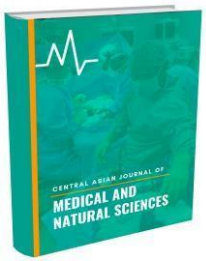

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Article

New Thiadiazole Derivative Shows Promising Bioactivity with Transition Metals in Rats

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Abstract: This study explores the synthesis and characterization of new transition metal complexes using 1,3,4-thiadiazole-2-amino,5-thiol derivatives as novel ligands, with CrCl3.6H2O, FeCl3, and NiCl2.6H2O. Characterization was achieved through magnetic susceptibility, molar conductance, 1H NMR, IR spectroscopy, mass spectrometry, and elemental microanalysis (C.H.N.). The biological effects were evaluated on rats, focusing on hemoglobin (Hb), packed cell volume (PCV), liver enzymes, urea, and creatinine levels. Results indicated that the thiadiazole derivative increased Hb and PCV, while reducing liver enzymes, urea, and creatinine levels, suggesting no toxic effect and potential anti-inflammatory properties. Further studies are recommended to investigate potential anti-cancer, anti-bacterial, and anti-fungal activities. This research fills a knowledge gap by providing new insights into the bioactivity and structural characteristics of thiadiazole metal complexes.

Keywords: Thiadiazole, Characterization, Liver Enzymes, Magnetic Susceptibility, Blood Parameters.

1. Introduction

Heterocyclic compounds are organic substances with a ring structure that include elements other than carbon, such nitrogen, sulfur, or oxygen acting as the heteroatom. Because of their intriguing physiological properties, a number of five-membered aromatic systems, including azole, pyrole, thiazole, thiadiazole, oxadiazole, triazene, and others, with three heteroatoms arranged symmetrically, have been studied[1][2]. These systems also demonstrate a wide range of biological activities. Thiadiazole is a heterocyclic molecule with an aromatic five-membered ring that contains one sulfur atom and two nitrogen atoms. 1, 3, 4-thiadiazole is the name for thiadiazole and related chemicals. The remaining four isomeric forms of thiadiazole, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,2,4-thiadiazole, are found in nature. 1,3,4-thiadiazoles are significant substances used in numerous technological domains, medicine, and agriculture[3]. In the medical area, several thiadiazoles have been patented for the treatment of various disorders, and some of them have been turned into commercial products[4]. Many thiadiazoles have been patented in the medical area to cure a broad range of illnesses, and due to their beneficial properties, some of them have turned into commercially available compounds in medicinal chemistry[5]. It is also recognized to possess special anti-inflammatory and antibacterial properties[6]. Other intriguing properties of differently substituted

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thiadiazole moieties include analgesic, antibacterial, anti-tubercular, anticonvulsant, and anti-hepatitis B viral properties. The –N=C-S moiety that exists in the structure of 1,3,4-thiadiazoles allows for a variety of biological activities[7][8].

2. Materials and Methods

ChemistryExperimental :

B.D.H. Chemicals and Fluka were the suppliers of all chemicals. Using CsI disc for the metal ion complexes and KBr disc for the produced ligands, the Shimadzu FT-IR-spectrometer was used to record the IR spectra. Thermofinigan flash was used to do elemental analysis. Using a Shimadzu A-A-500 AFG, Japan, S/N 23-0932-21-0015 power-150, voltage-AC110/220V, 50-60 Hz) flame spectrophotometer, the transition metals percentages in the produced complexes were ascertained. 1H NMR spectra were obtained using a 500MHz Bruker DRX System AL. Using an energy of (70 eV), the mass spectra of the ligand and complexes were recorded using the (HP)/MS Model 5973 Network Mass Selective Detector. The Gouy technique was used to conduct magnetic measurements with the balance magnetic susceptibility model M.S.B Auto. A conductivity meter called the Inolabcond 720 was used to measure the complexes' molar conductances in DMSO at room temperature.

