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Biological Activities of Thiadiazole Derivatives: A Review

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Abstract: Thiadiazole and its derivatives are important organic reaction intermediates and they have been widely used as anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, antiviral, diuretic and muscles relaxant activity. Generally, synthesis of the thiadiazole derivations needs high temperature ($\geq 100^0$C) or low temperature ($< 0^0$C) or high pressure (at least higher than 1 atmospheric pressure), and the yields of those reactions are low. Otherwise, they could be synthesized by reacting thiocarbonyl dichloride with dithizone. A series of thiadiazole have been synthesized using an appropriate synthetic route and characterized by elemental analysis and spectral data.
Key words: Thiadiazole, Biological activity, Synthesis.

1. INTRODUCTION:

The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as "hydrogen binding domain" and "two-electron donor system". It also acts as a constrained pharmacophore. 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. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms viz. 1,2,3- thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole.

Thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system, which leads to great in vivo stability and generally, a lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties are obtained.

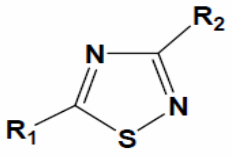
1.1. Chemistry of Thiadiazole moiety:

A series of thiadiazole have been synthesized using an appropriate synthetic route and characterized by elemental analysis and spectral data.

There are various types of thiadiazole rings are present:

- 1, 2, 4-Thiadizole
- 1, 3, 4-Thiadizole
- 1, 2, 5-Thiadizole
- 1, 2, 3-Thiadizole

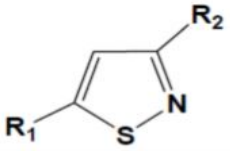
1, 2, 4-Thiadiazole moiety:



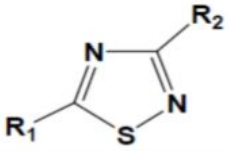
1,2,4-thiadiazole

1,2,4 –Thiadiazole moiety contain sulfur at position -1, and two nitrogen atom at position -2 & position -4.

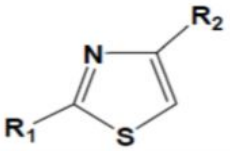
The photochemistry of 1, 2, 4-thiadiazoles is of interest because the ring system can be viewed as a combination of a thiazole and an isothiazole[1].



isothiazole



1,2,4-thiadiazole

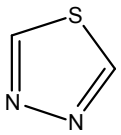


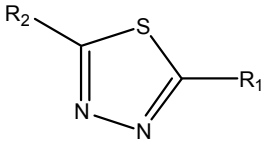
thiazole

Therefore, 1, 2, 4-thiadiazoles would be expected to undergo phototransposition reaction, via sulfur migration around four sides of the photochemically generated bicyclic intermediates, and photocleavage of the S-N bond similar to those of thiazoles and isothiazoles.

1, 3, 4 –Thiadiazole moiety:

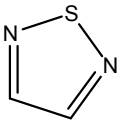
1,3,4- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1, and two nitrogen atom at position -3 & position -4.

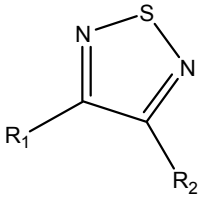




1, 2, 5-Thiadiazole moiety:

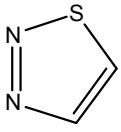
1,2,5- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1, and two nitrogen atom at position -2 & position -5.

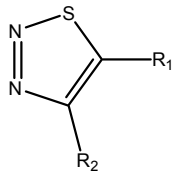




1, 2, 3-Thiadiazoles moiety:

1,2,3- Thiadiazole moiety contain a heterocyclic nucleus in which sulfur present at position -1, and two nitrogen atom at position -2 & position -3.





<u>1.2. Synthetic route:</u>

1.2.1. Synthesis of 1, 2, 4 –Thiadiazole derivatives:

The 1, 2, 4-thiadiazole ring can be synthesized by the four following methods;

(1) Oxidative cyclization of an N-thioacyl amidine (method A),

(2) Cycloaddition of nitrile sulfides with a nitrile (method B),

(3) Oxidation of thioamides or thioureas (method C),

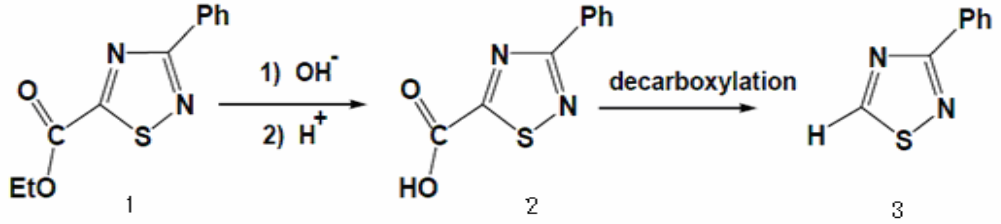
(4) Condensation of amidines with halogenated methylmercaptans (method D).

(A) (B) (C) (D)

Scheme1: Particular pathway for the synthesis of 1, 2, 4-thiadiazole ring system

Synthesis of 3-phenyl-1, 2, 4-thiadiazole:

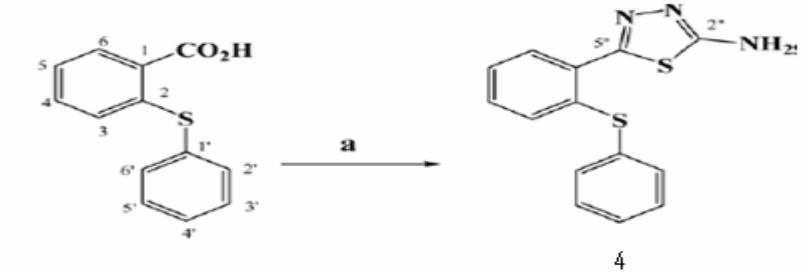
In the case of 3-phenyl-1,2,4-thiadiazole **3**, a cycloaddition of benzonitrile sulfide with ethyl cyanoformate led to the formation of ethyl 3-phenyl-1,2,4-thiadiazole-5- carboxylate **1**. Base catalyzed ester hydrolysis of 4 followed by decarboxylation of the resulting carboxylic acid produced **3** in 72% as a white solid.



