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Spectroscopic studies and biological activity of some transition metal complexes of unusual Schiff base

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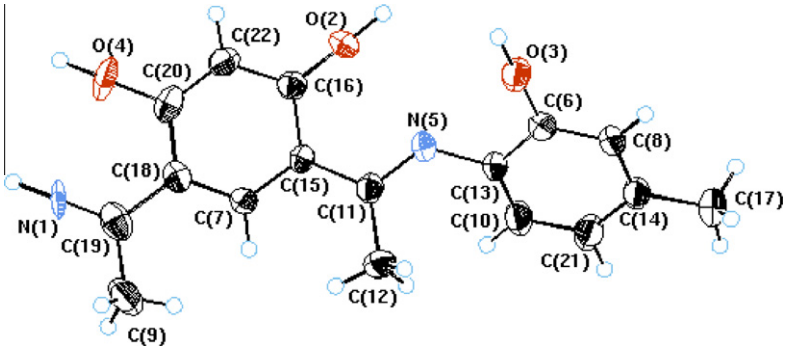
HIGHLIGHTS

- Synthesis and analysis of unusual Schiff base from a macrocycle Schiff base (**L**).
- Synthesis and spectroscopic of some transition metal complexes derived from **L**.
- Crystal structure of **L** was determined through X-ray single crystal analysis.
- Biological activity of **L** and complexes against bacteria and fungus were screened.
- Cytotoxicity of $[Pt^{II}L(Cl)_2]$ complex was checked as an antitumor agent.

GRAPHICAL ABSTRACT

Unusual Schiff base ligand, 4-ethanimidoyl-6-[(1*E*)-N-(2-hydroxy-4-methylphenyl)ethanimidoyl]benzene-1,3-diol, **L**, was synthesized via catalytic process. Some transition metal derivatives were also synthesized from the corresponding metal species with **L**. The biological activities of **L** and metal complexes were screened.



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ABSTRACT

Unusual Schiff base ligand, 4-ethanimidoyl-6-[(1*E*)-N-(2-hydroxy-4-methylphenyl)ethanimidoyl] benzene-1,3-diol, **L**, was synthesized via catalytic process involving the interaction of some metal ions with a macrocyclic Schiff base (**MSB**). The transition metal derivatives $[ML(H_2O)_4](NO_3)_3$, M = Cr(III) and Fe(III), $[NiL(H_2O)_4](NO_3)_2$, $[ML(H_2O)_2](NO_3)_2$, M = Zn(II) and Cd(II), $[Cl_2Pd(\mu\text{-}Cl)_2PdL]$, $[PtL(Cl)_2]$ and $[PtL(Cl)_4]$ were also synthesized from the corresponding metal species with **L**. The Schiff bases and complexes were characterized by elemental analysis, mass spectrometry, IR and ^{1}H NMR spectroscopy. The crystal structure of **L** was determined by X-ray analysis. The spectroscopic studies revealed a variety of structure arrangements for the complexes. The biological activities of **L** and metal complexes against the *Escherchia coli* as Gram-negative bacteria and *Staphylococcus aureus* as Gram-positive bacteria, and the two fungus *Aspergillus flavus* and *Candida albicans* were screened. The cytotoxicity of $[PtL(Cl)_2]$ complex, a *cis*-platin analogous, was checked as an antitumor agent on two breast cancer cell lines (MCF7 and T47D) and human liver carcinoma cell line (HepG2).

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Introduction

Coordination chemistry of macrocyclic ligands has shown to be interesting subject of current research in the last two decades [1,2]. Importance in designing new macrocyclic ligands arises mainly from their use as models for protein-metal binding sites in a substantial array of metalloproteins in biological systems, such as the synthetic ionophores, models for the magnetic exchange phenomena, therapeutic reagents in chelate therapy for treatment of metal intoxication and the cyclic antibiotics that retain their antibiotic actions to specific metal complexation [3–6]. On the other hand, the synthesis of binuclear complexes in which a ligand structure accommodates two metal centers in close proximity but in a different compartments separated by an intervening group represents important criteria in the study of transition-metal systems. In such molecularly designed ligands, the aromatic rings are expected to act as a bridge and a rigid separator between the two compartments. The interest in these complexes corresponds to their ability to serve as simple models for multi-metal-centered catalysts [7,8]. From these types of ligands, the macrocyclic Schiff bases exhibited great importance in macrocyclic chemistry because they can selectively chelate certain metal ions depending on the number, type and position of their donor atoms, the ionic radii of the metal centers, and the coordinating property of the counter ions [9]. Thus, the coordination chemistry of these macrocyclic Schiff bases was appeared in many recent reports due to their important applications [2,10–12].

