



## Original Research Article

# Metal Complexes of Metronidazole Benzoate with Some Metal Ions: Synthesis and Characterization and Study Apart from Their Biological Applications

Waleed Alaa Aldeen Saleh\*, Nada Mutter Abbass

Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq

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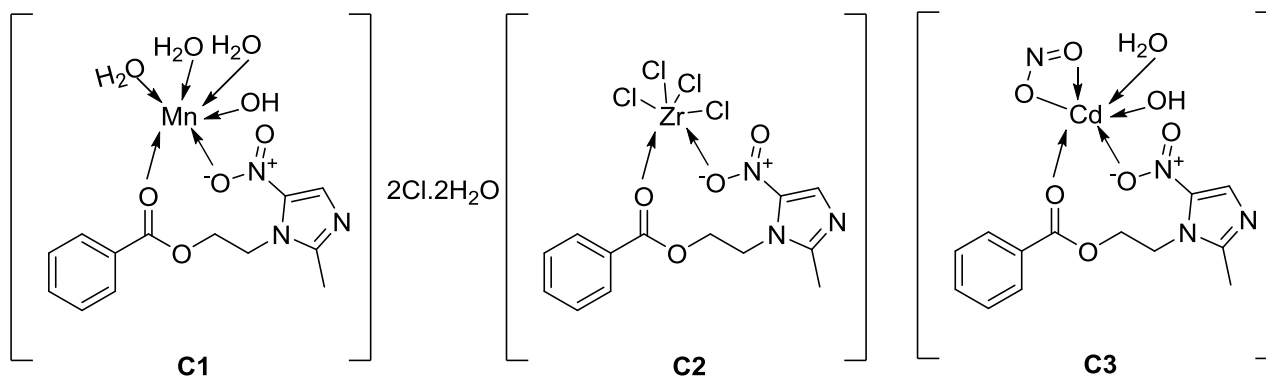
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## ABSTRACT

New metal complexes of metronidazole benzoate were prepared by the reacting of  $\text{Cd}(\text{NO}_3)_2$ ,  $\text{MnCl}_2 \cdot 6\text{H}_2\text{O}$  and  $\text{ZrCl}_4$  with ligands in L:M (1:1) mole ratio. All synthesized complexes were analyzed by FT-IR, UV-Vis, TG, DTG, AAS,  $^1\text{H-NMR}$ , elemental analysis (CHN), melting point determination, magnetic susceptibility determination, and chloride content determination. The proposed shape of all complexes was the octahedral. Some complexes were electrolyte and paramagnetic. All synthesized complexes are activated as antibacterial and antifungal against (*Candida*, *Pseudomonas auroginosa* (G-), *Escherichia coli* (G-), *Bacillus* (G+), and *Staphylococcus aureus* (G+)). The antioxidant activity of the ligand was also tested.

## GRAPHICAL ABSTRACT



\* Corresponding author: Waleed Alaa ALdeen Saleh

✉ E-mail: [waleedalaa1118@gmail.com](mailto:waleedalaa1118@gmail.com)

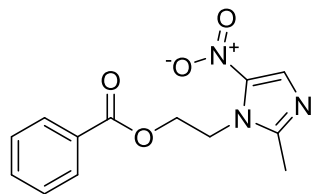
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## Introduction

Metronidazole benzoate (Scheme 1), is suggested for the wounds treatment caused by a broad panel of tested anaerobic bacteria and protozoa, including amebiasis, trichomoniasis, gingivitis, and vaginitis [1, 2]. The drug is effective against both anaerobic gram-negative and anaerobic spore-forming gram-positive bacilli [3]. Metronidazole benzoate suspensions are widely used to substitute metronidazole in pediatric oral formulations due to the bland taste of the ester compared with the bitterness of the free base [4]. Metronidazole benzoate has low solubility in water, but metronidazole is highly soluble (10.5 mg ml<sup>-1</sup> in water at 25 °C). No significant hydrolysis of the ester was observed in the simulated gastric fluid USP (up to 8 hours) and simulated intestinal fluid USP up to 5 hours [4].

