Int J Pharm Bio Sci 2013 July; 4(3): (P) 310 - 332

Review Article **Pharmaceutics**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

PHARMACOLOGICAL ACTIVITIES OF TRIAZOLE, OXADIAZOLE AND THIADIAZOLE

SHUBHANGI WAGHAMALE AND PRAVINA PISTE*

****P.G .Department of Chemistry, Y. C. Institute of Science, Satara (MS) India.***

ABSTRACT

Triazole, oxadiazole and thiadiazole a five member heterocyclic nucleus has attracted a wide attention of the Chemist in search for the new therapeutic molecules. This heterocyclic nucleus play vital role in biological fields such as, Antimicrobial, Anticonvulsant, Anticancer, Anti-inflammatory activity.These Skeletons have its multiple potential against several activities. This review provides a brief summary of the medicinal chemistry of triazole ,Oxadiazole and thiadiazole system and highlights some examples of recent drug containing this moieties in the current literature.

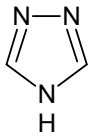
KEY WORDS: Triazole, Oxadiazole, Thiadiazole, Biological activities.

PRAVINA PISTE
P.G .Department of Chemistry, Y. C. Institute of Science, Satara (MS) India.

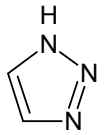
****Corresponding author***

1. INTRODUCTION

Nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications,especiallychemotherapy. That's why the search for new biological active agent is one of the most challenging tasks to the medicinal chemist. In recent years, the chemistry of triazoles And another five member heterocyclic derivatives has received considerable attention owing to their Synthetic and effective biological importance. There are two possible isomers of triazole depending on the position of nitrogen atom in the ring and are numbered as shown.



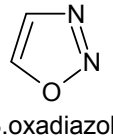
1, 2, 4 triazole



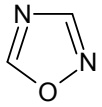
1,2,3 triazole

1, 2, 4- triazole have drawn great attention to chemists from two decades out of two triazole due to its wide variety of activity, low toxicity and good Pharmacokinetic and Pharmacodynamic profiles. Literature survey reveals that 1, 2, 4-triazole derivatives exhibit wide range of biological activities .

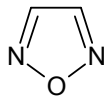
Oxadiazole, a heterocyclic nucleus having a five member ring containing one oxygen and two nitrogen atoms , in older literature it was referred as furadiazoles which attracted wide attention of chemist for preparation of different biological active drugs. Biological activities of oxadiazole are due to the presence of -N=C – O linkage. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring namely 1, 2, 3-, 1, 2, 4-, 1, 2, 5- and 1, 3, 4-oxadiazoles. Out of these 1, 3, 4-oxadiazoles are found to be most potent biologically.



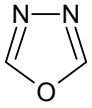
1,2,3.oxadiazole



1,2,4.oxadiazole

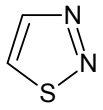


1,2,5 oxadiazole

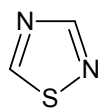


1,3,4 oxadiazole

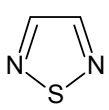
A large number of 1, 3, 4-oxadiazole derivatives have been found to exhibit various biological activities such as Anti-Inflammatory, Antimicrobial, Anticancer, Anticonvulsant, antihypertensive etc. Similarly, a recent literature survey revealed that the 1, 3, 4-thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole, etc. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. There are several isomers of thiadiazole, that is 1,2,3Thiadiazole (1), 1,2,4 Thiadiazole (2), 1,2,5 Thiadiazole (3)and 1,3,4 Thiadiazole (4)



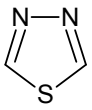
1) 1,2,3.thiadiazole



2) 1,2,4.thiadiazole



3) 1,2,5 thiadiazole

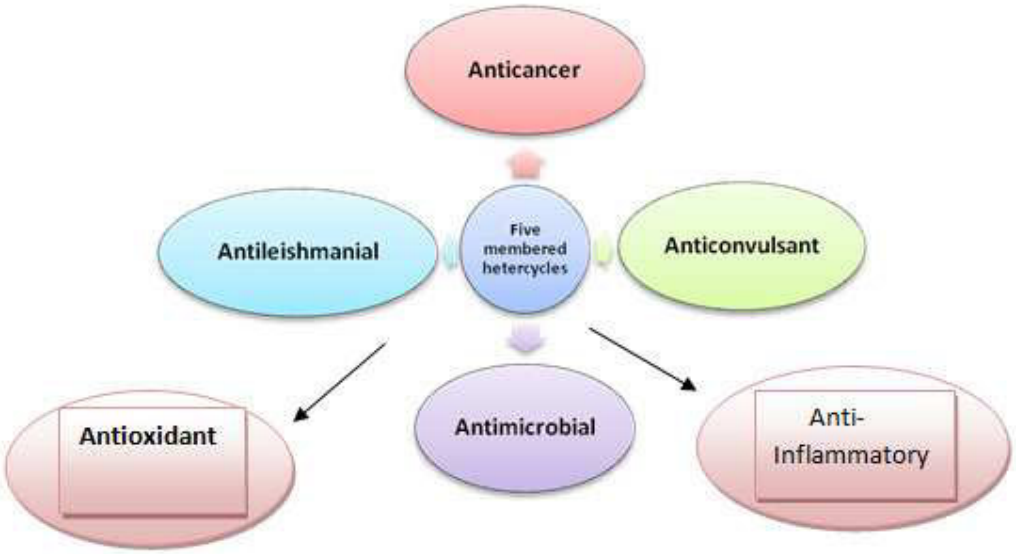


4) 1, 2, 4 .thiadiazole

1, 3, 4 Thiadiazole is the isomer of thiadiazole series. A review of standard reference works shows that more studies have been carried out on the 1, 3, 4 Thiadiazole than all the

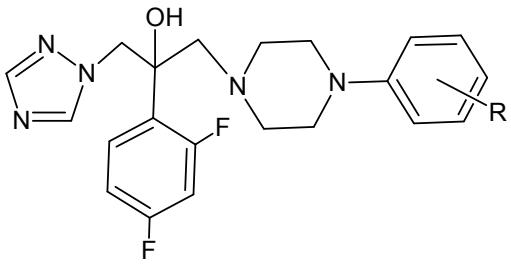
other isomers combined. Members of this ring system have found diverse applications such as pharmaceuticals, oxidation inhibitors, cyanide dyes, and metal complexing agents.

PHARMACOLOGICAL ACTIVITIES OF FIVE MEMBERED HETEROCYCLES

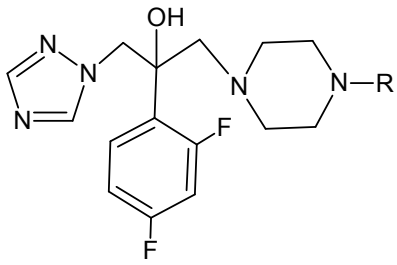


ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY

C. Sheng et al[1] synthesised 1-(1H-1,2,4-triazolyl)-2-(2,4-diflurophenyl)-3-(4-substituted-1- piperazinyl) -2-propanol derivatives on the basis of the active site of lanosterol 14α-demethylase. *In vitro* antifungal activities showed that some of the target compounds had higher antifungal activity and broader antifungal spectrum than fluconazole. Some of the target compounds showed good MIC values less than 0.125µg/mL and proved to be more potent than fluconazole. **5** and **3** had excellent potency against a broad range of fungal stains pathogen including *Aspergillus fumigatus*.

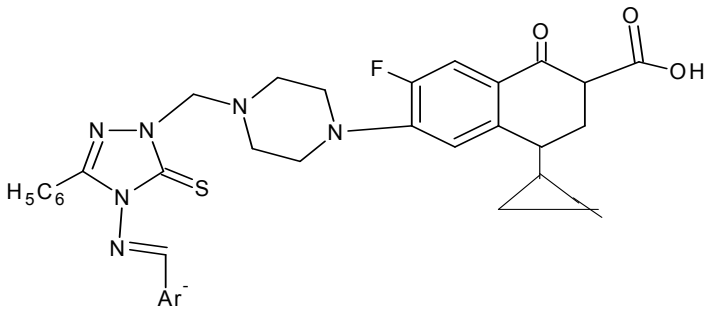


v



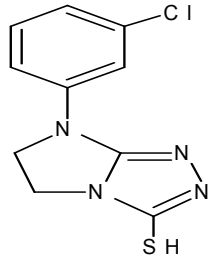
VI

S. Jubie et al [2] have synthesized some novel ciprofloxacin analogues (2) as antimicrobial agents. Ciprofloxacin have been incorporated to the new series of Schiff bases of 1, 2, 4-triazole via Mannich reaction. The new compounds have been evaluated in vitro for their antimicrobial activity against B. subtilis, K. pneumoniae, and P. aeruginosa at 10µg/ml concentration. All the compounds showed in vitro gram positive and gram negative activity generally comparable or superior to that of reference ciprofloxacin.

