Journal of the Serbian Chemical Society
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J. Serb. Chem. Soc. 74 (5) 537–548 (2009)
JSCS–3853

UDC 547.53'56+546.3–386:615.281–188
Original scientific paper

Preparation, characterization and antibacterial effect of 2-methoxy-6-(5-H/Me/Cl/NO_2-1*H*-benzimidazol-2-yl)phenols and some transition metal complexes

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(Received 10 June, revised 28 November 2008)

Abstract: 2-Methoxy-6-(5-H/methyl/chloro/nitro-1*H*-benzimidazol-2-yl)phenols (HL_x; x = 1–4, respectively) ligands and HL_1 complexes with $Fe(NO_3)_3$, $Cu(NO_3)_2$, $AgNO_3$ and $Zn(NO_3)_2$ were synthesized and characterized. The structures of the compounds were confirmed based on elemental analysis, molar conductivity, magnetic moment, FT-IR, ^{1}H- and ^{13}C-NMR. The antibacterial activity and minimum inhibitory concentration (*MIC*) of the free ligands, their hydrochloride salts and the complexes were evaluated using the disk diffusion method in dimethyl sulfoxide (DMSO) and the dilution method, respectively, against 9 bacteria. HL_1 and HL_3, as well as the Cu(II) and Zn(II) complexes, showed antibacterial activity against Gram-positive bacteria.

Keywords: benzimidazolylphenols; complexes; antibacterial activity.

INTRODUCTION

Benzimidazole and its derivatives possess a wide variety of useful biological properties due to their structural similarities with the common nucleobases.[1–4] While some are important potent antiviral agents,[5,6] many are the active components of biocides, such as fungicides, and insecticides.[7] For instance, 2-(4-thiazolyl)benzimidazole, known as thiabendazole, and several of its coordination compounds aroused considerable interest in medicine due to their strong antimicrobial activity.[8,9] Also in this range, 5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphinyl}-1*H*-benzimidazole (omeprazole) is used as the prototype antisecretory agent.[10] The compounds albendazole, mebendazole and flubendazole are effective anthelmintics.[11,12] Others, such as astemizole, are non-sedating antihistamines[13] and fenbendazole is effective against gastrointestinal nematode parasites.[14]

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doi: 10.2298/JSC0905537T

Investigation of the biological activity of complex compounds is a field that has developed over the years. When the ligands coordinate to transition metals, it is believed that the selectivity towards certain biological systems is improved.[15–18] In this work, 2-methoxy-6-(5-H/methyl/chloro/nitro-1*H*-benzimidazol-2-yl)-phenols (Fig. 1) ligands and the iron(III), copper(II), silver(I) and zinc(II) nitrate complexes with 2-methoxy-6-(1*H*-benzimidazol-2-yl)-phenol are reported. The antibacterial activities of the ligands and the complexes were evaluated by the disk diffusion method against nine bacteria.

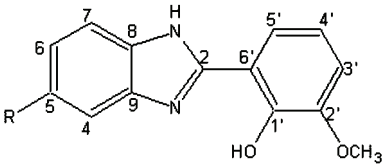


Fig. 1. Schematic view of the structure of the ligands; R = H in HL_1; R = CH_3 in HL_2; R = Cl in HL_3; R = NO_2 in HL_4.

EXPERIMENTAL

Materials and apparatus

All chemicals and solvents were of reagent grade and were used as purchased without further purification. Melting points were determined using a Gallenkamp melting point apparatus. The C,H,N content was determined on a Thermo Finnigan Flash EA 1112 analyzer (Istanbul University, Advanced Analyses Laboratory, Istanbul). The molar conductivity of the complexes was measured on a WPA CMD750 conductivity meter in dimethyl sulfoxide (DMSO, $c = 10^{-3}$ mol/L) at 25±1 °C. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity Inova 500 NMR spectrometer (in DMSO-d_6, $c \approx 10^{-4}$ mol/L). The residual DMSO-d_6 signal was used as an internal reference. The FT-IR spectra were recorded in KBr disks on a Mattson 1000 FT-IR spectrometer. The electronic spectra were recorded on a Perkin Elmer Lambda 25 UV/Visible Spectrometer. The magnetic measurements were performed on a Sherwood Scientific apparatus at room temperature by the Gouy method using $CuSO_4 \cdot 5H_2O$ as the calibrant and were corrected for diamagnetism by applying Pascal's constants.[19]

Syntheses of the ligands

The ligands were prepared according to literature procedures.[20,21]

2-Methoxy-6-(1*H*-benzimidazol-2-yl)phenol (HL_1) was prepared by reacting 2-hydroxy--3-methoxybenzaldehyde (1.52 g, 10.0 mmol) and an equivalent amount of $NaHSO_3$ (1.04 g, 10.0 mmol) at room temperature in ethanol (25 ml) for 4–5 h. The mixture was treated with 1,2--phenylenediamine (1.08 g, 10.0 mmol) in dimethylformamide (15 ml) and gently refluxed for 2 h. The reaction mixture was then poured into iced water (500 ml), filtered and crystallized from ethanol. Yield: 1.9 g; ≈ 80 %.