1 2 3

Scheme 2

1.2.2. Synthesis of 1, 3, 4 –Thiadiazole derivatives:



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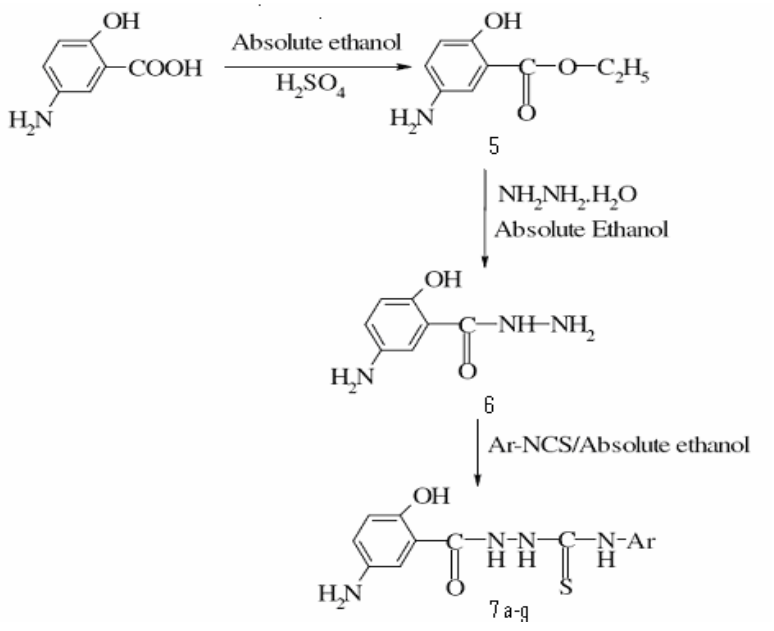
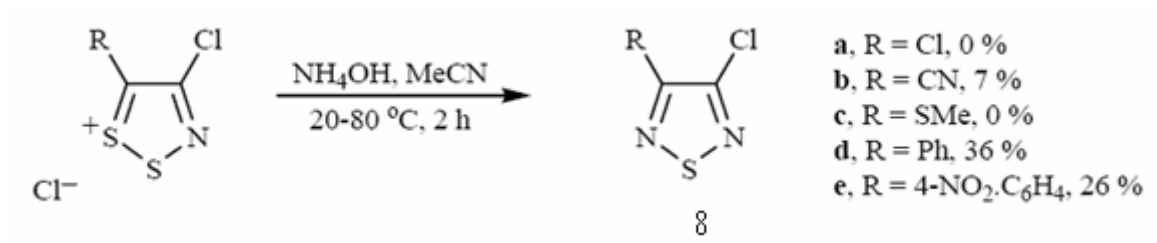
Scheme 3. 5-[2-(phenylthio) phenyl] - 1, 3, 4-thiadiazole derivatives (a: thiosemicarbazide, H_2SO_4, 120^0 C) [2]



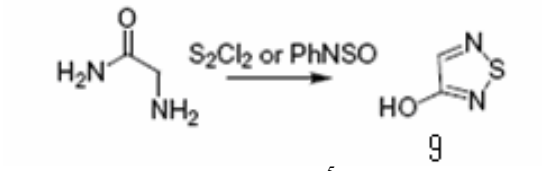
Scheme-4: Schiff bases of Thiadiazole [3]

1.2.3. Synthesis of 1, 2, 5–Thiadiazole derivatives:

Treatment of an acetonitrile solution of the 1, 2, 3-dithiazoles with aqueous ammonia gave corresponding 1, 2, 5-thiadiazoles[4].



Scheme 5

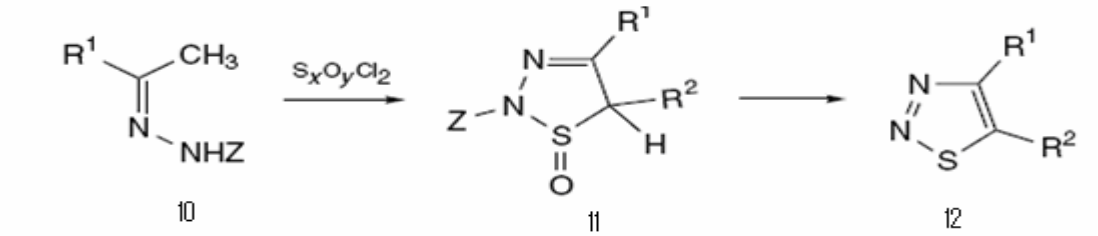


Scheme 6[5]

1.2.4. Synthesis of 1, 2, 3-Thiadiazoles:

The known methods leading to 1, 2, 3-thiadiazoles can be subdivided into five groups:
— cyclization of hydrazones with thionyl chloride (Hurd–Mori synthesis),
— cycloaddition of diazoalkanes onto a C=S bond (Pechmann synthesis),
— heterocyclization of α-diazo thiocarbonyl compounds (Wolff synthesis),
— ring transformation of other sulfur-containing heterocyclic compounds,
— Elaboration of preformed 1, 2, 3-thiadiazoles.

