Antimicrobial effects of bis(Δ²-2-imidazolinyl)-5,5′-dioxime and its mono- and tri-nuclear complexes

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Abstract

Bis(Δ²-2-imidazolinyl)-5,5′-dioxime (H$_2$L) and its nickel, cobalt, zinc, cadmium and mercury complexes have been prepared and tested *in vitro* against different microorganisms in order to assess their antimicrobial properties. We used *Bacillus subtilis* RSKK 244, *Micrococcus flavus*, *Streptococcus faecalis* RSKK 500, *Staphylococcus aureus* RSKK 490 from Gram-positive bacteria; *Pseudomonas aeruginosa* RSKK 356, *Salmonella typhimurium* RSKK 1017, *Escherichia coli* RSKK 550, *Enterobacter aerogenes* RSKK 720 from Gram-negative bacteria, *Candida tropicalis* RSKK 665 and *Penicillium raciborskii* IMI 40568.

Introduction

Metal ions play an important role in bioinorganic chemistry and metals such as Fe, Co, Cu, Ni, Zn, Cd, *etc.* may exist in trace amounts in biological systems. Structural studies of the complexes of these metals with biological compounds are extremely important. In order to understand the role of these metal ions it is useful to study analogous complexes such as metal dimethylglyoxime chelates [1, 2].

vic-Dioximes have received considerable attention as model compounds which mimic biofunctions, such as the reduction of vitamin B$_{12}$ [2, 3]. Oxime metal chelates are biologically active [4] and are reported to possess semiconducting properties [5, 6]. Various *vic*-dioximes and their transition metal complexes have been reported [3, 7–23]. Metals and their known compounds have antimicrobial effects but are all highly toxic. Many structural analogs of them have been prepared, in an attempt to lower their toxicity and enhance their biological activity as antimicrobial agents.

We have synthesized bis(Δ²-2-imidazolinyl)-5,5′-dioxime [23] (H$_2$L) (Scheme 1) and its mono- and tri-nuclear complexes. In this paper, we describe the antimicrobial effects of H$_2$L and its complexes.

Experimental

Synthesis

Bis(Δ²-2-imidazolinyl) (L) [24], anti-dichloroglyoxime [25, 26] and cyanogen-*di*-N-oxide [27] were prepared by known procedures [13, 18, 23]. ^{1}H-n.m.r. spectra were recorded on a Bruker 200 MHz spectrophotometer. I.r. spectra were obtained on a Pye Unicam SP 1025 spectrophotometer in KBr pellets. The magnetic moments of the complexes were measured according to the Gouy method with a Newport Instruments type D-104 magnet power supply (293 K). The metal contents of the complexes were determined on a Varian-Faction A-175 type atomic absorption spectrophotometer using solutions prepared by decomposing the compounds in aqua regia and subsequently digestion in concentrated HCl.

Bis(Δ²-2-imidazolinyl)-5,5′-dioxime (H$_2$L) [23]

Bis(Δ²-2-imidazolinyl) (L) (1.38 g, 10 mmol) was dissolved in CH$_2$Cl$_2$ (100 cm^3) and cooled to −10 °C. A solution of (CNO)$_2$ in CH$_2$Cl$_2$ (50 cm^3), prepared from (1.57 g, 10 mmol) anti-dichloroglyoxime and a 0.5 M Na$_2$CO$_3$ solution (120 cm^3) was added after stirring for 24 h at −10 °C, the white product was separated by filtration, washed with CH$_2$Cl$_2$ and EtOH and then dried *in vacuo*. Yield: 2.04 g, 92%. The compound is poorly soluble in DMSO, pyridine, DMF and THF. ^{1}H-n.m.r. (in DMSO-d$_6$) δ = 11.8 (s, 2H, disappears upon deuterium exchange), 3.40 (t, 4H), 3.86 (t, 4H).
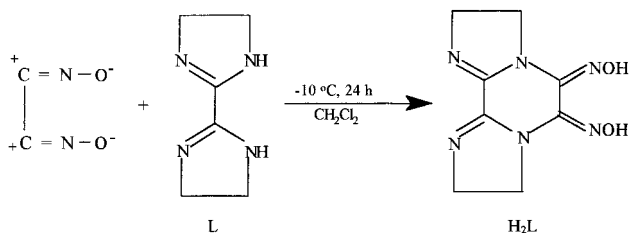
Scheme 1.

