

# Structural study and antimicrobial evaluation of some transition metal complexes with 3-(2-amino-4-methylphenyl)-2-thioxo-2,3-dihydroquinazolin-4(3H)-one

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## ABSTRACT

The quinazolin-4-one natural products are of high importance biological activity; thus, they were widely studied for pharmaceutical activities. Because of the previously mentioned in this research is underway to prepare a new derivative of quinazolin to know the coordination of the derivative to a number of transition metal ions. During the preparation of the complexes and then investigate biological activity of the derivative and complexes. The new preparation was ligand blending of paying disproportionate amounts of formaldehyde and amines presence of a compound carbon disulfide in ethanol solution. Use this ligand in the preparing many new complexes with ions of some transition elements (Cu II, Co II, and Ni II). Isolated as well as diagnosed and studied the structures of all solid-state complexes to study the physical properties and analytical technique using absorption flame and technical analysis clucking elements (C.H N. S) in addition to the FTIR spectroscopy and UV - visible and measurements of electrical conductivity and magnetic measurements at room temperature. It has been demonstrated a number of characteristics and behavioral composition shows that ligand wire bidented behavior in all the complexes prepared. Where it has been associated with metallic ion via nitrogen atom related to amino group, also sulfur atom.

**Keywords:** Thioxoquinazolin, complexes, biological activities and bidenteds

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## 1. Introduction

Thioxoquinazolin have been specified as sub-class quinazolinone with a lot of applications including biological and pharmacological activities, also significant building blocks and evaluating Crystals heterocycle [1]. Also, the quinazolinone is defined as a major faced heterocycle in the medicinal chemistry as well as building blocks for about 120 alkaloids which are naturally occurring. The derivatives of quinazoline have been major potent tyrosine kinase as well as being specified as inhibitors of the cellular phosphorylation, [2] they might be applied as DNA ligands [3], binding to the adenosine receptors [4] Furthermore, it is specified as a heterocycle of high importance and showing very good pharmacological properties including anti-microbial [5], antifungal [6], anti-tumor [7], anti-cancer [8], anti-inflammatory [9], anti-depressant [10], and anti-fungal activities[11].

## 2. Material and methods

All material and solvents used in the research of the two companies form Fluka and BDH applied with no modifications. The measurements have been done at Mustansiriya University laboratories and Technology University laboratories. FT-IR spectra have been recorded with the use of FT-IR.8300 Shimadzu spectrophotometer with range of frequency 4000-400 cm<sup>-1</sup>. Electronic spectra with the use of Varian UV-visible spectrophotometer as well as the molar conductivity measurement with the use of Philips conductivity meter. Also, melting points have been recorded in the Cos-lab melting point apparatus. Solid complex's magnetic susceptibility has been acquired at 25Celsius with the use of Magnetic Susceptibility Balance Johnson Matthey. Furthermore, the elemental analysis carried out using EA-Elemental analyzer, the contents of metal in solid complexes were determined via atomic absorption using Shimadzu model 6809 and Elemental C, H, N, and S analysis have been implemented with Fison EA 1108 analysis in Ibn –Sina company.

## 2.1. Synthesis ligand

Blending of carbon disulfide (25 mmoles, 1.9g) and the 4-methylbenzene-1,2-diamine (12mmoles, 1.46g) was add drop-wise to refluxed mixture related to anthranilic acid (10 mmoles, 1.37g) and potassium hydroxide (13 mmoles, 0.73g) in methanol (15ml). The mixture has been subjected to heat under reflux for three hours, white yellowish precipitate color has been indicated. Leave for 24hrs at a temperature of 5 °C after precipitate has been separated, filtered, after that washed with ethanol twice and left to dry at room temperature (Scheme 1). Recrystallization using absolute ethanol. The yield (8g, 65%) Anal. calcd. For (C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>OS): cala.(found) = %N 14.84 (14.1) , % C 63.6 (63.9) , % H 4.59 (4.7) , % S 11.3 (11.94) .

## 2.2. Synthesis of the transition metal (II) complexes

1 mmole of the metal chloride (Co II, Ni II and Cu II) has been subjected to dissolving in 10 ml of the absolute ethanol has been added to (1 mmole) regarding the ligand subjected to dissolving in (25ml) related to same solvent. Also, in molar ratio of 1:2 (metal: ligand) as well as refluxed 2hrs, the crystalline colored precipitates have been created at 25Celsius. Resultant solid has been subjected to washing via room hot ethanol as well as washed distilled water and after that left to dry.

