

Synthesis, characterization, and Biological Study of some transition Metal Complexes With Guaifenesin

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Abstract

The present work includes the preparation confirmation and bioassay of novel complexes of the ligand [3-(*o*-methoxy phenoxy-1, 2-propanediol)], with metal Cr (III), Co (II), Ni (II) and Cu (II) were also formed and studied. The new complexes were characterized by FT-IR Spectroscopy and UV-Visible spectroscopy.

The metal complexes have been tested in vitro against a number of microorganisms (gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Pseudomonas aeruginosa*)) in order to assess their antimicrobial properties. All our complexes showed considerable activity against all bacteria.

تحضير، تشخيص ودراسة بايولوجية لبعض معقدات العناصر الانتقالية مع الغوايفينيسين

الخلاصة

يتضمن البحث التحضير الكيميائي لبعض معقدات العناصر الانتقالية الجديدة المشتقة من المخلب 3-(اورثو ميثوكسي فينوكسي)-1 و2-بروبان دايلول (الغوايفينيسين) و ذلك لتفاعل هذا المخلب مع املاح العناصر الانتقالية التالية (Cr(III), Co(II), Ni(II) and Cu(II)).

تم تشخيص المخلب و معقداته باستخدام طيف الاشعة فوق البنفسجية والمرئية، طيف الاشعة تحت الحمراء . تم دراسة الفعالية المضادة للجراثيم لكل من المعقدات على نوعين من البكتريا هي (*Staphylococcus aureus*) و (*Pseudomonas aeruginosa*).

INTRODUCTION

Guaifenesin [3-(*o*-methoxyphenoxy)-1,2-propanediol] is used to relieve chest congestion or muscle relaxing action . Guaifenesin may help control symptoms but does not treat the cause of symptoms or speed recovery.

Guaifenesin [3-(*o*-methoxyphenoxy)-1,2-propanediol] has been extensively used as an expectorant and presented in a variety of pharmaceutical formulations^[1]. It helps loosen congestion in your chest and throat, making it easier to cough out through your mouth.

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Guaifenesin is used to reduce chest congestion caused by the common cold, infections, or allergies. Increasing physiological importance of oxygen donor compounds and active role played by certain metal ions coordinated to them have interested many workers in synthesizing and studying structural aspects of metal complexes with some oxygen donor ligands[2-4]. Various derivatives of 1,2-propanediol, 1,2-propanediol, and substituted 1,2-propanediol have shown anti-tubercular[5], bacteriostatic[6], antibacterial[7], antifungal[8], anti-inflammatory[9] activities.

The wide range of ligand application and its metal complexes aroused our interest to prepare a new series of some metal complexes.

Experimental

All chemicals used were of reagent grade supplied by either Merck or Fluka. The Fourier transform infrared spectroscopy (FTIR) spectra in the range (4000–200) cm^{-1} were recorded as cesium iodide disc on FTIR 8300 Shimadzu Spectrophotometer. The UV-Visible spectra were measured in ethanol using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200–1000) nm. Gallen Kamp M.F.B.600.010 F melting point apparatus were used to measure the melting point of all the prepared compounds [10].

Synthesis of ligand

Synthesis of ligand Guaiacol (2-methoxyphenol, (1.1 mL, 0.01 mole) is dissolved in 6 mL %95 ethanol in a fume hood, which is mixed with a solution prepared from (0.5 g., 0.01 mole) of crushed NaOH pellets in 2 mL water. The mixture is heated under reflux for 10 min.

Then, a mixture of 1.0 mL of 3-bromo-1,2-propanediol in 1.0 mL 95% ethanol is added drop wise to the phenoxide anion and the reflux is continued for 1 h. The ethanol is removed by evaporation on a sand bath, and 6 mL water is added to dissolve precipitated NaCl. The aqueous solution is extracted twice with 10 mL ethyl acetate, and the organic layer is dried using MgSO_4 . Removal of the drying agent and evaporation of the solvent affords pale yellow oil which is solidified by the addition of (10–20) mL hexane with cooling and stirring in an ice-bath. This crude solid is collected by vacuum filtration and is recrystallized from ethyl acetate-hexanes [11].

