

## Preparation, Characterization and Biological Activity of New Nickel(II) Complexes Containing Mixed Ligands\*

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### الخلاصة

حضرت معقدات جديدة للنكل الثاني حاوية لمزيج من الليكاندات : سميكاربازون (SCH) {بنزالديهايد سميكاربازون (BSCH) أو 2-فلوروبنزالديهايد سميكاربازون (FSCH)} والسالسالديهايد (SH) أو حامض الأنثرانيليك (AH) أو 2-ميثيل أمينوفوران (FH)، وشخصت بطرق فيزيائية وكيميائية . اقترحت الصيغة  $[Ni(SCH)(LH)_2](NO_3)_2$  للمعقدات (حيث SCH = BSCH أو FSCH ، LH = SH أو AH أو FH) . درست الفعالية البايولوجية للمعقدات على خمسة جراثيم مرضية باستخدام تقنية الانتشار على سطح الاكار كمضادات للجراثيم ايجابية وسلبية الغرام : *Bacillus subtilis* و *Streptococcus pyogenes* و *Staphylococcus aureus* و *Proteus vulgaris* و *Pseudomonas aeruginosa* وقد أثبتت الدراسة في الوسط التركيبي أن لهذه المعقدات فعالية كمضادات للجراثيم الموجبة والسالبة لصبغة الغرام . يتراوح التركيز المؤثر بين 31,25 - 500 مايكروغرام/مل . ان بكتريا *Pseudomonas aeruginosa* و *Staphylococcus aureus* هما الأكثر حساسية للمركبات وتلتهما بكتريا *Proteus vulgaris* .

### ABSTRACT

Nickel(II) complexes containing mixed ligands; semicarbazone (SCH) {benzaldehyde semicarbazone (BSCH) or 2-fluorobenzaldehyde semicarbazone (FSCH)} and salicylaldehyde (SH) or anthranilic acid (AH) or 2-methylaminofuran (FH) have been prepared and characterized physico-chemically. Complexes of the type  $[Ni(SCH)(LH)_2](NO_3)_2$  {where SCH = BSCH or FSCH, LH = SH or AH or FH} have been proposed . The biological activities of the resulted complexes have been evaluated by agar plate diffusion technique against five human pathogenic bacterial strains: *Bacillus subtilis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Proteus vulgaris*. The complexes were found

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to have antimicrobial activity on some gram-positive and gram-negative bacteria, in vitro. The effective concentrations ranging between 31.25-500 µg/ml. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the most sensitive bacteria followed by *Proteus vulgaris*.

## INTRODUCTION

Nickel complexes occurred in several nickel-containing enzymes and have been proposed to be involved in catalytic reaction. Nickel complexes with macrocyclic ligands have been prepared, and some of them are forming a coordination polymer [1-3] .

A good deal of work has been reported on the preparation and structural investigation of semicarbazone and their complexes [4-6]. This is due partially to their capability of acting as multidentate, NO, NNO, ONNO, donor with the formation of either mono- or bi- or poly-nuclear complexes [7,8]. In addition to their interesting ligational properties, semicarbazones and their complexes have important biological applications [9-10] .

There has been growing interest in the formation of mixed ligands chelates involving ligands containing different functional groups and transition metals of different oxidation states which can form chelates with ligands containing different donation sites [11]. On the other hand, coordination compounds with mixed ligands are of considerable importance in the field of metalloenzymes and other biological activities [12,13]. Hence a large body of the coordination chemistry of mixed ligands with transition and non-transition metal ions have been reported recently [14,15]. Due to the importance of mixed ligands complexes, we took a humble part in the chemistry of mixed ligands containing semicarbazones and their complexes, and some articles have been published on their coordination chemistry with transition and non-transition metal ions [16-18] .

In view of this, and since mixed ligands complexes of semicarbazones and salicylaldehyde or anthranilic acid or 2-methylaminofuran with nickel (II) ion have not yet been reported, it is a matter of interest to determine the extent to which the biological properties of these ligands would be affected by incorporating nickel (II) ion.

In the present work, nickel (II) complexes with mixed ligands {semicarbazones and salicylaldehyde or anthranilic acid or 2-methylaminofuran} have been prepared and characterized physicochemically.

Also this work includes the study of antimicrobial activity of these complexes against *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Proteus vulgaris*.

## EXPERIMENTAL

### I- Chemicals :

2-fluorobenzaldehyde, Nickel (II) nitrate, semicarbazide hydrochloride, 2-methylaminofuran, anthranilic acid (Fluka) have been used as supplied, whereas benzaldehyde and salicylaldehyde (Fluka) have been used after purification by distillation.

