BIOLOGICAL ACTIVITY OF SOME NICKEL(II) COMPLEXES

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ABSTRACT

The biological activity of some nickel (II) complexes containing mixed ligands {having the formulaes $[Ni_2(Sch)_2(Py)_4(NO_3)_2](NO_3)_2$ and $[Ni_2(Sch)_2(Py)_4(NO_3)_3]NO_3$ (where Sch=benzaldehyde semicarbazone - Bsch or 2-fluorobenzaldehyde semicarbazone - Fsch; Py = substituted pyridine: 2-aminopyridine - Py_1, 4-aminopyridine – Py_2, 2,3-dicarboxypyridine - Py_3, 2-amino-3-hydroxypyridine - Py_4, 2-amino-4-methylpyridine - Py_5 or 3,4-dicarboxypyridine - Py_6)} in dimethylsuphoxide solutions(DMSO) have been evaluated by agar plate diffution technique against five human pathogenic bacterial strains: *Bacillus subtilis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa and Proteus vulgaris* . The complexes were found to have antimicrobial activity on some gram-positive and gram-negative bacteria, *in vitro*. The effective concentration ranging between 62.5-500 µg/ml. *Pseudomonas aeruginosa* were the most sensitive bacteria followed by *Staphylococcus aureus* bacteria .

Key Ward : Nickel , Semicarbazone , Substituted-pyridine , Mixed-ligands , Biological activity

الفعالية البايولوجية لبعض معقدات النيكل (II)

الملخص

تم في هذا البحث دراسة الفعالية لبعض معقدات النيكل (II) الحاوية على مزيج من الليكاندات ذات الصيغ $[Ni(Sch)_2(Py)_4(NO_3)_2](NO_3)_2$ و $[Ni(Sch)_2(Py)_4(NO_3)_3]NO_3$ (حيث Sch = بنزالديهايد سميكاربازون – Bsch أو 2-فلوروبنزالديهايدسميكاربازون – Fsch ، Py = بريدين معوض: 2-أمينوبريدين – Py_1 أو 4- أمينوبريدين – Py_2 أو 2،3- ثنائي كاربوكسي بريدين – Py_3 أو 2- أمينو-3-هيدروكسي بريدين- Py_4 أو 2- أمينو-4-ميثيل بريدين– Py_5 أو 3،4- ثنائي كاربوكسي بريدين – Py_6) في محلول ثنائي ميثيل سلفوكسيد (DMSO) على عدد من الجراثيم باستخدام تقنية الانتشارعلى سطح الاكار كمضادات للجراثيم ايجابية وسلبية الغرام : *Bacillus subtilis* و *Streptococcus pyogenes* و *Staphylococcus aureus* و *Pseudomonas aeruginosa* و *Proteus vulgaris* ، وقد أثبتت الدراسة في الوسط الصنعي أن لهذه المعقدات فعالية كمضادات للجراثيم. يتراوح التركيز المؤثر بين 62.5 – 500 مايكروغرام/مل. ان بكتريا *Pseudomonas aeruginosa* هي الأكثر حساسية للمركبات وتلتها بكتريا *Staphylococcus aureus*

الكلمات المفتاحية : نيكل ، سميكاربازون ، بريدين معوض ، مزيج من الليكاندات ، الفعالية البايولوجية .

INTRODUCTION

Some aromatic compounds have been shown to possess antimicrobial activity against gram-positive and gram-negative bacteria (1), while others reported that Schiff bases have

been shown to possess antibacterial activity by themselves (2,3). Ismail showed that Schiff base complexes demonstrated good or remarkable activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Salmonella typhimurium* (4). Schiff bases and their complexes have received renewed attention, recently, due to their proven antitumer and antimicrobial activities (5). They are known to exhibit a wide variety of pharmacological properties such as antiflammatory, antimalarial, antihelmintic activity, hypotensive action, anti- convulsant activity (6,7). Singh studied the biological activity of triorganosilicon (IV) compounds and have been shown that some of them were very active against *Proteus mirabilis* while others were active against *Streptococcus viridans* bacteria (8).

