Synthesis and Characterization of $\alpha, \alpha'$-Dimethyl-4-[1-Hydroxy-4-[4-(Hydroxyldiphenyl- Methyl)-1-Piperidinyl]Butyl] Benzeneacetic Acid Metal Complexes of Biological Interest

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Abstract

$\alpha, \alpha'$-Dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzene acetic acid generically known as fexofenadine or carboxyterfenadine is a second generation H1-receptor antagonist, much widely used due to its non-sedative effects. Metal complexes of fexofenadine with various essential and trace elements of biological interest, have been synthesized and characterized by FT-IR, 1H-NMR, UV, CHN elemental analysis. Conductometric titration was carried out to determine the mole ratio of interaction of the drug and metal. Spectral data clearly showed the complexation of fexofenadine with nitrogen of the piperidine ring in case of magnesium, calcium, chromium and manganese complexes while oxygen of carboxylato group is involved in complexation with iron, cobalt nickel, copper, zinc and cadmium. Elemental analysis reveals monodentate character of these complexes.

Keywords: Fexofenadine; H1-receptor antagonist; Essential and trace elements; FT-IR; 1H-NMR

Introduction

Fexofenadine (carboxyterfenadine) (Figure 1), is $\alpha, \alpha'$-Dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl] benzeneacetic acid generically known as fexofenadine or carboxyterfenadine is a second generation H1-receptor antagonist, much widely used due to its non-sedative effects. Metal complexes of fexofenadine with various essential and trace elements of biological interest, have been synthesized and characterized by FT-IR, 1H-NMR, UV, CHN elemental analysis. Conductometric titration was carried out to determine the mole ratio of interaction of the drug and metal. Spectral data clearly showed the complexation of fexofenadine with nitrogen of the piperidine ring in case of magnesium, calcium, chromium and manganese complexes while oxygen of carboxylato group is involved in complexation with iron, cobalt nickel, copper, zinc and cadmium. Elemental analysis reveals monodentate character of these complexes.

Literature survey reveals few studies on the interaction of metal ions with fexofenadine [8]. Metals are considered essential to a human body being an integral part of an organic structure in performing physiologically important and vital functions in the body [9]. It seems that the role of metal ions is imperative for the way of function of fexofenadine. Synthesis and characterization of new metal complexes with fexofenadine are of great importance for better understanding of drug-metal interactions [10]. A thorough survey of the literature has revealed that no work has been reported on the synthesis of fexofenadine metal complexes with other co-administered drugs as levofloxacin [11], enoxacin [12,13], sparflaxacin [14], gatifloxacin [15], gliclazide [16] and atenolol [17].

In this paper, we present the synthesis of a series of fexofenadine–metal complexes with metals of biological interest in an attempt to find the mode of coordination as well as to study drug–metal interactions. More specifically, the complexes have been synthesized and characterized by elemental analysis and diverse spectroscopic techniques (IR, UV-Vis and NMR techniques).

Experimental

Materials

Fexofenadine was a kind gift from Getz Pharmaceuticals (Pvt.) Ltd. Karachi, Pakistan. The metal salts and other chemicals were of analytical grade (Merck Germany). All the glassware's were washed with chromic acid followed by a thorough washing with deionized water which was freshly prepared in the laboratory.

Instrumentation

Conductometric studies were carried on Vernier LabPro. Data acquisition and analysis were carried out by using the Logger pro 3.2 software. Thin Layer Chromatography (TLC) was performed on a HSF-254 TLC plate and the samples were visualized under a UV lamp, melting point of complexes was recorded on a Gallenkamp electrothermal melting point apparatus and is uncorrected. The characterization of fexofenadine metal complexes was carried out by FT-IR spectrophotometer (Shimadzu Prestige-21 200 VCE), coupled to a P IV-PC and loaded with IR resolution software. The disks were

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Received April 23, 2014; Accepted May 28, 2014; Published June 02, 2014

Citation: Arayne SM, Sultana N, Shehnaz H, Haider A (2014) Synthesis and Characterization of $\alpha, \alpha'$-Dimethyl-4-[1-Hydroxy-4-[4-(Hydroxydiphenyl- Methyl)-1-Piperidinyl]Butyl] Benzeneacetic Acid Metal Complexes of Biological Interest. Mod Chem appl 2: 127. doi:10.4172/2329-6798.1000127
placed in the holder directly in the IR beam. Spectra were recorded at a resolution of 2 cm⁻¹, and 50 scans were accumulated. Stability of these complexes was studied for 4.5 CF stability chamber from PARAMETER Generation and Control USA with constancy control ± 0.5%.