However, serology, urology, etc. from patients treated with metronidazole benzoate show only metronidazole and not non-aqueous metronidazole benzoate [5]. We have also developed a new metronidazole controlled-release formulation by using metronidazole benzoate as the base of metronidazole [6]. Therefore, to assess the dissolution of metronidazole benzoate, an analytical method that can quantify low concentrations (because of their low water solubility) is important in the presence of its dissolution products metronidazole and benzoic acid.

In this work, we synthesize metal complexes from the direct reaction of metronidazole benzoate with metal salts and test their antibacterial and antioxidant activities.



**Scheme 1:** Metronidazole benzoate

## Materials and Methods

FT-IR spectrophotometry was investigated for ligand (400-4000 cm<sup>-1</sup> in KBr) and complexes (250-4000 cm<sup>-1</sup> in CsI). The UV-Vis spectra were recorded by Shimadzu 1800 UV spectrophotometer (240-1100 nm) with DMSO as a solvent. Elemental analyses (CHN) were recorded by the elemental analyzer EuroEA 3000/Italy. Thermal analysis (TG and DTG) was recorded by tga-dta-sta300 Germany. The magnetic susceptibility measurements at ambient temperature were recorded by using Sherwood Scientific's Auto Magnetic Susceptibility Balance Model. Metal content was determined by atomic absorption spectroscopy on a Nova350 spectrophotometer. The Mohr method was used to determine the chloride content of the complex. NMR Bruker 500 MHz Germany measured <sup>1</sup>H NMR spectra in DMSO-*d*<sub>6</sub>. The melting points were determined on a Gallenkamp melting point apparatus.

*Preparation of [(Tetraaqua(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate) manganese(II)aquaChloride)]*

*Preparation a mole ratio of L:M (1:1)*

A 1.5 g solution of L (0.0054 mol) was dissolved in 75 mL of ethanol (pale white) and refluxed with constant stirring for 20 min until completely dissolved, and then the 0.636 g of metal salt MnCl<sub>2</sub>·6H<sub>2</sub>O (0.0027 mol) was added to 25 mL and a white color appeared immediately upon stirring. The solvent revealed a pale white product, which was cooled in an ice bath, scratched, and then washed with ethanol and dried in an oven at 85 °C.

*Preparation of [(tetrachloro(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate) zirconium(IV))]*

A solution of 1.5 g L (0.0054 mol) in 75 mL ethanol was refluxed with stirring for 20 minutes until completely dissolved, and then 0.634 g metal salt ZrCl<sub>4</sub> (0.0027 mol) was added to 25 mL

of ethanol immediately appeared and the solution was refluxed for 4.5 hours with constant stirring. The solvent evaporation gave a pale white product which was scraped off and cooled in an ice bath before being washed with ethanol and oven dried at 85 °C.

*Preparation of (Diaqua(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate)nitrito Cadmium(II) nitrate)*

A 1.5 g solution of L (0.0054 mol) in 75 mL of ethanol was refluxed with continuous stirring for 20 min until completion, and then 0.644 g metal salt Cd(NO<sub>3</sub>) (0.0027 mol) was added, refluxed for 5 min. After 15 min, the color had evaporated and the product was scratched, washed with ethanol, and dried in an oven at 85 °C. The physical properties and analysis data were illustrated in following:

**L<sub>3</sub>:** Pale white, 99-102 °C (decomposition), IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 2980, 1717, 1591, 1523, 1464, 1429, 1360, 1267, 1185, 1092, Anal. Calcd C, 55.87; H, 3.95; N, 14.56; M, Found: C, 56.67; H, 4.72; N, 15.25.

**C<sub>1</sub> Mn(II):** Pale white, yield 96%, 124 °C (decomposition), IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 2983, 1700, 1608, 1539, 1479, 1429, 1269, 1188, 1076, 759, 457. Anal. Calcd C, 29.83; H, 4.31; N, 7.87; M, 10.63; Cl, 13.21. Found: C, 30.64; H, 4.91; N, 8.24; M, 10.78; Cl, 13.94.

