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BIOLOGICAL ACTIVITIES OF 1, 3, 4- THIADIAZOLES AND SOME OF THEIR METAL COMPLEXES: A CONCISE REVIEW

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ABSTRACT

The rise of synthetic drug resistance, the emergence of novel pathogens, and the limitations of existing drugs in treating complex infections necessitate the development of new drug formations with potential effectiveness and new therapies. The nitrogen-containing heterocyclic compounds are crucial across various scientific and industrial fields due to their unique chemical properties and versatility. Thiadiazole is a five-membered heterocyclic compound having two nitrogen and one sulfur atom. Among the four isomers, 1,3,4-thiadiazole showed remarkable biological activity. The 1,3,4-thiadiazole derivatives and their metal complexes have gained attention in medicinal chemistry due to their versatile biological activities as antimicrobial, anticancer, anti-inflammatory, antitubercular, antioxidant, and anticonvulsant activities. The study provides a comprehensive overview of the diverse pharmacological properties exhibited by these compounds and gives an insight into the position of different substituents and their complexation with different metal ions for pharmacological values. Their impact on biological activity, emphasizes the importance of 1,3,4-thiadiazole derivatives in drug development and suggests future research directions to enhance their efficacy and specificity in targeting diseases, combat resistance, and paving the way for the development of novel therapeutic agents.

Keywords: 1,3, 4-thiadiazole derivatives, metal complexes, antimicrobial, anticancer, anti-inflammatory, anticonvulsant activity.

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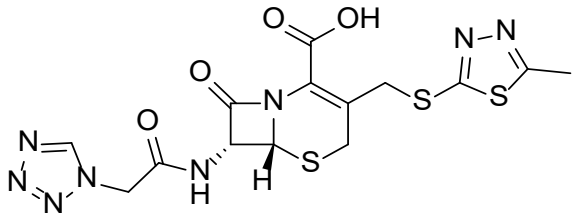
1. INTRODUCTION

The increasing death rate is a serious public health issue. One of the major causes is increasing infection and disease, due to the rise of synthetic drug resistance and the limitations of existing drugs in treating complex infections at global level has enforced the medical world to search for the novel antibiotics classes that can target the infective organisms more effectively. The development of bioactive compounds is now become the need of the hour. The nitrogen containing compounds are well known for its diverse medicinal properties due to the unique structure and chemical properties. Thiadiazole is a five –membered heterocyclic system containing one sulphur and two nitrogen atoms with broad variety of biological activity. Thiadiazole have four isomeric forms which have nitrogen atom at different position, namely 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole **1a.** Among all 1,3,4-thiadiazole isomer is most widely used due to its potential biological activity. This increases its demand in pharmaceutical industries to use as a core component in several drug categories as antimicrobial, antibacterial, antifungal, anti-inflammatory, anticancer,

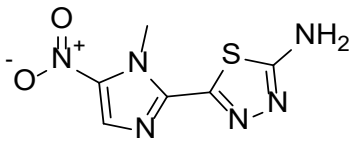
antiparasitic agents etc. The new compounds synthesised from 1,3,4- thiadiazoles have appeared as a great interest of researchers due to their potent biological activity. The presence of sulphur atom in thiadiazole nucleus enhances liposolubility and mesoionic character of thiadiazoles enable these compounds better to cross cellular membranes.The 1,3,4-thiadiazole derivatives have tremendous biological activities and hence occupied significant place in medicinal field. 1,3,4-thiadiazole moiety are found in several FDA-approved marketed drugs **1b.**[1,2,3] This paper contains a concise review on 1,3,4-thiadiazole derivatives as antibacterial, antifungal, anti-inflammatory, anti-cancer and anti-leishmanial activity and anticonvulsant activity, and antiviral activity and exploring the position of different substitutions for pharmacological values.

1a



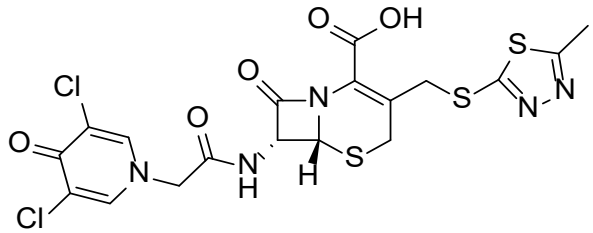
Cefazolin

(Antibacterial)



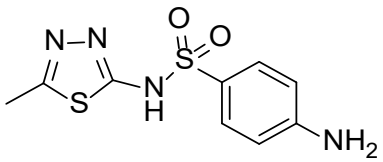
Megazol

(Antiprotozoal)



Cefazedon

(Antibacterial)



Sulfamethizole

(Antibacterial)

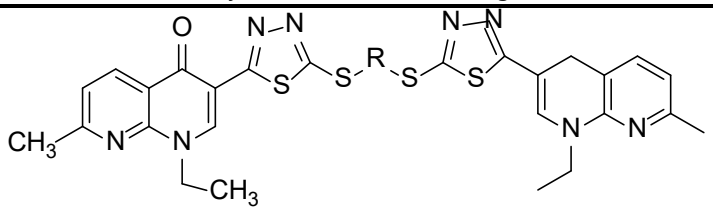
1b

2. BIOLOGICAL ACTIVITIES OF 1,3,4-THIADIAZOLE DERIVATIVES: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY:

1,3,4-thiadiazole has potential activity against pathogens. Therefore several researches have been worked on synthesis of new derivatives as antibacterial and antifungal agents.

Aggarwal et al [4] described the antibacterial activity of novel nalidixic acid –based 1,3,4- thiadiazole derivative **2**, by using disk diffusion. The bacterial stain contained gram- positive bacteria, *staphylococcus aureus* and *Bacillus subtilis,* and gram-negative bacteria are *Escherichia coli, Pseudomonas aerginosa* and *Klebsiella pneumonia.* The standard drug used was streptomycin. Some of the compounds showed potential antimicrobial activities as compared to standard drugs. The compound containing 1,4-bis-(methylene) benzene group and two 1,3,4-thiadiazoles displayed significant antibacterial activity(MIC, 31.25-125 lµg/Ml) against the tested organism.

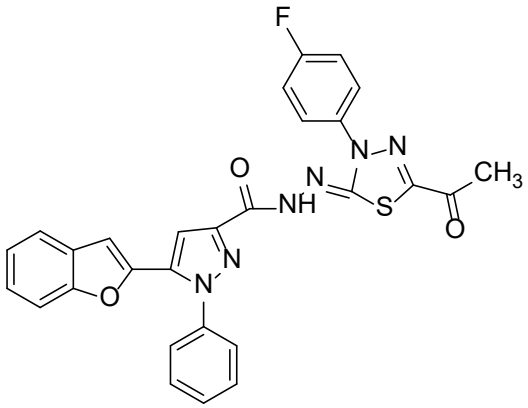
1,3,4- thiadiazole and its derivatives has serves a significant role as antibacterial agents and gained the interest of various researchers to synthesize and add new series of 1,3,4- thiadiazole derivatives in the medicinal field.



2

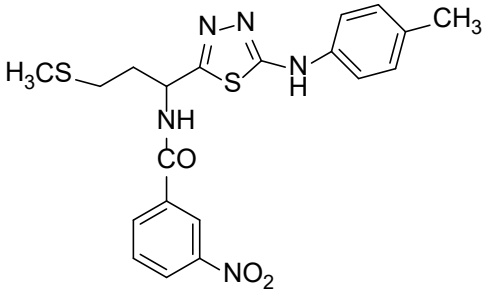
R = -$CH_2C_6H_4CH_2$-, -$(CH_2)_0$, -$(CH_2)_4$, -$(CH_2)_6$, $(CH_2)_8$

Abdel- Wahab et al. [5] reported synthesis of new 1,3,4- thiadiazole derivatives of 5-(benzofuran-2-yl)- 1-phenylpyrazole moiety through the reactions of the potassium salt of hydrazinecarbodithioate with substituted hydrazonoyl chlorides. Compound **3** among these synthesized compounds showed potential activity against *E. coli* and *C. albicans.*



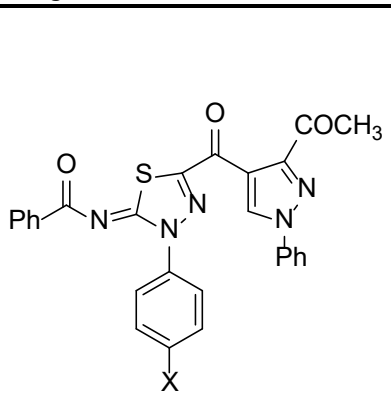
3

Pintilie et al [6] synthesized few novel N-(5-(3-(methylthio)propyl)-1,3,4-thiadiazole-2yl) benzamide derivatives **4** and by double dilution method tested their antimicrobial activities against five standard bacterial strains *Staphyloccus aureus, Bacillus antracis, Bacillus cereus, Sarcinatutea* and *Escherichia coli*. Some of the tested compounds showed significant antimicrobial activities as compared to the standard drugs. Compound of 4-methylphenyl moiety on heterocyclic ring was found the most active against *B. antracis and B. cereus.*



4

Farghaly et al [7] synthesized a new series of 1,3, 4-thiadiazoles including pyrole, triazolopyrimidin and benzimidazolpyrimidines via reaction of 1,3,4-thiadiazolenaminones with hydrazonoyl chloride and nitrogen nucleophiles. The antimicrobial activities were investigated against four fungal strains, namely *Aspergillus fumigatus, P.italicum, Geeotrichum candidum and Candida albicans* as well as four bacteria species including, Gram positive(*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative bacteria(*Pseudomonas aeruginosa* and *Escherichiacoli*. The standard drugs used for Gram positive bacteria were Amphotericin B(antifungal agent) and ampicillin(antibacterial agent) and for Gram negative bacteria, gentamicin (antibacterial agent)was used. Minimum inhibitory concentrations (MICs) of compounds **5, 6, 7** and **8** were also determined. Most of the synthesized compounds showed excellent effects on comparison with standard drugs.



