

Full Length Research Paper

Design, synthesis and bioassay of novel metal complexes of 3-amino-2-methylquinazolin-4(3H)-one

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New ligand 3-amino-2-methylquinazolin-4(3H)-one (L) has been synthesized in good yield by the reaction of anthranilic acid with acetic anhydride then replaced the oxygen with nitrogen of hydrazine. When the ligand react with Co(II), Ni(II) and Cu(II) new complexes are formed. The chemical structure of all prepared compounds were characterized by FT-IR, elemental analysis, ¹H-NMR and UV/visible spectra, moreover determination of molar ratio M:L, molar conductance in D.M.F solution, magnetic moments (μ_{eff}) and determination of metal content M% by flame atomic absorption spectroscopy. The free ligand and their metal complexes have been tested *in vitro* against a number of microorganisms (gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and gram negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus vulgaris*)) in order to assess their antimicrobial properties. All our complexes showed considerable activity against all bacteria.

Keywords: Metal complexes, methylquinazolin, anthranilic acid, *Bacillus cereus*.

INTRODUCTION

Interest in coordination chemistry is increasing continuously with the preparation of organic ligands containing a variety of donor groups (Hancock and Martell, 1989; Bhyrappa et al., 1996; Castillo-Blum and Barba-Behrens, 2000) and it is multiplied many fold when the ligands have biological importance (Mohan and Rajesh, 1992; Kong et al., 2003). Quinazoline compounds are widely used in agrochemicals as plant virucides (Hung et al., 1996), antifungal agents (Dandia et al., 2004) and herbicides (Khan et al., 2003). According to recent data, quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity and many substituted quinazoline derivatives have recently earned great interest in chemotherapy as antitumor drugs (Jin et al., 2005; Wissner et al., 2000). Compounds containing the 4(3H)-quinazolinone ring have been reported to possess different biological activities such as antibacterial (Nesrin et al., 2009), antifungal (Bartoli et al., 1998; Aysel et al., 2005), anti-tubercular (Kumar et al., 1983), antiviral (Corbett et al.,

2000), anticancer (Hour et al., 2000; Hamel et al., 1996) and anticonvulsant (Usifoh and Scriba, 2000) activity depending on the substituents in the ring system. In addition, literature surveys show that quinazolinone hydrazones exhibit antimicrobial (Radhakrishnan et al., 1984; Karalı et al., 1998) and anticonvulsant (Aysel et al., 2005; Abdel-Hamide et al., 1997) activity. Furthermore and taking into consideration the use of metal complexes in the treatment of some diseases, mentioned above, we have tested the antimicrobial activity of the prepared ligand and complexes using strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereu* and *Proteus vulgaris*, from different pathological products from patients. In view of the above considerations we planned the present study to further investigate this ring system.

EXPERIMENTALS

All chemical used were of reagent grade (supplied by Either Merck or Fluka) and used as supplied. The FTIR spectra in the range (4000–200) cm^{-1} were recorded as cesium iodide disc on FTIR 8300 Shimadzu Spectrophotometer. Proton NMR spectra were recorded on Bruker -DPX 300 MHz spectrometer with TMS as

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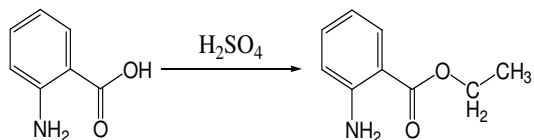
Table 1. Physical data of complexes.

No.	Complexes	Color	M.P. °C	Yield (%)	M:L
C ₁	CoL ₂ Cl ₂	Green	115	83	1:2
C ₂	NiL ₂ Cl ₂	Light green	55	80	1:2
C ₃	CuL ₂ Cl ₂	Brown	360	75	1:2

internal standard in Jordan University. The UV-Visible spectra were measured in DMF using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200 - 1000) nm. Magnetic susceptibility measurements for complexes were obtained at room temperature using (Magnetic susceptibility Balance Model MSB-MKI). Elemental microanalysis was carried out using CHNOS elemental analyzer model 5500 Carlo-Erba instruments (Italy made). Gallen Kamp M.F.B.600.010 F melting point apparatus were used to measure the melting point of all the prepared compounds.

