

Preparation, Characterization and Biological Study of New Derivatives of 1, 3, 4 - Thiadiazole and Its Complexes with Some Transitional Element Ions.

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Abstract:

The current study involved preparation of ligand [2,5-bis-(2-(diphenyl methylene) hydrazineyl)-1,3,4-thiadiazole] (L_1) from reacting between thiadiazole derivative [(2,5-dihydrazineyl-1,3,4 -thiadiazol) and Benzphenone by the ratio (1:2) .

Attended the transitional elements ions complexes [Cr^{+3} , Fe^{+3} , Co^{+3} , Ni^{+2} , Cu^{+2}] with ligand (L_1) Complexes were diagnosed using the precision analysis of elements (C.H.N), Infrared spectrum (FTIR), Spectrum of Nuclear Magnetic Resonance proton (1H -NMR), Mass spectroscopy, measurement magnetic sensitivity and measurement molar conductivity the results were practical exactly matching with the molecular and structural formulas of the proposed compound .Hyperchem was used to draw ligand (L_1) and its complexes and to show the distribution of electronic density.

Data obtained indicates that the stereochemistry figure of the complexes [Cr^{+3} , Fe^{+3} , Co^{+3}] was octahedral , the proposed stereochemistry figure of the complexes [Ni^{+2} , Cu^{+2}] is square planer.

A study was conducted testing the biological activity for the prepared ligand (L_1) and its complexes against two types of bacteria *staphylococcus aureus* and *Escherichia coli* compared to the standard inhibitor (Cipro.), the results obtained confirmed that ligand(L_1) and their complexes did not show any biological activity towards the bacteria *aureus staphylococcus aureus*, while the ligand(L_1) and their complexes showed different activity towards the second type of bacteria *Escherichia coli*, some showed greater activity than the standard inhibitor and some showed less activity than the standard inhibitor.

Keyword: Mass spectral, Thiadiazole, Metal complexes, *staphylococcus aureus*, *Escherichia coli*.

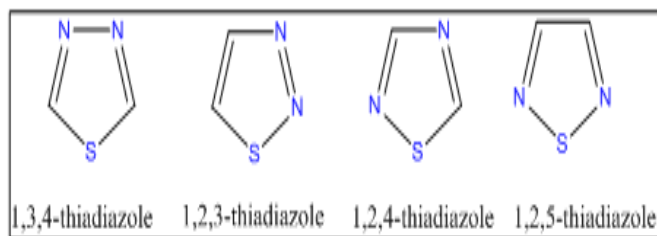
1. Introduction:

Heterocyclic chemistry has now become a separate field of chemistry with long history, present society and future prospects. Nitrogen, oxygen and sulfur are considered the most hetero atoms known. Heterocyclic compounds are considered one of an important type of organic compounds due to their implication in drugs and industrial studies (Ibtisam, K. J et. al.2012 and Carey, F et. al.1980). A little work has been done concerning the preparation and investigation of the metal complexes having 1,3,4- thiadiazole nucleus. Metal complexes has been used as photographic

layer stabilizer (Khalil, K. Abid et. al.2006), and in marine anti-fouling and anti- corrosion paints (Rajendran, et. al.; 1995). The ligand has also been used as an analytical reagent in the detection and determination of metal ions (David, B. T et. al. 2006) . Mono and disubstituted 1,3,4-thiadiazole ligands and their complexes have pharmacological properties (Margaret et. al.; 1960). Five membered aromatic systems containing three hetero atoms at symmetrical positions have been studied due to their interesting physiological properties (Sabir, H et. al.; 2008), 1,3,4-Thiadiazole can act as a ligand and its complexes have a wide variety applications especially as antifungal and antibacterial agents

(Samee, W et. al.2011 and- Kumar, J et. al.2010). 1,3,4-Thiadiazole was first described in 1882 by Fischer and further developed by Busch and his coworkers. The advent of sulfur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in this field (Stellings et. al.; 1986).

Thiadiazole is a 5-membered ring system containing hydrogen-binding domain, sulfur atom, and two electron donor nitrogen system ($-N=C-S$) that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,3,4 -thiadiazole (1); 1,2,3- thiadiazole (2); 1,2,4-thiadiazole (3); and 1,2,5- thiadiazole (4) five-member ring (Gupta R et. al. 2005) . (Figure1).



(Figure1)

Among these four types of thiadiazole, 1, 3, 4thiadiazole is well known. 1,3,4-Thiadiazole and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical and industrial importance (Holla B et. al.2002).

2.1. Materials and Methods:

All chemicals used are supplied from Fluka and Merck companies and used without any further purification. Infrared spectra were performed using a Bruker affinity (FT-IR) 8400S spectrophotometer in the range ($400-4000\text{ cm}^{-1}$), Spectra (FT-IR) were recoded as potassium bromide(KBr) and (CsI) discs, the compounds were determined using an elemental analyzer CHNS Model Fison EA 1108, (Tehran University, Iran) and melting points were obtained using an electrothermal apparatus Stuart melting point.¹H NMR, spectra were measured on

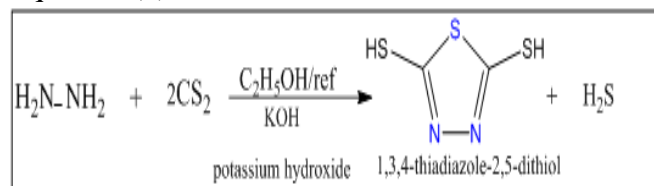
a Bruker Avance II 400 spectrometer, operating at 400, 100.6 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) and TMS as an internal standard. Molecular weights were determined with TOF MS ES Mass spectra. Reactions were monitored by thin layer chromatography (TLC) on silica gel (aluminum foil-backed, 0.25mm silica gel 60 F₂₅₄; Merck)., plates were visualizing with ultraviolet light or iodine.