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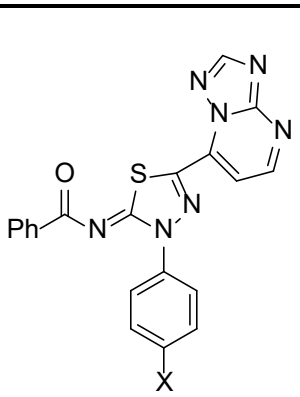

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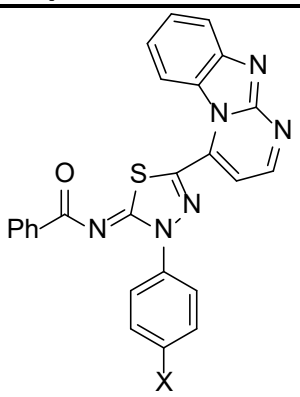

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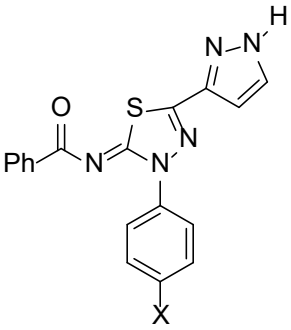
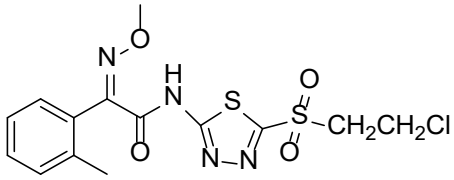


8

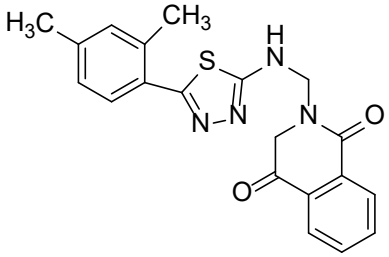
X = OCH_3, CH_3, Cl, NO_2

Wu el at [8] designed and synthesized a series of novel 1,3,4-thiaziazole derivatives containing an amide moiety, and their antimicrobial activities were tested. Compound **9** was designed and synthesized according to comparative molecular field analysis and displayed higher antimicrobial activities against *Xanthomonas oryzae* pv. *Oryzicola* and *Xanthomonas oryzae* pv. *Oryzae,* with EC_{50} values of 2.1 and 1.8 mg/L respectively, found better than those of thiodiazole copper(99.6 and 92.5 mg/L) used as a positive control. Also, the protective and curative activities of the compound against rice leaf streak were superior than those of thiodiazole copper.



9

Sahu et al [9] synthesized 1,3,4- thiadiazole derivatives and evaluated the antimicrobial activity against gram positive bacteria *Bacillus subtilis* and gram negative bacteria *Escherichia coli* by Agar diffusion method. The standard drug used for the investigation was Ciprofloxacin. Compounds **10** and **11**, showed prominent antimicrobial activity than the standard drug used.



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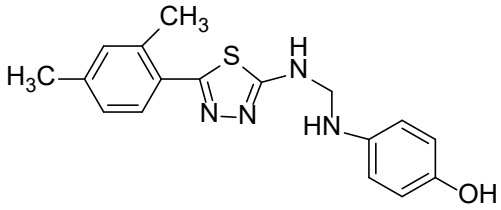
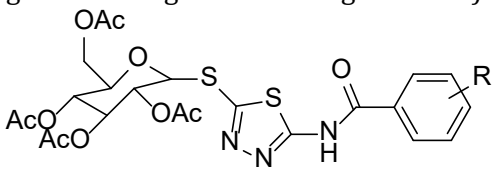


11

Chen et al [10] prepared a series of novel 1,3,4-thiadiazole derivatives of glucosides and tested the bioactivities of these compounds. The *in vitro* antifungal activities of these compounds against five different fungus namely *P. infestans, G. zeae, B. dothidea, Phomopsis* sp., and *T. cucumeris* showed that compound **12** exhibited better antifungal activity against *P. infestans* with EC_{50} values of 3.43 which is higher than that of the standard drug (Dimethomorph) used. Moreover, it was

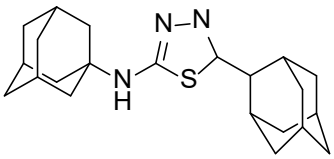
revealed by structure- activity relationships(SAR) analysis that the type and position of substituent groups in phenyl ring plays an important role in enhancing the antifungal activities against *P. infestans.*



R=4-F

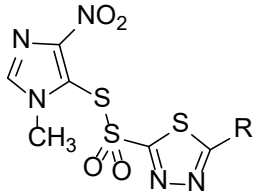
12

Kadi et al [11] described the synthesis of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. The evaluation of antibacterial activity showed that compound **13** acquired better activity as compared to the reference drugs Gentamicin and Ampicillin against *e. coli and P. aeuroginosa.* The results showed that antibacterial activity was decreased on introducing the benzyl- or 4-substituted benzyl moieties whereas introduction of another adamantyl moiety on C-5 of thiadiazole nucleus increased the antifungal activity.[12]

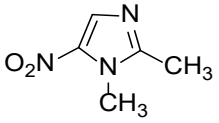
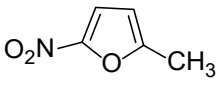


13

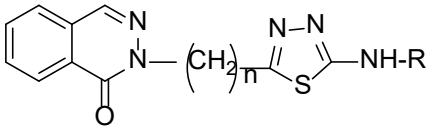
Bahram et al [13] reported *in vitro* antibacterial screening of a series of 2-(1-methyl-4-nitro-1H-imidazol-5-ylsulfonyl)-1,3,4-thiadiazoles **14(a-c)** by agar dilution method against gram-negative and gram-positive bacteria. Among the three compounds 14c with 5-(5-nitrofuran-2-yl)-residue on 1,3,4-thiadiazole displayed significant antibacterial activities against gram-positive bacteria namely *S. aureus, Staphylococcus epidermidis* and *B. subtilis.*



14(a-c)

R =a)CH_3CONH- , b)  , c) 

Onkal et al [14] synthesized and evaluated antimicrobial activity of new 1,3,4-thiadiazole derivatives **15(a-l)**, against two gram-positive bacteria(*Staphlococcus aureus, Bacillus subtilis),* two gram-negative bacteria*(Pseudomonas aeruginosa, Escherichia coli)* and two yeast-like fungi *Candida albicans* and *Candida parapsilosis* by using broth microdilution method. Most of the derivatives showed significant antimicrobial activity against *B. subtilis* and the fungi.



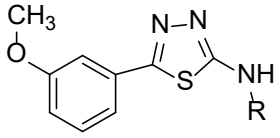
15(a-l)

Comp.	n	R
15a	1	Phenyl
15b	1	Benzyl
15c	1	Phenethyl
15d	1	4-Chlorophenyl
15e	1	4-Methoxyphenyl

15f	1	4-Methylphenyl
15g	2	Phenyl
15h	2	Benzyl
15i	2	Phenethyl
15j	2	4-Chlorophenyl
15k	2	4-Methoxyphenyl
15l	2	4-Methylphenyl

3. ANTI-CANCER ACTIVITY

Janowska et al [15**]** designed and synthesized new 1,3,4-thiadiazole derivatives, and also investigated their the anti-cancer activity. Among all tested compounds, the compound **16,** 2-(2-trifluorophenylamino)-5-(3-methoxyphenyl)-1,3,4 thiadiazole was showed strongest anti-proliferative activity against MCF-7 and MDA-MB-231 breast cancer cells with IC_{50} values 49.6μM and 53.4 μM, respectively.

