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Review Article

The Study of Biological Activities of Various Mixed Ligand Complexes of Nickel(II)

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Abstract

This review focuses on research undertaken over the past decades about biological activities of nickel complexes with mixed ligands of different types such as mixed ligand complexes of Ni(II) with furfuralurea and thiourea, mixed ligand complexes of Ni(II) dialkyldithiophosphates with 2-acetylpyridine semicarbazone and 2-acetylpyridine benzoylhydrazone, Ni(II) complexes of thiosemicarbazone and isothiosemicarbazone-based ligands, Ni(II) complexes of morpholinedithiocarbamates and diamines, mixed ligand complex of Ni(II) with nicotinanilide and thiocyanate, mixed-ligand Ni(II) complexes containing sulfathiazole and cephalosporin, Ni(II) complexes with sparfloxacin in the presence or absence of N,NO-donor ligand, Ni(II) mixed ligand complexes of bis(phenylimine) Schiff base ligands incorporating pyridinium moiety, Ni(II) complexes of azo dyes and thiamine hydrochloride, Ni(II) complexes of moxifloxacin imidazole mixed ligands, Ni(II) thiosemicarbazone complexes, mixed ligand Ni(II) complexes with isatinmonohydrazone Schiff base ligands and heterocyclic nitrogen base, mixed ligand complexes of Ni(II) based on 1,10-phenanthroline and novel thiosemicarbazone, Ni(II) mixed ligand complexes of 2-Amino-3-Hydroxypyridine (AHP) and imidazoles. This study focuses on the antimicrobial biological activities of various kinds of mixed ligands Ni(II) complexes.

Keywords: Mixed ligands; Ni(II) complexes; Biological activities; Anti-bacterial activities; Anti-fungal activities; Shiff base ligands

Abbreviations

M: Ni(II); Fu: Furfural-urea; A: Thiourea; CHP: Chloramphenicol, G+ve: Gram positive, Pr: Propyl; G-ve: Gram negative; MICs: Minimum Inhibitory Concentrations; NI: No Inhibition; C: *Candida;* S: *Staphylococcus*; E: *Escherichia*; H_2L^1: (4-(p-fluorophenyl) thiosemicarbazone); H_2L^2: (4-(p-bromophenyl) thiosemicarbazone), H_2L^3 : (4-(p-methoxyphenyl)thiosemicarbazone) of salicylaldehyde; PPh_3: Triphenylphosphine; μ-4,4'-byp: (4,4'-bipyridine); Py: Pyridine; Imz: Imidazole; (4-Pic): 4-picoline; MOX: Moxifloxacin; Him: Imidazole; Hstz: Sulfathiazole; L1: Cefazolin; HL_2: Cephalothin; HL_3: Cefotaxime; HL_4: Ceftriaxone; HL_5: Cefepime; Hstz: sulfathiazole.

Introduction

Transition metal ions are playing an important role in biological processes in the human body [1,2]. Coordination compounds combine the features of metals, which have a wide range of coordination numbers, geometries, variable oxidation states, and ability to bind a variety of organic ligands or mixed ligands in an attempt to get the optimal stability and the biological *in vitro* activity, where the action of many drugs depends on the coordination with metal ions or the inhibition on the formation of metallo-enzyme [3,4]. Researchers have published reviews about complex metals and their contributions to biological activities; it was made clear that a number of antibiotics contain a metal-binding site. Sometimes, transition metal ions are tightly bound forming stable coordination connections, which have an important structural function and/or are responsible for effective antibiotic action. There are a number of antibiotics that require metal ions to function properly and complexes often show better physicochemical properties and are much more effective than parents drugs. Therefore, bioinorganic chemistry provides a powerful weapon for overcoming numerous challenges encountered in antibiotic chemistry [5], researchers showed the importance of metal chelation to tetracycline which is an antibiotic used to treat many different bacterial infections, such as urinary tract infections, acne, gonorrhea, chlamydia, and others [6]. Coordination chemistry of mixed-ligands with transition and non-transition metal ions is important in metallo-enzymes and other biological activities [7]. In most cases, metal complexes show higher bioactivities than the free ligands[8], and some side effects and drug-resistance may be reduced upon complexation [9]. Mixed ligand complexes differ from traditional complexes in the sense that they are having at least two different kinds of ligands associated with the same metal ion in a complex. The presence of more than one type of ligand in a complex increases chances of variation in properties expected for the complex. This makes the researchers interested in the synthesis of mixed ligand complexes with varying properties. In recent years, many publications are devoted to synthesis and characterization of mixed ligand complexes [10]. Numerous mixed ligands transition metal complexes have been investigated by various techniques and their biological activitiesand, exhibit many neurophysiological and neuro pharmacological effects like antimicrobial, antiviral, anticonvulsant, anticancer, anti-mycobacterial, antimalarial, cysticidal, herbicidal and anti-inflammatory activity were extensively studied [11-15]. Chelating ligands containing O, S and N donor atoms and metal complexes containing nitrogen and Sulphur donors have been proved

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Table 1: Antimicrobial activity of the complex $[M(Fu)_2A_2]$ [(66)].

Test Organisms	Concentration µg/ml/disc			Positive control CHP (60 µg/ml/ disc)
	15	30	60	
	Zone of inhibition (mm)			
P. mirabilis	NA	10	13	21
S. aureus	NA	NA	10	23
E. coli	7	7	10	21
K. pneumonia	13	13	14	21
P. aeriginosa	NA	9	11	21