**C<sub>2</sub> Zr(IV):** Pale white, yield 94%, 100 °C (decomposition), IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 2958, 1725, 1608, 1537, 1481, 1431, 1371, 1269, 1188, 1076, 439, 306. Anal. Calcd C, 29.73; H, 2.71; N, 7.34; M, 17.89; Cl, 27.87; Found: C, 30.69; H, 2.55; N, 8.26; M, 17.94; Cl, 27.93.

**C<sub>3</sub> Cd(II):** Light yellow, yield 93%, 140 °C (decomposition), IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3440, 2983, 1700, 1606, 1535, 1481, 1429, 1267, 1188, 1157, 1074. Anal. Calcd C, 27.69; H, 2.93; N, 12.34; M, 20.47; Found: C, 28.48; H, 3.10; N, 12.78; M, 20.52.

## Results and Discussion

### FT-IR spectroscopy

The FT-IR spectra of Mn(II), Zr(IV), and Cd(II) complexes show that the stretching vibrations of NO<sub>2</sub> and CO groups related to the ligand coordination with metal ions *via* the NO<sub>2</sub> and CO groups. The C=O group was absent and a new low-frequency band appeared in the complex spectrum due to the coordination with metal ions. Finally, new stretches occurred at lower frequencies assigned to M-N, M-O, and M-Cl [7-12].

### <sup>1</sup>H-NMR spectroscopy

The metal complex and ligand (L) were characterized by <sup>1</sup>H NMR in DMSO-*d*<sub>6</sub>. The characteristic peaks of imidazole protons, CH<sub>2</sub> protons, and a benzene ring were appeared due to the complexions ligand with metals, according to the previous studies [13]. The <sup>1</sup>H-NMR spectra of the ligands are displayed in Figure S1 (Supporting information) and data are presented in Table 1.

### Thermo-gravimetric of ligand and its complexes

TG and DTG data were analyzed by Ar gas with rate 10 °C.min<sup>-1</sup> in the range 0 to 1000 °C. TGA can be used to evaluate the thermal stability of a material. In a favorable temperature range, if a species is thermally stable, no mass change will be observed. Negligible mass loss corresponds to a low slope or no TGA trace. TGA also gives the high temperature of a substance use. Beyond this temperature, the material starts to degrade. Figure 1 and Table 2 demonstrate the thermograms of the ligands [14-18].

### Electronic spectra

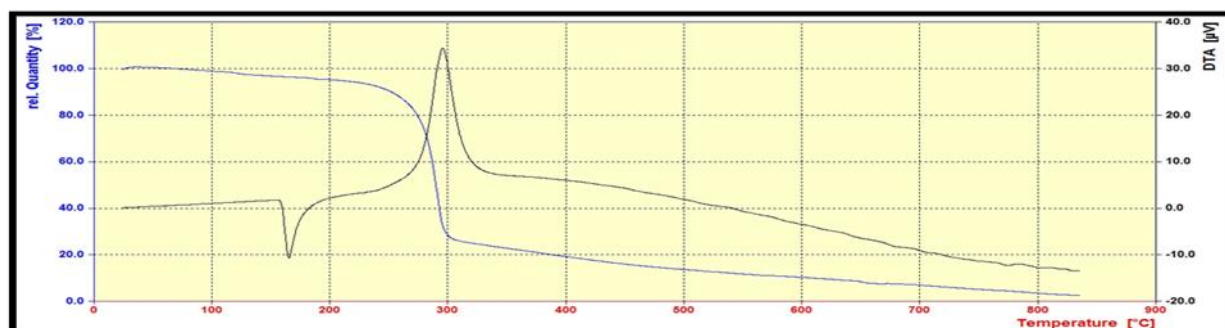
The electronic spectra of the desired compounds were observed in DMSO (10<sup>-4</sup> M) at room temperature. The ligand's spectrum in distilled water provided a sharp intense band appearing at 320 nm (31250 cm<sup>-1</sup>) assigned to the π-π\* of the conjugated system, as depicted in Table 3.