2.2. Experimental:

2.2.1. Synthesis 2,5-bis(2-(Diphenylmethylene)hydrazineyl)-1,3,4-thiadiazole (L₁):

1. Synthesis of 2,5-dimercapto-1,3,4-thiadiazole (X₁)

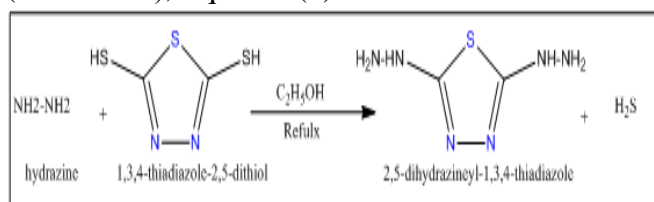
The compound (X₁) prepared by the reaction (16.5ml, 0.32mole) of hydrazine hydrate with (33.7gm, 0.6mole) potassium hydroxide dissolved in 200 ml of ethanol absolute and then add (0.2mole,13ml) of carbon disulfide, the reaction mixture was refluxed for (15hrs), then add (15 ml) hydrochloric acid (10%) where thiadiazole derived where precipitate the progress of the reaction was followed by TLC. After completion, the precipitate where filtered and leave to dry and then recrystallizes using absolute ethanol to get the yellow glossy crystals (Ahemd Ahmed et. al.2011 and S. Joshi et. al.2011), yield of the product compound 78% and melting point (163-165 °C), Equation (2).



Equation (2): Synthesis of 2,5-dimercapto-1,3,4-thiadiazole (X₁)

2. Synthesis of 2,5-dihydrazineyl-1,3,4-thiadiazole(X_2)

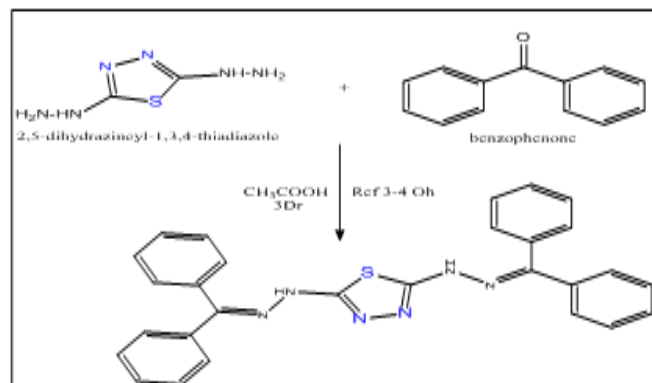
To 2,5-dimercapto-1,3,4-thiadiazole (X_1) (1.5 g, 0.01 mole) dissolved in ethanol, hydrazine hydrate (5 mL, 0.02 mole) was added drop wise with stirring and the mixture was then refluxed for (6 h), then the excess solvent was distilled off. Filtered the solid resulting which was separated out on cooling and recrystallized from ethanol to give the crystals Pale yellow color resulting from (X_2) (2,5-dihydrazino-1,3,4-thiadiazole (Jumat Salimon et. al.2010 and Sunny Jalhan et. al.2012), the yield of the product compound 71% and melting point (198-200°C), Equation(3)



Equation (3): Synthesis of (X_2)

3. 2,5-bis (2-(diphenyl methylene) hydrazineyl)-1,3,4-thiadiazole (L_1)

The ligand (L_1) was prepared by dissolving (3.5gm, 0.02mole) of the compound benzophenone in (50 ml) of ethanol absolute and add (3-4drops) of glacial acetic acid, then add (0.01 mole, 1.46gm) of the compound (X_2) that dissolved in ethanol absolute (50ml) to the mixture in the form of a small defenses, the mixture was refluxed for (6hr.), the reaction was followed by TLC. After completion the precipitate was formed, cooled the mixture by using ice path for (1hr), The precipitate where filtered, washed and then recrystallizes using solution of ethanol (1:1) and water to get crystals with cream-colored, where the yield of the product compound (82%) and melting point (175-177 °C).



2,5-bis(2-(diphenylmethylene)hydrazineyl)-1,3,4-thiadiazole

Figure (4): 2,5-bis(2-(Di phenyl methylene)hydrazineyl)-1,3,4-thiadiazole (L_1)

2.2.2. Synthesis of Metal complexes of ligand (L_1):

Complexes of ligand (L_1) preparation were performed by adding a hot solution of each of (0.001mole) [$CrCl_3 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, $CoCl_3 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2$] in absolute hot ethanol (20 ml) to (0.47g ,0.001mole) of (L_1) in absolute ethanol (20 ml). The mixtures were refluxed with stirring for four hours, the resulting precipitates were filtered and washed with water and recrystallized from hot ethanol, and it was then dried at room temperature (Ahemd Ahmed et. al. 2014). Table (1) shows the physical properties of the ligand and metal complexes.