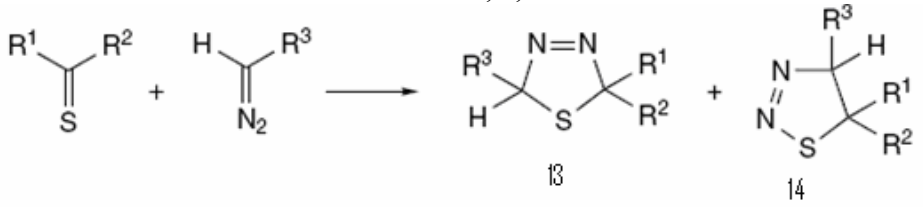
Hurd–Mori synthesis: Hydrazone derivatives10 that are substituted at N2 with an electron- withdrawing group (Z = CONH2, COOMe, COR, SO2R) and are possessing an adjacent methylene group can cyclize in the presence of thionyl chloride with the formation of 1, 2, 3-thiadiazoles **12**.



Scheme 7

Pechmann synthesis: This synthetic method, leading to 1, 2, 3-thiadiazoles, includes the reactions of diazo compounds with various thiocarbonyl compounds (thioketones, thioesters, thioamides, carbon disulfide, thioketenes, thiophosgene and isothiocyanates).

The reaction of diazoalkanes with thioketones gives mixtures of 1, 3, 4-thiadiazolines and 1, 2, 3-thiadiazolines. The ratio of the region isomers depends on the solvent polarity and steric effect. Increasing the solvent polarity and decreasing the steric hindrance favors the formation of the 1, 2, 3-thiadiazoles.



Scheme 8

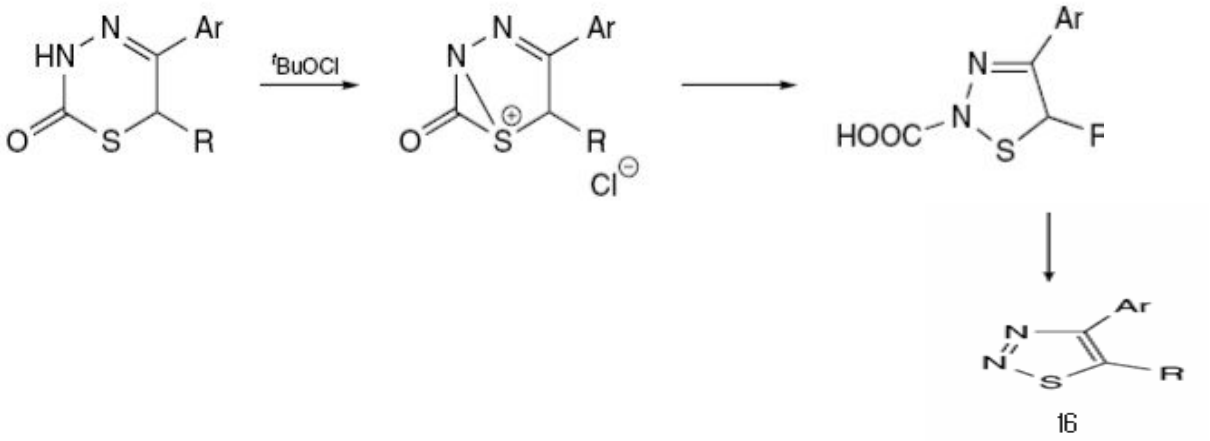
Wolff synthesis: An efficient method for the preparation of 1, 2, 3-thiadiazoles involves the generation and subsequent heterocyclization of α-diazothiocarbonyl compounds.

Wolff reported the synthesis of 5-alkyl-1, 2, 3-thiadiazoles by the reaction of 2-diazo-1, 3-dicarbonyl compounds with ammonium sulfide.

Scheme 9

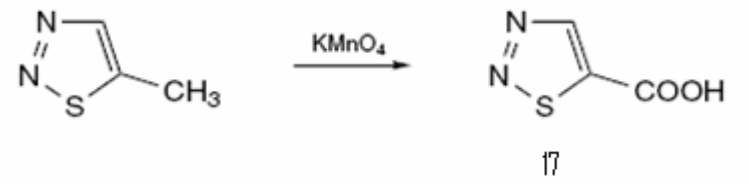
Ring transformation of other sulfur-containing heterocyclic compounds:

The 1, 2, 3-thiadiazole ring can also be obtained by the transformation of other sulfur-containing heterocycles.



Scheme 10

Elaboration of preformed 1, 2, 3-thiadiazoles: A number of 1, 2, 3-thiadiazole derivatives are best prepared by transformations of the 4- and 5-substituents of a preformed thiadiazole ring. Oxidation of 5-methyl-1, 2, 3-thiadiazole by potassium permanganate at 100^0C in water affords 1, 2, 3-thiadiazole-5-carboxylic acid in 51%yield.



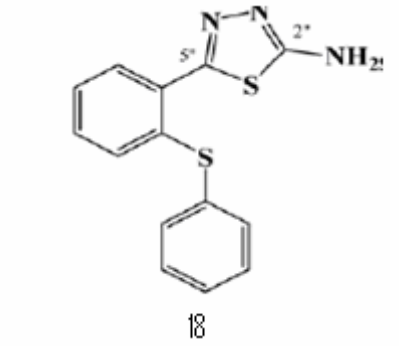
Scheme 11

2. Biological activity of Thiadiazole:

2.1. Anticonvulsant Activity

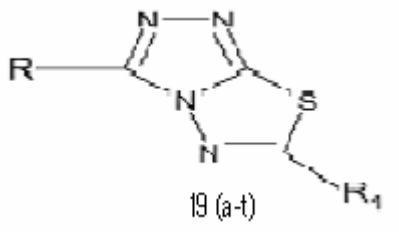
Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archived during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity.

