



Review Article

PHARMACOLOGICAL ACTIVITY OF 1,3,4-THIADIAZOLE DERIVATIVES AND ITS COMPLEXES: A REVIEW

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ABSTRACT

In recent years 1,3,4-Thiadiazole derivatives and their transition metal complexes with biological activity have been widely studied. These compounds show a wide range of biological effectiveness like antibacterial, antifungal, antitumor as well as anti-inflammatory activity. This review provides a broad view of the synthesis and pharmacological activities of 1,3,4-Thiadiazole derivatives and its complexes.

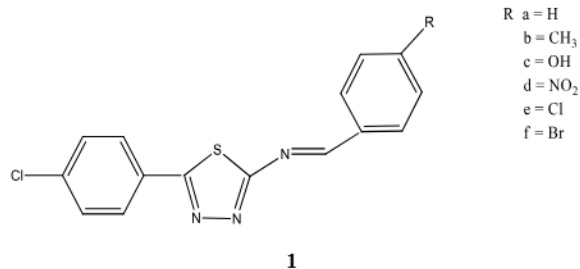
Keywords: 1,3,4-Thiadiazole, Metal complexes, Antimicrobial activity.

INTRODUCTION

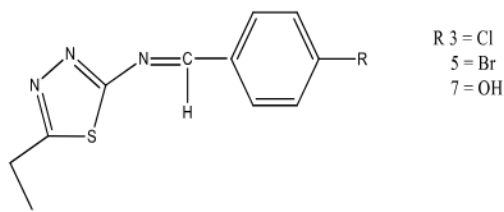
Bioinorganic chemistry is at the gateway of inorganic chemistry and biochemistry, i.e. it describes to the two mutual relationships between these two sub-disciplines, with a focus upon the feature of inorganic "substances" two in dwelling systems, which includes the transport, speciation, eventually, mineralization of inorganic materials, to which include two the use of inorganic in medical therapy and diagnosis. These "substances" can be steel ions (such as K^+ , Fe^{+2} and Fe^{+3}), composite ions (e.g. molybdate), coordination compound (like cisplatin and carbonyl technetium) or inorganic molecules such as CO , NO and O_2 . In other words, medicinal inorganic chemistry and biomineralization are necessary integral phase ¹⁻³. The development of the area of bioinorganic chemistry has extended the activity in Schiff bases and thiol derivative complexes, due to the fact that it has been identified that many of these complexes might also serve as models for biologically vital species ^{4,5}. Schiff bases derived from an amino and carbonyl compound are a necessary classification of ligands that coordinate to metal ions by using azomethine nitrogen and have been studied extensively. In azomethine derivatives, the C,N linkage is essential for biological activity, various azomethine have been pronounced to possess terrific antibacterial, antifungal, anticancer and antimalarial things to make ⁶. Schiff bases are usually bi-or tri- dentate ligands successful of forming very secure complexes with transition metals. Some are used as liquid crystals. In organic synthesis, Schiff base reactions are beneficial in making carbon-nitrogen bonds⁷. Thiadiazole is a 5-membered ring device containing two nitrogen and one sulfur atom. They happen in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4thiadiazole⁸. The chemistry and the purposes of these new Schiff base thiadiazole derivatives should be appreciably studied through coordinating to a number metal ion moieties. As a result, the structural-activity relationship study of 1,3,4-thiadiazoles should be elevated in the near future⁹.

BIOLOGICAL ACTIVITY OF 1,3,4-THIADIAZOLE DERIVATIVES

Mousa¹⁰ synthesized new six compounds (5a-5f) containing Schiff base and 1,3,4-thiadiazole and evaluated for antimicrobial activity. All the newly synthesized compounds were screened for their antimicrobial activity using four microorganisms, (*S. Aureus* and *B. Cereus*) as gram-positive and (*E. coli* and *P. Aeruginosa*) as gram- negative bacteria. The compounds **5b** exhibited the least inhibition of bacterial while **5F** was the highest growth as compared to standard drugs.

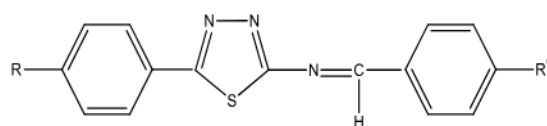


Naveen et al¹¹ have reported the synthesis and characterization of a series of Schiff base by the condensation of 5-ethyl-1,3,4-thiadiazol-2-amine with different aromatic aldehydes. These compounds were screened for *in vitro* antibacterial and antifungal activity against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Ralstonia solanacearum*, *Aspergillus Niger*, *Aspergillus flavus* and *Alternaria solani*. All the compounds were reported to exhibit potent antibacterial and antifungal activity.