Table (1): Physical properties for ligand (L_1) and its complexes

Symbol	Chemical Formula	M.WT	Physical appearance	M.P °C	Yield
L_1	$C_{28}H_{22}N_6S$	474	yellow crystal	175-177	82%
L_1A_1	$[L_1CrCl_2]Cl$	633.1	yellow crystal	276-278	81%
L_1A_2	$[L_1FeCl_2]Cl$	636.0	Brown crystal	266-268	80%
L_1A_3	$[L_1Co Cl_2]$	639.3	Brown crystal	257-260	84%
L_1A_4	$[L_1NiCl_2]Cl$	604.0	Grey Pale crystal	248-245	83%
L_1A_5	$[L_1Cu Cl_2]$	609.3	Pale yellow crystal	250-253	79%

3. Results and discussion:

3.1. Elemental Analysis:

The elemental analysis of the 2,5-bis(2-(Di phenyl methylene)hydrazineyl)-1,3,4-thiadiazole (L_1) has been carried out to identify the composition of each element.

Table (2): (C.H.N.S.) elementary micro analysis of the synthesized (L_1)

Sample	Experimental percent				Theoretical percent			
	C %	H %	N %	S %	C %	H %	N %	S %
L_1	70.52	4.57	7.57	6.73	70.86	4.67	7.71	6.76

3.2. IR Spectra:

FTIR spectrum of compound (L_1) was characterized by the appearance of absorption bands at $[(3254)] \text{ cm}^{-1}$ due to the vibration of the set of (N-H) ν and the spectrum showed absorption bands at $[(3056-3070)] \text{ cm}^{-1}$ attributed to the aromatic group (C-H), $[(1570) \text{ and } (1580)] \text{ cm}^{-1}$ were attributed to the (C= N) ν groups of the thiadiazole ring and the azomethine group respectively. The spectrum also showed absorption bands at sites $[(1320,1294,1026)] \text{ cm}^{-1}$ attributed to the structural motion and symmetric and asymmetric vibration of the (C-S-C) ν group of the thiadiazole ring (M.C.H amming et. al.; 1972, D.A. Skoog et. al.1964, R. D. Feltham et. al.1964 and Nakamoto K et. al.1963.

The (FTIR) spectrum of $[\text{Cr}^{+3} +, \text{Fe}^{+3} \text{ and } \text{Co}^{+3}]$ complexes with compound (L_2) showed an offset in the beam site of the (N-H) ν and at a rate of $[(113-159)] \text{ cm}^{-1}$ indicating consistency through this site, in addition to the displacement of the sites of the two bands (C = N) ν for thiadiazole and azomethine, the spectrum showed shift the beam of the group (C = N) ν and the thiadiazole loop towards a higher frequency at a rate of $[(10-24), (10-69)] \text{ cm}^{-1}$ respectively.

Which confirms the consistency of these two sites as well, there is further evidence of this consistency, the spectra of the complex showed new absorption bundles that were not present in the free compound spectrum (L_2) at the range $[(516-573) \text{ and } (265-298)] \text{ cm}^{-1}$ due to (M-N) ν and (M-Cl) ν Respectively.

Complexes (Ni^+ and Cu^{+2}) with compound (L_1) showed a shift to a higher frequency in the Packed (N-H) ν at the range $(99-129) \text{ cm}^{-1}$. The beam of the thiadiazole was characterized by a shift to a higher frequency and an average $(11-29) \text{ cm}^{-1}$ and lower frequency $(32-44) \text{ cm}^{-1}$ for azomethine, New matrices were also found in the spectrum of these Complexes at $(265-298)$ due to (M-Cl) ν . As shown in Table (3).

Table (3): gentel infrared absorption of the compound (L_1) and its complexes

NO	Compound	N-H	C-H (Ar)	C=N thiadiazole ring	C=N azomethine	C-S-C (Sy) and (Asy)	M-N	M-Cl
L_1	$\text{C}_{23}\text{H}_{22}\text{N}_6\text{S}$	3254	3070	1570	1580	1294 (Sy) 1320 (Asy)		
A_1	$[\text{Cr}L_1\text{Cl}_3]$	3370	3055	1591	1621	1292 (Sy) 1304 (Asy)	516	286
A_2	$[\text{Fe}L_1\text{Cl}_3]$	3367	3058	1594	1649	1285 (Sy) 1321 (Asy)	573	293
A_3	$[\text{Co}L_1\text{Cl}_3]$	3413	3056	1560	1590	1291 (Sy) 1320 (Asy)	571	298
A_4	$[\text{Ni}L_1\text{Cl}_2]$	3353	3056	1538	1591	1295 (Sy) 1320 (Asy)	571	292
A_5	$[\text{Cu}L_1\text{Cl}_2]$	3383	3057	1526	1609	1293 (Sy) 1320 (Asy)	571	265

