucleus are known to have excellent antibacterial, antifungal, antitubercular, antioxidant, anticancer, anti-inflammatory, analgesic, anticonvulsant, anxiolytic activities [1].

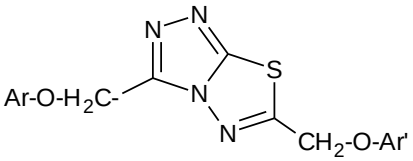
Biological Activities of 1, 2, 4-Triazoles:

As Antibacterial and Antifungal agents: Xin-Ping Hui *et al,* prepared variety of 5-(5-methylisoxazol-3-yl)-1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3,4-oxadiazoles and evaluated for their antibacterial potency [2].



[1]

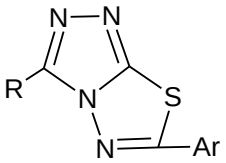
B. Shivarama Holla *et al*, prepared variety of diaryloxy-methyl-substituted-1,2,4-triazolo [3,4-b]-1,3,4-thiadi-azoles and evaluated for antibacterial activity [3].



3a, Ar, Ar' = 4-Cl-Phenyl,

[2]

B. Shivarama Holla *et al*, prepared a series of 6-(5-aryl-2-furyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoles and investigated for antibacterial potency [4].



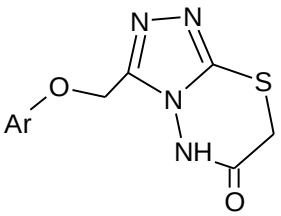
Ar = Aryl furyl

R' = NO_2, Cl, Br

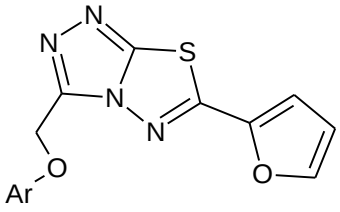
R= CH_3, C_2H_5, C_3H_7, C_6H_5, p-Cl-C_6H_4, o- OH-C_6H_4

[3]

B. Shivarama Holla *et al,* reported the synthesis of N-bridged heterocycles such as triazolothiadiazoles, bis-triazolothiadiazoles, triazolothiadiazines, triazolothiadiazinones derived from 3-aryloxymethyl-4-amino-5-mercapto-1,2,4-triazoles and evaluated for their antibacterial activity [5].



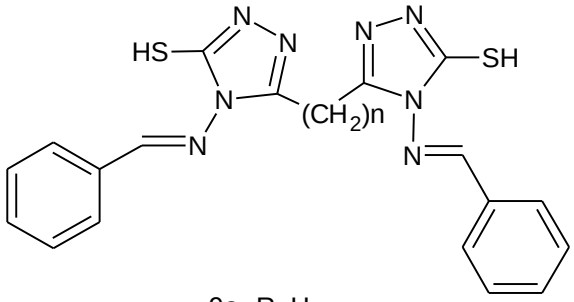
Ar = p-Cl-C_6H_4



3a, Ar = p-Me -C_6H_4

[4]

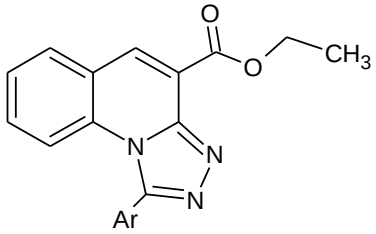
B. Shivarama Holla *et al*, reported the synthesis of various bis–(4-amino-5-mercapto-triazol-3-yl)alkanes, their schiffs bases and bis-(1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-4-yl]alkanes and investigated as potent antibacterial agents[6].



9a, R=H

[5]

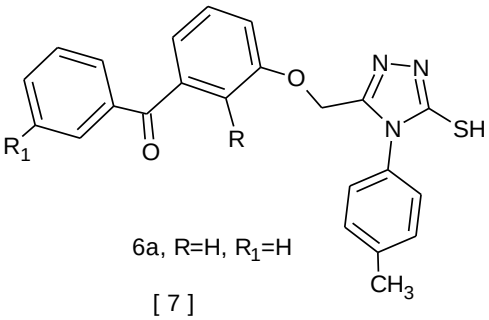
K. Mogilaiah *et al*, prepared a series of 1-arylazetidino [2,3-b][1,8]napthyridin2-(1*H*)-ones and 1-aryl-4-carbethoxy-1,2,4-triazolo[4,3-a][1,8] naphthyridines and tested for antibacterial potency[7].



6a, Ar=C_6H_5

[6]

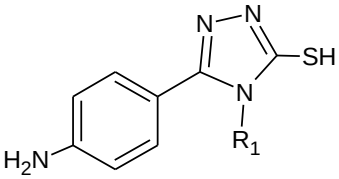
B. S. Sudha *et al*, reported the synthesis of 5-[(4-aroyl) aryloxymethyl]-2-(4-methylphenylamino)-1,3,4-thiadiazoles and 5-[(4-aroyl)aryloxymethyl]-4-(4-methyl)-3-mercapto-4*H*-1,2,4-triazoles and investigated as antibacterial agents[8].