The biological activity of thiosemicarbazone and semicarbazone complexes have been studied by many workers, some of those complexes possessed good antitumor activity in addition to the effect of other activities (9-17).

In view of this, and since the biological activities of mixed ligand – nickel (II) complexes have not yet been reported, it is a matter of interest to determine the extent of these complexes on the bacterial growth.

In the present work, the antimicrobial activity of some nickel (II) - mixed ligands complexes have been studied by agar plate diffusion technique against *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Proteus vulgaris*.

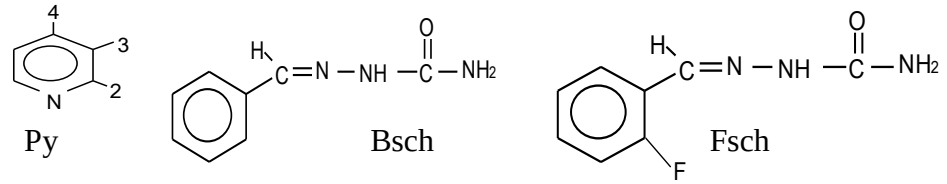
EXPERIMENTAL

1-Materials and methods:

Nickel (II) nitrate, 2-aminopyridine (Py_1), 4-aminopyridine (Py_2), 2,3-dicarboxypyridine (Py_3), 2-amino-3-hydroxypyridine (Py_4) ,2-amino-4-methylpyridine (Py_5) and 3,4-dicarboxypyridine (Py_6) have been used as supplied from Fluka.

2-Preparation of the ligands:

Benzaldehyde semicarbazone - Bsch and 2-fluorobenzaldehyde semicarba- zone Fsch) {Fig. 1} have been prepared according to the standard method (18): 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 $^{\circ}$C, Fsch= 240 $^{\circ}$C).



Py Bsch Fsch

Py	2	3	4
Py_1	NH_2	H	H
Py_2	H	H	NH_2
Py_3	COOH	COOH	H
Py_4	NH_2	OH	H
Py_5	NH_2	H	CH_3
Py_6	H	COOH	COOH

Figure-1:Model structure of the ligands

3-Preparation of the complexes:

Nickel (II)-mixed ligands complexes {Fig. 2} have been prepared according to the previous method (19). The complexes have been prepared by the reaction of aqueous solution of nickel (II) nitrate with ethanolic solution of semicarbazones (Bsch or Fsch) and substituted pyridine (Py) in 1:1:2 molar ratio. 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 .