2-Methoxy-6-(5-methyl-1*H*-benzimidazol-2-yl)phenol (HL_2) was synthesized by a procedure similar to that employed for HL_1 but using 2-hydroxy-3-methoxybenzaldehyde (305 mg, 2.00 mmol), $NaHSO_3$ (210 mg, 2.00 mmol) and 4-methyl-1,2-phenylenediamine (250 mg, 2.00 mmol). Yield: 355 mg; ≈ 70.0 %.

2-Methoxy-6-(5-chloro-1*H*-benzimidazol-2-yl)phenol (HL_3) was synthesized by a procedure similar to that employed for HL_1 but using 2-hydroxy-3-methoxybenzaldehyde (305 mg,

2.00 mmol), $NaHSO_3$ (210 mg, 2.00 mmol) and 4-chloro-1,2-phenylenediamine (285 mg, 2.00 mmol). Yield: 360 mg; ≈ 65.0 %.

2-Methoxy-6-(5-nitro-1*H*-benzimidazol-2-yl)phenol (HL_4) was synthesized by a procedure similar to that employed for HL_1 but using 2-hydroxy-3-methoxybenzaldehyde (305 mg, 2.00 mmol), $NaHSO_3$ (210 mg, 2.00 mmol) and 4-nitro-1,2-phenylenediamine (306 mg, 2.00 mmol). Yield: 430 mg; ≈ 75.0 %.

Syntheses of the complexes

$[Fe(L_1)(OH)(H_2O)_2]NO_3$ was prepared by treating a hot solution of the ligand HL_1 (120 mg, 0.500 mmol) in iso-propanol (10 ml) with $Fe(NO_3)_3·9H_2O$ (222 mg, 0.550 mmol) in iso-propanol (5.0 ml) at ≈ 60 °C for 3–4 h. The solution mixture was allowed to stand at ≈ 4 °C for several days whereby black solid products precipitated, which were collected by filtration and dried under vacuum over anhydrous calcium chloride. Yield: 180 mg; ≈ 95.0 %.

$[Cu(L_1)_2]·2H_2O$ was prepared by reacting 120 mg HL_1 (0.500 mmol) and 133 mg $Cu(NO_3)_2·3H_2O$ (0.550 mmol) in 10 ml methanol. After 4 h-reflux, the formed precipitate was filtered and dried at ≈ 80 °C. Yield: 150 mg; ≈ 65.0 %.

$[Ag(L_1)]$ was synthesized by reacting 120 mg HL_1 (0.500 mmol) and 94 mg $AgNO_3$ (0.550 mmol) in 10 ml ethanol at room temperature for 6 h with stirring. The obtained precipitate was filtered and dried at ≈ 80 °C. Yield: 135 mg; ≈ 80.0 %.

$[Zn(L_1)(H_2O)_2]NO_3$ was prepared by adding 164 mg $Zn(NO_3)_2·6H_2O$ (0.550 mmol) in 15 ml ethyl acetate to 120 mg HL_1 (0.500 mmol) suspended in ethyl acetate and refluxing the mixture for 2 h. The obtained dark yellow precipitate was filtered and dried under vacuum over calcium chloride. Yield: 145 mg; ≈ 75.0 %.

Determination of antimicrobial activity

The antimicrobial activities were evaluated against Gram-positive (*Staphylococcus aureus*, ATCC 29213, *Bacillus cereus*, ATCC 11778, *Bacillus subtilis*, ATCC 6633, *Staphylococcus epidermidis*, ATCC 12228) and Gram-negative (*Escherichia coli*, ATCC 25922, *Klebsiella pneumoniae*, ATCC 4352, *Pseudomonas aeruginosa*, ATCC 27853, *Salmonella enteritidis*, KUEN 349, *Proteus mirabilis*, CCM 1944) bacteria. The strains were provided by the Centre for Research and Application of Culture Collections of Microorganisms, Istanbul University (KUKENS).

Mueller–Hinton Agar (Fluka 70191) was used for the detection of the qualitative antibacterial effect and to maintain the strains. For the detection of the quantitative antibacterial effect, Mueller–Hinton broth (Fluka 70192) (CAMBH) with $MgCl_2·2H_2O$ (10 mg Mg^{2+}/L) and $CaCl_2·6H_2O$ (20 mg Ca^{2+}/L) was used as the medium.

