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Biological studies of newly synthesized ferrocenyl complexes containing triazinone moiety

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A new ferrocenyl ligand, 1,1′-bis[1-methyl-5-phenyl-4H-(1,3,4)-thiadiazolo(2,3-c)(1,2,4)triazin-4-one]ferrocene was prepared from the reaction of 1,1′-diacetylferrocene with 4-amino-2,3-dihydro-6-phenyl-3-thioxo[1,2,4]triazin-5(4H)one. The ligand, L, forms 1 : 1 complexes with Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) in good yield. Characterization of the ligand and its complexes was carried out using IR, ^{1}H NMR, magnetic susceptibility as well as elemental analysis. Biological activity of the ligand and its complexes were carried out against *Aspergillus niger, Cladosporium herbirum* and *Fusarium moniliformae* using filter paper discs; and against bacterial strains of *Escherichia coli, Staphylococcus aureus* using viable cell counting technique. The results indicated that the ligand is biologically active whereas the complexes are more active than the ligand. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: diacetylferrocene; triazinone; complexes; characterization; magnetic properties biological activity

INTRODUCTION

The chemistry of ferrocene is currently receiving much attention associated with its increasing applications in catalysis,[1–3] the design of new nonlinear optics materials,[4,5] the preparation of biosensors[6,7] or the preparation of new biologically active compounds.[8–10] Ferrocene is often incorporated into some organic molecules in order to obtain new compounds which have higher biological activity.[11–14] A successful example is a ferrocene–chloroquine analogue, i.e. ferrochlroquine {FQ: 7-chloro-4[2-(*N*′,*N*′-dimethylaminomethyl)-*N*-ferrocenyl-methylamino]quinoline}, in which one ferrocene unit was incorporated into chloroquine (CQ).[15–17] *In vitro*, FQ has proved to be about 22 times more active than CQ against chloroquino-resistant strains of *Plasmodium falciparum* and shows higher activity *in vivo* in mice infected with *P. berghei* N and P. yoelii NS.[15–17]

Ferrocenyl compounds are incompatible with the other treatments owing to the high stability and non-toxicity of the ferrocenyl moiety. Accordingly, the potential to use ferrocenyl compounds as medicals and chemotherapy agents for the treatment of cancer has attracted many authors in the last two decades.[18–20] The best example of the ferrocenyl derivative is ferrocifen, which is biologically active against some types of cancer and expected to enter phase I clinical trials very soon.[18–21] On the other hand, (1,3,4)thiadiazolo(2,3-c)(1,2,4)triazin-4-one derivatives are well known for their significant biological activities.[22–24] Some thiadiazole derivatives have found application as antitumour agents, pesticides, dyes lubricants and herbicidal and analytical reagents.[25,26]

These interesting applications of the ferrocenyl and thiadiazolo-triazinone compounds attracted us to continue our previous studies[27–29] on the preparation of heterobimetallic complexes since some ferrocenyl complexes show more biological activity than the parent ligand. The aim of this article is to prepare and characterize a new ferrocenyl ligand derived from the reaction of 1,1′-diacetylferrocene with 4-amino-2,3-dihydro-6-phenyl-3-thioxo[1,2,4]triazin-5(4H)one. The study has been extended to prepare and characterize the Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) complexes with the mentioned ligand in order to obtain the heterobimetallic complexes. The prepared ligand and its complexes have been characterized by IR, ^{1}H NMR spectra as well as elemental analysis and magnetic

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susceptibility. These compounds contain a ferrocene unit and so they were evaluated for their biological activity against *Escherichia coli, Staphylococcus aureus, Aspergillus niger, Cladosporium herbirum* and *Fusarium moniliformae* using filter paper discs.