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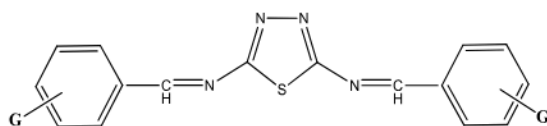
Pandey et al.¹² described synthesized new Schiff base of the type, 2-amino-5-aryl-1,3,4-Thiadiazole with different aromatic aldehyde and characterized through IR, and ¹H NMR. The synthesized compounds have been screened for antimicrobial activity, analgesic activity, and anti-inflammatory. The compounds **4a**, **4d**, **4e** and **4j** showed good antibacterial activity against gram-positive bacteria, while compounds **4b**, **4d**, **4e** and **4j** showed good antibacterial activity against gram-negative bacteria.



3

R = OCH ₃	R' = OH	R = OCH ₃	R' = NO ₂
R = OH	R' = OH	R = OH	R' = NO ₂
R = Cl	R' = OH	R = Cl	R' = NO ₂
R = NO ₂	R' = OH	R = NO ₂	R' = NO ₂
R = N(CH ₃) ₂	R' = OH	R = N(CH ₃) ₂	R' = NO ₂

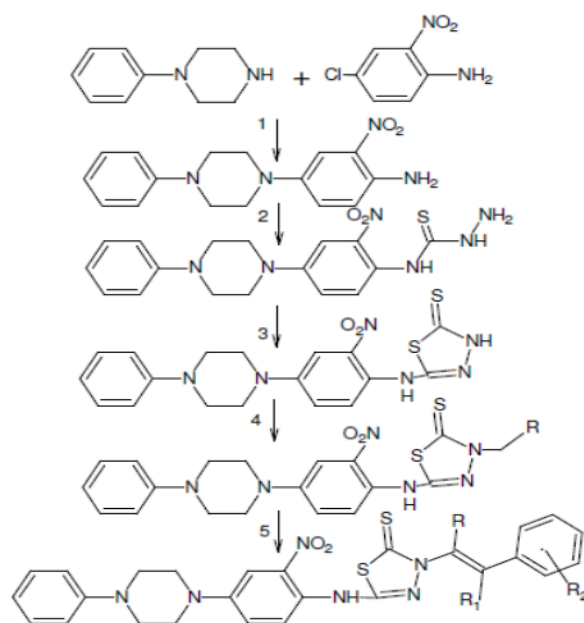
Series compounds (**0-10**) containing 1,3,4-thiadiazole and Schiff base were synthesized. The chemical structure of the prepared compounds was investigated by using analytical and spectral means. All the compounds were screened for their antioxidant activity. Compounds **5** exhibited the highest antioxidant activity¹³.



4

Compd.	G	Compd.	G
0	H	6	m-Cl
1	p-Cl	7	m-Br
2	p-Br	8	m-OCH ₃
3	p-OCH ₃	9	m-NO ₂
4	p-NO ₂	10	m-OH
5	p-OH		

Prakash¹⁴ has discussed synthesized series of new Schiff bases and hydroxyl derivatives of 1,3,4-thiadiazole containing N-phenyl Piperazine moiety. All the newly synthesized compounds were evaluated for their antibacterial activity against *S.aureus*, *E.coli*, *K.pneumoniae* bacterial strains and antioxidant activity *in vitro* by reducing power activity and Hydrogen peroxide-scavenging activity. The compounds (**Id_a**) and (**Ie_a**) showed significant antibacterial activity, while the other compounds showed moderate antibacterial.

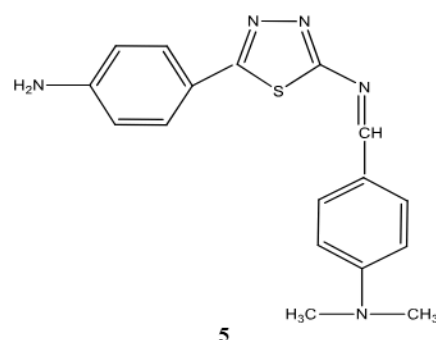


Scheme -1

NO.	Compound
1	Benzene
2	CS ₂ , NH ₂ -NH ₂ and ClCH ₂ COONa in NH ₃
3	CS ₂ in DMF
4	HCHO and Substituted amines in ethanol
5	Carbonyl compound and anhydrous sodium acetate in acetic acid