**Table 1:** <sup>1</sup>H-NMR data for ligand (L)

Chemical shifts (ppm)	No. of protons	Assignments in DMSO
8.00	1	Aromatic protons of imidazole (A)
5	5	Aromatic protons of phenyl (B)
2.98	2	protons of CH <sub>2</sub> (C)
3.88	2	protons of CH <sub>2</sub> (D)
4.4	3	protons of CH <sub>3</sub> (E)

**Table 2:** TG and DTG data for ligand and its metal complexes

Compound	M.F and M.W.	Step	Decomposition (°C)	DTG (°C)	Suggested Formula of loss	Mass loss%	
						Calculated	Found
L <sub>3</sub>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> (275.26)	1	25- 300	168	C <sub>9</sub> H <sub>9</sub> O <sub>4</sub> N	70.90	70
		2	300 -800	330 680	C <sub>3</sub> H <sub>4</sub> N <sub>2</sub>	24.73	26
		Residue	> 800		C	4.37	4
C <sub>1</sub>	[Mn(H <sub>2</sub> O) <sub>4</sub> (L <sub>3</sub> ).2Cl.2H <sub>2</sub> O (509.104)	1	45 - 345	140 150 300	CH <sub>3</sub> , 4H <sub>2</sub> O, 2Cl	31.03	30
		2	345 - 800	555 650 735	C <sub>7</sub> H <sub>7</sub> O <sub>2</sub>	24.18	24
		Residue	> 800		MnC <sub>5</sub> H <sub>9</sub> O <sub>4</sub> N <sub>3</sub>	45.15	46
C <sub>2</sub>	[ZrCl <sub>4</sub> (L <sub>3</sub> )] (508.28)	1	50 - 800	167 325 650 780	C <sub>10</sub> H <sub>12</sub> O <sub>2</sub>	32.03	32
		Residue	> 800		ZrC <sub>3</sub> HO <sub>2</sub> Cl <sub>4</sub> N <sub>3</sub>	68.09	68
C <sub>3</sub>	[Cd NO <sub>3</sub> (H <sub>2</sub> O) <sub>2</sub> (L <sub>3</sub> ) NO <sub>3</sub> (547.68)	1	38 - 275	153 225	NO <sub>3</sub> , 2H <sub>2</sub> O, C <sub>7</sub> H <sub>5</sub> O <sub>2</sub>	40.01	40
		2	275 - 800	320 350 640 750	C <sub>6</sub> H <sub>9</sub> O <sub>3</sub> N <sub>4</sub>	33.80	34
		Residue	> 800		CdO <sub>2</sub>	26.19	26

**Figure 1:** The thermal stability of the ligand

A very low intensity band was assigned to the  $n-\pi^*$  transitions. Due to the ligands complexation with metal ions, the  $\pi-\pi^*$  transition band was slightly shifted to the higher wavenumbers in the

spectra of Mn(II), Zr(IV), and Cd(II) ion complexes [19, 20]. Charge transfer bands were observed as listed in Table 3.

The Mn(II) complex (C1) is white in the solid state and gave a clear solution in D.W. which mentioned the involvement of solvent molecules in the coordination with metal ions, The spectrum of the complex in Figure 2 exhibited two bands in the visible region. The first band was of a very low extinction coefficient appeared at 9727 cm<sup>-1</sup> and was assigned to <sup>6</sup>S <sup>6</sup>A<sub>1g</sub>→<sup>4</sup>T<sub>2g</sub> (ν<sub>1</sub>) transition corresponding to octahedral Mn(II) complexes. The second band appeared with the maximum absorption at 9881 cm<sup>-1</sup> and was taken to assign to the transition <sup>6</sup>A<sub>1g</sub> →<sup>4</sup>T<sub>1g</sub> (ν<sub>2</sub>). Magnetic moment of the complex (μ<sub>eff</sub>. 6.01 B.M.) comes in agreement with those of octahedral geometries. The conductivity measurement (189.0 S.mol<sup>-1</sup>.cm<sup>2</sup>) shows that the complex is an electrolyte with ionic ratio of (1:1) [21-24].