6a, R=H, R_1=H

[7]

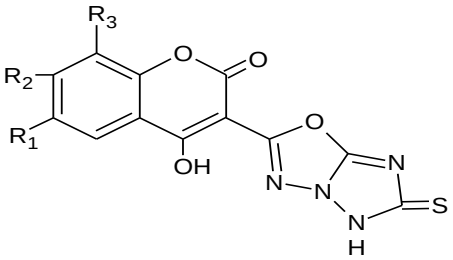
T. K. Ravi *et al*, reported the synthesis of 1,2,4-triazoles derivatives of anthranalic acid and for their antibacterial activity [9].



(4Aa) R_1= NH_2

[8]

V. V. Mulwad et al, had reported the synthesis of a series of oxadiazolo(1,3,5)-triazines, 1,2,4-triazoles and thiadiazolo 1,3,4-oxadiazole analogues and investigated for their antibacterial activity [10].



5a, R_1, R_2, R_3=H

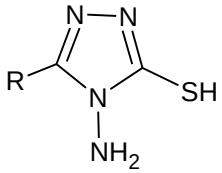
5b, R_1=CH_3, R_2, R_3=H

5c, R_1=H, R_2, R_3=CH_3

5d, R_1=, R_2=H,R_3=CH_3

[9]

Umesh Kumar *et al*, reported the synthesis of 4-amino-5-aryl-1,2,4-triazoles and screened for their antibacterial activity [11].

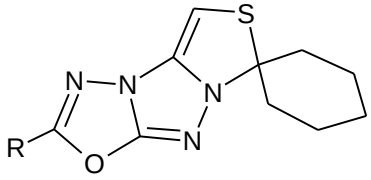


4a, R=C_5H_4N

4b, R=C_6H_5

[10]

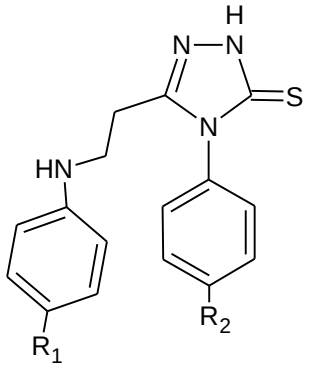
Nizamuddin *et al*, reported the synthesis of 2-Aryl/aryloxy methyl-1,3,4-oxa/thiadiazolo[4,5-b]1,2,4-triazolo[5,4-c]thiazolo-spiro-7-cyclohexanes and investigated as fungicidal agents [12].



4a,R= Ph

[11]

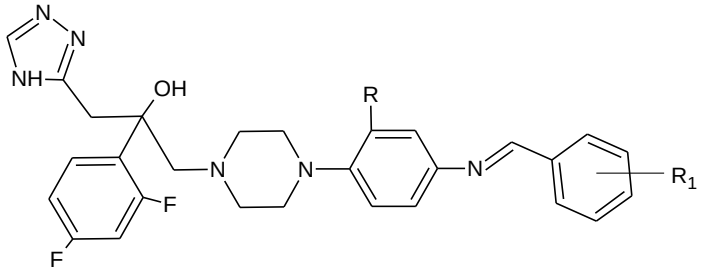
Anees A Siddiqui *et al,* reported the synthesis of a series of 3-(p-substituted anilinoethyl)-4-(p-substituted phenyl)-5-thioxo-1,2,4-triazoles and investigated as active antifungal agents [13].



3a, R_1, R_2= H

[12]

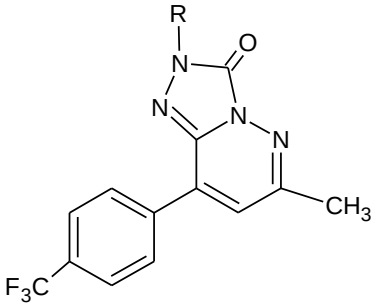
Qing-Yan Sun *et al*, prepared various 1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl)-propan-2-ols and investigated for their antifungal potency [14].



5a, R= H, R_1= 4-F-C_6H_4

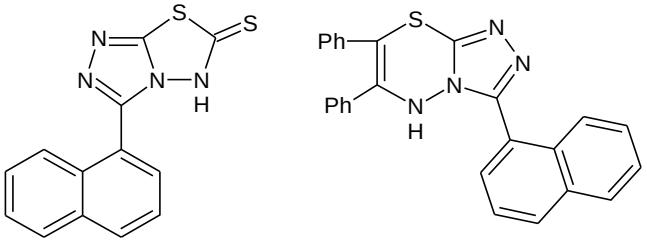
[13]

Yong Sun *et al*, synthesized 2-alkylamino-3-aryl-6-(1*H*)-1,2,4-triazol-1-yl)-thieno (2,3-d)-pyrimidin-4(3*H*)-ones and evaluated for fungicidal activity. Compound 6h showed excellent activity [15].