to show broad biological activity [16-18], to be potential antibacterial and fungal agents [19] as well as component of several vitamins and drugs [20,21]. Nickel(II) complexes with nitrogen and sulfur donor ligands are highly interesting because several hydrogenases and carbon monoxide dehydrogenases contain such nickel complexes as their active site [22,23]. The role of mixed ligand complexes in biological process has been well recognized. The stabilities of mixed chelates are of great importance in biological systems as many metabolic and toxicological functions are dependent upon this stability. Many attempts have been made to correlate the stability of the metal-ligand complexes with their antimicrobial activity [24], biological important metal ions with mixed ligands where mixed ligand complexes are used for storage as well as for transport of active material through membrane [25].Schiff bases were important class of ligands, such ligands and their metal complexes had a variety of applications including biological, clinical, analytical and industrial in addition to their important roles in catalysis and organic synthesis [26-28]. Mixed ligand complexes are found to be more active biologically than the ligand itself and its binary complexes and it was widely reported that transition metal mixed ligand complexes are used in fighting microbial infections [29-31]. In his most recent article for the first time, Lobana also reported some nickel(II) complexes of thiosemicarbazones with a co-ligand [32], the biological activities of both above mentioned ligands are attributed to their chelating ability with transition metal ions coordinating to them through either thione or thiolate sulfur, and one of the nitrogen atoms [33,34]. In addition, various applications transition metal complexes of thiocarbazones have been described such as catalytic activity [35, 36], imaging and therapy [37], in sensor [38], antimicrobial [39], antiviral [40], cytotoxic [41], antibacterial [42], anticancer [43], antioxidant activities [44], antiparasital [45], antitumor activities [46], fungicidal [47], and antineoplastic [48]. It is well known that some drugs exhibit increased activity when administered as metal complexes and several metal chelates have been shown to inhibit tumor growth [49,50]. Among all transition metals, this work is much emphasized on nickel, which is an important transition metal normally stable in the +2 oxidation state and it more attracted by the researchers in recent years because of their numerous importance in biological systems. The role of nickel in bioinorganic chemistry has been rapidly expanded since the discovery that urease is a nickel enzyme in 1975. Since then, the list of nickel-dependent enzymes has been significantly increased [51,52], Ni(II) complexes as antibacterial, antifungal, and anticancer agents have been studied and proposed as potent catalysts in homogenous and heterogeneous reactions [53-56]. The coordination chemistry of nickel ion is significant because of its participation in redox cycles of several metallo-enzymes. Square planar nickel complexes can cause cleavage of plasmid DNA, under special factors [57]. A large number of nickel complexes with capability of acting as vitamins are known [58]. Nickel possesses an important role in physiological processes as a co-factor in absorption of iron from the intestine. It can increase absorption of iron from the diet in iron deficient rats (female) under the condition that dietary iron is in the unavailable ferric form [59]. In this review, the focus is placed on anti-bacterial and anti-fungal activities of various kinds of mixed ligands nickel(II) complexes.

Anti-Microbial Activities of Various Kinds of Mixed Ligands Nickel(II) Complexes

Antimicrobial activities of mixed ligand complex of Ni(II) with furfuralurea and thiourea

In vitro antimicrobial efficacy of *pneumonia* the mixed ligands and their corresponding Ni(II) complexes which are discussed in this work were all evaluated by the agar well diffusion method [60-63] and the paper disc diffusion method [64, 65]. This mixed ligand complex of the Ni(II) with furfuralurea and thiourea was tested against *Proteus mirabilis*, *Staphlococus aureus*, *Klebsiella*, *Pseudomonas aeriginosa*, and *E. coli*. The results of antimicrobial activity of the complex were described in Table 1; the complex shows appreciable activity against all the test organisms at 60µg/ml/disc. It was carried out in dimethylsulfoxide solution at concentrations of 15, 30 and 60 µg/ml/disc. The positive control was chloranphenicol at 60µg. The highest zone of exhibition that was 14mm was seen against *Klebsiella* pneumonia compared to 21mm inhibition of the control. The complex showed activity against *E. coli* and *Klebsiella pneumonia* at all the concentrations used. The complex is active against *Staphylococcus aureus* at the concentration of 60µg/ml/disc while it showed no activity against *Proteus mirabilis* and *Pseudomonas aeriginosa* at 15µg/ml/disc. The higher the concentration, the higher the zone of inhibition. The *in vitro* evaluation of the biological studies of the mixed ligand complex showed greater activity against *Proteus mirabilis* and *Klebsiella pneumonia* at 60µg/ml/disc with the minimum zone of inhibition of 13mm and 14mm respectively [66].

Biological activities of mixed ligand complexes of Ni(II) dialkyldithiophosphates with 2-acetylpyridine

semicarbazone and 2-acetylpyridine benzoylhydrazone: Dialkyldithiophosphates Ni(II) complexes react with 2-Acetylpyridine Semicarbazone (Apsc) and 2-Acetylpyridine Benzoylhydrazone (HApBH) to yield mixed ligand complexes. The biological activities of the two organic ligands (Apsc and HApBH), some related complexes and Erythromycine (as a reference compound) were tested against a number of bacteria and fungi. The used bacteria were *B. cereus*G+ve, *M.luteus*G+ve, and *Streptonyces*G+ve; the tested fungi were *Asperrgillusflovus, Fusariumoxysporium, Chrysosporium Tropicm*, and *A. fumig. var. albus*. The organic compound (HApBH) shows a high degree of activity against bacteria and fungi. This activity may be due to the pyridyl ring and OH group in the compound (Enol form); which play an important role in the antibacterial and antifungal activity [67,68]. Detailed results of antibacterial and antifungal activity of Apsc, HApBH and some complexes are found in Table 2a, 2b respectively and the diameter of the inhibition zone was measured in mm [68].

In vitro antimicrobial study of four new biochemical active Ni(II) complexes of thiosemicarbazone and isothiosemicarbazone-based ligands

The antimicrobial efficacy of four Ni(II) complexes 1, 2, 3 and 4

Table 2a: Antibacterial of Apsc, HApBH and Ni(II) complexes.

Compound	*B. cereus* (G+ve)	*M. lutes* (G+ve)	*Streptonyces* (G+ve)
Apsc	10	12	15
[Ni{$(PrO)_2PS_2$}$_2$Apsc]	12	10	12
HApBH	16	15	30
[Ni{$(PrO)_2PS_2$}(HApBH)]	12	0	9
Erythromycin	0	0	0

Table 2b: Antifungal activity of Apsc, HApBH, and nickel (II) complexes.