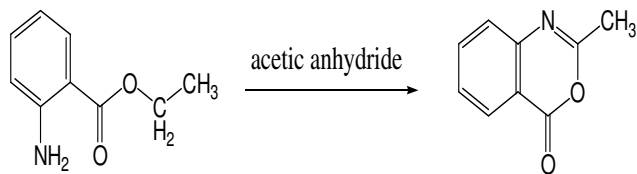
Synthesis of ethyl anthranilate

The mixture of anthranilic acid (0.246 mole) with 50 ml absolute ethanol and 2.5 ml. Concentrated sulfuric acid was refluxed for 4 h, yield 60% of ethyl anthranilate according to the following reaction:



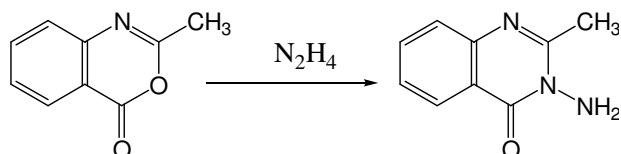
Synthesis of 2-methyl-4H-benzo[d][1,3]oxazin-4-one

The mixture of ethyl anthranilate (0.01 mole) with 100 ml absolute ethanol and acetic anhydride (0.01 mole) was refluxed for 48 h.



Synthesis of 3-amino-2-methylquinazolin-4(3H)-one(L)

The 3-amino-2-methylquinazolin-4(3H)-one(L) was prepared by stirring equimolar quantities of 2-methyl-4H-benzo[d][1,3]oxazin-4-one and hydrazine in benzene for 12 h, then refluxed for 24 h, cooled then washed with cold water and air dried to yield oily product. Proton NMR (S. 1.2(3H) for CH₃, 6.3(1H) for NH₂, m. 7.3 for H aromatic, m. 8.2 for H aromatic).



Synthesis of complexes

A hot ethanolic solution (20 ml) of corresponding metal salt (0.005 mole) was mixed with hot ethanolic solution of the ligand (0.01 mole). The mixture was refluxed for 5 h on a water bath. On cooling the contents, the colored complex separated out in each case. The same was filtered, washed with 50% ethanol and dried in vacuum over P₄O₁₀. Purity of the complexes was checked by TLC.

Study of complexes formation in solution

Complexes of ligand with metal ions were studied in solution using DMF as solvent in order to determine (M:L) ratio in the complex following the molar ratio method (Nada et al. 2001). A series of solutions were prepared having a constant concentration (10⁻³ M) of metal ion and ligand (L). The [M/L] ratio was determined from the relationship between the absorbance and the mole ratio of [M/L]. The results of complexes formation in DMF were listed in Table 1.

Antimicrobial activity assessment

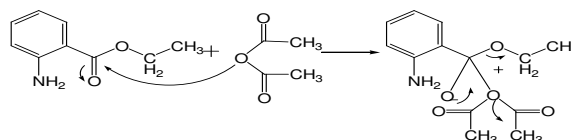
E. coli, *K. pneumoniae*, *P. vulgaris*, *P. aeruginosa*, *S. aureus* and *B. cereus* freshly isolated from different clinical sources from patients and purified, identified by conventional methods were cultivated on solid media and incubated at 37°C for 24 h prior to testing. The filter paper disk method was used to measure the inhibitory activity as indicated by the diameter of the inhibition zone. Filter paper (Whatman No. 4) discs (6 mm diameter) were saturated with different concentrations (1.0, 0.75, 0.50, 0.25, 0.125 mg/mL) of the ligand and metal complexes to be tested. They were dried in an oven at 60°C for 12 h. The dried disks were placed on already cultured nutrient agar plates concomitantly with the pathogens. The diameter of the clear zone around the disks was measured after 48 h of incubation at 37°C (Banty, 1979). The absence of a clear zone around the disks indicated inactivity. DMF was used as a solvent to prepare the solutions of the ligand and metal complexes. The results are shown in Figures 1, 2, 3 and 4.

RESULTS AND DISCUSSION

Synthesis of the ligand

The esterification of anthranilic acid than the reaction of the ester with acetic anhydride yield the cyclic compound 2-methyl-4H-benzo[d][1,3]oxazin-4-one as shown in the mechanism:

Suggested mechanism:



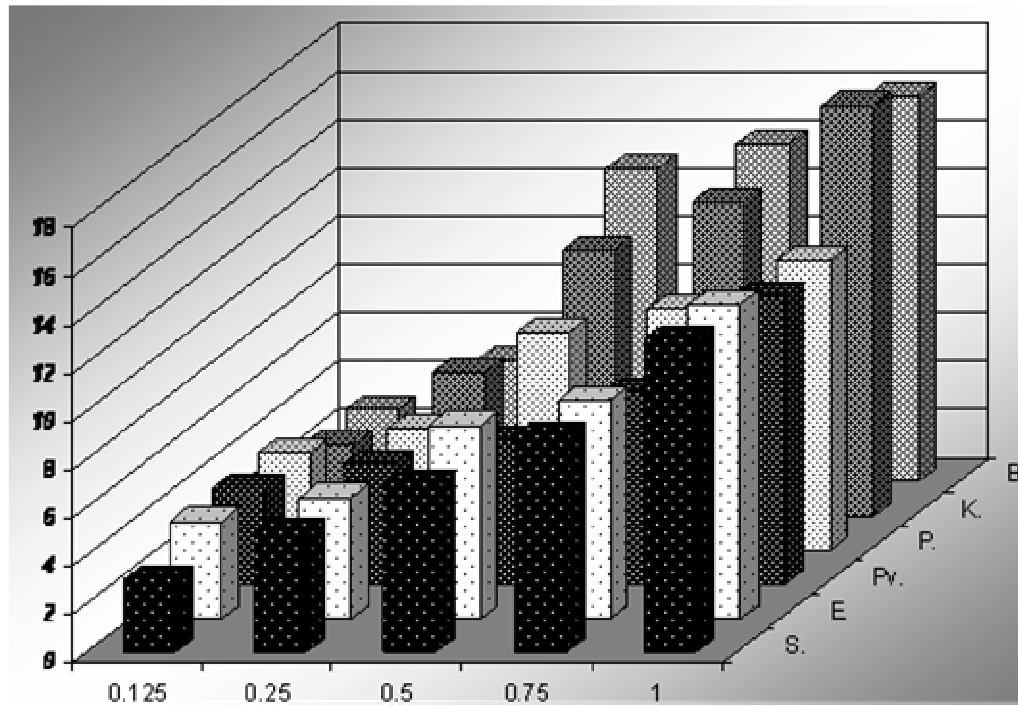


Figure 1. The effect the ligand toward studied bacteria. S = *S. aureus*, E = *E. coli*, Pv = *P. vulgaris*, P = *Pseudomonas*, K = *Klebsiella*, B = *B. cereus*.