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[Ni(HL)₂], [Co(HL)₂], [Cu₃(HL)₂Cl₄], [Zn(HL)Cl(H₂O)], [Hg(HL)Cl(H₂O)] and [Cd₃(HL)Cl₄(H₂O)₂] complexes

[Ni(HL)$_2$], [Co(HL)$_2$], [Cu$_3$(HL)$_2$Cl$_4$], [Zn(HL)Cl(H$_2$O)], [Hg(HL)Cl(H$_2$O)] and [Cd$_3$(HL)Cl$_4$(H$_2$O)$_2$] complexes

A solution of the nickel(II) (0.5 mmol), cobalt(II) (0.5 mmol), copper(II) (1.5 mmol), zinc(II) (1.00 mmol), mercury(II) (1.00 mmol) or cadmium(II) (3.0 mmol) chloride in hot absolute EtOH (30 cm^3) was added to a suspension of H$_2$L (222 mg, 1.0 mmol) in hot EtOH (50 cm^3). The solution changed to red, brown, green, yellow, white or yellow immediately and a sharp decrease in pH to 3.5–4.5 occurred. When the pH was raised to 5.0–5.5 with 0.5% NaOH solution in EtOH, precipitation started. The mixture was stirred on a waterbath at 60 °C for 2 h in order to complete the precipitation. The precipitates were then filtered and washed with hot EtOH and hot H$_2$O and dried *in vacuo*.

Heterotrinuclear complexes of H$_2$L, [MM′$_2$(HL)$_2$Cl$_4$]; M = Ni^{II}, Co^{II} or Cu^{II}, M′ = Cu^{II} or Cd^{II}

A suspension of the mononuclear complex (1.00 mmol; 501 mg [Ni(HL)$_2$] or 501 mg [Co(HL)$_2$]), in EtOH (50 cm^3) was treated with an excess of the second metal chloride prepared by dissolving copper(II) or cadmium-(II) (2 mmol) in EtOH (40 cm^3) and the mixture was refluxed for 10 h with continuous stirring. The precipitate was filtered off, washed with EtOH and Et$_2$O, and then dried *in vacuo*.

The colours, melting points, yields, elemental analyses, characteristic i.r. absorptions and magnetic moments of the complexes are give in Tables 1 and 2.

Antibacterial and antifungal activity

Cultures

The test microorganisms: *Escherichia coli* RSKK 550, *Bacillus subtilis* RSKK 244, *Enterobacter aerogenes* RSKK 720, *Staphylococcus faecalis* RSKK 500, *Staphylococcus aureus* RSKK 490 and *Pseudomonas aeruginosa* RSKK 356, *Salmonella typhimurium* RSKK 1017 and *Candida tropicalis* RSKK 665 were obtained from the Refik Saydam Central Hygiene Institute. *Micrococcus flavus* was obtained from Gazi University. *Penicillium raciborskii* IMI 40568 was obtained from the International Mycological Institute, UK. The cultures of bacteria were maintained in Nutrient Agar slants at 4 °C and subcultured twice in Nutrient Broth prior to use at 37 °C. The fungi cultures were maintained in Sabouraund Dextros Agar (Difco) at 4 °C and subcultured twice in Subouraund Dextros Broth (SDB) prior to use at 28 °C.

Inhibitory activity of microorganisms

The preliminary screening on the antibacterial activity of H$_2$L and of its metal complexes in dimethylsulfoxide (DMSO), was performed *in vitro* by the agar diffusion method [28]. H$_2$L and its metal complexes and metal salts were prepared by dissolving 0.1 g of each compound in 1 cm^3 of DMSO. The bacteria were grown in nutrient broth at 37 °C for 24 h and the fungi were grown in SDB at 28 °C for 48 h. All the materials used were sterilized and Mueller Hinton Agar (Difco) was melted in a water bath and cooled to 45 °C with gentle shaking to bring about uniform cooling. Each culture (0.5 cm^3) was then inoculated aseptically and was well mixed with gentle