Compound	*spergilus flovus*	*Fusarium oxysporium*	*Chrysosporium Tropicm*	*funig. var. albus*
Apsc	10	10	18	0
[Ni{$(PrO)_2PS_2$}$_2$Apsc]	12	10	12	15
HApBH	22	20	25	22
[Ni{$(PrO)_2PS_2$}(HApBH)]	10	15	12	15
Erythromycin	0	0	0	0

Table 3: The *in vitro* antimicrobial activity (inhibition zone, mm) of four Ni(II) Complexes (**1**, **2**, **3** and **4**) on the microorganisms.

Microbes	250(mg/ml)[a]				125 mg/ml				62.5 mg/ml				31.2 mg/ml				15.6 mg/ml			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
C. albicans	30	24	40	17	25	18	35	13	20	13	30	10	15	10	25	0	10	0	20	0
C. tropicalis	35	25	20	20	30	20	15	15	25	15	10	10	20	10	0	0	15	0	0	0
C. glabrata	30	23	27	35	25	18	22	30	20	13	17	25	15	8	12	20	10	0	8	15
S. aureus	25	30	18	22	20	25	13	17	15	20	8	12	10	15	0	8	0	10	0	0
E. coli	18	15	NI	13	13	10	0	10	8	0	0	0	0	0	0	0	0	0	0	0
P.aeruginosa	NI	18	17	18	0	13	12	13	0	8	7	8	0	0	0	0	0	0	0	0

[a] MICs: Minimum Inhibitory Concentrations (250 × 0.1 = 25, 12.5, 6.25, 3.12, 1.56 mg/ml); NI: No Inhibition; *C = Candida; S = Staphylococcus; E = Escherichia; P = Pseudomonas*. Complex**1** = Salicylidene S-propyl-isothiosemicarbazonato (N, N', O)-(triphenylphosphine) Ni(II), Complex**2** = 5-Bromo-2-hydroxobenzaldehyde S-propylisothiosemicarbazonato-(N, N', O) -(triphenylphosphine) Ni(II)hydro iodide, Complex**3** = Salicylidenethiosemicarbazonato (N, S, O)-2-methyl imidazole Ni(II), and Complex**4** = 5-Bromo-2-hydroxobenzaldehyde thiosemicarbazonato (N, S,O)-2-methyl imidazole Ni(II).

were tested against some bacteria such as *C. albicans*, *P.aeruginosa*, *E coli*, *S. aureus*, *C. glabrata*, *C. tropicalis*. Complexes 1 and 3 exhibited large inhibition zone (40, 35 mm) against *C. albicans* with a minimum inhibitory concentration (MIC) = 1.56mg/ml, while these complexes were not efficient against *P.aeruginosa* and *E. coli* (Gram-negative bacteria). Complex 2 revealed strong activity against *S. aureus* (Gram-positive bacteria) and 4 showed high property against *C. glabrata*. The complexes 2 and 4 revealed moderate activities against tested bacteria and fungi except *C. glabrata and S. aureus* (Table 3) [69]. The obtained results of tested complexes revealed no significant activity against two bacterial strains *(P. aeruginosa and S. aureus*) even at 500µg/ml, while revealed good antifungal activity against pathogenic Candida species, with MIC values in the range of 15.6-62.5 µg/ml for complexes 1, 2, 3 and 250 µg/ml for the inorganic salt. The best anti-candida property was observed for complex 2 against *C. parapsilosis*, while the complexes had the least effect on *C. krusei*. These complexes revealed lower negative effects on the viability of the MRC-5 cell line than nystatin as antifungal drug [70]. Other literature reported the thiosemicarbazones and some of their metal complexes are usually effective on *S. aureus*, *S. epidermidis, E. coli and C. albicans* [71]. The part of those microbial results including good antifungal activity against pathogenic *candida* species, strong activity against *S. aureus* and did not significant activity against *P. aeruginosa* have been consistent with our results. In contrast, Ni(II) thiohydrazide and thiodiamine complexes revealed significant activities against *P. aeruginosa, E. coli* and a selected of fungal *Aspergillus* strain [72]. From these four studied Ni(II) complexes, 1 and 3 exhibited the strongest antifungal properties especially against *Candida albicans* and 2 showed the highest antibacterial property, especially against *Staphylococcus aureus*, and the detailed results are summarized.

Antimicrobial studies of mixed ligand complexes of Ni(II) complexes with morpholinedithiocarbamates and diamines

These mixed ligand complexes of Ni(II) with morpholinedithiocarbamates and diamineswere tested for their fungicidal against *Candida albicans, Aspergillus niger, Rhizopus spp*. and bactericidal activities against *Staphylococcus aureus, E.coli, Pseudomonas aeruginosa, Aeromonas hydrophila and Vibrio spp*. All the complexes were inactive against *Rhizopus spp*. In case of Nickel(II) complexes, reasonable activity towards all the fungi is noticed. Though the Ni(II) complexes were active against all the bacteria, all the complexes were found to be least active at lower concentrations. All the complexes showed moderate activity at higher concentrations. The trien complex was found to show excellent activity towards *Staphylococcus aureus*, the evaluations of the antimicrobial activities of these complexes clearly reveal the fact that the nickel complexes exhibit a wide spectrum of activity, being active against all the bacteria and fungi studied. The Anti-fungal activity data and anti-bacteria data is furnished in Table 4 and Table 5 respectively [73].

Table 4: Anti-Fungal Studiesof Ni(II) complexes.

Complexes	Fungi	Zone of Inhibition(mm) Concentration(µg/ml)			Antibiotic (1mg/ml)
		1000µg	750µg	500µg	
[Nii(en)(morphdtc)$_2$]	*Candida albicans*	6	5	5	6
	Aspergillus niger	3	2	1	6
	Rhizopus spp.	8	7	5	10
[Nii(dien)(morphdtc)$_2$]	*Aspergillus niger*	5	5	2	6
	Aspergillus niger	3	2	1	5
	Rhizopus spp.	8	7	5	10
[Nii(trien)(morphdtc)$_2$]	*Aspergillus niger*	6	5	4	7
	Aspergillus niger	3	2	1	5
	Rhizopus spp.	7	6	6	10

Where en/dien/trien stand for diamines morphdtc stands for morpholinedithiocarbamate.