A series of **5-[2-(phenylthio) phenyl] - 1, 3, 4-thiadiazole derivatives** were synthesized **18**. Compounds were evaluated *in vivo* for their anticonvulsant and muscle relaxant activities using PTZ and rotarod tests, ED_{50} of this synthesized compound was found to be greater than 100.



18

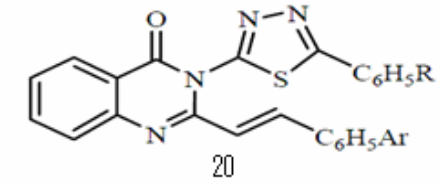
Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus system (triazolothiadiazoles) were found to have diverse pharmacological activities such as fungicidal, bactericidal, insecticidal, herbicidal, anticancer, antiinflammatory and CNS stimulant properties . They also find application as dyes, lubricants and analytical reagents[6]. The compounds that exhibited the most potent anti-MES activity included **19b, 19c, 19g, 19j, 19k, 19q** and **19r** which have activity comparable with phenytoin and carbamazepine.



19 (a-t)

R= C6H5CH2-, C6H5OCH2-, 2-OHC6H4-
R1=C6H5CONHCH2-, 2-BrC6H4-, 3-BrC6H4-, 4-BrC6H4-, 2-C6H5CO-C6H4-, C10H7CH2-, C8H6NCH2-, C6H5COCH2CH2-

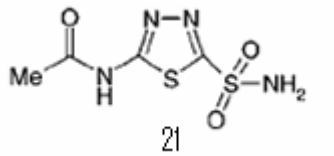
Thiadiazole with styryl and quinazoline **20** are reported to exhibit wide range of anticonvulsant, sedative, tranquilizer, analgesic, antimicrobial, anesthetic, anticancer, antihypertensive, antiinflammatory, diuretic and muscle relaxant properties.[7]



20

R=N (CH3)3, p-F, 3-NO2, 4-OH,
Ar=3-NO2, N (CH3)3, 4-Br, 4-FC6H4,

Anticonvulsant Sulfonamides Incorporating Valproyl and Other Lipophilic Moieties: The valproyl derivative of acetazolamide (5-valproylamido-1, 3, 4-thiadiazole-2-sulfonamide) was one of the best CA I and CA II inhibitor in the series and exhibited very strong anticonvulsant properties in an MES test in mice. In consequence, other 1,3,4-thiadiazolesulfonamide derivatives possessing potent CA inhibitory properties and substituted with different alkyl/ arylcarboxamido/sulfonamido/ureido moieties in the 5 position have been investigated for their anticonvulsant effects in the same animal model. It was observed that some lipophilic derivatives, such as 5-benzoylamido-, 5-toluenesulfonylamido-, 5-adamantylcarboxamido-, and 5-pivaloylamido-1,3,4-thiadiazole-2-sulfonamide, show promising in vivo anticonvulsant properties and that these compounds may be considered as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs.[8]



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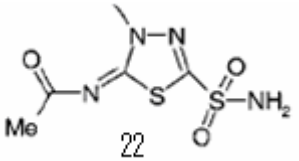

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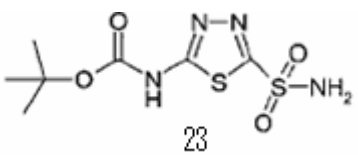

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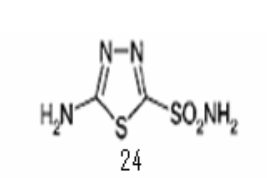

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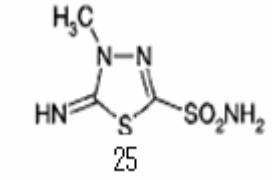

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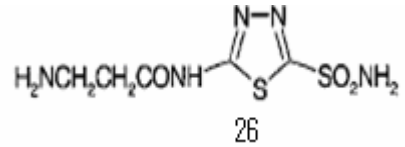

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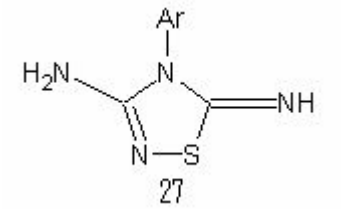
Recently, compound containing thiourea and urea groups have emerged as structurally novel anticonvulsants. Thus, a series of novel thiourea derivatives carrying the 5-cyclohexylamino-1, 3, 4-thiadiazole moiety were synthesized and their anticonvulsant activity was evaluated.[9]

A series of 3-aryl amino/amino-4-aryl-5-imino-Delta (2)-1, 2, 4-thiadiazoline compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (ScPTZ) induced seizure models in mice.[10]



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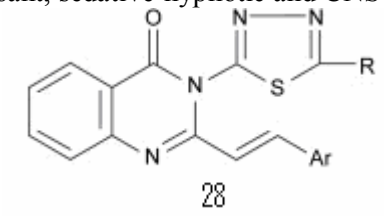
Ar = p-OC2H5-C6H4 (this is the most active compound % increase in sleep was found to be 55.6).