## 3. Results and discussion

### 3.1. Mass spectrum of 3-(2-amino-4-methylphenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one

The mass spectrum of ligand [3-(2-amino-4-methylphenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one] (Figure 2) showed the peaks at (*m/z*(%): 283) which corresponds to (M<sup>+</sup>), 268 (M-NH<sub>2</sub>) and 192 (M-CS<sub>2</sub>).

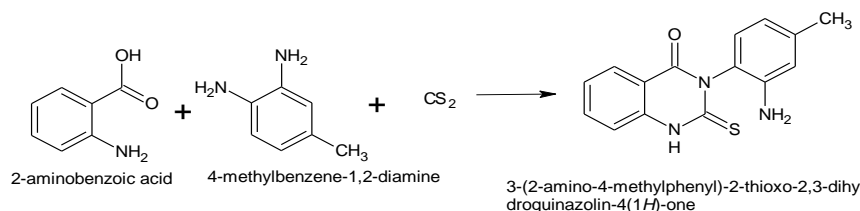


Figure 1. Preparation 3-(2-amino-4methylphenyl)-2-thioxo-2,3-di-hydroquinazolin-4(3H)-one

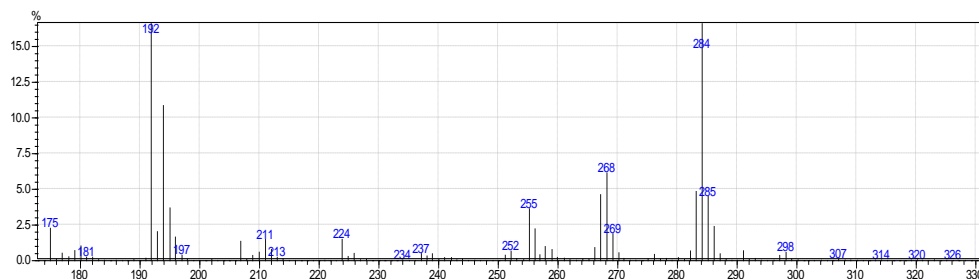


Figure 2. Mass spectrum of ligand

Table 1. Physical properties regarding prepared ligand and its metal complexes

Symb.	Molecular formula	Color, Yield%	m.p °c	M % Calc. (found)
L	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS	Yellowish, 65	174-176	-----
S <sub>1</sub>	[Co(C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS) <sub>2</sub> Cl <sub>2</sub> ]	light blue, 84	>320 dec	8.47(9.61)
S <sub>2</sub>	[Ni(C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS) <sub>2</sub> Cl <sub>2</sub> ]	Greenish yellow, 75	286 dec.	8.26(8.93)
S <sub>3</sub>	[Cu(C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> OS) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]Cl <sub>2</sub>	green, 78	> 300 dec.	8. 6 (9.88)

### 3.2. FTIR spectral studies of Schiff bases and their complexes

FTIR spectra related to the free ligand displayed bands at (3225, 3248) cm<sup>-1</sup> resulting from NH<sub>2</sub> stretching vibrations. Also, a band at (1618cm<sup>-1</sup>) has been a property related to azomethine (-C=N-) stretching vibration and band appears at (1263cm<sup>-1</sup>) because of (C=S) (quinazolin). The comparisons related to FTIR of the 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one with metal II complexes specified that the ligand has been coordinated principally to metal ions bidentately. FT-IR band at (1618cm<sup>-1</sup>) resulting azomethine (-C=N-) vibrations related to ligand was not modified in all complexes specifying the non-involvements in coordination. The next evidences are supporting the chelation's mod.