1. Preparation of 5-amino-1,3,4-thiadiazole-2-thiol [9]

Anhydrous sodium carbonate (0.054 mole, 5.82gm) and carbon disulfide (0.133 mole, 10.2gm) were added to thiosemicarbazide (0.109 mole, 10gm) suspended in anhydrous ethanol (50 ml). The reaction mixture was heated for seven hours while being stirred under reflux. TLC provided evidence that the reaction had finished. Using a rotary evaporator, the solvent was mainly evaporated at lower pressure. A 50 ml solution of water was used to dissolve the residue, and 9 ml of strong hydrochloric acid was used to acidify it.To get the pure chemical, the product was recrystallized from ethanol and water. The physical characteristics include a 70% yield, faint yellow crystals, and a melting point of 233–235 oC.

2. Preparation of (E)-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)phenol[10]

Add a few drops of glacial acetic acid to a solution of 5-amino-1,3,4-thiadiazole-2-thiol (0.21mol, 29.2 g) in 100 ml of 100% ethanol with 2-hydroxybenzaldehyde (0.1 mol, 13.4 g). For four hours, the reaction mixture was heated and refluxed. TLC provided evidence that the reaction had finished. Using a rotary evaporator, the solvent was mostly eliminated at low pressure, and the pure chemical was obtained by recrystallizing the ethanol/water mixture.The physical characteristics include yellow crystals, an 82% yield, and a melting point between 262 and 264 oC.,(scheme 1).

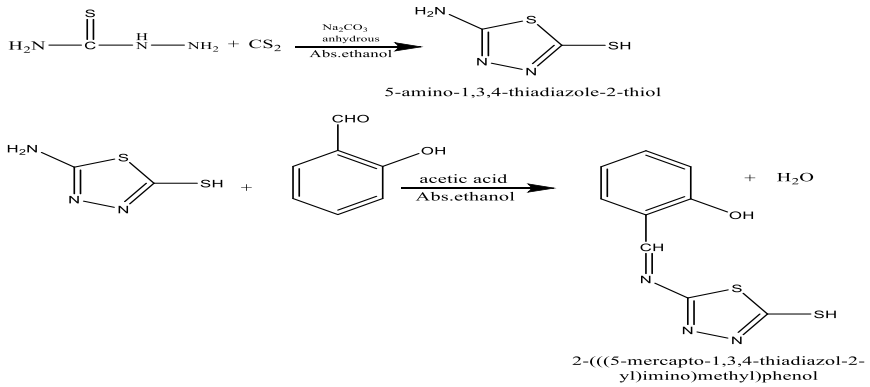


Figure 1. The physical characteristics include yellow crystals, an 82% yield, and a melting point between 262 and 264 Oc.

3. General procedure preparation of complexes of ligand

The transition metal salts (CrCl3.6H2OFeCl3 and NiCl2.6H2O) dissolved in hot absolute ethanol (30 ml) were mixed with a solution of (5 mmol) from the ligand dissolved in absoluteethanol (20 ml). For 1.5 hours, the mixture was refluxed. The solvent was eliminated after the mixture cooled by vacuum evaporation. Using DMF-ethanol (30–70 v/v) after filtering, the precipitate was crystallized[11].

Table 1. Displays the physical characteristics and molecular formula of the resulting complexes.

NO.	Formula	M.Wt	Color	(ʌm)[a]	M.P.°C	Yield %	μ_{eff}
1	Ligand	237	Faint yellow crystals	--------	(233-235)	70	----------
2	$[Cr(L)_2\ Cl_2]Cl$	632.94	violate	33	244-246	88	3.7
3	$[Fe(L)_2\ Cl_2]Cl_2$	636.79	black	41	261-263	76	2.3
4	$[Ni(L_1)\ Cl_2]$	366.89	Pale blue	17	284D	81.4	0.4

a= Ω-1 cm2 mol-1 (in DMSO solvent).