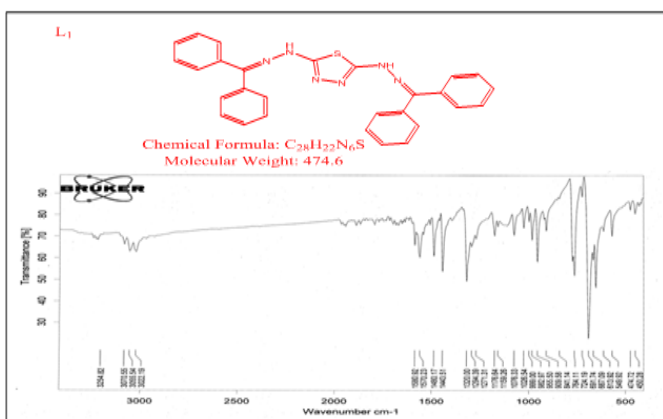


Figure (5): The infrared spectrum of the ligand (L₁) (C₂₈H₂₂N₆S) in the KBr disc

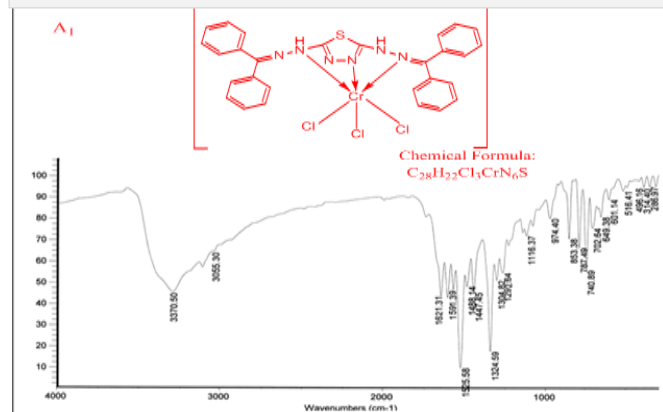


Figure (6): IR spectrum of the complex [Cr L₁ Cl₃] in the CsI disc

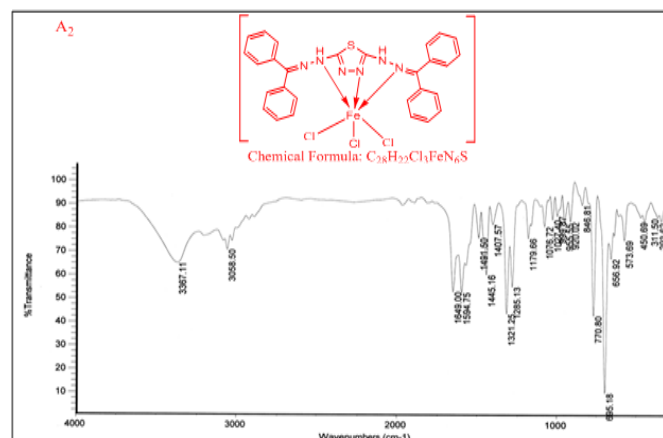


Figure (7): IR spectrum of the complex [FeL₁Cl₃] in the CsI disc

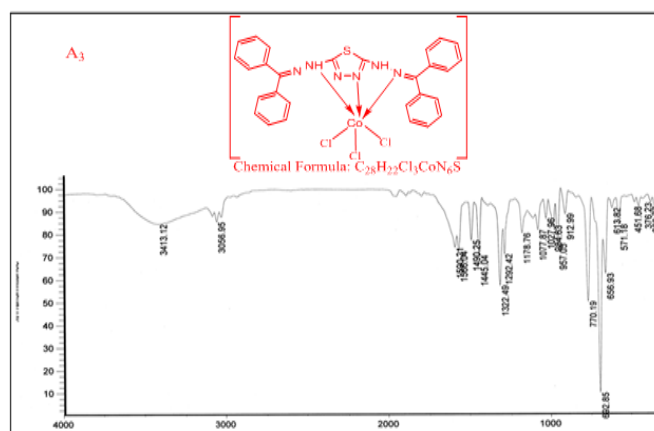


Figure (7): IR spectrum of the complex [CoL₁Cl₃] in the CsI disc

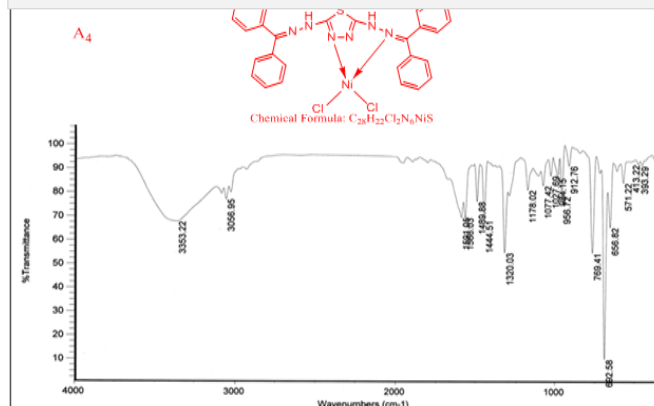


Figure (8): IR spectrum of the complex [NiL₁Cl₂] in the CsI disc

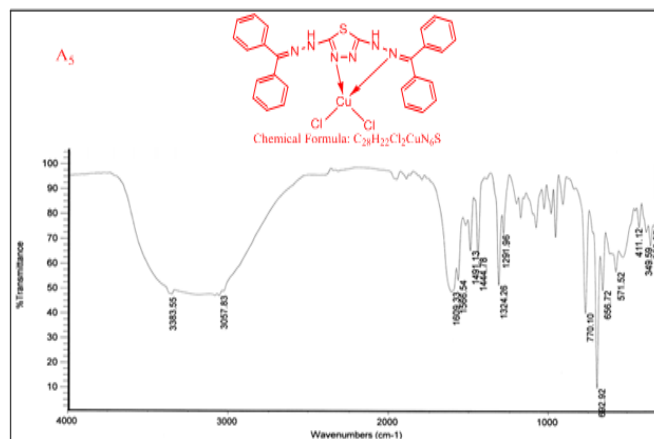


Figure (9): IR spectrum of the complex [CuL₁Cl₂] in the CsI disc.