EXPERIMENTAL

All chemicals and solvents were obtained from Merck. The starting materials, 4-amino-2,3-dihydro-6-phenyl-3-thioxo[1,2,4]triazin-5(4H)one[30] and 1,1′-diacetylferrocene,[31] were prepared by the method described in the literature. The yields refer to analytically pure compounds and were not optimized. Melting points were taken on a capillary melting point apparatus and are uncorrected. ^{1}H NMR was recorded on a Varian Gemini spectrometer in DMSO as a solvent. IR spectra were recorded on a Pye–Unicam SP300 FT-IR spectrometer, using KBr pellets. Elemental analyses were determined at the microanalytical centre, Cairo University. Magnetic susceptibilities were measured at 20 °C by the Gouy method at the Faculty of Science, Cairo University.

Synthesis of the ligand L

1,1′-Diacetylferrocene (5.0 mmol) was dissolved in small amount of dry pyridine (30 ml) and slowly added to a solution of 4-amino-2,3-dihydro-6-phenyl-3-thioxo[1,2,4]triazin-5(4H) one (10.0 mmol dissolved in 30 ml pyridine). The mixture was refluxed with stirring for about 2 h. The color began to change from reddish brown to brown within 30 min and the reflux continued to 2 h. The brown product was filtered, washed with cold ethanol and recrystallized from DMF.

General procedure for the synthesis of the complexes

The different complexes were prepared by the addition of 2.0 mmol of the metal acetates dissolved in ca. 30 ml DMF, into a warmed solution of the ligand (2.0 mmol/l) in DMF (30 ml). The mixture was refluxed for 2.0 h. The complex, which separated out with cooling at 5 °C, was filtered, washed twice with cold ethanol and dried.

Materials and methods

Microorganisms and culture conditions

All strains of fungi and bacteria used in this study were obtained from the Northern Regional Research Laboratory (NRRL) and American Type Culture Collection (ATCC), and maintained as pure cultures. The fungi *Asergillus niger, Cladosporium herbarum* and *Fusarium moniliforme* were maintained on Czapek-Dox agar. The bacteria *Escherichia coli* and *Staphylococcus aureus* were maintained on nutrient agar.

Bioassay for antifungal activity

The susceptibilities of the test fungal spores (*Asergillus niger, Cladosporium herbarum* and *Fusarium moniliforme*) as seeded in Dox's medium on filter paper discs (6 mm diameter) soaked with 0.5 mg/ml of each sample (dissolved in 2-propanol), were determined.[32] The soaked and completely dried filter paper discs were placed on the surface of the seeded Dox medium in triplicate tests for each sample. Plates were allowed to stand for 2 h to allow diffusion. Then, the plates were incubated at 28 °C for 48 h, after which the susceptibility of each organism to each sample was estimated by measuring the diameter of the zones of inhibition.

Minimum inhibitory concentration of the antifungal samples

The minimum inhibitory concentrations (MICs) of the ligand and its complexes on *Asergillus niger, Cladosporium herbarum* and *Fusarium moniliforme* were determined by the dilution method described by Nair *et al*.[33]

Antibacterial assessment

Bactericidal activity was evaluated based on the killing rate by the viable cell counting technique according to the method described by Olurinola *et al*.[33]

Statistics

All measurements of the fungicidal activity are the means of three replicates; the results obtained were processed by analysis of variance and the significance was determined as the least significant difference (LSD) levels of 1 and 5%.

RESULTS AND DISCUSSION

Synthesis and characterization of the ligand

The ligand, L, was prepared first by reacting 1,1′-diacetylferrocene dissolved in a small amount of dry ethanol with two equimolar of the triazonone with reflux (Fig. 1). The reaction proceeded but the yield was low (ca. 22–26% referred to diacetylferrocene). By replacement of ethanol with pyridine as a solvent, the reaction proceeded well with increasing yield to reach 88–90% referred to diacetylferrocene. This high yield may be due to the basicity of the pyridine, which accelerates the ligand formation. The ligand was separated easily from the mother liquor and recrystallized using DMF as a solvent.

