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Preparation and diagnosis of Zn(II), Cd(II) and Hg(II) complexes with Schiff base ligand derived from trimethoprim

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Abstract

Synthesis and identification of some new zinc(II), cadmium(II), and Mercury(II) complexes with ligand **3** were done. The resulting compounds were identified using various physicochemical techniques such as electrical conductivity, magnetic susceptibility, infrared spectroscopy, electronic (ultraviolet) spectra, 1H-NMR spectroscopy, atomic absorption, and CHN elemental analysis. Through magnetic measurements and ultraviolet and infrared electronic spectra, we found that the shape of the resulting complexes is tetrahedral around zinc(II), cadmium(II), and Mercury(II), while the molar electrical conductivity results of the complexes prepared in neutral medium confirmed that they are electrolytes in a solvent. DMF and DMSO in a ratio (1:1). The prepared complexes in the basic medium were non-electrolyte. Zn(II), Cd(II), and Hg(II), complexes showed tetrahedral geometry with the general formula $[M(L3)](NO_3)_2$ and [M(L3)] in neutral and basic medium respectively. Then the antibacterial activity of the prepared ligand and complexes against bacteria (*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella spp*). Neither the complexes nor ligand compounds showed antibacterial activity.

Keywords: Trimethoprim, Zn(II), Cd(II), Hg(II), Complexes, Antibacterial.

1. Introduction

Compounds containing nitrogen, sulfur, or oxygen particularly trimethoprim have piqued interest in chemistry due to their many pharmacological activities, including antiparasitic [1], antibacterial [2, 3], anticancer [4], antimalarial [5], antineoplastic [6], and antivira1 [7, 8]. Schiff base is a technique that is applied on compounds that are used as a ligand in formation of metal complexes and they were synthesized via reaction of carbonyl compounds with amine compounds. Schiff bases have a wide variety of biological activities such as antimicrobial, [9] antitumor [10]anti-inflammatory with pharmacological activity[11]. Metal complex is a mixture between metal and organic compounds named ligand which in general is a Schiff base of carbonyl compounds that condensed with primary amines. Metal ions are used in many drugs such as cisplatin which is one of the leading metal ions [12]. Metal Complexes have been reported to be particularly successful in inhibiting the growth of several bacterial species, and are utilized to reduce germ proliferation on contact surfaces in health care settings and hospitals [13, 14]. The growth inhibition effect, known as "contact killing," led to the United States Environmental Protection Agency (US EPA) approving metallic copper as the first solid antimicrobial substance [15].

The aforesaid facts prompted us to develop and characterise a variety of Some second-chain metal complexes such as Zn(II), Cd(II), and Hg(II) via reaction of terephthalaldehyde reacted with 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine to afford Schiff base as ligands to form octahedral complexes as multidentate and the obtained new complexes were screened as potential candidates against antibacterial agents.

2. Experimental

2.1. Materials

The primary compounds have been supplied from Merck, Aldrich, BDH, and Fluka. All the compounds and solvents have been used as supplied.

Elemental analysis of carbon, nitrogen, hydrogen were done at Iraq-Baghdad-Ibn Al Haytham University. Zinc, Cadmium, and Mercury contents have been determined by the Atomic absorption method after the decomposition of the complexes with concentrated nitric acid. Conductivity measurements have been carried out with an electrolytic conductivity measuring set LF-42 and Multiline f/SET-2WTW Wiscenschaf Technische Werketattem 82362 Weiheim using 10^{-3} M DMF & DMSO at 25 ^{o}c.

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Magnetic susceptibility of the complexes has been measured by SHERWOOD SCIENTIFIC Magnetic Susceptibility (MSB) at 25 °c. Electronic spectra have been recorded on Shimadzu UV-1650 PC UV-Visible Spectrophotometer for 10^{-3} solutions of the ligands and their complexes in DMF & DMSO at 25°c, using a 1 cm cell. The infrared spectra of the ligands and their complexes have been recorded on Model Alpha–Bruker in the range 400-4000 cm^{-1}, finally antibacterial activity evaluation.

2.2. Preparing the Ligand

1 mmol terephthalate and 2 mmol trimethoprim were dissolved in 40 ml ethanol, with heating until having homogenous mixture then 3-5 drops glacial acetic acid were added with refluxing for 2h. After completion (TLC), reaction mixture was evaporated under vacuum, to get precipitate that was filtered and left to dry. (M.p.: 200°C, ark yellow, yield 85%) (Scheme 1).[16]

2.3. Preparation of the complexes

Synthesis of metal complexes at base, acid and neutral media were done to conclude that acidic reaction condition is not suitable because of presence of acidic hydrogen proton that reacted with lone pair of amine group to afford NH_3 which decrease activity of coordination with (NH_2).

