J Therm Anal Calorim (2010) 99:639–647
DOI 10.1007/s10973-009-0421-9

Metal complexes of fenoterol drug

Preparation, spectroscopic, thermal, and biological activity characterization

M. H. Soliman · Gehad G. Mohamed · Eman A. Mohamed

Received: 25 February 2009 / Accepted: 14 August 2009 / Published online: 16 September 2009

Abstract Metal complexes of fenoterol (FEN) drug are prepared and characterized based on elemental analyses, IR, ^{1}H NMR, magnetic moment, molar conductance, and thermal analyses (TG and DTA) techniques. From the elemental analyses data, the complexes are formed in 1:2 [Metal]:[FEN] ratio and they are proposed to have the general formula $[Cu(FEN)_2]\cdot 2H_2O$; $[M(FEN)_2(H_2O)_2]\cdot yH_2O$ (where M = Mn(II) ($y = 2$), Co(II) ($y = 4$), Ni(II) ($y = 4$), and Zn(II) ($y = 0$) and $[Cr(FEN)_2(H_2O)_2]Cl\cdot H_2O$. The molar conductance data reveal that all the metal chelates are non-electrolytes except Cr(III) complex, having 1:1 electrolyte. IR spectra show that FEN is coordinated to the metal ions in a uninegative bidentate manner with ON donor sites of the aliphatic –OH and secondary amine –NH. From the magnetic moment measurements, it is found that the geometrical structures of these complexes are octahedral (Cr(III), Mn(II), Co(II), Ni(II), and Zn(II)) and square planar (Cu(II)). The thermal behavior of these chelates is studied using thermogravimetric and differential thermal analyses (TG and DTA) techniques. The results obtained show that the hydrated complexes lose water molecules of hydration followed immediately by decomposition of the coordinated water and ligand molecules in the successive unseparate steps. The FEN drug, in comparison to its metal complexes is also screened for their antibacterial activity against bacterial species (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*), Yeasts (*Candida albicans* and *Saccharomyces cervisiae*), and Fungi (*Aspergillus niger* and *Aspergillus flavus*). The activity data show that the metal complexes have antibacterial activity like that of the parent FEN drug against one or more species.

Keywords Fenoterol · Metal complexes · IR · Molar conductance · Magnetic moment · ^{1}H NMR · Thermal analyses · Biological activity

M. H. Soliman · E. A. Mohamed
Chemistry Department, Faculty of Science, Helwan University, Helwan, Egypt

G. G. Mohamed (✉)
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
e-mail: ggenidy@hotmail.com

Introduction

Fenoterol (FEN, Fig. 1) is β_2-adrenoceptor agonist that may have clinical value in the treatment of congestive heart failure [1, 2]. FEN possesses two chiral centers and the drug is supplied as a racemic mixture of (R,R)-FEN and (S,S)-FEN. Previous studies using cardiomyocytes contractility have demonstrated that (R,R)-FEN is the active component and this compound is currently under development as a therapeutic agent [1, 2]. As part of the preclinical studies, the pharmacokinetics of (R,R)-FEN in rats was investigated, and an assay was developed to quantify (R,R)-FEN concentrations in rat plasma. The determination of FEN in plasma requires a sensitive assay as the plasma concentrations of the drug were commonly <10 ng/ml due to the compound's poor bioavailability and extensive metabolism via phase II pathways [3]. Plasma concentrations of FEN had been measured using a radioimmunoassay [4] and enzyme immunoassay [5] techniques as well as gas chromatography–MS [6, 7], LC–APCI–MS [8], and HPLC with fluorescence detection [9]. However, these methods required either expensive antibodies, derivatization procedures, or were not sensitive enough for the