Table 1. Analytical and physical data for the *vic*-dioxime and its complexes

Compound	Colour	M.p.[a] (°C)	Yield (%)	Found (Calcd.) (%)					
				C	H	N	Cl	M	M′
H$_2$L C$_8$H$_{10}$N$_6$O$_2$	white	228–230	92	43.2 (43.0)	4.5 (4.8)	37.1 (37.7)	–	–	–
[Ni(HL)$_2$] C$_{16}$H$_{18}$N$_{12}$O$_4$Ni	red	> 320	97	38.3 (37.0)	3.6 (3.7)	33.5 (33.3)	–	11.7 (11.6)	–
[Co(HL)$_2$] C$_{16}$H$_{18}$N$_{12}$O$_4$Co	brown	> 320	78	38.3 (38.2)	3.6 (3.7)	33.5 (33.6)	–	11.8 (11.6)	–
[Cu$_3$(HL)$_2$Cl$_4$] C$_{16}$H$_{18}$N$_{12}$O$_4$Cl$_4$Cu$_3$	green	208–210	69	24.8 (24.5)	2.3 (2.5)	21.7 (21.4)	24.6 (24.3)	18.5 (18.6)	–
[NiCu$_2$(HL)$_2$Cl$_4$] C$_{16}$H$_{18}$N$_{12}$O$_4$Cl$_4$NiCu$_2$	dark green	228–230	96	24.0 (24.6)	2.4 (2.6)	21.7 (21.4)	18.4 (18.7)	7.6 (7.6)	16.5 (16.6)
[CoCu$_2$(HL)$_2$Cl$_4$] C$_{16}$H$_{18}$N$_{12}$O$_4$Cl$_4$CoCu$_2$	dark green	210–212	93	24.0 (24.7)	2.2 (2.3)	21.4 (21.6)	18.4 (18.6)	7.7 (7.6)	16.5 (16.6)
[NiCd$_2$(HL)$_2$Cl$_4$] C$_{16}$H$_{18}$N$_{12}$O$_4$Cl$_4$NiCd$_2$	red	> 300	95	22.1 (22.3)	2.1 (2.1)	19.4 (19.4)	16.5 (16.3)	6.8 (6.6)	25.9 (25.8)
[CoCd$_2$(HL)$_2$Cl$_4$] C$_{16}$H$_{18}$N$_{12}$O$_4$Cl$_4$CoCd$_2$	brown	245–247	95	22.1 (22.3)	2.1 (2.1)	19.4 (19.3)	16.3 (16.5)	6.8 (6.9)	25.9 (25.8)
[Zn(HL)Cl(H$_2$O)] C$_8$H$_{11}$N$_4$O$_3$ClZn	yellow	248–250	57	28.3 (24.6)	3.3 (3.3)	24.7 (24.8)	10.4 (10.2)	19.2 (19.1)	–
[Hg(HL)Cl(H$_2$O)] C$_8$H$_{11}$N$_4$O$_3$ClHg	white	222–224	64	20.2 (20.1)	2.3 (2.3)	16.7 (16.4)	7.5 (7.7)	–	–
[Cd$_3$(HL)Cl$_4$(H$_2$O)$_2$] C$_8$H$_{12}$N$_6$O$_4$Cl$_4$Cd$_3$	yellow	242–244	95	13.1 (13.3)	1.8 (2.0)	11.4 (11.3)	19.3 (19.5)	45.8 (45.0)	–

M′ = Cu^{II} or Cd^{II}; [a] with dec.

Table 2. Magnetic moments and characteristic i.r. bands[a] of bis(Δ^2-2-imidazolinyl) (L), *vic*-dioxime (H$_2$L) and their complexes

Compound	Magnetic moment (B.M.)	I.r. (cm^{-1}) v(N—H)	v(O—H)	v(CH)	δ(O—H$\cdots$O)	v(C=N)[b]	v(C=N)[c]	v(N—O)
L	–	3220	–	2950	–	1770–1700	–	–
H$_2$L	–	–	3190	2950	–	1690	1640	1000
[Ni(HL)$_2$]	diamag	–	–	2950	1710	1680	1630	1000
[Co(HL)$_2$]	1.97	–	–	2950	1710	1680	1630	995
[Cu$_3$(HL)$_2$Cl$_4$]	4.68	–	–	2950	1710	1670	1610	980
[NiCu$_2$(HL)$_2$Cl$_4$]	3.47	–	–	2950	1710	1670	1610	980
[CoCu$_2$(HL)$_2$Cl$_4$]	5.48	–	–	2950	1710	1670	1610	980
[NiCd$_2$(HL)$_2$Cl$_4$]	diamag	–	–	2950	1710	1690	1640	1000
[CoCd$_2$(HL)$_2$Cl$_4$]	1.95	–	–	2950	1710	1680	1630	1000
[Zn(HL)Cl(H$_2$O)]	diamag	–	3180	2950	–	1675	1635	980
[Hg(HL)Cl(H$_2$O)]	diamag	–	3180	2950	–	1675	1635	980
[Cd$_3$(HL)Cl$_4$(H$_2$O)$_2$]	diamag	–	–	2950	–	1675	1635	980