The ligand L was obtained from the reaction of 1,1′-diacetylferrocene with triazinone (1 : 2 molar ratio). The ligand was formed via the intermediate (i) in Fig. 1, which could not be separated from the reaction mixture. This is may be due to the high activity of SH group in triazinone ring. Thus it is suggested that the reaction of diacetylferrocene with 4-amino-2,3-dihydro-6-phenyl-3-thioxo[1,2,4]triazin-5(4H)one proceeded through two steps: the first is the condensation of the amino group of triazinone with C═O of diacetylferrocene to give (i) and the second is the addition of thiol group of triazinone to C═N as soon as it is formed with concurrent Michael-type addition.[26] All attempts to separate the intermediate were unsuccessful; presumably, such intermediate was converted under the conditions used to give the ligand L. The elemental analysis of the ligand is consistent with the calculated results (Table 1).

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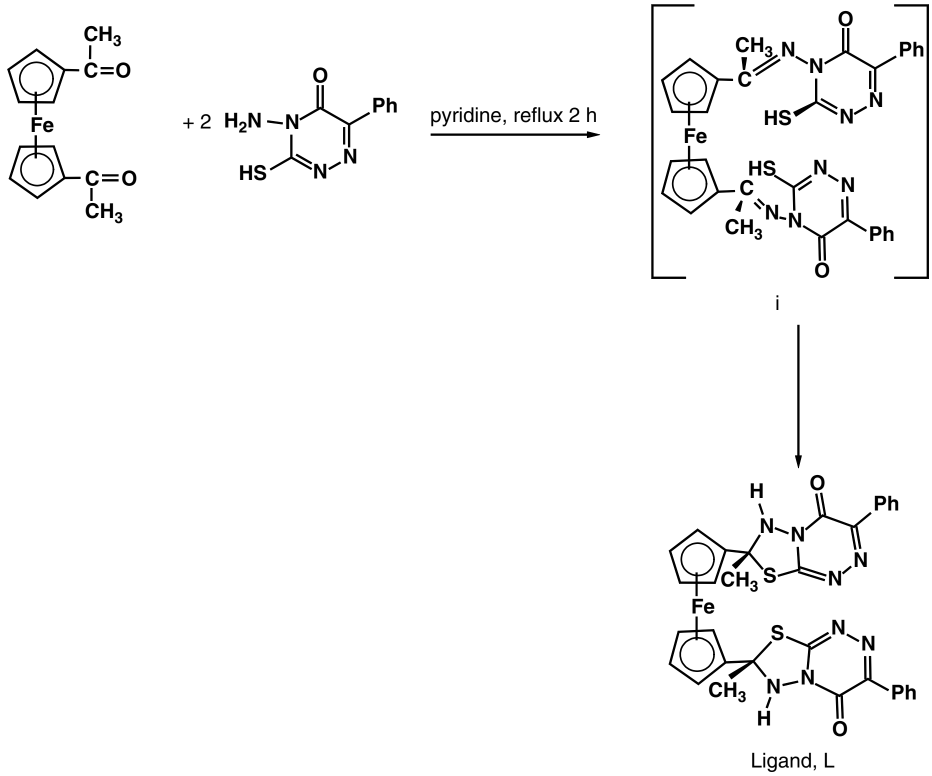


Figure 1. Preparation of the ligand.