Biological Experimental

1. Protocol of experiment:

16 male albino strain rats were kept in an experimental home with regulated temperatures. They were acquired from Thi-Qar University's College of Sciences. They were split into two groups, each with an average weight of between 130 and 200 grams. Commercial pellets were provided to the animals. In dimethylsulfoxide (DMSO), 2(mercapto-1,3,4-thiadiazole-2YI)amino)methyle) phenol was dissolved[12]. The control group and the treatment group were the two equal groups into which the experimental animals were split. For 14 straight days, the treatment group received an intraperitoneal injection of 0.5 ml of DMSO containing 25 mg / kg of 2(mercapto-1,3,4-thiadiazole-2YI)amino)methyle) phenol, whereas the control group received 0.5 ml of DMSO [13]. On day 15, all of the animals were butchered and put to death using anesthetic ether.

2. Blood and Biochemical parameters

Animals were used to provide blood. It was split into two sections: one was used for blood analyses (Hb, PCV), which were computed using the Baker and Silvorton (1976)[14] technique. The remaining portion was obtained by centrifuging the sample for 10 minutes at 2000 rpm and using it for biochemical analyses. The levels of urea and creatinine were measured, and the activities of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assessed using a kit that was specifically designed for this purpose.

4. Results

At room temperature, the newly synthesized ligand and its complexes exhibit high stability in the solid state. While their metal complexes are soluble in DMSO and DMF, the ligands themselves are soluble in typical organic solvents. The biological results were subjected to statistical analysis utilizing the T-test at statistical significance ($p<0.05$) to compare the treatment and control groups.

1. Molar conductance

(ʌm) of the complexes' 10-3MDMSO solutions were calculated. The values molar conductance are given in Table 1. The findings for the Cr (III) and Fe (III) complexes demonstrate that they are 1:1 electrolytes, indicating the presence of one chloride ion outside the coordination sphere. This is confirmed by the Ni (II) complex, which is seen as neutral since the molar conductance (ƛm) values are insufficient to indicate the

presence of an ionic complex.

2. Magnetic moments

Table 1 lists the magnetic moment (μeff) values for the complexes containing newligands.The Fe(III) complex 1's magnetoelectric moment value is 2.3 BM, which is equivalent to one unpaired electron[13]. This value may indicate an octahedral structure that is free of spin and the low spin state of Fe(III).For the Ni(II) complex, the magnetic moment of 0.4 BM indicates a low spin square planar configuration. The Cr(III) complex has a magnetic moment of 3.7 BM, which implies that there are three unpaired electrons present and maybe an octahedral form that is free of spin.

3. IR spectra

The infrared spectra technique was used to identify the generated coordination complexes, especially when comparing the position of the donor atom with the free ligand spectra. The infrared spectra were used to locate the absorption bands for the various active groups, such as (C=N), (C=S), (SH), (C=N–N=C), (M–S), (M–N), and (M–Cl), in addition to determining the ligand. Four bands, corresponding to the (C=N), (C=S), (SH), and (OH) groups, are seen in the ligand at (1622), (1258), (2556), and (3465) cm-1Additionally, the bands at (1535) cm-1 and (740) cm-1, respectively, suggest the formation of the (C=N–N=C) and (C–S–C) bands. In ligand-metal complexes, stretching frequencies for the (C=N), (C=S), and (SH) are diminished and moved to lower frequencies of around 5–30 cm-1. On the other hand, although they remain stationary, the stretching frequencies for the (C=N–N=C), (C–S–C), and (OH) also weaken [15]. This is because these groups do not coordinate with metal ions. Three newly discovered bands are identified as (M–N), (M–S), and (M–Cl); these bands are found in the ranges (442–485) cm–1, (356–425) cm–1, and (255–343) cm–1, respectively. These bands show coordination. As a result, the nitrogen and sulfur atoms in the ligand's (C=N) and (SH) groups have coordinated (Fig. 1-4 and Table 2).

Table 2. The nitrogen and sulfur atoms in the ligand's (C=N) and (SH) groups have coordinated

compound	ν C=N	ν OH	νC=S	νSH	νC=N-C=N	νC-S-C	νM-S	νM-N	νM-Cl
ligand	1622	3465	1258	2556	1535	740	--	--	--
Cr-L	1614	3465	1243	2551	1535	740	352	476	343
Fe-L	1620	3465	1253	2548	1535	740	425	442	276
Ni-L	1595	3465	1245	2535	1535	741	387	485	324

4. 1H NMR spectra

The ligand's 1H NMR spectra exhibit distinctive signals because of the (-OH) proton, which appears at 4.5 ppm. Furthermore, the presence of the band at 5.8 ppm may be attributed to the ligand's (–SH) proton. The band between 6.9 and 7.8 ppm may be attributed to protons in aromatic rings, whereas the band seen at 8.5 ppm may be attributed to ligand (CH=N) protons.(Figure 4).