2.2. Antidepressant agent:

A series of novel 3-[5-substituted phenyl-1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities.[11]



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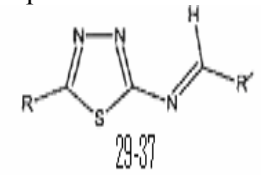
2.3. Anti- microbial agent:

Synthetic antibacterial compounds are divided into two major classes, topical agents and systemic agents. The topical agents or local anti-infective agents may be classified as antiseptics and disinfectants and constitute as important, if under appreciated, group of drugs. The topical are termed as disinfectants, antiseptics and preservatives based on how they are used.

Several five member aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties. It is also well established that various derivatives of 1, 2, 4-triazole, 1, 3, 4-thiadiazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activities. The available therapeutically important medicines are terconazole, itraconazole, fluconazole, cefazoline and ribavirin etc. are some of the examples which contain one of these heterocyclic nucleus.[12]

Schiff bases of Thiadiazole

Replacement of the morpholine C-ring of linezolid with a 1, 3, 4- thiadiazolyl ring leads to oxazolidinone analogues **33** having potent antibacterial activity against both gram-positive and gram-negative organisms. Conversion of the C5 acetamide group to a thioacetamide further increases the potency of these compounds.[13]



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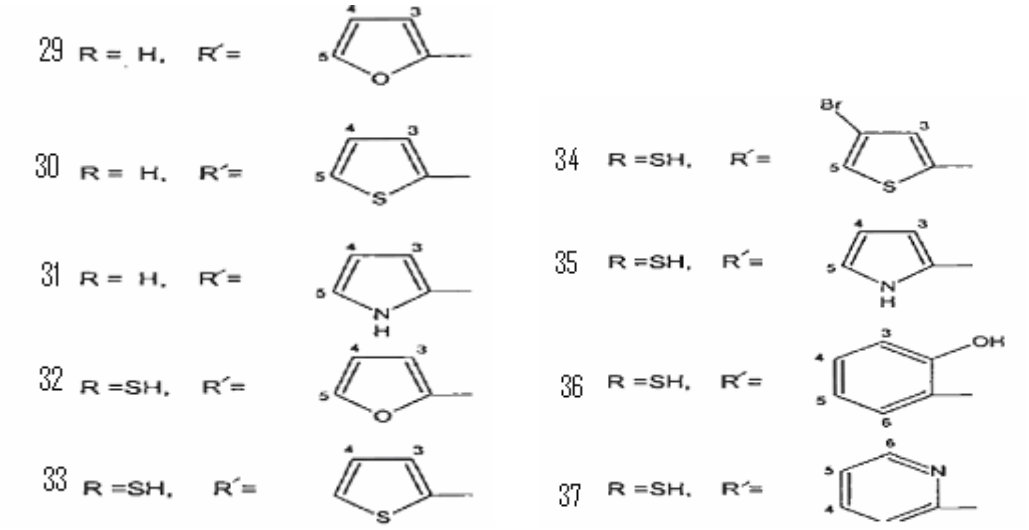
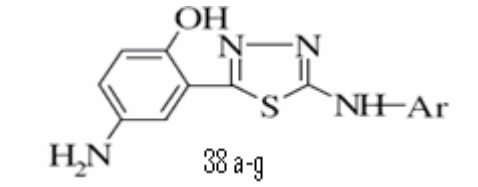
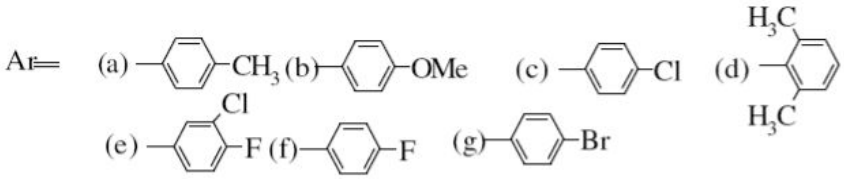


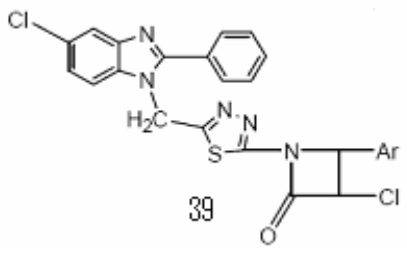
Various 4-amino-2-{5-[(4-substituted phenyl) amino]-1, 3, 4- thiadiazole-2-yl} phenol **38 a-g** were synthesized and evaluated for their antibacterial and antifungal activity. The compounds showed significant antibacterial activity against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger* fungi using cup plate technique. Compounds **38c, 38e & 38f** were found to be very good antibacterial activity against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger* (MIC value 25µg/ml).[14]





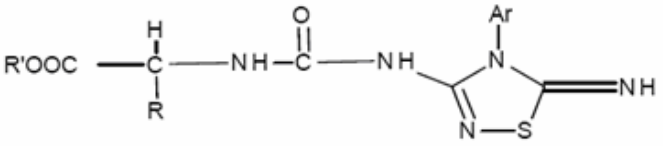
3-Chloro-1-[5-(5-chloro-2-phenyl-benzoimidazol-1-ylmethyl) - 1, 3, 4] thiadiazol-2-yl]-azetidin-2-one as Potent Antimicrobial agent:

A variety of azetidine derivatives have been successfully synthesized in appreciable yields and screened in vitro for their antimicrobial activities against both strains of Gram-positive and Gram-negative bacteria.[15] Good antibacterial activity was observed in **39b, 39c, 39e, 39g, 39h** against *B. Subtilis* compounds **39h, 39i, 39j** showed good activity against *S. aureus* compounds **39a, 39b, 39d, 39f, 39g** showed significant activity against *A. niger*.