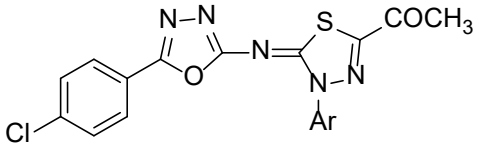


R=2-CF3C6H4

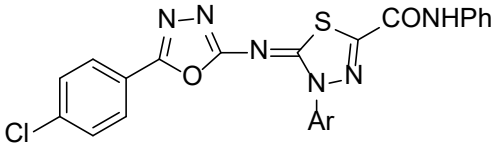
16

R=2-$CF_3C_6H_4$

Dawood et al [16] prepared and evaluated anti-cancer activity of 1,3,4-thiadiazole derivatives. The results revealed that the compound **17** and **18** have excellent antitumor activity against human colon carcinoma cell line (HCT- 116) with IC_{50} values of 0.73 and 0.86μg/mL, respectively due to the presence of chlorine atom (electron withdrawing group). Whereas most of the tested compounds showed moderate anticancer activity.



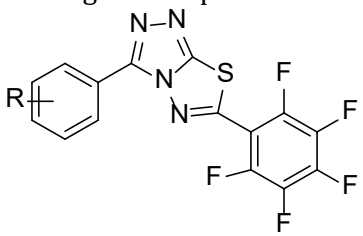
17



18

Ar= 4-ClC_6H_4

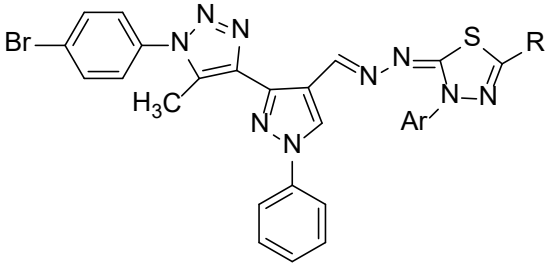
Chowrasia et al [17] synthesized a series of fluorinated 3,6-diaryl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazoles. Anti-cancer screening of the synthesized compounds were carried out against three cancerous cell lines namely MCF7(human breast cancer), SaOS-2(human osteosarcoma) and K562(human myeloid leukemia). The compound **19** showed excellent antiproliferative activity with IC_{50} values of 22.1, 19 and 15μM against MCF7, SaOS-2 and K562 respectively, whereas most of the tested compounds showed moderate to good antiproliferative property against the cell lines.



19

R=H

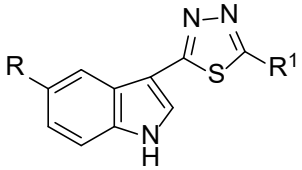
Rashdan et al [18] synthesized novel 1,3,4-thiadiazole derivatives under solvent free conditions and investigated for their anti-cancer activity against human lung carcinoma (A-549) and human breast carcinoma(MCF7). Most of the compounds showed significant anti-cancer activity against breast cells. Compounds **20 (a-b)** showed high cytotoxic activity with 81.9% and 89.2% against breast cells respectively and also had minimum toxicity on normal skin cells with value of 38.2 and 40.7 respectively.



20(a-b)

20a: R=COOEt, Ar=$C_6H_4CH_3$ 20b: R=$COCH_3$, Ar=C_6H_4Cl

Kumar et al [19] synthesized a series of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazoles and analysed their cytotoxicity against various human cancer cell lines. Compound **21(d)**having 4-benzyloxy-3-methoxyphenyl and 5-bromo indolyl substituents was found most active in suppressing cancer cells growth with a value of IC_{50} 1.5µM against PaCa2(pancreatic cancer cell lines). Moreover, SAR(structure activity relationship) study shown that C-2 substitution plays important role in cytotoxic activity in the compounds. The compounds **21(a-c)** with C-2 substituents benzyl, 3,4-dimethoxyphenyl and 4-benzyloxy-3-methoxyphenyl respectively shown good cytotoxicity against multiple human cancer cell lines.

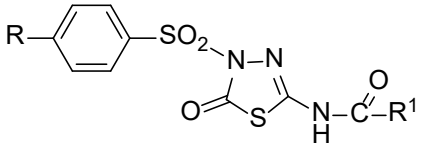


21(a-d)

Comp.	R	R^1
21a	$CH_2C_6H_5$	H
21b	3,4-$(OCH_3)_2C_6H_3$	H
21c	4-BnO-3-$OCH_3C_6H_3$	H
21d	4-BnO-3-$OCH_3C_6H_3$	Br

4. ANTI-INFLAMMATORY ACTIVITY

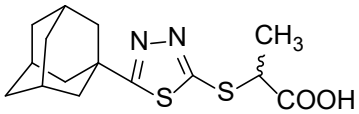
Schenone et al [20] synthesized a new series of N-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides and their in vivo anti-inflammatory activities were tested in carrageenan rat paw edema test, with a dose of 50mg/kg po. Indomethacin was used as reference drug(5mg/kg). compounds **22(a-d)** were found good in anti-inflammatory activity.



22(a-d)

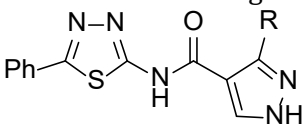
comp.	R	R^1
22a	H	4-Methoxyphenyl
22b	H	4-Fluorophenyl
22c	H	4-Trifluoromethylphenyl
22d	H	2-Furoyl

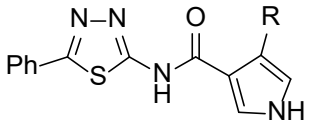
Kadi et al [12] described the synthesis and anti-inflammatory activity of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. The carrageenan-induced paw oedema method in rats was used to determine the in vivo anti-inflammatory activity of these compounds. The reference drug used was Indomethacin. Among all, the propionic acid derivative **23** showed highest anti-inflammatory activity, which produced strong dose-dependent inhibition(more than 50%).



23

Maddila et al [21] reported the synthesis anti-inflammatory activity of a new series of1,3,4-thiadiazole with pyrazole and pyrrole nucleus. The anti-inflammatory screening of the synthesized compounds were evaluated carrageenan – induced acute paw oedema in rats at 3h and 5h using indomethacin as standard drug. Most of the tested compounds were found to show significant anti-inflammatory activity, whereas the compound **24(a-b)** and **25** had shown highest activity as compared to the standard drug.





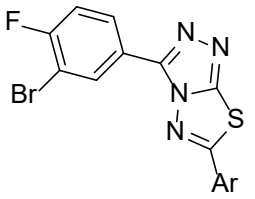
24(a-b)

24a: R= 4-NO_2-C_6H_4;24b: R=4-F-C_6H_4

25

R= 4-$NO_2C_6H_4$

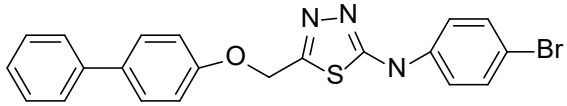
Chawla et al [22] synthesized a series of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives and evaluated in vivo anti-inflammatory activity by using carrageenan-induced rat paw oedema method[23]. Ibuprofen was used as standard drug and the oral dose was same for tested compounds and standard drug(20mg/kg). Among all, compound **26** containing fluorine atom showed highest activity of 51.86%.



26

Ar= 4-F-C_6H_4

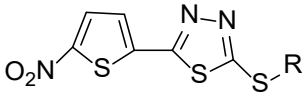
Kumar et al [24] synthesized a series of 1,3,4-thiadiazole derivatives of biphenyl-4-yloxy acetic acid and evaluated their anti-inflammatory activity using rat paw oedema induced by carrageenan. All the tested compounds showed anti-inflammatory activity ranging between 27.27% and 63.63%. The result showed maximum activity of compound having *p*-bromophenylamino **27** with value of 63.63%.



27

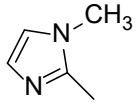
5. ANTI-LEISHMANIAL ACTIVITY

Sadat-Ebrahimi et al [25] synthesised a series of novel 5-(nitrothiophene-2-yl)-1,3,4-thiadiazole derivatives abd analysed their anti-leishmanial activity against *Leishmania major* promastigotes. Compound **28** amongst all tested compounds was found most active with IC_{50} values of 11.2µg/mL(after 24 h) and 7.1µg/mL(after 48 h) which were comparatively more effective than the reference drug Glucantime having IC_{50} 50µg/mL (after 24 h) and 25µg/mL (after 48h).

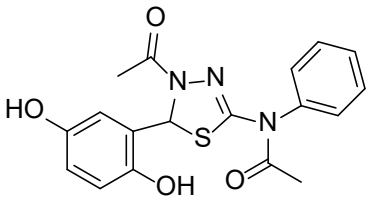


28

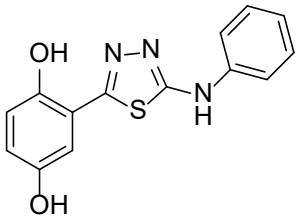
R=



Al-Qahtani et al [26] described various derivatives of 1,3,4-thiadiazole that have significant anti-leishmanial activity. The author revealed that Compound **29** showed highest activity at law concentration (50µM) and whereas compound **30** showed strong activity at high concentration against *L. donovani* promastigotes.