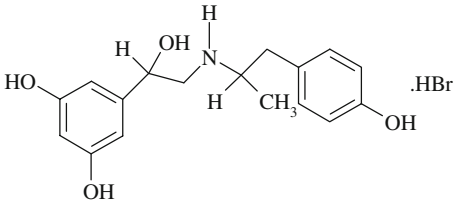


Fig. 1 Structure of FEN·HBr drug

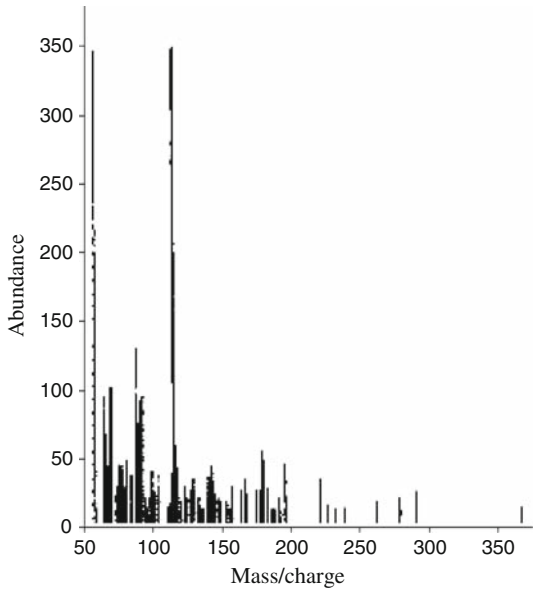


Fig. 2 Mass spectrum of FEN·HBr drug

determination of low FEN plasma concentrations that were required for pharmacokinetic studies.

However, in this work, metal chelates of Mn(II), Cr(III), Co(II), Ni(II), Cu(II), and Zn(II) transition metals with FEN drug molecule are prepared. The solid chelates are characterized using different physico-chemical methods like elemental analyses (C, H, N, and metal content), IR, ^{1}H NMR, magnetic moment, and thermal analyses (TG and DTA). Biological activities of the complexes are studied (Fig. 2).

Experimental

Materials and reagents

All chemicals used were of the analytical reagent grade (AR) and of the highest purity available. They included FEN (UniPharma), Cu(II) chloride dihydrate (Prolabo), Co(II) and Ni(II) chlorides hexahydrates (BDH), Zn(II) chloride dihydrate (Ubichem), Cr(III) chloride hexahydrate (Sigma), and Mn(II) chloride (Prolabo). Zinc oxide, disodium salt of ethylenediaminetetraacetic acid, EDTA were from Analar, ammonia solution (33% v/v), and ammonium chloride from El-Nasr pharm. Chem. Co., Egypt. Organic solvents used included absolute ethyl alcohol, diethylether, and dimethylformamide (DMF). These solvents were spectroscopic pure from BDH. Hydrogen peroxide, hydrochloric, and nitric acids (MERCK) were used. De-ionized water collected from all glass equipments was usually used in all preparations. The test organisms were kindly supplied from the microbiological resource center, Ain Shams University, Faculty of Agricultural, Egypt (CAIM, Cairo Mircen), and from Bacteriological Department of National Organization for Drug Control and Research (NODACR), ATCC, American type culture collection. Bacterial test organisms were inoculated on nutrient agar slants for 24 h at 37 °C. Yeast and Fungi organisms were inoculated on Sabouraud's dextrose-agar slants and incubated at 28 °C for 48 h (Jacobs and Gerstein, 1960). Several workers used these organisms repeatedly as test organisms.

Instruments

The molar conductance of the solid complexes in DMF was measured using Sybron-Barnstead conductometer (Meter-PM.6, $E = 3406$). Elemental microanalyses of the separated solid chelates for C, H, N, and S were performed at the Microanalytical Center, Cairo University. Infrared spectra were recorded on a Perkin-Elmer FT-IR type 1650 spectrophotometer in wave number region 4000–400 cm^{-1}. The spectra were recorded as KBr pellets. The ^{1}H NMR spectra were recorded using 300 MHz Varian-Oxford Mercury. The molar magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic corrections were made by Pascal's constant and Hg[Co(SCN)$_4$] was used as a calibrant. The thermogravimetric (TG and DTG) and differential thermal (DTA) analyses were carried out in dynamic nitrogen atmosphere (20 mL min^{-1}) with a heating rate of 10 °C min^{-1} using Shimadzu TG-60H and DTA-60H thermal analyzers.

