Novel 'quinolone' metal complexes: Synthesis and spectroscopic studies of Mg(II), Zn(II) and Ba(II) complexes with *N*-methyl (or *N*H)-3-acetyl-4-hydroxy quinolin-2-one ligands

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The complexation between *N*-methyl-3-acetyl-4-hydroxyquinolin-2-one (NMeQuin) and *N*-H-3-acetyl-4-hydroxy quinolin-2-one (NHQuin) with $MgCl_2$, $ZnCl_2$ and $BaCl_2$ has been accomplished. The structure of the resulting complexes **1-5** has been elucidated through elemental analyses, FT-IR and $^1H/^{13}C$ NMR Spectroscopy and Mass Spectrometry. The spectroscopic data show complexes of the general formula $Mg_2(OH)L_3(H_2O)_z$ and $ML_2(H_2O)_z$ where: M = Zn(II) and Ba(II), L = NMeQuin, NHQuin and z = 2, 4.

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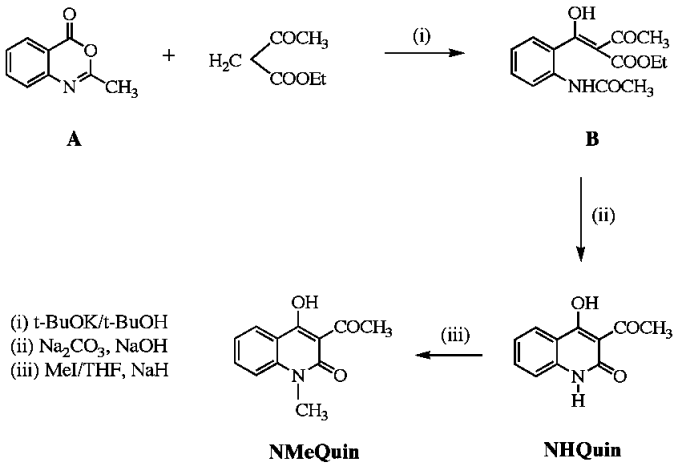
Introduction.

'Quinolones' is a group of antibacterial agents which comprises substituted quinolinone and 1,8-napthyridine derivatives containing the β-dicarbonyl moiety. These compounds exhibit interesting biological properties such as antimicrobial [1-3], anticoccidial [4] or antitumor [5] activities. It is known that blood-brain barrier transport of 'quinolone' derivatives is characterized by its dependence on lipophilicity [6]. Quinolinone derivatives have become important as *N*-methyl-D-aspartate (NMDA) receptor antagonists [7]. A series of 3-quinolinocarboxamides have been designed as serotonin 5-HT_3 receptor antagonists [8] and the inhibition of human erythrocyte calpain I by quinoline carboxamides has been reported [9]. In addition, 2-substituted-4-hydroxy-3-quinoline carboxamides have shown antiarthritic and analgetic activities [10].

Recently, we have developed a new methodology for the synthesis of quinoline-2,4-dione derivatives [11-13] involving the C-acylation of active methylene compounds with 3,1-benzoxazin-4-ones. (Scheme 1)

Scheme 1



Synthesis of NHQuin and NMeQuin

The β,β'-tricarbonyl moiety present in these compounds provides them with suitable sites for complexation with metal ions. It is known that nitrogen heterocycles, such as 3-acyl pyrrolidine-2,4-diones (tetramic acids), containing the β,β-tricarbonyl system are suitable substrates for bidentate complexation to a metal. 'Magnesidin' (Figure 1), a natural antibiotic, was isolated as a 1:1 mixture of the covalent magnesium chelates of 1-acetyl-3-hexanoyl and 3-octanoyl tetramic acid derivatives [14].

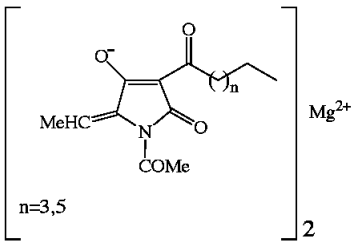
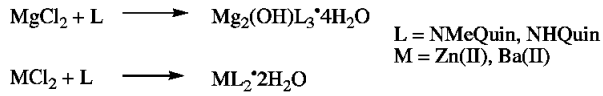


Figure 1 Magnesidine

The complexation of various tetramic acids with transition metals has been extensively studied in the last decade [15-18]. Many investigations have proved that binding of a drug to a metalloelement enhances its activity and in some cases the complex possesses even more healing properties than the parent drug [19]. This has prompted us to investigate the metal binding properties of quinolone derivatives.