Proton NMR studies of metal complexes were carried out on a Bruker AMX 500MHz instrument in deuterated methanol (CD₂OD) using TMS as an internal standard. CHN elemental studies were carried out by standard micro methods using Carlo Erba 1106.

Conductometric titrations

Prior to the synthesis of the metal complexes, the stoichiometry of complexes was determined using conductometric titration technique [18]. 0.1 mM metal solution was titrated against the drug solution at 298 K with constant stirring and change in conductivity was measured until the addition resulted in no change of conductivity values of the resulting solution. Similar process was repeated for all metals.

Synthesis of metal complexes

Metal complexes of fexofenadine were synthesized with magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium hydrated salts. The synthesis of magnesium, calcium, chromium and manganese complexes with fexofenadine were carried out in M:L ratio of 1:2 while for rest of the metals M:L ratio was 1:1. These ratios were determined earlier by conductometric measurements. Drug and metal salts were dissolved separately in hot methanol (20 mL) and deionized water (10 mL). Both solutions were mixed with constant stirring and then refluxed for about three hours. The reactions were monitored by thin layer chromatography. The volume of the reaction mixture was then reduced by evaporation, filtered while hot and then kept undisturbed for crystal growth at room temperature.

The growth of crystals depended upon many factors like type of crystal, environment, concentration of solution, temperature etc. Due to this all these metal complexes had variable time of crystallization. Crystals of magnesium, calcium, chromium and manganese complexes were obtained within 10 to 15 days, while the iron complex took one month for crystallization. Cobalt, nickel, copper, zinc and cadmium complexes were crystallized in 20~25 days. Crystals of different colors for different complexes were obtained. Finally, these were filtered, washed with water and methanol, and vacuum dried. Their melting points were recorded and were recrystallized from absolute methanol.

Metal complexes of magnesium, calcium, chromium, manganese, ferric hydrated salts. The synthesis of magnesium, calcium, chromium and manganese complexes with fexofenadine were carried out in M:L ratio of 1:2 while for the rest of the metals M:L ratio was 1:1. These ratios were determined earlier by conductometric measurements. Drug and metal salts were dissolved separately in hot methanol (20 mL) and deionized water (10 mL). Both solutions were mixed with constant stirring and then refluxed for about three hours. The reactions were monitored by thin layer chromatography. The volume of the reaction mixture was then reduced by evaporation, filtered while hot and then kept undisturbed for crystal growth at room temperature.

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Physical data

Fexofenadine: Color white, m.p. 190°C, UV nm (ε): 1.775(218 nm), IR (KBr) vmax: 3400-3350 cm⁻¹, 2926 cm⁻¹, 1781 cm⁻¹, 1691 cm⁻¹, 1588 cm⁻¹, 1466 cm⁻¹, 1437 cm⁻¹, 1377 cm⁻¹, 1310 cm⁻¹, 1215 cm⁻¹, 1006 cm⁻¹, 891 cm⁻¹, 834 cm⁻¹, 768 cm⁻¹, 755 cm⁻¹, 746 cm⁻¹, 739 cm⁻¹, 731 cm⁻¹, 720 cm⁻¹, 711 cm⁻¹, 698 cm⁻¹, 687 cm⁻¹, 676 cm⁻¹, 666 cm⁻¹, 655 cm⁻¹, 645 cm⁻¹, 634 cm⁻¹, 623 cm⁻¹, 612 cm⁻¹, 601 cm⁻¹, 590 cm⁻¹, 580 cm⁻¹, 570 cm⁻¹, 560 cm⁻¹, 550 cm⁻¹, 535 cm⁻¹, 526 cm⁻¹, 517 cm⁻¹, 508 cm⁻¹, 499 cm⁻¹, 490 cm⁻¹, 481 cm⁻¹, 472 cm⁻¹, 463 cm⁻¹, 454 cm⁻¹, 445 cm⁻¹, 436 cm⁻¹, 427 cm⁻¹, 418 cm⁻¹, 409 cm⁻¹, 400 cm⁻¹, 391 cm⁻¹, 382 cm⁻¹, 373 cm⁻¹, 364 cm⁻¹, 355 cm⁻¹, 346 cm⁻¹, 337 cm⁻¹, 328 cm⁻¹, 319 cm⁻¹, 310 cm⁻¹, 301 cm⁻¹, 292 cm⁻¹, 283 cm⁻¹, 274 cm⁻¹, 265 cm⁻¹, 256 cm⁻¹, 247 cm⁻¹, 238 cm⁻¹, 229 cm⁻¹, 220 cm⁻¹, 211 cm⁻¹, 202 cm⁻¹, 193 cm⁻¹, 184 cm⁻¹, 175 cm⁻¹, 166 cm⁻¹, 157 cm⁻¹, 148 cm⁻¹, 139 cm⁻¹, 130 cm⁻¹, 121 cm⁻¹, 112 cm⁻¹, 103 cm⁻¹, 94 cm⁻¹, 85 cm⁻¹, 76 cm⁻¹, 67 cm⁻¹, 58 cm⁻¹, 49 cm⁻¹, 40 cm⁻¹, 31 cm⁻¹, 22 cm⁻¹, 13 cm⁻¹, 4 cm⁻¹, 3 cm⁻¹, 2 cm⁻¹, 1 cm⁻¹, 0 cm⁻¹.

