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1,3,4- THIADIAZOLE AND ITS POTENCY: A REVIEW

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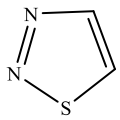
Abstract:
The Thiadiazole & their derivatives shown the number of pharmacological activities as anti-microbial, anti-inflammatory activity, anti-tubercular activity, ant diabetic activity, diuretics, anti-depressant, anti-viral, anticonvulsant, anti-oxidant, analgesic activity, antinociceptive & cytotoxic activity. These thiadiazole are the heterocyclic compound which contain the five-member ring & nitrogen & sulphur. In this paper we mention the recent derivatives of 1,3,4-thiadiazoles & their activity.

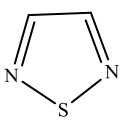
Key words: 1,3,4-thiadiazole, biological activity, Anti-Microbial, Antitubercular, Antiviral, Anticancer, Anti-inflammatory, Analgesic, Anticonvulsant, Antioxidant, Antinociceptive, Anxiolytic, Herbicidal, Triglycerides biosynthesis inhibitor etc.

Introduction:

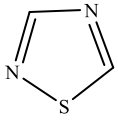
Thiadiazoles are clear to yellowish liquids which are soluble in alcohol, ether and slightly soluble in water; they are starting material for numerous chemical compounds including sulphur drugs. Thiadiazoles are easily metabolized by biochemical reactions and they are non-carcinogenic in nature. Thiadiazoles and their derivatives exhibit wide range of pharmacological activities such as antimicrobial activity, antidepressant, cardiotonic, antibacterial, anti-tubercular, anticonvulsant, antileshmanial, analgesic, anti-inflammtory, anticancer, phosphodiesterase inhibitors and effect on Tyrosinase enzyme. This diversity of biological activity may be due to the presence of -N=C-S moiety. There are four isomers of thiadiazole, among these 1,3,4-thiadiazole is the most thermally stable; which is only isomer doesn´t contain any sulphur- nitrogen bond. 1,3,4-thiadiazole relatively stable in aqueous acid solutions but the nucleus can undergo ring cleavage by aqueous base solutions.



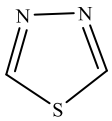
1,2,3 Thiadiazole



1,2,5 Thiadiazole



1,2,4 Thiadiazole



1,3,4 Thiadiazole

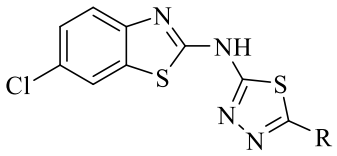
Chemistry of thiadiazole:

Thiadiazole moiety acts as a hydrogen binding domain and two electron donar system. Thiadiazole acts as a bioisosteric replacement of thiazole moiety. Thiadiazole nucleus are ring opening by strong base easy of nucleophilic attack and the formation of mesoionic compound by quaternization. The substituents in the 2,5 positions have a large effect in determining the reactivity of the molecules as a whole. Thus, the environment nucleophillicity of 2-amino thiazoles gives rise to electrophilic attack on both the amino group and the nuclear nitrogen atom. Nucleophiles easily displace halogen atom from the thiadiazole nucleus this is due to the electronegativity of the two nuclear nitrogen atom which impart a low electron density to the carbon atom of the nucleus.

BIOLOGICAL ACTIVITY OF 1,3,4 – THIADIAZOLE:

ANTIMICROBIAL ACTIVITY

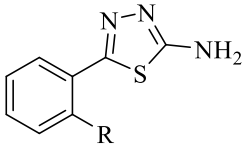
Arun Kumar et al synthesized thiadiazole from thiosemicarbazide. Thiosemicarbazide derivative on cyclisation with different aromatic carboxylic acids in the presence of $POCl_3$ formed 1, 3, 4 thiadiazole derivatives which were characterized by elemental analysis, IR, H1NMR and Mass spectral data's and screened for their antimicrobial activities and showed significant antimicrobial activities.[i]



[1]

R = Phenyl, 4-chlorophenyl, 2,4 Dichlorophenyl,4- Nitrophenyl
2-Aminophenyl, 2,4-Dichlorophenoxymethyl, 2-Naphthylmethyl,
4-Methoxyphenyl, 2-Acetoxyphenyl, 3-pyridyl