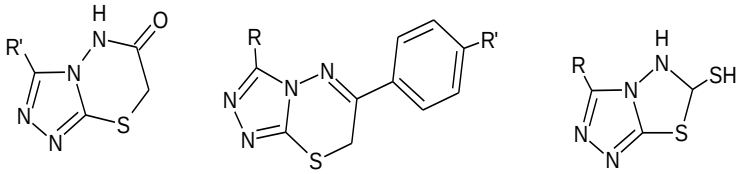
[14]

Jag Mohan *et al*, synthesized s-triazolo[3,4 b)[1,3,4] thiadizoles, s-triazolo(3,4 – b)[1,3,4]thiadiazines and s-triazolo(3',4'-2,3)[1,3,4-thiadizino[5,6-b]quinoxalines and evaluated for antimicrobial potency [16].



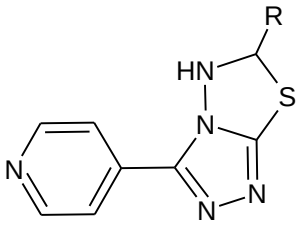
[15]

Jagmohan *et al*, prepared s-triazolo[3,4-b][1,3,4] thiadiazoles and s-triazolo[3,4-b][1,3,4]thiadiazines and evaluated for antifungal and antibacterial activities [17].



[16]

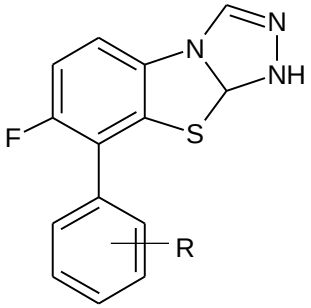
H. M. Hirpara *et al*, synthesized a series of 6-aryl-3-pyridin-4-yl-5,6-dihydro[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazoles and investigated for antimicrobial activity [18].



3a, R=C_6H_5

[17]

G. M. Srinivasa *et al,* reported the synthesis of 8-fluoro-9-substituted(1,3)-benzothiazolo(5,1-b)-3-substituted triazoles and investigated for their antimicrobial activities [19].

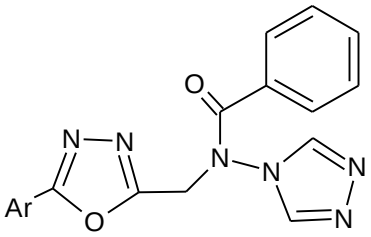


(H_1-H_3), R=o,m,p- NO_2

(H_4-H_5), R=o,m,- Cl

[18]

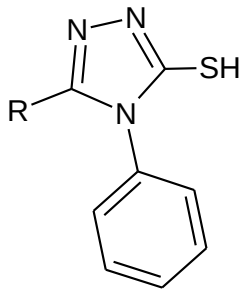
Arun Kumar Wahi *et al*, prepared N-(substituted benzylidene)-2-(N-(4*H*-1,2,4-triazole-4-yl)benzamido) acetohydrazides and N-((5-substitutedaryl)-1,3,4-oxadiazole-2-yl)methyl-N-(4*H*-1,2,4-triazole-4-yl)benzamides and screened for antibacterial and antifungal activity [20].



A_1=Ar= 2-OH-C_6H_4

[19]

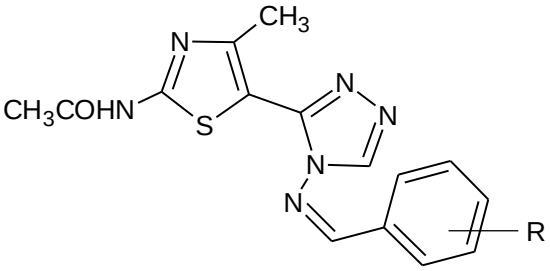
Mudasir Rashid Banday *et al*, reported the synthesis of substituted triazoles and thiazolidinones from fatty acids and screened for antimicrobial activity [21].



3a, R=CH_2=$CH(CH_2)_8$-

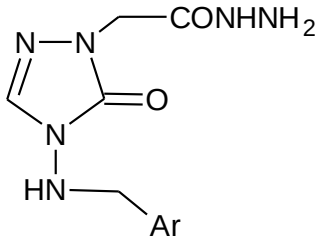
[20]

B. A. Baviskar *et al*, synthesized thiazolyltriazole substituted azetidinone derivatives and evaluated for their antimicrobial activity[22].



[21]

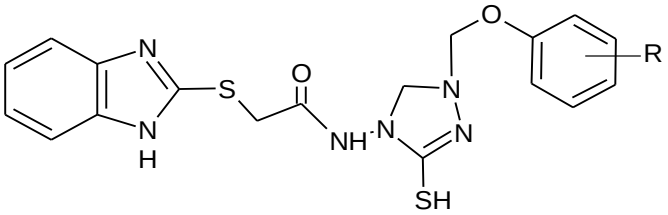
Bahittin Kahveci *et al*, reported the synthesis of 3-alkyl-4-(arylmethyleneamino) 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives and screened for the antimicrobial activity[23].