Fexofenadine magnesium complex: Colorless, Yield 50%, m.p. 112°C, UV nm (ε): 0.4615(207 nm), IR (KBr) vmax: 3421 ± 2967 dm⁻¹, 1680 dm⁻¹, 1446.45 sm, 1320 dm⁻¹, 0.4615(207 nm) 1300-1320 dm⁻¹, 1300 dm⁻¹, 1090 dm⁻¹, 1410 dm⁻¹, 1637 dm⁻¹, 1351 dm⁻¹, 704 dm⁻¹, 1000 dm⁻¹, 670 dm⁻¹, 570 dm⁻¹, 550 dm⁻¹, 535 dm⁻¹, 526 dm⁻¹, 517 dm⁻¹, 508 dm⁻¹, 499 dm⁻¹, 490 dm⁻¹, 481 dm⁻¹, 472 dm⁻¹, 463 dm⁻¹, 454 dm⁻¹, 445 dm⁻¹, 436 dm⁻¹, 427 dm⁻¹, 418 dm⁻¹, 409 dm⁻¹, 400 dm⁻¹, 391 dm⁻¹, 382 dm⁻¹, 373 dm⁻¹, 364 dm⁻¹, 355 dm⁻¹, 346 dm⁻¹, 337 dm⁻¹, 328 dm⁻¹, 319 dm⁻¹, 310 dm⁻¹, 301 dm⁻¹, 292 dm⁻¹, 283 dm⁻¹, 274 dm⁻¹, 265 dm⁻¹, 256 dm⁻¹, 247 dm⁻¹, 238 dm⁻¹, 229 dm⁻¹, 220 dm⁻¹, 211 dm⁻¹, 202 dm⁻¹, 193 dm⁻¹, 184 dm⁻¹, 175 dm⁻¹, 166 dm⁻¹, 157 dm⁻¹, 148 dm⁻¹, 139 dm⁻¹, 130 dm⁻¹, 121 dm⁻¹, 112 dm⁻¹, 103 dm⁻¹, 94 dm⁻¹, 85 dm⁻¹, 76 dm⁻¹, 67 dm⁻¹, 58 dm⁻¹, 49 dm⁻¹, 40 dm⁻¹, 31 dm⁻¹, 22 dm⁻¹, 13 dm⁻¹, 4 dm⁻¹, 3 dm⁻¹, 2 dm⁻¹, 1 dm⁻¹, 0 dm⁻¹.

Citation: Arayne SM, Sultana N, Shehnaz H, Haider A (2014) Synthesis and Characterization of α,α-Dimethyl-4-[1-Hydroxy-4-[4-(Hydroxydiphenyl-Methyl)-1-Piperidiny]Butyl] Benzeneacetic Acid Metal Complexes of Biological Interest. Mod Chem appl 2: 127. doi:10.4172/2329-6798.1000127
**Fexofenadine cobalt complex:** Color light green Yield 33%, m.p. 212°C, UV nm (ε): 0.78(204nm), IR (KBr) νmax: 3618 sm, 3376 db, 2924 m, db, 1717, 1697 db, m, 1605-1508 trp, m, 1480 s, 1310 db, sm, 1220 s, 1115 db, sm, 1033-1007 db, 753 m, 537 sm, 468 sm. 1H NMR (MeOD, 400 MHz) δ: 6.99, 7.08, 7.21 aromatic, 3.6 –CH2-COOCd, 2.29, 2.19 (t, J=7.69 Hz) CH2-N, 1.77 (t, J=7.0 Hz) 4.5(CH2)3-N open chain, 4.49 (J=4.8Hz) (piperidine)(Ph)-CH-OH, 2.0 (s) alcoholic. Calculated for C36H51CdNO4: C, 64.17; H, 7.62; N, 2.08. Found: C, 68.91; H, 8.26; N, 2.28.