5. Mass spectra

1. Ligand mass spectrum

The emergence of the base peak, series of peaks, and molecular ion peak (M+) in the ligand spectrum, as well as the process of breakup contained in the scheme (2), are shown in figures 5 and 3

Table 3. Important peaks of mass spectrum for ligand

No.	Fragmentation	m/z
1	$C_9H_7N_3OS_2$ (Molecular ion)	237
2	$C_8H_7N_3OS$	193
3	$C_3H_2N_3S_2$	144
4	$C_2H_3N_3S_2$	133
5	C_7H_7NO	121
6	$C_2HN_2S_2$	117
7	CHN_2S_2	105
8	C_6H_6O	94
9	C_6H_5 (base peak)	77
10	C_5H_5	65
11	CHNS	59

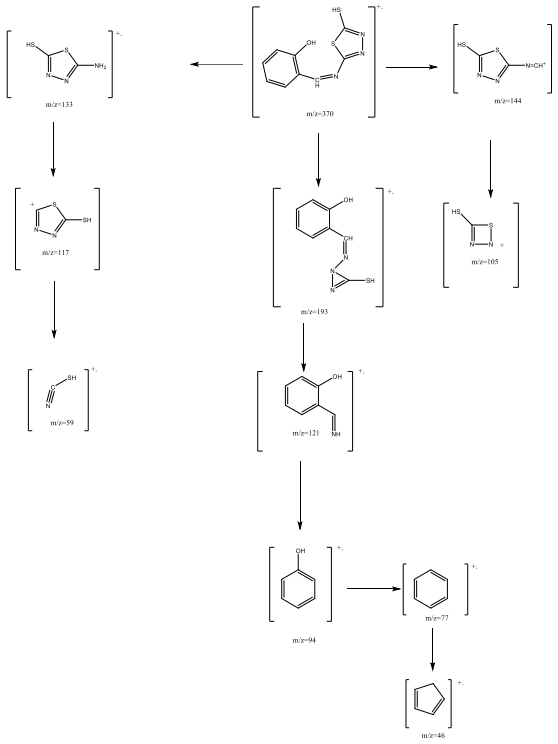


Figure 2. Important peaks of mass spectrum for ligand

Mass spectra of Cr-L

The Cr-L spectrum appearance of the molecular ion peak (M+) , base peak and series of important peaks belong to lose chloride atoms ,the break up embedded in the,(fig. 6 and table 4) .

Table 4. Important peaks of mass spectrum for Cr-L

No.	Fragmentation	m/z
1	$[Cr(L)_2Cl_2]^{+\cdot}Cl$	632
2	$[Cr(L)_2Cl_2]^{+\cdot}$	596
3	$[Cr(L)_2Cl]^{+\cdot}$	561
4	$[Cr(L)_2]^{+\cdot}$	525

Mass spectra of Fe-L

The Fe-L spectrum appearance of the molecular ion peak (M+) , base peak and series of important peaks belong to lose chloride atoms ,the break up embedded in the,(fig. 7 and table 5) .

Table 5. Important peaks of mass spectrum for Fe-L

No.	Fragmentation	m/z
1	$[Fe(L)_2Cl_2]^{+\cdot}Cl$	636
2	$[Fe(L)_2Cl_2]^{+\cdot}$	600
3	$[Fe(L)_2Cl]^{+\cdot}$	565
4	$[Fe(L)_2]^{+\cdot}$	529

Mass spectra of Ni-L

The Ni-L spectrum appearance of the molecular ion peak (M+) , base peak and series of important peaks belong to lose chloride atoms ,the break up embedded in the,(fig. 8 and table 6) .