2a , R= CH_3, Ar= C_6H_5

[22]

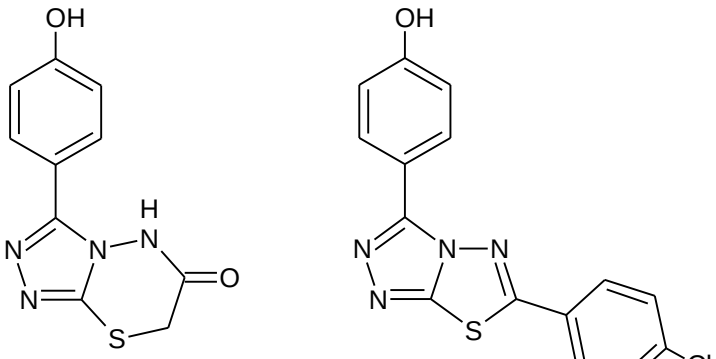
R. Shivakumar *et al*, synthesized 3-aryl-oxymethyl-4-[2-(benzimidazolyl thio)acetamide]-5-mercapto-1,2,4-triazoles and evaluated for their antimicrobial activities [24].



VIa, R= p-Cl

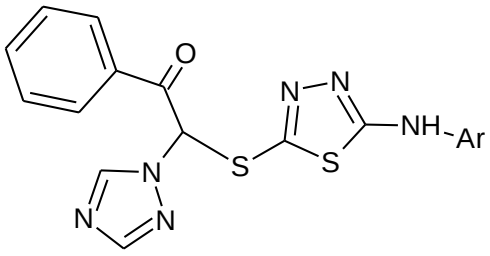
[23]

Jag Mohan prepared a series of s-triazolo(3,4-b)(1,3,4)thiadiazoles, s-triazolo (3,4-b)(1,3,4) thiadiazines and screened for their antibacterial and antifungal activities [25].



[24]

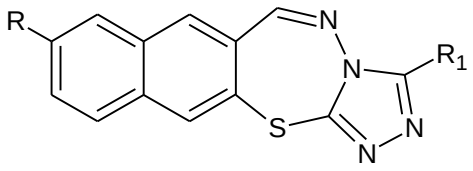
Chang –Hu Chu *et al*, prepared a series of ω-(5-arylamino-1,3,4-thiadiazol-2-thiol)-ω-(1*H*-1, 2, 4-triazol-yl)acetophenones and screened for antifungal and growth regulatory activities [26].



4a, Ar =m-Me-C_6H_4

[25]

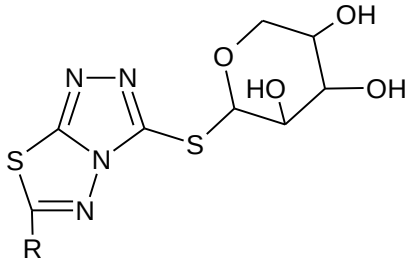
Balakrishna Kalluraya *et al,* prepared 3-alkyl-/aryl-9-substituted 1,2,4-triazolo[3,4-b][1,3,4]quinolino thiadiazipines and selected compounds were screened for their antibacterial and antifungal activities [27].



5a, R=H, R_1= Methyl

[26]

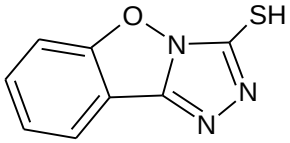
Nasser S. A. M. Kalil synthesized *N*-and *S*-α-L-arabinopyranosyl[1,2,4]triazolo[3,4-b][1,3,4]thiadi-azoles and investigated for antimicrobial potency [28].



7a, R= C_6H_5

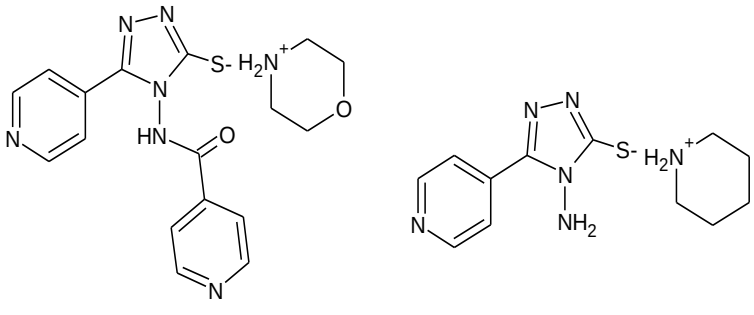
[27]

D. K. Swamy *et al*, synthesized 3-substituted(1,2,4)-triazolo[3,4-b]1,2-benzisoxazole derivatives and tested for their antimicrobial activity [29].