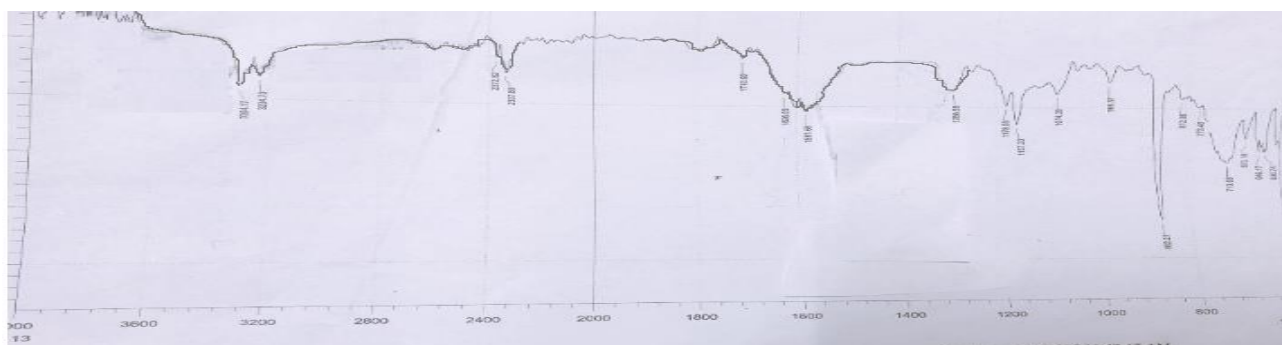


Figure 3. FTIR spectra of (a) 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one

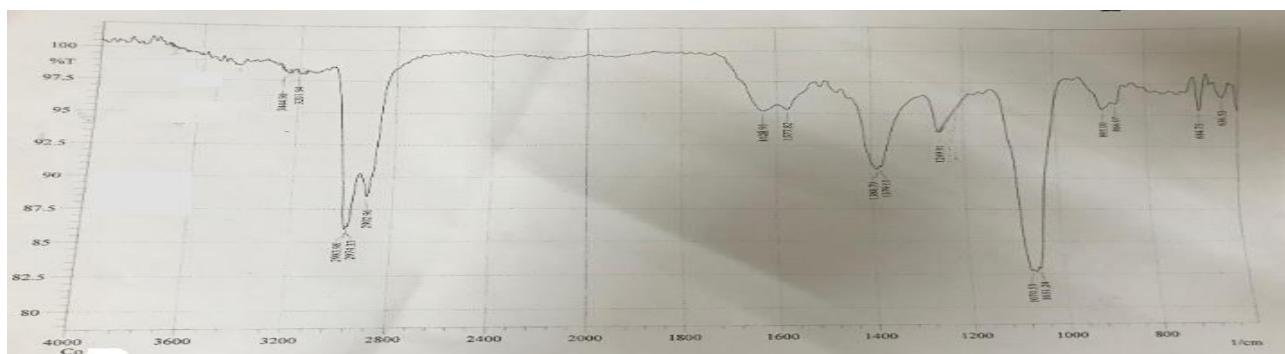


Figure 4. FTIR spectra of  $[\text{Co}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$  complex

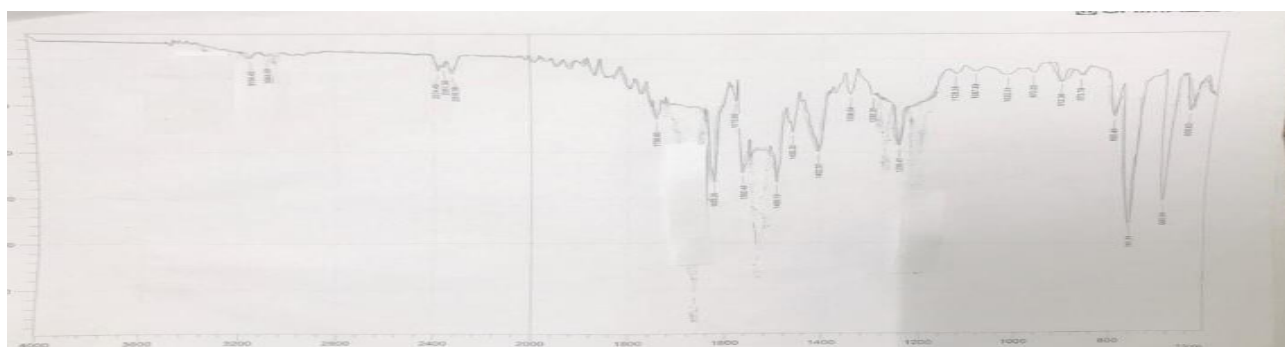


Figure 5. FT-IR spectra of  $[\text{Ni}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$  complex