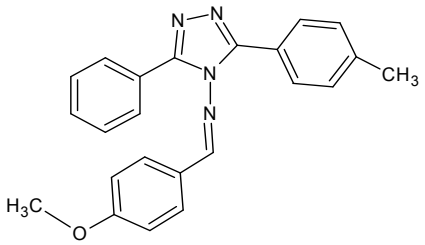


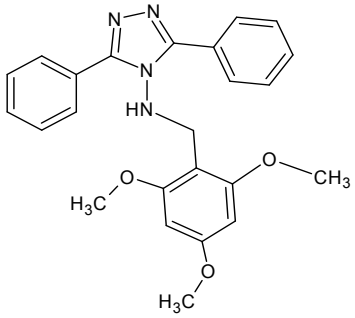
2 a - f

K. Sztanke et al[3] synthesise unsubstituted and 3-substituted-7-aryl-5*H*-6,7-dihydroimidazo [2,1-*c*][1,2,4]triazoles Their antifungal activity was investigated against *Aspergillus niger* and *Fusarium oxysporum.* Among the series of synthesized compounds, 7-(3-chlorophenyl)-6,7-dihydro- 5*H*imidazo[2,1-*c*][1,2,4]triazole-3-thiol showed the most significant activity .

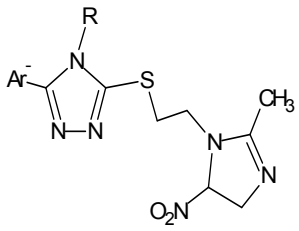


M. serdar et al [4] were used *Esherichia coli* ATCC 25922, *Pseudomonas auroginosa* ATCC 10145, *Yersinia pseudotuberculosis* ATCC 911, *Klepsiella pneumonia* ATCC 13883, *Enterococcus fecalis* ATCC 29212, *Staphylococcusaureus* ATCC 25923, and *Bacillus cereus* 709 ROMA.A simple susceptibility screening test using agar-well diffusion as adapted earlier was used used by them. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 *µ*g/50 *µ*L) served as control antibiotics. DMSO served as solved control. They found that compound shows good antibacterial activity against *staphylococcus aureus*.

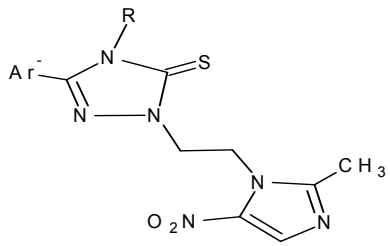




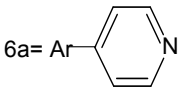
H. Saadeh et al[5] synthesise new 1, 2, 4-triazole-3-thiol metronidazole derivatives the antimicrobial activity of the newly prepared compounds derived by using Gram-positive, Gram-negative, and fungal cultures. With the exception of Clostridium sporogenes the reported antimicrobial activity was significantly lower than that of the reference tested antimicrobials.

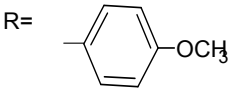


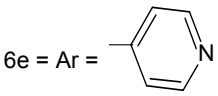
6a -6e

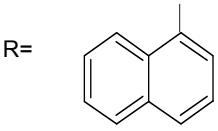


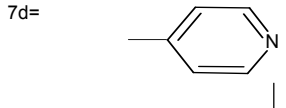
7a -7e

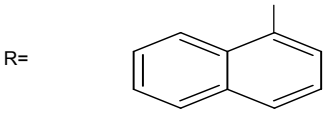




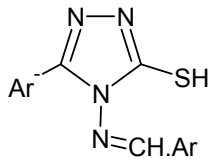




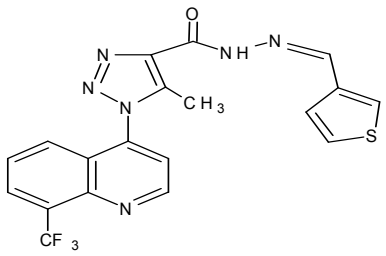




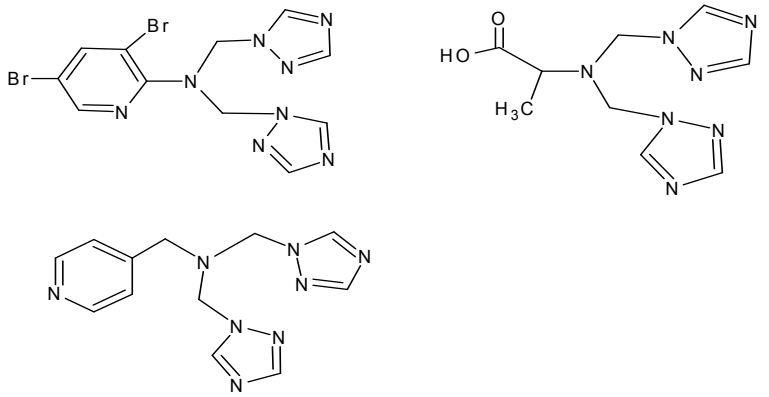
G. Rao et al [6] synthesised series of Schiff bases of triazole series(s) which show antibacterial as ewell as antifungal activity like 5-phenyl,4-(substituted) amino,3-mercapto 1,2,4-triazoles show antimicrobial activity.



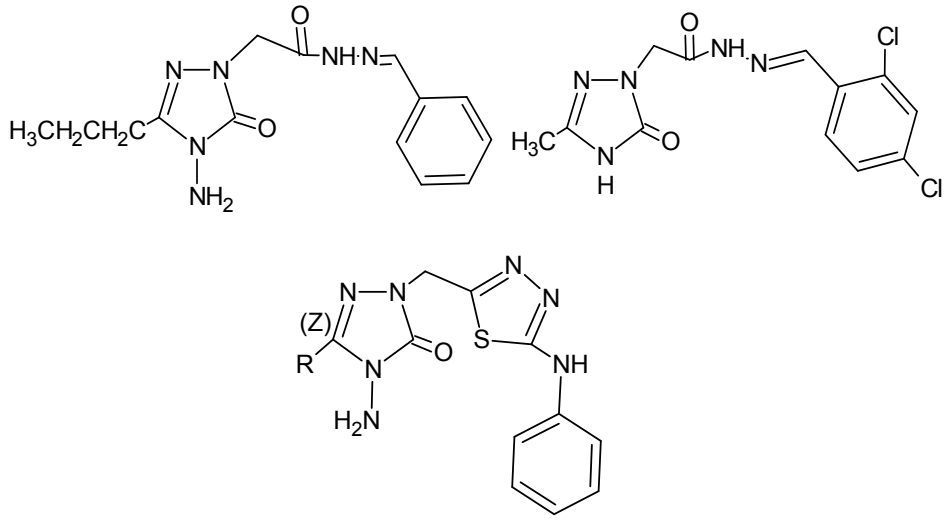
B. Bantwal et al [7] produced a set of Schiff's bases as N-[1-arylmethelene]-1-[8-(triafluromethyl) quinolin-4-yl]-5-methyl-1H-1,2,3-triazole-4-carbohydrazide & 1- aryl-4-{1-[8- (triafluro methyl) quinolin-4-yl]-5-methyl-1H-1,2,3-triazole-4-yl}prop-2-en-1-one containing triazole and quinoline moiety The compounds were screened for their antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Psuedomonus aeruginosa, Bacillus subtilis*, *Klebsiella pneumonia, Aspergilus flavus, Aspergilus fumigates, Candida albicans,Penicillium marneffei, Trichophyton mentagrophytes.*



H. Bay et al [8] synthesised a series of six new N,N-bis(1,2,4-triazole-1-yl methyl) amine, in one step condensation of 1-(hydroxymethyl) with different amines and compounds were evaluated for their antifungal activity against budding yeast *saccharomycces cerevisiae* and their antibacterial activity was found most active .

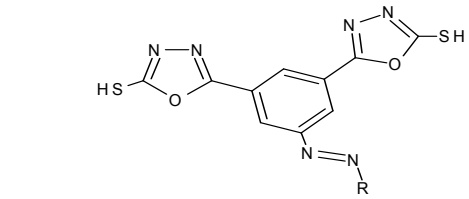


N. Demirbas et al[9] evaluate Antimicrobial activity of some newly synthesized compounds and resulted in potent activity against many microorganisms. The compounds prepare belongs to 1-(5-phenylamino-[1,3,4]thiadiazole-2-yl) methyl -5-oxo- [1,2,4]triazole and 1- (4-phenyl -5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo- [1,2,4] triazole derivatives.

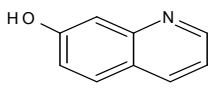


R:a=CH_3,b=$CH_2C_6H_5$,c=C_6H_5

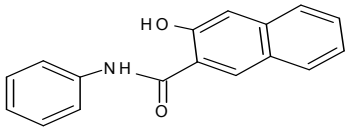
A.Shridhar et al[10] determine the antimicrobial activity of newly synthesized compounds by well plate method in nutrient agar , In this work, E. coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhi, were used to investigate the antibacterial activities. This investigation proposes a convenient, economical and useful method for the synthesis of 5, 5'-(5-nitrobenzene-1, 3-diyl) bis (1, 3, 4-oxadiazole-2-thiol) azo dye, coupled with quinoline, and napthols which are biologically active molecules possessing safer antimicrobial activity among all test compounds, compound1 14b, 14d and 14e showed significant antimicrobial activity when compared to other compounds. Specifically, compound 14b and 14c having methoxy, halogen and electron donating atom was more efficient than other compounds but less potent than standard drug ampicillin.