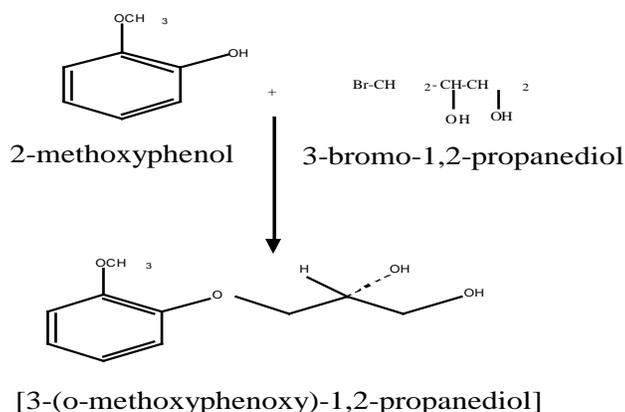


Figure (1): The reaction of the formation metal

Synthesis of metal complexes

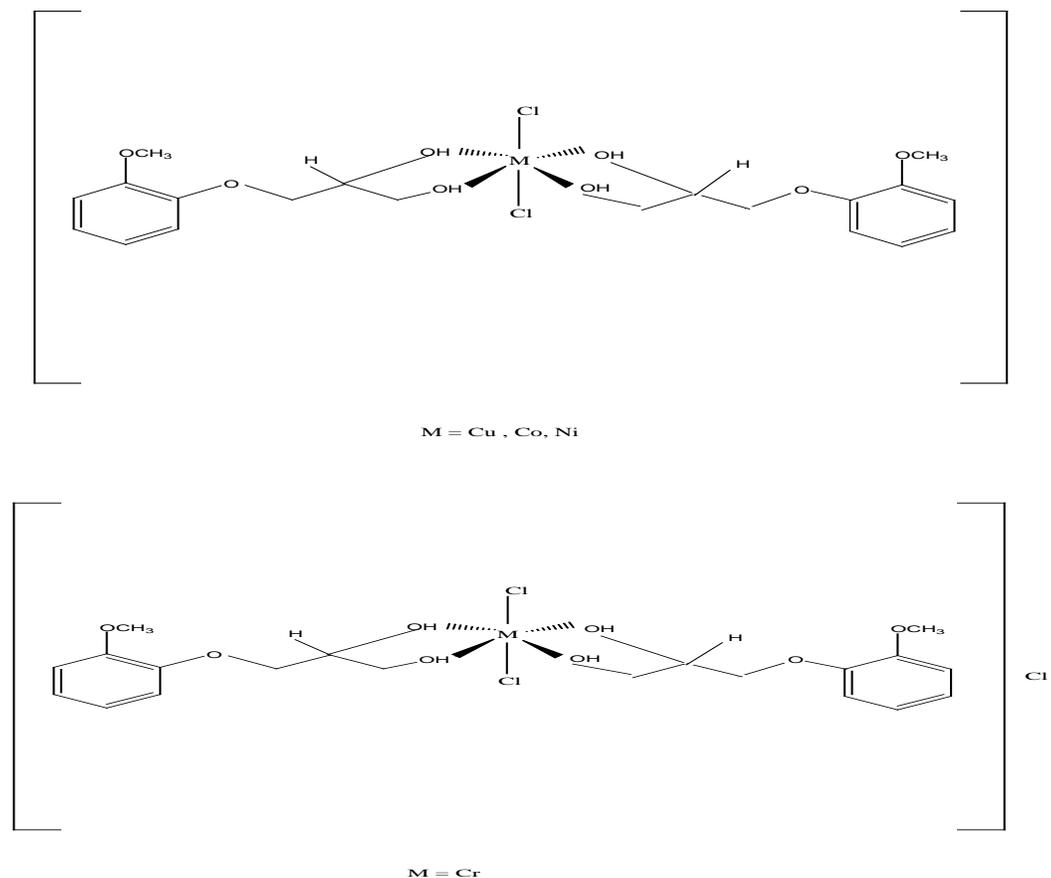
Bis ([3-(*o*-methoxyphenoxy)-1,2-propanediol]) metal complexes obtained by refluxing the mixture of (1 mmole) hydrated metal chlorides of Cr(II), Co(II), Ni(II) and Cu(II) (1 mmol.) and (2 mmol.) of the ligand in 50 ml. ethanol at pH (8-9), till the complexes precipitated out. The closed complexes were filtered with water, ethanol and dried under vacuum [12].

Study of complexes formation in solution

Complexes of ligands with metal ions were studied in solution using ethanol or Dimethylformamide (DMF) as solvents, in order to determine (M: L) ratio in the complex following molar ratio method [13]. A series of solution were prepared having a constant concentration 10^{-3} M of metal ion and ligands. The [M/L] ratio was determined from relationship between absorption of the absorbed light and mole ratio of [M/L]. The results of complexes formation in ethanol were listed in table (1).

Table (1): Physical analytical data for the ligands and metal complexes.