In this article, we report the synthesis of a molecularly designed macrocyclic Schiff base (4,6-di[(1*E*)-N-(2-hydroxy-4-methylphenyl)-ethanimidoyl]benzene-1,3-diol). Interaction of this compound with different transition metal species showed unusual catalytic process to yield the unusual ligand 4-ethanimidoyl-6-[(1*E*)-N-(2-hydroxy-4-methylphenyl)ethanimidoyl]benzene-1,3-diol, **L**, Scheme 1. The synthesis and spectroscopic studies of some transition metal complexes of that unusual ligand are also reported.

Experimental

Reagents

4,6-Diacetylresorcinol, 2-amino-5-methylphenol and the transition metal salts were purchased from Aldrich. All the solvents were of analytical reagent grade and were purified by standard methods.

Instruments

IR measurements (KBr pellets) were carried out on a Unicam–Mattson 1000 FT-IR spectrometer. NMR measurements were performed on a Spectrospin–Bruker 300 MHz spectrometer. Samples were dissolved in $(CD_3)_2SO$ and TMS was used as an internal reference. Thermogravimetric analysis measurements were carried out under N_2 atmosphere at a heating rate of 10 °C/min using a Shimadzu DT-50 thermal instrument. Elemental analyses were performed on Perkin–Elmer 2400 CHN elemental analyzer. Mass spectrometry measurements of the solid complexes (70 eV, EI) were carried out on a Finnigan MAT SSQ 7000 spectrometer.

Preparation of Schiff bases

*Preparation of 4,6-di[(1E)-N-(2-hydroxy-4-methylphenyl)-ethanimidoyl]-benzene-1,3-diol (**MSB**)*

Solutions of 4,6-diacetylresorcinol and 2-amino-5-methylphenol in absolute ethanol with molar ratio 1:2 were mixed together and heated to reflux for 1 h. The reaction mixture was then cooled and the formed yellow precipitate was isolated by filtration. The crude was recrystallized from hot ethanol to give yellow fine crystals. The compound was left to dry under vacuum for several hours (yield 86%).

*Preparation of 4-ethanimidoyl-6-[(1E)-N-(2-hydroxy-4-methylphenyl)ethanimidoyl]-benzene-1,3-diol (**L**)*

A mixture of **MSB** and $FeCl_3$ (1:1 mol ratio) in absolute ethanol was heated to reflux for 5 min and then left to stand at room temperature for few hours. The formed yellow residue was separated by filtration. The compound was recrystallized from hot ethanol to give yellow crystals. The crystals were left to dry under vacuum for several hours (yield 42%).

Preparation of complexes

A mixture of metal ion salt and 4-ethanimidoyl-6-[(1*E*)-N-(2-hydroxy-4-methylphenyl) ethanimidoyl]benzene-1,3-diol ligand (1:1 M ratio) in about 30 cm^3 aqueous ethanol was heated to reflux with stirring for *ca.* 2 h. The reaction mixture was cooled and solid complexes were separated by slow evaporation. The isolated complexes were recrystallized from hot ethanol (yield 68–79%). Table 1 gives the elemental analysis and mass spectrometry data for the Schiff bases and complexes.

Biological activity

In vitro antibacterial and antifungal activity of the ligand and the synthesized complexes were tested against the two bacteria: *Escherchia coli* as Gram-negative bacteria and *Staphylococcus aureus* as Gram-positive bacteria, and the two fungus: *Aspergillus flavus* and *Candida albicans*. The tests were carried out using paper disc diffusion method. The nutrient agar medium (peptone, beef extract, NaCl and agar-agar) and 5 mm diameter paper discs of Whatman No.1 were used. The test compound was dissolved in DMSO in 0.1–0.4% concentrations. The paper discs was soaked in different solutions of the compound, dried and placed in the Petri plates (9 cm diameter) previously seeded with the test organisms. The plates were incubated for 24–30 h at 27 ± 1 °C and the inhibition zones (mm) were measured around each disc. As the organism grows, except in the region where the concentration of antibacterial agent was above the minimum inhibitory concentration and a zone of inhibition was seen. The size of the inhibition zone depends upon the culture medium, incubation conditions, rate of diffusion and the concentration of the antibacterial agent. Comparison of the obtained data was carried out with the two standards: tetracycline antibacterial agent and Amphotericin B antifungal agent.