3.3.1. ¹H-NMR Spectra:

The spectra of proton Nuclear Magnetic Resonance ¹H-NMR of the prepared ligands (L₁) shown in Figures (15), characterize ¹H-NMR spectrum appearance of multiplet signal at chemical shift (δ) at range (7.2-7.7 ppm) due to the aromatic ring protons (Robert M. Silverstein et. al.2005) (Ar-H), and the appearance of a singlet signal at shift (δ) (10.6 ppm) due to the proton (-NH), ligands (L₁) spectra showed a signal at δ2.5 ppm for the DMSO-d₆ solvent (Donald L. Pavia et. al.2001and - A Huang, J et. al.2004), As shown in Table (4)

Table (4): ¹H-NMR spectra data of prepared compound

Compound	Group	Kind Of Signal	Shift (ppm)	Integration
L ₁	NH-C=N	Singlet	10.6	2H
	Benzene ring	Multiple	7.2 - 7.7	20H

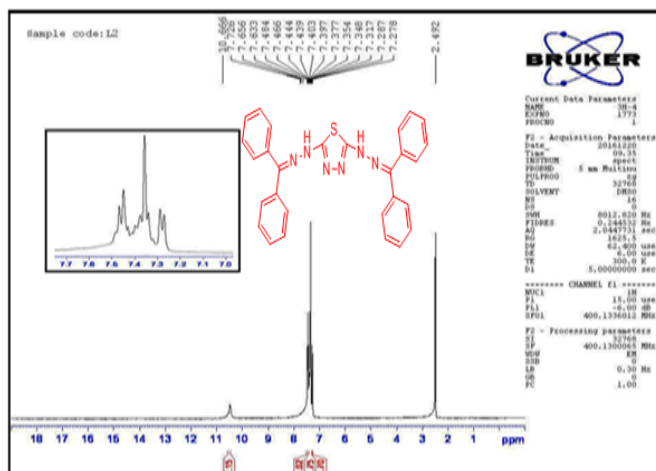


Figure (10): ¹H-NMR spectrum for L₁ (C₂₈H₂₂N₆)

3.4. Mass spectra:

Characterize mass spectra of the formazans (L₁) and its complexes which appearance of molecular ion (M⁺) at (474 m/z), and the fragmentation of (L₁) showed the peaks in [397, 365, 288, 247, 180 and 77 m/z] due

to {[C₂₂H₁₇N₆S]⁺, [C₂₂H₁₇N₆]⁺, [C₁₆H₁₂N₆]⁺, [C₁₅H₁₁N₄]⁺, [C₁₃H₁₀N]⁺ and [C₆H₅]⁺} respectively, The following figures show the mass spectra of the formazans (L₁) and their complexes.

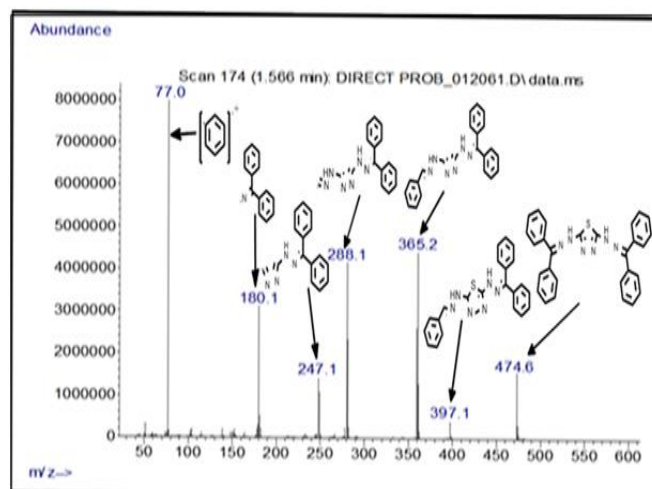


Figure (11) Mass spectra of (L₁)

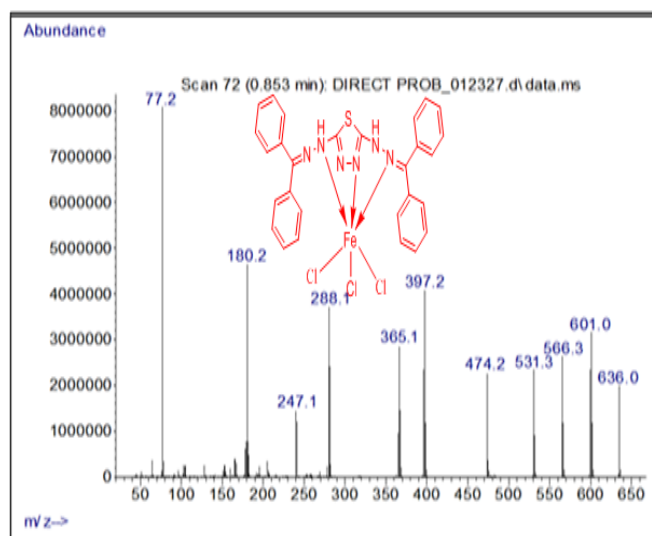


Figure (12) Mass spectra of [FeL₁Cl₃]

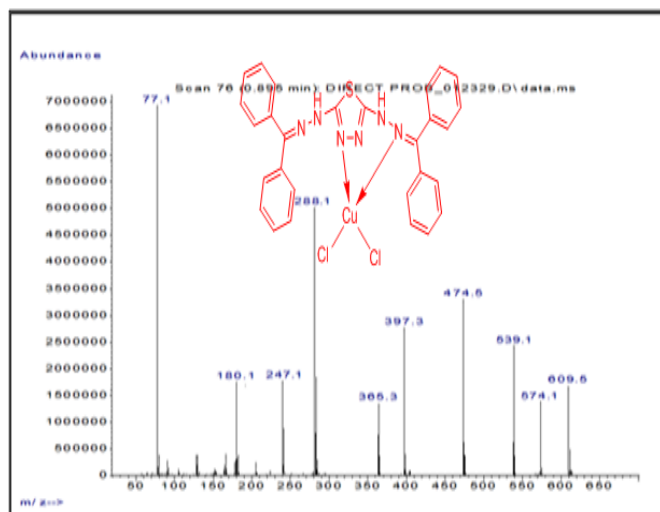


Figure (13) Mass spectra of $[CuL_1Cl_2]$.