In this report we present the synthesis of *N*-H-3-acetyl-4-hydroxy quinolin-2-one (NHQuin) and *N*-methyl-3-acetyl-4-hydroxy quinolin-2-one (NMeQuin) (Figure 2) complexes with Mg(II), Zn(II) and Ba(II) chloride salts in several ratios [20] (Equation 1). The structure of these compounds has been elucidated through elemental

analyses, FT-IR, $^1H/^{13}C$ NMR Spectroscopy and Mass Spectrometry (FAB-MS). Efforts to obtain crystals suitable for X-ray study of complexes **1-5** were unsuccessful.



Equation 1: Synthesis of complexes **1-5**

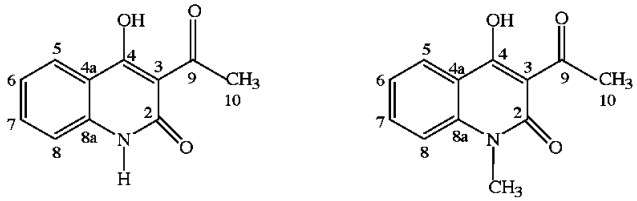


Figure 2 Atom numbering for NHQuin and NMeQuin

EXPERIMENTAL

General Remarks.

All manipulations were performed under aerobic conditions using reagents and solvents as received, except tetrahydrofuran which was distilled prior to use according to standard procedures [21]. Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded in KBr in the range 4000-400 cm^{-1} on a Nicolet Magna 560 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian Gemini-2000, 300 MHz spectrometer. Chemical shifts are quoted on ppm (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad); *J* values are given in Hz. The Mass spectra were recorded on a VG 707OE/DEC VAX 4000.60 instrument using Fast Atom Bombardment (FAB) at the University of Liverpool. Elemental analyses were obtained on a Euro EA3000 Series EuroVector CHNS Elemental Analyser at the National Technical University of Athens, Organic Chemistry Laboratory.

2-Methyl-3,1-benzoxazin-4-one (**A**) and Ethyl-[(2-acetylaminophenyl)-hydroxymethylidene]-acetoacetate (**B**) (Scheme 1) have been synthesized according to the previously reported method [11, 12].

3-Acetyl-4-hydroxy-quinolin-2-one (**NHQuin**).

Into a solution of sodium hydroxide (18.0 g, 0.45 mole) in water (100 mL) was added sodium carbonate (5.3 g, 0.05 mole) and ethyl-[(2-acetylaminophenyl)-hydroxymethylidene]-acetoacetate (**B**) (3.2 g, 0.011 mole). The mixture was stirred at room temperature overnight. The precipitated white solid was collected by filtration and treated with water (35 mL). The resulting mixture was cooled in an ice-water bath and treated with 10% aqueous hydrochloric acid until pH 1-2, when the formation of a white solid was observed. The product was obtained as a white solid (1.8 g, 77%), m.p.: 262-264 °C; IR (KBr, ν_{max}/cm^{-1}): (OH) 3360, (NH) 3160, (C=O) 1661, 1622 and (C=C) 1606; ^1H NMR(DMSO-d_6): δ 2.72 (s, 3H, $COCH_3$), 7.23 (t, 1H, H-6), 7.30 (d, 1H, H-8, $J_{7,8}$=8.3), 7.65 (t, 1H, H-7), 7.99 (dd, 1H, H-5, $J_{5,6}$=8.0, $J_{5,7}$=1.2), 11.53 (s, 1H, NH) and 17.04 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 205.7 (C-9), 174.7 (C-4), 161.1 (C-2), 140.5 (C-8a), 134.8 (C-7), 124.7 (C-5), 122.0 (C-6), 115.5 (C-8), 113.3 (C-4a), 105.7 (C-3) and 30.5 (C-10).

N-methyl-3-acetyl-4-hydroxy-quinolin-2-one (**NMeQuin**).