A. In neutral medium :

An equal mole ratio of metal salt such as $Zn(NO_3)_2.6H_2O$ and Ligand **3** dissolved in 20 ml absolute ethanol were refluxed for 3h (TLC). The reaction residue was cooled and evaporated to about half its volume to afford a complex that was filtered off, washed with diethyl ether, and dried (Scheme 2, Table 1).[17]

B. In basic medium

The foregoing steps was applied except addition of 2M NaOH drop-wise instead of glacial acetic acid until pH = 9-10 (Scheme 3, Table 1).

2.4. Calculation of Relative Molecular Weight

Relative molecular weight of the prepared complexes was calculated, an amount of the complex was weighed and dissolved in DMF to obtain a concentration of 0.001 molar.[18]

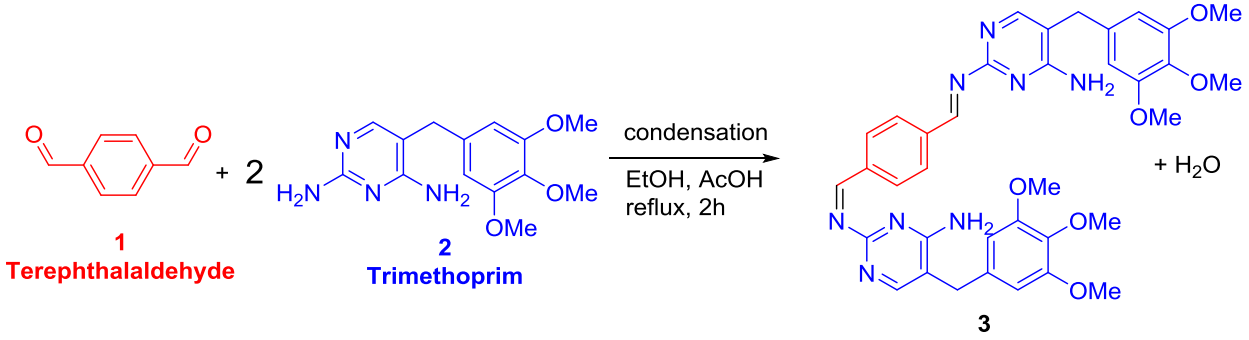
The solution was transferred to a test tube containing a Beckmann thermometer and placed in an ice bath. The solution was stirred slowly and we noticed a decrease in the temperature of the solution and at the freezing point of the solution the temperature was stabilized, and by knowing the freezing point of DMF we calculate the difference caused by the dissolved complex in the heat From the standard curve that was drawn for previously known compounds and given a straight line and using the Excel program(Compounds of known molecular weight are used, and a standard curve is drawn for these compounds. By projecting onto the straight line, the unknown compounds are calculated), a graph of the curve is made with a linear relationship between the difference in temperature and molecular weight. By projecting onto the obtained curve, we can determine the molecular weight of the prepared complex (Table 3).

2.5. Antimicrobial Assay

The antibacterial activity of new complexes has been investigated and expressed according to the agar plate diffusion method as the diameter of the inhibition zones [19] against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella spp*. All the bacterial strains were carried out and identified in this study is achieved at The Biology Department, College of Education for Pure Sciences, University of Mosul.

3. Results and Discussion

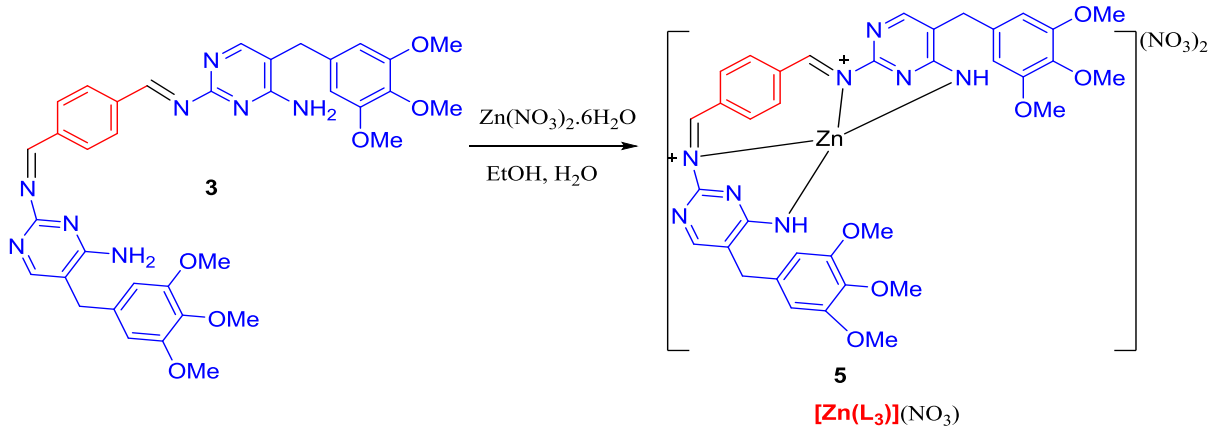
Terephthalaldehyde reacted with 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine via condensation reaction conditions to afford Schiff base 3 in excellent yield (Scheme 1). The structure of new Schiff base **3** was elucidated via elemental and spectroscopic analyses.