Cytotoxicity determination

Three human cancer cell lines were used for *in vitro* screening experiments: two breast cancer cell lines (MCF7 and T47D) and human liver carcinoma cell line (HepG2). The cancer cells were obtained frozen in liquid nitrogen (−180 °C) from the American Type Culture Collection. The tumor cell lines were maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing. Cell culture cytotoxicity assays were carried out as described in literature [13]. RPMI-1640 medium (Sigma Chemical Co., St. Louis, Mo, and USA) was used for culturing and maintenance of the human tumor cell lines. Cells were seeded in 96-well microliter plates at a concentration of 5×10^4–10^5 cell/well in a fresh medium and left to attach to the plates for 24 h. Growth inhibition of cells was calculated spectrophotometrically using a standard method with the protein-binding dye sulforhodamine B (SRB) [14]. The optical density (OD) of each well was measured at 564 nm with an ELIZA

microplate reader (Meter Tech. Σ 960, USA). The sensitivity of the human tumor cell lines to thymoquinone was determined by the SRB assay. The percentage of cell survival was calculated as follows:

Survival fraction = OD(treated cells)/OD(control cells)

The IC_{50} value is the concentration of thymoquinone required to produce 50% inhibition of cell growth. The results are compared with a similar run of *cis*-platin as an antitumor compound.

X-ray structure determination

All X-ray measurements were made at room temperature using suitable crystals for data collection. Accurate lattice parameters were determined from least squares refinements of well-centered reflections in the ranges $2.91 \leqslant \theta \leqslant 27.49$ for the compound. During data collection, three standard reflections were periodically observed and showed no significant intensity variations. The ranges of h, k and l are $0 \leqslant h \leqslant 14$; $0 \leqslant k \leqslant 12$ and $-17 \leqslant l \leqslant 16$. 5456 unique reflections were measured of which 2018 had $I > 3{:}00\sigma(I)$. These observed reflections were used for structure determination and refinements. All Diagrams and calculations were performed using maXus crystallographic software package (Nonius, Delft & MacScience, Japan). The structure was determined by direct methods SIR 92 [15] and refined by full matrix least-squares methods maXus [16]. The displacement factors of non-hydrogen atoms of the compound were refined with anisotropic thermal parameters. The hydrogen atoms were refined isotropically. The function minimized was $[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{½}$ with $w = 1/\delta^2(F_o)^2 + 0.0300(F_o)^2$. The final R and R_w values are given in Table 3.

Results and discussion

The Schiff base 4,6-di[(1*E*)-N-(2-hydroxy-4-methyl-phenyl)-ethanimidoyl]benzene-1,3-diol was prepared by the condensation reaction of 4,6-diacetylresorcinol and 2-amino-5-methylphenol in 1–2 M ratio (Scheme 1). This Schiff base was molecularly designed to be used as a bicompartment ligand. The IR spectrum of the compound showed characteristic stretching frequencies due to the functional groups, Table 2 [17]. Also, the presence of the OH groups was confirmed by ^{1}H NMR (Table 2). Direct interaction of this Schiff base with some transition metal species such as Fe(III), Ni(II)

Table 1
Elemental analysis and mass spectrometry data of the Schiff bases and complexes.