Table 6. Important peaks of mass spectrum for Ni-L

No.	Fragmentation	m/z
1	$[Ni(L)_2Cl_2]^{+\cdot}$	367
2	$[Ni(L)_2Cl]^{+\cdot}$	332
3	$[Ni(L)_2]^{+\cdot}$	296

Elemental analysis

The purity of ligand was checked by elemental analysis (C.H.N.S), tabulated in table (7).

Table 7. Elemental analysis for the prepared ligand

Ligand	Calculated %				Founded %			
$C_9H_7N_3OS_2$	H%	C%	N%	S%	H%	C%	N%	S%
	2.95	45.56	17.72	27.00	2.72	45.15	17.06	26.74

Biological effect

Table 8 displays the blood and biochemical data of the control group and the treatment group using a produced thiadiazole derivative. The produced thiadiazole derivative has a considerable ($p<0.05$) impact on the percentage of packed cells and hemoglobin (Hb) (FIG.1). When compared to the control group, it was observed that the treated group had higher levels of PCV and Hb.The latest research's findings concur with those of the previous study [16].

Results showed that the produced thiadiazole derivative had an impact on PCV and Hb, suggesting that this material enhances the capacity to release and transport significant quantities of energy as well as carry big amounts of oxygen.Because Hb gave red blood cells their color and oxygen-carrying capacity, an increase in Hb levels corresponds to an increase in the number of red blood cells. The capacity of red blood cells to transport significant quantities of oxygen was shown to be improved in the treated group as compared to the control group, according to all prior data.

Table 8. Effect of on Blood and Biochemical Parameters in Rats

BLOOD PARAMETERS		
	CONTROL GROUP	**TREATED GROUP**
Hb (g/dL)	9.11 ± 1.02	12.43 ± 0.91 *
PCV (%)	28.43 ± 1.82	34.53 ±2.73 *
BIOCHEMICALPARAMETERS		
AST (IU/ml)	215.59 ±7.33	185.88 ±9.69 *
ALT (IU/ml)	32.29 ±8.16	11.71 ±4.95 *
Creatinine (mg/dL)	0.93 ±0.22	0.73 ±0.2
Urea (mg/dL)	39.84 ±10.02	27.89 ±7.09 *

Mean ±Standard Deviation(SD)

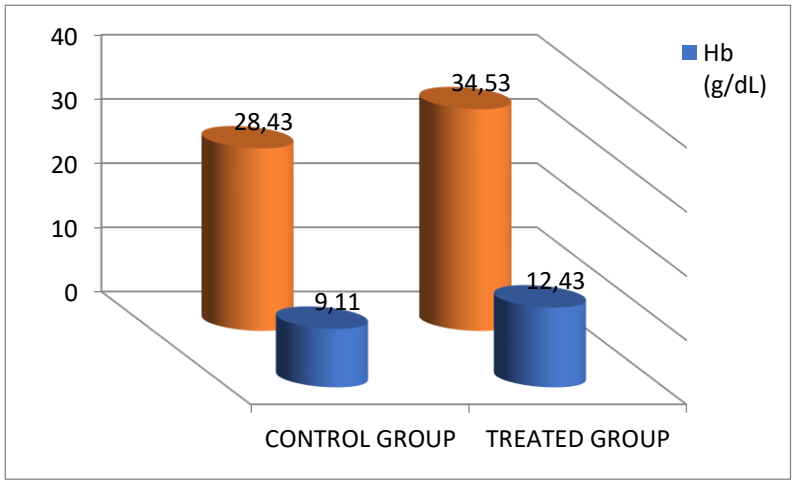


Figure 3. The relationship between prepared thiadiazole derivative and Hb, PCV percentage.

The current study's findings indicated that the liver enzyme levels had dropped. The treated group had decreased levels of AST and ALT. This suggested that the thiadiazole derivative that was made had an active impact on the liver enzymes. Furthermore, as compared to the control group, the treated group's levels of creatinine and urea were lower due to the effects of the synthesized thiadiazole derivative (FIG.2). These findings may account for the produced thiadiazole derivative's lack of notable liver damage. Moreover, the rate of urea, ALT, and AST increased liver function [17]. The thiadiazole derivatives' overall biological activity was dependent upon the presence of the N-C-S moiety, which was the basis for these results [18]. The synthesized thiadiazole derivative was shown to have anti-inflammatory properties based on the levels of AlT, AST, and urea in the treated group.