[a] KBr pellets; [b] imidazolinyl; [c] oxime.

shaking before pouring into the sterilized petri dishes. This material was allowed to set (1–2 h). Wells of 9 mm size were then cut in the medium. To each one of these, a solution of 0.1 cm^3 of the compound was added. The plates of bacteria were incubated at 37 °C for 24 h and the plates of fungi at 28 °C for 48 h. At the end of the incubation period the inhibition zones around the wells were measured in mm. DMSO was used as a control. Ampicillin (10 μg) and nystatine (30 μg) were also screened under similar conditions for comparison as a reference standard. According to the Bauer-Kirby method the doses of the ampicillin and nystatine were used as a high influence disc [29].

Results and discussion

^{1}H-n.m.r. and i.r. spectra

The structure of H$_2$L was determined by a combination of elemental analyses, i.r. and ^{1}H- n.m.r. spectral data. The i.r. data for bis(Δ^2-2-imidazolinyl) (L) and the *vic*-dioxime (H$_2$L) are summarized in Table 2. The dis-appearance of the N—H stretching band, along with the appearance of new absorptions at 3190 cm^{-1} (O—H stretching), 1640–1635 cm^{-1} (C=N stretching) and 1000–990 cm^{-1} (N—O stretching) are in agreement [6–20] with the structure shown in Scheme 1. Aliphatic C—H stretching vibrations occur at 2950–2850 cm^{-1}. Furthermore, the stretching vibration of the five-membered ring [23] structure, L, is at 1770 and 1700 cm^{-1} and for H$_2$L at 1690 cm^{-1}. In the ^{1}H-n.m.r. spectrum of H$_2$L the OH proton resonance singlet at 11.8 p.p.m. disappears upon deuterium exchange; two triplets at 3.40 and 3.86 p.p.m. correspond to imidazolinyl =N—CH$_2$—CH$_2$—N— protons.

Elemental analyses, i.r. spectroscopy and magnetic susceptibilities were used to determined the structural characteristics of the complexes (Tables 1 and 2). The reaction of H$_2$L with nickel(II), cobalt(II), copper(II), zinc(II), cadmium(II) and mercury(II) gives products with 1:2, 1:2, 3:2, 1:1, 1:1 or 3:1 metal–ligand ratios

(Figures 1, 2, 3 and 4). For nickel(II) and cobalt(II), only mononuclear complexes were obtained, even when the metal ions were used in excess [7] (Table 1). Since a distinct lowering in the pH of the solution was observed during complex formation, deprotonation of the ligand with subsequent N,N′-chelation with the
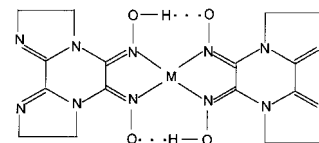

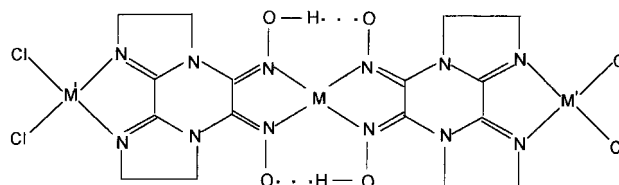Fig. 1. [M(HL)$_2$], M = Ni^{II} or Co^{II}.

Fig. 2. [MM′$_2$(HL)$_2$Cl$_4$], M = Ni^{II}, Co^{II} or Cu^{II}; M′ = Cu^{II} or Cd^{II}.
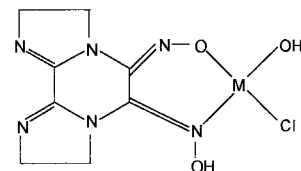
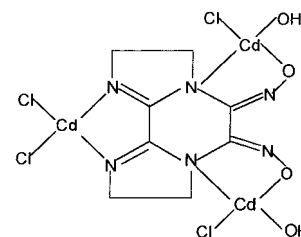Fig. 3. [M(HL)Cl(H$_2$O)], M = Zn^{II} or Hg^{II}.

