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Preparation of New Complexes of Bivalent Manganese, Iron, Cobalt, and Nickel with Mixed Ligands of Ciprofloxacin (Cip) and Metronidazole (Met) or 4-Aminoantipyrine (4AAP) with Study of Their Chemical, Physical Properties and Antibacterial Activity

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Abstract

Synthesis of mixed metal complexes were done through reaction of two drugs such as antipyrine, or ciprofloxacin with Metronidazole to have eight complexes. Physical, chemical and antibacterial activity of new complexes were studied. These mixed ligands were further coordinating with bivalent transition metals in a metal: ligands mixture ratio 1:1. These complexes were characterized by using elemental analysis and physical properties, in addition molar conductance in DMF which showed non-electrolytic behavior. FT-IR spectra revealed absorption bands for new ligands and metal complexes that agreed with the propose structures and the electronic spectra verified that these complexes display six-coordinate octahedral geometry. Antibacterial activity showed good results.

***Keywords*:** Ciprofloxacin, Metronidazole, 4-Aminoantipyrine, Mixed ligands, Antibacterial Activity.

1. Introduction

Widespread of antimicrobial resistance rises, which leads to explore new sources drug compounds as new classes of antibiotics. Meanwhile, metal complexes are with broad presence in medicinal chemistry as the anticancer drug cisplatin. Indeed, metal complexes have been largely ignored for antibiotic industry. However, they have unique modes of action with existence in a wide range of 3D geometries which more favorable than pure organic compounds. These lead to make them interesting starting materials for the development of new drugs. [1] Besides that, complexes which derived from the coordination between transition metal platin and organic moieties such as cyclobutane dicarboxylic acid, 1,2-diaminocyclohexane and oxalic acid in the second and third generation anticancer platin drugs carboplatin and oxaliplatin respectively. [2, 3] Meanwhile, metal complexes have long had only a niche presence in the medicinal chemistry landscape.[3] On the other hand, Ciprofloxacin (CIP) is one of a new generation of fluorinated quinolones structurally related to nalidixic acid[4] s a very common antibiotic drug for the treatment of different types of bacterial infections[5]. Also, Antipyrine (ANP) is considered one of the valuable discovery in the field of medicinal and organic chemistry because of its activity of such antipyretic, less toxic, nonpaid analgesic, anti-inflammatory drug together with its metabolism by liver to exert via urine [6]. Beside, antipyrine derivatives have an important roles in coordination chemistry[7]. In the same manner, the antibiotic importance of Metronidazole (MTR) as antibiotic in treatment of anaerobic bacterial infections and parasites that infect joints, brain spinal cord, skin, vagina, stomach and liver.[8] in addition to it is recently used in regime of COVID19[9] because of its role in decrease level of several cytokines in blood which already increase in COVID19 patients. Also, MTR could decrease neutrophil-generated ROS (Reactive Oxygen Species) during the inflammation process.[9] According to above survey and in continuation of our work in coordination synthesis, the present paper intended to report the synthesis of a new series of metal complexes that derived from mixing two antimicrobial drugs as mixed ligands and bivalent transition metals and study their characterization, and

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their antimicrobial activity (Figure 1).[10, 11].

Experimental

Chemistry and instruments:

The chemical reagents together with antipyrine, or ciprofloxacin with Metronidazole were provided from chemical companies that work in Iraq. Bivalent transition metal chlorides (manganese, iron, cobalt, and nickel) were supplied by Fluka. FT-IR spectra were recorded as cesium iodide disc on FT-IR 8300 Shimadzu spectrophotometer, in the range (200–4000) cm^{-1}. UV-Visible spectra were recorded on Shimadzu UV-Vis.160 A spectrophotometer in the range (200–1000) nm, and measured in DMF. Magnetic susceptibility balance model MSB-MKI was used to measure the magnetic susceptibility measurements at room temperature (25°C). Flame atomic absorption of elemental analyzer, Shimadzu AA-670, was used for metal determination . Elemental analyzer model 5500-Carlo Erba instrument is used to determine percentage of C, H, N, and metal. Gallen Kamp M.F.B.600.010 F was used to as melting point apparatus to get melting point of all the prepared compounds.