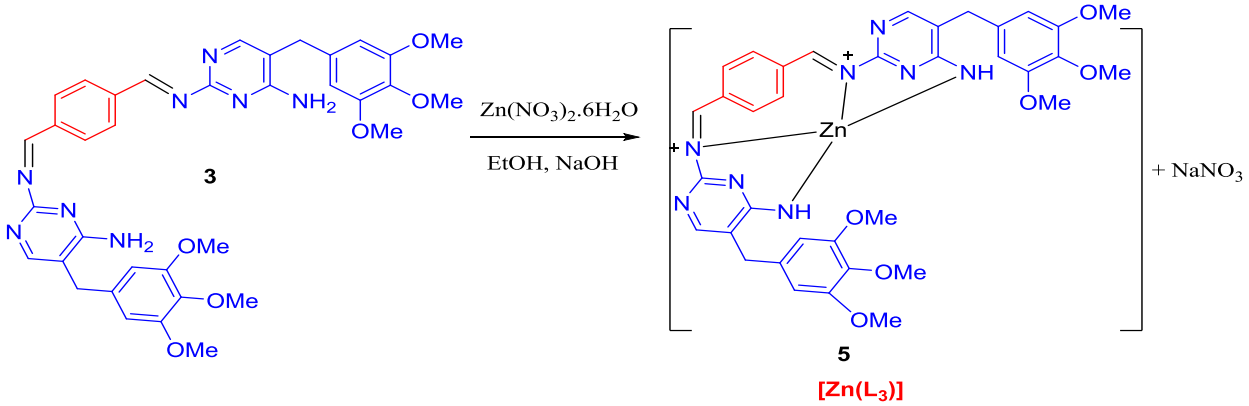
Scheme 1: Schiff base synthesis

New complexes were synthesized via reaction of ligand **3** with metal salt of Zn, Cd and Hg in basic, acid and neutral media. Acidic reaction condition is not suitable because of presence of acidic hydrogen proton that reacted with lone pair of amine group to afford NH_3 which decrease activity of coordination with (NH_2). So, reaction was done at neutral and basic medium (Scheme 2 and 3). Physical properties of new ligand and complexes were depicted in Table 1, while table 2 has amounts and medium of

new complexes preparation. Also, Relative molecular weight is cited in Table 3.



Scheme 2: Complex synthesis in neutral medium



Scheme 3: Complex synthesis in basic medium

Table 1: Physical properties new compounds

No.	% yield	Mp °C	Color
Ligand 3	85	200	Dark yellow
4a = [Zn(L3)](NO3)2	88	233	yellow
4b = [Zn(L3)]	85	245	yellow
4c = [Cd(L3)](NO3)2	88	268	yellow
4d = [Cd(L3)]	83	290	yellow
4e = [Hg(L3)](NO3)2	89	212	yellow
4f = [Hg(L3)]	89	250	yellow

Table 2- Amounts and medium for the preparation of the complexes

Complex	Medium	Wt. of NaOH	Wt of $Hg(NO_3)_2.H_2O$	Wt. of $Cd(NO_3)_2.4H_2O$	Wt. of $Zn(NO_3)_2.6H_2O$	Wt. of $TerTMPH_2$
4a = [Zn(L3)](NO3)2	Neutral				1	2.28
4b = [Zn(L3)]	Basic	1ml.			1	2.28
4c = [Cd(L3)](NO3)2	Neutral			1		2.20
4d = [Cd(L3)]	Basic	1ml	.	1		2.20
4e = [Hg(L3)](NO3)2	Neutral		1			1.98
4f = [Hg(L3)]	Basic	1ml	1.			1.98