Complex	Elemental analysis found (calc.)				Mass spectrometry	
	C	H	N	Cl	M.M.	*m*/*z*
MSB	71.20 (71.27)	6.03 (5.98)	6.88 (6.92)	–	404.47	388
L	68.38 (68.44)	6.12 (6.08)	9.30 (9.39)	–	298.34	299
$[CrL(H_2O)_4](NO_3)_3$	33.56 (33.53)	4.35 (4.31)	11.48 (11.51)	–	608.41	547, 549, 552
$[FeL(H_2O)_4](NO_3)_3$	33.31 (33.35)	4.32 (4.28)	11.40 (11.44)	–	612.27	551, 553
$[NiL(H_2O)_4](NO_3)_2$	36.83 (36.92)	4.85 (4.74)	10.05 (10.13)	–	553.11	491, 492, 493
$[ZnL(H_2O)_2](NO_3)_2$	38.91 (38.98)	4.31 (4.23)	10.62 (10.70)	–	523.77	460, 462, 463
$[Cl_2Pd(\mu\text{-}Cl)_2PdL]$	31.22 (31.27)	2.84 (2.78)	4.22 (4.29)	21.63 (21.72)	652.95	648, 649, 652
$[CdL(H_2O)_2](NO_3)_2$	35.69 (35.77)	4.32 (4.23)	9.73 (9.82)	–	570.79	549, 550, 552
$[PtL(Cl)_2]$	36.10 (36.18)	3.35 (3.22)	4.91 (4.96)	12.50 (12.57)	564.34	562, 563, 564, 565
$[PtL(Cl)_4]$	32.06 (32.14)	2.84 (2.78)	4.19 (4.29)	22.27 (22.32)	635.24	634, 635, 636, 638, 641

Table 2
IR and NMR data of the Schiff bases and complexes.

Compound	IR data (cm^{-1})				^{1}H NMR data (ppm)
	υ(OH)	υ(NH)	υ(C=N)	υ(C=C)	
MSB	3379 (m) 3310 (m)	–	1615 (sh) 1593 (vs)	1530 (vs) 1460 (s) 1433 (s)	12.70 (s, 2 H, OH), 9.46 (s, 2 H, OH), 8.41, 8.25 (d, 2 H, Ph), 6.88–6.1 (m, 6 H, Ph), 2.40 (s)–2.08 (s, 12 H, CH_3)
L	3431 (b)	3069 (m)	1636 (s) 1611 (s) 1592 (s)	1536 (s) 1463 (m) 1435 (m)	17.21 (s, 1H, C=NH), 12.72 (s, 1 H, OH), 9.71 (d, 2 H, OH), 8.26 (d, 2 H, Ph), 6.89–6.20 (m, 3 H, Ph), 2.65–2.25 (m, 9 H, CH_3)
$[CrL(H_2O)_4](NO_3)_3$	3319 (b)	2925 (m)	1603 (m)	1519 (s)	–
$[FeL(H_2O)_4](NO_3)_3$	3388 (vs) 3209 (s)	2928 (m)	1617 (s)	1542 (s) 1404 (s)	–
$[NiL(H_2O)_4](NO_3)_2$	3426 (vs)	2923 (m)	1628 (s)	1417 (m)	–
$[ZnL(H_2O)_2](NO_3)_2$	3398 (m) 3291 (m) 3162 (m)	3028 (m)	1692 (m) 1623 (s)	1528 (m) 1484 (m) 1440 (m)	12.48 (bs, 1 H, OH), 10.23 (bs, 2 H, OH), 8.41 (bs, 2 H, OH), 7.11–6.35 (m, 5 H, Ph), 1.35–1.03 (m, 9 H, CH_3)
$[Cl_2Pd(\mu\text{-}Cl)_2PdL]$	3399 (vs)	3196 (vs)	1616 (s) 1565 (m)	1499 (m) 1424 (s)	12.33 (bs, 1 H, OH), 10.15 (bs, 2 H, OH), 8.80 (bs, 2 H, OH), 7.30–6.59 (m, 5 H, Ph), 1.32–1.27 (m, 9 H, CH_3)
$[CdL(H_2O)_2](NO_3)_2$	3510 (b)	3075 (w) 2928 (w)	1612 (m)	1594 (m) 1531 (m) 1491 (m)	12.45 (bs, 1 H, OH), 10.20 (bs, 2 H, OH), 8.37 (bs, 2 H, OH), 7.10–6.10 (m, 5 H, Ph), 1.25–1.06 (m, 9 H, CH_3)
$[PtL(Cl)_2]$	3427 (b)	2927 (w)	1627 (m)	1500 (m) 1428 (m)	12.42 (bs, 1 H, OH), 10.15 (bs, 2 H, OH), 8.02 (bs, 2 H, OH), 7.31–6.18 (m, 5 H, Ph), 1.71–1.06 (m, 9 H, CH_3)
$[PtL(Cl)_4]$	3216 (m)	3076 (m)	1654 (s)	1587 (s) 1488 (m) 1425 (sh)	12.48 (bs, 1 H, OH), 10.22 (bs, 2 H, OH), 8.14 (bs, 2 H, OH), 7.27–6.37 (m, 5 H, Ph), 1.33–1.26 (m, 9 H, CH_3)