### II- Preparation of the ligands :

Semicarbazone ligands have been prepared according to standard methods [19]: 0.0890 mole of semicarbazide hydrochloride and 0.0163 mole sodium acetate dissolved in 10 ml water have been mixed with 0.0940 mole of the appropriate aldehyde. The mixtures were shaken and heated on a water bath for few minutes then refluxed for one hour. On cooling, the solid products were separated, filtered off, washed with water, recrystallized from ethanol and dried. White crystals were obtained (m.p. of BSCH=200 °C, FSCH= 240 °C ).

### III-Preparation of the complexes :

The complexes have been prepared by the reaction of aqueous solution of nickel (II) nitrate with ethanolic solution of semicarbazones (BSCH or FSCH) and salicylaldehyde or anthranilic acid or 2-methylaminofuran (SH, AH, FH ) in 1:1:2 molar ratio at pH 6-7. The mixtures have been refluxed for 3 hrs., evaporated to about half their volumes and cooled. The resulting products were filtered, washed with diethylether and dried .

### IV-Analytical & physical measurements

The metal contents have been determined by a standard precipitation method [20]. Relative molecular weights of the complexes have been determined cryoscopically [21]. Molar conductivities of the complexes have been measured in an electrolytic conductivity measuring set LF-42 using  $10^{-3}$  M absolute ethanol 25 °C. Magnetic susceptibilities of the complexes have been measured by Bruker B.M6. IR spectra of the ligands and their complexes have been recorded on a Pye-Unicam 1100 spectrophotometer in the 400-4000  $\text{cm}^{-1}$  range using KBr pellets. UV/Visible spectra have been recorded on Shimadzu-160 spectrophotometer for  $10^{-3}$  M solution of the ligands and their complexes in absolute ethanol at 25 °C using a 1 cm cell.

### V- Antimicrobial assay of the complexes

Five pathogenic microorganisms have been selected to study the antibacterial activity of the complexes in this research. These were gram positive {*Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilis*} and gram negative {*Pseudomonas aeruginosa* and *Proteus vulgaris*}. All the bacterial strains have been isolated from clinical samples (skin infection) and

identified before use in Biology Department, Science College, Mosul University. The antibacterial activity of the compounds has been evaluated by agar plate diffusion technique [22,23] against a variety of medically important gram-positive and gram-negative bacteria. In this method nutrient agar plates have been seeded with 0.1 ml. of the broth culture of the tested microorganism containing ( $10^8$ ) cells/ml., filter paper discs were impregnated with the tested materials then placed on the surface of seeded nutrient agar plates, the plates were incubated at  $37^\circ\text{C}$  for 24 hrs. The zone of inhibition have been measured using a special calibrated lences.

#### VI-Determination of minimum inhibitory concentration (MIC):

Different concentrations of the tested materials in dimethylsulphoxide solutions (7.600, 15.375, 31.250, 62.500, 125, 250, 500  $\mu\text{g/ml}$ ) were used for the determination of minimum inhibitory concentration (MIC) [22,23]. The lowest dilution which inhibits the growth have been recorded, each experiment were carried out in triplicates for each concentration of the complexes as well as for the microorganisms alone as positive controls for the growth.

### RESULTS AND DISCUSSION

The reaction of nickel (II) nitrate with the semicarbazone and Salicylaldehyde or anthranilic acid or 2-methylaminofuran ligands (The structures of the ligands are shown in Figure 1) in 1:1:2 molar ratio may be represented by the following reactions :



(where SCH = BSCH or FSCH; LH = SH or AH or FH)