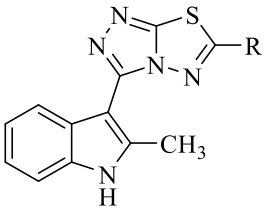
Mahendra singh M Raj et al synthesized thiadiazole derivatives by the reaction between benzoic acid 2-hydroxy benzoic acid with thiosemicarbazide using conc. H_2SO_4 as oxidising agent. The synthesized compounds were characterized by IR. H1NMR and nitrogen estimation and screened for their antibacterial and antifungal activities by paper disc diffusion technique. All the synthesized compounds showed moderate activity against bacteria and fungi. [ii]



R = H,OH

[2]

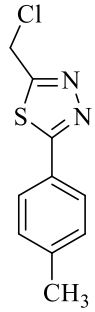
Sobhi M Gomha et al synthesized some novel compounds, namely, 3-(2-methyl-1Hindol-3-yl)-6-aryl-[1, 2, 4] triazolo [3,4-b][1, 3,4] thiadiazoles via bromination of 2methyl-3-[4-(arylideamino)-5-mercapto-4H[1,2,4triazol-3-yl]-1H indoles. New thiadiazoles, triazoles and oxadiazoles with indole moieties were prepared by the cyclization of corresponding thiosemicarbazides with microwave irradiation using different reaction conditions. The structure of the synthesized compounds was confirmed by elemental analysis and spectral analysis. The antibacterial activity of the newly synthesized compounds against Staphylococcus aureus, Bacillus subtilis, (gram-positive) E.coli(gram-negative) and antifungal activity against Candida albicans were studied under the same condition using trimethoprim as reference in Muller-Hinton agar medium by disc agar diffusion method. [iii]



R= C_6H_5, 4-CH_3 C_6H_4

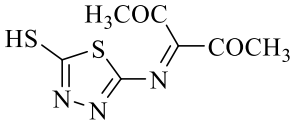
[3]

Murthy et al. synthesized some novel compounds, namely (3,5-dichloro-4-((5-aryl-1,3,4thiadiazol-2-yl) methoxy)phenyl) aryl methanones for their antimicrobial activities. The antimicrobial activity of the newly synthesized compounds was evaluated by agar well diffusion method. Antimicrobial activity of all the synthesized compounds was evaluated by measuring the zone of inhibition against the test microorganisms. Gentamicin (standard antibacterial drug) and Nystatin (standard antifungal drug) were used for comparision. The minimum inhibitory concentrations (MIC) were evaluated by the micro broth dilution technique. Some compounds showed good and other compounds showed moderate antimicrobial activities on comparision with their respective standard drugs.[iv]



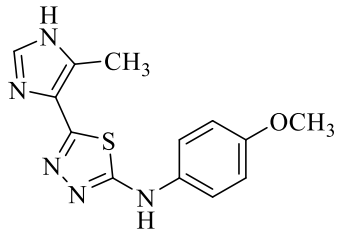
[4]

Dubey et al synthesized 1,3,4 thiadiazole1,3,5-triazine derivatives and evaluated their antimicrobial activity against bacterial stains like Pseudomonas aeruginosa, Bacillus cereus, Escherichia coli and Bacillus subtilis. The resultant MIC value for the title compounds were found in good agreement with the results of zone of inhibition. The tested compounds showed moderate antibacterial activity in comparison with cefixime as standard drug.[v]



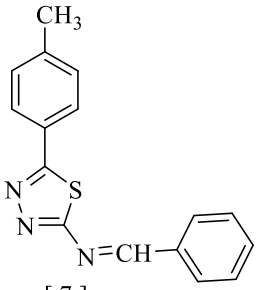
[5]

Liesen et al synthesized N-(4methoxyphenyl)-5-(5-methyl-1H-imidazol-4-yl)1,3,4-thiadiazole-2-amine derivatives. The synthesized derivatives were tested for antimicrobial activity by the disc diffusion method. In general, these results indicated weak antimicrobial activities for all compounds. However, some compounds showed significant mean zone inhibition (MZI), for bacterial stains Staphylococcus aureusand Bacillus subtilis, Escherichia coli and Mycobacterium smegmatis. One compound was found to be the most potent compound with MIC value 130µg/ml as compared with standard drug.[vi]