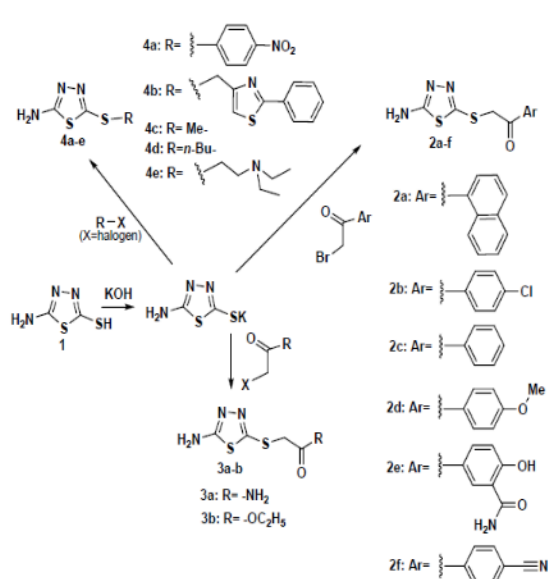
R	R ₁	R ₂
Anisidino	H	4-hydroxy
morpholino	CH ₃	3-methoxy-benzilidene
piperidino		4-hydroxy-benzilide

Hassan et al.¹⁵ synthesized 5-(4-aminophenyl)-2-amino-1,3,4-thiadiazole derivatives and evaluated anticancer activity against Breast cancer (MCF7) and human prostate cancer (DU 145). The anticancer results revealed that thiadiazole derivative exhibited more effect in breast cancer than in prostate cell line.

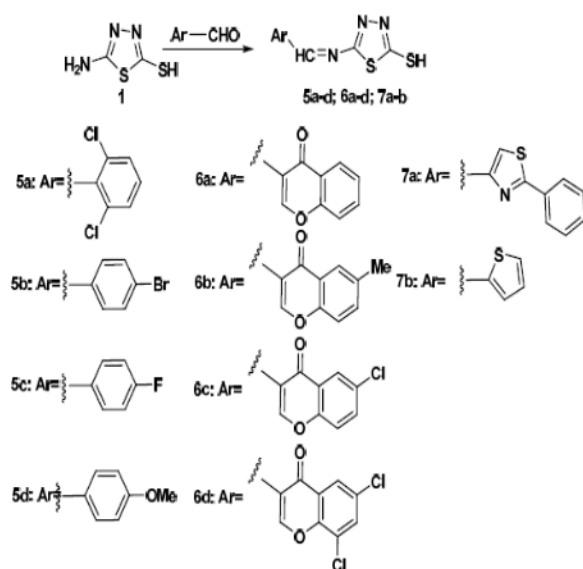


5

A new two series of compounds of S-substituted 5-amino-2-mercapto-1,3,4-thiadiazoles and Schiff bases (N-substituted 5-mercapto-1,3,4-thiadiazol-2-imines) derivatives were synthesized by reflux conditions, respectively, using microwave irradiation. The synthesized compounds were screened for antibacterial activity and were characterized by mass spectroscopy, ¹H NMR and elemental analysis¹⁶.

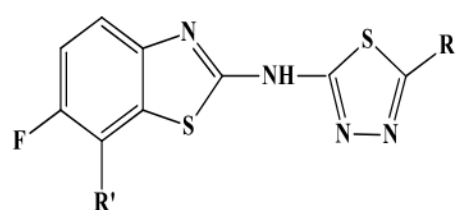
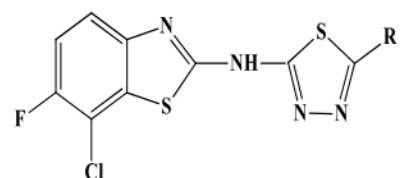
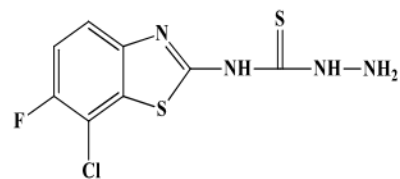
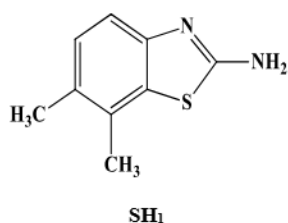


Scheme - 2



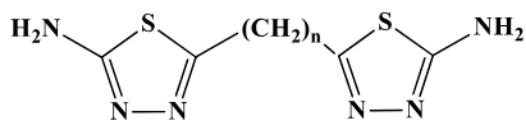
Scheme - 3

A series of fluoro benzothiazole incorporated 1, 3, 4 - thiadiazole (**SH₁-SH₁₁**), was presented by Sugumaran et al.¹⁷ The structure of the synthesized compounds was confirmed by UV, IR, ¹H NMR, Mass spectral analysis and evaluated for their antimicrobial and anti-inflammatory activity. Growth inhibitory activities of compounds **SH₆-SH₁₁** against revealed significant good bacterial activity. Compound **SH₁₁** was found to have superior anti-inflammatory activity in the inhibition than compound **SH₆**.