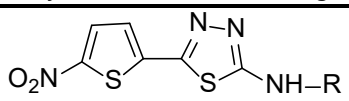


29



30

Tahghighi et al [27] synthesized new compounds of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines and 5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-amines, among these the derivatives, compounds **31(a-b)** containing hydroxypropyl and methoxypropyl groups respectively showed highest activity against promastigote form of *Leishmania major*, with IC_{50} values of 3µM as compared to the standard drugs glucantime(IC_{50}68.44µM) and fluconazole(IC_{50} 941.1µM).

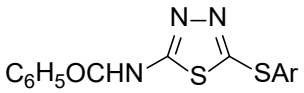


31(a-b)

31a: R=$(CH_2)_3OH$; 31b: R=$(CH_2)_3OMe$

6. ANTICONVULSANT ACTIVITY

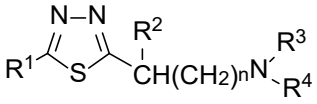
Pattanayak et al [28] reported the synthesis and evaluation of a series of 2-amino-5-sulfanyl-1,3,4-thiadiazoles anticonvulsant agents. The anticonvulsant screening was performed by using maximal electroshock(MES) test and pentylene tetrazole(PTZ) model in mice. The reference drug used for MES test was Phenytoin and Diazepam for PTZ-induced model. The results showed that compounds **32(a-c)** had potent anticonvulsant activity.



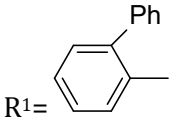
32(a-c)

32a: Ar= 4-$C_6H_4SO_2CI$, 32b: Ar=4-$C_6H_4SO_2NH_2$, 32c: Ar=4-C_6H_4F

Stillings et al[29] described the synthesis and pharmacological investigation of a series of substituted 1,3,4-thiadiazoles. 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole(compound **33**) was examined for anticonvulsant activity by using several test conditions in rats and mice. The standard drugs used were phenytoin, phenobarbital and carbamazepine. The results showed that compound **33** had significant anticonvulsant activity in comparison with standard drugs.

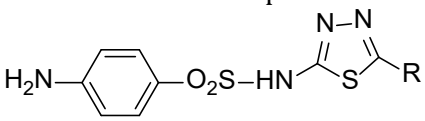


33



; R^2= H; R^3= H; R^4= H; n= 0

Singh et al [30] revealed the synthesis and anticonvulsant activity of some 1,3,4- thiadiazole derivatives. The anticonvulsant activity was investigated by using maximal electroshock test (MES)and phenytoin sodium as reference drug. The dose was 20 mg/Kg for tested compounds and reference drug. Among all, Compound **34(a-b)** showed potent anticonvulsant properties as compared to rest of the tested compounds.

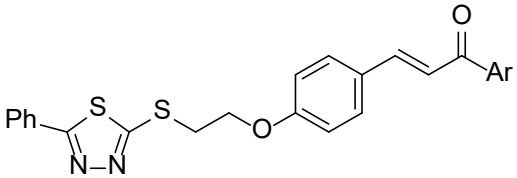


34(a-b)

34a: R= C_6H_5; 34b: R=p-$NO_2C_6H_5$

7. ANTIVIRAL ACTIVITY

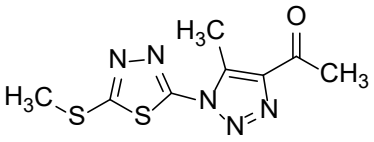
Gan et al [31] synthesized series of new 1,3,4-thiadiazole derivatives and evaluated their in vitro and in vivo antiviral activities. Result of in vitro study revealed good antiviral activity by the compound **35a** and **35b** against TMV(tobacco mosaic virus), having binding constant 6.02μM and 5.04μM respectively as compared to the Ribavirin and Ningnanmycin (positive control used). Result of in vivo study showed significant antiviral activity of compound **35a** and **35b** against TMV, having EC_{50} values of 33.87 and 30.57μg/mL, respectively as compared to Ribavirin and Ningnanmycin.



35(a-b)

35a: Ar=Ph; 35b: Ar=thiophene-2-yl

Rashdan et al [32] synthesized novel 1,3,4-thiadiazole based molecules containing 1,2,3- triazole moiety and identified their antiviral activity by *in silico* docking study against Coronavirus protease, which played essential role in propagating COVID-19 disease. Compound **36**, **37**, **38** and **39** displayed good docking scores to COVID-19 main protease, with the binding energy of -8.3 to -6.2 kcal/mol.



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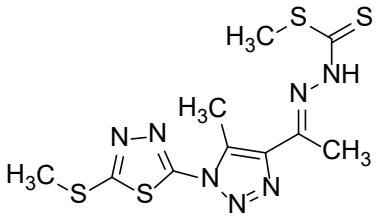
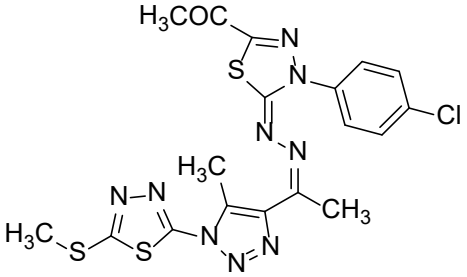


37



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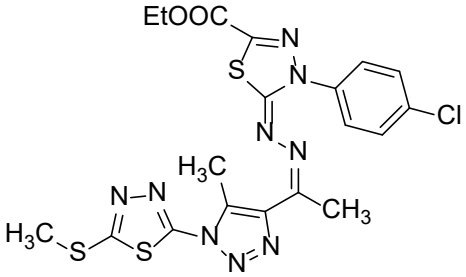
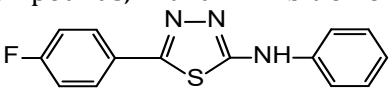


39

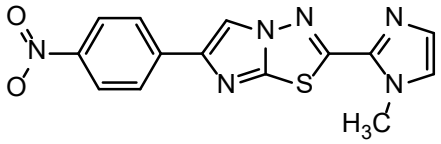
8. ANTITUBERCULAR ACTIVITY

Oruç et al. [33] prepared and investigated some 2,5-disubstituted-1,3,4-thiadiazoles for antituberculosis activity against *M. tuberculosis* H37Rv in BACTEC 12B medium using broth microdilution method. Compound **40** was found to have the highest activity among all the synthesized compounds, with an inhibition of 69%.



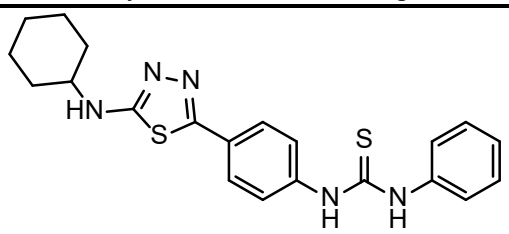
40

Patel et al. [34] synthesized a series of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives and evaluated their antitubercular activity against *Mycobacterium tuberculosis* H37Rv, using MABA method. Results revealed that most of the compounds showed antitubercular activity but, Compound **41** exhibited the highest inhibitory activity (98%) with MIC value 3.14 µg/ml. Moreover, the results of cytotoxicity analysis in a mammalian Vero cell line by using MTT test, revealed that these compounds had antitubercular activity at non-cytotoxic concentrations.



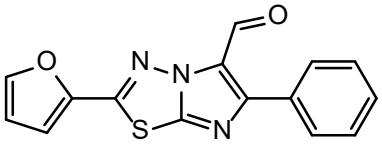
41

Karakuş et al. [35] performed the synthesis and antitubercular examination of eight N-phenyl-N'-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl)phenyl]thiourea derivatives, against *M. tuberculosis* H37Rv stain at MIC 6.25 µg/ml, using BACTEC 460 Radiometric System. It was observed that Compound 42 showed the highest antitubercular activity with an inhibition of 67%.

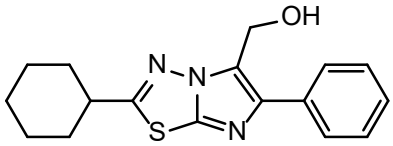


42

Kolavi et al. [36] performed synthesis of some 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles, and investigated their antitubercular activity against M. tuberculosis (H37Rv) by BACTEC 460 radiometric method. Study reported that some of the tested compounds showed moderate activity but, Compound **43** and compound **44** had excellent antitubercular activity with 100% inhibition.