Weight in gram

Table 3: Relative molecular weight

Compound	M.Wt calc. (Exp.) g. mol^{-1}
Ligand 3	678 (675)
4a = [Zn(L3)](NO$_3$)$_2$	867.41 (864)
4b = [Zn(L3)]	741.41 (738)
4c = [Cd(L3)](NO$_3$)$_2$	914.41 (910)
4d = [Cd(L3)]	788.41 (783)
4e = [Hg(L3)](NO$_3$)$_2$	1002.59 (999)
4f = [Hg(L3)]	876.59 (870)

A. Electrical conductivity

Molar electrical conductivity [20] of new complexes was measured at a concentration of 10^{-3}M by using DMF & DMSO as a solvent at 25ºc. The results showed that new complexes in neutral medium are good conductive electrolyte at a ratio of 1:2. While that prepared in basic medium (pH = 10) are non-conductive and their solution is non-electrolyte. (Table 4). Complexes **4a,c,e** are charged (electrically conductive), while neutral complexes **4b,d,f** are electrically non-conductive complexes (Table 4).

B. Magnetic Sensitivity Measurement

Magnetic measurements[21] of new metal complexes were measured to afford that new complexes showed diamagnetic properties[22]

C. CHN Elemental Analysis

Elemental analysis of carbon, nitrogen, hydrogen were done and Zinc, Cadmium, and Mercury contents have been determined by the Atomic absorption method after the decomposition of the complexes with concentrated nitric acid (Table 5).

Table 4: Molar electrical conductivity

Compound	M.Wt calc. (Exp.) g. mol^{-1}
4a = [Zn(L3)](NO$_3$)$_2$	^M in DMSO (^M in DMF)
4b = [Zn(L3)]	78 (132)
4c = [Cd(L3)](NO$_3$)$_2$	9 (14)
4d = [Cd(L3)]	76 (134)
4e = [Hg(L3)](NO$_3$)$_2$	5 (10)
4f = [Hg(L3)]	73(135)

Table 5: CHN Elemental Analysis

compound	**%C Calc. (Exp.)**	**%H Calc. (Exp.)**	**%N Calc. (Exp.)**	**%Zn Calc. (Exp.)**	**%Cd Calc. (Exp.)**	**%Hg Calc. (Exp.)**
L3	63.71 (60.82)	5.60 (5.21)	16.51(15.00)			
4a = [Zn(L3)](NO$_3$)$_2$	49.80 (48.99)	4.38 (4.33)	16.14 (16.00)	7.54 (7.33)		
4b = [Zn(L3)]	58.26 (57.98)	4.85 (4.67)	15.10 (14.88)	8.82 (8.65)		
4c = [Cd(L3)](NO$_3$)$_2$	47.24 (46.97)	4.15 (3.98)	15.31 (15.00)		12.29 (12.01)	
4d = [Cd(L3)]	54.79 (54.53)	4.56 (4.31)	14.20 (14.05)		14.25 (14.02)	
4e = [Hg(L3)](NO$_3$)$_2$	43.08 (42.89)	3.79 (3.62)	12.56 (12.06)			20.01 (19.56)
4f = [Hg(L3)]	49.28 (48.96)	4.10 (3.79)	12.77 (12.03)			22.89 (22.66)

D. Electronic spectra

Coloured complexes have transitions bands at spectrum visible region, accompanied by other bands in the near-infrared and ultraviolet region adjacent to the visibility of the spectrum. [23]The importance of electronic spectra showed in explaining the properties that were related to metals containing (d) orbitals that are partially filled with electrons. In our study, the electronic spectra of the prepared complexes were measured using DMF and DMSO as solvents, and the prepared compounds did not give (d-d) spectra, which are associated with the metal originally, while it gave the charge transfer spectra. It included transitions between the metal and the ligand and this indicates that the metal does not possess individual electrons, meaning that it does not possess (d-d) transitions, and this leads us to confirm that the complex was in the stereotyped tetrahedral form (Table 6).

Table 6: Electronic spectral data of complexes

Compounds.	C.T.
4a = [Zn(L3)](NO$_3$)$_2$	34013
4b = [Zn(L3)]	33783
4c = [Cd(L3)](NO$_3$)$_2$	34013
4d = [Cd(L3)]	34013
4e = [Hg(L3)](NO$_3$)$_2$	34013
4f = [Hg(L3)]	33783

E. IR spectra

IR spectrum of Ligand **3** revealed bands at 1701 cm^{-1} (C=N), at 3363 cm^{-1} (NH_2), this proves that the interaction between the amine group and the terphthalidehyde occurred, on the compound trimethoprim. Another amine group did not react because of molar ratio of reaction (2:1) and presence of steric hindrance by an ortho-compensator (trimethoxybenzyl).). We note that there are changes in the values of C = N and clear increases for the complexes, due to the electronic density transferred between the metal and the ligand when coordinating In addition to the changes that occur to the tertiary amines, which are converted to ammonium salt. Also, IR revealed bands of aliphatic and aromatic C-H and bands of symmetric and asymmetric C-O-C (Table 7)[24-26].