The spectrum of the Zr(IV) complex (C2) as illustrated in Figure 3 and Table 3 in D.W.

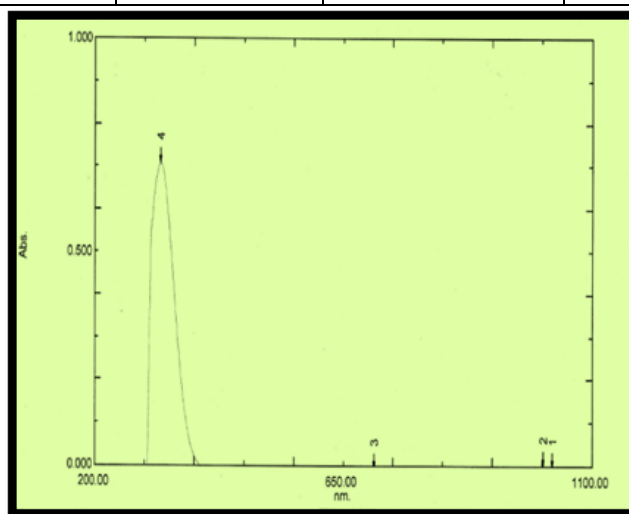
exhibited no transition bands in the visible region except that of CT transition which is quite familiar with the d<sup>0</sup> configuration where no d-d transition is involved. The solid complex was diamagnetic and conductivity in D.W. (30.0 S.mol<sup>-1</sup>.cm<sup>2</sup>) shows that the complex was of a non-electrolyte nature [21, 25, 26].

The spectrum of the Cd(II) complex (C3) as shown in Figure 4 and Table 3 in D.W. exhibited no transition bands in the visible region except that of CT transition which is quite familiar with the d<sup>10</sup> configuration where no d-d transition is involved. The solid complex was diamagnetic and conductivity in D.W. (127.0 S.mol<sup>-1</sup>.cm<sup>2</sup>) shows that the complex is an electrolyte with ionic ratio of (1:1) [21, 25, 26].

Consistent with the above-mentioned points, the molecular structure of the provided complexes may be taken after as exhibited in Scheme 2.

**Table 3:** Electronic spectra in D.W.

Compound	Band positions nm (cm <sup>-1</sup> )	Assignment	Molar Conductivity (S.cm <sup>2</sup> .mol <sup>-1</sup> ) in D.W.	μ <sub>eff</sub> . (B.M)	Suggested geometry
L	320 (31250)	(π-π*)	-	-	-
C <sub>1</sub> Mn(II)	ν <sub>3</sub> 705 (14184) ν <sub>2</sub> 1012(9881) ν <sub>1</sub> 1028(9727)	L → M(C.T.) <sup>6</sup> A <sub>1g</sub> → <sup>4</sup> T <sub>1g</sub> <sup>6</sup> S <sup>6</sup> A <sub>1g</sub> → <sup>4</sup> T <sub>2g</sub> ( <sup>4</sup> G)	189.0	6.01	Octahedral
C <sub>2</sub> Zr(IV)	ν <sub>1</sub> 649 (15408)	L → M(C.T.)	30.0	Diamagnetic	Octahedral
C <sub>3</sub> Cd(II)	ν <sub>1</sub> 1012 (9881)	L → M(C.T.)	127.0	Diamagnetic	Octahedral