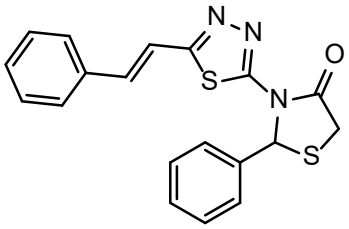
43



44

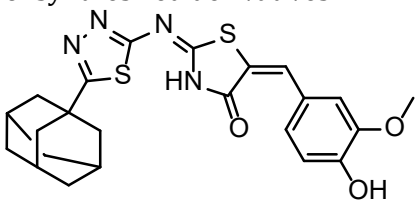
9. ANTIOXIDANT ACTIVITY

Joseph et al. [37] prepared a sequence of 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones and examined for in vitro antioxidant activity by using diphenylpicrylhydrazyl (DPPH) assay. Compound **45** showed potential activity with IC_{50} value 161.93 µmol L^{-1}.



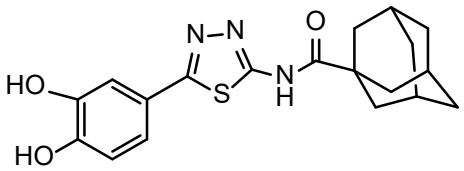
45

Djukic et al. [38] produced nine thiazolidinone derivatives and investigated for their antioxidant activity by using three in vitro assay: DPPH, FRAP, and TBARS. Vitamins E and C and α-lipoic acid were used as traditional antioxidants. Data revealed that Compound **46** had highest antioxidant activity as compared to other tested derivatives. The study demonstrated that phenyl-functionalized benzylidene, amino-carbonyl functional domains, and chelating ligand properties affected the antioxidant activity of synthesized derivatives.



46

Jakovljević et al. [39] synthesized some 1,3,4-thiadiazoles derived from phenolic acids. Their antioxidant activity was screened by using DPPH assay. Compound **47** and compound **48** having adamantyl group showed significant antioxidant activity with IC_{50} value lower than the reference antioxidant used (17.85 μM and 14.21 μM respectively).



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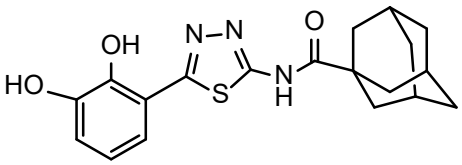
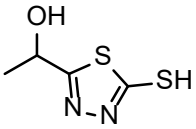
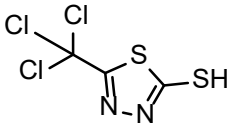


48

Rabie et al. [40] designed and synthesised thirteen 5-substituted-1,3,4-thiadiazole-2-thiols. On testing their antioxidant activity by two in vitro antioxidant assay(ABTS test and DPPH test), it was found that Compound **49**, compound **50**, and compound **51** exhibited very high antioxidant activities, with IC_{50} value 23.67 μM, 24.94 μM, and 23.36 μM respectively in ABTS assay, and 14.17 μM, 14.93 μM, and 12.08 μM respectively in case of DPPH assay. Their activity were found better than the reference antioxidants used.



49



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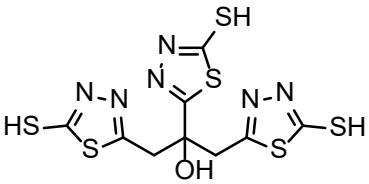
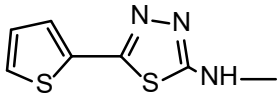


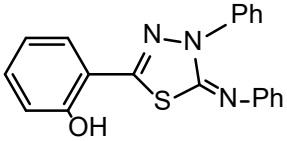
51

Muğlu et al. [41] synthesized and explored antioxidant property of seven 1,3,4-thiadiazole derivatives containing thiophene groups, by using TLC-DPPH and DPPH assays. Study demonstrated that Compound **52** exhibited highest antioxidant activity (81.13%).



52

Al-Omair et al. [42] synthesized novel thiadiazole derivatives and evaluated their antioxidant activity using SOD-like activity, DPPH free radical scavenging activity, ABST and NO assay. Compound **53** demonstrated promising results (more than 50 %).

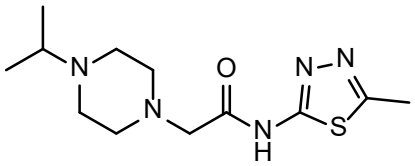


53

10. ANTIDEPRESSANT ACTIVITY

Can et al. [43] prepared some new thiadiazoles from acetylated 2-aminothiadiazole and piperazine derivatives. Later on tested for their antidepressant like activities by tail-suspension and modified forced swimming methods. Fluoxetine was taken as reference drug. Data showed that Compound **54, 55, 56, 57, 58,** and **59** exhibited notable antidepressant-like

activities. Moreover, theoretical calculation of absorption, distribution, metabolism, excretion (ADME) properties for the obtained compounds were also performed and results confirmed the antidepressant-like potential of these compounds.



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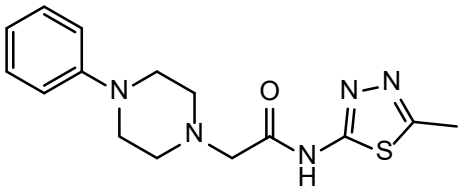

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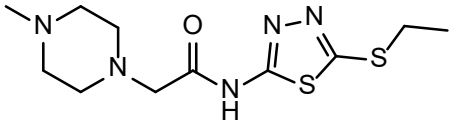

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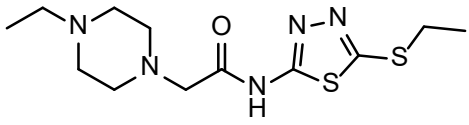

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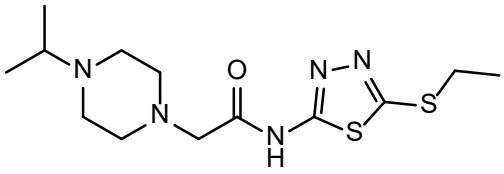

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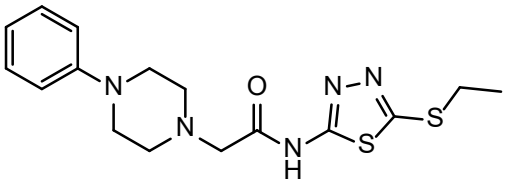
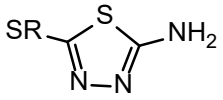


59

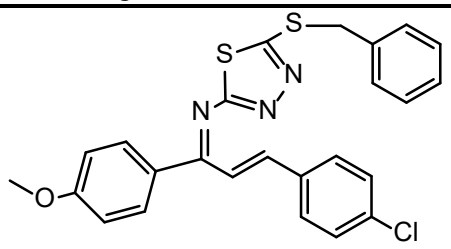
Clerici et al. [44] synthesized a sequence of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives containing different substituents. The compounds were examined pharmacologically to find out their central nervous system activity. Two reference drugs Imipramine and Diazepam were used for comparison. Most of the tested compounds were exhibited notable activity as compared to the reference drugs but, Compound **60** showed most significant antidepressant and anxiolytic activity, among all.



R=3-CH_3O-benzyl

60

Yusuf et al. [45] synthesized a series of 5-amino-1,3,4-thiadiazole-2-thiol derivatives bearing imine linkage and investigated for their antidepressant activities . Study revealed that Compound **61** and Compound **62** possessed potential antidepressant activity, which decreased immobility time by 77.99% and 76.26% respectively, as compared to reference drug imipramine, showed decreased immobility time by 82%.



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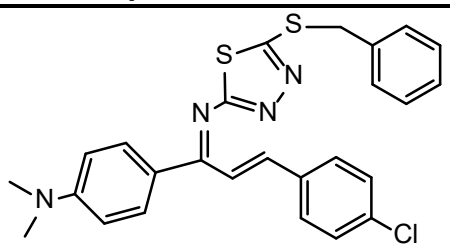
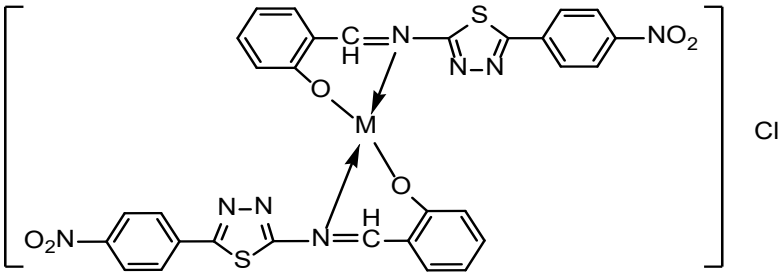


62

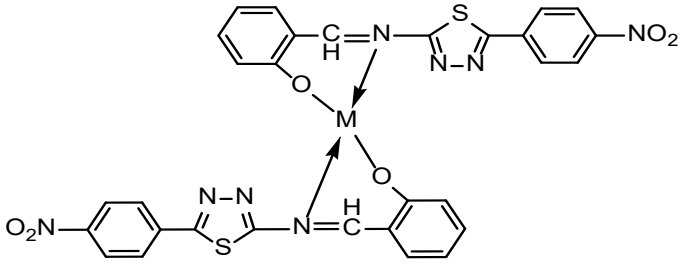
11. BIOLOGICAL ACTIVITIES OF METAL COMPLEXES

Yousif et al. [46] prepared five new metal complexes derived from 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole, with VO(II), Co(II), Rh(III), Pd(II) and Au(III) metal ions. complexes were examined for in vitro antibacterial activity against *Staphylococcus aureus*, *Salmonella typhi* and *Escherishia coli* by using agar diffusion method. Results showed that Complexes **63, 64,** and **65** were more activity than the free ligand.