Table 5: Antibacterial Studies of Ni(II) complexes.

Complexes	Bacteria	Inhibiton Zone(mm) Conc(µg)			Standard(1µg/ml)
		1000µg	750µg	500µg	
[Nii (en)(morph dtc)$_2$]	*Staphylococcus aureus*	9	7	7	15
	E.coli	7	5	2	10
	Pseudomonas aeruginosa	9	7	6	11
	Aeromonas hydrophila	12	8	4	12
	Vibrio spp.	6	5	3	11
[Nii(dien)(morphdtc)$_2$]	*Staphylococcus aureus*	9	7	6	13
	E.coli	7	6	5	10
	Pseudomonas aeruginosa	7	4	2	11
	Aeromonas hydrophila	6	5	2	13
	Vibrio spp.	6	4	3	10
[Nii(trien)(morphdtc)$_2$]	*Staphylococcus aureus*	11	9	6	10
	E.coli	6	5	3	10
	Pseudomonas aeruginosa	9	7	6	12
	Aeromonas hydrophila	8	7	5	10
	Vibrio spp.	6	5	3	10

Antimicrobial activities of mixed ligand complex of Ni(II) with nicotinanilide and thiocyanate

Mixed ligand Ni(II) complex of Nicotinanilide (NAL) and Thiocyanate (SCN) was prepared and tested against selected four bacteria which are *Klebsiella pneumonia* (MTCC 109), *Vibrio cholera* (ATCC 14035), *Micrococcus luteus* (ATCC 14452) and *Staphylococcus aureus* (MTCC 96). The observed antifungal activity of the complex against *Candida albicans* (MTCC 183), *Candida tropicalis* (MTCC 184) and *Candida parapsilosis* (MTCC 2509), and the observed antimicrobial activity values for the complex are given in Table 6. Complex containing nicotinanilide show apparently an enhanced antimicrobial activity [74]. The results are quite promising; the bacterial screening results in Table 6 revealed that the complex showed maximum activity against *Klebsiella* pneumonia. The antimicrobial data revealed that the complex is more bioactive. The enhanced activity of the metal complex may be ascribed to the increased lipophilic nature of the complex arising due to chelation. It is probably due to faster diffusion of the chelates as a whole through the cell membrane or due to the chelation effect. Although this complex $[Ni(NAL)_2(SCN)_2]$ shows biological activity but, some reports indicated other metal complexes like $[Zn(NAL)_{2(}SCN)_{2]}$ and $[Cu(NAL)_2(SCN)_2]$ that showed higher activity than the complex $[Ni(NAL)_2(SCN)_2]$. These results suggest that the nature of the metal and the coordinated metal ion play significant roles in the inhibition activity [75].

Antibacterial activityof mixed ligand Ni(II) complexes containing sulfathiazole and cephalosporin

Antibacterial activities of cephalosporins and their Ni(II) complexes were tested and the chosen strains were G(+) *Staphylococcus aureus* ATCC 25923 and G(−) *Escherichia coli* ATCC 11775, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumonia* ATCC 23357, *Salmonella enteritidis* CDC 64, and *Bacillus subtilis*

Table 6: Antimicrobial properties of the complex [75].

No.	Test Bacteria	Zone of Inhibition(mm) (µg/ml)	
		Complex $[Ni(NAL)_2(SCN)_2]$	
		50	100
1	*K. pneumonia*	18	26
2	*V. cholera*	20	25
3	*M. luteus*	13	15
4	*S. aureus*	15	18
Test Fungal			
5	*C. albicans*	9	13
6	*C. tropicalis*	8	14
7	*C. parapsilosis*	10	17

Table 7: Antibacterial activity of the drugs and the complexes [76].

Compound	Zone of inhibition (mm)					
	E.C.	S.E.	P.A.	S.A	K.P.	B.S.
Cefazolin	33.0 ± 1.5	36.0 ± 1.0	0.0 ± 0.0	34.0 ± 1.5	35.0 ± 0.5	57.0 ± 2.0
$[Ni(L_1)(stz)(H_2O)]$	20.0 ± 2.5	18.0 ± 0.0	0.0 ± 0.0	27.0 ± 1.0	23.0 ± 1.0	37.0 ± 1.0
Cephalothin	19.0 ± 0.5	29.0 ± 1.0	0.0 ± 0.0	25.0 ± 1.0	33.0 ± 1.5	60.0 ± 0.5
$[Ni(L_2)(stz)]$	10.0 ± 0.0	21.0 ± 0.5	0.0 ± 0.0	27.0 ± 0.5	20.0 ± 1.0	33.0 ± 1.0
Cefotaxime	40.0 ± 1.5	34.0 ± 0.0	23.0 ± 1.0	18.0 ± 2.0	39.0 ± 0.5	35.0 ± 1.0
$[Ni(L_3)(stz)]$	31.0 ± 1.0	37.0 ± 0.5	17.0 ± 0.0	13.0 ± 0.5	24.0 ± 0.5	37.0 ± 0.5
Ceftriaxone	33.0 ± 0.5	38.0 ± 1.0	35.0 ± 2.0	25.0 ± 1.0	40.0 ± 1.0	43.0 ± 0.5
$[Ni(L_4)(stz)(H_2O)]$	35.0 ± 1.0	32.0 ± 0.0	22.0 ± 0.5	15.0 ± 0.5	28.0 ± 1.0	35.0 ± 1.5
Cefepime	13.0 ± 2.0	25.0 ± 1.5	0.0 ± 0.0	0.0 ± 0.0	25.0 ± 2.0	30.0 ± 1.0
$[Ni(L_5)(stz)]Cl$	30.0 ± 1.5	33.0 ± 0.5	19.0 ± 1.0	15.0 ± 1.0	28.0 ± 0.0	35.0 ± 0.5
Sulfathiazole	8.0 ± 1.0	7.0 ± 0.5	7.0 ± 0.5	6.0 ± 0.0	7.0 ± 1.0	8.0 ± 1.5

Where E.C: *Escherichia coli* ATCC 35939; S.E: *Salmonella enteritidis* ATCC 497; P.A: *Pseudomonas aeruginosa* ATCC 10145; S.A: *Staphylococcus aureus* ATCC 25923; K.P: *Klebsiella pneumonia* ATCC 10031; B.S: *Bacillus subtilis* ATCC 6051. Values are the mean ± Standard deviation of the mean.