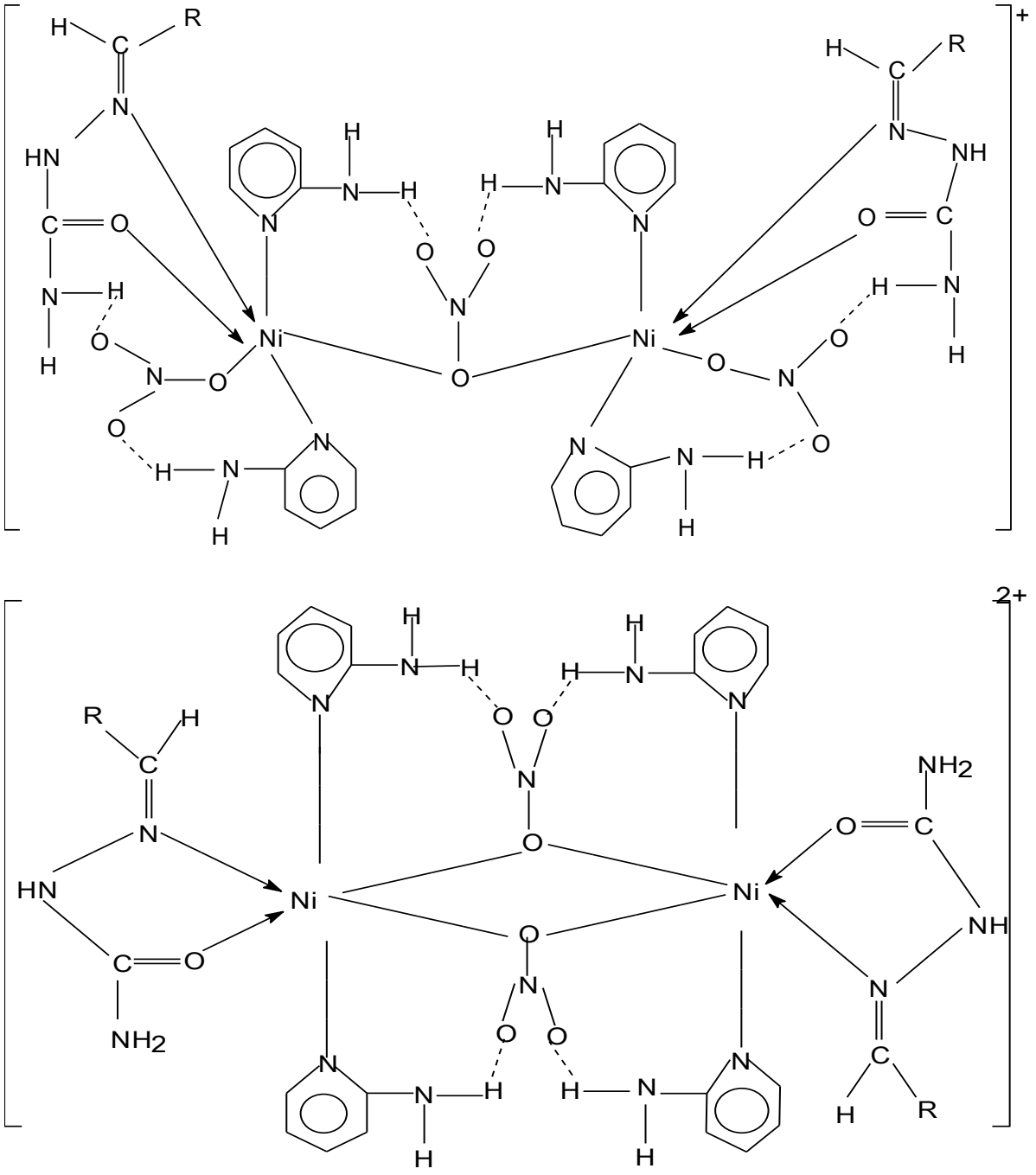


Figure-2: Model structures of the complexes

4- Antimicrobial assay of the complexes:

Five pathogenic bacteria have been selected to study the antibacterial activity of the complexes in this research . These were gram positive {*Bacillus subtilis*, *Streptococcus pyogenes*, *Staphylococcus aureus*} and gram negative {*Pseudomonas aeruginosa* and *Proteus vulgaris*}. All the bacterial strains have been isolated and identified before use in Department of Biology, College of Science, University of Mosul. The antibacterial activity has been evaluated by agar plate diffusion technique (20,21)against a variety of medicinally important gram-positive and gram-negative. In this method nutrient agar plates have been seeded with 0.1ml. 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 ^oC for 24 hr. The zone of inhibition have been measured using a special calibrated lences .

5-Determination of the minimum inhibitory concentration (MIC):

Different concentration of the tested materials in dimethylsulphoxide solutions (500, 250, 125, 62.50, 31.25, 15.62, 7.80, 3.90 µg/ml) were used for the determination of minimum inhibitory concentration (MIC). The highest dilution which inhibits the growth have been recorded, each experiment were carried out in triplicate for each concentration of the complexes as well as for the microorganisms alone as positive controls for the growth.

RESULTS & DISCUSSION

The complexes under investigation have been previously characterized by elemental analysis, molar conductance values, magnetic moment data, infrared spectrophotometry and electronic spectral data (19).

