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Thiadiazoles: Progress Report on Biological Activities

Kempegowda, Senthil Kumar G.P.*, Dev Prakash and Tamiz Mani T.

Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Mandya District. Karnataka State

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ABSTRACT

Chemical properties of 1,3,4-thiadiazole have been reviewed in last fast five year. However, usefulness of 1,3,4-thiadiazole has a privileged system in the medicinal has been promoted advance on therapeutic potential of the system. This review provides a brief summary of medicinal chemistry of 1,3,4-thiadiazole system. The highlight some example of 1,3,4-thiadiazole containing the drug substance in the current literature. Several five membered aromatic systems having a three heteroatom at symmetrical position such as thiadiazole owing a several pharmacological activity. It covers the most active thiadiazole derivative and structural activity relationship of the most potent compounds. It acts as an important tool for medicinal chemist to develop a newer compound possessing the thiadiazole moiety that could be better agents in term of efficiency and safety.

KEYWORDS: 1,3,4-Thiadiazole, biological activity, structural activity relationship.

INTRODUCTION

Five membered heterocyclic compounds show various types of biological activity among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activity probably virtue of –N=C-S- grouping. Therapeutic importance of these rings prompted us to develop selective molecules in which substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities. Thiadiazoles have occupied an important place in drug industry, 1,3,4-thiadiazoles have wide applications in many fields. Earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs. Some of other uses are antitumor, antiinflammtory, pesticides, dyes, lubricants, and analytical reagents [1].

1,3,4-thiadiazole derivatives posses interesting biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring [2]. Approach to practice of medicinal chemistry has developed from an empirical one involving synthesis of new organic compounds based on modification of chemical compounds of known biological

activities could be better explored. It is well established that slight alteration in the structure of certain compounds are able to bring drastic changes to yield better drug with less toxicity to the host it observed that chemical modification not only alters physiochemical properties but also pharmacological properties [3].

Chemistry of Thiadiazole [4]**:**
Thiadiazole moiety act as a "hydrogen binding domain" and "two-electron donar system". Thiadiazole act as a bioisosteric replacement of thiazole moiety. So, it acts as third and fourth generation cephalosporin. Thiadiazole is a five membered ring system containing sulphur and nitrogen atom. They occur in four isomeric form *viz.*, 1,2,3-thiadiazole (1), 1,2,4-thiadiazole (2), 1,2,5-thiadiazole (3), 1,3,4-thiadiazole (4). Its dihydro derivative provides bulk of literature on thiadiazole.

1, 2 , 3-Thiadiazole

(1)

1, 2 , 4-Thiadiazole

(2)

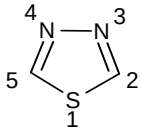
1, 2 , 5-Thiadiazole

(3)

1, 3 , 4-Thiadiazole

(4)

The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence, the numbering of 1,3,4-thiadiazole (4) is done in the following manner. This designated that one sulphur group is present in the ring.

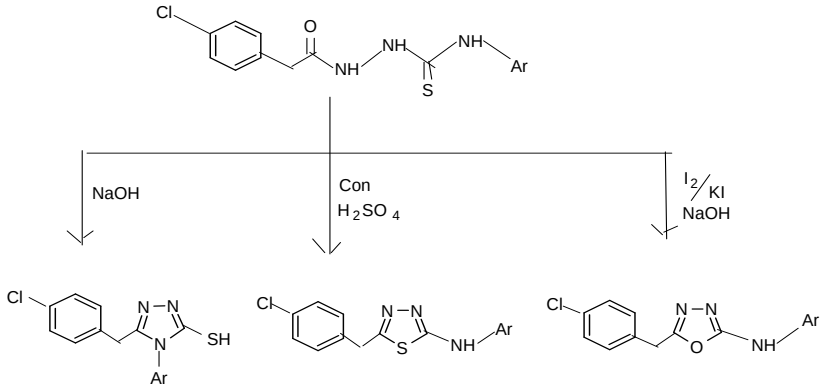


(4)