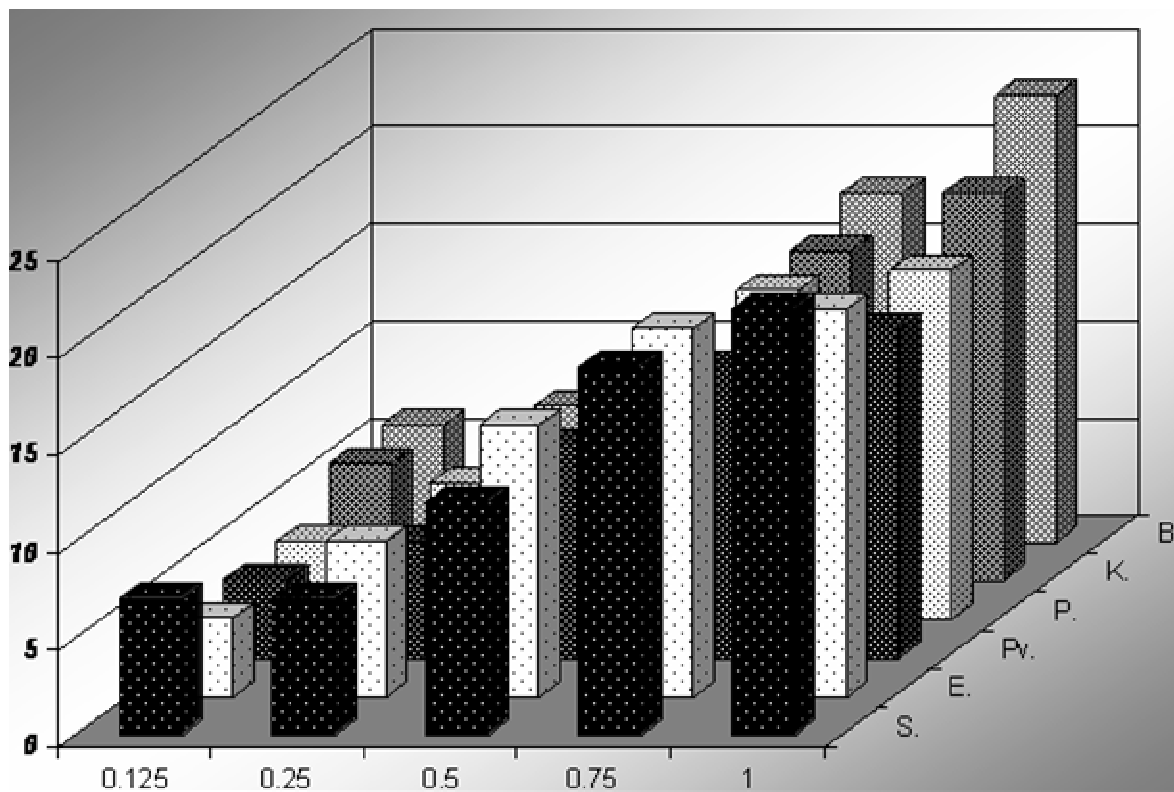


Figure 2. The effect the complex (C_1) toward studied bacteria. S = *S. aureus*, E = *E. coli*, Pv = *P. vulgaris*, P = *Pseudomonas*, K = *Klebsiella*, B = *B. cereus*.

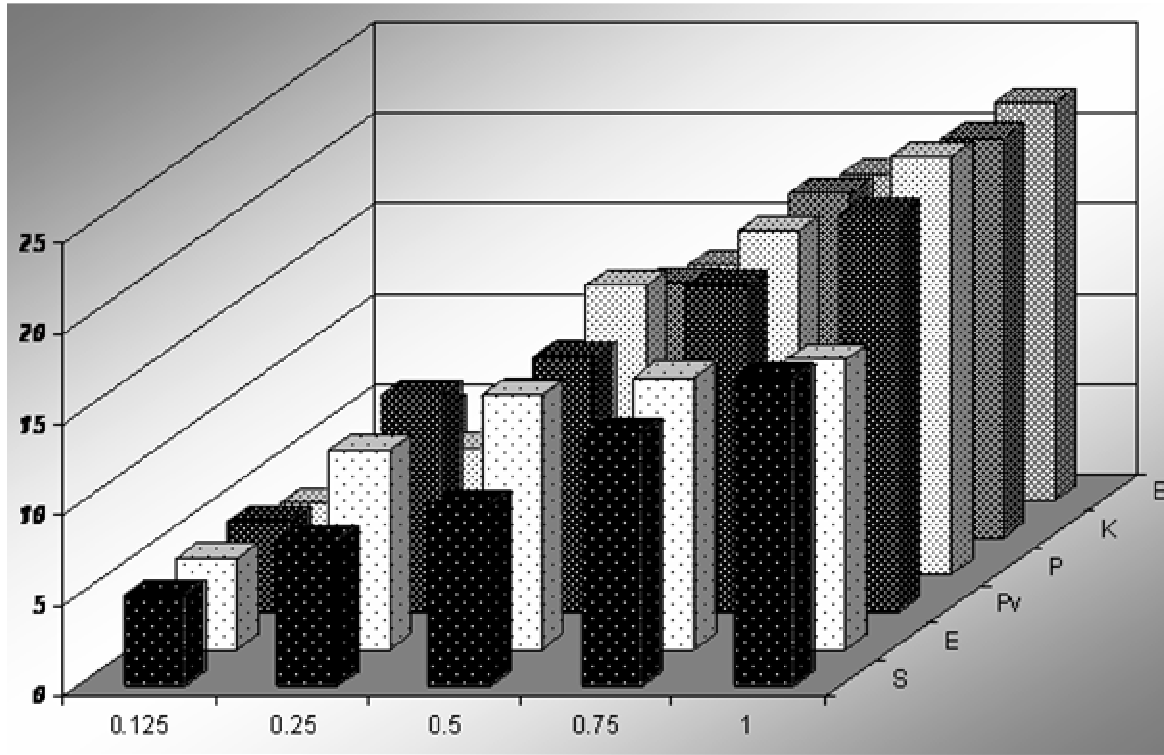


Figure 3. The effect the complex (C₂) toward studied bacteria. S = *S. aureus*, E = *E. coli*, Pv = *P. vulgaris*, P = *Pseudomonas*, K = *Klebsiella*, B = *B. cereus*.