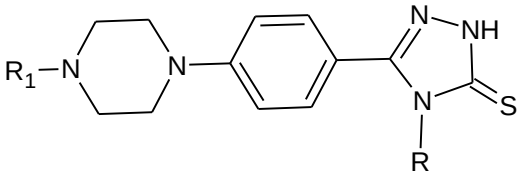
[28]

A.M. Manikaro *et al*, reported the synthesis of substituted 4-(N-pyridyl-5-4-amino-s-triazole-5-thiolate and evaluated for antimicrobial activity [30].



[29]

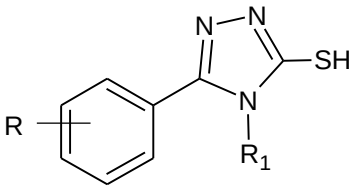
Harish Rajak *et al*, prepared 4-substituted piperizin-1yl)phenyl]-4-substituted 2,4-dihydro[1,2,4] triazole-3-thiones and evaluated for antimicrobial activity [31].



1, R= CH_2-CH_3, R_1=H

[30]

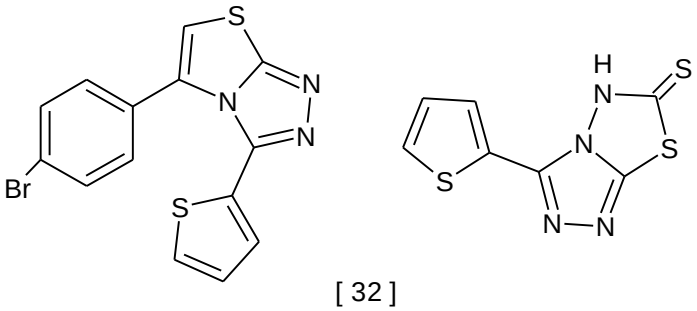
Rajkumar Agarwal *et al*, synthesized 5- aromatic substituted -4*H*-1,2,4-triazol-3-thiol and evaluated for antimicrobial activity [32].



[31]

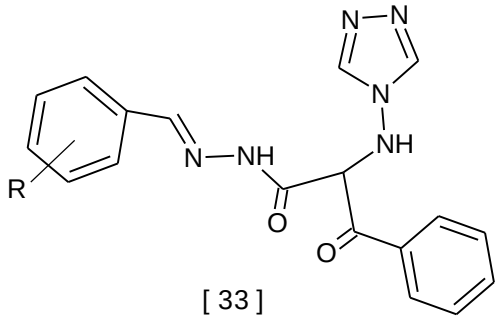
Mrs. Arti Singh *et al*, reported the synthesis of N-(disubstituted amino)methyl(4*H*)-1,2,4-triazole-4-yl)benzamide and investigated for antimicrobial activity [33].

As diuretic agents: Jag Mohan reported the synthesis of 3-(2-thienyl)-s-triazolo[3,4-b][1,3,4]-thiadiazole, 2-(2-thienyl)thiazolo[3,2-b]-s-triazole and isomeric 3-(2-thienyl)-thiazolo(2,3-c)-s-triazole and screened for their diuretic, antibacterial and antifungal activities [34].



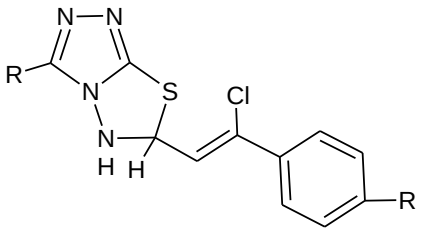
[32]

As anti-inflammatoty agents: Arun K. Wahi *et al*, synthesized the series of N-substituted benzylidene)-2-N-(4*H*-1,2,4-triazole-4yl)benzamido acetohydrazides and evaluated for antimicrobial and anti-inflammatory activities [35].



[33]

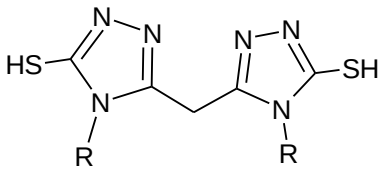
Rajive Gupta *et al*, synthesized a series of 3-alkyl/aryl-6-(2-chloro-2- substituted-phenylethenyl)-5-b-dihydro-s-trizolo[3,4-b][1,3,4].thiadiazoles and evaluated for anti-inflammatory, antibacterial and antifungal activities [36].



(3), R_1= 4' -OMe -C_6H_4, R=Cl

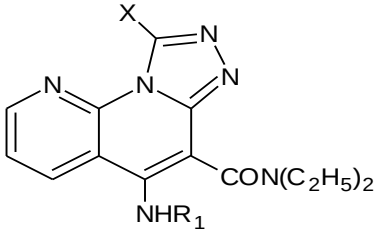
[34]

Rohini Diwedi *et al*, synthesized several 5,5'-Methylene bis(4-substituted phenyl/alkyl)-4*H*-1,2,4-triazole-3-thiol and investigated for their antioxidant, anti-inflammatory activities[37].