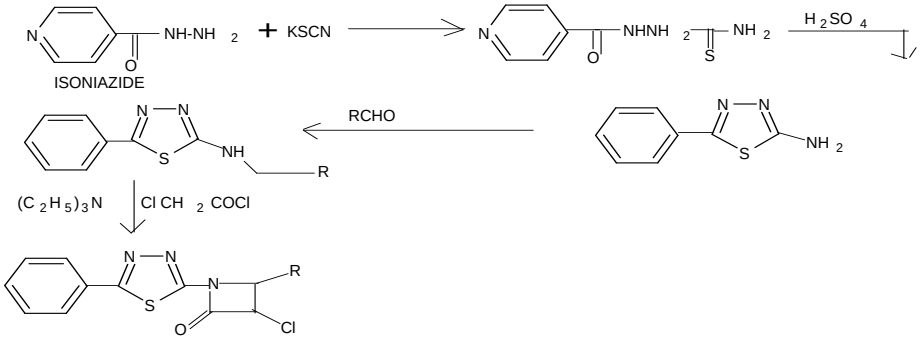
Synthesis of 1.3,4-thiadiazoles:
Thiadiazoles can be synthesized from mainly thiosemicarbazide or hydrazide that is thiadiazole can cyclized from thiosemicarbazide or hydrazide by methods like conventional method, ultrasound or microwave using catalyst like H_2SO_4, $POCl_3$, CS_2, polyphosphoric acid and HCl.

Methods of synthesis of 2,5-disubstituted-1,3,4-thiadiazoles:
Important new general routes of 1,3,4-thiadiazole have been reported, The major routes are:

From Thiosemicarbazides:
a. Desai *et. al.* [5] synthesized 2-(2-(4-chlorophenyl)acetyl)-*N*-aryl hydrazine carbothioamides were prepared by reacting 4-chlorophenyl acetyl hydrazide and aryl isothiocyanate in the presence of ethanol. Various 5-(4-chloro-benzyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols 2,5-(4-chloro benzyl)-N-aryl-1,3,4-thiadiazole-2-amine have been prepared by the cyclization with sodium hydroxide, sulphuric acid and iodine in potassium iodide in presence of sodium hydroxide.

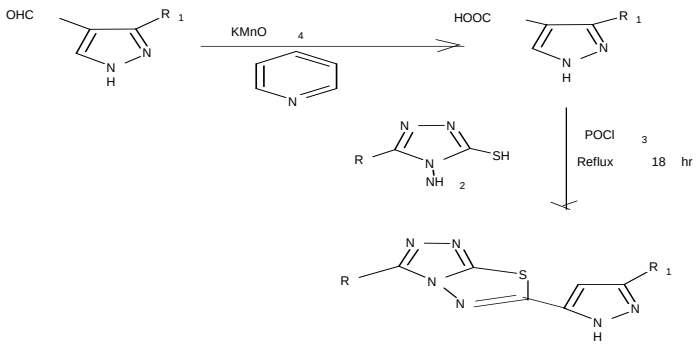


b. Joseph Valarmathy *et. al.* [6] synthesized 5-(pyridine-4yl)-1,3,4-thiadiazole-2-amine has been synthesized by reacting isonicotinohydrazide with potassium thiocyanate on further cyclo condensation with concentrated sulphuric acid. The compound reacted with various aromatic aldehydes in the presence ethanol which on further cycloaddition with chloroacetyl chloride and triethylamine in DMF.



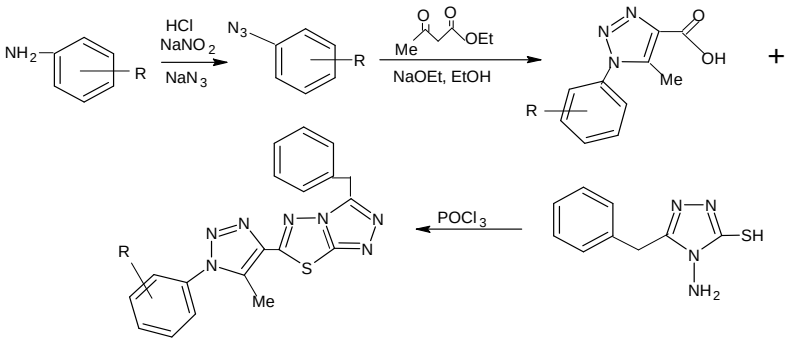
By using phosphorous oxychloride

a. Dhanya Sunil *et. al.* [7] synthesized 3,6,-disubstituted 1,2,4-triazolo(3,4-b)-1,3,4-thiadiazole from 3-substitued-4-amino-5-mercapto-1,2,4-triazoles and 3-substituted 4-caboxy pyrozoles, naphthyl oxymethyl and flurophenyl group as substituent. Presence of fluoro-substituent and aromatic naphthalene ring was found to enhance activity. The difference in electro negativity between fluorine and carbon created a large dipole moment which contributed to the molecule ability to be engaged in intermolecular interactions.