ATCC 6051. The antibacterial activities of the complexes were better than those of both the sulfathiazole (Hstz) and the starting metal salt. These provided reasons to believe that antibacterial activities of the complexes synthesized do not correlate with the toxicity of them against the bacterial tested. The results are shown in Table 7, where it can be appreciated that except cefepime complex in most cases the antimicrobial activity of complexes was similar or less than the activity of pure antibiotics. The cefazolin $[Ni(L_1)(stz)H_2O]$ complex showed lower bactericidal activity than the free ligand against all tested bacteria. The complexed cefotaxime $[Ni(L_3)(stz)]$ showed better activity against *Salmonella enteritidis* and *Bacillus subtilis* than the uncomplexedcefotaxime, while ceftriaxone and cephalothin complexes showed better activity against *Escherichia coli* and *Staphylococcus aureus* than the free antibiotics, respectively. The cefepime adduct, at difference of all the others, shows better antibacterial activity than that of the free ligand against all tested bacteria. The cefepime $[Ni(L_5)(stz)]Cl$ complex is only electrolyte that showed better activity than free cefepime against all bacteria strains, including against *P. aeruginosa* and *S. aureus* where cefepime is inactive. The cefepimecomplexe activity could be slightly higher because of the different structure of cefepime compared to other cephalosporins tested (it has a zwitterionic structure possessing the pyrrolidinium ring). Antibacterial activity of mixed-ligand nickel ion complexes depends mainly on the type of cephalosporin used, the metal ion, and the type of microorganism [76].

Antimicrobial activity of Ni(II) complexes with sparfloxacin in the presence or absence of N, N O-donor ligand

The anti-microbial activity of mononuclear Ni(II) complexes with the third-generation quinolone antibacterial agent sparfloxacin (sf) in the absence or presence of nitrogen donor heterocyclic ligands 1,10-phenanthroline (phen) or 2,2'-bipyridine(bipy) has been tested. It has been found that $NiCl_2 .6H_2O$ does not exhibit antimicrobial activity at the concentration range used to assay the activity of the complexes in this study. These compounds have important factor that show antimicrobial activities; that is the chelate effect provided by both the sparfloxacinato ligand and the N, N'-donor ligand (bipy, phen) and the nature of the ligands. The test was done on three different microorganisms named *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, and the test has revealed that the inhibition provided by the complexes is slightly decreased in comparison to free sparfloxacin. The results are presented in Table 8, complex 5 exhibits better activity than the other two ones against *S. aureus* (MIC = 16µgmL^{-1}), while the best activity against *E. coli* is provided by complexes 5 and 6 (MIC = 16µgmL^{-1}), and complexes

Table 8: Minimum inhibitory concentration in μgmL^{-1} [79].

Compounds	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*S. aureus* ATCC 29213
Hsf	8	0.5	0.5
$NiCl_2.6H_2O$	>1024	>1024	>1024
Phen	32	32	32
Bipy	256	256	256
$Ni(sf)_2(H_2O)_2$, **5**	16	128	16
$Ni(sf)_2$(phen), **6**	16	32	32
$Ni(sf)_2$(bipy), **7**	128	32	128

Table 9: Antibacterial activity of free Schiff base ligands (L^1 and L^2), their mixed ligand complexes and some known antibiotics [28].

Compounds	Gram positive						Gram negative					
	Staphylococcus aureus			*Bacillus subtillis*			*Pseudomonas aereuguinosa*			*Escherichia coli*		
	5[a]	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
L^1	++	++	nd	++	++	+	+	+	nd	++	+	+
$[Ni(L^1)(L')Br_2]\cdot 2H_2O$	+	+	+	Nd	nd	Nd	++	+	nd	++	nd	nd
L^2	++	+	+	+	+	Nd	+	+	+	++	+	nd
$[Ni(L^2)(L')Br_2]\cdot 2H_2O$	++	nd	nd	+	nd	Nd	+	nd	nd	++	+	nd
Chloroamphinicol (Standard)	++	++	++	+++	+++	++	+++	+++	++	++	++	++

nd: non detected; Inhibition values: 0.1-0.5 cm; beyond control = + (less active); Inhibition values = 0.6-1.0 cm; beyond control = ++ (moderate active); Inhibition values = 1.1-1.5 cm; beyond control = +++ (highly active); [a] Concentration in mg ml^{-1}.

6 and 7 present better activity (MIC = 32 μgmL^{-1}) than 7 against *P. aeruginosa*. Considering the nature of the N,N'-donor heterocyclic ligand, the results suggest that 6 is much more active than 7 against *E. coli* and *S. aureus*, while against *P. aeruginosa* both complexes provide the same inhibition [58]. In general, the inhibition increases in the order bipy<phen, which is in accordance with the activity observed for the free N, N'-donor ligands and for a series of other ternary N, N'-donor ligands and quinolones complexes [10,77,78].

Antibacterial activity of Ni(II) mixed ligand complexes of bis(phenylimine) schiff base ligands incorporating pyridinium moiety

The biological activity of these Schiff base ligands 2, 6-pyridinedicarboxaldehydebis(o-hydroxyphenylimine, L2), 2,6-pyridinedicarboxaldehydebis(p-hydroxyphenylimine, L1) , 2-aminopyridne (L') , their mixed ligand Ni(II) complexes and chloroamphenicol (as a standard compound) was tested against bacteria. The organisms used in this investigations included *Staphylococcus aureus* and *Bacillus subtillis* (as gram-positive bacteria) and *Pseudomonas aereuguinosa* and *Escherichia coli* (as gram-negative bacteria). The results of the bactericidal screening of the synthesized compounds are recorded in Table 9. The data obtained reflect the following findings: The two Schiff base ligands; L1 and L2, have moderate activity in comparison with *Staphylococcus aureus*, *Escherichia coli* and less active in comparison with *Pseudomonas aeruginosa*. L1 ligand shows a moderate activity towards *Bacillus subtillis* while L2 ligand is less active [28]. The remarkable activity of the two Schiff base ligands may be arise from the pyridyl-N and the hydroxyl groups, which may play an important role in the antibacterial activity [68], as well as the presence of two imine groups which imports in elucidating the mechanism of transformation reaction in biological systems [80]. Antibacterial activity of all mixed ligand complexes towards *Bacillus subtillis* not detected; except Ni(II) mixed ligand complex of L2 which has less active action, while their activities toward all other bacteria have remarkable degree [28]. The activity of the two Schiff base ligands and their mixed ligand complexes increases as the concentration increases because it is a well-known fact that concentration plays a vital role in increasing the degree of inhibition [81].