The disc diffusion method was used for the detection of the qualitative antibacterial effect of the chemical agents.[22] For this purpose, filter papers (Whatman, No:1) with 6 mm diameter were autoclaved and dried at 37 °C overnight. Each chemical agent (21.27 mg) was dissolved in DMSO and 23.5 µl of this solution (containing 500 µg chemical agent) were soaked onto the sterile discs. Bacterial suspension with $1–2×10^8$ cfu/ml (McFarland 0.5) were prepared from each bacterial strain and streaked onto the agar. The discs impregnated with the chemical agents were placed onto the agar surface and incubated at 37 °C for 24 h. Chemical agents with growth inhibition zones were used for the further examinations.

For the detection of the antibacterial effect of the chemical agents, quantitatively, the macro-dilution broth method according to clinical and laboratory standards institute (formerly NCCLS) was performed.[23] Serial dilutions of the chemical agents between 531.75–0.26 µg/ml with CAMBH were prepared in sterile tubes. A bacterial suspension with 10^7 cfu/ml final

concentration was inoculated. Positive (without tested chemical agent) and negative (without bacterial suspension) tubes were used at the end of each organism tested. The tubes were incubated at 37 °C for 24 h. The minimum inhibitory concentration, *MIC*, value was defined as the lowest concentration of the chemical agent giving complete inhibition of visible growth.

RESULTS AND DISCUSSION

Physical properties

The analytical data and physical properties of the ligands and the complexes are summarized in Table I. The melting points of the ligands HL_2–HL_4 suggest that a methyl substitution on the 5-position of the benzimidazole moiety decreases the melting point and a chloro or nitro group increases it with respect to the HL_1 ligand.

TABLE I. The analytical data and physical properties of the HL_1–HL_4 ligands and the complexes

Compound	Found (Calcd.), %			M.p. °C	Color	Λ[a] S cm^2 mol^{-1}
	C	H	N			
HL_1 ($C_{14}H_{12}N_2O_2$)	70.3 (70.0)	4.8 (5.0)	11.4 (11.7)	278	White	–
HL_2 ($C_{15}H_{14}N_2O_2$)	70.5 (70.8)	5.8 (5.6)	10.6 (11.0)	259	White	–
HL_3 ($C_{14}H_{11}ClN_2O_2$)	61.5 (61.2)	3.9 (4.0)	9.9 (10.2)	304	Dirty white	–
HL_4 ($C_{14}H_{11}N_3O_4$)	59.2 (58.9)	4.1 (3.9)	14.4 (14.7)	329	Greenish yellow	–
$[Fe(L_1)(OH)(H_2O)_2]NO_3$[b] $C_{14}H_{16}FeN_3O_8$	40.7 (41.0)	3.6 (3.9)	9.9 (10.2)	227	Black	37
$[Cu(L_1)_2]\cdot 2H_2O$[b] $C_{28}H_{26}CuN_4O_6$	57.8 (58.2)	3.9 (4.5)	10.3 (9.7)	212	Khaki-green	12
$[Ag(L_1)]$ $C_{14}H_{12}AgN_3O_5$	48.8 (48.4)	3.2 (3.2)	8.5 (8.1)	184	Grey	9
$[Zn(L_1)(H_2O)_2]NO_3$ $C_{14}H_{13}N_3O_6Zn$	41.5 (41.8)	3.2 (3.7)	10.8 (10.4)	322	Dark-yellow	35

[a]In DMSO, t = 25±1 °C; [b]μ_{eff} values for $[Fe(L_1)(OH)(H_2O)_2]NO_3$ and $[Cu(L_1)_2]\cdot 2H_2O$ are 3.85 and 1.61 μ_B, respectively

The molar conductivity values of the complexes were 37 and 35 S cm^2 mol^{-1} for the Fe(III) and Zn(II) complexes, respectively. These results are indicative for 1:1 electrolyte complexes. The Cu(II) and Ag(I) complexes had a non-ionic character according to the molar conductivity measurements.[24,25]

The magnetic moment value of the $[Fe(L_1)(OH)(H_2O)_2](NO_3)$ complex was 3.85 μ_B, which is lower than the spin only value of ≈ 5.90 μ_B for Fe(III) d^5 with s = 5/2 (high spin under a weak field) and higher than the spin only value of ≈ 2.0 μ_B in the case of s = 1/2 (low spin in the presence of a strong field). The intermediate value of the magnetic moment indicates stabilization of the species having an intermediate ferric spin (s = 3/2) state for this complex. The occurrence of

such an intermediate spin state is typical for five coordinated Fe(III) d^5 ferric complexes.[26,27] The magnetic moment value of the $[Cu(L_1)_2]\cdot 2H_2O$ complex was 1.63 μ_B, which is to be expected for a typical d^9 Cu(II) complex.