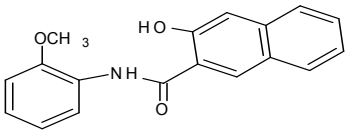
R=



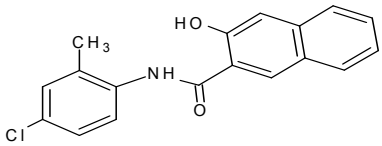
14b



14c

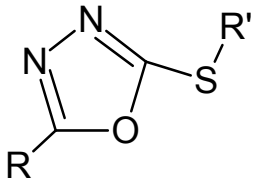


14d

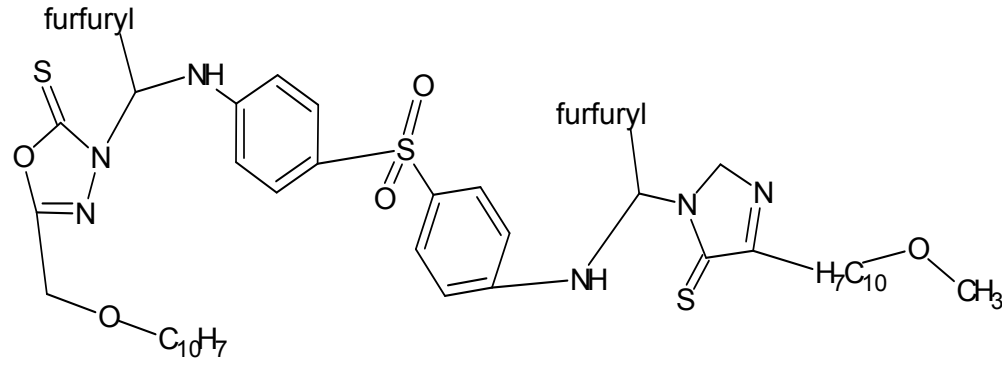


14e

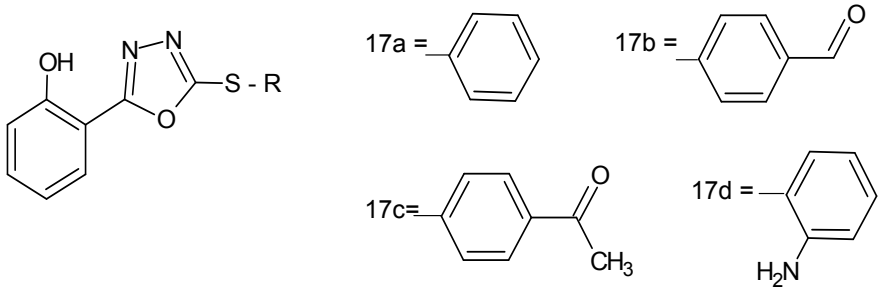
M. Mohammed-Ali et al [11]synthesised two new series of 2-alkylthio-5-aryl-1, 3, 4-oxadiazole (aryl = 2-hydroxyphenyl, 5-bromofuryl and alkyl = H,CH_2CH_3, $CH_2(CH_2)_2CH_3$, CH_2Ph, $CH_2CO_2CH_2CH_3$, CH_2CO_2H) were synthesized. The prepared compounds were examined against two bacterial strains, Gram negative (E. coli) and Gram positive (S. aureus), and against pathogenic fungi Aspergillus niger. MIC was determined for all compounds against two bacterial strains. LD50 values were determined for some selected compounds which have showed a good antimicrobial activity.



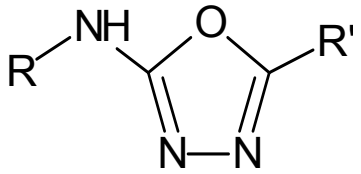
M. Ashraf Ali et. Al. [12] synthesized a series of oxadiazole mannich bases by reaction between oxadiazole derivatives, dapsone, and appropriate aldehydes and was evaluated against Mycobacterium Tuberculosis. Compound 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3yl]methyl amino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4 oxa-diazole-2-thione from all the synthesized compounds have shown best activity against M. Tuberculosis and isoniazide resistant M. Tuberculosis.



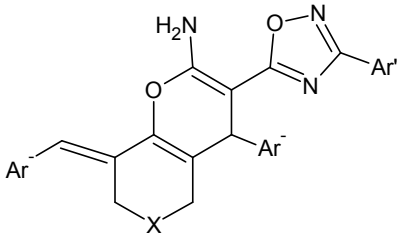
P.Parikh *et al.*[13] synthesized and investigated 1, 3, 4 oxadiazoles (17a-d) for their *in-vitro* antibacterial activity against Gram-positive: *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa*) and Gram-negative: *Escherichia coli*.



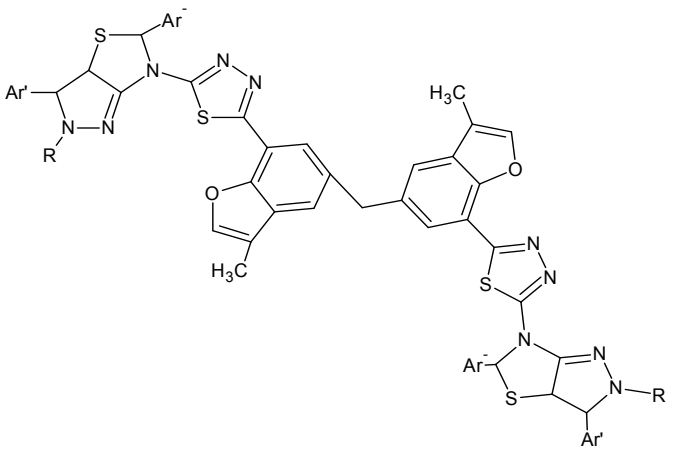
P. Ilangovan et al[14] synthesise a new series of 1, 3, 4-oxadiazole derivatives .All newly synthesized compounds were screened for antibacterial and antifungal activity by zone of inhibition and minimum inhibitory concentration. microorganisms used are *Staphylococcusaureus(G+ve),Escherichiacoli(G-ve),Vibriocholera(G-ve),Klebsillapneumonie (G-ve),Pseudomonasaureginosa(G-ve),Bacillussubstillis(G+ve), Carynebacterium (G+ve), Statusalbus(G+ve), Bacillus.lintus(G+ve),Salmonellatyphi* etc .whereas antifungal activity was screened by fungus *Streptomyces griseus, Monoscus rubrum, Candida albicans* etc.



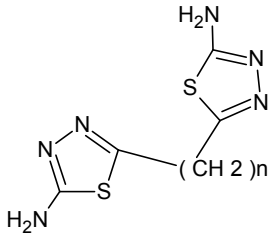
R. Kumar et al[15] synthesise novel 1, 2, 4-oxadiazole-pyranopyridine/chromene hybrid heterocycles in moderate yields. In vitro screening of these compounds against Mycobacterium tuberculosis H37Rv (MTB) disclosed that the 1, 2, 4-oxadiazole-pyranopyridine hybrids display enhanced activity relative to the 1, 2, 4-oxadiazole-chromene hybrids. Among the synthesised compound compounds, 21b, 21c and 21f–21i were more potent than the standard drug ethambutol (MIC: 7.64 lM), while four of them 21b, 21c, 21g, and 21h were more active than ciprofloxacin (MIC: 4.71 lM). Compound 21h, was found to be the most potent in the library, being 1.2, 15.2, and 24.6 times more active than isoniazid, ciprofloxacin, and ethambutol, respectively. However, all the compounds were less active than rifampicin (MIC: 0.12 lM).



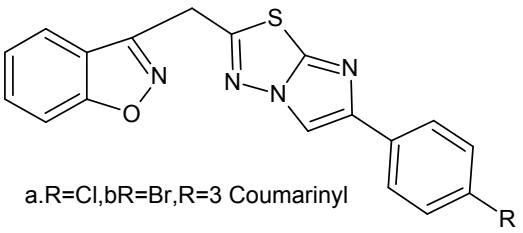
S. Cherkupally et al[16] synthesise a new series of Bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes. The compounds were evaluated for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis* (ATCC 6633),*Staphylococcus aureus* (ATCC 6538p) and *Micrococcus luteus* (IFC 12708), and Gram-negative bacteria *viz.Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922).



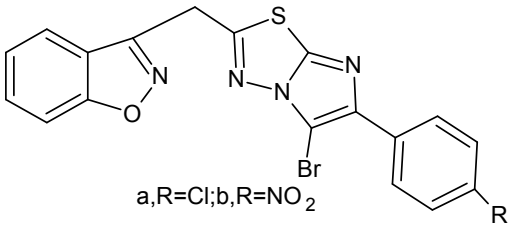
A.Barve et al[17] synthesise a series of dichlorides followed by 1,3,4 –thiadiazole-2-amine.The newly synthesised compound were evaluated for the antibacterial &antifungal activity Microbial strains used are-Staphylococcus aureus NCIM 2602; Bacillus subtilis NCIM 2613; Escherichia coli NCIM 2666; Pseudomonas *aeruginosa* NCIM 5225; *Saccharomyces cerevisiae* NCIM 3220*; Candida albicans* NCIM 3471*;* Aspergillus niger NCIM 813. Ciprofloxacin and Gresiofluvin were used as standard drug for the antibacterial and antifungal activity the title compounds have showed the better antibacterial activity and antifungal activity compared with the standard drug.