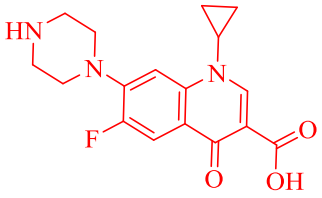
General Procedures of synthesis Mixed Ligands Metal Complexes 1a-d and 2a-d

Equimolar of metal chlorides (MCl_2, 5 mmol) and the parent ligand of CIP with ANP or MTR were mixed together in ethanol (10 mL). This mixture was gradually added to KOH solution (0.5 M) then was refluxed for 2h . After completion, reaction was cooled to afford a precipitate which was filtrated and washed with 20 mL H_2O then 20 mL ether. The precipitate was dried in the oven at 70°C.

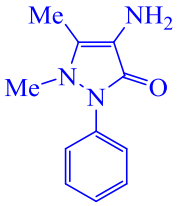
The percentage weight of metals and ligands were listed in Table (1).

1. Results and Discussion

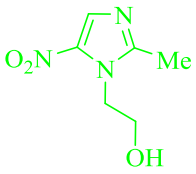
Ciprofloxacin (CIP) was mixed with Antipyrine (ANP) or Metronidazole (MTR) in alcoholic potassium hydroxide under reflux temperature for two hours with the addition of metal chlorides of Manganese, Iron, Cobalt, and Nickel to afford two groups of complexes **1a-d** and **2a-d** (Figure 2). This reactions depends on the coordination of bivalent transition metal chlorides with size of the chelate rings, together with bidentate ligands that with a flexible organic backbone of five and six membered rings have almost no strain and stable complexes. [12-14]



Ciprofloxacin
CIP



Antipyrine
ANP



Metronidazole
MTR

Figure 1: Antibiotic drugs against bacteria

Table 1: The percentage weight of metals and ligands

	CIP (g)	MTR (g)	ANP (g)	$MCl_2.XH_2O$ (g)	Complexes
1a	1.6	0.86	-----	0.625	$[Mn(MTR)(Cip)(H_2O)_2]$
1b	1.6	0.86	-----	0.63	$[Fe(MTR)(Cip)(H_2O)_2]$
1c	1.6	0.86	-----	1.19	$[Co(MTR)(Cip)(H_2O)_2]$
1d	1.6	0.86	-----	1.185	$[Ni(MTR)(Cip)(H_2O)_2]$
2a	1.6	-	1.1	0.625	$[Mn(ANP)(Cip)((H_2O)_2]$
2b	1.6	-	1.1	0.63	$[Fe(ANP)(Cip)((H_2O)_2]$
2c	1.6	-	1.1	1.19	$[Co(ANP)(Cip)((H_2O)_2]$
2d	1.6	-	1.1	1.185	$[Ni(ANP)(Cip)((H_2O)_2]$