Synthesis of metal complexes

The metal complexes were prepared by the addition of hot solution (60 °C) of the appropriate metal chloride salts (0.12, 0.13, 0.24, 0.24, 0.14, and 0.14 g of Cr(III), Mn(II), Ni(II), Co(II), Cu(II), Zn(II), respectively, 1 mmol) in an ethanol–water mixture (1:1, 25 mL) to the hot solution (60 °C) of FEN (1.04 g, 2 mmol) in the same solvent (25 mL). The resulting mixture was stirred under reflux for 1 h whereupon the complexes precipitated. They were collected by filtration, washed with a 1:1 ethanol: water mixture and diethyl ether.

Biological activity

The antimicrobial activities were carried out by disc diffusion technique as described in British pharmacopoeia (2003). Nutrient agar was melted at 45 °C and inoculated by the cell suspension (1 mL/100 mL) bacteria or yeast. The flask was shaken well and poured into a petri-dish (15 cm in diameter). Filter paper discs (6 mm) Whatman No. 2 were thoroughly moistened by antibiotics (50 µg), the treated discs were aseptically transferred and placed upon the surface of the inoculated plates with tested organisms and kept in a refrigerator for 1 h to permit diffusion of antimicrobial substances. The plates were incubated at 37 °C for 24 h in case of bacteria and at 28 °C for 48 h in case of yeast. The zones of inhibition were measured in mm the mean values of inhibitions were calculated from triple reading in each test [10].

The following media were used in studying the antimicrobial properties of FEN drug and its complexes. The weights are given in gram per one-liter medium.

Nutrient agar medium (pH 7.4)

It consists of beef extract (1.0 g), yeast extract (2.0 g), peptone (5.0 g), sodium chloride (5.0 g), agar (15.0 g), and distilled water (100 mL).

Sabouraud's dextrose agar medium (pH 5.6)

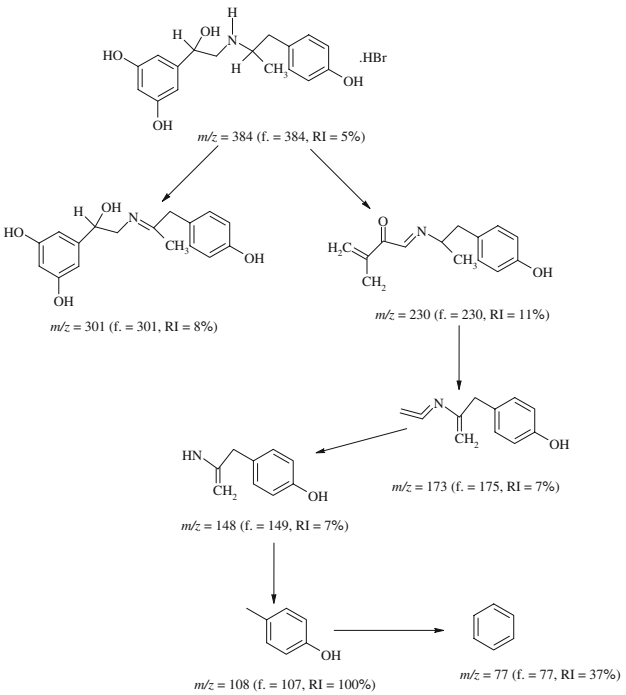
It consists of peptone (10 g), dextrose (20 g), agar (15 g), and distilled water (100 mL).

Results and discussion

The formation of metal complexes with organic compounds has long been recognized. However, the binary complexes of the cited drug with metal ions have not been studied yet, although they may be an area of interest. This is because they may affect the bioavailability of these drugs as certain metal ions were present in relatively appreciable concentration in biological fluids [11].

Mass spectrum of FEN·HBr

The electron impact mass spectrum of FEN is recorded and investigated at 70 eV of electron energy. The mass spectrum of the studied drug is characterized by moderate to high relative intensity molecular ion peaks at 70 eV. The abundance of the molecular ion depends mainly on the structure (and therefore the potential energy surface) of the molecular ion. The mass spectrum of FEN shows a well-defined parent peak at $m/z = 384$ (M+) with a relative intensity = 5%. The parent ion and the fragments obtained by cleavage in different positions in FEN molecule are shown in Scheme 1.