Ar= a. 2-hydroxy-4-methoxy, b. 4-clorophenyl, c. 2-nitrophenyl, d. 4-nitrophenyl, e. 4-chloro-2-nitrophenyl, f. 2-ethoxyphenyl, g. 4-ethoxyphenyl, h. 2, 4-diclorophenyl, i. 2-clorophenyl, j. phenyl, k. 2-hydroxyphenyl, l. 4-methoxyphenyl, m. 4-hydroxyphenyl, n. 3,4,5-trimethoxyphenyl, o. dimethylaminophenyl.

The antimicrobial activity of synthesized compound was determined by paper disc method. The organisms selected for antimicrobial activity were *Bacillus substilis, Escherichia coli, Sachromyces cerviceae, Staphylococcus aureus, Pseudomonas aeruginosa, Corynebacteriun diphtheriae, Bacillus megaterium.*The synthesized compound give good antimicrobial response against the selected organisms.[16]



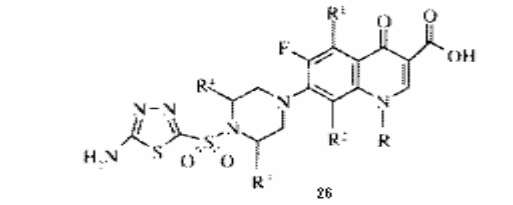
alkyl{[(5-imino-4-aryl-4,5-dihydro-1,2,4-thidiazol-3-yl) carbamoyl]amino}acetate

40

Ar	R	R'
$C_6H_5NH_2$	CH_3	CH_3
p-Cl-C_6H_4-NH_2	CH_3	CH_3
p-NO_2-C_6H_4-NH_2	CH_3	CH_3
p-CH_3-C_6H_4-NH_2	CH_3	CH_3

2.4. Anti-tubercular agents:

7-[4-(5-amino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl] fluoroquinolones have been synthesized by the reaction of appropriate N-piprazinyl FQs and 5-acetylamino-[1,3,4]thiadiazole-2-sulfonyl chloride.Compound tested exhibited pronounced antibacterial activity against the Gram-(+)ve bacteria and moderate poor activity against Gram-(-)ve bacteria and *Mycobacterium tuberculosis* strain H37Rv.[17]

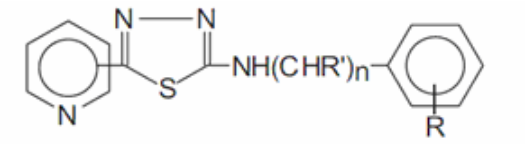


26

R= Cyclopropyl/ Ethyl;
R^1 = H, H, NH_2 H; R^2 = H, H, F, OCH_3;
R^3 = H, H, CH_3, H; R^4 = H, H, CH_3, CH_3.

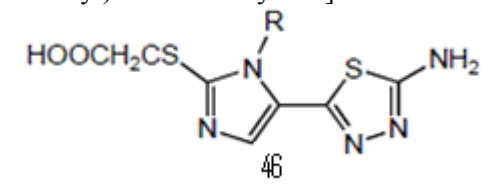
41

Synthesis of some new 2, 5-disubstituted 1, 3, 4-thiadiazoles containing Isomeric pyridyl as potent antimicrobial agents



42 a. n=1, R=R'=H
43 b. n=2, R=R'=H
44 c. n=1, R=H, R'=CH3
45 d. n=0, R=*o*- CH3

α-[5-(5-Amino-1, 3, 4-thiadiazol-2-yl)-2- imidazolylthio] acetic acids as an anti- tubercular activity.[18]

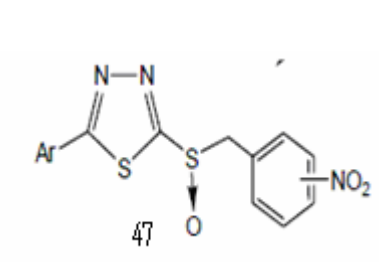


46

R= (a) CH3, (b) CH2C6H5

In continuation of research program for new antitubercular agents, some hybrid compounds containing a 5-nitrohetrocyle and 1, 3, 4-thiadiazole ring havae been synthesized and their antituberculosis activity have been evaluated.

2-(nitroaryl)-5-(nitrobenzylsulfinyl and sulfonyl)-1, 3, 4-thiadiazole derivatives, have been synthesized and evaluated against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC27294) in BACTEC 12B medium using a broth micro dilution assay.[19]



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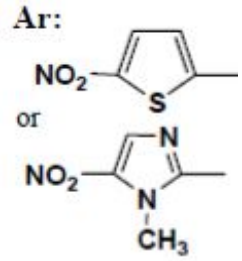
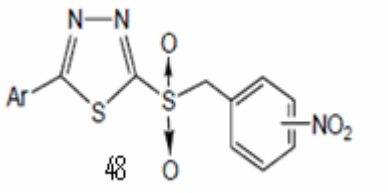
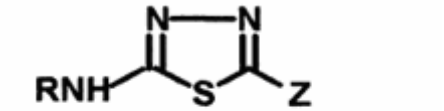




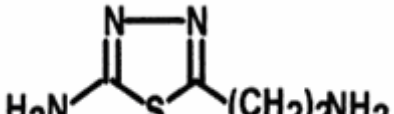
48

2.5. Anti-tumor agents:

5-amino-l,3,4-thiadiazole-derivatives such as the thiol **49**, a compound used as radioprotective agent, as well as an investigational antitumor**52** and gastroprotective drug; acetazolamide **50**, which was the first non-mercurial diuretic drug, used clinically thereafter as antiglaucoma, antiepileptic or antiulcer drug, together with a large series of its congeners derived from 5-amino-1,3,4-thiadiazole-2-sulfonamide **51**.[20]



49 R=H, Z=SH
50 R=Ac, Z=SO_2NH_2
51 R=H, Z=SO_2NH_2



52

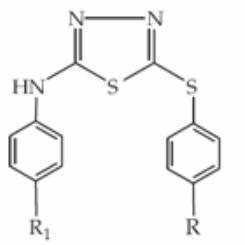
2.6. Analgesic and anti-inflammatory activity:

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the thiadiazole moiety present in some compounds possess a pharmacophoric character for the inhibition of COX.