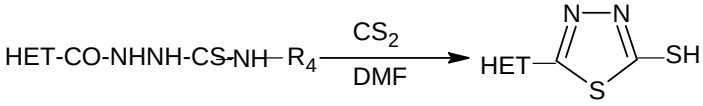
b. Pokhodylo *et. al.* [8] synthesized 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol with 5-methyl-1-aryl-1*H*-1,2,3-trazole-4-carboxylic acids in phosphorus oxychloride. It was established reaction performed with closuring thiadiazole ring. Thus by the reaction of 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol with 5-methyl-1-aryl-1*H*-1,2,3-triazole-4-

carboxylic acid new 3-benzyl-6-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-yl)(1,2,4)triazolo(3,4-b)(1,3,4)thiadiazole.

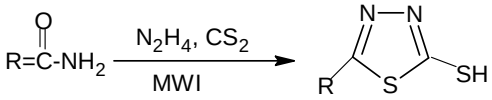


By using carbon disulphide

a. Dhiman *et. al.* [9] synthesized thiosemicarbazide with carbon disulphide and DMF under result formation of 5-(3-aryl-1*H*-pyrazole-5-yl)-2-mercapto-1,3,4-thiadiazoles.



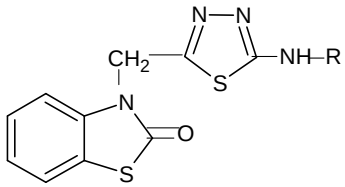
b. Mazaahir Kidwai *et. al.* [10] synthesized thioamides were treated with hydrazine hydrate followed by carbon disulphide solution. The reaction mixture was irradiated in a microwave oven to yield 5-substituted-2-mercapto-1,3,4-thiadiazoles.



Biological activities of 1,3,4-thiadiazole

Antinociceptive activity.

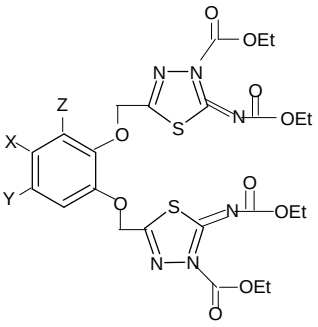
Tijen Onkol *et. al.* [11] synthesized and antinociceptive activity of 2-(2-oxobenzothiazolin-3-yl)methyl)-5-aminoalkyl/aryl-1,3,4-thiadiazole the compound were screened antiallergenic and antihistaminic agents.



R=ethyl, methyl, allyl, phenyl,cyclohexyl

Antitumor Activity

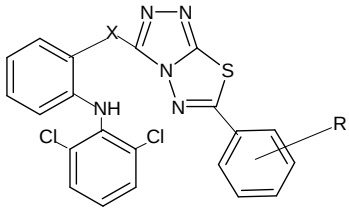
Kemal Sancak *et. al.* [12] synthesized 2-acylamino 2-aroylamino and ethoxycarbonyl imino-1,3,4-thiadiazoles as antitumor agents.



X=H, Y=H, Z=H,OCH_3

Cytotoxic Activity

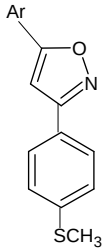
Kaliappan Ilango *et. al.* [13] synthesized and cytotoxic activity of 3,6-disubstituted 1,2,4-triazole-(3,4-b)-1,3,4-thiadiazoles as potential antileishmanial activity aganist standard drug Doxorubicin at concentration 10µM.



R=-3-Chloro, -4-Chloro, -4-nitro, -2-methoxy,
X= $-CH_2$, $-CH_2COOCH_2$

Anti-inflammatory Activity

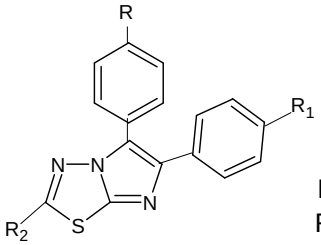
Karabasanagouda *et. al.* [14] synthesized some new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety as potential analgesic and anti-inflammatory activity aganist standard drug Analgin and Diclofenac Sodium at concentration 25 mg/kg.