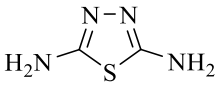
[6]

Seelam et al synthesized a novel series of N-benzylidene-5-ptolyl-1,3,4-thiadiazole derivatives and screened their antimicrobial activity. The screened compounds showed high antibacterial activity against all the stains employed. In this view some compounds showed potent activity as compared with standard drug Streptomycin against B. subtilis and B. thuringiensis.[vii]



[7]

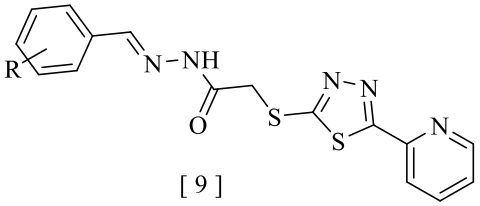
Adediji et al synthesized Cu(II) Metal Complexes of 1,3,4-thiadiazole-2,5-diamine with some semicarbazide derivatives and investigated their antimicrobial activity. Antitubercular activity was investigated against Mycobacterium tuberculosis using Microplatealamar blue assay. Amoxicillin was used as standard drug. Some compounds showed excellent antimicrobial activities on comparision with standard drug.[viii]



[8]

ANTI - TUBERCULAR ACTIVITY:

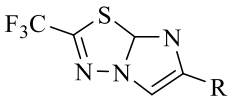
Mamolo M.G et al (2009) synthesized [5(pyridine-2yl)-1,3,4-thiadiazole-2-ylthio] acetic acid arylidenes hydrazides which showed MIC in the range of 2080µg/ml against M. tuberculosis H37RV. Another series of [5(pyridine-2-yl)-1,3,4-thiadiazole-2-ylthio] acetic acid-(3,4-diaryl-3H-thiadiazole-2-ylidene) hydrazide were found less active than the former series of compounds.[ix]



R = Methyl or Methoxy or Chlorine Group

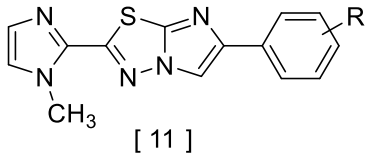
[9]

Gadad A.K et al (2004) evaluated 6-aryl-2triflouromethylimidazo [2,1-b] 1,3,4-thiadiazole derivatives against M. tuberculosis against H37RV strain by radiometric BACTEC and broth dilution method. it was found that 4-flouro phenyl derivative causes maximum inhibition at 6.25µg/ml concentration. All the synthesized compounds were reported to be less active than standard drug Isoniazid.[x]



[10]

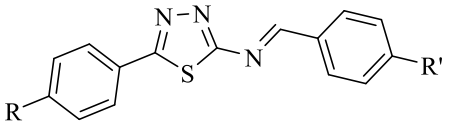
Noovi M.N et al (2013) synthesized a series of imidazo [2,1-b] 1,3,4-thiadiazole derivatives and the synthesized compounds were evaluated for their invitro antitubercular activity against M. tuberculosis H37RV strain by using Alamar Blue susceptibility test. Among the tested compounds, 2-(1-methylimidazol-2-yl)-6-(4-nitrophenyl) imidazo [2,1-b] 1,3,4-thiadiazole have shown the highest inhibitory activity with MIC of 3.14µg/ml as compared to other compounds.[xi]



R = 3-NO_2, 4 - F, 4-Br, 4- NO_2, 4-Cl, 4- CH_3, 2,4- Cl, 4-CH_3, 2,4-OH, H

[11]

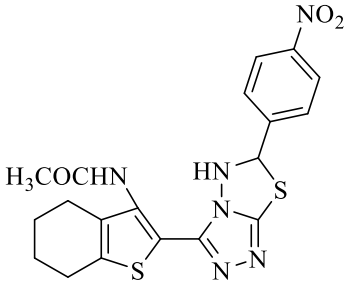
Pandey A et al (2011) synthesized a series of 2amino-5-aryl-1,3,4-thiadiazoles and screened them for their antitubercular, analgesic and anti-inflammatory activities. Antitubercular activity of compounds was judged by Rema plate method. Among the synthesized series of compounds, derivatives with chloro, hydroxy, methoxy and nitro groups were shown to possess significant activity. [xii]