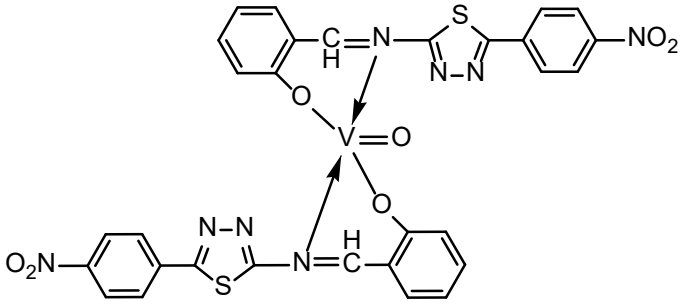
M=Rh, Au

63



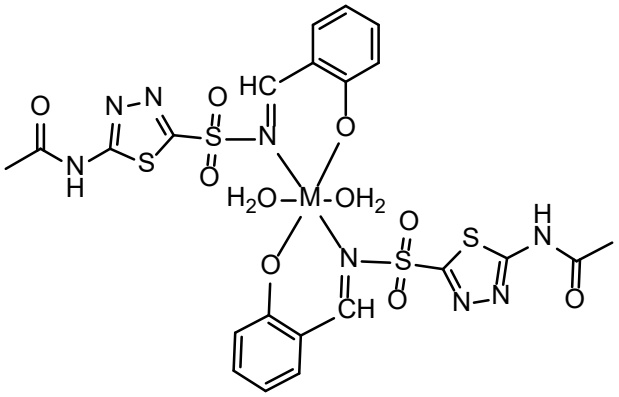
M=Pd, Co

64



65

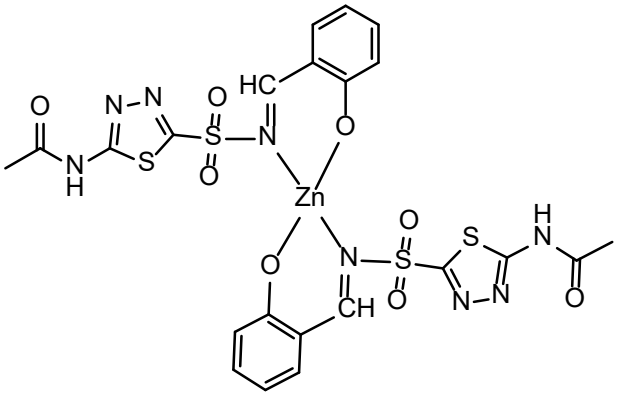
Malik et al. [47] introduced some metal complexes with a Schiff base derived from 5-acetamido-1,3,4-thiadiazole-2-sulphonamide and performed their antifungal screening against two fungal strains *Aspergillus niger* and *A. flavus.* Data elucidated that Compound **66** had excellent activity than the Schiff base and the reference drug (Netamycin) used.



M=Mn(II), Fe(II), Ni(II), Cu(II)

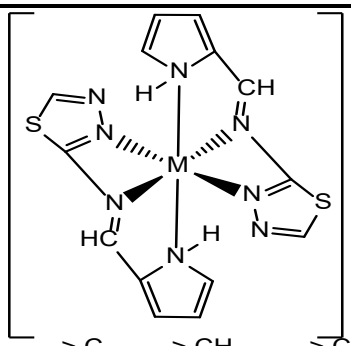
66

Ghosh et al. [48] also synthesized metal complex derived from 5-acetazolamido-1,3,4 - thiadiazole-2- sulphonamide in the same manner mentioned above, and investigated its diuretic activity on albino rats. It was found in the study that Compound **67** had promising activity as compared to the Schiff base and the reference drug (Acetazolamide pure drug).



67

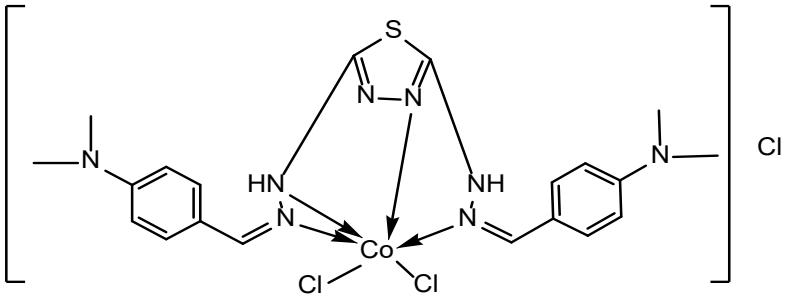
Chohan et al. [49] prepared complexes of a thiadiazole-derived pyrrolyl schiff base, having different anions.(SO_4^{2-}, NO_3^-, $C_2O_4^{2-}$, and $CH_3CO_2^-$). Complexes were tested for antibacterial activities against various bacterial strains(*Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa*). Results showed the potential activity of Compound **68**. It was found that the antibacterial activity of the ligand was increased due to coordination with metal ions, demonstrating potential for combating antibiotic-resistant strains.



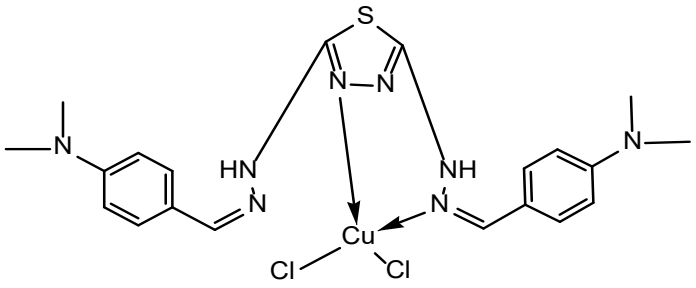
X= NO_3^- > $C_2O_4^{2-}$ > $CH_3CO_2^-$ > Cl- > SO_4^{2-}, M Cu(II) or Zn(II), n =1 or 2

68

Basher et al. [50] prepared some complexes derivatives from1,3,4– thiadiazole Schiff base and evaluated their antibacterial activity against two bacterial strains *Staphylococcus aureus* and *Escherichia Coli*. Ciprofloxacin was taken as standard drug for comparison. Results showed that ligand had better biological activity with 17 mm area of inhibition zone than the standard drug (9 mm) against *Escherichia coli*, also the complexes **69** and **70** showed greater biological activity (inhibition area 15 mm and 11 mm respectively) than Ciprofloxacin against *Escherichia coli* (Gram-negative), the ligand and its prepared complexes showed no activity against *Staphylococcus aureus*(Gram-positive).

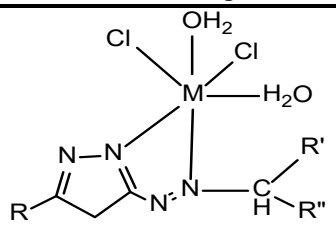


69



70

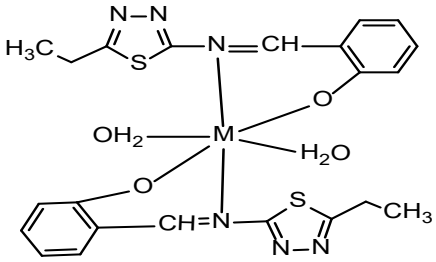
Jha et al. [51] performed synthesis of 2,5-disubstituted thiadiazoles by both conventional method and microwave irradiation method, which further condensed to form metal complexes. The prepared complexes were examined for anticancer activities on *HL-60 Human leukemia cell Line* and *U-937 Lymphoma cell lines*. Also the antimicrobial activity of the ligands and their complexes against bacteria and fungi were tested. Compound **71** demonstrated significant biological activity.



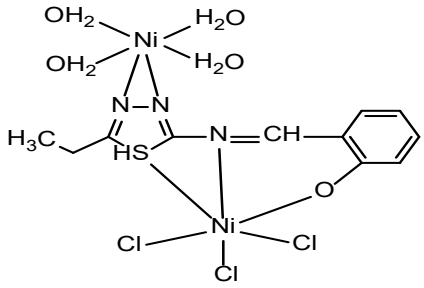
Where R=CH_3,for L1,L2,L3
or R=CH$_3$CH$_2$,forL4,L5,L6
R' & R''=COCH$_3$=L1&L4
R'=CN & R''=COOC$_2H_5$=L2&L5
R' & R''=CN=L3&L$_6$

M=Ni(II), Cu(II), Ru(II) **71**

Turan et al. [52] introduced 1,3, 4-thiadiazole-based Schiff base and its metal complexes and investigated their pro-oxidant on serum antioxidant vitamins (i.e., vitamins A, E, and C) and malondialdehyde (MDA) levels were measured in blood serum, liver, and kidney tissues.and in vitro antiproliferative effects on the human breast carcinoma MCF-7 and murine leukemia L1210 cell lines. The pro-oxidant effects of compound **72** and **73** were found lower than the control group. But all the compounds inhibited cell proliferation of MCF-7 and L1210 cancer cell lines.