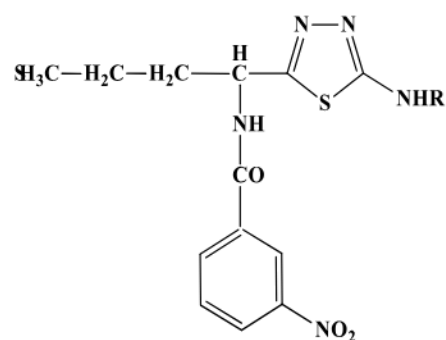
6

Ashutosh et al.¹⁸ presented a series of 1, 3, 4-Thiadiazol-2-Amine (**4a-h**) derivatives and their evaluation an antimicrobial activity against *B. Subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* bacterial strains and *S. cerevisiae*, *A. niger*, *C.albicans* fungal strains . Compounds **30e**, **30f** and **31** showed good anti-inflammatory and analgesic activity.



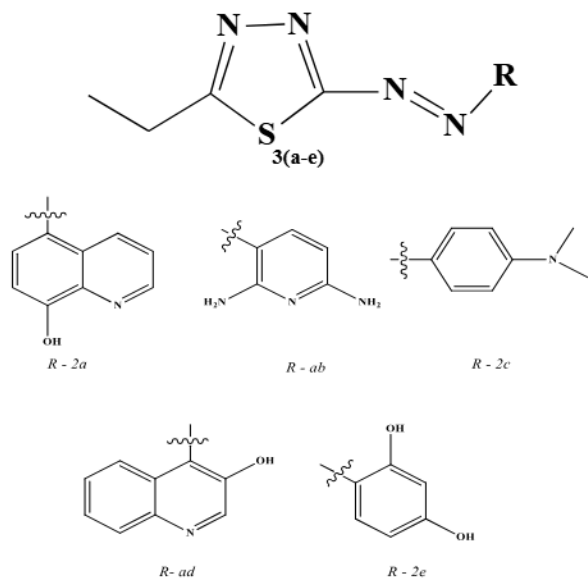
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Profire et al¹⁹ introduced the synthesis and antimicrobial activity of a new 1,3,4-thiadiazole derivatives (**27a-e**). The compounds were tested in vitro against a panel of microorganisms, including *Staphylococcus aureus*, *Bacillus anthrax*, *Bacillus cereus*, *Sarcina lutea* and *Escherichia coli* strains. The results revealed that the newly synthesized compounds exhibited promising antibacterial activities against *Bacillus anthracis* and *Bacillus cereus*.



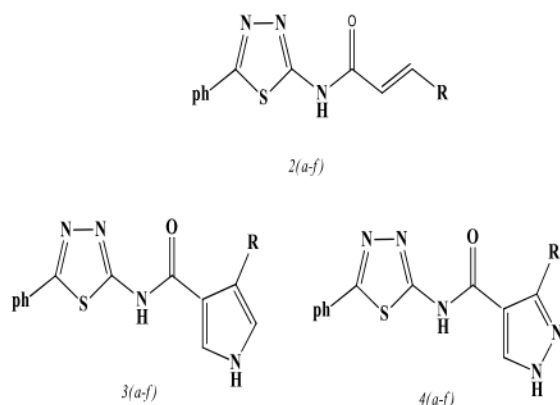
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Kumar et al²⁰ synthesized a series of 5-Ethyl-1,3,4-thiadiazole-2-amine **3** (**a-e**) and were evaluated for antibacterial activity against gram (+ve) *B. megaterium*, *B. subtilis* and gram(-ve) *E. coli* and *A.aerogens* and antifungal activity against *Aspergillus Flavus*, *Chrysosporium Keratinophilum* and *Candida Albicans*. Compound **3a** and **3b** showed good antimicrobial activities as compared with other compounds. However, compounds **3a** was found to show good antifungal activity.



9

3 new series of (E)-3-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide derivatives (**2a-f**), 4-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1Hpyrazole-3-carboxamide derivatives (**3a-f**) and 4-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1Hpyrrole-3-carboxamide derivatives (**4a-f**) were synthesized and characterized by elemental analysis LCMS mass, FT-IR spectra ¹H and ¹³C NMR. All the synthesized compounds were screened for their anti-inflammatory activity. Compounds **3c**, **3d**, and **4c** showed potent anti-inflammatory activities when compared with the standard drugs²¹.