R = Cl, $N(CH_3)_2$, OCH_3, NO_2
R' = OH, NO_2

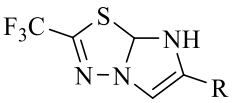
[12]

Shiradhkar M et al (2005) synthesized a series of Striazolo [3,4-b] 1,3,4-thiadiazoles and screened for their antitubercular activity against M. tuberculosis H37RV. The final data of the MIC was compared with the standard drug Rifampicin at 0.03µg/ml concentration which showed more than 95% inhibition. Among the derivatives, nitrophenyl derivatives was shown to possess maximum activity against M. tuberculosis.[xiii]



[13]

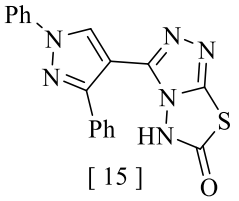
Gadad A.K et al (2004) evaluated 6-aryl-2triflouromethylimidazo [2,1-b] 1,3,4-thiadiazole derivatives against M. tuberculosis against H37RV strain by radiometric BACTEC and broth dilution method. it was found that 4-flouro phenyl derivative causes maximum inhibition at 6.25µg/ml concentration. All the synthesized compounds were reported to be less active than standard drug Isoniazid.[xiv]



[14]

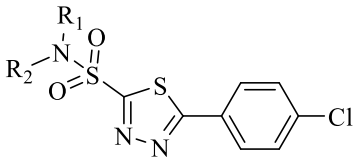
ANTIVIRAL ACTIVITIES:

Farghaly A et al (2006) synthesized a series of new 1,3,4-thiadiazoles starting from 4-amino-3-(1,3 diphenyl-1H-pyrazol-4-yl)-4,5-dinitro 1,2,4-triazolo-5- (1H)-thione and are screened for their antiviral potential. Synthesized compounds showed moderate to good activity.[xv]

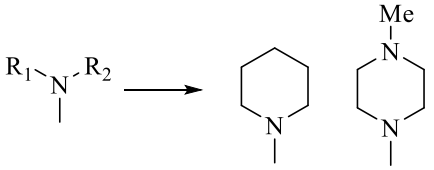


[15]

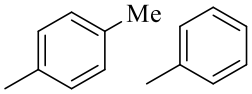
Yang S et al (2010) synthesized some new 5-(4chlorophenyl)-N-substituted-1,3,4-thiadiazole-2 sulphonamide derivatives starting from 4-chloro benzoic acid and screened for their antiviral activity against Tobacco mosaic virus by the Half Leaf method. All the synthesized compounds showed a certain degree of antiviral activity. [xvi]



[16]

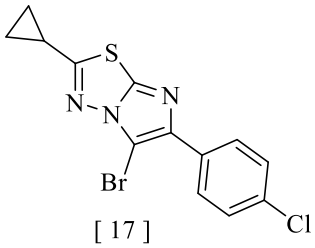


R1 = - H

R2 = 

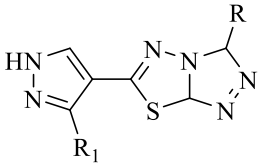
ANTICANCER ACTIVITY:

Noolvi M.N et al (2011) synthesized a series of 2,5,6trisubstituted imidazo [2,1-b] 1,3,4-thiadiazole derivatives and screened for antitumor activity. Among the synthesized compounds 5-bromo-6-(4chlorophenyl)-2-cyclopropyl imidazo [2,1-b] 1,3,4thiadiazole was found to be most active.[xvii]



[17]

Isloor A.M et al (2009) synthesized a series of 3,6disubstituted-1,2,4-triazolo [3,4-b] 1,3,4-thiadiazoles from 3-substituted-4-amino-5-mercapto-1,2,4-triazoles and 3-substituted-4-carboxypyrazoles. Newly synthesized compounds were screened for their anticancer activity in hepatic cell lines.[xviii]