Electronic spectra

UV–visible spectral data of the ligands and the complexes are given in Table II. The electronic spectra of the ligands and the complexes exhibit intense bands in the 220–310 nm region, which may be assignable to n → p* and p → p* transitions.

TABLE II. UV–visible spectral data of the HL_1–HL_4 ligands and the complexes (in methanol)

Compound	Wavelength, nm
HL_1	245, 283, 306, 361
$[Fe(L_1)(OH)(H_2O)_2]NO_3$	258, 318, 367, 381, 575
$[Cu(L_1)_2]\cdot 2H_2O$	251, 298, 305, 357, 456, 645
$[Ag(L_1)]$	285, 293, 303, 341
$[Zn(L_1)(H_2O)_2]NO_3$	274, 302, 335, 390, 445
HL_2	236, 265, 290, 371
HL_3	221, 300, 310, 352
HL_4	265, 295, 345, 363, 401, 415

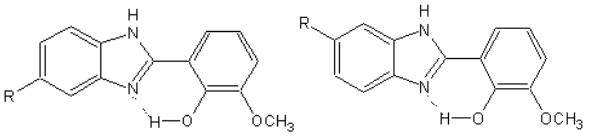
The electronic spectra of the Fe(III) complex is of little help in the present case, since the d → d transitions are masked by broad strong charge-transfer bands (575 nm, L → Fe, charge transfer).[28] The broad band at 445 nm in the spectrum of the Zn(II) complex is a charge-transfer band.

The electronic spectra of the Cu(II) complex showed three bands at 645, 456 and 357 nm. The 357 nm-band is assigned to a metal–ligand charge transfer. The other two bands are assigned to a $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transition, respectively. These assignments are typically characteristic for a square-planar geometry of Cu(II) complexes (Fig. 2).[29,30]

FT-IR spectra

FT-IR spectral data of the ligands and the complexes are given in Table III. The characteristic ν(O–H) and ν(N–H) vibrations of the ligands exhibit only a single strong band at *ca.* 3290 cm^{-1} in the IR spectra, which is probably caused by doubly intramolecular hydrogen bonding between the phenoxyl hydrogen atom and one of the imine nitrogen atoms (Table III, Fig. 2).[15,31,32] The 3295 cm^{-1} band in HL_1 changed significantly upon metal complexation, indicating deprotonation and subsequent involvement of the phenoxyl group in metal coordination. The coordination of the phenolic oxygen atom could also be supported by the appearance of medium-to-strong bands at a lower frequency region, *ca*. 500 cm^{-1}, assignable to ν(M–OC) vibration.[33]

The appearance of a strong broad band at *ca*. 3400 cm^{-1} in the Fe(III), Cu(II) and Zn(II) complexes strongly supports the presence of coordinated water molecules (Fig. 3). The characteristic ν(C–H) and δ(C–H) modes of the ring residues and aliphatic groups (methyl and methoxy substituents) are observed in the wavelength region between 3100–2940 cm^{-1} and 1500–800 cm^{-1} (Table III). The ν(C=C) frequencies of the ring residue are expected to appear at *ca*. 1630 cm^{-1} with their own characteristics for the ligands in the IR spectra. These frequencies are expected to shift to lower frequencies upon complex formation. Similarly, the (C=N) asymmetric stretching frequencies are expected to appear at *ca*. 1590 cm^{-1}. Thus, the IR band at 1593 cm^{-1} in the spectrum of the HL_1 ligand shifts to *ca*. 1600 cm^{-1} upon complex formation. These frequency changes may support the argument that coordination possibly occurs *via* an imine nitrogen atom.



Isomer **A** Isomer **B**

Fig. 2. Schematic presentation of the isomeric structures for the HL_2 (isomer **A**) and HL_4 (isomer **B**) ligands (R = CH_3, NO_2).

Fe(III) and Zn(II) complexes show strong bands at 1386 cm^{-1} in their IR spectra, supporting the presence of an uncoordinated nitrate ion, which was also confirmed by conductivity data.[28,34]