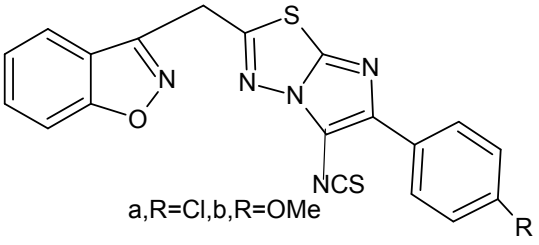
I. Khazi et.al.[12] were synthesized novel ethylene bridged benzisoxazolyl imidazo [2, 1-b] [1, 3, 4] - thiadiazoles. The investigation of antibacterial screening revealed that some of the tested compounds showed moderate to good bacterial inhibition. The high attributed to the activity is presence of electron withdrawing chloro-and bromo functional groups as comparable to that of standard.



a.R=Cl,bR=Br,R=3 Coumarinyl

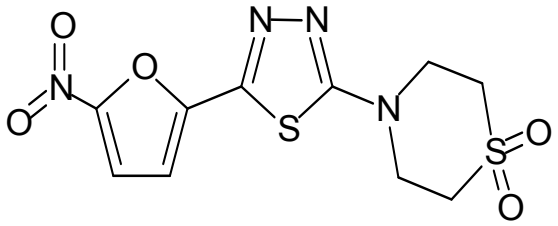


a,R=Cl;b,R=NO_2

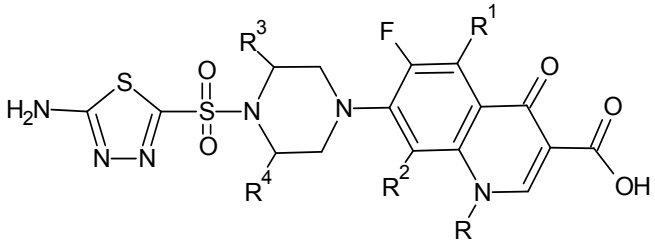


a,R=Cl,b,R=OMe

A. Foroumadi et.al.[19] have synthesize and evaluated invitro anti-*Helicobacter pylori* activity of N-[5-(5-nitro-2-heteroaryl)-1, 3, 4-thiadiazol-2-yl] thiomorpholines and some related compounds. They found that nitrofuran analog containing thiomorpholine S, S-dioxide moiety was the most potent compound tested.



S. Talath et al [20] synthesized a series of 7-[4-(5-amino-1, 3, 4-thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives. The compounds were evaluated for their *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data of the tested *N*-sulfonylfluoroquinolones indicated that all the synthesized compounds showed better activity against Gram-positive bacteria *S. Aureus.*



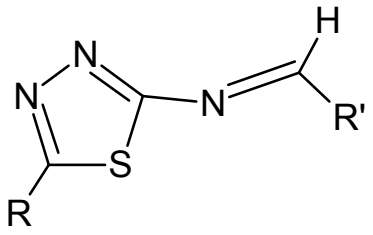
R =C_3H_5, C_2H_5

R_1= H, $NHCOCH_3$, NH_2

R^3= H, F, OCH_3

R^4=H, CH_3

K. Srivastava et al[21] *synthesise Schiff bases as new ligands* the synthesized ligands and their corresponding metal (II) complexes were screened in vitro for their antibacterial activity against four Gram-positive (*E.coli, P.aeruginosa, S.typhi & S.flexeneri*) and two Gram-positive (*B.subtilis & S.aureus*) bacterial strains by the agar-well diffusion method. It was concluded that the ligands act as tridentate (NNO donor) forming octahedral complexes with Co (II), Cu (II), Ni (II) and Zn (II) ions. Furthermore, the current study strongly demonstrates that these complexes are more effective antibacterial agents than the parent ligands.



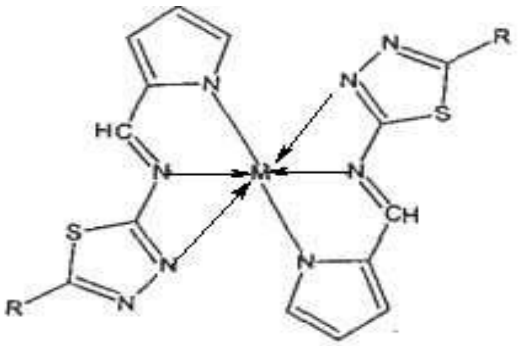


Figure-1

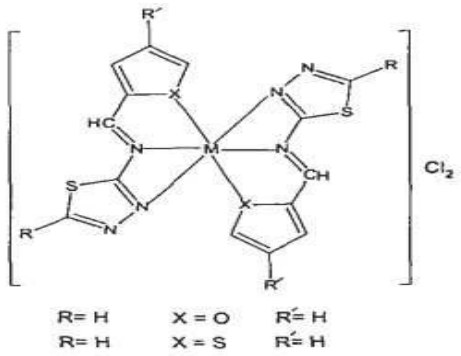
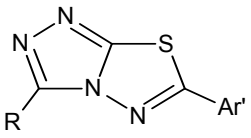


Figure-2

M = Co(II), Cu(II), Ni(II) or Zn(II)

Proposed structural formulae of the investigated metal complexes

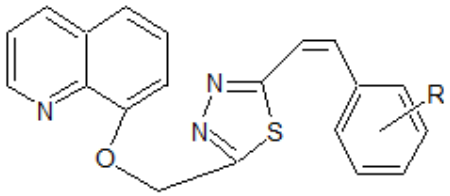
V. Mathew et al[22] synthesized several 3, 6-Disubstituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4-Thiadiazole and their dihydro analogues (34). Synthesized compounds are studied for their antibacterial, antifungal, anti-inflammatory and analgesic activities. The antimicrobial results showed that some of the compounds are active against both Gram-positive and Gram-negative bacteria. Compounds also showed good inhibition of growth of the yeast-like *Candida albicans* and the fungi *Aspergillus niger.*



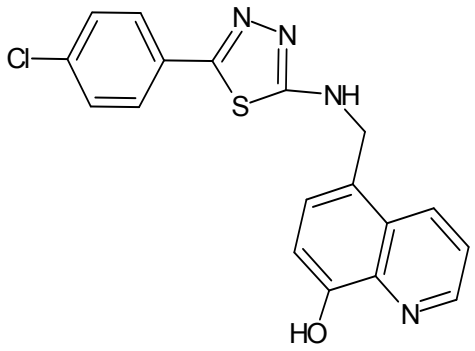
R=2 -Chloro -methoxy phenyl,3,4 -Dimethoxy benzyl
2 - Methyl -3 -Furanyl

Ar'=2 -phenyl -4 -quinolinyl,2 -methyl -4 -quinolinyl, 4 Quinolinyl
6 - Dihydroxy - 4 -piperydinyl,5 -methoxy -3 -indolyl methyl

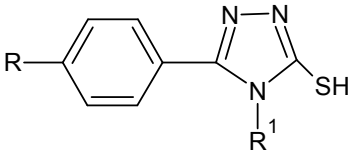
N.Madhev et al[23]synthesised Some new series 1, 3, 4-thiadiazoles and further evaluated antimicrobial Activity.



D.Patel et al, [24] have been Synthesise metal chelates of 5-[4- Chlorophenyl (1, 3, and 4) thiadiazol-2-ylaminomethylene]-8-hydroxy quinoline, characterized and evaluated its anti-microbial activity.



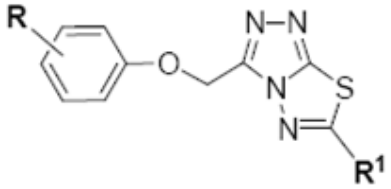
S. Prajapati et.al [25] synthesize some new 4-Aryl triazole and its derivative and screened for their antibacterial activity against and antifungal activities aginst Bacillus cereus, Pseudomonas aeriginosa, Klebsiella pneumoniae, Micrococcus flavus and Citrobactor freundii by ager well diffusion method and antifungal activity examined against Candida tropicalis, Candida albicans, Cryptococcus neofomans, Trichospor onbeigelii, and Aspergillius flavus by agar well diffusion method.