Scheme 1 Mass fragmentation pattern of FEN·HBr drug

Composition and structures of metal complexes

The aim of this work is to prepare the solid complexes of the drug under investigation and carrying out complete characterization using different physicochemical techniques. The isolated solid complexes of Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions with the FEN ligand are subjected to elemental analyses (C, H, N, and metal content), IR, ^{1}H NMR, magnetic moment studies, molar conductance, and thermal analyses (TG and DTA), to identify their tentative formulae in a trial to elucidate their molecular structures. The results of elemental analyses listed in Table 1 suggest that the complexes are formed in 1:2 [Metal]:[FEN] ratio and they proposed to have the general formulae $[Cu(FEN)_2]\cdot 2H_2O$ and $[M(FEN)_2(H_2O)_2]\cdot yH_2O$ (where M = Cr(III) ($y = 1$), Mn(II) ($y = 2$), Co(II) ($y = 4$), Ni(II) ($y = 4$), and Zn(II) ($y = 0$).

Molar conductivity measurements

The chelates are dissolved in DMF and the molar conductivities of 10^{-3} M of their solutions at 25 °C are measured. Table 1 shows the molar conductance values of the complexes. It is concluded from the results that, the divalent metal chelates are found to have molar conductance

Table 1 Analytical and physical data of FEN metal complexes

Complexes	Color/ % yield	Mp/°C	%Found (calcd.)				μ_{eff}/ B.M.	Λ_m/Ω^{-1} mol^{-1} cm^2
			C	H	N	M		
$[Cr(FEN)_2(H_2O)_2]Cl{\cdot}H_2O$ $C_{34}H_{48}CrN_2O_{11}$	Dark green (68)	>300	44.62 (44.80)	5.43 (5.30)	3.54 (3.10)	5.99 (5.70)	4.95	68.00
$[Mn(FEN)_2(H_2O)_2]{\cdot}2H_2O$ $C_{34}H_{50}MnN_2O_{12}$	Brown (70)	>300	38.11 (37.90)	5.32 (5.50)	5.11 (5.30)	6.53 (6.10)	4.82	18.50
$[Co(FEN)_2(H_2O)_2]{\cdot}4H_2O$ $C_{34}H_{50}CrN_2O_{12}$	Violet (62)	>300	45.26 (45.30)	5.39 (5.50)	2.90 (3.10)	6.13 (6.50)	5.28	24.50
$[Ni(FEN)_2(H_2O)_2]{\cdot}4H_2O$ $C_{34}H_{54}NiN_2O_{14}$	Yellowish green (73)	>300	36.17 (36.61)	5.38 (5.70)	2.53 (2.90)	6.69 (6.30)	3.66	16.80
$[Cu(FEN)_2]{\cdot}2H_2O$ $C_{34}H_{46}CuN_2O_{10}$	Brown (72)	>300	57.40 (57.81)	5.56 (5.95)	4.10 (3.95)	9.10 (9.00)	1.74	19.80
$[Zn(FEN)_2(H_2O)_2]$ $C_{34}H_{46}N_2O_{10}Zn$	White (65)	>300	46.43 (46.80)	4.85 (5.30)	2.82 (3.20)	6.26 (6.10)	Diam.	15.40

values of 15.40–24.50 Ω^{-1} mol^{-1} cm^2 indicating that all the divalent metal chelates are non-electrolytes. The Cr(III) complex is found to have a molar conductance value of 68 Ω^{-1} mol^{-1} cm^2 indicating its electrolytic nature and of the type 1:1 electrolyte.

IR spectral studies

The IR data of the spectra of FEN drug and its complexes are listed in Table 2. The IR spectra of the complexes are compared with this of the free FEN drug in order to determine the coordination sites that may be involved in chelation. The position and/or the intensities of these peaks are expected to be changed upon chelation. These characteristic peaks are listed in Table 2. Upon comparison it is found that:

(1) The υ(OH), υ(C–O), and δ(OH) stretching vibrations are observed at 3397–3219, 1227, and 1391 cm^{-1} for FEN drug, respectively. The participation of the hydroxyl O atom in the complex formation is evidenced from the shift in position of these bands to 3567–3152, 1235–1306, and 1403–1466 cm^{-1} for FEN–metal complexes, respectively.