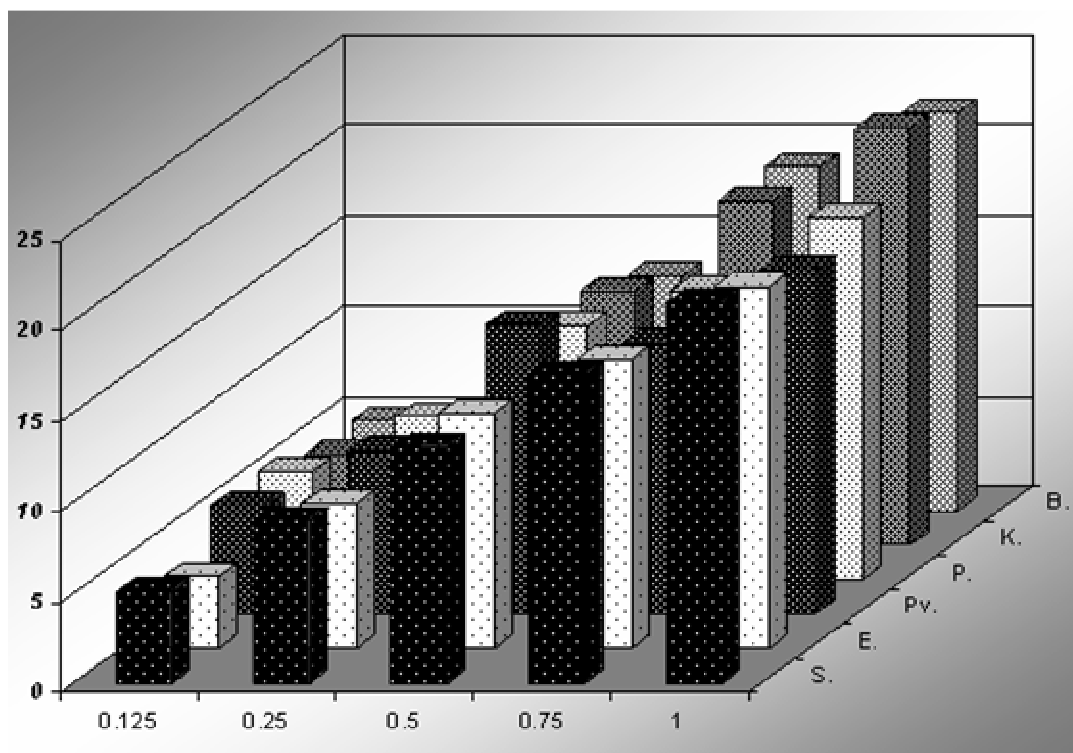
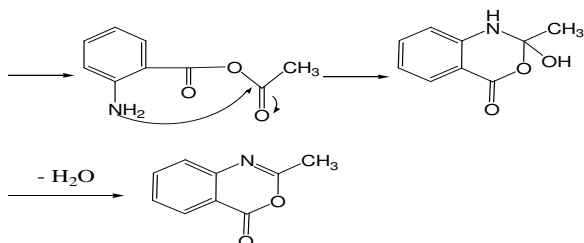


Figure 4. The effect the complex (C₃) toward studied bacteria. S = *S. aureus*, E = *E. coli*, Pv = *P. vulgaris*, P = *Pseudomonas*, K = *Klebsiella*, B = *B. cereus*.

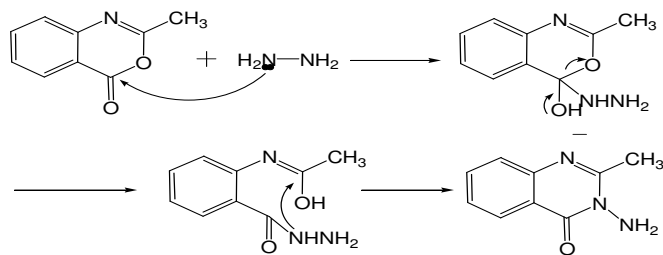
Table 2. Molar conductance values and element chemical analysis data of the complexes.

No.	Complexes	$\Omega\text{M (Ohm cm}^2\text{ mol}^{-1}\text{)}$	Elemental analysis							
			Theoretically calculated values				Actual calculated values			
			C%	H%	N%	M%	C%	H%	N%	M%
C_1	CoL_2Cl_2	18	45.02	3.78	17.50	12.27	44.02	3.21	16.72	11.89
C_2	NiL_2Cl_2	19	45.04	3.78	17.51	12.23	43.93	2.96	16.65	11.93
C_3	CuL_2Cl_2	16	44.59	3.74	17.33	13.11	44.11	2.96	16.23	12.45



The reaction of this compound with hydrazine yield the novel ligand 3-amino-2-methylquinazolin-4(3H)-one as shown in the mechanism:

Suggested mechanism:



Synthesis of complexes

The complexes were synthesized by the reaction of the ligand with the metal ions in 1:2 molar ratios in ethanolic medium. The ligand behaves as bidentate coordinate through oxygen and nitrogen donor atoms.