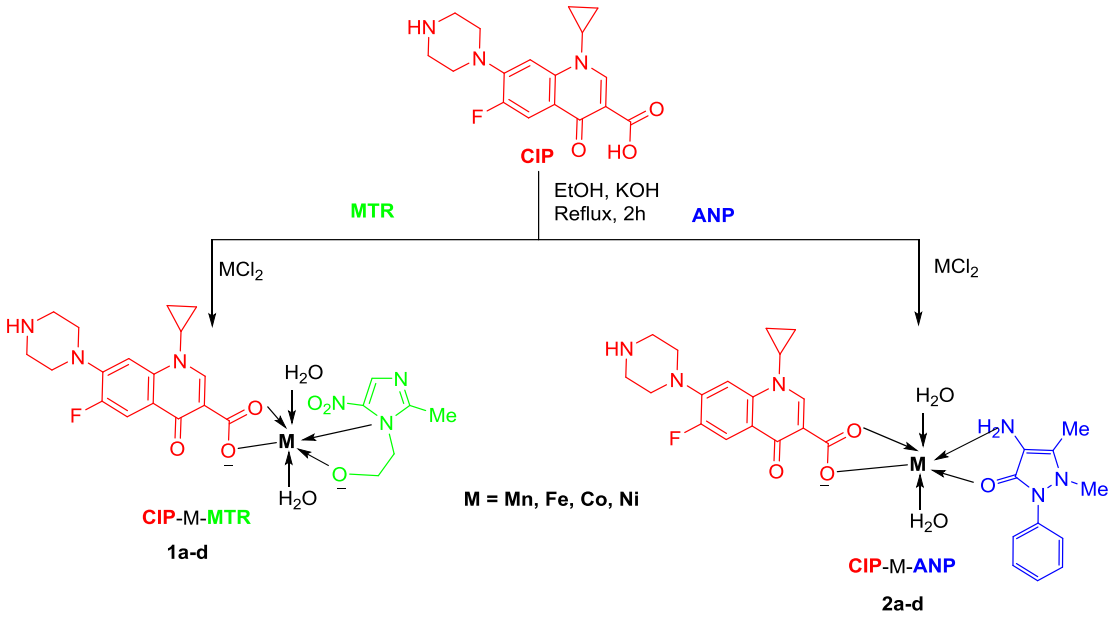


Figure 2: New synthesized complexes

Ciprofloxacin (CIP) was coordinated with transition metals of Manganese, Iron, Cobalt, and Nickel through the carboxylate oxygen atom and the carbonyl oxygen atom in CIP to generate an octahedral geometry and antipyrine (ANP) was coordinated through amino group and oxygen of carbonyl group while coordination of Metronidazole (MTR) is occurred through hydroxyl group and nitrogen at position one of imidazole ring (Figure 3).[15-17]

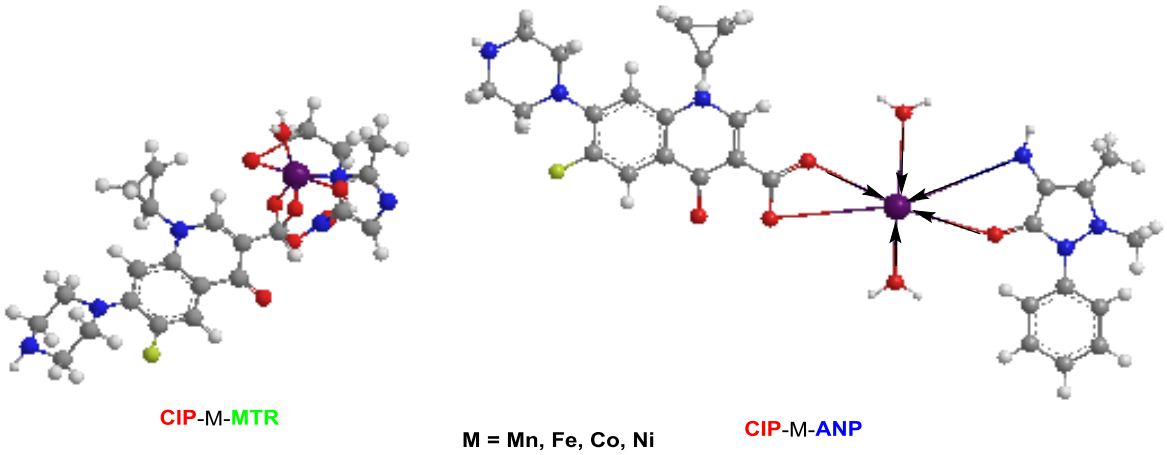


Figure 3: New synthesized complexes as 3D structures (Mn complex as an example), using PerkinElmer ChemBioDraw Ultra, version 14.0.0.117, Cambridge Soft Corporation (2014).

The new synthesized metal complexes were characterized through CHNS analysis and Physical properties, molar conductance, FT-IR, Electronic spectra, and magnetic moment data.

a. CHNS analysis and Physical properties

All new complexes were physically characterized as depicted in Table 2. Color of new complexes ranged from brown, green to dark brown according to metals and ligands. Also, most of melting point are decomposed during measuring [20]

b. FT-IR spectra

Also, FTIR measurements were subjected to confirm the structures of new complexes. Most of characteristic bands that are included in FTIR spectra were listed in table 3. The bands showed that ligands of Ciprofloxacin (CIP), Antipyrine (ANP) and Metronidazole (MTR) have characteristic bands at 1284-1310 cm^{-1} that related to C-N, 1175-1185 cm^{-1} that related to C-O while symmetrical C=O of CIP at 1310s cm^{-1} and unsymmetrical at 1625s cm^{-1} (Table 3).