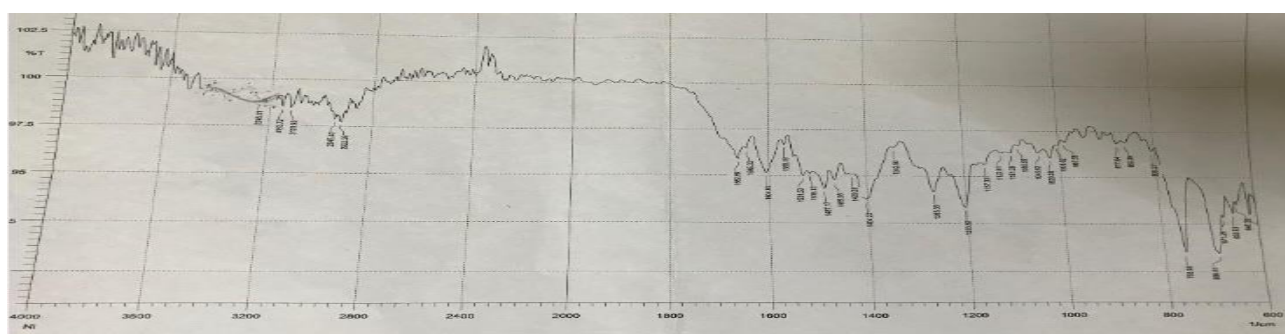


Figure 6. FT-IR spectra of  $[\text{Cu}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2(\text{H}_2\text{O})_2]\text{Cl}_2$  complex.

- The appearance regarding new bands in the metal complexes at  $(504\text{cm}^{-1} - 535\text{cm}^{-1})$  was allocated to the (M-N) stretching vibrations [12-14] and (M-S) stretching vibration [15-17] appearance at  $(433 - 485)\text{cm}^{-1}$ , such bands have been absent in ligand, this supports participate of amino group and (C=S) (quinazolin) in coordination compared to the free 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one. Cu (II) complex displayed new broad peak at  $(3435)\text{cm}^{-1}$  has been allocated to OH stretching vibration regarding coordinated molecules of the water. Spectra of the complexes of Ni (II) and Co (II) showing weak bands in range of  $(418-425\text{cm}^{-1})$  that might be allocated to  $\nu(\text{M-Cl})$  [18]. The assignments, vibrations, and characteristics of 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one as well as its complexes were indicated in the Table 2.

Table 2. FTIR spectra of 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-and their complexes

Compound	$\nu\text{NH}_2$ (asy.aym)	$\nu\text{C=S}$	$\nu\text{C=N}$	$\nu\text{M-N}$	$\nu\text{M-S}$	$\nu\text{M-Cl}$
$\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$	3225, 3248	1263	1618	-	-	-
$[\text{Co}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	3068, 3228	1215	1618	504	461	425
$[\text{Ni}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	3097, 3020	1209	1618	523	485	418
$[\text{Cu}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2(\text{H}_2\text{O})_2]\text{Cl}_2$	3135, 3120	1203	1618	535	433	422

### 3.3. Molar conductance's of the metal complexes

The molar conductance is another technique used to conform the structures regarding prepared complexes, molar conductance related to chelate complexes and the free ligand using DMSO solvent at 25 Celsius. All complexes' data have been recoded as well as tabulated in Table 3, this data indicating Co (II) and Ni (II) Complexes nonelectrolytic naturein but Cu (II) complex electrolytic naturein [19].

Table 3. Molar conductance's of metal complexes

Compound	$\lambda(\text{ohm}^{-1}\text{cm}^2\text{mole}^{-1})$
$[\text{Co}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	12
$[\text{Ni}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	16
$[\text{Cu}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2(\text{H}_2\text{O})_2]\text{Cl}_2$	30

### 3.4. Magnetic moment of metal complexes

The magnetic moment (BM) values that are related to all metal (II) complexes have been acquired at 25Celsius (Table 4). Also, the magnetic moment value that is related to CoII complex has been indicated at 4.12 B.M specifying CoII complex as one of the high spins indicating 3 un-paired electrons in octahedral environments [20].