The analytical data of these complexes are presented in Table 1. All the complexes are fairly stable and can be stored for long periods at room temperature.

Elemental analysis, molar conductance

The compositions of the complexes are summarized in Table 2. The C, H, N and M contents (both theoretically calculated values and actual values) are in accordance with the formula ML_2Cl_2 indicating that the ligand is neutral. This can be explained by the absence of any deprotonating agent during the synthesis. The complexes are generally soluble in common organic solvents. The molar conductance values of all the complexes

determined in nitrobenzene at room temperature are given in Table 2.

Infrared spectra

A study and comparison of the infrared spectra of the ligand and its complexes imply that the ligand is bidentate, with the carbonyl-oxygen and nitrogen as the 2 coordination sites. The presence of ring vibrations and C-H absorption makes the spectra fairly complicated for complete assignments of individual bands. The partial infrared data are presented in Table 3. In the infrared spectra of the complexes a considerable negative shift in $\nu(\text{C}=\text{O})$ is observed, indicating a decrease in the stretching force-constant of the $\text{C}=\text{O}$ bond as a consequence of coordination through the carbonyl-oxygen atom of the free base. Another important band, which occurs at 1525 cm^{-1} , is attributed to $\nu(\text{C}=\text{N})$ (azomethine) mode (Radhakrishnan et al., 1984; Agarwal and Prakash, 1991) and remains unaffected after complexation. The band due to NH-stretching in free ligand occurs in the 3325 cm^{-1} region, in the spectra of all the complexes, this band is shifted to lower frequency and appears in the $3283 - 3260\text{ cm}^{-1}$ region, indicating the involvement of the N-atom of the ligand in coordination.

Magnetic moment and UV-Vis spectra

The ultraviolet spectrum of the synthesized ligand in DMF showed two absorption bands, the position of the first band at 235 nm which represents the $(\pi \rightarrow \pi^*)$ transition while the position of the second band (which has higher intensity than the first band due to conjugated system) appeared at 300 nm which represents the $(n \rightarrow \pi^*)$ transition. Generally, the bands of the newly synthesized complexes are either shifted to shorter or longer wavelengths than that of ligands, but the high intensity of the bands is an indication for complex formation. The origin of the band observed at about 700 nm in the electronic spectra of complexes has been identified as d-d transition. In these complexes the bands observed at $300 - 400\text{ nm}$ could be assigned to nitrogen-metal charge transfer absorption. The electronic absorption bands for the ligand and com-

Table 3. Infrared absorption frequencies (cm^{-1}) of ligand and its complexes.

No.	Compounds	ν (NH)	ν (C=N)	ν (C=O)	M-O	M-N
L	$\text{C}_9\text{H}_9\text{N}_3\text{O}$	3325	1525	1650	-	-
C_1	CoL_2Cl_2	3273	1490	1650	484	426
C_2	NiL_2Cl_2	3260	1541	1616	493	430
C_3	CuL_2Cl_2	3280	1558	1670	500	425

plexes are classified into two distinct groups: those that belong to ligand transitions appeared in the UV region while d-d transitions appeared in the visible region. These transitions are assigned in relevance to the structures of complexes. The high spin octahedral Co(II) and Ni(II) complexes exhibit magnetic moment values around 4.85 and 2.79 B. M. respectively and three transitions each in the electronic spectra. The Co(II) complex exhibits three electronic transitions (16286.644, 32573.289, 37453.183) from ground state ${}^4\text{T}_{1g(\text{F})}$ to the excited states ${}^4\text{T}_{2g(\text{F})}$, ${}^4\text{A}_{2g(\text{F})}$ and ${}^4\text{T}_{2g(\text{P})}$ respectively. In the case of Ni(II) complex, the three observed absorptions (23809.5, 29673.5, 42016.8) can be attributed to the transitions, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(\text{F})}$ and ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(\text{P})}$. The parameters like β , B and Dq have been evaluated from the electronic spectral absorptions of Co(II) and Ni(II) complexes. The β values are found to be less than 1.0, indicating that the M-L bond is covalent. The magnetic moment values evaluated from the spectra are in good agreement with the experimentally determined values (Table 1). The Cu(II) complexes of the ligand with $\mu_{\text{eff}} = 1.93$, exhibit a broad absorption centered at 39525.69 cm^{-1} , 33783.78 cm^{-1} and 25252.52 cm^{-1} (could be assigned to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition) respectively suggesting a distorted octahedral geometry (Rajib et al., 2002; Bernhardt and Lawrence, 1989; Masoud et al., 2005; Kamal et al., 2004).