Fig. 4. [Cd$_3$(HL)Cl$_4$(H$_2$O)$_2$].

vic-dioxime groups probably occurs. The usual hydrogen bridges (H—O···H) associated with the square-planar *vic*-dioxime complexes were characterized by the weak deformation bands [4, 5, 7–20] at 1710–1700 cm^{-1} in [Ni(HL)$_2$] and [Co(HL)$_2$] (Figure 1), (Table 2).

In contrast to nickel(II) and cobalt(II), copper(II) gives trinuclear complexes with H$_2$L with a 3:2 metal–ligand ratio. Even when the ratio of the reactants was 1:2, the same product, [Cu$_3$(HL)$_2$Cl$_4$], was formed. The stability of the univalent anion and bicyclic imide complexes of these two metal ions in solvents such as water is the most important reason for the formation of the trinuclear complexes. In the i.r. spectra, hydrogen bridges of the trinuclear complexes exhibit a weak deformation band [7, 10, 13, 18] at 1710 cm^{-1}. The aliphatic (C—H, N—O) and (C=N) stretching vibrations are similar for H$_2$L as well as the nickel(II), cobalt(II) and copper(II) complexes [4–20].

In order to synthesize heterotrinuclear complexes of the type [MM$'_2$(HL)$_2$Cl$_4$] [M = nickel(II) or cobalt(II); M$'$ = copper(II) or cadmium(II)], heterogeneous reactions of mononuclear [Ni(HL)$_2$] and [Co(HL)$_2$] with a solution of copper(II) or cadmium(II) chloride in EtOH were carried out. In the products, while nickel(II) or cobalt(II) are still coordinated to the *vic*-dioxime groups, two other metal ions are coordinated to two bicyclic imide groups and to a four univalent anion [7] (Figure 2).

H$_2$L reacts with zinc(II) and mercury(II) salts in a 1:1 metal–ligand ratio to give complexes with two of the four metal coordination sites occupied by the N atom of each oxime group and the O atom of the other group. Chloride ion and a water molecule are also coordinated to the metal ion in [M(HL)Cl(H$_2$O)], (Figure 3). The physical data and i.r. spectra are consistent with such a structure [6, 7, 16] (Tables 1 and 2). In contrast, to zinc(II) and mercury(II), cadmium(II) gives trinuclear

Table 3. Antimicrobial activity[a,b] of the ligand, metal complexes and metal salts (mm)

Compound	A	B	C	D	E	F	G	H	I	J
H$_2$L	–	–	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–	–
[Ni(HL)$_2$]	–	–	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–	–
[Co(HL)$_2$]	21	12	12	16	–	–	–	13	–	15
	(0.71)	(0.84)	(1.01)	(1.14)	–	–	–	(1.64)	–	(1.34)
[Cu$_3$(HL)$_2$Cl$_4$]	11	11	–	14	11	11	–	–	–	10
	(0.71)	(1.30)	–	(0.84)	(1.14)	(1.79)	–	–	–	(1.40)
[NiCu$_2$(HL)$_2$Cl$_4$]	–	–	–	10	–	–	–	–	–	–
	–	–	–	(1.48)	–	–	–	–	–	–
[CoCu$_2$(HL)$_2$Cl$_4$]	–	13	14	14	13	12	12	–	–	–
	–	(1.14)	(1.48)	(1.64)	(0.84)	(1.21)	(1.14)	–	–	–
[NiCd$_2$(HL)$_2$Cl$_4$]	20	19	20	29	29	19	20	21	25	23
	(0.55)	(1.22)	(1.16)	(0.84)	(1.67)	(1.22)	(1.09)	(0.51)	(0.45)	(0.71)
[CoCd$_2$(HL)$_2$Cl$_4$]	16	15	16	26	19	13	22	17	42	34
	(0.84)	(1.14)	(0.78)	(0.71)	(1.30)	(1.58)	(0.97)	(0.84)	(1.10)	(1.30)
[Zn(HL)Cl(H$_2$O)]	–	–	–	11	–	–	–	–	–	–
	–	–	–	(1.19)	–	–	–	–	–	–
[Hg(HL)Cl(H$_2$O)]	30	28	20	29	22	27	29	14	25	34
	(1.58)	(1.44)	(1.09)	(1.52)	(1.58)	(1.64)	(1.48)	(0.71)	(0.55)	(0.84)
[Cd$_3$(HL)Cl$_4$(H$_2$O)$_2$]	22	34	16	31	20	21	15	19	23	33
	(0.55)	(1.14)	(1.41)	(0.71)	(1.67)	(1.92)	(1.00)	(1.13)	(1.30)	(1.01)
DMSO	–	–	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–	–
Ampicillin (10 μg)	19	25	14	–	–	16	–	–	NT	NT
	0.84	0.84	1.14	–	–	1.14	–	–	–	–
Nystatine (30 μg)	NT	NT	NT	NT	NT	NT	NT	NT	18	20
	–	–	–	–	–	–	–	–	(0.55)	(1.79)
NiCl$_2$·6H$_2$O	19	19	23	25	26	20	19	18	29	12
	(0.55)	(1.00)	(1.48)	(0.55)	(0.86)	(1.11)	(0.90)	(0.89)	(1.14)	(0.59)
CoCl$_2$·6H$_2$O	24	22	14	24	31	18	21	16	28	12
	(0.85)	(0.89)	(0.91)	(0.58)	(0.52)	(0.84)	(0.85)	(1.30)	(1.14)	(0.55)
CuCl$_2$·2H$_2$O	28	39	26	24	36	24	20	25	25	34
	(1.14)	(0.84)	(0.89)	(1.30)	(0.88)	(0.84)	(1.17)	(0.51)	(0.89)	(1.30)
ZnCl$_2$·2H$_2$O	19	22	20	20	25	20	16	20	21	36
	(1.67)	(1.58)	(0.98)	(1.41)	(1.16)	(1.12)	(0.70)	(1.14)	(0.56)	(1.40)
CdCl$_2$·2H$_2$O	21	37	20	37	34	26	19	21	38	45
	(1.00)	(0.89)	(0.84)	(1.14)	(0.71)	(0.55)	(1.03)	(1.34)	(0.84)	(1.15)
HgCl$_2$·2H$_2$O	33	39	35	21	48	27	32	33	49	21
	(1.30)	(0.84)	(1.02)	(1.22)	(0.55)	(1.13)	(0.89)	(1.21)	(0.89)	(1.23)