Sodium hydride (60% sodium hydride in oil; 0.84 g, 0.019 mole) was added in portions to a stirred solution of *N*-H-3-acetyl-4-hydroxy-quinolin-2-one (1.3 g, 0.006 mole) and iodomethane (7.2 g, 0.051 mole) in anhydrous tetrahydrofuran (35 mL). The reaction mixture was then stirred and heated at 130-140 °C for 2.5 hours. The resulting mixture was concentrated under reduced pressure and the resulting solid was treated with diethyl ether (25 mL) and the evaporation was repeated. The residue was treated with water and the mixture was extracted three times with diethyl ether (3 x 30 mL). The aqueous layer was separated, cooled in an ice-water bath and acidified with 10% aqueous hydrochloric acid solution. The resulting precipitate was collected by filtration to afford a yellowish solid, which was recrystallised from hot ethanol as a white solid (1.1 g, 79%), m.p.: 140-142 °C (from ethanol) (lit. 143-146 °C); IR (KBr, ν_{max}/cm^{-1}): (OH) 3250, (C=O) 1658, 1623 and (C=C) 1598; ^1H NMR ($CDCl_3$): δ 2.79 (s, 3H, $COCH_3$), 3.52 (s, 3H, N-CH_3), 7.30 (t, 1H, H-6), 7.50 (d, 1H, H-8, $J_{7,8}$=8.1), 7.78 (t, 1H, H-7), 7.96 (dd, 1H, H-5, $J_{5,6}$=8.4 $J_{5,7}$=1.5) and 17.04 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 206.7 (C-9), 173.3 (C-4), 160.6 (C-2), 141.6 (C-8a), 135.7 (C-7), 125.4 (C-5), 122.3 (C-6), 114.4 (C-8), 115.3 (C-4a), 105.7 (C-3), 31.3 (C-10) and 28.9 (N-CH_3).

General Procedure for the Synthesis of Complexes **1-5**.

N-Me (or *N*-H)-3-Acetyl-4-hydroxy-quinolin-2-one (1 mmol) was dissolved in warm methanol and the solution was treated with 0.1 mol dm^{-3} NaOH up to pH 8. In succession, the solution was concentrated under reduced pressure and the resulting suspension was treated with water (30 mL) and 0.1 mol dm^{-3} NaOH up to pH 9.5-10. The hot mixture was filtered and the filtrate was treated with 10% aqueous solution of the metal salt (3 mmol of $MgCl_2$, $ZnCl_2$ or $BaCl_2•6H_2O$) and stirred for 1 hour. The precipitated solid was collected by filtration, washed with water and dried under *vacuo*.

$Mg_2(OH)(NMeQuin\text{-}H)_3•4H_2O$ (**1**).

The product was obtained as a white solid (0.56 g, 72%); IR (KBr, ν_{max}/cm^{-1}): (OH) bridge 3417, (OH) 3370, (C=O) 1630 and (C=C) 1605; ^1H NMR (DMSO-d_6):δ 2.47 (s, 3H, $COCH_3$), 3.41 (s, 3H, N-CH_3), 7.06 (t, 1H, H-6), 7.27 (d, 1H, H-8, $J_{7,8}$=8.4), 7.53 (t, 1H, H-7) and 8.04 (d, 1H, H-5, $J_{5,6}$=8.1); ^{13}C NMR (DMSO-d_6): δ 199.3/200.1 (C-9), 176.6 (C-4), 164.4/165.6 (C-2), 140.2/141.4 (C-8a), 132.5/132.9/133.2 (C-7), 126.7 (C-5), 124.1 (C-6), 114.1/114.7 (C-8), 120.7/121.8 (C-4a), 108.6 (C-3), 32.7/33.1 (C-10) and 28.4 (N-CH_3); FAB-MS: *m/z* (%) = 696 (18) [Mg_2L_3-$3H^+$], 457 (42) [MgL_2-$2H^+$].

Anal. Calcd. for $Mg_2C_{36}H_{39}N_3O_{14}$ (785): C, 55.03; H, 4.97; N, 5.35. Found: C, 55.36; H, 5.30; N, 5.06.

$Zn(NMeQuin\text{-}H)_2•2H_2O$ (**2**).