More recently, researchers reported 1, 3, 4-thiadiazole derivatives that exhibited analgesic and anti-inflammatory activities. 5-Arylamino substituted 3-nicotinoyl/isonicotinoyl-1,3,4-thiadiazol-2(3H)-one, 5-arylamino-1,3,4-thiadiazol-2(3H)-one,3-(5-bromo-2-thienyl)-1-phenyl-4-[3-acetyl-5-(N-substitutedacetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl]-1H-pyrazol, and 2-(2-naphthyloxymethyl)-5-substituted amino-1,3,4-thiadiazole derivatives showed anti-inflammatory and analgesic activities.

2-Amino-5-sulfanyl-1, 3, 4-thiadiazoles:

A series of diaryl substituted 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives, and perform their pharmacological testing *(Sharma etal2008)*.Compound **53 & 54** show very good anti-inflammatory activity.[21]

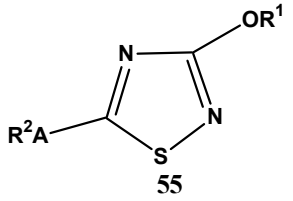


Compd. No.	R	R_1
53	$-SO_2NH_2$	–Br
54	$-SO_2Cl$	–Br

2.7. Anti-diabetic agent:

1, 2, 4- thiadiazole compound for the treatment of type-II diabetes mellitus Orally administrate pharmaceutical compositions in the form of tablets, comprising glibenclamide and metformin, or pharmaceutically acceptable salts thereof, as active ingredients, maintained separate from one another within the same composition, are described for the treatment of type-II diabetes mellitus.

The present invention relates to a novel l, 2, 4-thiadiazole compound represented by the formula: "1, 2, 4-thiadiazole compound"



55

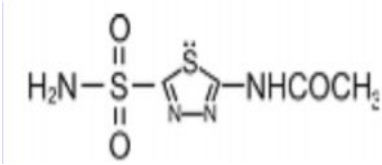
Wherein, R1 represents C3-C7 alkynyl that may he substituted with halogen; R2 represents C3-C8 cycloalkyl which may be substituted with C1-C4 alkyl, halogen atom and tritluoromethyl or the like; A1 represents a single bond, C1-C2 alkylene or C2-C3 alkylidene. The 1, 2, 4-thiadiazole compound has an excellent arthropod controlling activity, and can effectively control an arthropod pests such as insect pests, acarine pests and the like.

Sulfonylureas are the most widely used antidiabetic agents. These agents act on pancreatic ß-cells stimulating insulin secretion. 1, 3, 4-Thiadiazole, is a versatile pharmacophore which exhibits a wide variety of biological activities. A few of them which are worthy of mention are diuretic, CNS depressants, hypoglycemic, anti-inflammatory, and anti-microbial activities. It was planned to suitably incorporate the sulfonylurea moiety into the 1, 3, 4-thiadiazole ring system and to explore the possibilities of some altered biological action; hence, the following sulfonylurea derivatives were synthesized and screened for antidiabetic and antibacterial activity.[22]

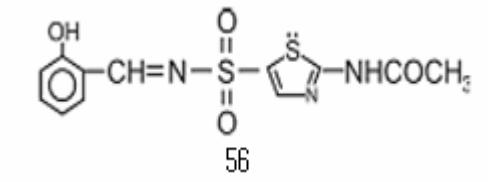
2.8. Diuretic agents:

Reaction of 3- and 4-carboxybenzenesulfonyl chloride with 5-amino-1,3,4-thiadiazole-2-sulfonamide/5-imino-4-methyl-2-1,3,4-thiadiazoline-2-sulfonamide afforded two series of benzolamide analogues to which the carboxyl moiety has been derivatized as esters or amides, in order to reduce their very polar character. The new derivatives showed low nanomolar affinity for three carbonic anhydrase (CA) isozymes, CA I, II and IV, and were effective as topical antiglaucoma agents in normotensive rabbits. Efficacy of several of the new sulfonamides reported was better than that of the standard drugs dorzolamide and brinzolamide, whereas their duration of action was prolonged as compared to that of the clinically used drugs.