Bactericidal screening

The antimicrobial screening data show that the compounds exhibit antimicrobial properties and it is important to note 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. 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 (Om Prakash et al.2005). This increases the lipophilic character of the metal chelate and favours 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.

The activity of the ligand and metal complexes was tested against some human pathogenic microbes including Gram-positive (*S. aureus* and *B. cereus*) Gram negative (*E. coli*, *P. aeruginosa*, *K. pneumoniae* and *P. vulgaris*) by the paper disk method (see Figures1, 2, 3 and 4). From the results obtained from the method (Figures 2, 3 and 4), it was found that some of the tested complexes were highly active even at low concentrations. The ligand and its complexes in dimethylformamide (DMF) are active against all the tested pathogens, with a (7-23 mm) inhibition zone diameter.

Results of antibacterial screening, indicate that the complexes, inhibit the growth of *B. cereus*, *S. aureus* and *E. coli* whereas, the ligand have no activity and other complexes are have less activity against other tested bacteria.

Stability study

These data show that the atomic charge have been affected by the presence of substituent of rings as shown in data (Appendix)). As a reference compound the unsubstituted ligand (Figure 5) the data for minimized geometry data (Appendix) and the 3d-geometrical structure (Figure 5) is shown in. The data obtained show that the heat of formation is about 47.05345 kcal/mole) and the highest atomic charge in ligand molecule is at [$\text{O}_{(11)}$ -0.954] the next charge value is at [$\text{N}_{(1)}$ -0.367] and [$\text{N}_{(13)}$ (-0.132)]. These data show clearly that these three atoms are the most reactive toward the bonding with the metal.

The determined bond angle and twist angle and 3D-geometrical structure, indicate that this molecule is planar (ChemOffice 2005).

The stability for the prepared complexes was studied theoretically by the Density Function Theory (DFT). The

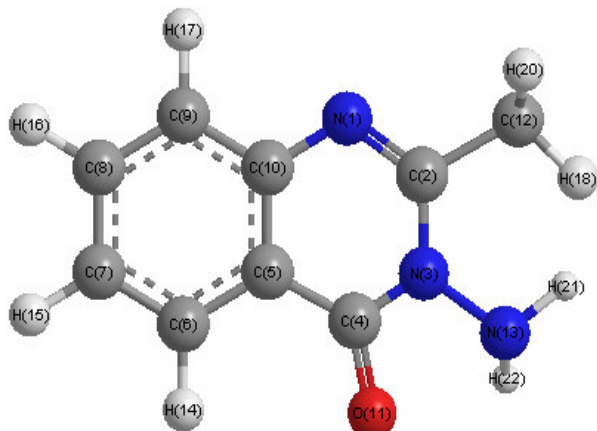


Figure 5. 3D-geometrical structure for the ligand.

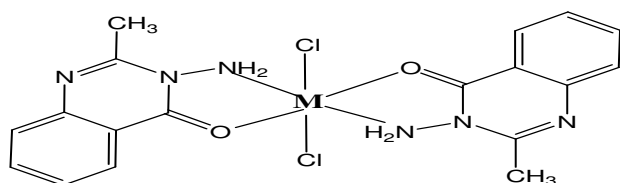


Figure 6. Proposed structure for the complexes.

total energy for the complexes was calculated and it was shown that the copper complex is the most stable and the cobalt complex is the least stable as follows: Cu-complex > Ni-complex > Co-complex.

Conclusions

Based on the reported results, it may be concluded that ligand act as bidentate uni-negative ligand, coordinating through one of the nitrogen atom and the oxygen. In the present work, which facilitates formation of five member rings, shifts the nitrogen atom of the other ring away from the coordination site. In the present investigations, all the complexes are found to be mononuclear, based on the FT-IR spectral data. The coordination number five is attained by coordination with the two bidentate ligand molecules and to two chloride atoms. Based on the physicochemical and the spectral studies the tentative structures proposed for the complexes are shown in Figure 6.