No.	Compound	Mole Ratio	Color	M.P.
[1]L	[3-(<i>o</i> -methoxyphenoxy)-1,2-propanediol]	-	white	79-81.
[2][Co (L) ₂ Cl ₂]	Bis([3-(<i>o</i> -methoxyphenoxy)-1,2-propanediol])Cobalt(II) chloride	1:2	blue	121-123
[3] [Ni(L) ₂ Cl ₂]	Bis([3-(<i>o</i> -methoxyphenoxy)-1,2-propanediol])Nickel(II) chloride	1:2	light-Yellow	95-97
[4] [Cu(L) ₂ Cl ₂]	Bis([3-(<i>o</i> -methoxyphenoxy)-1,2-propanediol])Copper(II) chloride	1:2	Dark-green	Oily
[5] [Cr(L) ₂ Cl ₂]Cl	Bis([3-(<i>o</i> -methoxyphenoxy)-1,2-propanediol])Chromium(III) chloride	1:2	green	Oily



**Figure (2): The proposed structure for the complexes where M = Co, Ni, Cr, Cu.
L₁ & L₂: [3-(o-methoxy phenoxy-1, 2-propanediol]**

Biological activity (Antibacterial activity)

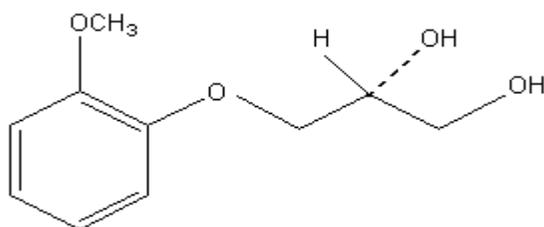
Biological activity is any activity of a substance that is demonstrable in living organisms. Biologically active substances are often of biological origin themselves.

The antibacterial activity of the prepared new ligand and its metal complexes were studied against selected types of bacteria which include *Staphylococcus aureus*, as gram positive and *Pseudomonas aeruginosa* as gram negative, cultivated in brain heart broth agar media, which is used DMF (dimethylformamide) as a solvent and as a control for the disc sensitivity test^[14-16]. This method involves the exposure of the zone of inhibition toward the diffusion of micro-organism on agar plate. The plates were incubated for 24 hours at 37 °C. The antibacterial activity was recorded as any area of bacterial growth inhibition that occurred in the diffusion area^[17]. The quantitative antibacterial activity

assay was performed by the nutrient broth for bacterial (Before turbidimetric measurements can be made, the spectrophotometer must be adjusted to 100% transmittance (0% absorbance). This is done using a sample of uninoculated medium. Percent transmittance of various dilutions of the bacterial culture is then measured and the values converted to optical density, based on the formula: Absorbance (O.D.) = $2 - \log \% \text{ Transmittance}$. A wavelength of 420 nm is used when the solution is clear, 540 nm when the solution is light yellow, and 600-625 nm is used for yellow to brown solutions).

Results & Discussion

The complexes were synthesized by reacting ligand with the metal ion in 1:2 molar ratio in ethanoic medium. The ligand behaves as bidentate coordinate through oxygen and oxygen donor atoms (Figure 3).



[3-(o-methoxyphenoxy)-1,2-propanediol]

Figure (3): The structure of the metal

Infrared Spectroscopy

OH stretching vibration:

The band at (3325 cm^{-1}) of the ligand due to asymmetrical OH stretching decreased to $\approx (3244 \text{ cm}^{-1})$ on complexation.

2. C-H (alph.) stretching vibration:

The band at (2943 cm^{-1}) in the spectrum of the ligand due to symmetrical $\nu(\text{C-H})$ stretching decreased to $\approx (2935.5 \text{ cm}^{-1})$ in the complex.

The low frequency bands of complexes:

New bands which appeared at low frequencies in the spectra of the synthesized complexes were probably due to (M-O) and (M-Cl) bond vibration frequencies. The facts are further supported by newly formed low frequency bands:

1: The band at ($432-530 \text{ cm}^{-1}$) have been assigned to $\nu(\text{M-O})$ [18,19].

2: The bands at ($311-364 \text{ cm}^{-1}$) have been assigned to $\nu(\text{M-Cl})$ [20-22]. On the basis of the above evidence is an indication of complex formation.