**Figure 2:** UV-Vis spectra of C<sub>1</sub>

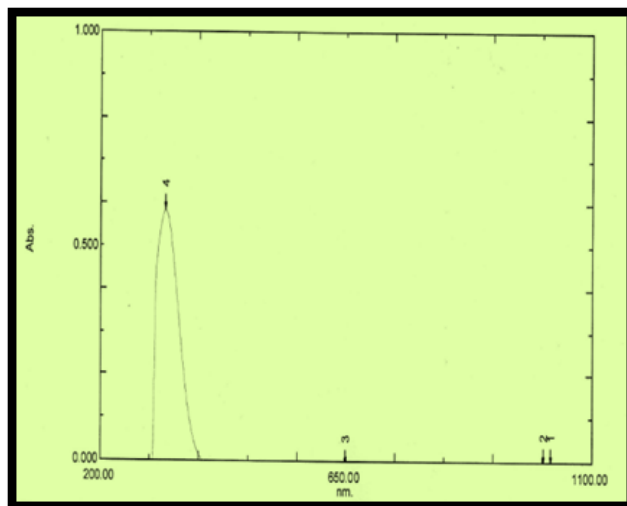


Figure 3: UV-Vis spectra of C<sub>2</sub>

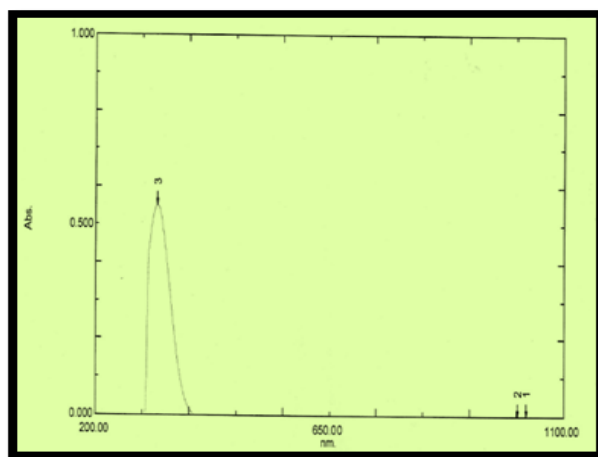
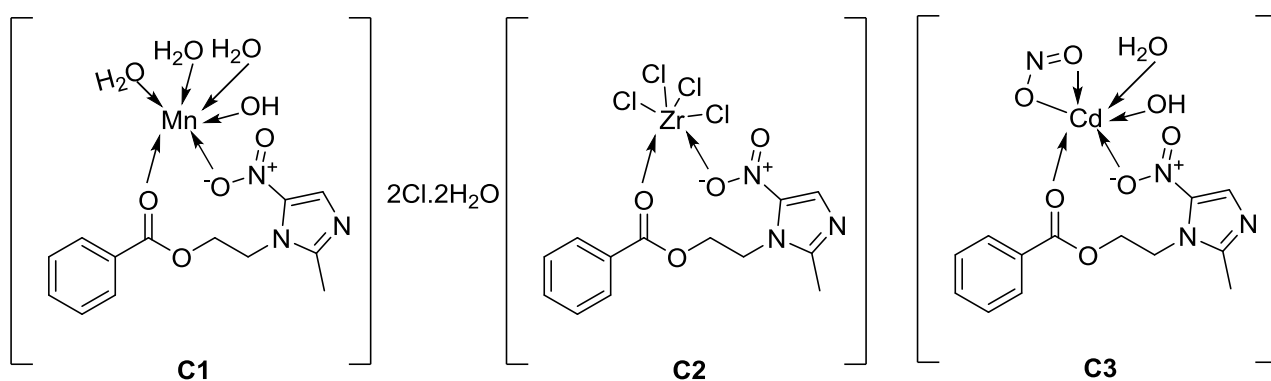


Figure 4: UV-Vis spectra of C<sub>3</sub>



Scheme 2: The complexes of metronidazole benzoate

### Biological activity

The antibacterial activities of ligands and their prepared metal complexes were investigated by using the  $2 \times 10^{-2}$  M dissolution method with

DMSO as a solvent. The antibacterial and antifungal activity of the prepared compounds was tested against (*Candida*, *Pseudomonas auroginosa* (G-), *E. coli* (G-), *Bacillus* (G+), and *Staphylococcus aureus* (G+). The results revealed that ligands and their conjugates had different

effects on the above-mentioned fungi and bacteria. However, cadmium complexes proved more effective than ligands and other complexes. The antibacterial and antifungal data results are listed in Table 4 and the inhibition zones are represented in Figure 5 [27].