The product was obtained as a white solid (0.38 g, 72%); IR (KBr, ν_{max}/cm^{-1}): (OH) 3350, (C=O) 1675, 1640 and (C=C) 1595; ^1H NMR (DMSO-d_6): δ 2.49 (s, 3H, $COCH_3$), 3.40 (s, 3H, N-

CH_3), 7.07 (t, 1H, H-6), 7.25 (d, 1H, H-8, $J_{7,8}$=8.1), 7.53 (t, 1H, H-7) and 8.03 (d, 1H, H-5, $J_{5,6}$=7.8); ^{13}C NMR (DMSO-d_6): δ 201.7 (C-9), 177.4 (C-4), 164.3 (C-2), 140.9 (C-8a), 132.9 (C-7), 126.6 (C-5), 121.7 (C-6), 114.2 (C-8), 120.9 (C-4a), 108.2 (C-3), 32.9 (C-10) and 28.4 (N-CH_3); FAB-MS: *m/z* (%) = 497 (21) [ZnL_2-2H$^+$].

Anal. Calcd. for $ZnC_{24}H_{24}N_2O_8$ (531.5): C, 54.18; H, 4.52; N, 5.27. Found: C, 54.00; H, 4.22; N, 5.18.

Ba(NMeQuin-H)$_2$•2H$_2$O (**3**).

The product was obtained as a white solid (0.32 g, 53%); IR (KBr, v_{max}/cm^{-1}): (OH) 3350, (C=O) 1641 and (C=C) 1599; ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H, $COCH_3$), 3.42 (s, 3H, N-CH_3), 7.06 (t, 1H, H-6), 7.26 (d, 1H, H-8, $J_{7,8}$=8.4), 7.52 (t, 1H, H-7) and 8.07 (d, 1H, H-5, $J_{5,6}$=8.1); ^{13}C NMR (DMSO-d_6): δ 199.9 (C-9), 175.0 (C-4), 163.7 (C-2), 141.1 (C-8a), 132.5 (C-7), 126.3 (C-5), 121.5 (C-6), 114.1 (C-8), 120.6 (C-4a), 108.0 (C-3), 32.4 (C-10) and 28.3 (N-CH_3); FAB-MS: *m/z* (%) = 571 (9) [BaL_2-2H$^+$].

Anal. Calcd. for $BaC_{24}H_{24}N_2O_8$ (605): C, 47.60; H, 3.97; N, 4.63. Found: C, 47.33; H, 3.80; N, 4.82.

Mg_2(OH)(NHQuin-H)$_3$•4H$_2$O (**4**).

The product was obtained as a white solid (0.59 g, 79%); IR (KBr, v_{max}/cm^{-1}): (OH) bridge 3420, (OH) 3355, (C=O) 1631 and (C=C) 1599; ^{1}H NMR (DMSO-d_6): δ 2.48/2.54 (s, 3H, $COCH_3$), 6.94-7.12 (m, 2H, H-6 and H-8), 7.40 (t, 1H, H-7), 7.92 (d, 1H, H-5, $J_{5,6}$=7.5) and 10.40/10.64 (two s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 199.1/199.5 (C-9), 178.0/179.4 (C-4), 165.4/166.6 (C-2), 139.0/140.4 (C-8a), 132.0/132.5 (C-7), 126.0/126.3 (C-5), 121.2/122.9 (C-6), 114.7/115.3 (C-8), 120.4/120.7 (C-4a), 106.7/108.4 (C-3) and 32.5/32.8 (C-10); FAB-MS: *m/z* (%) = 654 (6) [Mg_2L_3-3H$^+$], 428 (34) [MgL_2-2H$^+$].

Anal. Calcd. for $Mg_2C_{33}H_{33}N_3O_{14}$ (743): C, 53.30; H, 4.44; N, 5.65. Found: C, 53.44; H, 4.29; N, 5.80.

Zn(NHQuin-H)$_2$•2H$_2$O (**5**).