Biological activity of Ni(II) complexes of azo dyes and thiamine hydrochloride as antimicrobial agents

Mixed ligand Ni(II) complexes of Thiamine hydrochloride (Thi) as a primary ligand and four azo compounds as secondary ligands (A_{1-4}), were tested against gram positive (*Staphylococcus aureus*, Streptococcus pyogenes) and gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and also the antifungal activity against *Candida albicans*, Aspergillus nigar and *Aspergillus clavatus* was studied. The complexes were tested in concentration of 100, 200 and 300 mmol and in DMF as a negative control. On the other hand, media with ciprofloxacin (standard antibiotic for gram-positive), gentamicin (standard antibiotic for gram-negative) and Griseofulvin (standard antifungi) were used as positive control, the antibacterial and antifungal data is given in Table 10 and Table 11, inspection of the data given shows that: The percent inhibition increases with increasing the concentration of the complexes from 100 to 300 mmol [82]. In general, antifungal activity of metal-ligand complexes better than their antibacterial activities. The tested complexes are more active against gram-negative than gram-positive bacteria. It was reported that the antimicrobial activity is related to the cell wall structure of the bacteria because the latter is essential to the survival of bacteria. Gram-positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acid, but in contrast, gram- negative bacteria have a relatively thin cell wall consisting of few layers of peptidoglycan [83].This difference in cell wall structure can produce differences in antibacterial susceptibility and some

Table 10: Percentage inhibition of the investigated bacteria after three days using 100, 200 and 400 mmol of the mixed ligand complexes.

Complexes	*S. aureus*			*S. pyogenes*			*E. coli*			*P. aeruginosa*		
	100	200	400	100	200	400	100	200	400	100	200	400
Thi- A_1-Ni	44.4	48.2	53.8	46.4	52.3	60.3	52.3	58.4	69.3	50.2	57.2	69.4
Thi- A_4-Ni	44.9	50.1	56.3	43.8	53.6	60.6	47.2	56.4	63.7	45.2	57.6	64.8
Ciprofloxacin: 95%												
							Gentamicin 92%					

Table 11: Percentage inhibition of the investigated fungi after three days using 100, 200 and 400 mmol of the mixed ligand complexes**.**

Complexes	*Candida albicans*			*Aspergillus niger*			*Aspergillus clavatus*		
	100	200	400	100	200	400	100	200	400
Thi- A_1-Ni	43.3	52.6	66.6	47.3	58.5	70.1	46.3	57.6	68.9
Thi- A_4-Ni	49.9	56.4	68.2	50.1	61.0	71.3	44.6	57.4	69.3
Griseofulvin	92 %			90%			93%		

Table 12: The inhibition diameter zone values (mm) for MOX–HIm complexes [93].

Compounds	Inhibition zone diameter growth (mm)			
	Escherichia coli (G^-)	*Staphylococcus aureus* (G^+)	*Aspergillus flavus* (fungus)	*Condida albicans* (Fungus)
Control DMSO	0.0	0.0	0.0	0.0
Tetracyclin	31	29	--	
Antibacterial agent			--	--
Standard Amphotericin			19	21
Antifungal agent	--	--		
MOX*	22	40	--	
Ni(MOX)(HIm)Cl.H_2O	31	44	--	18

Where –no activity, [94]*

antibiotics can kill only gram-positive (or gram-negative) bacteria and is ineffective against the other type. Obtained results in Table 10 and Table 11 indicated that the metal complexes exhibited better antimicrobial and antifungal activities [82].

Antimicrobial activities of Ni(II) complex of moxifloxacin–imidazole mixed ligand

This mixed ligand complex was evaluated for its antibacterial activity against two bacterial species, namely *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*). Several authors reported that the antibacterial activities of fluoroquinolones were affected by the presence of divalent cations [84]. In addition, fluoroquinolones in vivo behavior as antibacterial agents was strongly affected by their physicochemical properties, in particular, their acid-base properties, as well as their capability to form complexes with metal ions [85]. Certain bacterial infections now defy all known antibiotics, and antibiotic resistance is a growing problem. It is obvious that there is a great need for new antibacterial agents and metal complexes that could be active against multi resistant micro-organisms [86]. Studies have shown that the antibacterial activity of Ni-MOX complexes against *E. coli* was in the range 6-10 mm and that the percentage inhibition of fungal growth measured for *C. albicans* fungus were 11-40%, depending on the concentration of the complexes. The antibacterial and antifungal activities of the synthesized moxifloxacin-imidazole mixed ligand complex was screened against a gram-negative (*E. coli*) and gram-positive (*S. aureus*) bacteria in addition to *A. flavus*, and *C. albicans* fungi. The results of the biological activities are summarized in Table 12, the complex showed a much better antibacterial effect on the selected bacterial strains as compared to standard and MOX ligand alone. This Ni(II) complex has the highest effect compared to the other complexes, and all of the synthesized MOX-HIm mixed ligand complex showed an excellent activity against *E. coli* and *S. aureus* [87]. The results were promising compared with previous studies [88-90]. It is very clear from the inhibition zone values in Table 12 that all the complexes are more active against gram-positive bacteria while, gram-negative bacteria are more resistant. This may be due to the presence of a double membrane surrounding each bacterial cell. Although all bacteria have an inner cell membrane, gram-negative bacteria have a unique outer membrane. This outer membrane excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why gram-negative bacteria are generally more resistant to antibiotics than are gram-positive bacteria. Such an increase in activity of metal chelates as compared to the moxifloxacin can be explained based on chelation theory [91]. Moxifloxacin showed no inhibition of *in vitro C. albicans* growth [92]. The chelation of Ni(II) to the mixed ligands MOX-HIm resulted in enhancing the antifungal activity of *C. albicans* to a certain extent [93].