TABLE III. Prominent IR bands for the HL_1–HL_4 ligands and the complexes

Compound	Frequency, cm^{-1}
HL_1	3295 *s*, 3068 *w*, 2930 *w*, 1628 *m*, 1593 *m*, 1478 *s*, 1424 *m*, 1255 *s*, 1062 *m*, 781 *m*, 743 *m*, 605 *m*, 502 *w*, 433 *w*
$[Fe(L_1)(OH)(H_2O)_2]NO_3$	3411 *m*,*br*, 3276 *m*, *br*, 2933 *w*, 1621 *m*, 1605 *sh*, 1562 *m*, 1547 *m*, 1493 *m*, 1478 *m*, 1386 *s*, 1305 *m*, 1278 *m*, 1066 *w*, 793 *w*, 746 *m*, 589 *m*, 508 *w*, 458 *w*
$[Cu(L_1)_2]\cdot 2H_2O$	3423 *m*, *br*, 3254 *m*, *br*, 2946 *m*, 1623 *m*, 1608 *m*, 1538 *w*, 1485 *s*, 1462 *m*, 1315 *m*, 1246 *m*, 1208 *m*, 1069 *m*, 854 *w*, 746 *m*, 572 *m*, 517 *m*, 445 *w*
$[Ag(L_1)]$	3434 *m*, *br*, 3361 *m*, *br*, 3280 *m*, *br*, 3049 *w*, 2934 *w*, 1621 *m*, 1594 *m*, 1532 *m*, 1497 *m*, 1447 *m*, 1255 *s*, 1070 *s*, 750 *s*, 735 *m*, 654 *m*, 604 *m*, 445 *w*
$[Zn(L_1)(H_2O)_2]NO_3$	3449 *m*, *br*, 3307 *m*, *br*, 2941 *w*, 1624 *m*, 1605 *w*, 1497 *s*, 1482 *s*, 1386 *s*, 1312 *s*, 1286 *m*, 1243 *m*, 1197 *m*, 1112 *m*, 1066 *m*, 793 *m*, 743 *m*, 572 *w*, 517 *m*, 445 *w*
HL_2	3291 *s*, 3076 *w*, 2933 *w*, 1632 *m*, 1593 *m*, 1482 *s*, 1424 *m*, 1255 *s*, 1062 *m*, 789 *m*, 735 *m*, 604 *m*
HL_3	3295 *s*, 3072 *w*, 2937 *w*, 1628 *w*, 1594 *m*, 1482 *s*, 1424 *m*, 1386 *m*, 1255 *s*, 1058 *m*, 935 *m*, 739 *m*, 735 *m*, 608 *m*
HL_4	3291 *s*, 3087 *w*, 2941 *w*, 1632 *m*, 1593 *m*, 1520 *s*, 1478 *m*, 1424 *m*, 1336 *s*, 1255 *s*, 1055 *m*, 843 *m*, 792 *m*, 739 *s*, 608 *m*

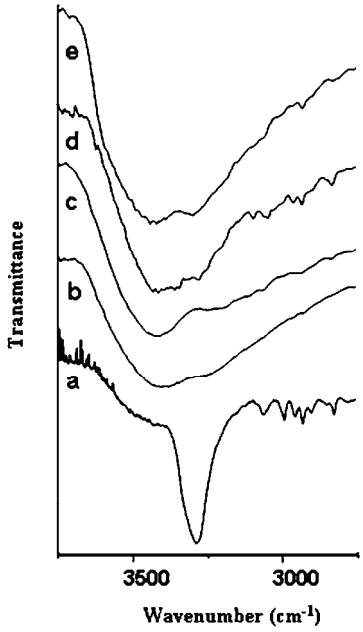


Fig. 3. FT-IR spectra of HL_1 and its complexes in the 3750–2750 cm^{-1} region.
a, HL_1;
b, $[Fe(L_1)(OH)(H_2O)_2]NO_3$;
c, $[Cu(L_1)_2]\cdot 2H_2O$; d, $[Ag(L_1)]$;
e, $[Zn(L_1)(H_2O)_2]NO_3$.

NMR spectra

The ^{1}H- and ^{13}C-NMR spectral data are given in Tables IV and V, respectively. The ligands HL_2 and HL_4 have two isomeric forms according to their ^{1}H-NMR spectra (Figs. 2 and 4, Table IV). The isomer structures are observed for the benzimidazole protons only. The OH and NH protons show only a broad single band in the spectra of HL_1. This observation results from strong hydrogen bonding between the imine nitrogen with a double bond and the phenolic hydrogen atoms (Fig. 2).[35,36] The other ligands, HL_2, HL_3 and HL_4 give two broad bands for the OH and NH protons, probably because of the 5-position substitutions (Fig. 4). This means that these ligands have weaker hydrogen bonding than HL_1 in DMSO-d_6.

In the ^{1}H-NMR spectra of the Ag(I) and Zn(II) complexes, considerable changes are observed. The broad signal in the ^{1}H-NMR spectrum of HL_1 at 13.15 ppm, due to the NH and OH protons sharpens on complexation and its intensity changes to only single proton, namely the NH proton (Fig. 5). The OH proton signal is absent in the ^{1}H-NMR spectra of the complexes. This is evidence that the phenolic oxygen is coordinated to the metal ions and that the phenolic hydrogen is eliminated on complexation (Fig. 6).