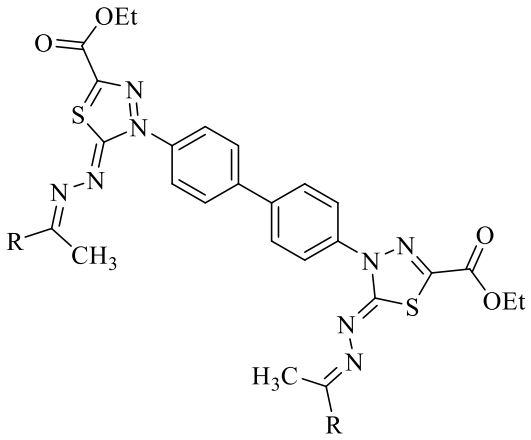


R = Phenoxymethyl
o- cresyloxymethyl
o- chloromethoxyphenyl
2- napthyloxymethyl

R1 = p- methoxyphenyl
p- fluorophenyl

[18]

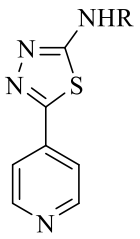
Gomha S M, Kheder N A, Abdelhamid A O, Mabkhot Y N et al., (2016) synthesized bis (1, 3, 4-thiadiazole) derivatives and evaluated for its anticancer activity.[xix]



R = Naphthalene

[19]

Abdo N Y, Kamel M M. et al., (2015) synthesized 1, 3, 4-thiadiazole derivatives and evaluated for its anticancer activity.[xx]

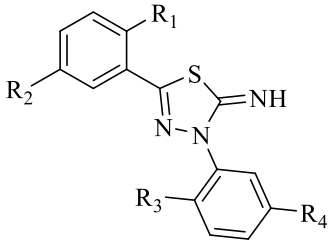


R = anisole/ toluene

[20]

ANTI -INFLAMMATORY ACTIVITY:

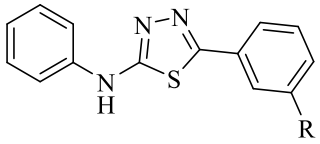
Asif M et al (2009) synthesized 2,4-diphenyl-5imino-1,3,4-thiadiazole derivatives by reaction of benzoyl chloride and phenyl hydrazines. Formed phenyl hydrazone derivatives heated with phosphorous pentachloride and then cyclized with potassium thiocynate yields the target compound. The newly synthesized compounds were screened for their in-vitro anti-inflammatory activity by using Carrageenan induced rat paw method.[xxi]



R1 = H, Cl
R2 = H, Cl, NH2
R3 = H, NO2
R4 = H, NO2

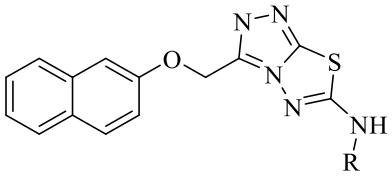
[21]

Kumari R, Sharma B B, Dubey V et al., (2017) synthesized 1, 3,4-thiadiazole derivatives and evaluated for its anti-inflammatory activities.[xxii]



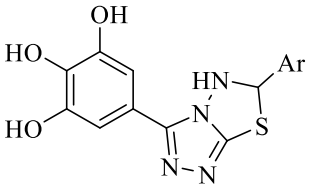
[22]

Amir M et al., (2017) Synthesized 6-substituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4thiadiazole from naphthoxy acetic acid and evaluated for anti-inflammatory activity.[xxiii]



[23] R= phenyl, methyl, propyl…

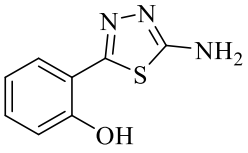
Subramani A et al (2007) synthesized a series of 5{6-(substituted phenyl))-5,6-dihydro-1,2,4-triazolo1,3,4-thiadiazole-3-yl} benzene-1,2,3-triol and evaluated for anti-inflammatory activity by carrageenan induced acute rat paw oedema in rats taking Diclofenac sodium as standard drug for comparison.[xxiv]



[24]