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 gyrase enzyme including the separation of supercoiling or decantenation or unknotting of the DNA (22-25). Moreover, the Antibacterial agents were known to attack the cell in avariety of ways such as : killing or inhibiting the growth of microorganisms 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 complex (2,12). Numerous experiments have been done to determine the antimicrobial influence of the complexes. Table 1 showed that the complexes number 3, 4, 6, 9 and 10 have antimicrobial activity against all gram negative and most of the gram positive bacteria. While, complexes number 1, 2, 5 and 11 have antimicrobial activity against all gram negative and only one gram positive (*Staphylococcus aureus*) bacteria, whereas complexes number 7 and 8 have antimicrobial activity against only two microorganism one gram-negative and one gram-positive bacteria , while complex 12 showed only activity against one gram-positive bacteria. 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 competitive equilibria involving the SH group of the cell enzyme. Therefore, we concluded that most of the complexes aquire a good biological activity (Fig.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 (14) and should have lower MIC (Table 2) than complexes (Table 1) consequently , these observations have been consistent with that observed by many workers (13) .

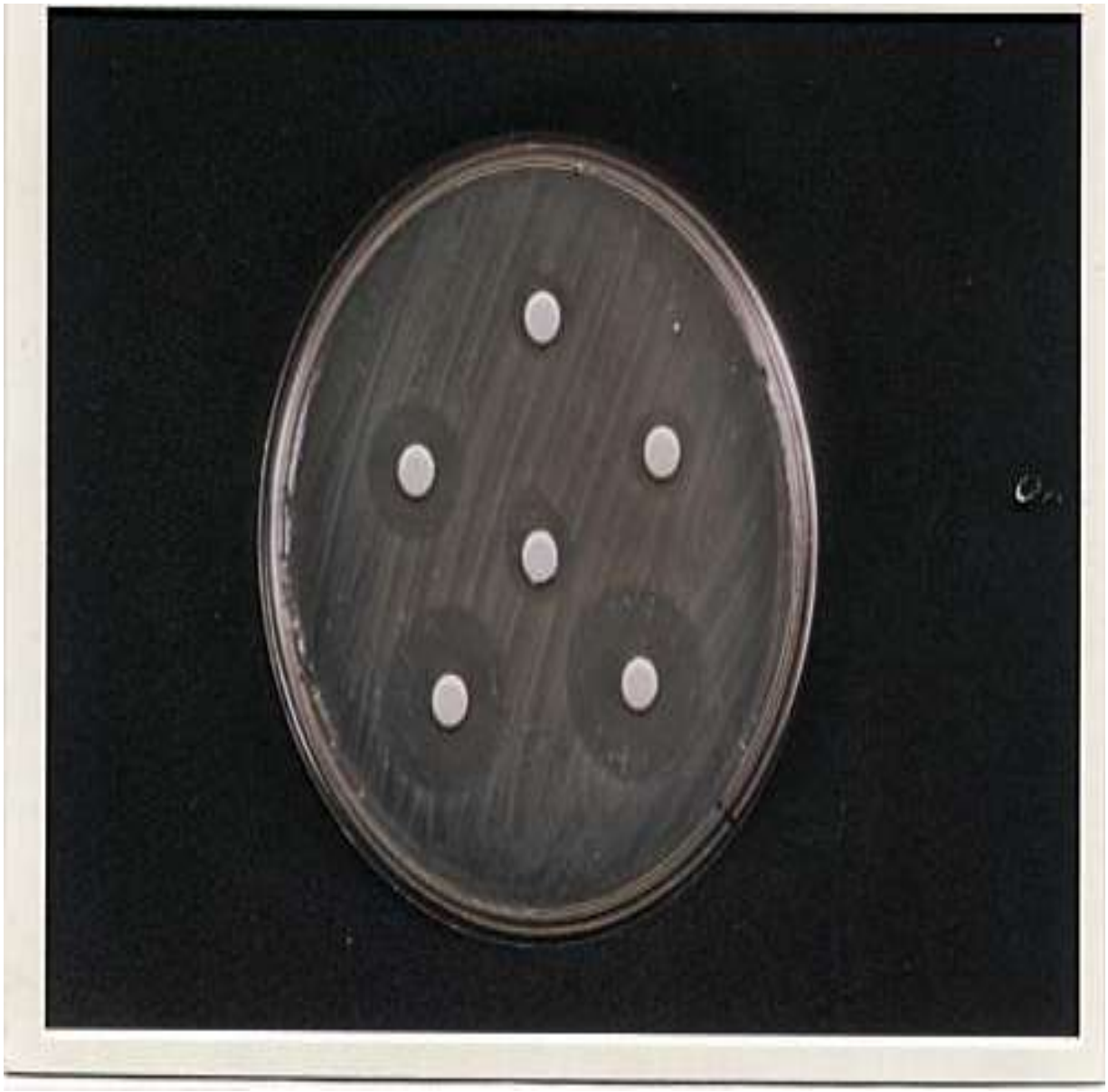


Figure- 3 : Antimicrobial activity of different concentrations of complex on *staphylococcus aureus*

CONCLUSION

From the above data we could conclude the following :

1- All the complexes showed a good antimicrobial activity against *Staphylococcus aureus* .
2- All the complexes except complex 8 and 12 showed a good antimicrobial activity against *Proteus vulgaris* .