FTIR of new complexes have new bands that related to metal-oxygen in range of 614-623 cm^{-1} and 645-680m cm^{-1}, while metal-nitrogen bonds appeared at 430-438m cm^{-1} and metal-OH_2 appeared at 680-760m cm^{-1}(Table 3). Also, carbon-nitrogen or -oxygen bonds appeared with slight shielding due to coordination at 1226 $cm^{-1}$and 116-1167s cm^{-1} with absence of symmetrical and unsymmetrical CO bands [21].

Table 2: CHNS and physical properties of complexes

No	Mwt	Color	m.p	%C	%H	%N	%M
				Theoretical (Practical)			
1a	589.39	Brown	300d	50.25 (50.12)	4.17 (4.11)	3.04 (3.00)	12.38 (12.30)
1b	590.19	Brown	260d	50.14 (50.10)	4.16 (4.03)	3.04 (2.98)	12.58 (12.60)
1c	648.39	Dark brown	277d	49.89 (48.99)	4.13 (4.01)	3.09 (3.02)	13.16 (13.20)
1d	647.89	Green	300d	49.82 (49.65)	4.14 (3.99)	3.09 (3.00)	13.11 (13.16)
2a	461.39	Brown	270d	51.09 (50.98)	4.19 (4.11)	6.64 (6.58)	13.24 (13.26)
2b	462.19	Brown	272d	50.83 (50.62)	4.70 (4.53)	6.62 (6.59)	13.43 (13.38)
2c	465.39	Dark brown	295d	56.18 (56.02)	4.64 (4.52)	6.57 (6.52)	14.07 (14.02)
2d	464.89	Green	288d	56.21 (56.03)	4.67 (4.43)	6.57 (6.53)	14.02 (14.08)

Table 3: FT-IR spectra data of the three ligands and complexes in (cm^{-1})

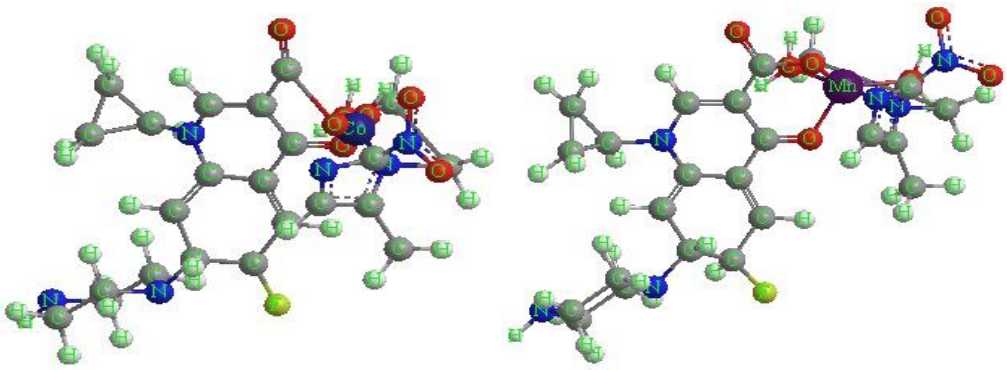
No	Compounds	M-O	M-N	M-OH_2	C=N	C-N	C-O	Sym CO_2	Asym CO_2
CIP	Ciprofloxacin	--------	--------	--------	-------	1284 m	1176 s	1381s	1625 s
MTR	Metronidazole	--------	--------	--------	1589 m	1310 m	1185 s	------	------
ANP	4-Aminoantipyrine	--------	--------	--------	--------	1290 m	1175 s	------	-----
1a	[Mn(CIP)(MTR)(H_2O)$_2$]	623 m,645m	430 m	734 m, 760 m	1590 m	1240 s	1167s ,1192 s	1378 s	1623 s
2b	[Fe(CIP)(MTR)(H_2O)$_2$]	620 m,671 m	431 m	680 m ,691m	1600 m	1230 s	1162 s,1183 s	1325 s	1594 s
1c	[Co(CIP)(MTR)(H_2O)$_2$]	619 m,668m	435 m	724 m, 766 m	1589 m	1235s	1158 s, 1181 s	1327 s	1591 s