**Fexofenadine copper complex:** Color light blue Yield 44%, m.p. 110°C, UV nm (ε): 1.16(244nm), IR (KBr) vmax: 3390sm, 2986db,m, 1717 sm db, 1447 m, 1380 db, sm, 1300 sm, 1150-1098 db, 950-990 trp, sm, 850 sm, 750 sm, 707 m, 637-619 db, m, 1H NMR (MeOD, 400 MHz) δ: 6.99, 7.07 aromatic, 4.45 –CH2-CH2-N, 2.29, 2.19 (t, J=3.5 Hz) CH2-N, 1.39, 1.34 -CH2-CH2-N, 2.36 (t, J=14.0 Hz) 1.39 (t, J=7.0 Hz) 1.77 (t, J=6.3 Hz) 4.5(CH2)3-N open chain, 3.49 (J=4.8Hz) Ph-CH-OH, 3.9 (s) alcoholic. Calculated for C36H51CuNO4: C, 69.14; H, 8.22; N, 2.24. Found: C, 69.10; H, 8.29; N, 2.27.

**Fexofenadine zinc complex:** Color dirty white Yield 46.64%, m.p. 102°C, UV nm (ε): 0.86(217nm), IR (KBr) vmax: 3618 sm, 3376 db, 2924 m, db, 1717, 1697 db, m, 1605-1508 trp, m, 1480 s, 1310 db, sm, 1220 s, 1115 db, sm, 1033-1007 db, 753 m, 537 sm, 468 sm. 1H NMR (MeOD, 400 MHz) δ: 6.96, 7.08, 7.21 aromatic, 3.49 –CH2-COOZn, 2.29, 2.19 (t, J=2.0 Hz) CH2-N, 1.59, 1.34 (t, J=1.34 Hz), -CH2-CH2-N, 3.9 (t, J=14.0 Hz), 1.39 (t, J=8.0 Hz), 1.77 (t, J=7.0 Hz) 4.5(CH2)3-N open chain, 2.51 (J=4.8Hz)(piperidine)(Ph)-CH-OH, 5.5 (s) alcoholic. Calculated for C36H51ZnNO4: C, 68.94; H, 8.20; N, 2.23. Found: C, 68.91; H, 8.26; N, 2.28.

**Fexofenadine cadmium complex:** Colorless Yield 42.5%, m.p. 132°C, UV nm (ε): 1.95(221nm), IR (KBr) vmax: 3629 sm, 3450 s, 3070 db, m, 1710-1725 db, sm, 1491-1972, db, sm, 1447 m, 1410 db, m, 1270 db sm, 1154 m, 1099-1017 db, m, 950 db, sm, 860 sm, 940 sm, 750 sm. 1H NMR (MeOD, 400 MHz) δ: 6.99, 7.30 aromatic, 3.6 –CH2-CH2OCd, 2.29, 2.19 (t, J=3.75 Hz)(t, J=7.69 Hz) CH2-N, 1.59, 1.34 (t, J=5.75 Hz), -CH2-CH2-N, 2.36 (t, J=14.0 Hz) 1.39 (t, J=8.0 Hz), 1.77 (t, J=7.0 Hz) 4.5(CH2)3-N open chain, 3.49 (J=5.7Hz) piperidine-CH-OH, 4.4 (s) alcoholic. Calculated for C36H51CdNO4: C, 64.13; H, 7.62; N, 2.08. Found: C, 64.17; H, 7.67; N, 2.11.

**Results and Discussion**

Fexofenadine is a zwitterion having good solubility in stomach and small intestinal fluids. Grapefruit juice decreases the dissolution of fexofenadine because of its interaction with excipients included in formulation to impair this process [19]. In the light of this study was initiated to explore fexofenadine interactions with metals of biological interest.

Transition metal complexes of fexofenadine were synthesized in molar ratios as described earlier in methanol. Prior to synthesis complexation studies between fexofenadine and metals were investigated by conductometric titrations. The effects on conductivity caused by the increased volume of reaction medium were compensated by correcting it for dilution by correction term [(V + V')/ V'] and equivalence point were calculated. Molar conductivity values (Λm) were then calculated by correcting conductivity values (µS) using the formula Λ m= K/C, where, K is the measured conductivity and C is the electrolyte concentration.