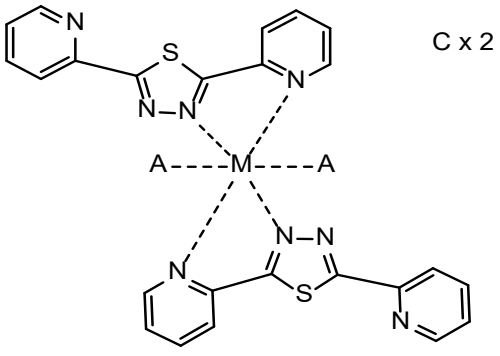


M=Co(II) and Mn(II)
72



73

Ahmed et al. [53] presented in vitro effects of 2,5-bis(2-pyridyl)-1,3,4-thiadiazole metal complexes on T lymphocyte proliferation and intracellular redox status. The study reported that Compound **74** showed potential activity as compared to free ligand.



C x 2

M= Cu, A=NO_3^-
M=Ni, A=H_2O, C=ClO^{4-}

74

12. CONCLUSION

The exploration of 1,3,4-thiadiazole derivatives and their metal complexes reveal their significant potential in various biological activities, including antimicrobial, anti-inflammatory, anticancer, anti-leishmanial, anticonvulsant, antitubercular, antioxidant, antidepressant, and antiviral activities. And the potency of thiadiazoles increased upon complexation. These compounds not only demonstrate promising mechanisms of action but also offer a strategic advantage in overcoming drug resistance, a major challenge in modern therapeutics. Their varied structures allow for further improvements in how they work, which could lead to safer and more effective drugs. Overall, 1,3,4-thiadiazole derivatives and the complexes formed upon coordination with metal ions represent a vital area of interest in medicinal chemistry, with the potential to yield novel therapeutic agents that can significantly impact the fight against drug-resistant conditions.

Future studies should focus on developing innovative synthetic approaches to enhance their biological applicability.

CONFLICT OF INTERESTS

None.

ACKNOWLEDGMENTS

None.

REFERENCES

Jain A. K., Sharma S., Vaidya A., Ravichandran V., & Agrawal R. K. 2013.1,3,4-thiadiazole and its derivatives:A review on recent progress in biological activities, *Wiley & Sons*

Singh A. K., Mishra G.,& Jyoti K. 2011. Review on biological activities of 1,3,4-thiadiazole derivatives, *Journal of Applies Pharm*

aceutical Science. 01(05): 44-49.

Li, Y., Geng, J., Liu, Y., Yu, S., & Zhao, G. 2013. Thiadiazole—A promising structure in medicinal chemistry. ChemMedChem, 8(1), 27-41.

Aggarwal N., Kumar R., Dureja P. & Khurana J. M. 2012. Synthesis of novel nalidixic acid-basrd 1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives as potent antibacterial agents, *Chem. Biol. Drug Dis*.79, 384-397.

Abdel-Wahab, B.F., Abdel-Aziz, H.A., & Ahmed, E.M. 2009. Synthesis and antimicrobial evalution of some 1,3-triazole, 1,3,4-thiadiazole, 1,2,4-triazole, and 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazine derivatives including a 5-(benzofuran-2-yl)- 1-phenylpyrazole moiety, *Monatsh Chem*. 140: 601-605.

Pintilie O., Profire L., Sunel V., Popa M. & Pui A.2007. Synthesis and antimicrobial activity of some new 1,3,4-thiadiazole and 1,2,4-triazole compounds having a D, L-methionine moiety, *Molecules*. 12, 103-113.

Farghaly T. A., Abdallah M. A.& Aziz M. R. A. 2012. Synthesis and antimicrobial activity of some new 1,3,4- thiadiazole derivatives, *Molecules*. 17:14625-14636.

Wu Z., Shi J. C., Hu D.,& Song B. 2021. Design, synthesis, antibacterial activity, and mechanisms of novel 1,3,4- thiadiazole derivatives containing an amide moiety, *Journal of agricultural and food chemistry*, https://doi.org/10.1032/acs.jafc.1c01626

Sahu S., Sahu T., Kalyani G., and Gidwani B. 2021. Synthesis and evaluation of antimicrobial activity of 1,3,4-thiadiazole analogues for potential scaffold, *Journal of pharmacopuncture.* 24(1): 32-40.

Chen M., Zhang X., Lu D., Luo H., Zhou Z., Qin X., Wu W. & Zhang G. 2021. Synthesis and bioactivities of novel 1,3,4-thiadiazole derivatives of glucosides, *Frontiers in chemistry*. 9:645876.

Kadi A. A., Al-Abdullah E. S., Shehata I. A., Habib E. A., Ibrahim T. M., & El-Emam A. A. 2010. Synthesis, antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives, *Euro J Med Chem*. 45(11): 5006-5011.

Kadi A. A., El-Brollosy N. R., Al-Deeb O. A., Habib E. E. Ibrahim T. M., & El-Emam A A. 2007. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles, *Euro J Med Chem*.42(2):235-242.

Bahram L., Negar M., Ali A., & Alireza F.2011. Synthesis and in vitro antibacterial activity of new 2-(1-methyl-4-nitro-1H-imidazol-5-ylsulfonyl)-1,3,4-thiadiazoles, *E-J Chem*. 8(3):1120-1123.

Onkal T., Dogruer D. S., Uzun L., Adak S., Ozkan S., & Sahin M. F. 2008. Synthesis and antimicrobial activity of new 1,2,4-triazole and 1,3,4-thiadiazole derivatives, *Journal of enzyme inhibition and medicinal chemistry*. 23(2):277-284.

Janowska S., Khulyuk D., Bielawska A., Szymanowska A., Gornowicz A., Bielawski K., Noworol J., Mandziuk S., & Wujec M. 2022. New 1,3,4-thiadiazole derivatives with anticancer activity, *Molecules*. 27:1814.

Dawood K. M., & Gomha S. M. 2014. Synthesis and anti-cancer activity of 1,3,4-thiadiazole and 1,3-thiazole derivatives having 1,3,4-oxadiazole moiety, *J. Heterocyclic Chem*. 00: 00.

Chowrasia D., Karthikeyan C., Choure L., Sahabjada, Gupta M., Md Arshad, & Trivedi P. 2013. Synthesis, characterization and anti cancer activity of some fluorinated 3,6-diaryl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, *Arabian Journal of Chemistry*.

Rashdan R. M., Mohammad Farag M., El-Gendey M. S., & Mounier M. M. 2019. Toward rational design of novel anti-cancer drugs based on targeting ,solubility, and bioavailability exemplified by 1,3,4-thiadiazole derivatives synthesized under solvent-free conditions, *Molecules*. 24:2371.

Kumar D., Kumar N. M., Chang K. H., & Shah K. 2010. Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles, *European journal of medical chemistry*. 45: 4664-4668.

Schenone S., Brullo C., Bruno O., Bondavalli F., Ranise A., Filippelli W., Rinaldi B., Capuano A., & Falcone G. 2006. New1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities, *Bioorganic & medical chemistry*.14:1698-1705.

Maddila S., Gorle S., Sampath C., & Lavanya P. 2012. Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus, *Journal of Saudi Chemical Society*.

Chawla G., Kumar U., Bawa S., & Kumar J. 2012. Synthesis and evaluation of anti-inflammatory , analgesic and ulcerogenic activities of 1,3,4-oxadiazole and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives, *Journal of Enzyme Inhibition and Medicinal Chemistry*. 27(5):658-665.

Winter C. A., Risley E. A., & Nuss G. W. 1962. Carrageenan-induced edema in hind paw of the rats as an assay for anti-inflammatory drugs, *Proc So Exp Biol Med*. 111:544-547.

Kumar H., Javed S. A., Khan S. A., & Amir M. 2008. 1,3,4 Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: Synthesis and preliminary evaluation of biological properties, *Euro J Med Chem*. 43:2688-2698.

Sadat-Ebrahimi S. E., Mirmohammadi M., Tabatabaei Z. M., Arani M. A., Ashtiani S. J., Hashemian M., Foroumadi P., Meymandi A. Y., Moghimi S., Moshafi M. H., Norouzi P., Aedestani S. K.,& Foroumadi A. 2019. Novel 5-(nitrothiophene-2-yl)-1,3,4-thiadiazole derivatives: Synthesis and antileishmanial activity against promastigote stage of Leishmania major, *Iranian Journal of Pharmaceutical Research*. 18(4): 1816-1822.