The product was obtained as a white solid (0.40 g, 76%); IR (KBr, v_{max}/cm^{-1}): (OH) 3360, (C=O) 1660, 1651 and (C=C) 1595; ^{1}H NMR (DMSO-d_6): δ 2.49/2.52 (s, 3H, $COCH_3$), 7.02 (t, 1H, H-6), 7.11 (d, 1H, H-8, $J_{7,8}$=7.8), 7.43 (t, 1H, H-7), 7.92 (d, 1H, H-5, $J_{5,6}$=7.5) and 10.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 200.8 (C-9), 179.2 (C-4), 165.5 (C-2), 139.4 (C-8a), 132.5 (C-7), 126.2 (C-5), 122.0 (C-6), 115.1 (C-8), 121.0 (C-4a), 107.6 (C-3) and 32.8 (C-10); FAB-MS: *m/z* (%) = 469 (51) [ZnL_2-2H$^+$].

Anal. Calcd. for $ZnC_{22}H_{20}N_2O_8$ (503.5): C, 52.43; H, 3.97; N, 5.56. Found: C, 52.20; H, 3.67; N, 5.38.

Results and Discussion.

The reaction of ligands **NMeQuin** and **NHQuin** with metal halides of Mg(II), Zn(II) and Ba(II) afforded the metal complexes **1-5** in good yields listed in the experimental section. A typical experimental procedure for the preparation of complexes **1-5** requires treatment of a solution of the ligand (1 equiv.) in warm methanol with an aqueous solution of 0.1 mol dm^{-3} NaOH up to pH 8; the resulting solution is concentrated *in vacuo*, dissolved in water, the pH adjusted at 9.5-10 and treated with 10% aqueous solution of the metal salt (3 equiv.). The same complexes are formed irrespective of the ligand to metal ratio used (1:3 or 1:5).

The elemental analyses are generally in accordance with the structures $M_2(OH)L_3$•zH_2O or ML_2•zH_2O. Reaction of the ligands with MCl_2 (M = Zn^{2+}, Ba^{2+}) yields the complexes Zn(NMeQuin-H)$_2$•2H$_2$O (**2**), Ba(NMeQuin-H)$_2$•2H$_2$O (**3**) and Zn(NHQuin-H)$_2$•2H$_2$O (**5**) as proposed from their elemental analyses. On the other hand, reaction of the ligands with $MgCl_2$ yields complexes Mg_2(OH)(NMeQuin-H)$_3$•4H$_2$O (**1**) and Mg_2(OH)(NHQuin-H)$_3$•4H$_2$O (**4**).

The IR spectra of ligands **NMeQuin** and **NHQuin** show two strong bands at 1658/1661 and 1623/1622 cm^{-1} characteristic for the lactam and the enolic CO, respectively. The shift of the carbonyl absorption to lower wavenumbers (*ca* 10-30 cm^{-1}) in metal complexes **1-5** is characteristic for the coordination of the CO function [22]. New bands at higher frequencies (3350-3370 cm^{-1}) appear when the ligand is complexed to the metals. These bands can be attributed to the stretching vibration of the OH group from water molecules which are either coordinated to the metals or captured in the crystal lattice [22]. However, the OH stretching mode involving the hydroxyl bridge appeared at 3420/3417 cm^{-1} (complexes **1**, **4** respectively) [23].

In the ^{1}H NMR spectra of **NHQuin** and **NMeQuin** there is a broad signal at 17.04 ppm which is assigned to the enolic proton of position 4. The disappearance of this signal in the ^{1}H NMR spectra of complexes **1-5** is an indication of complexation between the oxygen at position 4 and the metal ion. In addition, complexation *via* the amide nitrogen of **NHQuin** is excluded by