According to Turkoglu et al. (2013), there isn't an increase in AST or ALT enzyme activity, which suggests that there won't be any liver damage. Stated differently, these chemicals have a far lower toxic impact and also have a preventive effect against liver damage.[19] In a research, however, that used 6-substituted 1, 2, 4-triazole-[3,4-b] - 1, 3, 4-thiadiazole 1, 3, 4-oxadiazole compounds of isoniazid, it was noted that the levels of AST and ALT activities increased when comparing the implementation groups to the control group. [20].

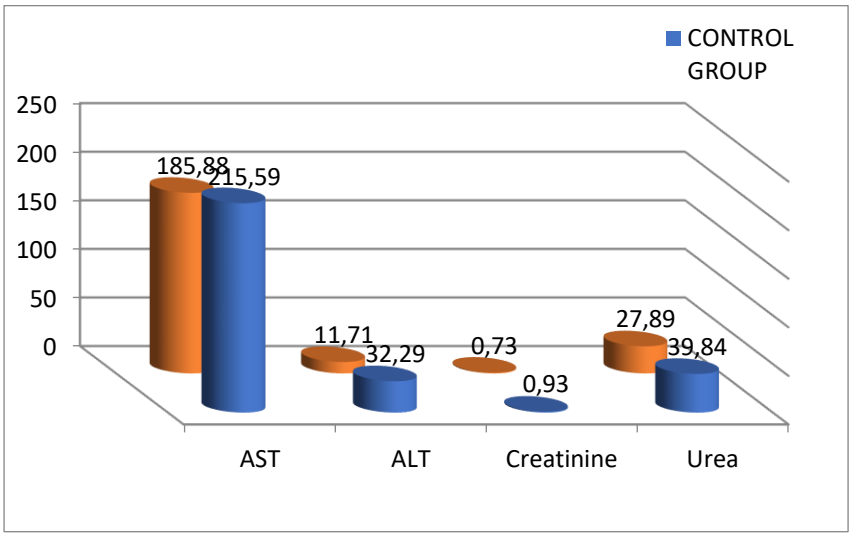
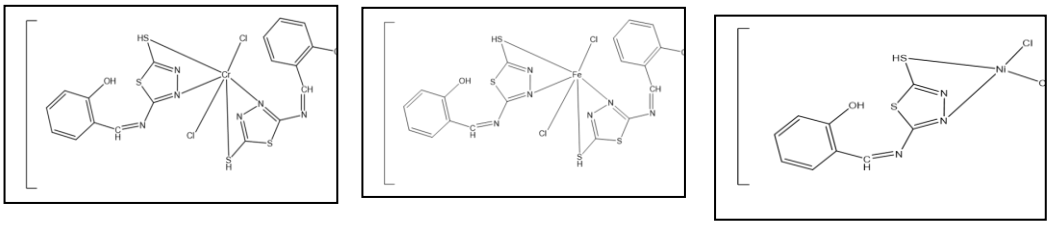


Figure 4. The relationship between prepared thiadiazole derivative and liver enzymes,urea and creatinine levels.

5. Conclusion

The structure of ligands and their complexes is determined by the results of various analytical techniques such as infrared spectroscopy, element analysis, H1-NMR spectroscopy, mass spectroscopy, molar conductivity, and magnetic moments. The nickel complex has a square plainer configuration, while the chromium and iron complexes have an octahedral configuration.



In terms of biological characteristics, the produced thiadiazole derivative effectively increases hemoglobin and compresses blood volume, boosting blood's capacity to transport more oxygen. Additionally, based on the level of biochemical markers that were assessed in the research, the drug has no toxic impact on the liver or unfavorable and negative influence on organ functioning. In addition to the aforementioned benefits, this material, like other thiadiazole derivatives, exhibits anti-inflammatory properties.Further research is advised to determine if it has any other biological impacts.

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