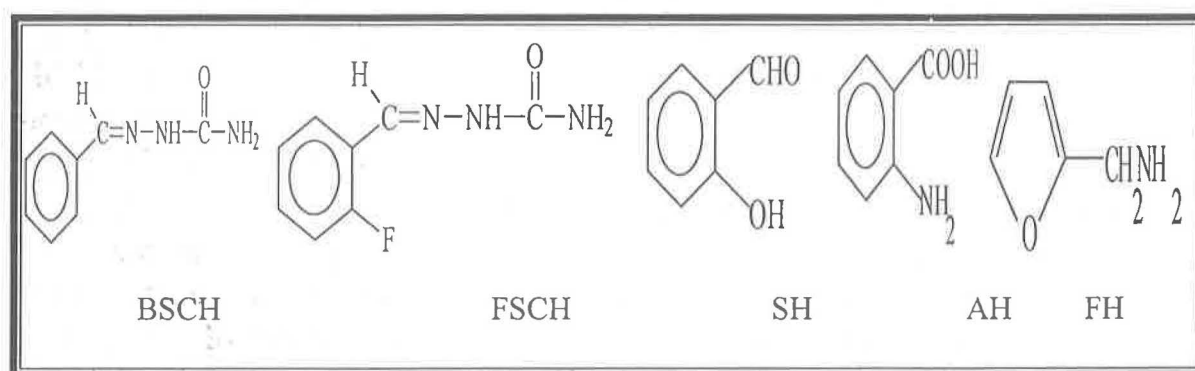


Figure (1) : Structures of the ligands

The resulted complexes are colored solid, moderately soluble in ethanol, soluble in dimethylformamide and dimethylsulfoxide. The elemental analyses reveal that the complexes have the composition  $[\text{Ni}(\text{SCH})(\text{LH})_2](\text{NO}_3)_2$ . The molar conductivities of the complexes in  $10^{-3}\text{M}$  absolute ethanol are determined, the values shown in Table-1 approach those expected for 1:2 electrolytes [24]. The magnetic moments of the complexes calculated from the corrected magnetic susceptibilities

determined at room temperature are shown in Table-1. The  $\mu_{\text{eff}}$  values reported for the complexes (2.63-2.71 B.M.) supported the monomeric structures indicating octahedral geometry around the metal ions [17].

**Table (1) : Analytical data and physical properties of the complexes**

No	Compounds	Colors	M.P. °C	* $\Lambda_M$	** $\mu_{\text{eff}}$	M.Wt (Calc./Obs.)	%Ni (Calc./Obs.)
1	[Ni(BSCH)(SH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Black	217-219	82.8	2.710	557.70 566.98	10.52 9.77
2	[Ni(BSCH)(AH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Green	193d	89.3	2.630	619.70 629.29	9.47 9.08
3	[Ni(BSCH)(FH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Green	205-206d	83.6	2.645	539.70 549.25	10.88 10.50
4	[Ni(FSCH)(SH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Dark green	176-178	82.5	2.700	575.70 584.85	10.20 9.33
5	[Ni(FSCH)(AH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Pale green	137-138	78.2	2.670	637.70 647.39	9.20 8.92
6	[Ni(FSCH)(FH) <sub>2</sub> ](NO <sub>3</sub> ) <sub>2</sub>	Dark brown	102-103	70.9	2.690	557.70 567.73	10.53 10.20

\* $\Lambda_M$  = molar conductivities in  $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ ; \*\*values in Bohr magneton (B. M.)

The infrared spectra of semicarbazone ligands showed a strong band at about  $1675 \text{ cm}^{-1}$  which was attributed to the C=O group [7]. This value shifted towards a lower frequency on coordination indicating the formation of a chelation between the oxygen of the carbonyl group and the metal ion [7]. The next strong band at  $1580 \text{ cm}^{-1}$  which was attributed to C=N group shifted towards a lower frequency on coordination [7,8] due to the decrease of the bond order as a result of metal nitrogen bond formation [7,8]. The position of the ligand in the range  $3300\text{-}3500 \text{ cm}^{-1}$  remained unaltered in the complexes indicating that there is no coordination through the NH group [7,8]. The infrared spectra of salicylaldehyde showed bands at  $1700, 3150\text{-}3250, 1250 \text{ cm}^{-1}$  which were due to  $\nu_{\text{C=O}}, \nu_{\text{OH}}, \nu_{\text{C-O}}$ , respectively, upon complexation these bands were shifted (Table 2). The shift in these vibrations indicated their coordination with  $\text{C} \cdots \text{O} \cdots \text{C}$  the metal ion [30]. The positive shift in the stretching frequency upon complexation indicated that there was a Cu-O bond. Such increase in frequency  $\text{C} \cdots \text{O} \cdots \text{C}$  may be related to an increase in the dipolar contribution of [30]. The infrared spectra of anthranilic acid showed a wide bands in the region  $3500\text{-}3600$  and  $3400 \text{ cm}^{-1}$  due to the stretching vibration of carboxylic OH and NH<sub>2</sub> groups, respectively, this wide range was due to the hydrogen bonding. In the spectra of the complexes, it is more difficult to observe the coordination due to the presence of different groups and hydrogen bonding. Whatever this wide band was shifted to lower frequency [25]. The other two bands observed at  $1350\text{-}1430 \text{ cm}^{-1}$  and  $1550\text{-}1600 \text{ cm}^{-1}$  were due to the symmetric and asymmetric stretching frequencies of carboxylic group, respectively. On complexation these bands were shifted to  $1350\text{-}1420 \text{ cm}^{-1}$