Table 4. Magnetic moment of the metal complexes

Compound	$\mu_{\text{eff}}$ cal. (found) B.M
$[\text{Co}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	3.872 (4.65)
$[\text{Ni}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	2.828 (3.17)
$[\text{Cu}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2(\text{H}_2\text{O})_2]\text{Cl}_2$	1.732 (1.76)

The Ni II complex indicated magnetic moment value 3.42 BM, specifying the 2 un-paired electrons for each Ni II ion and such complex has octahedral [21] geometry. Furthermore, the magnetic moment value 1.93 B.M with regard to Cu II complex specified single un-paired electron for each Cu II ion for  $d^9$ - system octahedral [22].

### 3.5. Uv-vis. spectral properties

The electronic spectra of 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(3H)-one shows band in  $35578\text{cm}^{-1}$  has been due to the  $\pi-\pi^*$  as well as the band at  $33113$  is attributed to  $n-\pi^*$ .

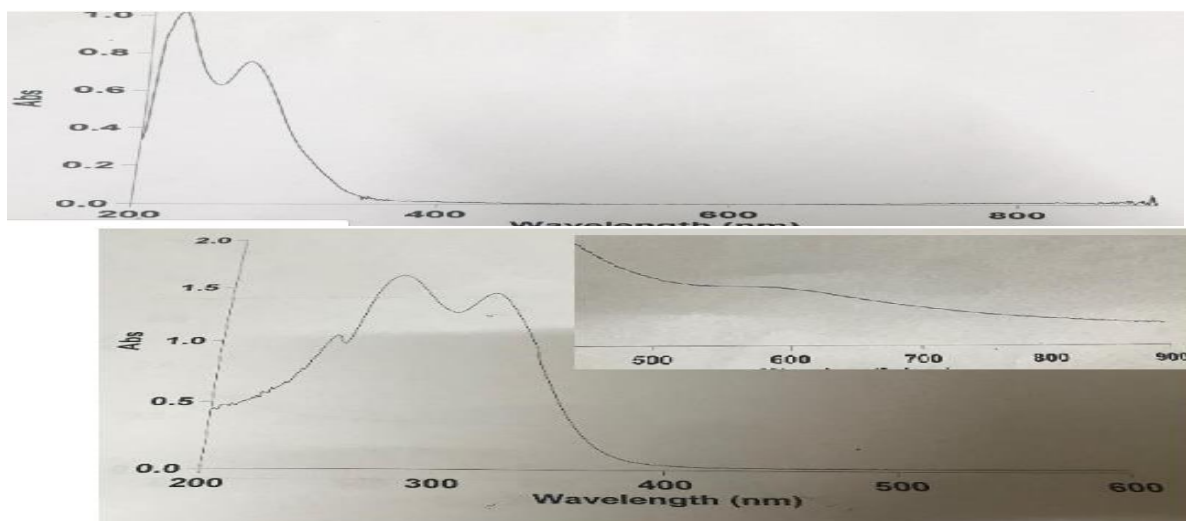


Figure 7. Electronic Spectral data of 3-amino-2- methyl -2-phenyl- 2H-benzol [e][1,3]thiazin-(3H)- one and copper complex

Electronic spectra related to the cobalt complex showed 3 absorption bands which are in the regions 15384, 20000 as well as 24938 $\text{cm}^{-1}$  that might be allocated to the transitions of  ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$  (F),  ${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$  (F) and  ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}$  (p) have been suggesting octahedral geometry around CoII ion[23-25]. Electronic spectra related to the Ni II complex indicated the [26] band in that is in region of (17094, 22676 and 25316)  $\text{cm}^{-1}$  allocated to  ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}$  (F),  ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$  (F) and  ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$  (p). Also, the electronic spectra related to copper complex showed [27] absorption band at (17214 $\text{cm}^{-1}$ ) that might be allocated to transition  ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$  depending on electronic spectra octahedral geometry around Cu (II) ion has been indicated.