1d	[Ni(CIP)(MTR)$(H_2O)_2$]	623 m,680m	438 m	690 m, 731 m	1588 m	1235 s	1160 s,1192 s	1333 s	1611 s
2a	[Mn(CIP)(ANP)$(H_2O)_2$]	614 m,681m	471 m	756 m	--------	1237 s	1115s, 1156 s	------	------
2b	[Fe(CIP)(ANP)$(H_2O)_2$]	615 m,683 m	477 m	743 m, 771 m	--------	1238 s	1118 s, 1152 s	------	------
2c	[Co(Cip)(ANP)$(H_2O)_2$]	620 m,685 m	438 m	735 m, 772 m	--------	1221 s	1123 s, 1161 s	------	------
2d	[Ni(Cip)(ANP)$(H_2O)_2$]	625 m,678 m	435 m	780 m, 803 m	--------	1226 s	1116 s, 1143 s	------	------

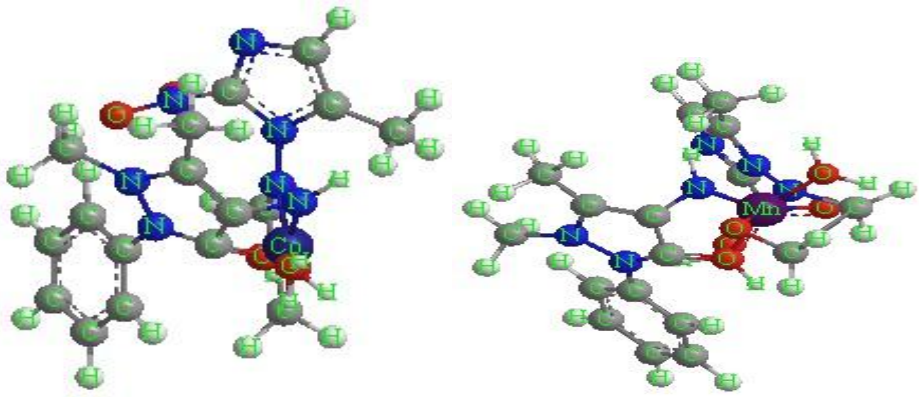
s = strong , m = medium

c. Molar conductance

Molar conductance was measured in DMF as a solvent. It showed values in range of 16-23 $\Omega^{-1}cm^2$ mol^{-1} to indicate these complexes have non-electrolytic behaviour [19] Also, compositions of complexes had the formula CIP-M-MTR.$2H_2O$ in **1a-d** or CIP-M-ANP.$2H_2O$ in **2a-d** where M= divalent Mn, Fe, Co, Ni. Besides, bidentate CIP, MTR and ANP ligands formed two bonds with central metal ion, which allowed water to coordinate with these metals, and owing to its monodentate nature, it was not a chelating ligand (Table 4).[22]



3D chemical structure a. [Co(CIP)(MTR)$(H_2O)_2$] b. [Mn(CIP)(MTR)$(H_2O)_2$]



3D chemical structure of c.[Co(Cip)(ANP)$(H_2O)_2$] d. [Mn(Cip)(ANP)$(H_2O)_2$]

Figure 4: New synthesized complexes as 3D structures

Table 4: Conductivity data of the complexes

No	Complexes	Conductivity in DMF $\Omega^{-1}cm^2mol^{-1}$
1a	$[Mn(CIP)(MTR)(H_2O)_2]$	18
2b	$[Fe(CIP)(MTR)(H_2O)_2]$	20
1c	$[Co(CIP)(MTR)(H_2O)_2]$	23
1d	$[Ni(CIP)(MTR)(H_2O)_2]$	16
2a	$[Mn(CIP)(ANP)(H_2O)_2]$	25
2b	$[Fe(CIP)(ANP)(H_2O)_2]$	20
2c	$[Co(Cip)(ANP)(H_2O)_2]$	22
2d	$[Ni(Cip)(ANP)(H_2O)_2]$	19

d. Electronic absorption spectra

Three spin-allowed transition observed in low spin state for Mn(II) υ_1= 12525, 12550.02 cm^{-1}, υ_2= 29910.4, 29998.23 cm^{-1} and υ_3= 25200.2, 25144.76 cm^{-1}. Also, three metals (divalent Fe, Co and Ni) showed three bands Table (5), these complexes exhibit six-coordinate octahedral geometry.[23]