Table 1. Physical and analytical data of the ligand and its complexes

Ligand/complex	Formula (F.W.)	Yield (%)	%C found (calcd)	%H found (calcd)	%N found (calcd)	Magnetic moment, μ_{eff}
L	$C_{32}H_{26}FeN_8O_2S_2$ (674.59)	89	56.71 (56.98)	3.69 (3.88)	16.93 (16.61)	dia
$Mn(L)(OAc)_2$	$C_{36}H_{32}FeMnN_8O_6S_2$ (847.62)	78	51.07 (51.01)	3.65 (3.81)	13.12 (13.22)	5.94
$Fe(L)(OAc)_3$	$C_{38}H_{35}Fe_2N_8O_8S_2$ (907.57)	76	50.39 (50.29)	3.74 (3.89)	12.28 (12.35)	5.82
$Co(L)(OAc)_2$	$C_{36}H_{32}CoFeN_8O_6S_2$ (851.61)	78	50.58 (50.77)	3.67 (3.79)	13.09 (13.16)	4.46
$Ni(L)(OAc)_2$	$C_{36}H_{32}FeN_8NiO_6S_2$ (851.37)	82	50.65 (50.79)	3.64 (3.79)	13.09 (13.16)	3.16
$Cu(L)(OAc)_2$	$C_{36}H_{32}CuFeN_8O_6S_2$ (856.23)	80	50.39 (50.50)	3.57 (3.77)	13.02 (13.09)	1.91
$Zn(L)(OAc)_2$	$C_{36}H_{32}FeN_8O_6S_2Zn$ (858.06)	76	50.53 (50.39)	3.85 (3.76)	13.00 (13.06)	dia

The ligand, L, was characterized using different spectroscopic tools. In IR spectra, it was found the new broad band centred at 3448/cm. This band was assigned to an N–H bond.[34] Also observed (Table 2) was a medium band at 860/cm, assigned to C–S–C (ring) stretching vibration.[27,35] No bands were found due to the C=N or SH groups, which confirmed the conversion of i to the ligand L. The characteristic peaks of the ferrocenyl moiety were appeared in the expected region. The band appearing at 1658/cm was assigned to C=O group in the triazinone moiety.

In the ^1H NMR spectra (Table 3), the absence was noticed of N–NH_2 and SH proton signals of the starting compound, which appeared at 5.2 and 10–12 ppm, respectively.[30] The spectra showed a broad band at 8.0 ppm, which was assigned to the N–H group (Fig. 1). The protons of the ferrocenyl moiety appeared as two multiplets at 4.36 and 4.49 ppm. These bands were assigned to the α- and β-protons for the substituted cyclopentadienyl rings.[36,37] The signal of the methyl group was observed at 1.12 ppm and the signals of the phenyl ring appeared in the expected region.

Synthesis and characterization of the complexes

The complexes of Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) ions were prepared easily and in good yield from the equimolar ratio of the ligand and the corresponding metal salts in DMF with reflux for 2 h (Fig. 2). All the complexes are deeply brown, and stable in air and light. They are slightly soluble in DMF and soluble in warm DMSO. The elemental

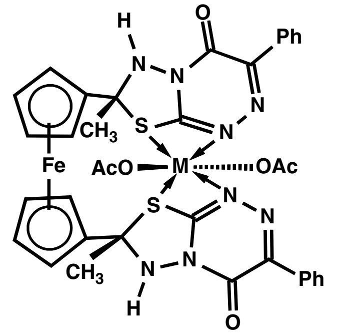
Table 2. The important IR spectral data of the ligand and its metal(II) complexes (ν/cm)

Ligand/complex	(N–H)	(C=O)	(Fc moiety)	C–S–C in ring	(M–O)	(M–S)	(M–N)
L	3448 br	1658 s	3047 m, 1438 w, 1099 m, 1005 m, 802 m, 466 m	860 m			
Mn(L)(OAc)$_2$	3425 br	1651 s	3051 m, 1434 w, 1095 m, 1004 m, 802 m, 470 m	850 m	468 m	563 w	455 w
Fe(L)(OAc)$_3$	3421 br	1658 s	3083 w, 1415 w, 1114 m, 1006 m, 817 m, 494 m	846 m	462 w	582 s	452 m
Co(L)(OAc)$_2$	3417 br	1658 s	3038 w, 1434 w, 1095 m, 1008 m, 810 m, 470 m	851 m	469 m	586 s	456 m
Ni(L)(OAc)$_2$	3422 br	1654 s	3048 w, 1433 w, 1110 m, 1009 m, 804 m, 480 m	853 m	472 m	594 s	447 m
Cu(L)(OAc)$_2$	3433 br	1658 s	3048 w, 1442 w, 1095 m, 1004 m, 806 m, 472 m	843 m		594 s	433 w
Zn(L)(OAc)$_2$	3417 br	1658 s	3049 w, 1434 w, 1103 m, 1016 m, 806 m, 470 m	849 m	469 w	578 s	420 w

Fc = ferrocene.