Ar= 8-quinolinyl, 2-furyl,
2-amino-3-pyridyl

Cyclooxygenase Activity

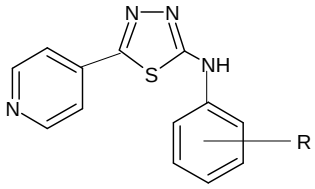
Andanappa Gadad *et. al.* [15] synthesized and biological evaluation of 2-trifluoromethyl/Sulfonamido-5,6-diaryl substituted imidazo(2,1-b)-1,3,4-thiadiazoles: a novel class of cyclooxygenase-2-inhibitiors as potential the anti-inflammatory activity using standard drug Celecoxib at concentration 10 mg/kg.



R=H, OCH_3
R_1= SCH_3, SO_2CH_3,
R_2=CF_3, SO_2NH_2

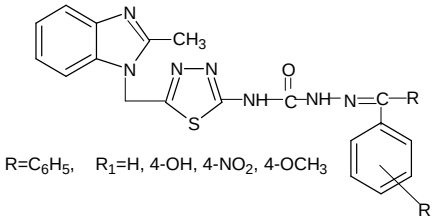
Anticonvulsant Activity

Mohammad Shahar Yar *et. al.* [16] synthesized and anticonvulsant activity of substituted oxidiazole and thiadiazole derivatives using eletrocovulsometer using standard drug Phenytoin Sodium at concentration 25 mg/kg.



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

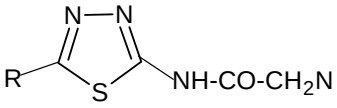
Harish Rajak *et. al.* [17] synthesized novel 2,5-disubstituted 1,3,4-thiadiazoles as potential anticonvulsant activity using standard drug Carbamazepine and Phenytoin at concentration 30 and 100 mg/kg.



R=C_6H_5, R_1=H, 4-OH, 4-NO_2, 4-OCH_3

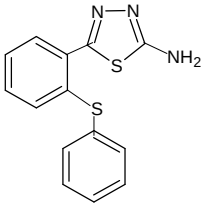
CNS Depressant Activities

Ashok Shakya *et. al.* [18] synthesized and biological activity of 2-substituted ethanamido-5-alkyl-1,3,4-thiadiazoles as potential the CNS depressant, spasmolytic activity using standard drug Acetylcholine at concentration 12 to 32 mg/ml.



Muscle Relaxant Activites

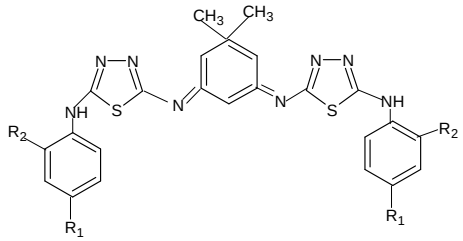
Ali Almasirad *et. al.* [19] synthesized anticonvulsant and muscle relaxant activities of substituted 1,3,4-oxidiazole, 1,3,4-thiadiazole and 1,2,4-triazole using standard drug Diazepam at concentration 10ml/kg.



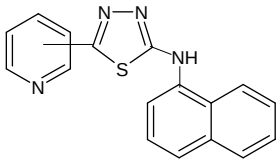
Antimicrobial Activity

Anti bacterial activity

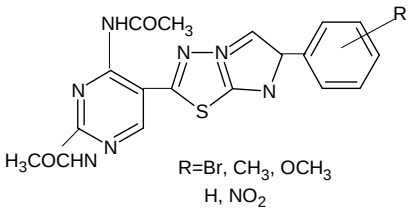
Vijay Dabholkar *et. al.* [20] synthesized and biological studies of *bis* thiadiazole/triazole by sonication as potential antibacterial activity using standard drug Ampicillin Trihydrate at concentration 50µg/ml.



Khosrow Zamani *et. al.* [21] synthesized and antimicrobial activity of some pyridyl and napthyl substituted 1,2,4-triazole and 1,3,4-thiadiazole derivatives against *S. aureus* and *E. coli*.

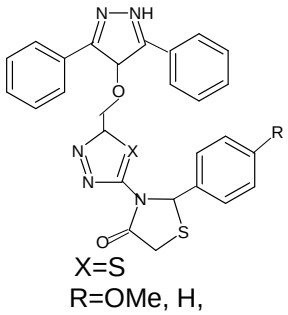


Ramappa *et. al.* [22] synthesized and evaluations of antibacterial activity of some new *N*,*N*-(5-(6-(4-subsitutedphenyl) imidazo(2,1-b) (1,3,4)-thiadiazole-2-yl)-pyrimidine-2,4-diyl) di acetamide derivatives against *E. coli, Staphylococcus aureus* and *Bacillus subtillis* using cup-plate-agar diffusion method using standard drug Methotrexate at concentration 50 µg/ml.