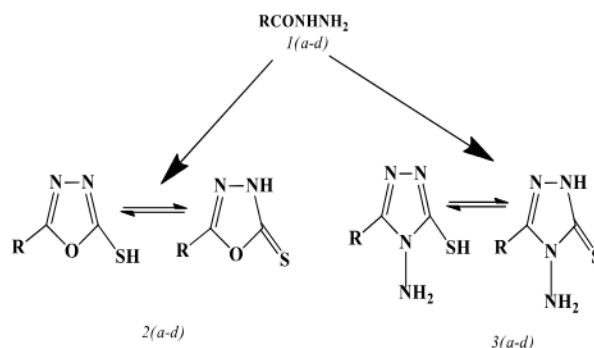


R = C₆H₅, 4-Br-C₆H₄, 4-NO₂-C₆H₄, 4-F-C₆H₄, 4-I-C₆H₄, 4-Cl-C₆H₄

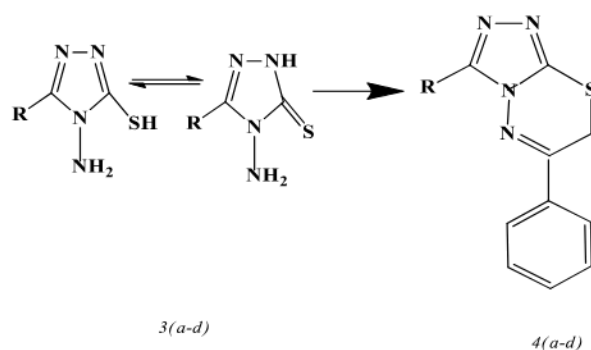
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Ahmad et al²² have synthesized a series of three novel 5-long chain alkenyl/hydroxyalkenyl-1,3,4-oxadiazol-2-thiones, **2(a-d)**, 4-amino-5-long chain alkenyl/ hydroxyalkenyl-1,2,4-triazol-3-thiones, **3(a-d)** and 3-long chain alkenyl/ hydroxyalkenyl-6-phenyl-7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines, **4(a-d)** and

investigated for *in vitro* anticancer activity against three different human cancer cell lines namely; human hepatocellular carcinoma (Hep3 B), human breast adenocarcinoma (MCF 7) and human cervical carcinoma (HeLa) and PBMCs. All compounds have shown possess moderate to good activity but compounds **4c** and **4d** were the most promising cytotoxic agent with IC₅₀.



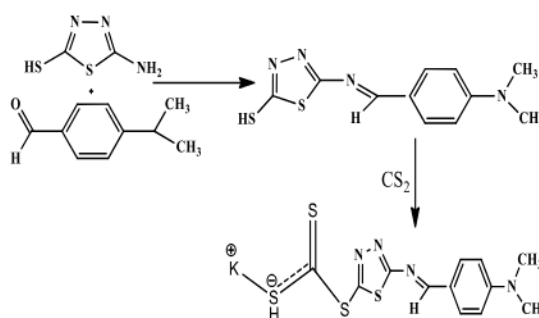
Scheme-4



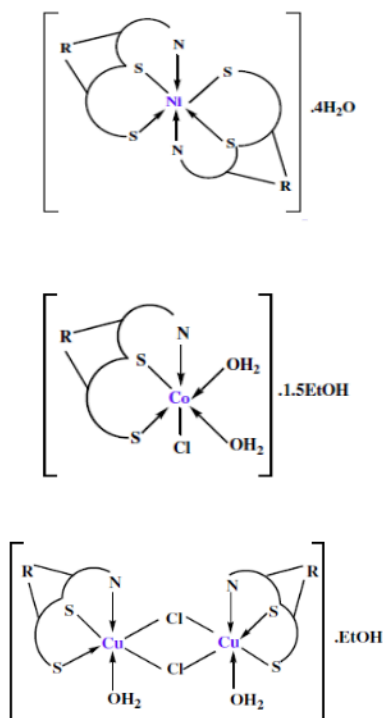
Scheme - 5

1,3,4-THIADIAZOLE DERIVATIVES LIGAND AND THEIR COMPLEXES

Novel complexes of copper, nickel, and cobalt individually with novel Schiff base derived from potassium 2-N (4-N,N-dimethylaminobenzylidene)-4-trithiocarbonate thiadiazole and 4-N,N-dimethylaminobenzylidene (Scheme-6) was investigated. The structure geometry of the ligand and their metal complexes had been resolved, the ligand acts as a tridentate chelating and coordinated with metal ion via the two sulfur atoms as well as N atom of the azomethine group. All of the complexes have octahedral geometry. The ligand and their complexes were investigated for *in vitro* antibacterial activity for both gram negative and gram positive bacterial strain. The Ni(II) complex showed higher action against bacterial strain than other complexes and ligand when compared them with ampicillin as a standard drug²³.