The benzimidazole moiety protons of the Ag(I) and Zn(II) complexes show broad signals in the ^{1}H-NMR spectra because of the perturbing effect of the metal ion. On complexation, the acidic character of the benzimidazole moiety protons is increased.

TABLE IV. ^{1}H-NMR spectral data of the HL_1–HL_4 ligands, and the Ag(I) and Zn(II) complexes (in DMSO-*d*6)

Compound	Benzimidazole protons					Phenolic protons				
	H4	H5	H6	H7	NH	H3'	H4'	H5'	OH	OCH_3
HL_1	7.65 *m*	7.29 *m*	7.29 *m*	7.65 *m*	13.15 *s, br*	7.65 *m*	6.95 *t* J^a = 7.8, 8.3	7.08 *d-d* *J* = 8.3, 1.5	13.15 *s, br*	3.84 *s*
A[b]	7.64 *d* *J* = 7.8	7.29 *s, br*	7.29 *s, br*	7.64 *d* *J* = 7.8	13.16 *s, br*	7.10 *d* *J* = 8.2	6.96 *t* *J* = 8.2, 7.8	7.10 *d* *J* = 8.2	–	3.84 *s*
B[c]	8.73 *s*	7.22 *s, br*	7.22 *s, br*	7.98 *s, br*	13.49 *s, br*	7.61 *s*	7.30 *d,br* *J* = 7.3	7.56 *d* *J* = 7.3	–	3.85 *s*
HL_2, Isomer **A** (54 %)	7.48 *d* *J* = 7.8	7.12 *d* *J* = 7.8	2.46[d] *s*	7.52 *s*	13.30 *s, br*	7.61 *d* *J* = 7.8	6.94 *t* *J* = 7.8, 8.3	7.08 *m*	13.04 *s, br*	3.83 *s*
HL_2, Isomer **B** (46 %)	7.38 *s*	2.43[d] *s*	7.08 *m*	7.59 *d, br* *J* = 6.8	13.34 *s, br*	7.61 *d* *J* = 7.8	6.94 *t* *J* = 7.8, 8.3	7.08 *m*	13.07 *s, br*	3.83 *s*
HL_3	7.68 *s, br*	–	7.66 *d, br*	7.30 *d-d* *J* = 8.3, 1.9	13.26 *s, br*	7.63 *d-d* *J* = 7.8, 1.5	6.97 *t* *J* = 7.8, 7.8	7.11 *d-d* *J* = 7.8, 1.5	12.88 *s, br*	3.84 *s*
HL_4, Isomer **A** (60 %)	7.79 *s, br*	8.17 *s, br*	–	8.45 *s, br*	13.63 *s, br*	7.68 *d* *J* = 7.4	7.00 *t* *J* = 7.8, 7.8	7.16 *d* *J* = 7.8	12.40 *s, br*	3.86 *s*
HL_4, Isomer **B** (40 %)	8.61 *s, br*	–	8.17 *s, br*	7.87 *s, br*	13.56 *s, br*	7.68 *d* *J* = 7.4	7.00 *t* *J* = 7.8, 7.8	7.16 *d* *J* = 7.8	12.29 *s, br*	3.86 *s*

[a]In Hz; [b]$[Ag(L_1)]$; [c]$[Zn(L_1)(H_2O)_2]NO_3$; [d]3H (CH_3)

TABLE V. ^{13}C-NMR spectral data of HL_1 and its Ag(II) and Zn(II) complexes

Compound	Chemical shift in DMSO-d_6 (δ_C / ppm)
HL_1	152.64, 149.30, 149.09, 124.62, 119.39, 118.35, 114.69, 113.24, 56.45
$[Ag(L_1)]$	152.95, 149.05, 148.85, 124.30, 119.20, 118.50, 114.20, 113.40, 56.35
$[Zn(L_1)(H_2O)_2]NO_3$	155.70, 148.60, 148.10, 124.20, 122.40, 120.75, 115.50, 114.12, 57.85

In the ^{13}C-NMR spectra of HL_1 and its Ag(I) and Zn(II) complexes, the signal around 152.64, 152.95 and 155.70 ppm, respectively, belongs to the imidazole C=N (C-2) carbon atom. The low ppm signal, 56.45, 56.35 and 57.85 ppm, respectively, is due to the methoxy carbon atom in HL_1 and its Ag(I) and Zn(II) complexes. The signals around 149 ppm are due to C-8, C-9, C-2', C-1' carbon atoms of the HL_1 ligand and the complexes. The other signals belong to the benzimidazole benzene and phenol ring carbon atoms (Table V).