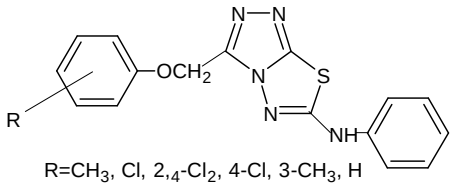


Antifungal activity

Anand Kumar Dubey *et. al.* [23] synthesized and antifungal activity of 5-(3,5-diphenyl pyrazol-4-yloy methyl)-2-(4-oxo-2-substituted phenyl-3-thiazolidinyl)-1,3,4-oxidiazoles/thiadiazoles and related compounds against *F. oxysporum, C. capsicum* and *R. solani* using standard drug Dimethyl formamide at concentration 25 µg/ml.



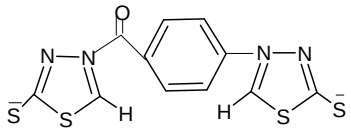
Nizamudin *et. al.* [24] synthesized and fungicidal activities of 3-aryloxymethyl-6-substituted-1,2,4-triazolo(3,4-b)-1,3,4-thiadiazoles against species *Aspergillus flavus* and *Aspergillus niger* using standard drug Dithane at concentration 100 ppm.



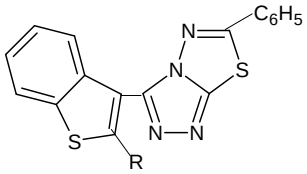
R=CH_3, Cl, 2,4-Cl_2, 4-Cl, 3-CH_3, H

Antitubercular activity

Johnson *et. al.* [25] synthesized 3-(2-sulphido-1,3,4-thiadiazolium-4-carbonyl-phenyl)syndones and 4-(4-(2-sulphido-1,3,4-thiadiazolium)benzoyl)-1,3,4-thiadiazolium-2-thiolates from 3-(4/3-(hydrazine carbonyl)phenyl) syndones, and their antimicrobial and anti tubercular activity against *M. tuberculli* using standard drug Cotrimoxazole and Fluconazole at concentration 100 µg/ml.



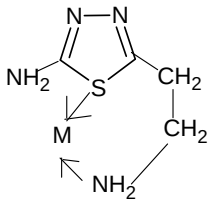
Mahendra Shiradkar *et. al.* [26] synthesized and bioactivity of *s*-triazolo(3,4-b)(1,3,4)thiadiazoles, *s*-triazolo(3,4-b)(1,3,4) thiadiazines and *s*-triazolo(3,4:2,3)-thiadiazino(5,6-b)quinoxaline as potential anti-tubercular activity against *M. tuberculli* using standard drug Rifampicin at concentration 0.03 µg/ml.



R=$NHCOCH_3$

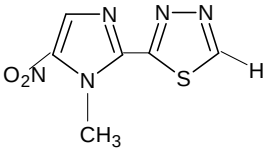
Metal Complexes

Mihai Barboiu *et. al.* [27] synthesized and biological activity of metal complexes of 5-(2-aminoethyl)-2-amino-1,3,4-thiadiazole as potential antifungal activity against *Aspergillus* and *Candida spp* using standard drug Clotrimazole at cocentration10µM.



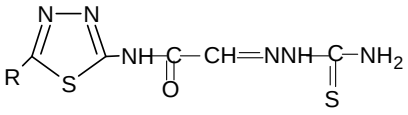
Antiprotozoal Activites

Shafiee Yazdikarimy *et. al.* [28] synthesized 1-methyl-2-(1,3,4-thiadiazole-2-yl)-5-nitroimidazole and 1-methyl-2-(1,3,4-oxidiazoles-2-yl)-5-nitroimidazole as potential antiprotozoal agents.



Antiviral Activities

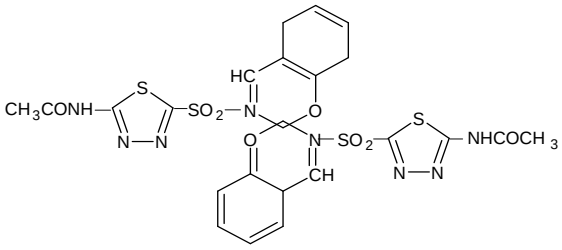
Giri *et. al.* [29] synthesized *N*-(5-Aryl/aryloxymethyl-1,3,4-thiadiazole-2-yl)glyoxylamide thiosemicarbazone as potential antiviral and antifungal agents against *Alternaria brassicae* and *Helminthosporium oryzae* using standard drug Bavistin and Dithane at concentration 45 µg/ml.