and 1500-1575  $\text{cm}^{-1}$ , respectively [26]. The difference between the symmetry and asymmetry stretching vibration of  $\text{COO}^-$  group ( $\Delta\nu$  which was equal to 150-155  $\text{cm}^{-1}$ ) gave indication about the manner of coordination of carboxylic group, this value showed that the anthranilic acid coordinated through  $\text{COO}^-$  group which was acted as monodentate [26]. On the other hand, the spectra of all the complexes showed new bands at 1380-1385  $\text{cm}^{-1}$  as due to ionic nature of nitrate group [17,26]. In addition, new bands were observed in the spectra of the complexes at 480-500 and 580-590  $\text{cm}^{-1}$  as due to  $\nu_{\text{Ni-N}}$  and  $\nu_{\text{Ni-O}}$ , respectively. The presence of these bands (Table 2) supported the coordination of the ligands to the metal ion.

Table (2) : IR spectral data of the ligands and their complexes (values in  $\text{cm}^{-1}$ )

Comp.	$\nu_{\text{C=N}}$	$\nu_{\text{NH}}$	$\nu_{\text{C=O}}$	$\nu_{\text{C-O}}$ Ph	$\nu_{\text{COO}^-}$ (s)	$\nu_{\text{COO}^-}$ (as)	$\nu_{\text{C=O=C}}$	$\nu_{\text{C=O}}$ ald.	$\nu_{\text{Ni-O}}$	$\nu_{\text{Ni-N}}$
BSCH&SH	1580	3200-3500	1675	1250	-	-	-	1710	-	-
1	1560	3200-3500	1650	1300	-	-	-	1690	550	600
BSCH&AH	1580	3200-3500	1675	-	1350	1550	-	-	-	-
2	1560	3200-3500	1645	-	1350	1500	-	-	540	600
BSCH&FH	1580	3200-3500	1675	-	-	-	1490	-	-	-
3	1550	3200-3500	1650	-	-	-	1525	-	560	610
FSCH&SH	1580	3200-3500	1675	1250	-	-	-	1710	-	-
4	1550	3200-3500	1650	1320	-	-	-	1690	540	610
FSCH&AH	1580	3200-3500	1675	-	1420	1620	-	-	-	-
5	1555	3200-3500	1650	-	1420	1575	-	-	540	600
FSCH&FH	1580	3200-3500	1675	-	-	-	1495	-	-	-
6	1560	3200-3500	1640	-	-	-	1520	-	550	650

The electronic spectra of the Ni (II) complexes (Table 3) showed absorption bands at 9035-10846  $\text{cm}^{-1}$ , 16666-20000  $\text{cm}^{-1}$  and 21570-24570  $\text{cm}^{-1}$  due to  $\nu_1$ ,  $\nu_2$  and  $\nu_3$ , respectively, (attributed to  $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{2g}(\text{F})$ ,  $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F})$  and  $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$  transitions) which were expected for  $d^8$  system having high spin octahedral geometries [27]. The ligand field parameter B and the ligand field splitting energy (10Dq) have been calculated (27). The values of  $\hat{a}$  of the complexes were between 0.70-0.78 indicating the covalent character of the bond concerned. However, the electronic spectral data suggested octahedral geometries of all the complexes (Figure 2)[27].