Antimicrobial activity of mixed-ligand Ni(II) thiosemicarbazone complexes

The antibacterial activity of the compounds (ligands and complexes) was studied against *Escherichia coli* (*E. coli*) and *Bacillus*. The effectiveness of an antibacterial agent in sensitivity was based on

Table 13: Minimum Inhibitory Concentration (MIC) value in µg/mL of the Schiff base ligands (H_2L^{1-3}), Ni(II) complexes and standard drugs against pathogenic strains [62].

Compounds	*E. coli*	*Bacillus*
H_2L^1	500	250
$[Ni(L^1)(PPh_3)]$ (**8**)	125	125
$[Ni(L^1)(Py)]$ (**9**)	62.5	125
H_2L^2	125	250
$[Ni(L^2)(PPh_3)]$.DMSO (**10**)	31.2	125
$[Ni(L^2)(Imz)]$ (**11**)	15.6	15.6
H_2L^3	125	250
$[Ni(L^3)(4\text{-Pic})]$ (**12**)	31.2	31.2
$[\{Ni(L^3)_2(\mu\text{-}4,4'\text{-byp})\}]$.2DMSO (**13**)	62.5	125
Vancomycin	30	30

the diameter of the zones of inhibition, which was measured to the nearest millimeter (mm). The standard drug Vancomycin was tested for its antibacterial activity at the same concentration and under similar conditions to that of the compounds as a positive control. DMSO was used as a negative control under the same conditions for each organism, these synthesized compounds (8, 9, 10, 11, 12, 13) showed potential antibacterial activity against the pathogens tested (*E. coli* and *Bacillus*) and in some cases they showed promising results by giving MIC values less than the standard drug examined [62]. The results in Table 13 also indicate that the corresponding Ni(II) complexes showed much better antibacterial activity with respect to the individual ligands against the same microorganism under identical experimental conditions, which is in agreement with reported results. A possible explanation is that, by coordination, the polarity of the ligand and the central metal ion are reduced through the charge equilibration, which favors permeation of the complexes through the lipid layer of the bacterial cell membrane [4, 95, 96]. From the zone of inhibition, it is observed that complex 11 showed the most promising results, as compared to the other compounds of this study, and the difference in value may be attributed to the nature of the compounds synthesized with imidazole as co-ligands [97,98]. The minimum inhibitory concentration of these complexes and antibacterial activity indicates that complex 11 is the potential lead molecule for drug designing [62].

Antimicrobial activity of mixed ligand complex of Ni(II) based on 1,10-phenanthroline and novel thiosemicarbazone

Mixed ligand Ni(II) complex of 2-(1-(2-phenyl-hydrazono)-propan-2-ylidene)hydrazine-carbothioamide (TPHP) and 1,10-phenanthroline (1,10-Phen) , [Ni(1,10-phen)(TPHP)Cl] has been synthesized and the antimicrobial activities of this metal complex was studied against gram (+) bacteria as *Bacillus subtillis* RCMB 010067, *Staphylococcus aureus* RCMB 010028); gram(-) bacteria as *Pseudomonas aeuroginosa* RCMB 010043, *Escherichia coli* RCMB 010052) and fungi as *Aspergillus flavus* RCMB 02568, *Pencicilliumitalicum* RCMB 03924, *Candida albicans* RCMB 05031, *Geotricumcandidum* RCMB 05097. Standard discs of Gentamicin and Ampicillin (antibacterial agents), Amphotericin B (antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10µl of solvent (DMSO) were used as a negative control. The antibacterial results of the compounds were compared with the standard. The results of antimicrobial assessment, Table 14 exhibit that TPHP has a high antibacterial activity against B. subtillis (RCMB 010067) with 19.4 mm inhibition zone. The TPHP ligand and its complexe did not exhibit antibacterial activity against P.euroginosa (RCMB 010043). Ni(II) complex has high antimicrobial activity against *S. aureus* (RCMB 010028), the inhibitions zones are 27.5, 24.9 and 23.7 mm .The results of antibacterial and anti-fungal activities of Ni(II) complex are summarized in Table 14 and Table 15 [99].

Table 14: Antibacterial activity ligands and their Ni(II) complex.

Compounds	Diameter of inhibition zone (in mm)[a]							
	(G^-)				(G^+)			
	Pseudomonas euroginosa		*Escherichia coli*		*Bacillus subtillis*		*Staphylococcus aureus*	
Conc. (mg/ml)	1 mg/ ml	Activity index	1 mg/ ml	Activity index	1 mg/ ml	Activity index	1 mg/ ml	Activity index
TPHP	NA	-	14.0 ±0.64	62.78	19.4 ±0.64	70.80	18.1 ± 0.35	55.86
[Ni(1,10-phen)(TPHP)Cl]	NA	-	19.5 ± 0.37	82.95	23.1 ± 0.39	84.30	24.9 ± 0.37	76.85
Standard[b]	17.3 ±0.15		22.3 ± 0.18		27.4 ± 0.18		32.4 ± 0.10	

[a]Mean zone of inhibition in mm ± standard deviation beyond well diameter (6mm) produced on a range of environmental and clinically pathogenic microorganisms using (1mg/ml) concentration of tested samples.
[b]The standard antibacterial agents used are Gentamicin for G^- and Ampicillin for G^+.

Table 15: Antifungal activity of Ni(II) complex.