(2) The NH stretching vibration: υ(NH), is found in FEN drug at 3050 cm^{-1}. Whoever, the participation of the NH group in the chelation is ascertained from the shift of this band from 3040 to 3199 cm^{-1} in the spectra of the complexes.

(3) New bands are found in the spectra of the complexes in the regions 520–559 cm^{-1}, which is assigned to υ(M–O) stretching vibrations [12–16]. The bands at 436–510 have been assigned to υ(M–N) mode [12–16].

Therefore, from the IR spectra, it is concluded that FEN behaves as a uninegative bidentate ligand coordinated to the metal ions via the deprotonated hydroxyl O and NH groups.

Magnetic susceptibility and electronic spectral studies

The magnetic moment values of Cr(III) and Mn(II) complexes are found to be 4.95 and 4.82 B.M., respectively, which indicate their presence in octahedral structure [17].

The Ni(II) complex reported herein is found to has a room temperature magnetic moment value of 3.66 B.M.; which is in the normal range observed for octahedral Ni(II) complexes (μ_{eff} = 2.9–3.3 B.M.) [12, 17]. This indicates that, the Ni(II) complex is probably octahedral.

Table 2 IR spectra (4000–400 cm^{-1}) of the FEN drug and its metal complexes

Compounds	ν(OH)	ν(C–O)	δ(OH)	ν(NH)	ν(M–O)	ν(M–N)
FEN·HBr	3397–3219br	1227m	1391sh	3055br	–	–
$[Cr(FEN)_2(H_2O)_2]Cl{\cdot}H_2O$	3390–3200br	1306m	1466m	3172br	555s	497s
$[Mn(FEN)_2(H_2O)_2]{\cdot}2H_2O$	3396–3226br	1272m	1457m	3050m	552s	506w
$[Co(FEN)_2(H_2O)_2]{\cdot}4H_2O$	3410–3250br	1270m	1413m	3075br	520s	510s
$[Ni(FEN)_2(H_2O)_2]{\cdot}4H_2O$	3520–3170br	1237m	1465m	3087br	559s	498s
$[Cu(FEN)_2]{\cdot}2H_2O$	3412–3152br	1235br	1403m	3040br	554s	436s
$[Zn(FEN)_2(H_2O)_2]$	3567–3328br	1243m	1404m	3199br	537s	502s

sh Sharp, *m* medium, *s* small, *w* weak, *br* broad

The magnetic susceptibility value for Co(II) complex is found to be 5.28 B.M. (normal range for octahedral Co(II) complexes is 4.3-5.2 B.M.), is an indicative of octahedral geometry [17–19]. The magnetic moment value of 2.15 B.M. falls within the range normally observed for octahedral Cu(II) complexes [11, 17]. The Zn(II) complex is diamagnetic and according to the empirical formula of this complex, an octahedral geometry is proposed.

^{1}H NMR spectra

The ^{1}H NMR spectra of FEN drug and its Zn(II) complex are recorded in d_6-dimethylsulfoxide (DMSO) solution using tetramethylsilane (TMS) as internal standard. The chemical shifts of the different types of protons of the FEN drug and its diamagnetic Zn(II) complex are listed in Table 3.

The spectrum of the complex is examined in comparison with those of the parent Schiff base. Upon examinations it is found that:

(1) The OH signal, appeared in the spectrum of FEN drug at 4.760 ppm (Table 3), completely disappeared in the spectrum of its Zn(II) complex indicating that the OH proton is removed by the chelation with metal ion.
(2) The signal observed at 8.536 ppm for FEN drug, is assigned to NH protons. This signal is found at 8.90 ppm for Zn(II) complex. This indicates that the NH group is coordinated to the Zn(II) ion without proton displacement.

Therefore, it is clear from these results that the data obtained from the elemental analyses, IR, and ^{1}H NMR spectral measurements are in agreement with each other.