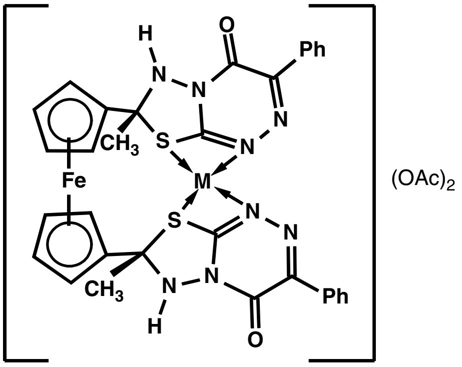
Table 3. ^{1}H NMR data of the ligand and its metal(II) complexes

Ligand/complex	^{1}H NMR (DMSO-d6), δ in ppm
L	1.12 (s, 6H, 2CH$_3$), 4.36 (m, 4H, C$_5$H$_4$), 4.49 (m, 4H, C$_5$H$_4$), 7.38–7.62 (m, 10H, ph), 8.0 (s, 2H, NH)
Mn(L)(OAc)$_2$	1.48 (s, 6H, 2CH$_3$), 4.39 (m, 4H, C$_5$H$_4$), 4.51 (m, 4H, C$_5$H$_4$), 7.33–7.57 (m, 10H, ph), 8.06 (s, 2H, NH)
Ni(L)(OAc)$_2$	1.66 (s, 6H, 2CH$_3$), 4.42 (m, 4H, C$_5$H$_4$), 4.51 (m, 4H, C$_5$H$_4$), 7.35–7.60 (m, 10H, ph), 8.08 (s, 2H, NH)
Cu(L)(OAc)$_2$	1.49 (s, 6H, 2CH$_3$), 4.42 (m, 4H, C$_5$H$_4$), 4.53 (m, 4H, C$_5$H$_4$), 7.32–7.57 (m, 10H, ph), 8.07 (s, 2H, NH)
Zn(L)(OAc)$_2$	1.74 (s, 6H, 2CH$_3$), 4.41 (m, 4H, C$_5$H$_4$), 4.52 (m, 4H, C$_5$H$_4$), 7.28–7.53 (m, 10H, ph), 8.11 (s, 2H, NH)



M = Mn(II), Fe(III), Co(II), Ni(II) and Zn(II)

Figure 2. Proposed structure of the octahedral complexes.



M = Cu(II)

Figure 3. Proposed structure of the Cu(II) complex.

analysis data of the ligand and its complexes are consistent with the calculated results from the empirical formula of each compound (Table 1).

The IR spectra of the free ligand and its metal complexes were recorded in KBr and are given with their assignments in Table 2. It was found that the characteristic band of the N–H bond in the free ligand at 3449/cm was shifted to a lower frequency to ca. 3420/cm in the complexes.[38] This shift indicates that the nitrogen atom coordinates to the metal ions in the complexes. The medium band at 860/cm, observed in the free ligand, was assigned to C–S–C (ring) stretching vibration.[28,35] This band shifted to lower values with 11–13/cm for all complexes, which indicates the involvement of the sulphur atom in the bonding with the metal ions.[28,35]

Further conclusive evidence of the coordination of the ligand with the metal ions was the appearance of new two weak bands at ca. 578 and 438/cm assigned to metal–sulfur (M–S) and metal–nitrogen (M–N) stretching, respectively. These new bands were observable only in the spectra of the metal complexes and not in the spectra of the ligand, thus confirming the participation of the sulfur and nitrogen atoms in the complexation.[39,40] In the low frequency region, a band was observed in the spectra of Mn(II), Fe(III), Co(II), Ni(II) and Zn(II) at ca. 468/cm, which was attributed to ν(M–O). This band suggested that the acetate group bonded directly with the Mn(II), Fe(III), Co(II), Ni(II) and Zn(II) complexes, forming octahedral structure (Fig. 2).[27] The later band was not found in the spectra of the Cu(II) complex, suggesting that it has square planar geometry of the Cu(II) complex (Fig. 3).[27]