From the graph it is found that magnesium, calcium, chromium and manganese metal ions bind to ligand in the 2:1 ratio, whereas nickel, copper, zinc, cadmium and iron complexes are formed in equimolar ratio (Figure 2).

Metal complexes of fexofenadine were synthesized by refluxing fexofenadine with metal salt solutions in a mixture of methanol and water in equimolar ratios and then crystallizing them at room temperature. Solubility and melting points were noted; all these complexes are 50% soluble in methanol and 25% soluble in ethanol, ethyl acetate and acetone.

Stability of these complexes was studied by taking their melting points at an interval of 24 hours for seven days according to Q1A (R2) compliant [20]. Samples were stored at 25°C/60% RH, 30°C/65% RH, 30°C/75% RH, 30°C/75% RH and 25°C/40% RH. Melting points of the complexes were recorded after 24 hours for 7 days. No appreciable changes in the melting points were observed, and the estimated error was ± 1°C. It was concluded that the complexes were stable according to ICH guidelines [21]. Their structures were established from the elemental analyses, which agree well with their proposed formulae.
Infrared studies

Fexofenadine metal complexes were characterized by studying the most typical vibrations in the IR spectrum in the region 400–4000 cm⁻¹. In the IR spectra of metal complexes, some very prominent peak shifting has been observed along with a change in intensities of several important peaks indicating complexation of fexofenadine with metals (Figures 3 and 4).

The major infrared absorption bands of fexofenadine for -OH stretching occurred in the region 3300-3370 cm⁻¹ and out of plane bending at 965 cm⁻¹, C-H stretching at 3058.04 cm⁻¹ due to strained molecule because of the substitution of aromatic rings, a sharp band of C=O stretching at 1700 cm⁻¹, at 1600 and 1475 cm⁻¹, C=C aromatic medium weak bands, at 1447.60 cm⁻¹ bending absorptions of –CH₂, C-O medium stretching vibration at 1279 cm⁻¹, at 1099 cm⁻¹ C-N stretching region and at 1167 and 747 cm⁻¹ four or more CH₂ groups.

On comparing the IR spectrum of fexofenadine with its magnesium, manganese, iron and cobalt complexes it is found that the major doublet band of -OH group shifted to 3420 cm⁻¹ as the singlet sharp band which was due to –O-metal and N-metal stretching [22,23]. In calcium complex two very weak bands appeared at 3650 cm⁻¹ and another at 3411 cm⁻¹ as sharp band, in chromium complex as a sharp band it was at 3400 cm⁻¹, in case of manganese complex a very weak band was at 3647 cm⁻¹. In case of iron ammonium citrate this band appeared as broadband in the region 3440-3380 cm⁻¹ which was due to the N-H stretching of ammonium ion. In iron sulfate complex it was at 3400-3390 cm⁻¹ as a medium band. In nickel and copper complex a sharp stretching band appeared at 3390 cm⁻¹. Fexofenadine zinc complex showed three consecutive small singlet at 3618 and sharp doublet at 3376. In cadmium complex a small band at 3629 cm⁻¹ and 3450 cm⁻¹ was recorded. Water bands are also appeared above 3000 cm⁻¹ (Figures 5 and 6).

Fexofenadine showed C=O stretching at 1700 cm⁻¹ due to carboxylic group which shifted to 1680 cm⁻¹ as doublet strong band in magnesium.
complex whereas in cadmium, calcium, chromium, manganese, iron chloride, iron sulfate, iron ammonium citrate, cobalt, nickel, copper and zinc complexes this band appeared in the region 1715-1720 cm$^{-1}$ [24,25] complexes indicating the coordination of this moiety to the metal ions [26] (Figure 7).

Fexofenadine C=O stretching appeared at 1279 cm$^{-1}$ as single band of medium stretching, while in magnesium, calcium and cobalt complex this band appeared at 1300 cm$^{-1}$, in chromium it was in the form of broadband, whereas in manganese and iron chloride it was in the region of 1300-1280 cm$^{-1}$, iron sulfate it was at 1264 cm$^{-1}$ as weak band, in iron ammonium citrate it appeared at 1253 cm$^{-1}$ as a medium intensity band. In nickel complex at 1300 cm$^{-1}$ as medium band whereas
in copper it was a doublet of weak intensity, in zinc complex a weak doublet appeared at 1248 cm$^{-1}$ and in cadmium complex at 1260 cm$^{-1}$. The change in the C-O stretching showed that the carboxylate ion also coordinated to a metal [27].