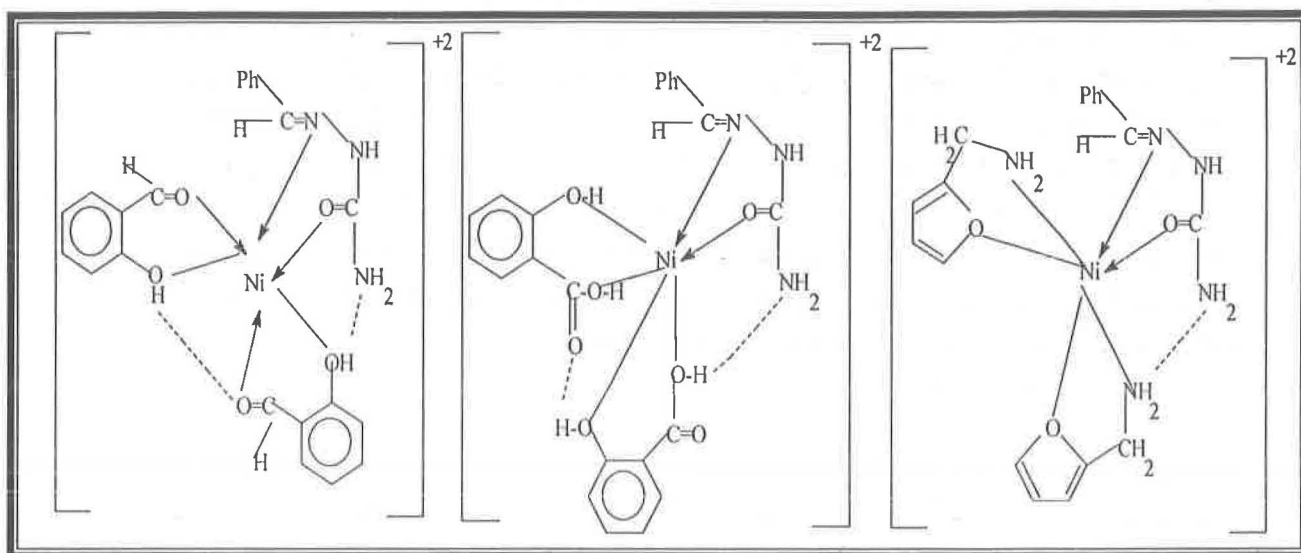


Figure (2) : Proposed structures of the complexes

Table (3) : Electronic spectral data of the complexes

Comp.	$\nu_1^*$ $\text{cm}^{-1}$	$\nu_2$ $\text{cm}^{-1}$	$\nu_3$ $\text{cm}^{-1}$	C.T $\text{cm}^{-1}$	B $\text{cm}^{-1}$	10Dq	$\beta$	Dq/B	C.F.S.E
1	9035	16666	21570	26520	722	9035	0.70	1.25	10845
2	10845	20000	24568	28480	802	10845	0.78	1.35	13015
3	9037	16667	21575	28160	722	9037	0.70	1.25	10845
4	9038	16666	21576	27700	722	9038	0.70	1.25	10845
5	10845	20000	24568	26300	802	10845	0.78	1.35	13015
6	10846	20000	24570	28500	802	10846	0.78	1.35	13015

\* calculated

Many chemical compounds had a good ability to attack the bacteria through their effects on the synthesis of ribonucleic acid which could be resulted from the inhibition action of these compounds on the DNA of the bacteria which caused inhibition of the activities of DNA enzyme including the separation of supercoiling or decatenation or unknotting of the DNA [28,29]. Moreover, the antibacterial agents were known to attack the cell in a variety of ways such as: killing or inhibiting the growth of micro-organisms by affecting special target sites like the synthesis of cell wall, protein and nucleic acid, or by inhibiting the function of the cell membrane, binding of the sulfhydryl groups of the cell enzymes with the complexes (30-32). Numerous experiments have been done to determine the antimicrobial influence of the complexes. Table 4 showed that the complexes numbers 1 and 2 have anti-microbial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Proteus vulgaris*, whereas complex 4 have antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus* and

*Pseudomonas aeruginosa*. Complex 3 have only antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, meanwhile complex 5 have antimicrobial activity against *Streptococcus pyogenes* and *Pseudomonas aeruginosa*. As heavy metal ions preferentially bind to SH group of the cell enzyme more strongly, it is logical to assume that the complexes screened were involved in a competitive equilibria involving the SH group of the cell enzyme. Therefore, we concluded that most of the complexes acquire a good biological activity (Figure 3). If this is the case, the complexes which were expected to bind to SH group of the cell enzymes acted more strongly than the nitrogen donor atom in the ligands (33) and should have lower MIC (Table 5) than complexes (Table 4) consequently, these observations have been consistent with that observed by many workers (33).