The characteristic frequencies of the ferrocenyl moiety in the spectra of the ligands were observed at 3047, 1438, 1100, 1005, 802 and 466/cm. These bands were attributed to ν(C–H), ν(C=C), ν(C–C), δ(C–H), π(C–H) and δ(Fe-ring), respectively.[41,42] The corresponding frequencies of the complexes appeared at nearly the same position, which indicates that the ferrocenyl moiety is not directly coordinated to the Mn(II), Fe(III), Co(II), Ni(II) or Zn(II) ions.[41,42]

The ^{1}H NMR spectra of the complexes were recorded at room temperature using DMSO as a solvent (Table 3). The signal of the N–H group appeared at ca. 8.1 ppm in the complexes compared with 8.0 ppm in the ligand. These signals were shifted slightly downfield in the spectra of the complexes, which may be due to complexation of the sulfur and nitrogen atoms with the metal ions.[28,39,40] The spectra showed also two multiplets for the α- and β-protons for the substituted cyclopentadienyl rings appeared at ca. 4.40 and 4.51 ppm.[36] The signals of the methyl group was observed at ca. 1.56 ppm in the complexes. The other signals of the phenyl group appeared in the expected region.

The magnetic moments of the ligand and its complexes with Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) are given in Table 1. The magnetic moments were calculated from the corrected magnetic susceptibilities. The effective magnetic value (μ_{eff}) of the Co(II) complex was found to be 4.46 B.M., which suggested the octahedral geometry of the complex[43] (Fig. 2). Furthermore, the effective magnetic moment of the Ni(II) complex, 3.16 B.M., suggests the presence of two unpaired electrons in this complex. This result indicates that the Ni(II) complex may have an octahedral structure.[43] The magnetic moments of the Mn(II) and Fe(III) complexes are 5.94 and 5.82 B.M., respectively, which deviates slightly from the theoretical value for five unpaired electrons (5.92 B.M.). This value suggested that the Mn(II) and Fe(III) complexes may be high-spin six-coordinated (Fig. 2). On the other hand, the magnetic moment of the Cu(II) complexes was observed at 1.91 B.M. This value is consistent with the theoretical value of one unpaired electron. This result and the absence of a Cu–O band in the IR spectra suggested that the Cu(II) complex may have a square-planar structure (Fig. 3).[43]

On the basis of the different spectral data of the complexes discussed previously; and also by comparison the obtained results with others described in the literature,[27,28,37,43] one can conclude that the metal ions are bonded to the ligands via the nitrogen and sulfur atoms in all complexes. The Mn(II), Fe(III), Co(II), Ni(II) and Zn(II) complexes may have octahedral structure, whereas Cu(II) complex may have a square-planar geometry. Both structures are illustrated in Figs 2 and 3.

Antimicrobial properties

The ligand and its metal complexes were evaluated for their biological activity against the standard fungal strains of *Aspergillus niger*, *Cladosporium herbarum* and *Fusarium moniliforme* and against bacterial strains of *Escherichia coli* and *Staphylococcus aureus*. The compounds were tested at concentration of 0.5 mg/ml using the paper disc diffusion method.[28,33,37] The inhibition zones were measured in mm and the results are represented in Tables 4 and 5 for fungi and killing rate in Figs 4 and 5 for bacteria. The inhibition zones are the clear zones around the discs. It was found that the complexes have higher biological activity than the free ligand. The results show that the biological activity depends on the nature of the metal ion as well as the tested

Table 4. Antifungal activity data of the ligand and its complexes (inhibition zone diameter in mm)

Complex	A	B	C
L	17.4	15.3	20.1
$Mn(L)(OAc)_2$	23.6	20.3	26.0
$Fe(L)(OAc)_3$	17.6	16.7	21.2
$Co(L)(OAc)_2$	21.8	19.7	25.3
$Ni(L)(OAc)_2$	21.2	19.5	25.1
$Cu(L)(OAc)_2$	28.2	26.7	30.1
$Zn(L)(OAc)_2$	29.4	28.7	34.0
LSD 5%	1.3	1.6	1.4
1%	2.8	3.0	2.9

A = *Asergillus niger*, B = *Cladosporium herbarum* and C = *Fusarium moniliforme*; LSD = least significant difference.