and Pd(II) in ethanol exhibited a catalytic process to give the unusual Schiff base, 4-ethanimidoyl-6-[(1*E*)-N-(2-hydroxy-4-methylphenyl)ethanimidoyl]-benzene-1,3-diol, **L** (Scheme 1). Due to the expected unusual structure arrangement of this Schiff base with a free azomethine group, C=NH, the crystal structure was determined by X-ray analysis. The crystallographic data are presented in Table 3. The ORTEP representation of the compound is illustrated in Fig. 1. Selected bond lengths and angles are given in Table 4. The crystal analysis revealed that the compound crystallized in the monoclinic space group $P2_1/c$ with a Z value of 4. From the structural analysis of the compound (Fig. 1), it can be noted that it is totally unsymmetrical having the point group C_s. The fragments N1—C19—C18 and N1—C19—C9 are planar which revealed the sp^2 hybridization of the N1, C19 and C18 atoms. The bond angles between these atoms lie in the range of 120° (Table 4). Also, the bond angle C19—N1—H1 of the free azomethine is linear (179.9°). Furthermore, the bond length of C19—N1 is 1.212 Å, which is shorter than the normal single C—N bond, indicated the presence of double bond character [18,19]. The bond lengths in the other azomethine (C11—N5—C13) showed the presence of conjugation between the C—N bonds and the two phenyl groups attached to the group (1.431 and 1.324 Å). The X-ray analysis of **L** also showed that it contains three OH groups attached to the phenyl rings. Interestingly, the C—O bond length of the OH group attached to the position *para* to the C=N—H group (C16—O2 = 1.281 Å) is shorter than the other C—O bonds (C6—O3 = 1.355 Å and C20—O4 = 1.339 Å). The content of one unit cell (Fig. 2) showed that the dihydroxy phenyl moieties of every two molecules are located in opposite faces and are parallel. This could be due to a charge transfer between every two moieties with π–π* type of interaction [20].

According to the unusual structure of the ligand **L**, it was expected that its transition metal complexes may have unique chemical and structure features. Therefore, we have prompted to carry out the interaction of some transition metal ions *ca.* Cr(III), Fe(III), Ni(II), Zn(II), Pd(II), Cd(II), Pt(II) and Pt(IV) with the **L**, 1:1 M ratio, in aqueous ethanol solutions. A variety of complexes were isolated; mainly: $[ML(H_2O)_4](NO_3)_3$, M = Cr(III) and Fe(III), $[NiL(H_2O)_4](NO_3)_2$, $[ML(H_2O)_2](NO_3)_2$, M = Zn(II) and Cd(II), $[Cl_2$-

Table 3
The crystal structure parameters for the ligand **L**.

Crystal parameters	
Empirical formula	$C_{17}H_{18}N_2O_3$
Fw	298.34
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	11.4842 (3)
b (Å)	9.7771 (3)
c (Å)	13.1498 (4)
α (°)	90.00°
β (°)	99.988 (2)°
γ (°)	90.00°
V (Å)	1454.11 (7)
Z	4
T/K	298
ρ_{calc} (g cm^{-3})	1.363
μ (cm^{-1})	0.09
R[a]	0.087
R_w[b]	0.178
(Mo $K\alpha$) Å	0.71073

[a] $R = \Sigma[|F_o| - |F_o|\Sigma|F_o|]$.
[b] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$; $w = 1/\delta^2(F_o)^2 + 0.0300\ (F_o)^2$.

Table 4
Selected bond lengths (Å) and bond angles (°) for the ligand **L**.