R=aryloxy methyl

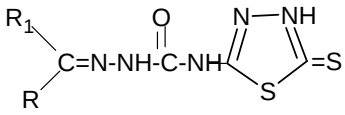
Diuretic Activites

Suparana Ghosh *et. al.* [30] synthesized, characterization and biological studies of Zn(II) complex of schiff base derived from 5-acetazolamido 1,3,4-thiadiazole-2-sulphonamide as potential diuretic agents using standard drug Acetazolamide.



Carbonic anhydrase inhibitor activity

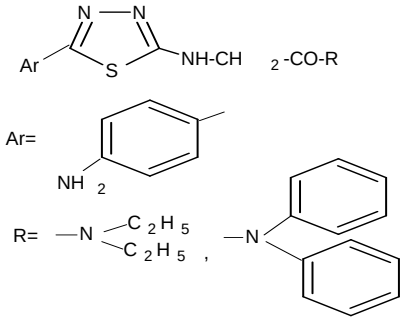
Mohammed *et. al.* [31] synthesized and docking studies of new 1,3,4-thiadiazole-2-thione derivatives with carbonic anhydrase inhibitory agents using standard drug Acetazolamide.



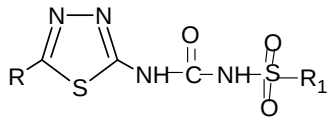
R=H, CH_3, C_6H_5,
R_1=C_6H_5, 4-(OH)C_6H_4,
3(Br)C_6H_4, 4-(F)C_6H_4,
C_6H_5, 3-pyridyl, 2-furyl,

Antidiabetic Activities

Shashikant Pattan *et. al.* [32] synthesized and biological evaluation of some 1,3,4-thiadiazoles as potential the anti-diabetic.



Ameya Chavan *et. al.* [33] synthesized and biological activity of sulphanyl urea as potential anti-diabetic agent using standard drug Gliclazide at concentration 200mg/kg.

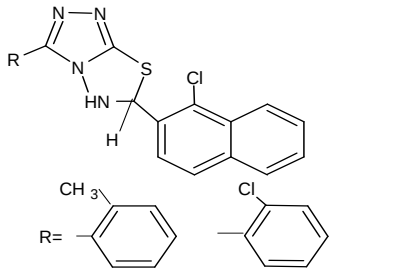


R= phenyl, methyl phenyl, chloro phenyl, methyl

R_1= phenyl methyl

Antioxidant Activities

Poonam Kamotra *et. al.* [34] synthesized and biological activity of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6-dihydro-*s*-trizolo (3,4-b) (1,3,4) thiadiazoles as potential the antioxidant and antibacterial agent against *Escherichia coli* and *Staphylococcus aureus* using standard drug Sodium Nitroprusside at concentration 5µM.

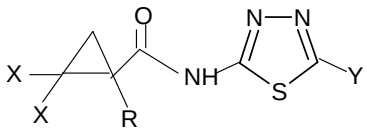


Phenyl, CH_3, C_2H_5, $CH_2CH_2CH_3$

R_1=H,OH, Cl, NO_2 R_2=OH, NO_2, Cl, R_3=OH, H, NO_2 R_4=H, OH, OCH_3

Acaricidal Activites

Yasushi Shiga *et. al.* [35] synthesized and acaricidal activity of *N*-(1,3,4-thiadiazole-2-yl)cyclopropanecarboxamides against *Tetranychus urticae.*



R=H, CH_3, C_2H_5, n-C_3H_7, i-C_3H_7

X=H, Cl, Br

Y=CF_3, CF_2CF_3, H, CH_3, C_2H_5

CONCULSION

Thiadiazole are the most important classes of heterocyclic compounds and possess versatile type of biological activities; have exist anti-cancer, anti-tubercular, anti-bacterial, anti-fungal, anti-malarial, anti-inflammatory, anti-helmentic and anti-hypertensive activities. Thiadiazole heterocycles that have been reported to date illustrates different approaches to the challenge of preparing these bioactive products. In general, thiadiazole are prepared by appropriate rearrangements, ring opening and substitution reaction. Thiadiazole rings continues to grow, and the organic chemistry will provide more and better methods, more active, more specific and safer.

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