Table 5. The minimum inhibitory concentration of the ligand and its complexes on the tested fungi (μg/ml)

Complex	A	B	C
L	125	100	75
$Mn(L)(OAc)_2$	25.0	25.0	5.0
$Fe(L)(OAc)_3$	50.0	25.0	10.0
$Co(L)(OAc)_2$	40.0	20.0	8.0
$Ni(L)(OAc)_2$	40.0	20.0	10.0
$Cu(L)(OAc)_2$	10.0	5.0	2.0
$Zn(L)(OAc)_2$	10.0	10.0	5.0
LSD 5%	1.3	1.6	1.4
1%	2.7	2.9	2.8

A = *Asergillus niger*, B = *Cladosporium herbarum* and C = *Fusarium moniliforme*; LSD = least significant difference.

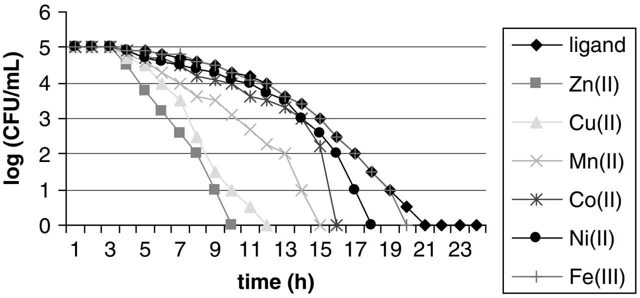


Figure 4. Viable cell number of *E. coli* as a function of time of the ligand and its complexes.

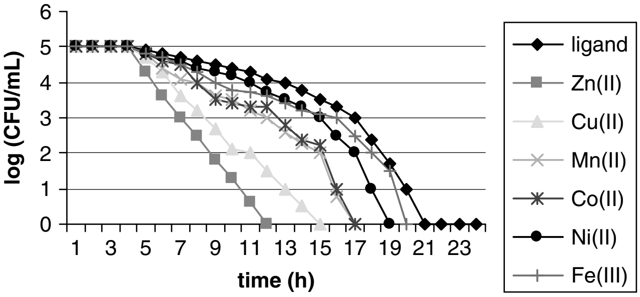


Figure 5. Viable cell number of *S. aureus* as a function of time of the ligand and its complexes.

fungi and bacteria. An increase in the biocidal activity of the ligand as a consequence of coordination with the metal ions was observed in terms of MIC values, as shown in Table 5. The results revealed also that the trend of growth inhibition of the complexes in the order: Zn(II) > Cu(II)> Mn(II) > Co(II) > Ni(II) > Fe(III). It is known[27,28,37] that the complexation tends to make the ligands more powerful and potent bactericidal agents, thus killing more of the bacteria than the parent ligand. A possible explanation is that the positive charge of the metal is partially shared with the donor atoms present in the ligands and there is π-electron delocalization over the whole chelated ring.[27,28,37] This, in turn, increases the lipophilic character of the metal complex and favors its permeation through the lipoid layers of the microorganism membranes. Furthermore, other factors, such as solubility, conductivity and dipole moment (influenced by the presence of metal ions) may also be possible reasons for this increasing in activity.[27,28,37] On the other hand, the inhibition of the growth of the microorganisms may be due to the inhibition of the glucose uptake,[44] inhibition of RNA and protein synthesis.[45] This result revealed that the metal complexes induced bacterial cell death, as shown in Figs 4 and 5.

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