Ar = 2 OH-C_6H_4
3 OH-C_6H_4
4 OH-C_6H_4
3 NO2-C_6H_4
3 Cl- C_6H_4
3,4,5 - $(OCH_3)_2C_6H_2$

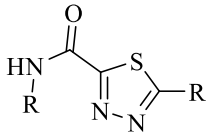
Gupta et al., synthesized disubstituted thiadiazole derivatives by reaction between salicylic acid and thiosemicarbazide in presence of conc. H_2SO_4. *In vivo* anti-inflammatory activity was evaluated and compared with standard drug ibuprofen and all compounds showed moderate anti-inflammatory activity.[xxv]



[25]

ANALGESIC ACTIVITY:

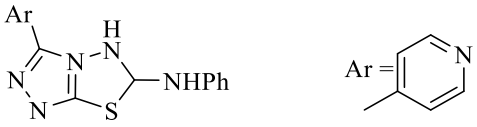
Singh K.A et al (2009) synthesized a series of 1,3,4-thiadiazoles derivatives from thiosemicarbazide by treatment with different benzoyl chlorides. Newly synthesized compounds were studied for analgesic activity. Analgesic activity was determined by using the method based on acetic acid induced writhing response in mice. Standard group received 100mg/kg body weight of Aspirin orally. The entire compound showed good analgesic activity.[xxvi]



R = 4-Cl C_6H_4
3-Cl C_6H_4
2-Cl C_6H_4

[26]

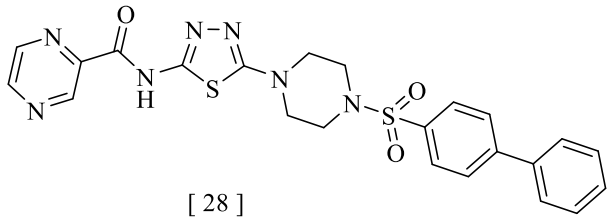
Abdel-Rahman RM et al(2011) synthesized some 1,2,4-triazolothiadiazole derivatives by the interaction between 4-amino-3-(pyridin-4-yl)-5-mercapto-1,2,4triazole and α,β-bifunctional compounds such as isothiocynate and screened for analgesic activity. Salicylic acid was selected as the standard drug. Activity was determined by Eddy's Hot Plate method. All the synthesized compounds tested for analgesic activity.[xxvii]



[27]

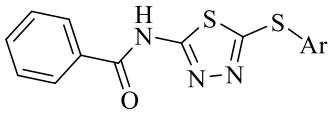
ANTICONVULSANT ACTIVITY

Harish et al. (2013) synthesized new pyrazine substituted 1, 3, 4-thiadiazole derivatives and carried out the reaction of pyrazine substituted 1, 3, 4 thiadiazoles with various sulfonyl chlorides. The anticonvulsant activity of the synthesized compounds was evaluated by MES model at the dose of 100mg/kg. [xxviii]



[28]

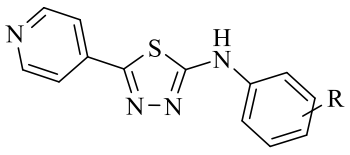
Patanayak P et al (2010) synthesized a series of 2amino-5-sulphanyl-1,3,4-thiadiazole derivatives and tested it for their anticonvulsant activity by using PTZ animal model. Phenytoin 40mg/kg was used as standard drug**.**[xxix]



Ar = 4-$C_6H_4SO_2Cl$
4-$C_6H_4SO_2NH_2$

[29]

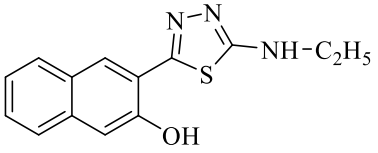
Mohammad Shahar Yar et al (2017) synthesized a series of heterocyclic compounds by the reaction between isoniazid and various substituted isothiocyanates and was tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electro convulsometer comparing with standard drug phenytoin sodium. Among the synthesized compounds, 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1,3,4-thiadiazole and 2(4-chlorophenyl) amino-5-(4-pyridyl)-1, 3, 4- oxadiazole were found promising compounds of the series.[xxx]



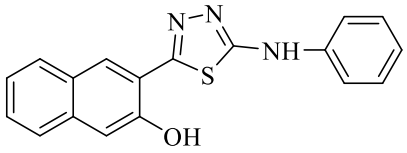
[30]