The C-N stretching in the reference compound was recorded at 1167 cm$^{-1}$ as medium stretching but in magnesium, chromium, manganese, ferric chloride, cobalt, copper, zinc and cadmium complex this appeared in the region 1149-1151 cm$^{-1}$, a sharp doublet appeared at 1100-1140 cm$^{-1}$ in calcium, whereas in nickel complex it was at 1120 cm$^{-1}$ as a medium band. In iron sulfate a doublet band was found at 1114 cm$^{-1}$ because of metal to nitrogen bonding and was absent in iron ammonium citrate [28-30].

The medium intensity bands of metal nitrogen absorptions were recorded in the region 1370-1395 cm$^{-1}$ as medium bands whereas in the range 670-580 cm$^{-1}$ as low intensity bands. From the above stretching modes of metal nitrogen stretching in fexofenadine metal complexes, there is no coordination of metal with nitrogen as there are no strong bands in these regions in the spectrum of fexofenadine [26,31].

Metal oxygen stretching was recorded at 1510-1490, weak bands of metal oxygen appeared in low intensity region in between 500-600 cm$^{-1}$ as sharp and weak singlets and medium doublets [24,29]. When atoms of higher atomic masses were attached to the oxygen of carboxylate ion the stretching frequency lowered and another reason is that if metal oxygen bond was weaker the stretching frequency will also lower. That's why weaker bands are recorded at lower intensity.

The methylene stretching frequencies were recorded in the region 2890-2870 cm$^{-1}$ as strong bands in calcium, chromium and cadmium but prominent bands in the rest of the complexes [22].

$^{1}$H NMR studies
The NMR spectra of fexofenadine and its metal complexes were recorded in deuterated methanol on 400 MHz Avance 500 spectrophotometer.

On comparing main peaks of fexofenadine with its complexes, it is observed that all the signals of the free ligand are present in the 1HNMR spectra of the complexes. Fexofenadine showed the aromatic proton resonating at δ 7.19 (s, J=1.16 Hz), 7.11 (s, J=0.5 Hz) and 7.06. The proton resonating at 6.20 is assigned to N-H proton, at 61.52 are assigned for two methyl on tertiary carbon. Protons of piperidine ring CH$_2$-N and -CH$_2$-CH$_2$-N resonate at δ 2.29, 2.19 and 2.34 (t, J=12.2 Hz), respectively, at δ 4.95 (s) are alcoholic protons.

At 1.42, 1.52 and 1.64 ppm shifting of methyl protons of tertiary carbon adjacent to carboxylic group were observed in fexofenadine iron chloride and iron sulfate complex, whereas there was a shift to 2.92 ppm for iron chloride and 2.19 for iron sulfate complex which confirms that the coordination of metal with nitrogen of piperidine ring and carboxylic group was evidenced from $^{1}$H NMR data.

At 1.46-1.64 ppm and methylene protons of piperidine ring shifted to 2.24 ppm confirmed that the coordination of metal with nitrogen of piperidine ring and carbonylic group was evidences from $^{1}$H NMR data of cobalt complex.

Spectroscopic studies as UV, IR, $^{1}$H NMR, and CHN analysis fully supports the formation of fexofenadine metal complexes in which fexofenadine is coordinated to the metal through piperidine nitrogen, oxygen of carboxylic group and oxygen of alcoholic group (Figures 2 and 3).

Conclusion
Fexofenadine metal complexes with magnesium, calcium, chromium, manganese, iron (ferric and ferrous); cobalt, nickel, copper, zinc and cadmium were synthesized and characterized by FT-IR, $^{1}$H-NMR and elemental analysis. Fexofenadine coordinate to metal ions to form stable monodentate complexes. The coordination being through piperidine nitrogen in case of magnesium, calcium, chromium and manganese complexes and with oxygen of carboxylato group in complexation with iron, cobalt nickel, copper, zinc and cadmium.

Disclosure Statement
There are no actual or potential conflicts of interest in this paper.

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Citation: Arayne SM, Sultana N, Shehnaz H, Haider A (2014) Synthesis and Characterization of α,α-Dimethyl-4-[1-Hydroxy-4,4-(Hydroxydiphenyl)-Methyl]-1-Piperidinyl]Butyl] Benzeneacetic Acid Metal Complexes of Biological Interest. Mod Chem appl 2: 127. doi:10.4172/2329-6798.1000127

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