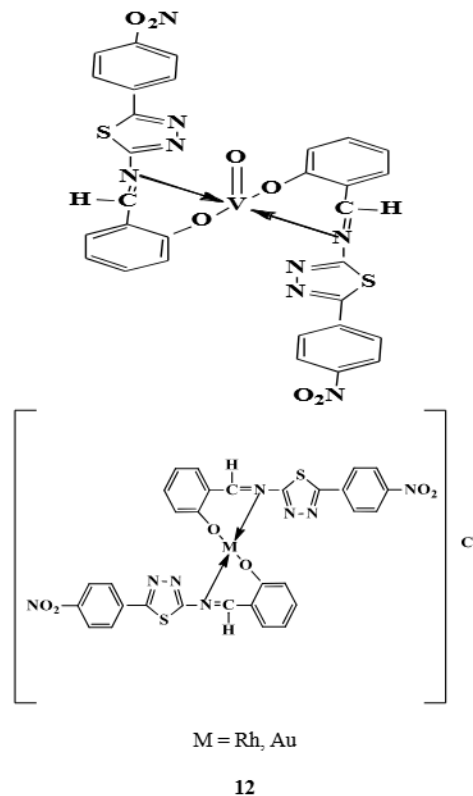
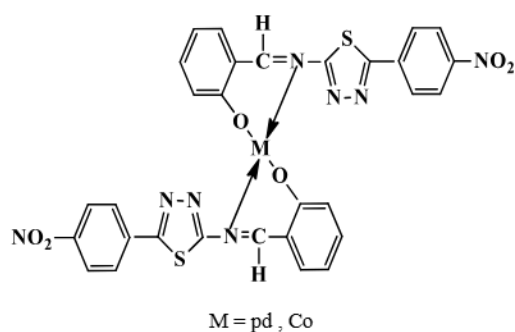


Scheme - 6



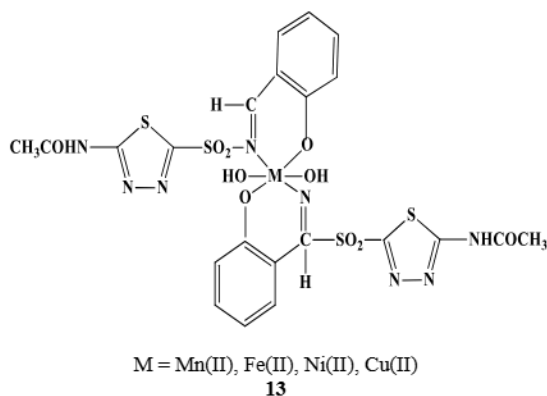
11

Yousif et al.²⁴ studied the effect of metal complexes of Schiff base on the biological activity. A novel five new metal complex derivatives of 2N-salicylidene-5-(p-nitro phenyl)-1,3,4-thiadiazole with the metal ions Vo(II), Co(II), Rh(III), Pd(II) and Au(III) (Fig.12) had been prepared. The ligand and their metal complexes were screened for their *in vitro* antibacterial activity. The result demonstrated that all complexes have moderate activity against tested bacterial strains and slightly higher compared to the ligand, HL.



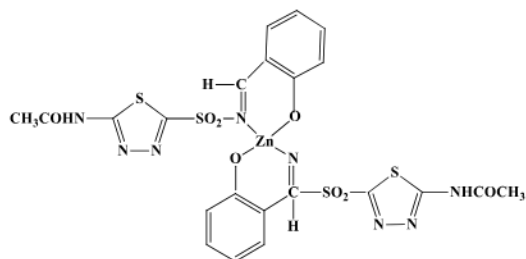
12

The metal complexes of Mn(II), Fe(II), Ni(II) and Cu(II) with Schiff bases of 5-acetamido-1,3,4-thiadiazole-2-sulphonamide (Fig.13) were screened against *Aspergillus niger* and *A. flavus*. The ligands presented here and their transition metal complexes gave better results against the growth of fungi. From the results, it can be observed that the complexes showed greater activity as compared to the Schiff base. It is found that the activity increases upon coordination. The increased activity of the metal chelates can be explained on the basis of the chelation theory²⁵.