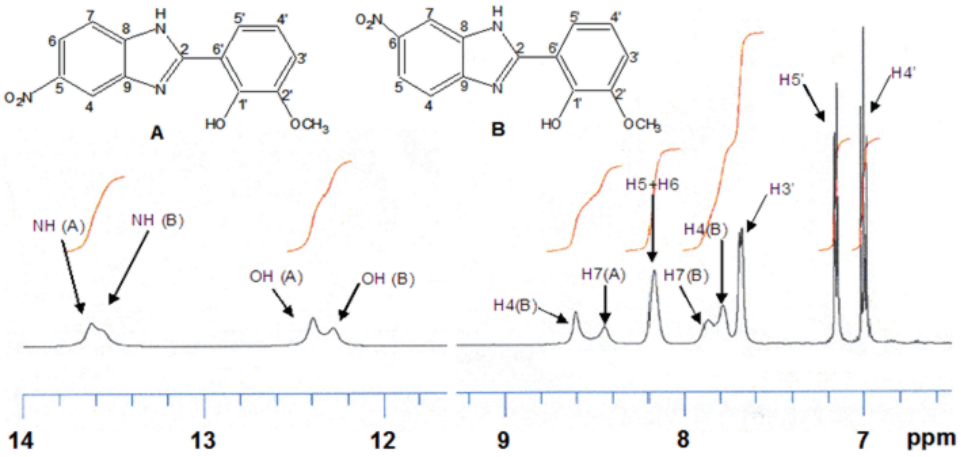


Fig. 4. ^{1}H-NMR spectra of the HL_4 isomers (**A** and **B**) in the 6.5–14 ppm region.

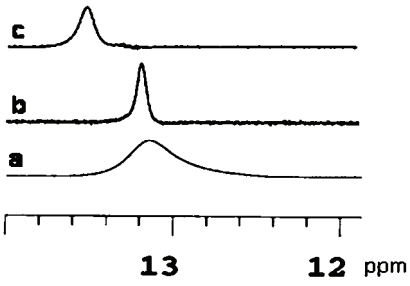


Fig. 5. ^{1}H-NMR spectra of HL_1 and its Ag(I) and Zn(II) complexes in the 12–14 ppm region. a, HL_1; b, $[Ag(L_1)]$; c, $[Zn(L_1)(H_2O)_2]NO_3$.

In conclusion, the optimized structures for the complexes presented in Fig. 6 are in best accord with the experimental data obtained from the analytical data, molar conductivity, magnetic moments, FT-IR and NMR spectroscopic measurements.

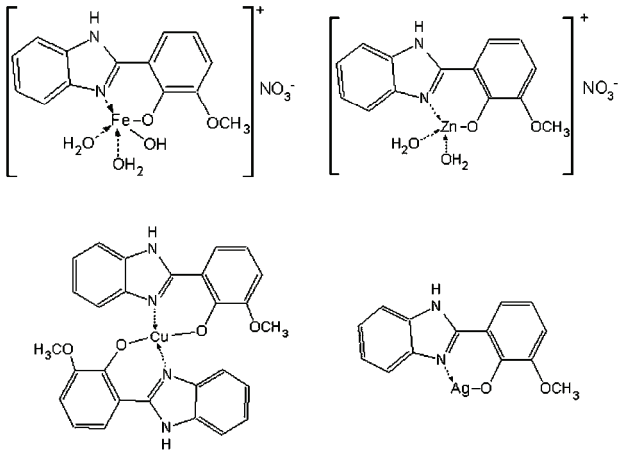


Fig. 6. Schematic view of the proposal structures of the studied complexes.

Antibacterial activity

The results concerning the *in vitro* antibacterial activity of the ligand and their complexes, together with the inhibition zone (mm) and *MIC* values, are presented in Tables VI and VII.

TABLE VI. *In vitro* antimicrobial activity of the compounds (inhibition zone, mm)

Compound	Microorganisms[a]								
	1	2	3	4	5	6	7	8	9
HL_1	–[b]	–	–	–	–	8	–	–	8
$HL_1 \cdot HCl$	–	–	–	–	–	8	–	–	–
HL_3	14	–	–	–	–	–	10	8	–
$HL_3 \cdot HCl$	12	–	–	–	–	–	–	–	–
HL_4	14	–	–	–	–	–	–	–	–
$[Fe(L_1)(OH)(H_2O)_2]NO_3$	14	–	>20	–	–	–	–	–	–
$[Cu(L_1)_2] \cdot 2H_2O$	–	–	–	–	–	–	8	8	–
$[Ag(L_1)]$	10	–	10	–	12	–	12	8	–
$[Zn(L_1)(H_2O)_2]NO_3$	–	–	–	–	8	–	8	10	10
$Fe(NO_3)_3 \cdot 9H_2O$	–	–	–	–	7	–	–	–	–
$Cu(NO_3)_2 \cdot 3H_2O$	10	7	7	7	–	7	7	10	12
$AgNO_3$	–	–	10	–	10	–	–	8	8
$Zn(NO_3)_2 \cdot 6H_2O$	–	12	7	–	10	7	–	12	16