Bond lengths (Å)					
N1—C19	1.212 (5)	C7—C18	1.382 (5)	C18—C20	1.441 (6)
O2—C16	1.281 (4)	C8—C14	1.370 (5)	C20—C22	1.353 (5)
O3—C6	1.355 (4)	C11—C12	1.514 (5)	C9—C19	1.514 (7)
O4—C20	1.339 (5)	C11—C15	1.438 (5)	C10—C13	1.382 (5)
N5—C11	1.324 (5)	C14—C17	1.505 (6)	C10—C21	1.382 (6)
N5—C13	1.431 (5)	C14—C21	1.410 (5)	N1—H1	0.960 (3)
C6—C8	1.392 (5)	C15—C16	1.455 (5)	O2—H2	0.960 (2)
C6—C13	1.400 (5)	C16—C22	1.415 (6)	O3—H3	0.960 (3)
C7—C15	1.396 (5)	C18—C19	1.469 (5)	O4—H4	0.960 (3)
Bond angles (°)					
C11—N5—C13	127.2 (3)	O4—C20—C18	119.3 (3)	C6—O3—H3	179.9 (9)
O3—C6—C8	123.3 (3)	C6—C8—C14	121.4 (3)	O4—C20—C22	119.5 (4)
O3—C6—C13	117.4 (3)	C13—C10—C21	120.7 (3)	C20—O4—H4	179.6 (3)
C8—C6—C13	119.3 (3)	N5—C11—C12	120.4 (3)	N5—C13—C6	117.4 (3)
C15—C7—C18	123.4 (3)	N5—C11—C15	118.2 (3)	N5—C13—C10	122.7 (3)
N1—C19—C9	119.9 (4)	C12—C11—C15	121.5 (3)	C6—C13—C10	119.6 (3)
N1—C19—C18	121.3 (4)	C19—N1—H1	179.9 (7)	C8—C14—C17	121.1 (3)
C9—C19—C18	118.8 (4)	C16—O2—H2	180.0 (2)	C8—C14—C21	119.0 (4)

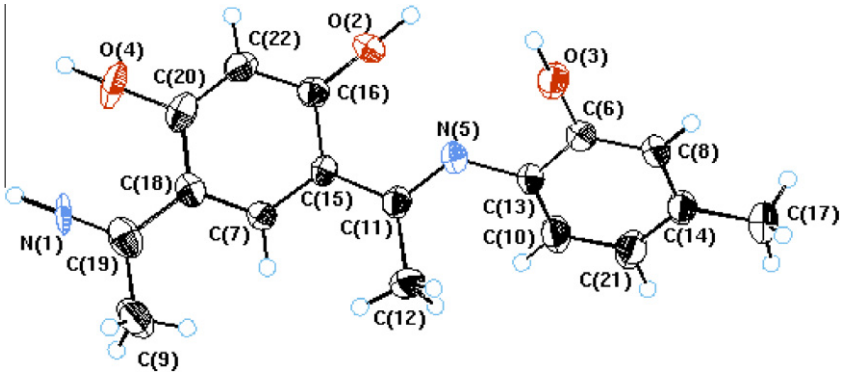

Fig. 1. The ORTEP projection of **L**.

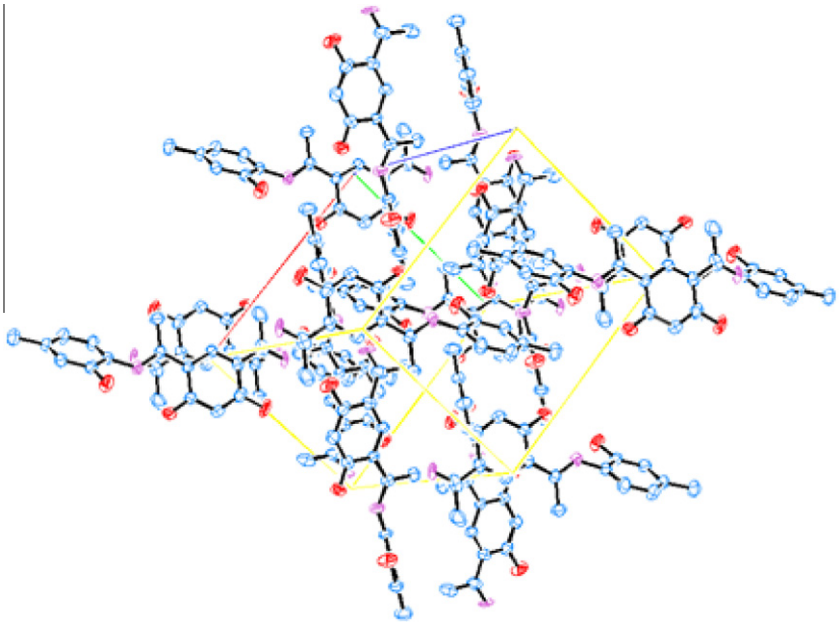

Fig. 2. The unit cell packing of **L**. Hydrogen atoms are omitted for clearance.