[a] The result of five experiments; [b] Standard deviation in parentheses; A: *E. coli*, B: *B. subtilis*, C: *E. aerogenes*, D: *M. flavus*, E: *S. faecalis*, F: *S. aureus*, G: *P. aeruginosa*, H: *S. typhimurium*, I: *C. tropicalis*, J: *P. raciborskii*; NT: Not tested.

complexes with H_2L with a 3:1 metal–ligand ratio. Even when the ratio of the reactants was 1:1, the same product, $[Cd_3(HL)Cl_4(H_2O)_2]$, was formed.

Magnetic moments

The common features of the H_2L complexes are their insolubility which hinders solution spectral investigations. However, magnetic susceptibility measurements provide sufficient data to characterize the structures (Table 2). The mononuclear complex $[Ni(HL)_2]$ is diamagnetic as expected for a d^8 metal ion in a square-planar field [7, 12, 13, 18–20]. The magnetic moment of $[Co(HL)_2]$ at 20 °C is 1.97 B.M. When the magnetic moment of the trinuclear complex, $[Cu_3(HL)_2Cl_4]$, is calculated as per copper(II) the result is 1.56 B.M., comparable with values reported for slightly distorted tetrahedral and square-planar copper(II) complexes of *vic*-dioximes [7, 10, 18]. $[MCd_2(HL)_2Cl_4]$ ($M = Ni^{II}$ or Co^{II}) is diamagnetic whereas other heterotrinuclear complexes of H_2L are paramagnetic. The magnetic susceptibility results closely follow the spin-only formula calculated for a square-planar central metal ion and two tetrahedral coordinated one.

Antibacterial and antifungal activity

The antimicrobial activity of H_2L and its metal complexes are presented Table 3. The results reveal that H_2L had no antimicrobial activity but of which some metal complexes that were $[NiCd_2(HL)_2Cl_4]$, $[CoCd_2(HL)_2Cl_4]$, $[Hg(HL)Cl(H_2O)]$ and $[Cd_3(HL)Cl_4(H_2O)_2]$ showed high antimicrobial activities against all the test microorganisms. While $[Co(HL)_2]$, $[Cu_3(HL)_2Cl_4]$ and $[CoCu_2(HL)_2Cl_4]$ demonstrated antimicrobial activities on some microorganisms. $[NiCu_2(HL)_2Cl_4]$ and $[Zn(HL)Cl(H_2O)]$ had effect only on *M. flavus*.

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