R= -OC_2H_5

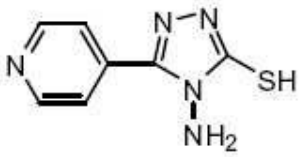
R^1= -Aryl

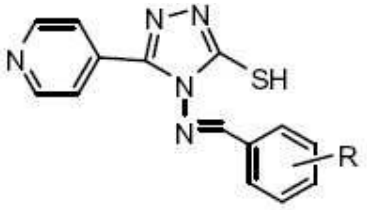
R Hunashal et al [26] synthesized 3-(substituted phenoxymethy)-6-phenyl/substituted phenoxymethyl-1,2,4-triazolo(3,4-B)-thiadiazole derivatives and were screened for their in-vitro antimicrobial activity and exhibited equipotent antibacterial and antifungal activity at MIC of 1 ,g/mL when compared with standard drug respectively. They showed comparable antitubercular activity against M. tuberculosis H37Rv at MIC of 0.50 ,g/mL, when compared with standard drug Rifampin and INH which showed MIC of 0.25 ,g/mL

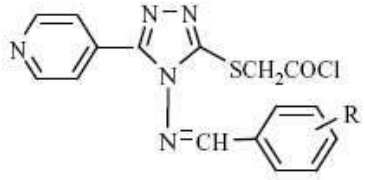
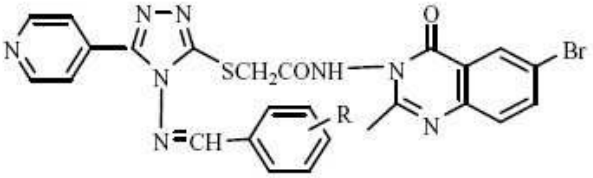


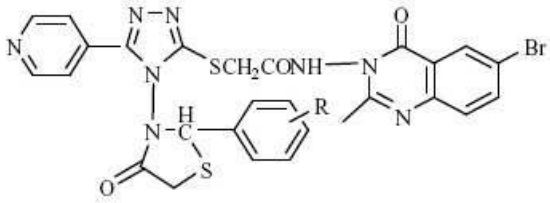
I Singh et al [27] synthesized a series of N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl)-5-(pyridin-4-yl)-5-thio)acetamido-1,2,4-triazoles

All the newly synthesized compounds were screened for their antibacterial activity against S.aureus, E.coli, P.vulgaris, K. pneumonia and showed better activities.



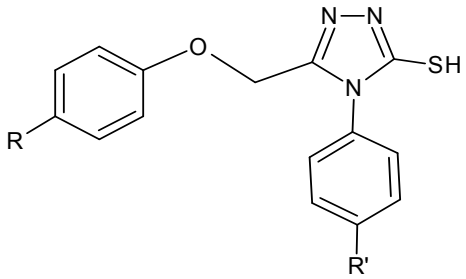


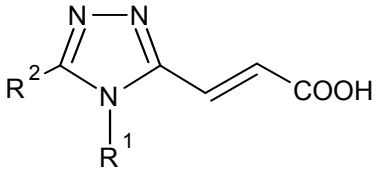


ANTICONVULSANT ACTIVITY

S.Pandey et al [28] synthesised series of new substituted mercapto triazoles & thiazolidiones derivatives & evaluate their MAO inhibitory & anticonvulsant activity.



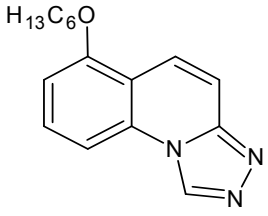
B Banachiewicz et al [29] carried Condensation reaction of the N3- substituted amidrazones and with malice anhydrides provided with newer derivatives of 3- (3, 4-diaryl-1, 2, 4-triazole-5-yl)propenoic acid which were evaluated for the anticonvulsant activity.



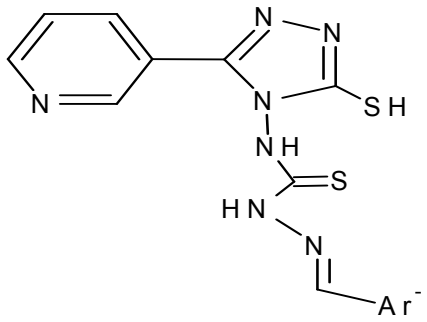
a: R^1=2 -C_5H_4N

R^2=C_6H_5

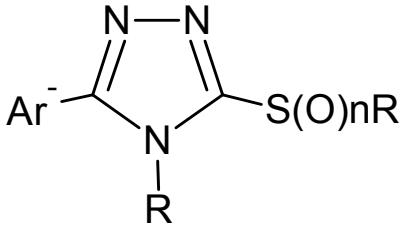
L Guoet et al [30] synthesised 5-hexyloxy- [1, 2, 4] triazolo [4, 3-a] quinoline and evaluated, found potent anticonvulsive in nature with low level of neurotoxicity. All the possible mechanism of anticonvulsive activity was done in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test.



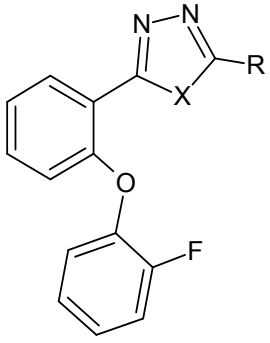
A Kshirsagar et al [31] synthesised1, 2, 4-triazole nucleus, therapeutically interesting drug candidate as anti-inflammatory, anti-infective and CNS stimulant. Heteroaryl semicarbazones and thiosemicarbazone have emerged as structurally novel anticonvulsants and found to possess antifungal properties and anti-HIV properties. Therefore thiosemicarbazide derivatives of 5-mercapto-3-(3'- pyridyl)-4H-1, 2, 4-triazole 4 were synthesized.



J Kane et al [32] prepared a series of isomeric alkylthio-1, 2, 4-triazole derivatives and examined for anticonvulsant activity versus strychnine, maximal electroshock, pentylene tetrazole and 3-mercapto propionic acid induced seizures in mice. The compounds were showed the anticonvulsant activity against maximal electroshock induced seizures.



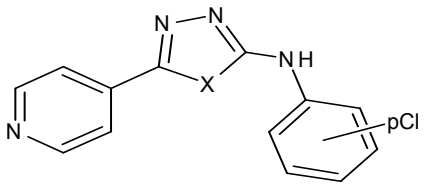
A.Almasirad et al. [33]A series of new 2-substituted-5-[2-(2-fluorophenoxy) phenyl] - 1, 3, 4-oxadiazoles (a-f) has been synthesized and screened for their anticonvulsant activities. Compound (a) shows considerable anticonvulsant activity both in PTZ and MES models.



	X	R
a	O	NH_2
b	O	SH
c	O	SCH_3
d	O	OH
e	N	SH
f	N	OEt

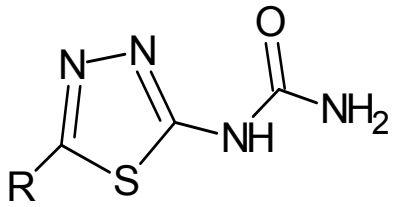
(a - f)

M Shaharyar et.al [34] synthesized a series of five membered heterocyclics and was tested for convulsion. From the synthesized compounds (If) 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1, 3, 4-thiadiazole and (IIf) 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1, 3, 4oxadiazole showed potent activity.

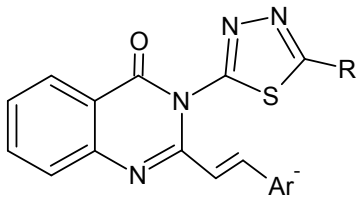


IFX=S
IIFX=O

B. Gowramma et al[35] synthesise1-(5-aryl-1, 3, 4-thiadiazol-2-yl) urea . The compounds were screened for their anticonvulsant activity by Pentylene Tetrazol Method (PTZ). Some of the synthesized compounds exhibited prominent anticonvulsant activity.



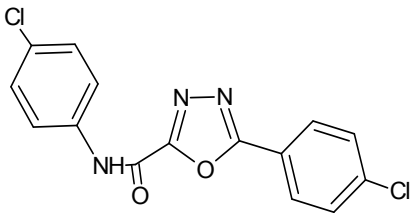
Jatav et al [36] synthesise a series of new 3-[5-substituted phenyl-1, 3, 4-thiadiazol-2-yl]-2-styryl quinazoline-4(3*H*)-ones and evaluated for anticonvulsant activity .Compounds were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Compound showed good anticonvulsant activity in the test models.

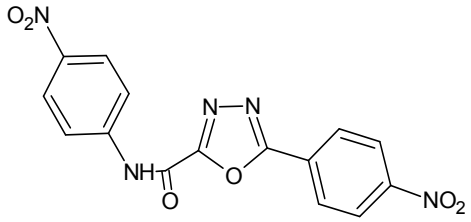


a = R = C_6H_5; Ar =4 - Cl C_6H_4
b = R = 3 - Cl C_6H_4 ; Ar = 4 -Cl C_6H_4
c = R = 4 - Cl C_6H_4 ; Ar = Pyridyl

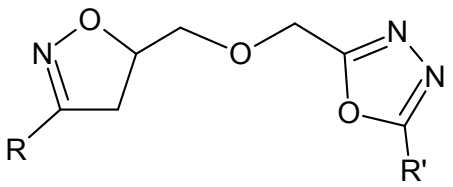
ANTI-INFLAMMATORY AND ANALGESICS

A Singh et al [37] synthesised 2, 5 Di-substituted 1, 3, 4-oxadiazole derivatives. These compounds were tested for their anti-inflammatory activity determined by rat paw oedema method .The entire compound gives good response for anti-inflammatory activity for this activity indomethacine was used as standard drug and compared to new synthesized drugs. Compound [3-Chloro-N-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl]benzamide and [4-Nitro-N-[5-(4-Nitrophenyl)-[1,3,4] oxadiazole-2yl] benzamide have greater anti-inflammatory activity.