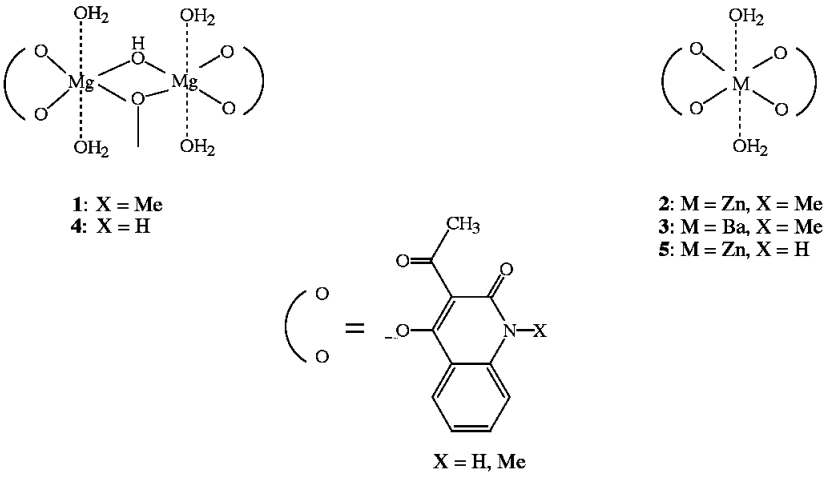


Figure 3 Proposed structures of the synthesized complexes

the existence of a signal attributed to the NH group at the region of 10.6-11.5 ppm in the ^{1}H NMR spectra of the ligand as well as the complexes **4** and **5**.

As for the ^{13}C NMR spectra of complexes **1-5**, the signals with the major importance are those of the carbonyl atoms at positions 2, 4 and 9. The signals of the carbonyl atoms C-2 and C-4 in the ^{13}C NMR spectra of complexes **1-5** are shifted upfield in comparison with these signals in the free ligands **NHQuin** and **NMeQuin**, in contrast to the signal of C-9 which is shifted downfield, indicating complexation with the the metal ions. Another observation of great importance is that the ^{13}C NMR spectra of compounds **1** and **4** (complexes with Mg^{2+}) exhibit two resonances for each carbon at positions 2, 4 and 9, suggesting an unequivalent coordination environment of three ligand molecules coordinated to Mg^{2+} cations, as depicted in Figure 3. In fact, the two ligands are symmetrical and the third one is complexed in a different way, a pattern which explains the two resonances of each carbon. On the contrary, complexes **2**, **3** and **5** exhibit only one signal for each carbon at positions 2, 4 and 9 because the two ligands are symmetrically complexed with the metal ion.

The FAB-MS Spectra of compounds **1-5** were recorded in 3-NOBA (3-nitro-benzyl alcohol) and revealed their nuclearities. The FAB-MS spectrum of compound **1** shows peaks at m/z 696 and 457 corresponding to the fragments $[Mg_2(NMeQuin)_3\text{-}3H]^+$ and $[Mg(NMeQuin)_2\text{-}2H]^+$ respectively. Moreover compound **4** shows peaks at m/z 654 and 429 corresponding to the fragments $[Mg_2(NHQuin)_3\text{-}3H]^+$ and $[Mg(NHQuin)_2\text{-}2H]^+$ respectively. On the other hand, compounds **2**, **3** and **5** show peaks at 497, 571 and 469 respectively corresponding to the formulae $[Zn(NMeQuin)_2\text{-}2H]^+$, $[Ba(NMeQuin)_2\text{-}2H]^+$ and $[Zn(NHQuin)_2\text{-}2H]^+$. No peaks corresponding to higher ions were observed, indicating the exclusion of the formula M_2L_3. The revealed nuclearities of the studied complexes are presented in several similar complexes of Ba(II) with oxygenated ligands where the metal centers are connected by bridging oxygen atoms of various kinds [24].

Conclusion.

Five novel mononuclear and binuclear Mg(II), Zn(II) and Ba(II) complexes with **NMeQuin** and **NHQuin** ligands have been succesfully synthesized and characterized by means of elemental analyses, FT-IR and ^{1}H/^{13}C NMR Spectroscopy and Mass Spectrometry. Mg(II) complexes follow the general molecular formula $Mg_2(OH)L_3$ (where L = **NMeQuin** or **NHQuin**) whereas Zn(II) and Ba(II) complexes follow the molecular formula ML_2. The ^{13}C NMR spectra of these compounds play an important role for the elucidation of their structure. In Mg(II) complexes the three ligands are not symmetrical to each other, they act in monodentate and bidentate mode, as explained through the existence of two signals for each carbon atom at positions 2, 4 and 9 in the ^{13}C NMR spectra. On the contrary, the two ligands in the Zn(II) and Ba(II) complexes are symmetrical, they act as bidentate ligands, since there is only one signal for each carbon atom at the same positions in the ^{13}C NMR spectra.

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