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APPENDIX

Bond lengths

Bond	Actual	Optimal	Bond	Actual	Optimal	Bond	Actual	Optimal
N(13)-H(22)	1.0200		H(17)-C(9)	1.1000	1.1000	N(13)-H(21)	1.0200	1.0200
C(12)-H(20)	1.1130	1.1130	C(8)-H(16)	1.1000	1.1000	C(10)-C(9)	1.3370	1.4200
C(12)-H(19)	1.1130	1.1130	C(7)-H(15)	1.1000	1.1000	C(8)-C(9)	1.3370	1.4200
C(12)-H(18)	1.1130	1.1130	H(14)-C(6)	1.1000	1.1000	C(8)-C(7)	1.3372	1.4200
C(7)-C(6)	1.3370	1.4200	O(11)-C(4)	1.2080	1.2080	N(3)-C(2)	1.2660	1.4620
C(5)-C(10)	1.3370	1.4200	N(3)-C(4)	1.1244	1.4620	C(2)-N(1)	1.2600	1.2600
C(5)-C(6)	1.3370	1.4200	N(13)-N(3)	1.3520	-	N(1)-C(10)	1.2600	1.4560
C(5)-C(4)	1.3510	1.5170	C(12)-C(2)	1.4970	1.4970			

Bond angles

Angle	Actual	Optimal	Angle	Actual	Optimal
H(21)-N(13)-H(22)	109.4418	104.5000	H(18)-C(12)-H(20)	109.4618	109.0000
N(3)-N(13)-H(22)	109.4418	-	H(20)-C(12)-C(2)	109.4618	110.0000
N(3)-N(13)-H(21)	109.5000	-	H(18)-C(12)-H(19)	109.4418	109.0000
C(5)-C(10)-C(9)	119.9988	120.0000	H(19)-C(12)-C(2)	109.4418	110.0000
N(1)-C(10)-C(9)	119.9988	120.0000	H(18)-C(12)-C(2)	109.5000	110.0000
C(5)-C(10)-N(1)	120.0000	120.0000	H(17)-C(9)-C(10)	120.0000	120.0000
H(19)-C(12)-H(20)	109.5200	109.0000	C(8)-C(9)-H(17)	120.0000	120.0000
C(8)-C(9)-C(10)	120.0000	-	C(6)-C(5)-C(4)	122.3986	117.6000
H(16)-C(8)-C(9)	119.9953	120.0000	C(2)-N(1)-C(10)	115.0000	115.0000
C(7)-C(8)-H(16)	120.0080	120.0000	C(5)-C(4)-O(11)	129.0461	123.0000
C(7)-C(8)-C(9)	119.9967	-	N(3)-C(4)-O(11)	111.0693	122.6000
C(8)-C(7)-H(15)	120.0081	120.0000	C(5)-C(4)-N(3)	119.8847	122.0000
H(15)-C(7)-C(6)	119.9953	120.0000	N(13)-N(3)-C(4)	113.2029	-
C(8)-C(7)-C(6)	119.9966	-	N(13)-N(3)-C(2)	125.2817	-
C(7)-C(6)-H(14)	120.0000	120.0000	C(2)-N(3)-C(4)	121.5153	124.0000
C(5)-C(6)-H(14)	120.0000	120.0000	C(12)-C(2)-N(3)	117.2671	125.3000
C(7)-C(6)-C(5)	120.0000	-	C(12)-C(2)-N(1)	116.7329	115.1000
C(6)-C(5)-C(10)	119.9987	120.0000	N(3)-C(2)-N(1)	126.0000	126.0000
C(4)-C(5)-C(10)	117.6000	117.6000			

Close contacts

Atom	Close contacts	Atoms	Close contacts
O(11)-H(22)	2.0630	N(3)-C(10)	2.5394
H(18)-H(21)	1.3972	H(17)-N(1)	2.5208
N(13)-H(18)	2.2270	C(6)-C(9)	2.6741
N(3)-H(18)	2.4497	C(8)-C(5)	2.6740
C(12)-N(13)	2.7422	C(5)-C(2)	2.4611
N(13)-O(11)	2.0945	C(4)-N(1)	2.5951
C(7)-C(10)	2.6740	-	-

Atomic charge

Atoms	Charges	Atoms	Charges	Atoms	Charges	Atoms	Charges
[N(1)]	-0.367	[C(7)]	-0.085	[N(13)]	-0.132	[H(19)]	0.050
[C(2)]	0.293	[C(8)]	-0.051	[H(14)]	0.015	[H(20)]	0.050
[N(3)]	0.733	[C(9)]	-0.085	[H(15)]	0.020	[H(21)]	0.117
[C(4)]	0.335	[C(10)]	0.160	[H(16)]	0.020	[H(22)]	0.111
[C(5)]	-0.066	[O(11)]	-0.954	[H(17)]	0.016	-	-
[C(6)]	-0.038	[C(12)]	-0.200	[H(18)]	0.059	-	-