Schiff base metal chelates **56 & 57** are widely applicable because of their industrial and biological importance.[23]

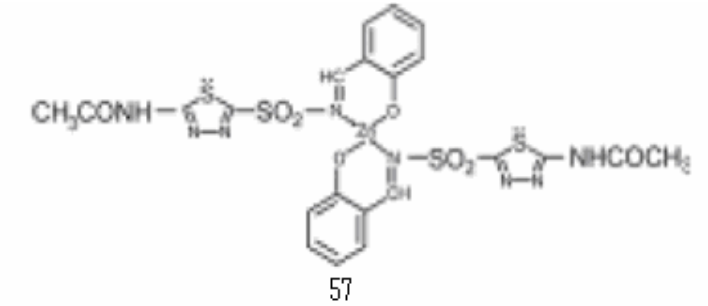


Structure of acetazolamide



56

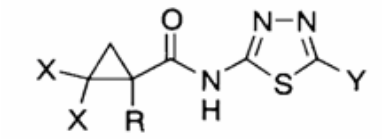
Structure of schiff base



57

Structure of complex

2.9. Thiadiazole compounds useful as Pesticides: [24]



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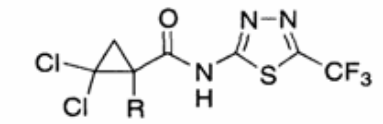
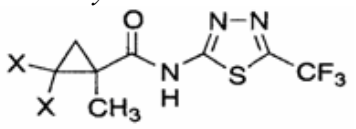


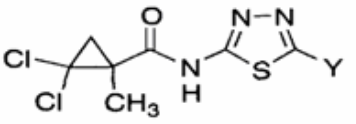
59

R=CH3 was found to be most active against *Tetranychus urticae.*



60

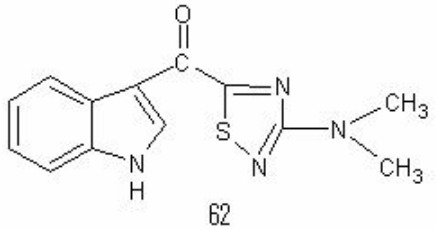
X= Cl was found to be most active against *Tetranychus urticae.*



61

Y= CF3, CF2CF3, (CF2)2CF3 was found to be most active against *Tetranychus urticae.*

2.10. Antioxidant:

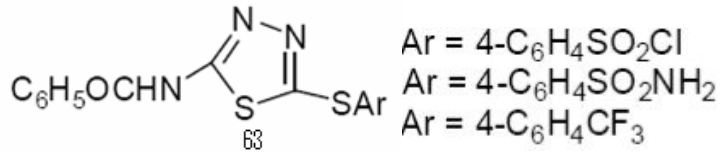


62

Dendrodoine

Dendrodoine (5-[(3-N-dimethylamino)-1, 2, 4- thiadiazolyl]-3-indanyl methanone) is an alkaloid extracted from the marine algae Dendrodoa grossularia. It possesses a 1, 2, 4- thiadiazole unit, a rarity among natural products. It is use as antioxidant.[25]

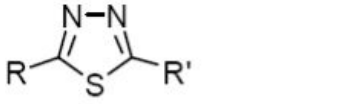
Some novel **5-[(2-(substituted phenyl)-1*H*-benzimidazole-1-yl) methyl]-*N*-methyl-1, 3, 4- thiadiazole-2-amines** were synthesized and tested for antioxidant properties by using various *invitro* systems. Compound **63** which is the most active derivative inhibited lipid peroxidation slightly at 10-3 M concentration.[26]



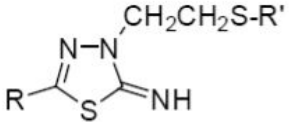
63

2.11. Radioprotective agents:

Thiol and aminothiol compounds are among the most efficient chemical radioprotectors.[27] Synthesized thiol and aminothiol compounds derived from thiadiazole structures **64a, 64b**.They examined them for their ability to scavenge free radicals (DPPH·, ABTS·+, ·OH). Thiol derivatives with a thiadiazole structure are the most active compounds scavenging DPPH· and ABTS·+ free radicals, with an IC50 of 0.053 ± 0.006 and 0.023 ± 0.002 mM, respectively, for the derivative **64a**. Moreover compound **64a** at 60 mM gave 83% protection against 2-deoxyribose degradation by ·OH. In both the test thiol derivatives were most efficient. Compound **64a** totally inhibits DNA strand breaks at the concentration of 50 mM.



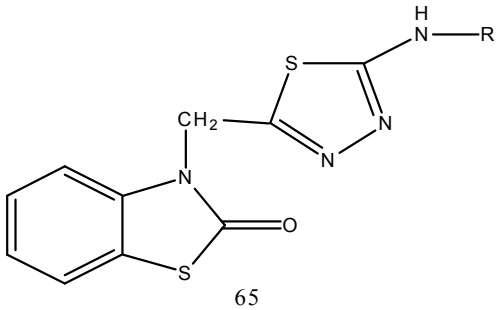
64a = R = -SCH2CH3, -CH2CH3;
R' = -SH,-NHCH2CH2SH



64b R = -SCH2CH3, -CH2CH3;
R' = -SO3H, -PO(OH)2

2.12. Antihistaminic agents:

2-Oxobenzothiazoline derivatives bearing substituents at position 3 with thiadiazole moiety have reported to exhibit antihistaminic activity.[28] Compounds **65a, 65b, 65d, 65e** and **65h** were more potent than others and the standards in tail flick test.



65

65 a. methyl, 65 b. ethyl, 65 c. allyl, 65 d. cyclohexyl, 65 e. phenethyl, 65f. phenyl, 65 g. 4-methylphenyl, 65 h. 4-clorophenyl, 65 i. 4-methoxyphenyl, 65 j. 4-nitrophenyl.

2.13. Antiplatelet agents:

Twenty 1, 3, 4-thiadiazole-2-nitrosimines and two 1, 2, 4-thiadiazole-5-nitrosimines were synthesized and assayed in the Born-test for their antiplatelet activity. Only two 1, 3, 4-thiadiazoles inhibited the aggregation at IC50 < 10 mumol/L. In an in vivo thrombosis model only in arterioles a small inhibition of thrombus formation was observed. The poor test results correspond to a very high chemical stability of the titel nitrosimines.

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