Hatice N. Dogan et al. (2002) synthesized two new series of 2,5-disubstituted-1,3,4-thiadiazoles and evaluated them for anticonvulsant activity. Among them, compounds 31 (90%) and 32 (70%) showed maximum protection. The acetylation of thiadiazoles retained

anticonvulsant effectiveness to a lesser degree. The ED50 values of these compounds were 33 and 66 mg/kg, respectively. Therefore, the dose of 100 mg/kg was selected as the best one.[xxxi]

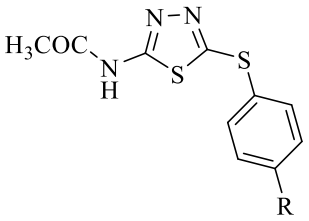


[31]



[32]

K. P. Harish et al. (2014) synthesized a series of 2-amino-5-sulphanyl-1,3,4-thiadiazole derivatives and evaluated for the anticonvulsant activity.[xxxii]

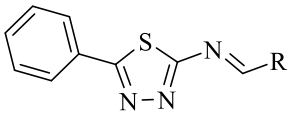


R = SO_2NH_2, CF_3, F

[33]

ANTIOXIDANT ACTIVITY

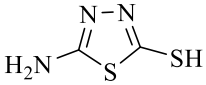
Kumar B.S et al (2011) synthesized 2,5-disubstituted-1,3,4-thiadiazole derivatives and investigated them for their in vivo antioxidant activity. [xxxiii]



[34]

R = 4 F- C_6H_4
4 OH-C_6H_4
4 N-$(CH_3)_2$-C_6H_4
4 CH_3- C_6H_4
2- Furyl

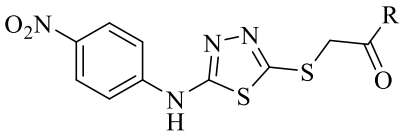
Kothawade P, Bhalerao R, Kulkarni G et al., (2017) synthesized 1, 3, 4- thiadiazole derivatives and evaluated for its antidiabetic and antioxidant activity. [xxxiv]



[35]

ANTINOCICEPTIVE ACTIVITY

Altıntop M. D (2016) synthesized 1,3,4 thiadiazole derivatives and evaluated its antinociceptive effects on sensory neurons pathways of nervous system. The effects of these compounds against mechanical, thermal and chemical stimuli were evaluated by tailclip, hot-plate and acetic acid-induced writhing tests, respectively. In addition, activity cage was performed to assess the loco motor activity of animals. The obtained data indicated that compounds 36b-e and 36g-h increased the reaction times of mice both in the hot-plate and tail-clip tests, indicating the centrally mediated antinociceptive activity of these compounds. Additionally, the number of writhing behaviour was significantly decreased by the administration of compounds 36a, 36c, 36e and 36f, which pointed out the peripherally mediated antinociceptive activity induced by these four compounds. According to the activity cage tests, compounds 36a, 36c and 36f significantly decreased both horizontal and vertical loco motor activity of mice. Antinociceptive behaviour of these three compounds may be non-specific and caused by possible sedative effect or motor impairments.[xxxv]

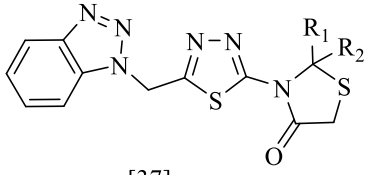


[36 a-h]

a - diethylamino
b - (3-chlorophenyl)amino
c - (4-chlorophenyl)amino
d - (4-nitrophenyl)amino
e - (1,3-benzodioxol-5 yl- methyl)amino
f - Morpholin- 4- yl
g - (benzothiazol-2-yl)amino
h - (6-Nitrobenzothiazol-2-yl)amino

ANXIOLYTIC ACTIVITY

Singh V. K (2018) synthesized derivatives of 5-[(N-benzotriazolomethyl)-1,3,4-thiadiazolyl]-4- thiazolidinone 37a-f and evaluated for their anxiolytic activity. The antianxiety activities of the synthesized derivatives were evaluated using Equine Protozoal Myeloencephalitis (EPM) test and Bright and dark box test experimental models of anxiety. All results were expressed as mean± standard error means (SEM) and analysed by one-way ANOVA. Post-hoc comparisons were performed by applying Dunnet's test.[xxxvi]