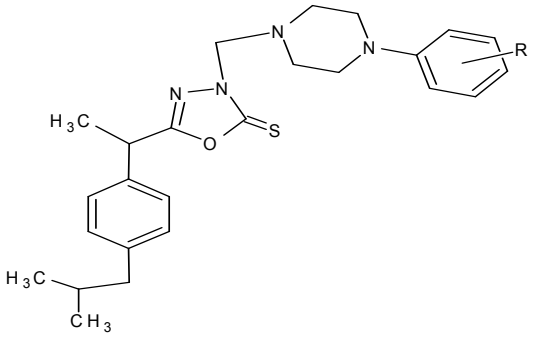
B. Jayashankar et.al[38] synthesized a series of novel ether-linked bis (heterocycle) s. All the Synthesized compounds were screened for anti-inflammatory and analgesic activities against ibuprofen and aspirin.



48d -R,R' =3 -O_2N C_6H_4

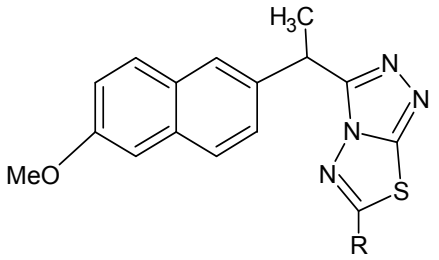
48g - R,R' =2,4 -Cl_2 C_6H_3

K.Manjunatha et al [39] synthesise a series of oxadiazole derivatives of ibuprofen which contains the arylpiperazine unit at position 3 of the oxadiazole ring as well as they investigate the Anti-inflammatory activity using paw edema induced by carrageenan with sodium Diclofenac as the reference. From synthesised compound, Compounds containing 4-Cl, 4-NO2, 4-F and 3-Cl groups were more active than sodium diclofenac, whereas compounds with 4-MeO and 2-EtO groups showed less activity.

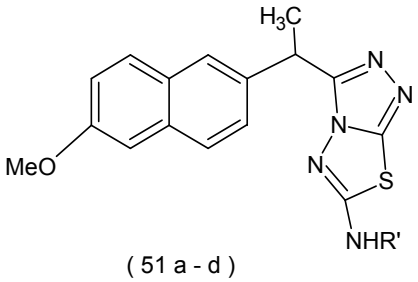


R = 4-Cl , 4-NO_2,4F,4MeO,2-EtO,3-Cl

M.Amir *et al*.[40] Some 6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives by cyclisation of 4-amino-5-[1-(6-methoxy-2-naphthyl)ethyl]-3-mercapto-(4*H*)-1,2,4-triazole with various substituted aromatic acids and aryl/alkyl isothiocyanates, through a single step reaction. All compounds were screened for anti-inflammatory activity.

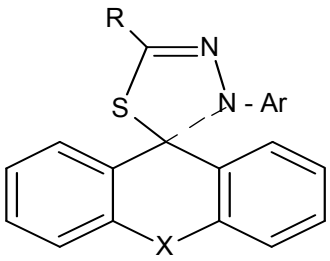


(50a - f)



(51 a - d)

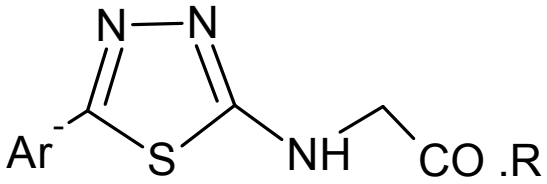
H.Hafez *et al*.[41] Synthesized a series of novel spiro-thioxanthene and spiro-xanthene-9'2-[1, 3, 4] thiadiazole derivatives. Some of newly synthesized compounds were tested for anti-inflammatory and analgesic activities comparable to ibuprofen



(52 a - g) , X = S

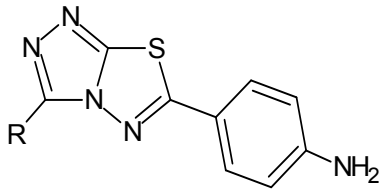
(53 a - g) , X = O

S Pattan et al[42] synthesised various substituted thiadiazoles all the compounds in addition were also screened for anti-inflammatory activity by winter et al method with standard drug (Diclofenac Sodium). However, Compounds have shown promising anti-inflammatory activity.

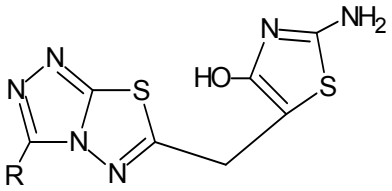


ANTICANCER ACTIVITY

D.Ibrahim et , al [43] Synthesized a new series evaluation of 3,6-disubstituted triazolo[3,4-b] thiadiazole derivative. 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. Compounds and maintained the highest growth inhibition

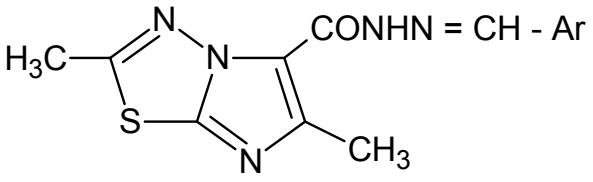


R = -CH_2O - Ph (p - Cl)



R = - CH_2O - Ph (p - Cl)

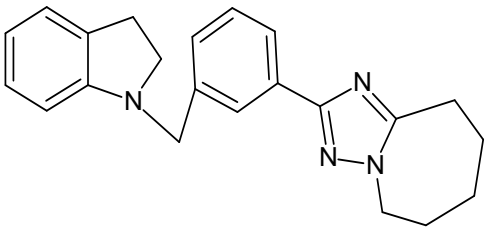
N.Terzioglu *et, al*. [44] synthesized some novel 2, 6-dimethyl-N'-substituted phenylmethylene-imidazo [2, 1-b] [1, 3, 4] thiadiazole-5-carbohydrazides. The newly synthesized compounds were evaluated in the National Cancer Institute's 3-cell line, one dose in vitro primary cytotoxicity assay Compounds which passed the criteria for activity in this assay (20-29% growth percentages) were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10- fold dilutions. 2,6-Dimethyl-N'-(2-hydroxyphenylmethylidene)imidazo[2,1 b][1,3,4] thiadiazole- 5-carbo hydrazide showed the most favorable cytotoxicity.



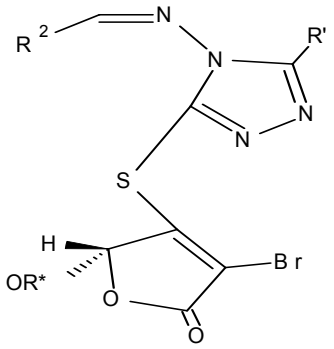
(a - h)

a = C_6H_4
b = 4 - $CH_3C_6H_4$
c = 2 - HOC_6H_4
d = 4 - $CH_3OC_6H_4$
e = 4 - BrC_6H_4
f = 4 -ClC_6H_4
g = 4 - FC_6H_4
h = 4 -$NO_2C_6H_4$

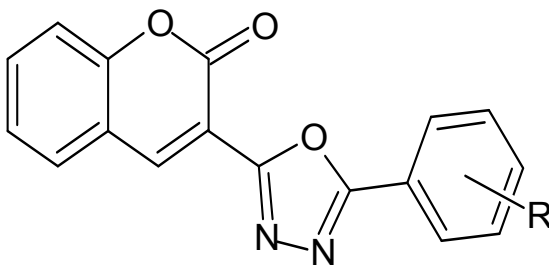
H. Mujagic et al [45] synthesise compound 1-(6,7,8,9 –tetrahydro-5H- [1,2,4]-triazolo[1,5,- a]-azepine – 2-yl)benzyl]indole &evaluated for anticancer activity against human tumour cell lines derived from nine cancer cell lines . The anticancer activity was moderate or weak in comparison to other lead series of compounds namely vincristine & vinblastine.



L Xiang et al synthesis [46] 12- hybrid 1, 2, 4-triazole Schiff bases bearing γ-substituted Butenolide moiety. These compounds were synthesized by utilizing the tandem asymmetric Michael addition elimination reaction as the key step. All the new compounds were evaluated for their in vitro anticancer activity. All these chiral 1, 2, 4-triazole derivatives exhibited good anticancer activities towards Hela. of all the tested compounds, the chiral compound 59l with an IC50 of 1.8 μM was found to be the most active.

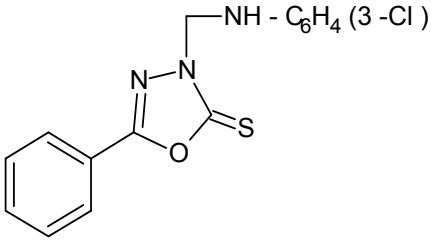


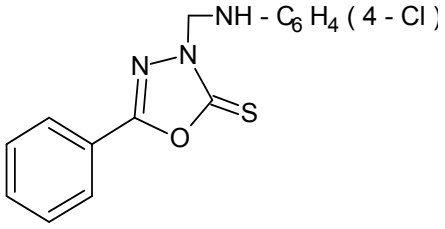
C.Biju et al[47] incorporate the coumarin ring system into oxadiazole moiety to explore the possibilities of some altered biological action. The new series of compounds bearing 1, 3, 4 –oxadiazole moiety with substitution in the 2nd & 5th position they carried out doking studies by using Gold software. The cytotoxicity activity of synthesised Compounds was tested by MTT assay and the Compounds show good activity on MCF -7 cell lines. Among the synthesised compound 60a, 60b, 60c shows maximum activity.