3.5. Molar Electrical Conductivity:

The electrical conductivity is regarded as one of the important and simple means for knowing the ionic formulas of the compounds (I. B. Foresman et. al.1996) Molar conductivity measured for solid complexes solutions of ions $[Cr^{+3}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+3}]$ with (L_1) concentration of 10^{-3} M dissolved in Dimethyl sulfoxide (DMSO) each separately at a laboratory temperature, has been used distilled water as a reference. The results are included in Tables (5) was found from the conductivity values of the complexes behave neutral compounds (non-electrolytic) the lack of any adjective-ionic, because of the lack of chloride ions out of the coordination sphere as counter ions of the central ion. The obtained results were appropriate with the molecular formulas and stereochemistry proposed of the prepared complexes.

Table (5): Molar electrical conductivity of (L_1) complexes

Electrolyte Type	Λ_m (S. $cm^2 \cdot mole^{-1}$) In (DMSO)	Complexes
$[CrL_1Cl_3]$	15	Non Electrolyte
$[FeL_1Cl_3]$	17	Non Electrolyte
$[CoL_1Cl_3]$	16	Non Electrolyte
$[NiL_1Cl_2]$	18.7	Non Electrolyte
$[CuL_1Cl_2]$	19.1	Non Electrolyte

3.6. Magnetic sensitivity:

The values of the effective magnetic torque (μ_{eff}) of the prepared complexes were calculated for the purpose of obtaining additional evidence to reinforce the conclusion of the proposed structural formula of the prepared complexes. The results shown in Table (6) showed a decrease in the values of the magnetic moments of the prepared complexes, which confirms that these complexes are of low-pitched type, which means that the prepared ligand (L_1) are classified as strong ligand, the measured results confirmed that the magnetic susceptibility value of the iron in the complex are (2.3).

This confirms the existence of a single electron only due to the duplication of the remaining electrons, the iron magnetic susceptibility values shown in the table below confirm an orthopedic contribution, this is evident from the value of the actual magnetic torque measured in practice was greater than the theoretical values when there is only a thermal contribution and this confirms that the octagonal iron complex. The value of the calculated magnetic torque of the chromium ion (Cr^{+3}) showed three single electrons and there is no presence of the European contribution. This is consistent with the literature. The low values of the calculated magnetic torque of nickel and cobalt confirmed that their luminescent complexes were of the strong ligand, which resulted in the coupling of the electrons. The nickel showed a square shape and eight octahedral cobalt. The calculated magnetic sensitivity values of the copper complex were characterized by having one single electron. The magnetic momentum values must be approximated to the calculated theoretical values, there is no

European contribution, and it is suggested that the copper complex is a square rather than a tetrahedron, Because the strong ligand will push the electron in the (3d) orbital to (4p), which is confirmed by the theoretical study.

Table (6): Magnetic effect (μ_{eff}) of prepared ligands (L_1) complexes

Complexes	μ_{eff} (BM)
[CrL ₁ Cl ₃]	3.8
[FeL ₁ Cl ₃]	2.3
[CoL ₁ Cl ₃]	0.6
[NiL ₁ Cl ₂]	0.6
[CuL ₁ Cl ₃]	1.8

3.7. Study of the electronic density of the ligand (L_1) using Hyperchem:

Hyperchem was used to draw the prepared ligand (L_1) using the PM3 (R. D. FELTHAM et al. 1964) method and the Electrostatic Potential Distribution. The study of the electrical voltage of the molecule is very important for finding effective sites in the molecular system, The voltage was drawn for the prepared ligand (L_1), As shown in the forms below.

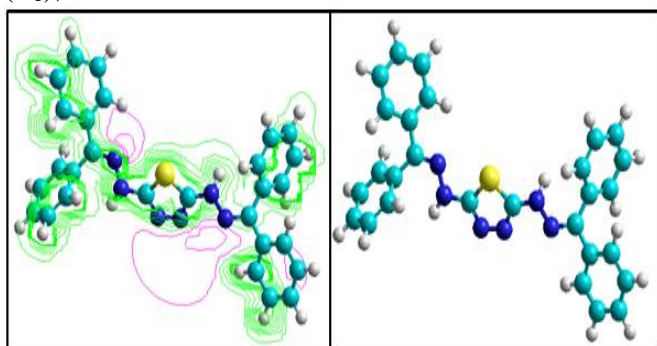


Figure (14): Distribution of electronic density in

Through spectroscopic and analytical studies of the thiadiazole derivative (L_1) and its

complexes, it was concluded that ligand (L_1) is an eight-surface complex with the salts of the triple oxidation element [Cr⁺³, Fe⁺³, Co⁺³]. While the square complexes of the standard with the salts of the two elements of the transition of oxidation [Ni⁺², Cu⁺³], As shown in the forms below.