Al-Qahtani A., Siddiqui Y. M., Bekhit A. A., El-Sayed O. A., Aboul-Enein H. Y., & Al-Ahdal M. N. 2009. Inhibition of growth of Leishmania donovani promastigotes by newly synthesized 1,3,4-thiadiazole analogs, *Saudi Pharmaceutical Journal*. 17:227-232.

Tahghighi A., Emami S., Ramzi S., Marznaki F. R., Ardestani S. K., Dastmalchi S., Kobarfard F., Shafiee A., & Foroumadi A. 2013. New 5-(nitroheteroaryl)-1,3,4-thiadiazoles containingacyclic amines at C-2: Synthesis and SAR study for their antileishmanial activity, *Journal of Enzyme Inhib. Med. Chem*. 28: 843-852.

Pattanayak P., Sharma R., & Sahoo P. K.2009. Synthesis and evaluation of 2-amino-5-sulfanyl-1,3,4-thiadiazoles as antidepressant, anxiolytic, and anticonvulsant agents, *Medicinal Chemistry Research*. 18:351-361.

Stillings M. R., Welbourn A. P., & Walter D. S. 1986. Substituted 1,3,4-thiadiazoles with anticonvulsant activity. 2 aminoalkyl derivatives, *Journal of Medicinal Chemistry*. 29: 2280-2284.

Singh A. K., Sarthy R. P., & Lohani M. 2012. Design, synthesis and anticonvulsant activity of some 1,3,4-thiadiazole derivatives, *Int. J. Chem. Sci.*10(3): 1487-1492.

Gan X., Hu D., Chen Z., Wang Y., & Song B. 2017. Synthesis and antiviral evaluation of novel 1,3,4-oxadiazole/thiadiazole-chalcone conjugates, *Bioorganic & Medicinal Chemistry Letters.*

Rashdan H., Abdelmonsef A. H.,& Abou-Krisha M. M. 2022. Synthesis and identification of novel potential thiadiazole based molecules containing 1,2,3-triazole moiety against COVID-19 main protease through structure-guided virtual Screening approach, *Biointerface Research in Applied Chemistry*. 12:8258-8270.

Oruç, E. E., Rollas, S., Kandemirli, F., Shvets, N., & Dimoglo, A. S. (2004). 1, 3, 4-thiadiazole derivatives. Synthesis, structure elucidation, and structure− antituberculosis activity relationship investigation. *Journal of medicinal chemistry*, *47*(27), 6760-6767.

Patel, H. M., Noolvi, M. N., Sethi, N. S., Gadad, A. K., & Cameotra, S. S. (2017). Synthesis and antitubercular evaluation of imidazo [2, 1-b][1, 3, 4] thiadiazole derivatives. *Arabian Journal of Chemistry*, *10*, S996-S1002.

Karakuş, S. E. V. G. İ., & Rollas, S. J. I. F. (2002). Synthesis and antituberculosis activity of new N-phenyl-N′-[4-(5-alkyl/arylamino-1, 3, 4-thiadiazole-2-yl) phenyl] thioureas. *Il Farmaco*, *57*(7), 577-581.

Kolavi, G., Hegde, V., ahmed Khazi, I., & Gadad, P. (2006). Synthesis and evaluation of antitubercular activity of imidazo [2, 1-b][1, 3, 4] thiadiazole derivatives. *Bioorganic & medicinal chemistry*, *14*(9), 3069-3080.

Joseph, A., Shah, C. S., Kumar, S. S., Alex, A. T., Maliyakkal, N., Moorkoth, S., & Mathew, J. E. (2013). Synthesis, in vitro anticancer and antioxidant activity of thiadiazole substituted thiazolidin-4-ones. *Acta pharmaceutica*, *63*(3), 397-408.

Djukic, M., Fesatidou, M., Xenikakis, I., Geronikaki, A., Angelova, V. T., Savic, V., ... & Saso, L. (2018). In vitro antioxidant activity of thiazolidinone derivatives of 1, 3-thiazole and 1, 3, 4-thiadiazole. *Chemico-Biological Interactions*, *286*, 119-131.

Jakovljević, K., Matić, I. Z., Stanojković, T., Krivokuća, A., Marković, V., Joksović, M. D., ... & Joksović, L. (2017). Synthesis, antioxidant and antiproliferative activities of 1, 3, 4-thiadiazoles derived from phenolic acids. *Bioorganic & medicinal chemistry letters*, *27*(16), 3709-3715.

Rabie, A. M., Tantawy, A. S., & Badr, S. M. (2018). Design, synthesis, and biological evaluation of new 5-substituted-1, 3, 4-thiadiazole-2-thiols as potent antioxidants. *Researcher*, *10*(7), 21-43.

Muğlu, H., Akın, M., Çavuş, M. S., Yakan, H., Şaki, N., & Güzel, E. (2022). Exploring of antioxidant and antibacterial properties of novel 1, 3, 4-thiadiazole derivatives: Facile synthesis, structural elucidation and DFT approach to antioxidant characteristics. *Computational biology and chemistry*, *96*, 107618.

Al-Omair, M. A., Sayed, A. R., & Youssef, M. M. (2015). Synthesis of novel triazoles, tetrazine, thiadiazoles and their biological activities. *Molecules*, *20*(2), 2591-2610.

Can, N. Ö., Can, Ö. D., Osmaniye, D., & Demir Özkay, Ü. (2018). Synthesis of some novel thiadiazole derivative compounds and screening their antidepressant-like activities. *Molecules*, *23*(4), 716.

Clerici, F., Pocar, D., Guido, M., Loche, A., Perlini, V., & Brufani, M. (2001). Synthesis of 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives and evaluation of their antidepressant and anxiolytic activity. *Journal of medicinal chemistry*, *44*(6), 931-936.

Yusuf, M., Khan, R. A., & Ahmed, B. (2008). Syntheses and anti-depressant activity of 5-amino-1, 3, 4-thiadiazole-2-thiol imines and thiobenzyl derivatives. *Bioorganic & medicinal chemistry*, *16*(17), 8029-8034.

Yousif, E., Majeed, A., Al-Sammarrae, K., Salih, N., Salimon, J., & Abdullah, B. (2017). Metal complexes of Schiff base: preparation, characterization and antibacterial activity. *Arabian Journal of Chemistry*, *10*, S1639-S1644.

Malik, S., Ghosh, S., & Mitu, L. (2011). Complexes of some 3d-metals with a Schiff base derived from 5-acetamido-1, 3, 4-thiadiazole-2-sulphonamide and their biological activity. *Journal of the Serbian Chemical Society*, *76*(10), 1387-1394.

Ghosh, S., Malik, S., Jain, B., & Ganesh, N. (2009). Synthesis, Characterization and biological studies of Zn (II) complex of schiff base derived from 5-acetazolamido-1, 3, 4-thiadiazole-2-sulphonamide, a diuretic drug. *Asian J. Exp. Sci*, *23*(1), 189-192.

Chohan, Z. H., Pervez, H., Rauf, A., & Supuran, C. T. (2002). Antibacterial Role of SO 4 2−, NO 3−, C 2 O 4 2− and CH 3 CO 2− Anions on Cu (II) and Zn (II) Complexes of a Thiadiazole-derived Pyrrolyl Schiff Base. *Metal-Based Drugs*, *8*(5), 263-267.

Basher, N. A., Flifel, I. A., & Mashaf, A. A. (2020, September). Synthesis, characterization and antibacterial study of some complexes derivatives from1, 3, 4–Thiadiazole Schiff base. In *IOP conference series: Materials Science and Engineering* (Vol. 928, No. 5, p. 052009). IOP Publishing.

Jha, A., Murthy, Y. L. N., Sanyal, U., & Durga, G. (2012). Rapid synthesis, characterization, anticancer and antimicrobial activity studies of substituted thiadiazoles and their dinucleating ligand metal complexes. *Medicinal Chemistry Research*, *21*, 2548-2556.

Turan, N., Topçu, M. F., Ergin, Z., Sandal, S., Tuzcu, M., Akpolat, N., ... & Karatepe, M. (2011). Pro-oxidant and antiproliferative effects of the 1, 3, 4-thiadiazole–based Schiff base and its metal complexes. *Drug and Chemical Toxicology*, *34*(4), 369-378.

Ahmed, Y. B., Merzouk, H., Harek, Y., Medjdoub, A., Cherrak, S., Larabi, L., & Narce, M. (2015). In vitro effects of nickel (II) and copper (II) complexes with 2, 5-bis (2-pyridyl)-1, 3, 4-thiadiazole on T lymphocyte proliferation and intracellular redox status. *Medicinal Chemistry Research*, *24*, 764-772.