$Pd(\mu\text{-}Cl)_2PdL]$, $[PtL(Cl)_2]$ and $[PtL(Cl)_4]$. Table 1 gives the elemental analysis and mass spectrometry data of the complexes. The fragmentation patterns in the mass spectra of the complexes as well as the elemental analysis data revealed the correctness of the suggested molecular formula. The numbers of water molecules in the complexes were determined using the thermogravimetry (TG) technique. The electrical molar conductance in DMSO at room temperature for the Pd and Pt complexes lies in the 23–36 μS range, which indicates that these complexes are nonelectrolytes. The other complexes showed higher molar conductance due to their electrolytic characteristics.

The IR spectrum of **L** showed characteristic bands corresponding to the υ(OH), υ(NH), υ(C═N) and υ(C═C) functional groups in the compound [17]. The IR spectra of the complexes also exhibited the characteristic bands of the ligand with the corresponding shifts due to complex formation (Table 2). In addition, the IR spectra of the chromium, iron, nickel, zinc and cadmium complexes displayed a broad band in the range 3510–3320 cm^{-1}, which can be ascribed to the stretching vibrations of water molecules coordinated to the metal ion in consistent with the elemental and thermal analyses. Furthermore, all the spectra showed non-ligand bands in the range 651–419 cm^{-1} corresponding to the stretching frequencies of M—O and M—N bonds [21–23]. The appearance of the υ(NH) in all the IR spectra of the complexes indicated that the free azomethine (C═NH) group was not involved in the coordination. The ^1H NMR spectra of the diamagnetic complexes ($[ZnL(H_2O)_2](NO_3)_2$, $[Cl_2Pd(\mu\text{-}Cl)_2PdL]$, $[CdL(H_2O)_2](NO_3)_2$, $[PtL(Cl)_2]$ and $[PtL(Cl)_4]$) gave more insight on the structure of the complexes. All the spectra displayed signals due to the protons of OH, phenyl and methyl groups with the corresponding shifts due to complex formation (Table 2). Interestingly, the signal due the C═NH group (17.21 ppm) disappeared from all the spectra of the complexes probably due to their involvement in intermolecular hydrogen bonding. From the spectroscopic data, it can be concluded that the ligand acted as a bidentate through the two donor sites CH_3C═N and adjacent OH group. It is worth to mention that the OH group coordinated without proton displacement in consistent with ^1H NMR data. Therefore, according to the elemental analysis and the spectroscopic studies, the complexes may have the proposed structures shown in Scheme 2.

Antibacterial and antifungal activity

The free ligand and its respective metal complexes were screened against the *E. coli* as Gram-negative bacteria and *S. aureus* as Gram-positive bacteria, and the two fungus *A. flavus* and *C. albicans* to assess their potential activity relative to the two standards: Tetracycline antibacterial agent and Amphotericin B antifungal agent, Fig. 3. The data showed that the free ligand has the capacity of inhibiting the metabolic growth of the investigated bacteria and one of the fungus to different extents, which may indicate broad-spectrum properties. The activity of this compound may be arising from the benzene diol and free azomethine moieties. The mode of action may involve the formation of hydrogen bonding between the OH and C═NH groups and the active centers of the cell constituents, resulting in interference with the normal cell process [24]. All the tested metal complexes showed activity against both *E. coli* and *S. aureus*. However, although the complexes showed promising activities against the two bacteria, their activities were less than the standard Tetracycline. On the other hand, only the three complexes $[NiL(H_2O)_4](NO_3)_2$, $[Cl_2Pd(\mu\text{-}Cl)_2PdL]$ and $[PtL(Cl)_2]$ showed antifungal activities against the tested fungus, while the other tested complexes were inactive. It is important to point out that nickel complex is more toxic against the *C. albicans* fungus, while palladium complex is more toxic against the *A. flavus* fungus compared to the standard Amphotericin B antifungal agent (Fig. 3). The antibacterial data revealed that the $[Cl_2Pd(\mu\text{-}Cl)_2PdL]$ and $[PtL(Cl)_2]$ complexes are more bioactive than the free ligand. The enhanced activity of the metal complexes may be retained to the increased lipophilic nature of the complexes which arose from the chelation. It was also noted that the toxicity of the metal complexes increases on increasing the metal ion concentration. This elevation is probably due to faster diffusion of the chelates as a whole through the cell membrane. The chelated metal may block the enzymatic activity of the cell or it may catalyze the toxic reactions among cellular constituents.