[a]1 – *P. aeruginosa*, 2 – *S. enteriditis*, 3 – *E. coli*, 4 – *P. mirabilis*, 5 – *K. pneumoniae*, 6 – *B. cereus*, 7 – *S. epidermidis*, 8 – *S. aureus*, 9 – *B.subtilis*; [b]zone did not form

TABLE VII. *In vitro* antimicrobial activity of the compounds (*MIC* / μg ml^{-1})

Compound	Microorganisms								
	1	2	3	4	5	6	7	8	9
HL_1	–[a]	–	–	–	–	532	–	–	*[b]
$HL_1 \cdot HCl$	–	–	–	–	–	532	–	–	–
HL_3	*	–	–	–	–	–	66.5	66.5	–
$HL_3 \cdot HCl$	*	–	–	–	–	–	–	–	–
HL_4	532	–	–	–	–	–	–	–	–
$[Fe(L_1)(OH)(H_2O)_2]NO_3$	532	–	*	–	–	–	–	–	–
$[Cu(L_1)_2] \cdot 2H_2O$	–	–	–	–	–	–	*	532	–
$[Ag(L_1)]$	66.5	–	33.2	–	66.5	–	33.2	66.5	–
$[Zn(L_1)(H_2O)_2]NO_3$	–	–	–	–	*	–	*	133	*

[a]No antibacterial activity qualitatively; [b]*MIC* value was not detected in the test concentrations (< 532 μg/ml)

The chloride substituted ligand, HL_3, and the $[Ag(L_1)]$ and $[Zn(L_1)(H_2O)_2](NO_3)$ complexes exhibit moderate antibacterial activity. Of all the compounds tested, the ligands and some complexes show antibacterial activity against Gram-positive bacteria. As an example, the inhibition zone and *MIC* values of HL_1, HL_3, $[Cu(L_1)_2] \cdot 2H_2O$ and $[Zn(L_1)(H_2O)_2]NO_3$ for the *B. cereus*, *S. epidermidis*, *S.*

aureus and *B. subtilis* (Gram+) organisms are exceptionally effective compared with the other compounds (Tables VI and VII, microorganisms 6–9).

A noteworthy result is that the Cu(II), Zn(II) and Ag(I) complexes show antibacterial activity toward *S. epidermidis* and *S. aureus* while the HL_1 ligand has no activity on them. On the other hand, it was observed that $AgNO_3$ has no activity on *P. aeruginosa* and *S. epidermidis*; however the $[Ag(L_1)]$ complex has considerable antibacterial activity toward these two bacteria. The Fe(III) complex exhibited antibacterial activity against *P. aeruginosa* and *E. coli* while $Fe(NO_3)_3 \cdot 9H_2O$ itself did not show any antibacterial effect on them.

Acknowledgement. This work was supported by Istanbul University Research Fund, Project number: 262/23082004.

ИЗВОД

ДОБИЈАЊЕ, КАРАКТЕРИЗАЦИЈА И АНТИБАКТЕРИЈСКИ ЕФЕКАТ 2-МЕТОКСИ-6(5-*H*/Me/Cl/NO_2-1*H*-БЕНЗИМИДАЗОЛ-2-ИЛ)-ФЕНОЛА И КОМПЛЕКСА НЕКИХ ПРЕЛАЗНИХ МЕТАЛА

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Добијени су и окарактерисани 2-метокси-6-(5-*H*/метил/хлоро/нитро-1*H*-бензимидазол-2-ил)-фенолни (HL_x; x = 1–4, редом) лиганди и HL_1 комплекси са $Fe(NO_3)_3$, $Cu(NO_3)_2$, $AgNO_3$, $Zn(NO_3)_2$. Структуре комплекса су потврђене на основу елементалне анализе, моларне проводљивости, магнетног момента, FT-IR, ^{1}H- и ^{13}C-NMR. Антибактеријаска активност слободних лиганада, њихових хидрохлоридних соли и комплекса је проверена коришћењем диск дифузионе методе у диметил-сулфоксиду (DMSO) као и минимална инхибиторска концентрација (*MIC*) методом разблажења, према 9 сојева бактерија. HL_1, HL_3, Cu(II) и Zn(II) комплекси показују антибактеријску активност према Грам-позитивним бактеријама.

(Примљено 10. јуна, ревидирано 28. новембра 2008)

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