Compounds	Diameter of inhibition zone (in mm)[a]							
	Aspergillus flavus		*Pencicilliu mitalicum*		*Candida albicans*		*Geotricum candidum*	
Conc. (mg/ml)	1mg/ml	Activity index	1mg/ml	Activity index	1mg/ml	Activity index	1mg/ml	Activity index
TPHP	15.6 ± 0.58	65.82	14.7 ± 0.44	67.12	NA	-	18.7 ± 0.64	65.15
[Ni(1,10-phen)(TPHP)Cl]	17.9 ± 0.51	75.55	16.8 ± 0.57	74.88	NA	-	21.3 ± 0.23	74.21
Amphotericin (B)	23.7 ± 0.10		21.9 ± 0.12		19.8 ± 0.20		28.7 ± 0.22	

[a]Mean zone of inhibition in mm ± standard deviation beyond well diameter (6mm) produced on a range of environmental and clinically pathogenic microorganisms using (1mg/ml) concentration of tested samples.

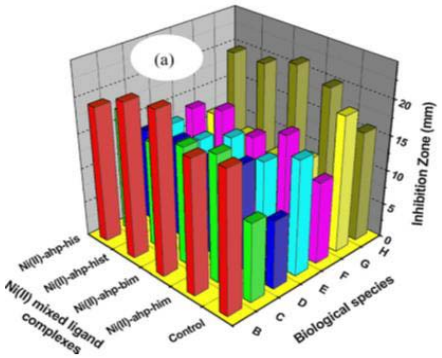

Figure 1: Biological activities of mixed ligand: (a) Ni(II) complexes (zone formation in mm). B: *Staphylococcus aureus*; C: *Klebsiella pneumoniae*; D: *Proteus vulgaris*; E: *Escherichia coli*; F: *Pseudomonas aeruginosa*; G: *Aspergillus niger*; H: *Candida albicans* [65].

Antimicrobial activity of Ni(II) mixed ligand complexes of 2-amino-3-hydroxypyridine and imidazole

Mixed ligand Ni(II) complexes of 2-Amino-3-Hydroxypyridine (AHP) and imidazoles that are imidazole (him), benzimidazole (bim), histamine (hist) and l-histidine (his) have been synthesized and the *in vitro* biological activity of the mixed ligand complexes was tested against the gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*), fungus (*Aspergillus niger*) and yeast (*Candida albicans*). Commercially available ampicillin was used as antibacterial control, while nystatin was used as antifungal control [65,100]. It was found that the Ni(II) complexes show effective antimicrobial activities against the studied microbes (Figure 1). Generally, the Ni(II) complexes have more effective inhibition on the gram positive bacteria *S. aureus* than the gram negative bacteria *E. coli*. The fact may be attributed to their different cell walls. *S. aureus* has cell wall fully composed of peptide polyglycogen as mentioned earlier. The peptidoglycan layer is composed of networks with plenty of pores, which allow foreign molecules to come into the cell without difficulty. However, *E. coli* has cell walls made up of a thin membrane of peptide polyglycogen and an outer membrane constituted of lipopolysaccharide, lipoprotein and phospholipids. Because of the bilayer structure, the outer membrane is a potential barrier against foreign molecules. In the case of other gram negative bacteria such as *Klebsiella species*, *Proteus species*, the activity of nickel complexes is more considerable than the zinc complexes and control Ni(II) complexes have the highest activity against the yeast, *Candida species* [65]. From the zone of inhibition (Figure 1), it is clear that the inhibition zone of Ni(II) mixed ligand complexes are higher than those of the control, which can be explained by (i) the chelation reduces the polarity of the central metal atom, mainly because of partial sharing of its positive charge with the ligand [101] and (ii) the normal cell process may be affected by the formation of hydrogen bond through the nitrogen atom of the ligand with the active centers of cell constituents [102].

Conclusion

Currently, microbial infections have become an important clinical threat, with significant associated morbidity and mortality, which is mainly due to the development of microbial resistance to the existing antimicrobial agents. Certain bacterial infections now defy all known antibiotics, and antibiotic resistance is a growing problem. It is obvious that there is a great need for new antibacterial agents and metal complexes that could be active against multi resistant microorganisms. Therefore, shiff's base mixed ligands and their corresponding Ni(II) complexes were investigated to show whether they are active microbial or not. The evaluation of the antimicrobial activities of these complexes clearly reveal the fact that the Ni(II) complexes exhibit a wide spectrum of activity, being active against all the bacteria and fungi studied. Ni(II) complexes show better inhibitory action against both gram-positive bacterial species, and it showed activity at all the concentrations used. The higher the concentration, the higher the zone of inhibition. The antimicrobial study revealed that the synthesized complexes showed better activity as compared to the parent ligands under identical experimental conditions. It was found that, the Ni(II) complexes have inhibition that is more effective on the gram-positive bacteria *S. aureus* than the gram-negative bacteria *E. coli*. The fact may be attributed to their different cell walls. *S. aureus* has cell wall fully composed of peptide polyglycogen. It may be concluded that antibacterial activity of the compounds is related to cell wall structure of the bacteria. It is possible because the cell wall is essential to the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. The Structure Activity Relationship (SAR) studies suggested that there is an inverse correlation between the dipole moment and the activity of the complexes against the studied bacterial and fungal species. The relationship between structural and biological properties has been explored which could be helpful in designing more potent antibacterial agents. It was found that Ni(II) complexes exhibited considerable amount of antibacterial activity at the time of screening, and have inhibition that is more effective on the gram-positive bacteria *S. aureus* than the gram-negative bacteria *E. coli* due to their different cell walls. Whereby, gram-positive bacteria have thick cell walls composed mostly of a substance unique to bacteria known as peptidoglycan, gram-negative bacteria have cell walls with only a thin layer of peptidoglycan, and an outer membrane with a lipopolysaccharide component not found in gram-positive bacteria. The enhanced activity of Ni(II) complexes may also be ascribed to the increased lipophilic nature of the complex arising due to chelation. It is due to faster diffusion of the chelates as a whole through the cell membrane or due to the chelation effect. The reported results indicated that the corresponding Ni(II) complexes showed much better antibacterial activity with respect to the individual ligands against the same microorganism under identical experimental conditions. A possible explanation is that, by coordination, the polarity of the ligand and the central metal ion are reduced through the charge equilibration, which favors permeation of the complexes through the lipid layer of the bacterial cell membrane.

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