3- All the complexes except complex 7 and 12 showed a good antimicrobial activity against *Pseudomonas aeruginosa* .
4- Complexes 3, 4, 6, and 9 showed a good antimicrobial activity against *Streptococcus pyogenes* , where as other complexes did not show any activity .
5- All the complexes except complex 10 showed no activity against *Bacillus subtilis*, where as complex 10 showed good activity against this kind of bacteria .

Table (1) : Antibacterial activity of the complexes

No.	Complexes	*S aureus*	*S. pyogenes*	*B. subtilis*	*P. vulgaris*	*P. aeruginosa*
1	$[Ni_2(Fsch)_2(Py_1)_4(NO_3)_2](NO_3)_2$	S	R	R	S	S
2	$[Ni_2(Fsch)_2(Py_2)_4(NO_3)_3]NO_3$	MS	R	R	MS	S
3	$[Ni_2(Fsch)_2(Py_3)_4(NO_3)_3]NO_3$	S	MS	R	MS	S
4	$[Ni_2(Fsch)_2(Py_4)_4(NO_3)_3]NO_3$	S	S	R	S	S
5	$[Ni_2(Fsch)_2(Py_5)_4(NO_3)_2](NO_3)_2$	S	R	R	MS	S
6	$[Ni_2(Fsch)_2(Py_6)_4(NO_3)_2](NO_3)_2$	S	MS	R	S	S
7	$[Ni_2(Bsch)_2(Py_1)_4(NO_3)_2](NO_3)_2$	S	R	R	S	R
8	$[Ni_2(Bsch)_2(Py_2)_4(NO_3)_3]NO_3$	MS	R	R	R	S
9	$[Ni_2(Bsch)_2(Py_3)_4(NO_3)_3]NO_3$	S	MS	R	MS	S
10	$[Ni_2(Bsch)_2(Py_4)_4(NO_3)_3]NO_3$	S	R	S	S	S
11	$[Ni_2(Bsch)_2(Py_5)_4(NO_3)_2](NO_3)_2$	S	R	R	S	S
12	$[Ni_2(Bsch)_2(Py_6)_4(NO_3)_2](NO_3)_2$	S	R	R	R	R

S = Sensitive ; zone diameter not more than 6 mm less than control (26,27); 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 (2) : Minimum inhibitory concentration (µg / ml) of the complexes

No.	*S. aureus*	*S.pyogenes*	*B.subtilis*	*P.vulgaris*	*p.aeruginosa*
1	62.50	-	-	62.50	125
2	500	-	-	500	125
3	125	500	-	500	125
4	62.50	125	-	125	62.50
5	62.50	-	-	500	62.50
6	62.50	500	-	125	62.50
7	62.50	-	-	125	-
8	500	-	-	-	62.50
9	125	500	-	500	62.50
10	62.50	-	250	250	62.50
11	62.50	-	-	62.50	125
12	250	-	-	-	-

-means that there is no activity appeared of these compounds this can be observed in Table1

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