R = substituted acids

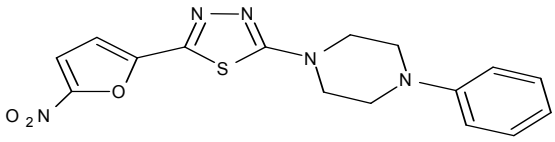
S.Aboraia et al [48] synthesized a series of 5-(2-hydroxyphenyl)-3-substituted-2, 3-dihydro-1, 3, 4-oxadiazole-2-thione derivatives and 13 of them were selected by the National Cancer Institute (NCI) and evaluated for their *in vitro* anticancer activity. These compounds have been selected for a full anticancer screening against a 60-cell panel assay where they showed Non- selective broad spectrum and promising activity against all cancer cell lines. Compounds proved to be the active members in this study compared to 5-fluorouracil and Cyclophosphamide as reference drugs, respectively.



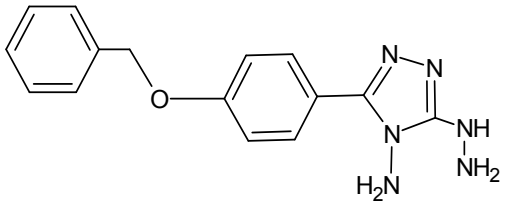


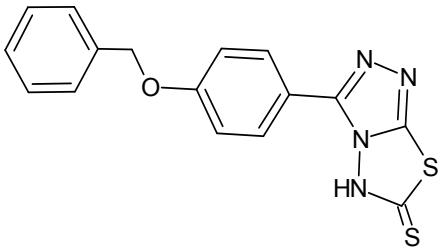
ANTILEISHMANIAL ACTIVITY

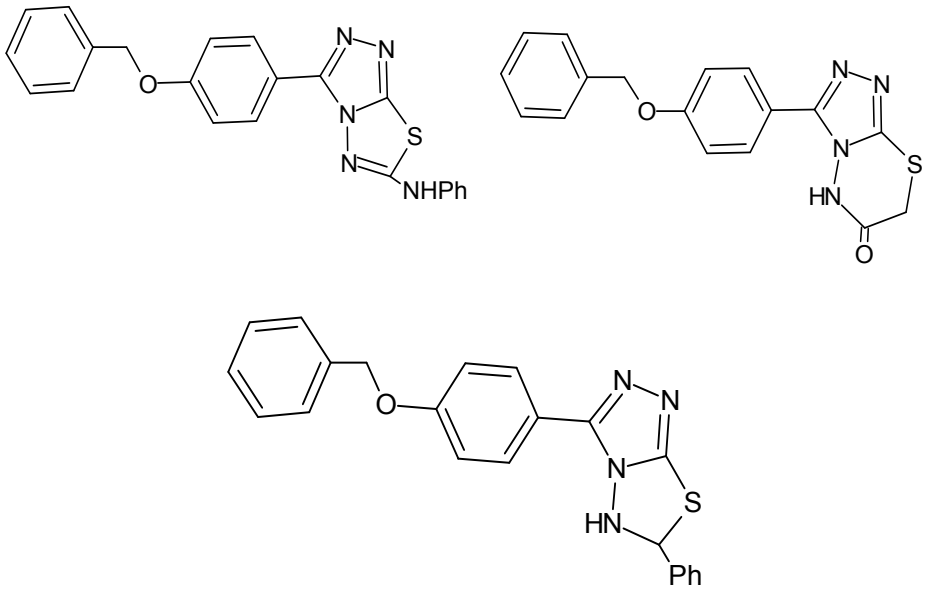
V.Ram *et al* [49] presented 2, 4 disubstituted 1, 3, 4 thiadiazole derivatives and evaluated for *invitro* antileishmanial activity. Among these, compound 63a showed 73% *in-vitro* inhibition of promastigote of *Leishmania donovani*.



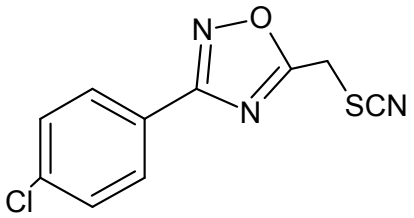
N.Rastogi et al[50] prepared a series of 4-Amino-3-(4'-benzyloxyphenyl)-5-mercapto-1, 2, 4- triazole compounds. These were screened for their antileishmanial activity against *Leishmani donovani*. Compound showed maximum inhibition among all tested compounds.





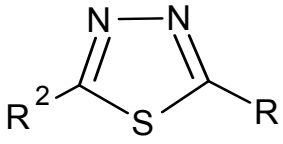


K.Werbovetz et al [51] synthesized a series of 3-aryl-5-thio cyanatomethyl-1, 2, 4-oxadiazoles. These compounds were tested against amastigotes of *Leishmania donovani*. In these 3-(4 chlorophenyl)-5-(thiocyanatomethyl)-1, 2, 4 oxadiazole showed more selectivity for *Leishmania donovani* (IC50=4.5±1.8 µM).



ANTIOXIDENT ACTIVITY

A.Padmaja et al **[52]** synthesise Some new disubstituted 1, 3, 4-oxadiazoles / thiadiazoles and 1, 2,4-triazoles some compounds are tested for antioxidant property by nitric oxide and DPPH methods. The results revealed that the compounds with oxadiazole moiety showed high antioxidant property when compared with compounds having thiadiazole and triazole moieties in both nitric oxide and DPPH methods at a 100 mM concentration. Further, it was observed that the benzyl series and exhibited greater antioxidant activity than aryl series, C.Kus et al [53] some novel 5-[(2-(substituted phenyl)-1*H*-benzimidazole-1-yl) methyl]-*N*-methyl-1, 3, 4-thiadiazole-2-amines were synthesized and tested for antioxidant properties, using various *invitro* systems. Compound , which is the most active derivative.



K Sancak et al[54] synthesise new 4-(3,4-dimethoxyphenethyl)-3,5-alkyl/aryl-4H-1,2,4-triazole and 4-(2,3-diaryl-4*H*-1,2,4-triazole-4-yl) ethyl)benzen-1,2-diol derivatives. In addition, the newly synthesized chemicals were screened for their antioxidant properties.

REFERENCES

1. Chun Q S, Wan Nian Z, Hai T J, Yun L S,Min Z, Jun Z, Jia Guo L, Jü Z, Design, Synthesis and Antifungal Activity of Novel Triazole Derivatives. Chemical Letters, 15(4): 404-407,(2004).
2. Jubie S, Sikdar P, Kalirajan R, Gowramma B, Gomathy S, Sankar S, Elango K, Synthesis and antimicrobial activity of some novel ciprofloxacin analogues. Journal of Pharmacy Research, 3: 511-13, (2010**)**.
3. Sztanke K, Tuzimski T, Rzymowska J, Pasternak K, Kandefer-Szerszeń M, Synthesis determination of the lipophilicity, Anticancer and Antimicrobial propertirs of some fuesed 1,2,4-triazole derivatives. *Eur. J. Med. Chem, 43:* 404–419, **(**2008).
4. Mevlut S, Nurhan G, Sengiil A K, Neslihan D, Synthesis of Some Novel 3,5-Diaryl- 1,2,4- Triazole Derivatives and Investigation of Their Antimicrobial Activitie .Turk J .Chem, 31;315-326, (2007).
5. Haythem A, Ibrahim M, Amal G, Mohammad S, Synthesis and Antimicrobial activity of new 1,2,4-triazole-3-thiol metronidazole derivatives. Monatsh Chem , 141:471–478, (2010) .
6. Rao G, Rajasekran S and Attimarad M ,synthesis and anti-microbial activity of some 5- phenyl-4- substituted amino-3-mercapto(4H),1,2,4-triazoles.Ind J. Pharm. Sci., 47:5-477, **(**2000).
7. Holla B , Mahalinga M, Karthikeyan M , Poojary B, Akberali P and Kumari N , European Journal of Medicinal Chemistry,40: 1173,(2005).
8. Hanane A ,Bouchra Q, Abdelkarim A, Rachid T, Nour-eddin B, Abdellah H, Mustafa T, Mohammed B and Sghirel K ,Synthesis and biological activity of new triazole compounds. Letters in drug design and discovery,7:41-45, **(**2010).
9. Demirbas N, Karaoglu S , Demirbas A, Sancak K, Synthesis and Antimicrobial activities of some new 1- (5-phenylamino-[1,3,4]thiadiazole-2 yl)methyl-5-oxo-[1,2,4]triazole and1-(4-phenyl-5-thioxo-[1,2,4]triazole-3-yl)methyl-5-oxo-[1,2,4] triazole Derivatives.European Journal of Medicinal Chemistry , 39: 793–804, (2004).
10. Shridhar A , Keshavayya J, Hoskeri J , Synthesis of 1,3,4 –oxadiazole incorporated azo dye derivatives as a potent biological activity molecules .International Journal of Pharmacy & pharmaceutical sciences , 4: 386-390, (2012).
11. Munther A and Nesreen N . Synthesis,characterization and study of antibacterial and antifungal activities of some 1,3,4- oxadiazole compounds. Journal of Chemical and Pharmaceutical Research , 4(1):315-321, (2012).
12. Mohamed A , Mohammad S, Bioorganic & Medicinal Chemistry Letters, 17: 3314–3316, (2007).
13. Parikh P, Marvaniya H, Sen D, Synthesis and biological evaluation of 1,3,4-oxadiazole derivatives as potential antibacterial and antifungal agents. Int J Drug Dev and Res , 3 (2): 248-255, (2011).
14. Ponnilavarasan I, Ayaluraja S, Sundaramoorthi C, Bhalchandra K , Synthesis ,characterisation & antimicrobial activity of 1,3,4 –Oxadiazole derivatives.Journal of