**Table 4:** Biological activity of the compound

Sample No.	Compound	<i>Escherichia Coli</i> Inhibition zone diameter (mm)	<i>Pseudomonas auroginosa</i> Inhibition zone diameter(mm)	<i>Staphylococcus aureus</i> Inhibition zone diameter (mm)	<i>Bacillus</i> Inhibition zone diameter (mm)	<i>Candida</i> Inhibition zone diameter (mm)
0	DMSO	-ve	-ve	-ve	-ve	10
12	L	13	14	12	9	20
6	C <sub>1</sub>	10	13	16	12	19
7	C <sub>2</sub>	12	12	12	13	21
8	C <sub>3</sub>	20	20	23	20	21



**Figure 5:** The inhibition zone for ligand and its complexes and DMSO against (*Candida*, *Pseudomonas auroginosa* (G-), *Escherichia Coli* (G-), *Bacillus* (G+), and *Staphylococcus aureus* (G+))

#### Antioxidant activity/DPPH radical scavenging activity

The prepared complexes exhibited the antioxidant activity against DPPH free radicals and the excellent scavenging rates [28]. Therefore, test compounds exhibited the anti-oxidant properties were chosen for encourage testing. Therefore, inhibitory concentration (IC<sub>50</sub>) values

were recorded in Table 5. In this work, we utilized a classification of antioxidant activity dependent on IC<sub>50</sub> range values published by Phongpaichit, as reported in Table 6. It is shown in Figures 6, 7, and 8.

- 1- All selected compounds indicated the strong antioxidant activities, as provided in Table 5.
- 2- a-Compounds (C<sub>1</sub>) and (C<sub>3</sub>) possess a strong anti-oxidant activity.

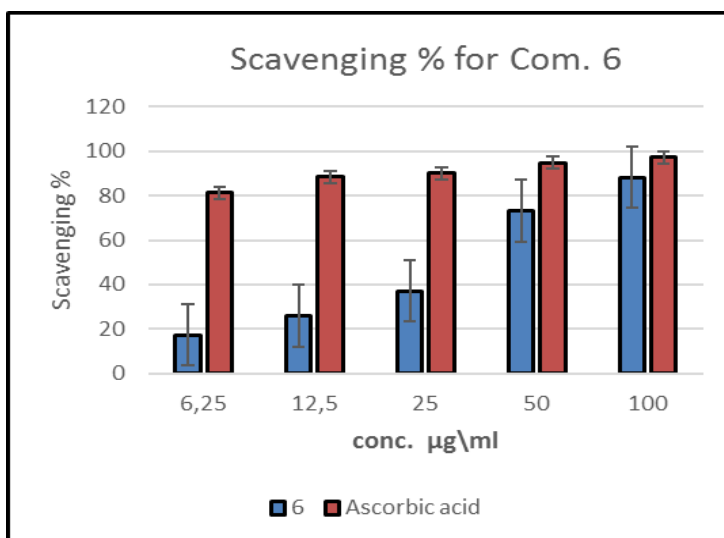
3-β-Compounds (C<sub>2</sub>) possess an intermediate antioxidant activity.