[35]

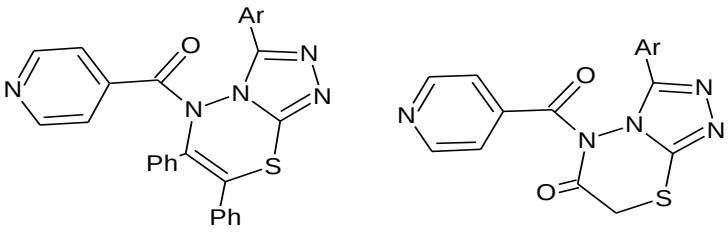
Mario Di Braccio *et al,* prepared 5-(alkylamino)-N-N-diethyl[1,2,4]triazolo[4,3-a][1,8]napthyridine carboxamide and its derivatives and screened for their anti-inflammatory activity [38].



3a, R_1= 1-C_4H_9, X=$COOC_2H_5$

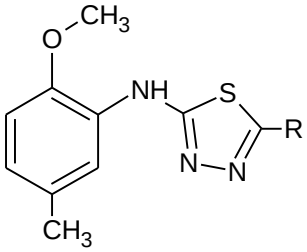
[36]

Ram Janam Singh *et al*, synthesized 1,2,4-triazolothiadiazines, 1,2,4-triazolothiadiazinones and evaluated for anti-inflammatory activity [39].



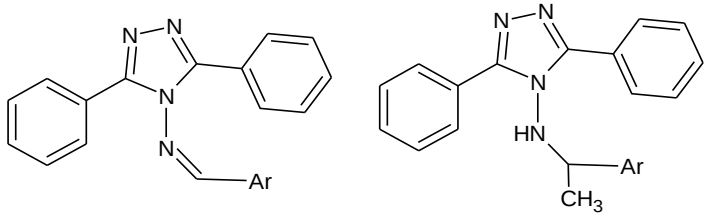
[37]

As anticancer agents: S. B. Hipara *et al*, reported the synthesis of 2-aryl 5-(2'-methoxy-5'-methylphenylamino)-1,3,4-thiadiazoles and 2-Phenyl-4-arylidine-1-(2'-methoxy-5'-methylphenyl thiourido-5-oxo-imidazolines and investigated for their antibacterial, antifungal and anticancer activities[40].



[38]

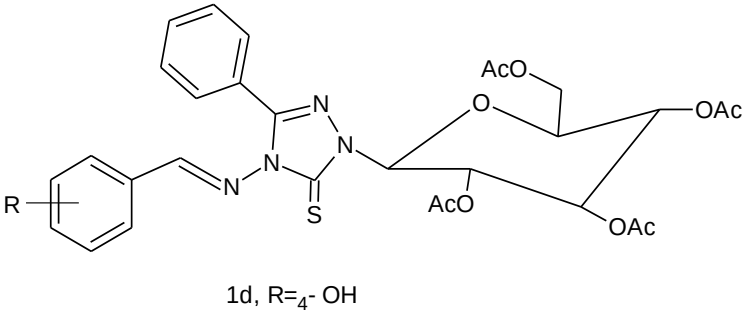
Olcay Bekircan *et al*, reported the synthesis of various 4-arylidenamino-4*H*-1,2,4-triazoles, 4-(1-aryl)ethylidenamino-4*H*-1,2,4-triazoles, 4-arylmethyl amino-4*H*-1,2,4-triazoles, 4-(1-aryl)ethylamino-4*H*-1,2,4-triazoles and investigated as weak anticancer agents [41].



2, Ar= 4- CH_3- C_6H_4 30, Ar=$_4$-NO_2-Phenyl

[39]

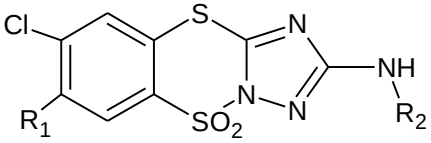
Zhi Zhang Li et al, were prepared various 4-(arylmethyl benzylidene amino)-5-phenyl-2*H*-1,2,4-triazole-3-(3*H*)-thiones and N-2,3,4,6-tetra-O-acetyl-acetyl-σ-D-glucopyranosyl-4-(arylmethylideneamino)-5-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione and investigated for their antiproliferative agents [42].



1d, R=$_4$- OH

[40]

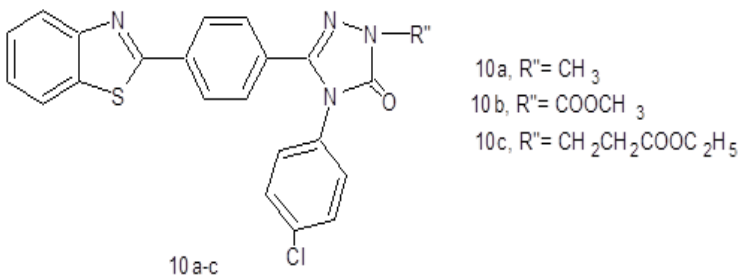
Elzbieto Pomarnacka *et al*, synthesized 2-arylamino-8-chloro-5,5-dioxo[1,2,4]-triazolo[2,3-b][1,4,2]benzodithi-azines and investigated for their anticancer and antibacterial activities [43].