Table 5: Electronic spectra data for complexes

No	Complexes	υ_1 cm^{-1}	υ_2 cm^{-1}	υ_3 cm^{-1}
1a	$[Mn(CIP)(MTR)(H_2O)_2]$	12525.00	29910.4	25200.2
1b	$[Fe(CIP)(MTR)(H_2O)_2]$	19890.02	31460.87	39910.00
1c	$[Co(CIP)(MTR)(H_2O)_2]$	7742.99	16657.67	23320.55
1d	$[Ni(CIP)(MTR)(H_2O)_2]$	10195.39	11155.96	26658.77
2a	$[Mn(CIP)(ANP)(H_2O)_2]$	12550.02	29998.23	25144.76
2b	$[Fe(CIP)(ANP)(H_2O)_2]$	19978.64	31480.53	39860.96
2c	$[Co(Cip)(ANP)(H_2O)_2]$	7790.33	16665.65	23330.33
2d	$[Ni(Cip)(ANP)(H_2O)_2]$	19180.44	11175.52	26700.21

e. Magnetic moment data

Magnetic moments were measured at room temperature. The effective magnetic moment values for Mn(II) complexes and Co(II) complexes **1a,c** and **2a,c** were ranges (1.72-1.83)B.M. while for Fe(II) complexes **1b,f** were (Zero)B.M. and for Ni(II) complexes **1d** and **2d** were (2.87,2.81)B.M. respectively as shown in Table (6), These values suggested that presence of one unpaired electron in the complexes of Mn(II) and Co(II) and the presence of two unpaired electron in the complexes of Ni(II),while the complexes of Fe(II) are diamagnetic. All these values have corresponded to octahedral geometries.[24-26]

Table 6: Magnetic moment data for complexes

No	Complexes	μ_{eff} (theoretical)	μ_{eff} (practical)	$X_A \times 10^{-6}$ (e.g.s.u)	$X_m \times 10^{-6}$ (e.g.s.u)	$X_g \times 10^{-6}$ (e.g.s.u)
1a	$[Mn(CIP)(MTR)(H_2O)_2]$	1.73	1.72	1170.22	866.17	1.35
1b	$[Fe(CIP)(MTR)(H_2O)_2]$	0	0	0	0	0

1c	[Co(CIP)(MTR)(H_2O)$_2$]	1.73	1.83	1150.16	925.55	1.60
1d	[Ni(CIP)(MTR)(H_2O)$_2$]	2.83	2.87	3620.64	3355.86	4.87
2a	[Mn(CIP)(ANP)(H_2O)$_2$]	1.73	1.75	1155.95	830.87	1.23
2b	[Fe(CIP)(ANP)(H_2O)$_2$]	0	0	0	0	0
2c	[Co(Cip)(ANP)(H_2O)$_2$]	1.73	1.83	1174.31	930.43	1.56
2d	[Ni(Cip)(ANP)(H_2O)$_2$]	2.83	2.81	3590.74	3268.65	4.75

2. Antibacterial Activity

Antibacterial activity of new complexes is subjected on *Escherichia coli, Pseudomonas aeruginosa* via using disc diffusion method in DMSO. [27-29]The results are listed in table 7. Role of negative results are effective so, all new complexes exhibited no activity against *Escherichia coli, Pseudomonas aeruginosa* except complex **2a,d** .

Table (7): antibacterial activity of new complexes

Comp. No.	10^{-3} M		10^{-4} M		10^{-5}M		10^{-6} M	
	E.	**P.a.**	**E.c.**	**P.a.**	**E.c.**	**P.a.**	**E.c.**	**P.a.**
1a	-	-	-	-	-	-	-	-
1b	-	-	-	-	-	-	-	-
1c	-	-	-	-	-	-	-	-
1d	-	-	-	-	-	-	-	-
2a	+	+	-	-	-	-	-	-
2b	-	-	-	-	-	-	-	-
2c	-	-	-	-	-	-	-	-
2d	+	+	-	-	-	-	-	-
E.c.: Escherichia coli, P.a.: Pseudomonas aeruginosa								

3. Conclusion

From pervious results, we can concluded that mix two antibacterial drugs with metal ions to form new metal complexes is depends on the ratio of addition together with reaction conditions. All new compounds were characterized, and antimicrobial activity has a negative results except two complexes of **2a,d**. Also, these new complexes proved that non-electrolytic behavior, exhibit six-coordinate octahedral geometry, and coordination is metal: ligand mixture ratio 1:1.

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4. Conflict of Interest

The authors declare no conflict of interest.

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