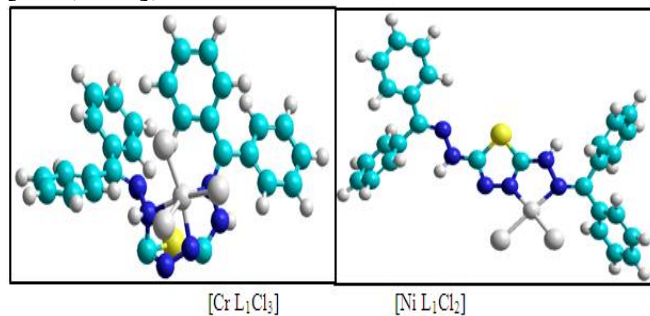
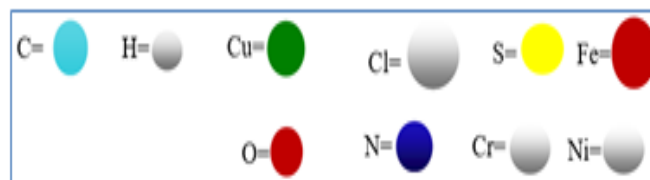


Figure (15): The geometric shape of the chromium and nickel complex of (L_1)



3.8. Evaluation Biological Activity of ligand (L_1) and its complexes 3-8-:

With a view to explore the possibility of obtaining biologically useful complexes that contain 1,3,4- thiadiazole ring system, such biological activity prompt us to prepare some new series containing the above mentioned unite. The antimicrobial activity of these compounds was determined by the agar diffusion method (G.P. Ford et al. 1993 and Thakar A et al. 2010) used were *Staphylococcus aureus* and *Escherichia coli*. In this method a standard 5mm diameter sterilized filter paper disc impregnated with the compound (1 mg per 1 ml of acetone) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 hours at (37⁰C). The zone of inhibition formed was measured in mm and are represented by (+), (++) and (+++) depending upon the diameter and clarity, Table (7). The preliminary screening result that compound

(L₁) and its complexes exhibits highest antibacterial activity against *Escherichia coli* and no biological effect was shown towards bacteria *Staphylococcus aureus*. The results shown in the table (7) and Figures (16) to (17).

Table (7): Antibacterial -biological activity of studied (L₁) and its complexes

Symbol	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
	Inhibition zone(mm)	Inhibition zone(mm)
22(L ₁)	16+++	0-
6 (Cr L ₁ Cl ₃)	7+	0-
7 (Fe L ₁ Cl ₃)	6+	0-
8 (Co L ₁ Cl ₃)	9+	0-
9 (Ni L ₂ Cl ₂)	6+	0-
10 (Cu L ₁ Cl ₂)	12++	0-
Cipro	9+	7+

Note: +++ Very good Inhibition, ++ Good Inhibition, + middle Inhibition, - Not Inhibition.

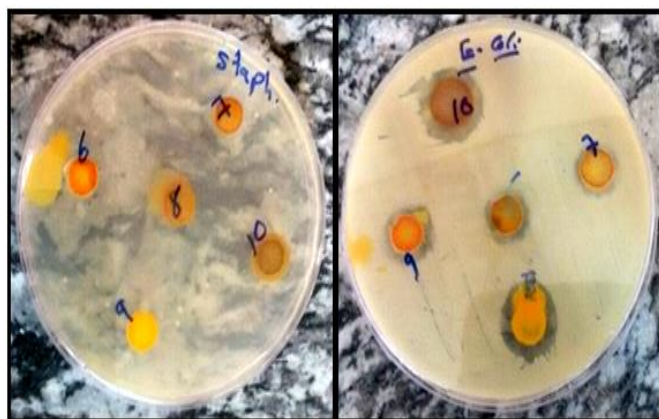


Figure (16): Biological effectiveness of complexes 6,7,8,9 and 10 against *E. coli* on the right and *Staph* at the left

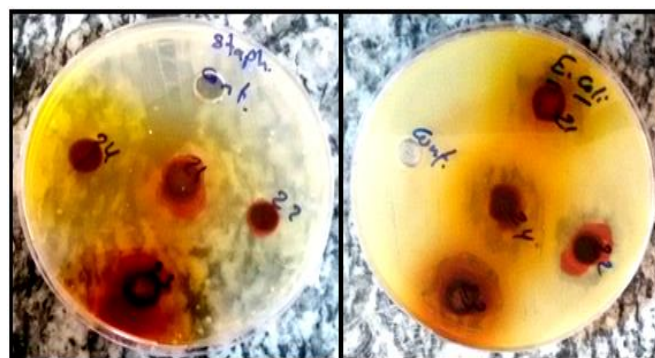


Figure (17): Biological effectiveness of ligand (L₁) against *E. coli* on the right and *Staph* at the left

4. Conclusions:

1. The triangular metal ions (Cr⁺³, Fe⁺³, Co⁺³) with thiadiazole derivative (L₁) gave the eight-surface complexes, while the binary metal ions (Ni⁺² and 2 Cu⁺²) gave a square level.
2. Through the results of the magnetic sensitivity measured for the prepared complexes, it was confirmed that the prepared is strong ligand
3. Spectral studies, which included the results of the infrared spectra (FTIR), finite element analysis, ¹H-NMR spectrum and mass spectrometry, as well as molar electrical conductivity measurements and magnetic susceptibility, confirmed the molecular and structural formulas of the proposed compound (L₁) and its complexes.
4. Ligand (L₁) prepared from 1,3,4-Thiadiazole derivative and its Complexes showed a strong inhibitory effect to medium strength against a type of negative bacteria (*Escherichia coli*) While the ligand did not show the record or its Complexes any biological effect on the bacteria positive type (*Staphylococcus aureuse*).