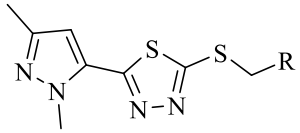


[37]

37	**R1**	**R2**
A	H	C_6H_5
B	C_6H_5	4Br- C_6H_5
C	H	4Cl- C_6H_5
D	CH_3	C_6H_5
E	CH_3	C_2H_5
F	C_6H_5	C_6H_5

HERBICIDAL ACTIVITY

Ding X (2017) synthesized derivatives containing 1,3,4- thiadiazole moiety 38a-k under microwave irradiation, and their structures were confirmed by 1H NMR and HRMS. They were evaluated for herbicidal and antifungal activities, and the results indicated that two compounds with a phenyl group 38a and 4-tertbutylphenyl group 38k possess good herbicidal activity for dicotyledon Brassica campestris and Raphanus sativus with the inhibition of 90% for root and 80%–90% for stalk at 100 ppm respectively. The structure-activity relationship of compounds 38a and 38l was also studied by density function theory method.[xxxvii]

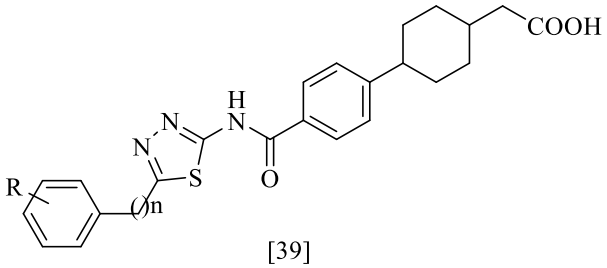


[38 a-k]

a. R Ph
b. 2-ClPh
c. 4-CNPh
d. 2-FPh
e. 2,4-diClPh
f. 3-ClPh
g. 3,4-diClPh
h. 4-BrPh
i. t-BuPh
j. CN
k. $CH=CH_2$

TRIGLYCERIDES BIOSYNTHESIS INHIBITORY ACTIVITY

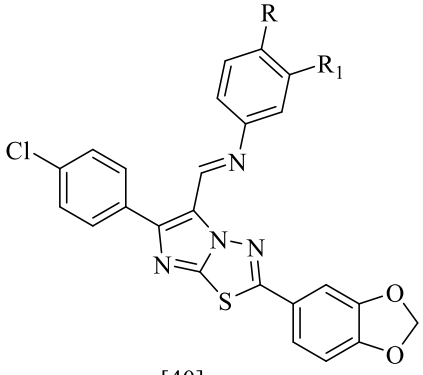
Various 1,3,4-thiadiazole-carboxamide derivatives 39 (n = 0-3; R = H, halo, alkyl, alkoxy) were reported as inhibitors of biosynthesis of triglycerides for treating pathologies in which such inhibition is beneficial. The inhibitory activity of compounds 39 towards the biosynthesis of triglycerides was found to be ranging from 0.01 μM to 10 μM.[xxxviii,xxxix]



[39]

ANTIHYPERLIPIDEMIC ACTIVITY

Synthesis of the 2,5,6-trisubstituted-imidazo[2,1-b] [1,3,4] thiadiazole derivatives 40 was reported and the products were screened for their in vitro antihyperlipidemic activity using standard drug Fenofibrate by following trition induced hyperlipidemic model. Bioassay data showed that compounds 40 (R/ R1 = SO_2NH_2/ H, CO_2H/ H, F/ Cl) demonstrated a significant decrease in the serum TCH (Total Cholesterol), LDL (low-density lipoprotein), VLDL (very low-density lipoprotein) and TG (Triglycerides) values along with an increase in serum HDL (high density lipoprotein) levels as compared to the standard drug Fenofibrate.[xl]



[40]

CONCLUSION

This review thus gives an overview of the various synthetic routes used to form a biologically rich thiadiazole moiety as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the therapeutic properties of the thiadiazole ring and the availability of varied drugs in the market containing the ring. Thus, this account of thiadiazole shows significant aspect of the bioactive thiadiazole ring.

ACKNOWLEDGEMENT

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