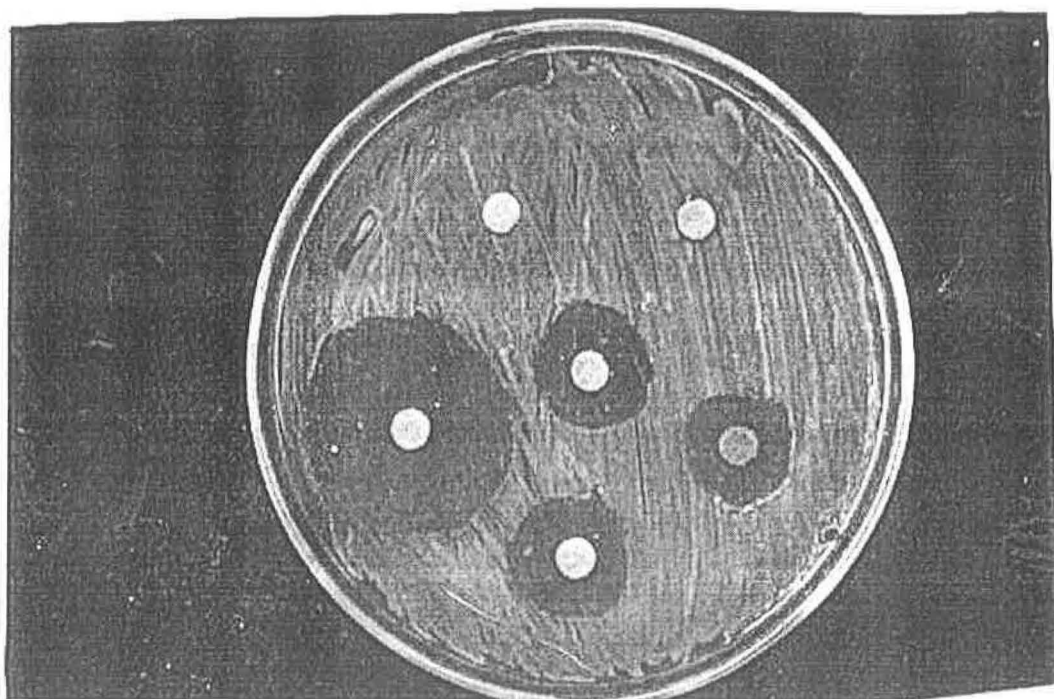


Figure (3) : Antimicrobial activity of different concentrations of complex 1 on *Proteus vulgaris*

Table (4) : Antibacterial activity of the complexes

No.	<i>Bacillus subtilis</i>	<i>Streptococcus pyogenes</i>	<i>Staphylococcus aureus</i>	<i>Proteus volcarus</i>	<i>Pseudomonas aeruginosa</i>
1	R	R	MS	S	S
2	R	R	S	S	S
3	R	R	S	R	S
4	MS	R	MS	R	MS
5	R	MS	R	R	S
6	R	R	R	R	R

S = Sensitive; zone diameter not more than 6 mm less than control[34,35]

MS=Intermediate; Moderately sensitive zone diameter of 6-12 mm less than control

R = Resistant; zone diameter of 12 mm or less than control .



**Table (5) : Minimum inhibitory concentrations ( $\mu\text{g} / \text{ml}$ ) of the complexes**

No.	<i>Bacillus subtilis</i>	<i>Streptococcus pyogenes</i>	<i>Staphylococcus aureus</i>	<i>Proteus vulgaris</i>	<i>Pseudomonas aeruginosa</i>
1	-	-	500	125	125
2	-	-	62.50	31.25	62.50
3	-	-	62.50	-	31.25
4	500	-	500	-	500
5	-	500	-	-	62.50
6	-	-	-	-	-

- means that there is no activity appeared of these compounds this can be observed in Table(1)

## CONCLUSION

This work in fact is a continuation of our studies including mixed ligand complexes. In this work some observations have been achieved that lead to establish the following points:

- 1- Semicarbazones acted as bidentate chelating ligands joint to nickel (II) ion through the carbonyl-oxygen and azomethane-nitrogen atoms. Salicylaldehyde, anthranilic acid and 2-methylaminofuran acted as bidentate chelating ligands
- 2- Nitrate ion joint in an ionic manner to the metal ion .
- 3- Nickel (II) ion is probably hexacoordinated, leading to high spin octahedral geometry.
- 4- Complexes 1, 2, 3, 4 and 5 showed good antimicrobial activities against *Pseudomonas aeruginosa*.
- 5- Complexes 1, 2, 3 and 4 showed good antimicrobial activities against *Staphylococcus aureus* .
- 6- Complexes 1 and 2 showed good antimicrobial activities against *Proteus vulgaris* .
- 7- Complex 4 showed good antimicrobial activity against *Bacillus subtilis* while Complex 5 showed good antimicrobial activity against *Streptococcus pyogenes* .
- 8- Complex 6 had no antimicrobial activity against the five micro-organism.

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