5.Reference:

Ahemd Ahmed,Reyahd Ahmed and IsmaeelMajed,Synthesis and Characterization of New Schiff Bases and Using Them Us Tri Dentate,Ligands in Metal Complexes,International Journal of Applied

- Science and Technology, Vol. 4, No. 6; November (2014).
- Ahemd Ahmed, Reyahd Ahmed and Ismaeel Majed, Synthesis and Characterization of New Schiff Bases and Using Them as Tridentate Ligands in Metal Complexes, International Journal of Applied Science and Technology.
- A Huang, J. J. Kodanko, L. E. Overman and J. Am. Chem. Soc., 126, 14043-4053, (2004)
- 25- I. B. Foresman and C. Frisch, "Exploring Chemistry with Electronic Structure Methods," 2nd ed., Gaussian Inc., Pittsburgh, PA. (1996).
- Carey, F. Organic Chemistry. McGraw-Hill Inc, America. (1980).
- David, B. T., Paul, B. The Science and Practice of Pharmacy. Lippincott Williams & Wilkins, 21st edition, America. (2006).
- D.A. Skoog, "Fundamentals of Analytical Chemistry", 5th ed., New York, 87, 24-44, (1988).
- Donald L. Pavia, Gary M. Lampman and George S. Kriz, (Introduction to Spectroscopy), 3rd Edition, ISBN: 0-03-031961-7, (2001).
- Gupta R. R.; Kumar, M.; Gupta, V. Five membered heterocycles with more than two heteroatoms. In Heterocyclic Chemistry II, 3rd edition. Springer (India) Pvt. Ltd. 491-573. (2005).
- G.P. Ford and B. WANG. J. Comp., 14:1101-111, (1993).
- Holla B. S., Poorjary N. K., Rao S. B., Shivananda M. K., New bis-amino mercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents, Eur. J. Med. Chem., 37, 511-517. (2002).
- Ibtisam, K. J., Sawsan, S. H., Rua, M. D., and Ali O. A. Synthesis and study the biological activity of some six, five and fused ring heteroatom systems derived from 2-mercaptobenzothiazole. Tikrit J. Pharmaceutical Sci., 8(1), 96-105. (2012).
- Jumat Salimon, Nadia Salih, Emad Yousif, Ayad Hameed and Hiba Ibraheem. Synthesis, Characterization and Biological Activity of Schiff Bases of 2, 5-Dimercapto-1,3,4-thiadiazole, Australian Journal of Basic and Applied Sciences, 4(7): 2016-2021, (2010).
- Kumar, J. G., Yadav, R. K., Dudhe, R., Sharma, P. K. Recent Advancements in the Synthesis and Pharmacological Evaluation of Substituted 1, 3, 4-Thiadiazole Derivatives. International J. of Pharm Tech Research, 2(2), 1493-1507. (2010).
- Khalil, K. Abid. Lanthanide metal complexes of 1, 3, 4-thiadiazole ligands. National J. Chem., 24, 596-607. (2006).
- Margaret, M., C., Stewart, R. H., John, M. V., Abraham, G. The Ant-leukemic Action of Two Thiadiazole Derivatives. Cancer Res, 20, 1195-1201. (1960).
- M.C. Hamming and N.G. Foster, "Interpretation of Mass Spectra of Organic Compounds" Academic Press, New York, (1972).
- Rajendran, N., Ravichandran, K., Rajeswari, S. Influence of substituents in thiadiazole on the localized corrosion of 316L stainless steel in simulated flue gas desulfurization environment, Anti-Corrosion Methods and Materials. Anti-corrosion method and materials, 42, 8-10. (1995).
- R.D. Feltham and R.G. Hayter, J. Amer. Chem. Soc., 82, 587-459, (1964)

- Nakamoto K, Infrared spectra of Inorganic and coordination Compounds, John Willey, New York, (1963).
- Robert M. Silverstein, Francis X . Webster and David J. Kiemle , (Spectroscopy identification of organic compounds), John Wiley & Sons, ISBN :0-471-39362-2, New York ,(2005).
- R. D. FELTHAM and R. G. HAYTE, “The Electrolyte Type of Ionized Complexes,” J. Chem. Soc., vol. 857, pp. 4587–4591, (1964).
- Sabir, H., Jyoti, S., Mohd, A. Synthesis and Antimicrobial Activities of 1,2,4-Triazole and 1,3,4Thiadiazole Derivatives of 5-Amino-2-Hydroxybenzoic Acid. CODEN ECJHAO E-J. Chem., 5(4), 963– 968. (2008).
- Samee, W., Vajragupta, O. Antifungal, cytotoxic activities and docking studies of 2,5-dimercapto-1,3,4thiadiazole derivatives. African J. Pharmacy and Pharmacology, 5(4), 477-485 .(2011).
- Stellings M.R., Welbourn A.P., Walter D.S., Substituted 1,3,4thiadiazoles with anticonvulsant activity. 2-Aminoalkyl derivatives, J. Med. Chem., 29 . 2280 – 2284 (1986).
- S. Joshi and V. Pawar; "Int.J.Pharma and Bio Sci.", 2,170-178; (2011).
- Sunny Jalhan, Anil Jindal, Avneet Gupta and Hemraj, Synthesis, Biological Activities and chemistry of thiadiazole derivatives and Schiff bases ,Asian Journal of Pharmaceutical and Clinical Research, 5, Issue 3, SSN - 0974-2441.(2012).
- Thakar A.S, Singh K. K, Joshi K.T., Pancholi A.M. and Pandya K.S. “Synthesis, Characterization and Antibacterial Activity of Schiff Bases and their Metal Complexes Derived from 4-Acyl-1-phenyl-3-methyl-2-pyrazolin-5-one and 2-Amino-4(4'-methylphenyl) thiazole”, E-Journal of Chemistry, 7(4), 1396-1406, (2010).