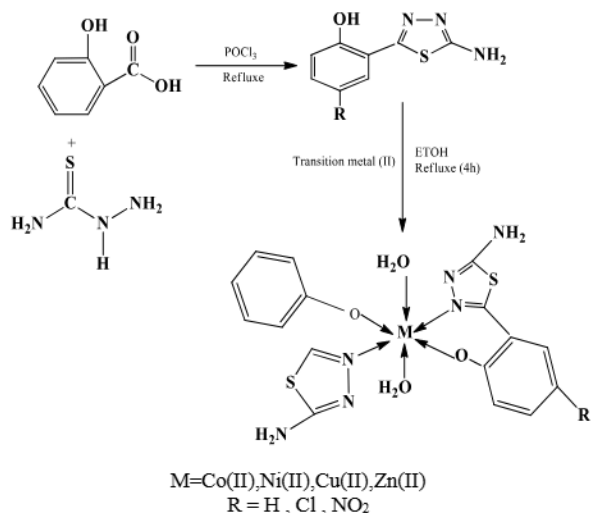
13

Ghosh et al.²⁶ described the synthesis Schiff base (Acetazolamide) derived from 5-acetazolamido-1,3,4-thiadiazole-2-sulphonamide and their zinc (II) complexes (Fig.14) in order to study the biological activity albino rats. The used parent drug as standard to compare the effect of the synthesized complexes screened albino rats. They found that the Zn (Acetazolamide) complex have encouraging activity compared with (parent drug) controlled rat and acetazolamide pure drug.



14

A novel set of ligands 2-amino-5-hydroxyphenyl-1,3,4-thiadiazoles obtained from the reaction of thio semicarbazide with substituted salicylic acid and its Co(II), Ni(II), Cu(II) and Zn(II) compounds (Scheme-7) were prepared and characterized by molar conductance, elemental analysis, ¹HNMR, infrared spectroscopy, electronic, magnetic susceptibilities, FAB-mass, ESR, and thermal studies. It is suggested that the ligands act as a bidentate coordinate to each metal by phenolic oxygen of salicylic acid moiety via deprotonation and through nitrogen at 4th position of thiadiazole moiety to form octahedral complexes with Co(II), Ni(II) and Zn(II) while complexes with Cu(II) have distorted octahedral geometry. These compounds have been screened for antibacterial, antifungal, and antitubercular activities 27.

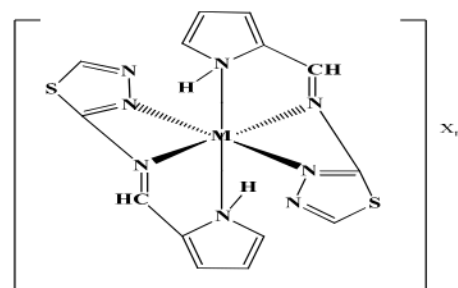


Scheme-7

Obaleye et al.²⁸ Synthesized, spectroscopic characterization and biological studies of Co(II), Ni(II), and Cu(II) complexes of 2,5-diamino-1,3,4-thiadiazole (L), derived from semicarbazide hydrochloride. The ligand coordinates through sulfur and nitrogen of the amines. The characterization involved elemental analysis, atomic absorption, molar conductance, thin layer chromatography, IR, UV-Vis, and magnetic susceptibilities. From the above studies, it is concluded that the ligands act as a tridentate molecule with stoichiometry being 1:2 (metal:ligand) obeying the general formula [(ML₂)]X₂. Co(II), Ni(II) and Cu(II) complexes possessing an octahedral geometry. The ligands and their corresponding complexes were investigated for *in vivo* antimicrobial activity for the fungal and bacterial strain. The biological studies showed that the metal complexes are not toxic at the dosage level administered. Based on various activities observed, metal complexes of 2,5-diamino-1,3,4-thiadiazole would be a better therapeutic drug for antibacterial treatment.

New metal complex derivatives of N-(2-pyrrolylmethylene)-2-amino-1,3,4-thiadiazole with the metal ions Zn (II) and Cu (II) (Fig.15) have been prepared and characterized quantitatively and

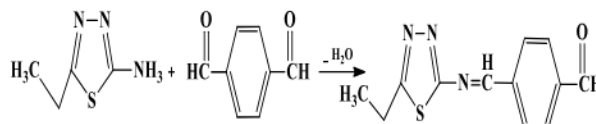
qualitatively by using various spectroscopic techniques, analytical, and physical data. From the spectral study, the ligand behaves as tridentate and coordinate with metal through nitrogen heteroatom. All of the complexes have octahedral geometry unless Cu(II) complexes have distorted octahedral geometry. The Schiff base ligand and its complexes were tested for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* 29.