20, R_1=Me, R_2= 4-MeOPh

[41]

Wageesh S.El Hamouly *et al,* reported the synthesis of N-substituted sulphonyl, 1,2,4-triazole, N-substituted benzylidene and pyrazole analogues bearing 4-(benzo(d)thiazol-2-yl)benzohydrazide and evaluated for antibreast cancer activity [44].

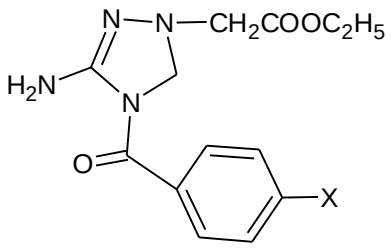


10a, R"= CH_3
10b, R"= $COOCH_3$
10c, R"= $CH_2CH_2COOC_2H_5$

10 a-c

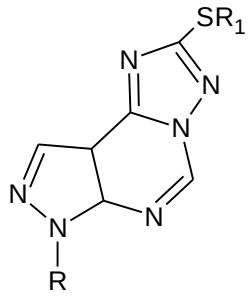
[42]

Hend A. A. Abd El-Wahab *et al,* synthesized substituted 1,2,4- triazole-3-acetic acid derivatives and evaluated for antitumor and anti-inflammatory activities [45].



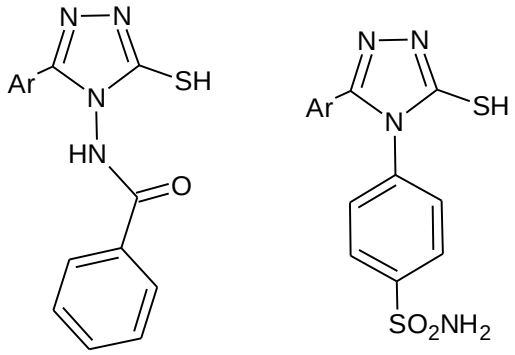
[43]

Ibrahim F. Nasser et al, were synthesized 2- alkylthio-7-tosyl-7*H*-pyrazolo (4,3-e)[1,2,4-]-triazolo[1,5-c] pyrimidines and other pyrazole derivatives and evaluated for their antitumour activity [46].



[44]

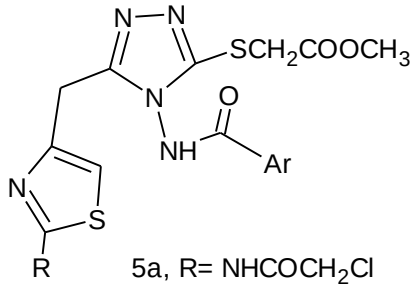
As antitubercular agents: Shashikant Patten *et al*, reported the synthesis of 5-mercapto 1,2,4-triazole derivatives and evaluated for antimicrobial, anti-inflammatory, antitubercular activities [47].



5g,h =Ar = p-NH_2-C_6H_4

[45]

Mahendra Ramesh Shiradkar *et al*, reported the synthesis of various derivatives of N-{4-[(4-amino-5-sulphanyl-4*H*-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amides and tested for antibacterial and antitubercular potency [48].

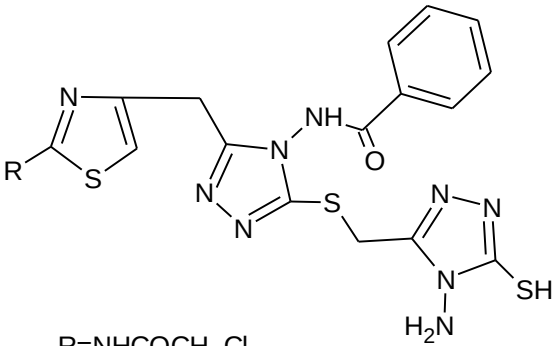


5a, R= $NHCOCH_2Cl$

Ar= 4-Cl- C_6H_4

[46]

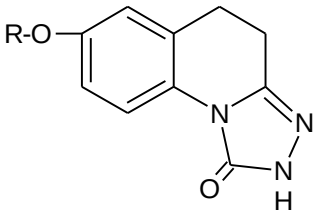
Mahendra Shiradkar *et al*, synthesized analogues of thiazolyl triazoles and tested for their antimycobacterial and antimicrobial activities [49].



R=$NHCOCH_2Cl$

[47]

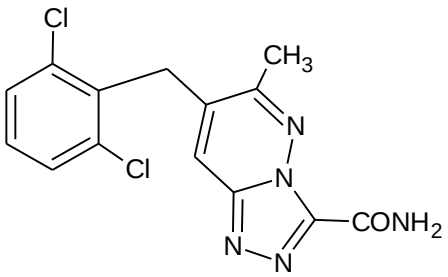
As anticonvulsant agents: Hong Guang Jin *et al.*, reported the synthesis of 7-alkoxy-4,5-dihydro[1,2,4]triazolo[4,3-a]quinoline1(2*H*)-ones and investigated for anticonvulsant activity and neurotoxicity [50].