**Table 5:** Antioxidant activities of all compounds

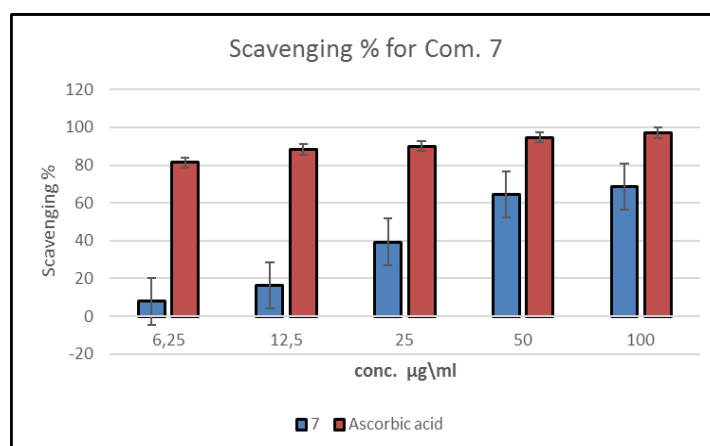
Compound No.	Scavenging %					Linear eq.	R <sup>2</sup>	Ic50
	6.25 (µg/ml)	12.5 (µg/ml)	25 (µg/ml)	50 (µg/ml)	100 (µg/ml)			
C <sub>1</sub>	17.32	25.98	37	73.22	88.18	y = 0.7693x + 18.537	0.9058	40.90
C <sub>2</sub>	7.87	16.53	39.37	64.56	68.5	y = 0.635x + 14.764	0.782	55.49
C <sub>3</sub>	27.11	37.2	50.44	70.95	86.82	y = 0.6133x + 30.739	0.9182	31.41
Ascorbic acid	81.4	88.4	90.1	94.7	97.2	y = 0.14x + 84.933	0.7609	-

**Table 6:** Antioxidant activity by Phongpaichit, 2007

IC50 (µg/ml)	Mark
10-50 (µg/ml)	Strong antioxidant activity
50-100 (µg/ml)	Intermediate antioxidant activity
> 100 (µg/ml)	Weak antioxidant activity

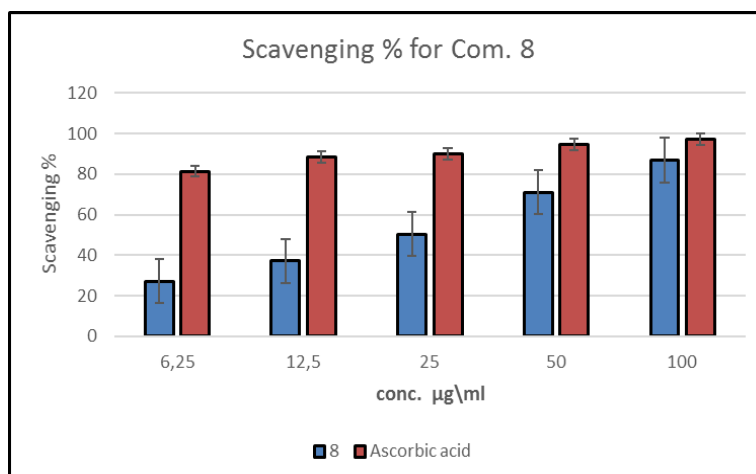


**Figure 6:** The antioxidant activity of C<sub>8</sub> (Mn(II))



**Figure 7:** The antioxidant activity of C<sub>9</sub> (Zr(IV))





**Figure 8:** The antioxidant activity of C<sub>10</sub> (Cd(II))

## Conclusion

Reactions of ligands with metal ions Mn(II), Zr(IV), and Cd(II) were prepared in a L:M (1:1) molar ratio. All synthesized complexes were analyzed. The proposed shapes were verified by using spectral and physicochemical methods. The results showed that all complexes had the octahedral shapes and partially electrolyte features. The biological results show that all synthesized compounds have an excellent antibacterial activity against (*Candida*, *Pseudomonas auroginosa* (G-), *Escherichia coli* (G-), *Bacillus* (G+), and *Staphylococcus aureus* (G+)). All compounds exhibited the potent antioxidant activity. The highest antioxidant activity and the lowest IC<sub>50</sub> values were found for compounds (C1) and (C3), with compound (C2) having a moderate antioxidant activity.

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## Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## Conflict of Interest

We have no conflicts of interest to disclose.

The Supporting Information is available free of charge at

<http://www.chemmethod.com/article/158549.html>

Detailed spectra of synthesized compounds ([PDF](#))

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