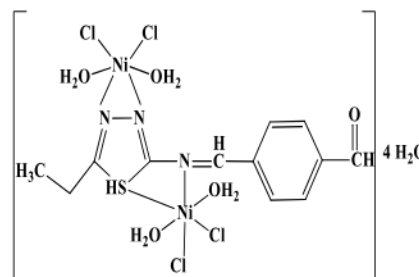
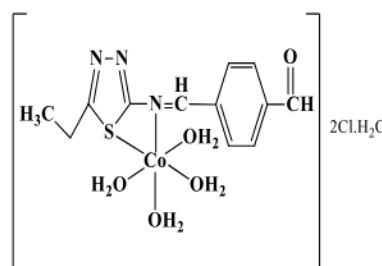
M = Cu(II) or Zn(II)
X = NO₃⁻ > C₂O₄²⁻ > CH₃CO₂ > Cl > SO₄²⁻
n = 1 or 2

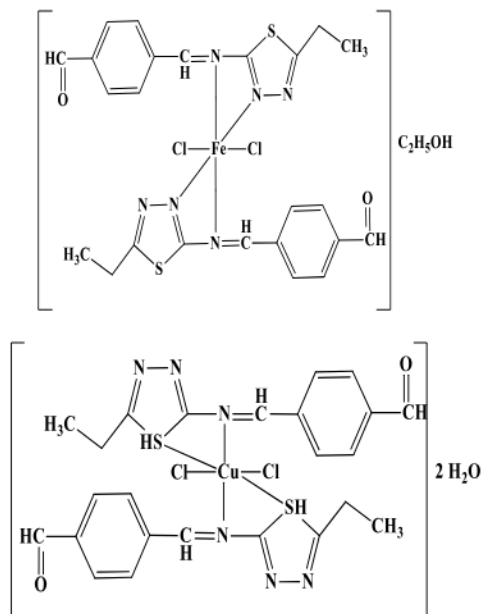
15

Furthermore, in continuation research by Turan et al.³⁰ in the field of Schiff base ligand synthesized from the condensation of 2-amino-5-ethyl-1,3,4-thiadiazole (1) with terephthalaldehyde (Scheme-8). Moreover Co(II), Ni(II), Cu(II) and Fe(II) of ligand were prepared (Fig.16) and their geometry structure was studied using different spectroscopic methods of analysis. On the basis of these studies, the geometrical structures of the prepared complexes are octahedral.



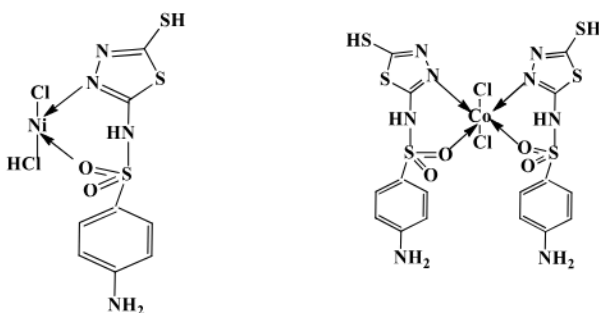
Scheme - 8





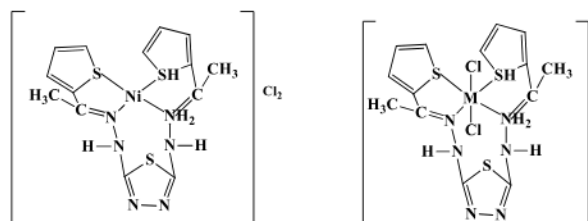
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Complexes of Co(III), Fe(III), Cr(III), Cu(II), and Ni(II) with 4-amino-N-(5-sulfanyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide were prepared, and their structures were studied by various spectroscopic methods. The infrared spectra of the complexes displays the same idea about the chelating of ligand to the metal ion and indicated that the ligand coordinated through thiadiazole nitrogen atoms and sulfonamide oxygen³¹.



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Eissa et al.³² discussed the synthesis, characterization and biological activities of Co(II), Ni(II), Cu(II) and Zn(II) chelates with [2,5-di(1-thiophen-2-yl-ethylidene)-hydrazine] 1,3,4-thiadiazole]. The antimicrobial activity against the bacterial and fungal microorganisms was studied and it has been noticed that all prepared complexes show good biological activity against microbial.



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

18

CONCLUSION

1, 3, 4-thiadiazole are one of the most important chemical classes of compounds having a common integral feature of a variety of medicinal agents. Literature review reveals that the compounds containing 1, 3, 4-thiadiazole nucleus and its complexes exhibited diverse biological activities, and very simple synthetic process too. This important functional group class has considerable potential and no doubt will offer new and exciting medicinal chemistries in the near future.

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