pharmacy research , 4(6):1696-1698, (2011).
15. Kumar R , Perumal S, Menéndez J , Perumal Y, Antimycobacterial activity of novel 1,2,4-oxadiazole- pyranopyridine /chromene hybrids generated by chemoselective 1,3-dipolar cycloadditions of nitrile oxides. Bioorg. Med. Chem, 19: 3444–3450, (2011).
16. Cherkupally S ,Chandrashekar R, Vookanti Y and Adki N, Synthesis & Antimicr- Obial study of bis –[thiadiazole-2-yl-tetrahydro-2H-pyrazolo[3,4-d][1,3 thiazole] methanes.Org.Communication, 3(3):57-69, (2010).
17. Barve A ,Joshi A , Kumar N , Gehlot S , Subhedar N ,Daniel V ,Singh P, Synthesis, characterisation &antimicrobial activity of Azole substituted derivatives. International Journal of Pharmaceutical sciences & Drug Research, 1(3):207- 210, (2009).
18. Lamani R, Shetty N, Kamble R, Khazi I, Synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazole derivatives. Eur J Med Chem ,xxx: 1-6. (2009).
19. Mirzaei F, Siavoshi S, Emami Safari F,, Khoshayand M, Shafiee A, Foroumadi A , Synthesis and in vitro anti-Helicobacter pylori activity of N-[5-(5-nitro-2-heteroaryl)-1,3,4-thiadiazol-2-yl]thiomorpholines and related compounds. Eur J Med Chem ,43: 1575-80, (2008).
20. Talath S, Gadad A, Synthesis, antibacterial and antitubercular activities of some 7- [4-(5-amino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl]fluoroquinolonic deriva tives. Eur J. Med Chem , 41: 918–24, (2006).
21. Srivastava K , Kumar A and Singh R, Bivalent transition metal complexes of tridentate schiff base ligands: An ecofriendly Study. J. Chem. Pharm. Res. ,2(6):68-77, (2010).
22. Mathew V, Keshavayya J, Vaidya V, Giles D, Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues. Eur J Med Chem,42:823-40, (2007).
23. Madhav N, Nayak A, Rao J, and Sarangapani M, Synthesis of Some new 1,3,4- thiadiazoles as antimicrobial agents. J Pharm Res, 4 (5):1396- 97, (2011).
24. Patel D and singh A, Synthesis, Charaterization and Antimicrobial activity of metal chelates of 5-[4-Chlorophenyl (1,3,4)thiadiazol-2-ylaminomethylene]-hydroxy quinoline. E-Jour Chem, 6(4):1017-22, (2009).
25. Prajapati S.,Goswami K and Patal A, Synthesis and characterisation of 4-Aryl thiazole ring system and its antimicrobial activity. Int J Pharm Bio Sci ; 4(1): 803 – 808 (2013).
26. Hunashal R and Satyanarayana D, One pot synthesis of 3-(substituted phenoxy methy) -6-phenyl /substituted phenoxymethyl-1,2,4-triazolo(3,4-B)-thiadiazole derivatives as antimicrobial agents. Int J Pharm Bio Sci ; 3(4):183 – 192 (2012).
27. Singh I, Kaur H ,Kumar S and Kumar A ,Synthesis and antimicrobial activity of some new Pyridinyl /Quinazolinyl /Azetidinyl /Thiazolidinonyl Triazoles. International Journal of Pharma and Bio Sciences ,V1(1) : 1-17, 2010.
28. Pandey S,Laxmi B, Biological activity of Mannich bases. Ind. J. Pharm. Sci. 65(3) 213-222, (2003).
29. Bozena M and Jacek B, Synthesis and biological activity of new derivatives of 3(3,4-diaryl-1,2,4-triazole-5-yl) propenoic acid. EuropeanJournal of Medicinal Chemistry ,39: 873–877, (2004).
30. Li-J G , Cheng-X W, Jing-H J , Li-M Z, Zhe-S Q, Design and synthesis of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives with anticonvulsant activity. Bioorganic & Medicinal Chemistry, 15: 6775–6781, (2007).
31. Kshirsagar A, Mrunmayee P T,Microwave assisted synthesis of Potential anti infective and anticonvulsant Thiosemicarbazones. Int.J. ChemTech Res, 1 (3): 696-701 , (2009)
32. John M, Kane et al,J. Med. Chem, 37: 125, (1993).

33. Almasirad A, Tabatabai S, Faizi M, Kebriaeezodeh A, Mehrabi N, Dalvandi A, Shafie A,Synthesis and anticonvalsant activity of new 2'-substituted-5-[2-(2-Fluro phenoxy)Phenyl]-1,3,4-Oxadiazole and 1,2,4-Triazoles. Bioorg Med Chem Lett , 14: 6057- 6059, **(**2004).
34. Mohammad S, Mohammad W ,Acta Poloniae Pharmaceutica Drug Research, 66 (4) :393-397, **(**2009).
35. Gowramma B,, Kulkarni A ,Gomathy S,, Kandula R , Synthesis And Anticonvul sant Screening Of Some Novel 1, 3, 4 - Thiadiazole Derivatives .Journal of pharmacy Research, 5(1):58-60,(2012).
36. Jatav V, Mishra P, Kashaw S, Stables J, Eur J Med Chem, 43: 1945-1954, (2008).
37. Singh A , Parthsarthy R. and Lohani M, Synthesis, characterization and Anti- infla mmatory activity *of some 1, 3, 4 - oxadiazole derivatives.* Journal of Chemica and Pharmaceutical Research, 4(1):779-782,(2012).
38. Jayashankar B, Lokanath Rai K, Baskaran N, Sathish H,, European Journal of Medici- nal Chemistry, 44: 3898–3902, (2009).
39. Manjunatha K, Poojary B, Lobo PL, Fernandes J, Kumari NS, Synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. Eur. J. Med. Chem, 45: 5225–5233, **(**2010).
40. Amir M, Kumar H, Javed SA, Bioorg Med Chem,17: 4504-4508, (2007).
41. Hafez H, Hegab M, Ahmed-Farag I, El-Gazzar A, Bioorg Med Chem Lett , 18,538-4543,(2008).
42. Shashikant R , Prajact K , Nachiket S , Sunil A ,Deepak S, Musmade I, Smita K ,Para- Pane I and Aarti V , Synthesis and biological evaluatition of some 1,3,4-thiadiazoles. Journal of Chemical and Pharmaceutical Research, 1(1):191-198, (2009).
43. Ibrahim D, Eur J Med Chem , 44: 2776-2781, (2009).
44. Terzioglu N, Gursoy A, Eur J Med Chem , 38: 781-786, (2003).
45. Mujagic H, Chen S, Geist R, Occhipinti S, Conger B, Smith C, Schuette W, Schackney S, Effects of Vincristine on cell survival, cell cycle progression and miotic accumulation in asynchronously growing Sarcoma 180 cells. Cancer Res, 43: 3591– 3597, (1983).
46. Xiang L, Xue Q , He-M, Xue X &Zhi H, Synthesis and evaluation of antitumour activities of novel chiral 1 , 2 , 4-triazole Schiff bases bearing γ- butenolide moiety. Organic and Medicinal Chemistry Letter , 2:26, (2012).
47. Biju. C, Ilango K,Docking Investigation,Synthesis&Cytotoxic studies of substituted Oxadiazole derivatives. International Journal of Pharmacy and Pharmaceutical Sciences. 4(3):262-265, (2012).
48. Aboraia S, Hamdy M, Abdel-R, Novel 5-(2-hydroxyphenyl)-3-substituted-2, 3-dihydro 1,3,4-oxadiazole-2-thione derivatives : Promising anticancer agents. Bioorganic and Medicinal Chemistry, 14: 1236–1246, 2006;
49. Ram V, Goel A, Kandpal A, Biorg. Med. Chem. Lett, 7: 651, **(**1997).
50. Rastogi N, Varma R, Singh A, *Indian J*. Heterocycl. Chem*,* 16: 112, (2006).
51. Werbovetz K, Cottrell D,Capers J, Salem M, Fradley K, Croft S, Bioorg. Med. Chem *,* 12: 2815, **(**2004).
52. Padmaja A, Rajasekhar C, Muralikrishna A and Padmavathi V,Synthesis and antioxi- dant activity of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4- triazoles. Journal of Chemical and Pharmaceutical Research, 4(1):294-302, (2012).
53. Kus C, Kilcigil G, Ozbey S, Kaynak F, Kaya M, Coban T, Eke B, Bioorg. Med. Che. 16: 4294-4303, **(**2008).
54. Kemal S, Yasemin U, Dilek U, Esra D, G¨ulcan K, Fatih C, Emrah B, Synthesis, Characterization, and antioxidant activities of new trisubstituted triazoles. Turk J Chem.36:457-466, (2012).