F. H NMR

1H NMR spectrum of ligand **3** revealed presence of a signal at 2.55 ppm to the two groups -CH2- group between the phenyl ring and the pyrimidine, a single signal at 3.89 ppm due to the 18 protons of the methoxy group substituted on the two benzene rings, and it gave a single signal at 6.99 ppm due to the 2H for two imine groups -CH=N-, and a group of signals (five different bands) in the region 7.06 until 7.99 ppm belongs to the group of protons attached to the phenyl and pyramidine to 8 protons, and finally a single signal at 8.94 ppm belongs to the stretching of the first amine group (Figure 1)[27-28].

Table 7: IR of new compounds

Comp. No.	M-N	N-H	C-H ar	C-H alph	C=N	C=N in ring	C-N	C-O-C
L3	--	3363,3242	2995	2939,2833	1680	1664	1328	1236,1004
4a = [Zn(L3)](NO$_3$)$_2$	520,611	3433,3340	3004	2966,2835	1685	1660	1353	1238,1000
4b = [Zn(L3)]	518,600	3433,3344	3002	2966,2837	1693	1644	1386	1236,997
4c = [Cd(L3)](NO$_3$)$_2$	526,592	3346,3334	2991	2937,2835	1697	1640	1382	1236,1004
4d = [Cd(L3)]	510,590	3367,3247	2993	2939,2833	1682	1670	1380	1236,1004
4e = [Hg(L3)](NO$_3$)$_2$	528,582	3397,3218	3030	2939,2833	1697	1602	1326	1234,1002
4f = [Hg(L3)]	516,592	3353,3278	3040	2937,2833	1697	1606	1325	1236,1002

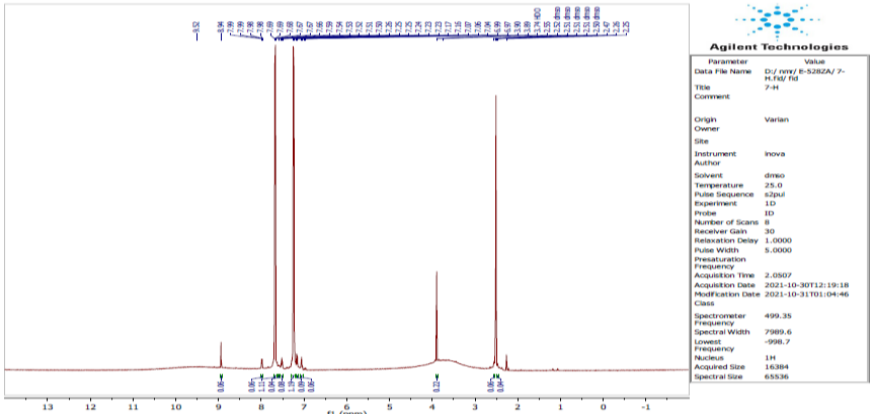


Figure 1: spectra H^{1}NMR for ligand

4. Antibacterial activity

The antibacterial activity of new complexes has been investigated and expressed according to the agar plate diffusion method as the diameter of the inhibition zones [29,30] against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella spp*. All new complexes have no activity , Cefotaxime and penicillin were used as references to compare with the complexes when measuring efficacy.

5. Conclusion

Based on the previous considerations from analytical and spectroscopic studies and physical and chemical properties, the following can be concluded:

- In the complexes resulting from the neutral medium, the ligand **3** coordinates with the zinc, cadmium and mercury binary ions through two nitrogen atoms azomethine and two nitrogen atoms of the two amine groups, as it acts in the form of a neutrally charged ketelete tetrahedron ligand. In the basic medium, the ligand **3** acts as a negatively charged ligand, as it loses two protons.
- The resulting complexes in the neutral medium are positively ionic with a general formula $[M(L3)](NO_3)_2$
- The resulting complexes in the basic medium are neutral with a general formula [M(L3)].
- The metal ion in all the complexes produced in the neutral and basic mediums is tetrahedral, taking the form of a tetrahedron, and producing mononuclear complexes.

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