Table(2) Selected IR bands in cm^{-1} for the ligand and its complexes

Compound	$\nu(\text{-OH})$	$\nu(\text{C-H})_{\text{alph.}}$	$\nu(\text{M-OC1})$	$\nu(\text{M-OC2})$	$\nu(\text{M-Cl})$
[1] L	3325	2943	-	-	-
[2] $[\text{Co}(\text{L})_2\text{Cl}_2]$	3318	2939.3	454	442	325
[3] $[\text{Ni}(\text{L})_2\text{Cl}_2]$	3320	2931	459	434	311
[4] $[\text{Cu}(\text{L})_2\text{Cl}_2]$	3244	2935.5	472	432	346
[5] $[\text{Cr}(\text{L})_2\text{Cl}_2]\text{Cl}$	3315	3338	530	523	364

Electronic absorption spectrum:

The Uv-visible spectrum of ligands solution in absolute ethanol shows three distinct peak at 340nm ($\epsilon_{\text{max}} \times 10^6 = 0.98$), 262nm ($\epsilon_{\text{max}} \times 10^6 = 0.308$), 222nm ($\epsilon_{\text{max}} \times 10^6 = 1.1$) for L which were assignable to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions respectively [16-18].

1. The electronic spectra of blue Cobalt (II) complex (L) showed two spin allowed transitions at 17950, and 21610cm^{-1} assignable to $T_{1g}(\text{F}) \rightarrow A_{2g}(\text{F})$ and ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{2g}(\text{P})$ transitions respectively, are in agreement with octahedral arrangements for Co(II) ion.

2. The electronic spectra of light yellow Ni (II) complex (L) showed spectral band at 400 nm assignable to ${}^3T_{1g}(\text{F}) \rightarrow {}^3T_{2g}(\text{F})$ transition was in agreement with octahedral arrangements for Ni(II) ion.

3. The electronic spectra of green copper (II) complex (L) shows strong band at 288 nm which belongs to the charge transfer. The second band found in the visible region at 440 nm was attributed to the electronic transition $E_{2g} \rightarrow {}^2T_{2g}$.

4. The electronic spectra of dark green chromium (III) complex (L) The Uv-visible spectrum of the dark green solution of chromium showed three bands with the absorbance maxima at 16266cm^{-1} , 20302cm^{-1} and 31830cm^{-1} which were considered as ν_1 and ν_2 absorption bands respectively. The third band of the octahedral coordination ν_3 which normally occurred at high energy was deduced by using Lever for d3 electronic configuration and it is found to be 320nm (31830cm^{-1}) and the bands may be assigned as

$$\nu_1 = {}^4A_{2g}(\text{F}) \rightarrow {}^4T_{2g}(\text{F})$$

$$\nu_2 = {}^4A_{2g}(\text{F}) \rightarrow {}^4T_{1g}(\text{F})$$

$$\nu_3 = {}^4A_{2g}(\text{F}) \rightarrow {}^4T_{1g}(\text{P})$$

Antibacterial Studies:

The antibacterial screening data show that the compounds exhibit antibacterial properties, and it is important to know that the metal chelates exhibit more inhibitory effects than the parent ligands. The increased activity of the metal chelates can be explained on the basis of chelation theory [23]. It is known that chelation tends to make the ligand act as more powerful and potent bactericidal agents, thus killing more of the bacteria than the ligand. It is observed that, in a complex, the positive charge of the metal

is partially shared with the donor atoms present in the ligands, and there may be π -electron delocalization over the whole chelating [24]. This increases the lipophilic character of the metal chelate and favors its permeation through the lipid layer of the bacterial membranes. The increased lipophilic character of these complexes seems to be responsible for their enhanced potent antibacterial activity. It may be suggested that these complexes deactivate various cellular enzymes, which play a vital role in various metabolic pathways of these microorganisms. It has also been proposed that the ultimate action of the toxicant is the denaturation of one or more proteins of the cell, which as a result, impairs normal cellular processes. There are other factors which also increase the activity, which are solubility, conductivity, and bond length between the metal and the ligand [25].

In conclusion, we can see that $[\text{Co}(\text{L})_2\text{Cl}_2]$ have high antibacterial activity among all the prepared complexes and also it has bacterial activity against *Staphylococcus aureus* bacteria more than that on *Pseudomonas aeruginosa* bacteria (table 4).

Table (4): Antibacterial screening data for the ligands and their complexes

Diameter of inhibition zone (6mm), (conc. 250 ppm)

Compound	<i>Pseudomonas</i> (dilute)	<i>Pseudomonas</i>	<i>Staphylococcus aureus</i> (dilute)	<i>Staphylococcus aureus</i>
L	12	13	20	25
$[\text{Co}(\text{L})_2\text{Cl}_2]$	9	11	10	21
$[\text{Ni}(\text{L})_2\text{Cl}_2]$	10	9	16	17
$[\text{Cu}(\text{L})_2\text{Cl}_2]$	8	8	12	13
$[\text{Cr}(\text{L})_2\text{Cl}_2] \text{Cl}$	11	11	10	19

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