3f, R=$CH_2C_6H_5$

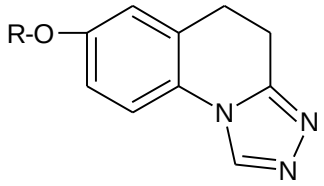
[48]

S. Moreau *et al.,* reported the synthesis of 3-amino-7-(2,6-dichlorobenzyl)-6-methyltriazolo[4,3-b]pyridine derivatives of amide and carboxylic acid and investigated for their anticonvulsant potency[51].



[49]

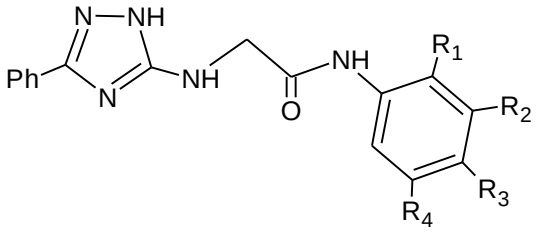
Zhi-Feng Xie *et al*, prepared various 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline analogues and were investigated for their anticonvulsant activity and neurotoxicity. Compound(4l) is found to be very active [52].



4l, R=CH_2-C_6H_4

[50]

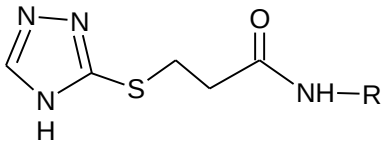
Dayanand Kadadevar *et al*., reported the synthesis and evaluation of N-(substitutedphenyl)-2-[5-phenyl-2*H*-1,2,4-triazol-3-yl-amino]acetamide for their anticonvulsant activity [53].



T_1=R_1=Cl, R_2=H, R_3=NO_2, R_4=NO_2

[51]

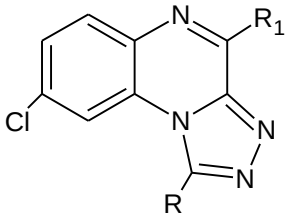
As Anxiolytic agents: Anil M. Manikaro *et al*, synthesized carboxamidoethylthio-(4*H*)-1,2,4-triazoles and evaluated for anxiolytic, anti-inflammatory, analgesic activity [54].



6a, R=C_6H_5

[52]

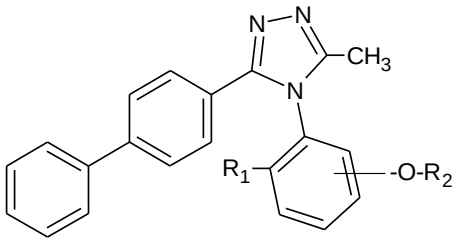
As Antioxidant agents: M. Suresh *et al*, reported the synthesis of 8-chloro-1,4-substituted (1,2,4[4,3-a]quinoxalines and evaluated for antioxidant and antimicrobial activity [55].



7b,R= C_6H_5, R_1=-SCH_2COOH

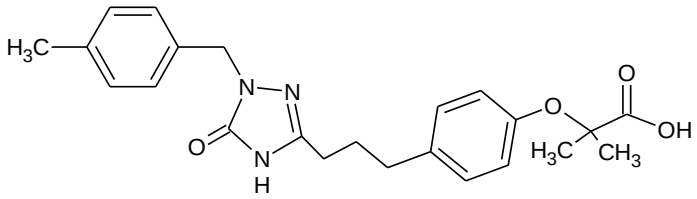
[53]

As Human V1A receptor antagonists: Akio Kakefuda *et al*, synthesized 5-(4-biphenyl)-3-methyl-4-phenyl-1,2,4-triazole derivatives and investigated as selective antagonists for the human vasopression V1A receptor [56].



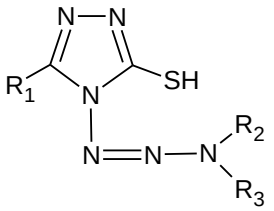
[54]

As PPARα agonists: Yan Ping Xu *et al.*, reported the design and synthesis of various 2, 4-dihydro-3*H*-1, 2, 4-triazol-3-one, and investigated as most potent and selective PPARα agonist [57].



[55]

As Analgesic agents: P. K. Goyal *et al*., were synthesized s-substituted -4-(3-disubtituted-1-triazenyl)-4*H*-1,2,4-triazol-5-thiol and tested for analgesic activity [58].



4a, R_1=CH_3, R_2=H, R_3=C_6H_5

[56]

CONCLUSION: The present study revealed that 1,2,4-triazole derivatives are the significant class of heterocyclic compounds and showed promising pharmacological activities like antibacterial, antifungal, antitubercular, antioxidant, anticancer, anti-inflammatory, analgesic, anticonvulsant, anxiolytic, activities. These observations have been useful for the development of 1, 2, 4-triazole nucleus which can be taken as a lead for future development to get safer and effective compounds.

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