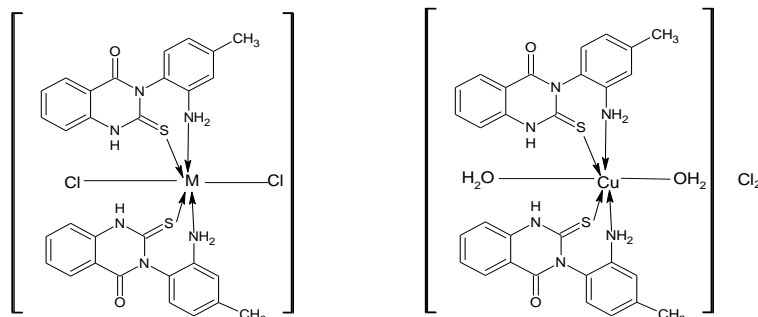


Figure 8. Suggested chemistry structure of metal complexes (Metal complexes of ligand where M= Ni (II) and Co (II).)

Table 5. Electronic spectral data of 3-(2-amino-4-methyl-phenyl)-2 thioxo-2,3-di-hydroquinazolin-4(3H)-one and its metal complexes

Compound	Wav number ( $\text{cm}^{-1}$ )	Assignments
$\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}$	35578	$\pi-\pi^*$
	33113	$n-\pi^*$
$[\text{Co}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	15384	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$ (F)
	20000	${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$ (F)
	24938	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}$ (p)
$[\text{Ni}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2\text{Cl}_2]$	17094	${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}$ (F)
	22676	${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$ (F)
	25316	${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$ (p)
$[\text{Cu}(\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS})_2(\text{H}_2\text{O})_2]\text{Cl}_2$	17214	${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$

### 3.6. Biological activity

The well diffusion technique has been utilized for screening the anti-microbial activity *in-vitro* with the use of Muller-Hinton Agar. Also, the plates have been prepared after pouring molten media of 15 ml in sterile Petri dishes. Bacterial suspension with  $1.5 \times 10^6$  has been inoculated for each one of the plates. Sterile cork borer with diameter of 5 mm has been utilized for boring 7 wells in all the agar plates. Volume of 1ml related to each of the compounds has been utilized via micropipette for each one of the wells. Also, one well has been filled with the solution of DMSO, as control (Mahmood et. al., 1989).

Table 6. Anti-microbial activity of the compounds against various bacterial isolates

Bacterial isolates	DMSO	Ligand/ DMSO	Ni-ligand/ DMSO	Co-ligand/ DMSO	Cu-ligand/ DMSO
<i>Staphylococcus aureus</i>	-	-	-	-	13
<i>Pseudomonas aeruginosa</i>	-	12	30	19	32
<i>E. coli</i>	-	-	-	-	14
<i>Acinetobacter</i>	-	11	-	27	29
<i>Klebsiella</i>	-	-	-	-	11
<i>Micrococcus</i>	-	16	-	35	-

All the plates have been set in the refrigerator for a period of 30mins and temperature of  $4\text{C}^\circ$  for allowing the occurrence of simple compound's diffusion (Crespo et al, 1990), after that subjected to incubation for 24 hours and a temperature of  $37\text{C}^\circ$ . The results related to all compounds have been indicated via evaluating the inhibition zone which is around wells. Abusive and inadequate use regarding the anti-microbial agents led to various

microbial infections which fails in responding to anti-microbial treatments as well as consequent resistance to such drugs [28-30]. A lot of studies indicated that the coordination related to organic compounds to metallic elements causing considerable modifications in biological activity of metal and organic ligand [31-33]. Generally, the cobalt isn't specified for being extremely toxic element [34] A lot of reports in terms of anti-bacterial properties related to the cobalt complexes were indicated, with the Co (II) complexes are the major examined because of their ease of synthesis, availability, and aqueous stability. Yet, just a few of cobalt (III) complexes have been specified for having bio-chemical roles. Furthermore, the Vitamin B12 has been cobaloxime, cobalt complex which contain glyoxime ligand, also a rare example regarding naturally occurring organometallic complexes, for instance, having metal carbon bond [35] The results indicated that there is not activity toward the *Staphylococcus aureus* or Gram-negative bacteria *E. coli* that is in agreement with other results [36]

#### 4. Conclusion

Ligand thioxoquinazolin base ligand 3-(2-amino-4-methyl-phenyl)-2thioxo-2,3-di-hydroquinazolin-4(1*H*)-one has been effectively synthesized, the ligand has been subjected to treatment for various ions salts for affording equivalent complexes. Its ligand coordinated via N- of the amino group as well as S – of the thione group. to metal atom result in the formation of 6-member ring chelate, the complexes have been suggested for being octahedral.

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