Cytotoxicity of $[PtL(Cl)_2]$ complex

To evaluate the potential usefulness of the reported platinum complex (*cis*-platin analogous) as antitumor agent, three human

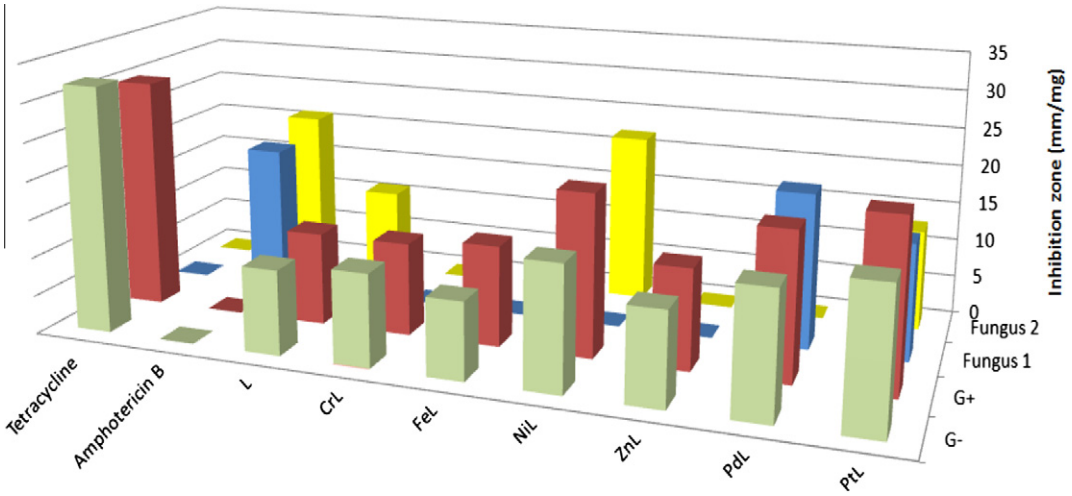

Fig. 3. *In vitro* antibacterial and antifungal activities of the ligand and the reported complexes. (G^-): Gram-negative *Escherchia coli* bacteria; (G^+): Gram-positive *Staphylococcus aureus* bacteria; fungus1: *Aspergillus flavus*; fungus2: *Candida albicans*.

cell lines (two breast cancer cell lines, MCF7 and T47D, and liver carcinoma cell line, HepG2) were treated by the compound and compared with *cis*-platin. The complex showed promising activity against the studied cell lines. The IC_{50} value (the concentration that produce 50% inhibition of cell growth) of $[PtL(Cl)_2]$ and *cis*-platin were determined. The IC_{50} values of the reported platinum complex were found to be: MCF7 (12.2 μg/ml, 21.6 μM), T47D (19.4 μg/ml, 34.4 μM) and HepG2 (20.7 μg/ml, 36.7 μM). According to the IC_{50} values, the $[PtL(Cl)_2]$ complex is, thus, considered as weak anticancer drug compared to *cis*-platin (11.9–9.9 μM) [25]. However, the validity of $[PtL(Cl)_2]$ complex as an anticancer drug requires further investigation such as *in vivo* study on the effect of the compound on Ehrlich solid carcinoma induced in mice including the study of tumor growth, apoptosis/necrosis ratio, hematological profile, liver and kidney functions and histological examination of the tumor cells and some organs.

Conclusion

Interaction of a macrocyclic Schiff base with some metal ions resulted in fragmentation of the compound to give unusual Schiff base with a free azomethine group. The spectroscopic studies of transition metal complexes of the latter Schiff base revealed unique structural arrangements.

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Appendix A. Supplementary material

Supplementary crystallographic data (Atomic positional parameters, all bond lengths and angles, anisotropic temperature factors and the calculated and observed structure factors) are available from the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK on request, deposition number: CCDC 821862. Schemes 1 and 2 are deposited as journal supplementary data. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2012.12.008.

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