Table 3 ^{1}H NMR spectral data of the FEN drug and its Zn(II) chelate

Compounds	Chemical shift (δ)/ppm	Assignment
FEN	9.284	(S, 3H, phenolic OH)
	8.536	(br, 1H, NH)
	5.994–7.019	(m, 7H, ArH)
	4.760	(br, 1H, aliphatic OH)
	3.360	(s, 3H, CH_3)
	2.896–3.096	(m, 2H, C–CH_2)
	2.489–2.569	(m, 2H, C–CH_2)
	1.078	(s, 2H, CH)
$[Zn(FEN)_2(H_2O)_2]$	9.280	(S, 6H, phenolic OH)
	8.900	(br, 2H, NH)
	6.062–6.917	(m, 14H, ArH)
	3.505	(s, 6H, CH_3)
	2.657–2.819	(m, 4H, C–CH_2)
	2.490–2.529	(m, 4H, C–CH_2)
	0.927	(s, 4H, CH)

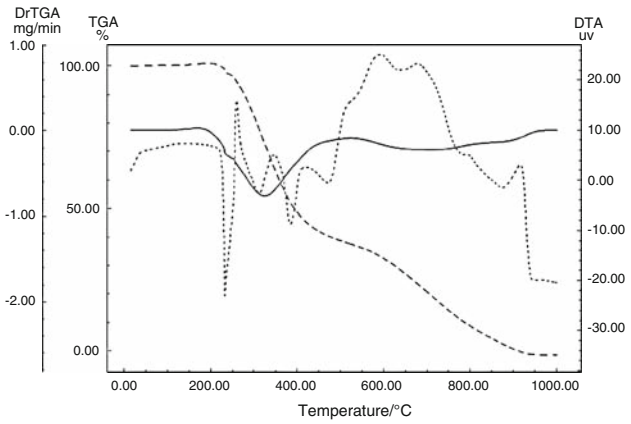


Fig. 3 TGA, DrTGA, and DTA curve of FEN·HBr drug

Thermal analyses (TG, DTG, and DTA) of FEN drug

The TG curve of FEN drug (Fig. 3), refers to two stages of mass losses at temperature ranges from 185 to 815 °C (Table 4). The first estimated mass loss of 39.30% (calcd. 39.80%) within the temperature range from 185 to 500 °C, may be attributed to the liberation of $C_8H_9O_3$ molecule as gases. In the 2nd stage within the temperature range from 500 to 815° C, fenoterol losses the remaining part with an estimated mass loss of 60.70% (calcd. 60.20%) with a complete decomposition as $C_9H_{13}NOBr$. Figure 3 shows the DTA curve which shows five exothermic peaks at 250, 300, 400, 480, and 650 °C and six endothermic peaks at 280, 370, 430, 600, 700, and 800 °C.

Thermal analyses (TG, DTG, and DTA) of the metal chelates

Figure 4 and Table 4 show the TG, DTG, and DTA results of thermal decomposition of FEN chelates. From these results it can be conclude that: the thermogram of $[Cr(FEN)_2(H_2O)_2]Cl{\cdot}H_2O$ chelate shows five decomposition steps within the temperature range from 30 to 600 °C. The first two steps of decompositions within the temperature range 30–120 °C correspond to the loss of water molecule of hydration and HCl with a mass loss of 5.99% (calcd. 5.11%). The subsequent steps (120–600 °C) correspond to the removal of the organic part of the drug leaving metal oxide as a residue. The overall weight loss amounts to 86.74% (calcd. 85.76%). The DTA data are listed in Table 4 and represented graphically in Fig. 4a. It is clear from these data that these mass losses are accompanied by exothermic (230 °C) and endothermic (90 and 435 °C) peaks.

The TG curve of the $[Mn(FEN)(H_2O)_2]{\cdot}2H_2O$ chelate is shown in Fig. 4b and listed in Table 4. It decomposes in six steps in the temperature range from 30 to 650 °C. The first step is the loss of the hydrated water with mass loss of

Table 4 Thermal analyses (TG and DTA) data of FEN drug and its metal complexes

Compounds	TG range/°C	DTG max/°C	DTA[a]/°C	Mass loss % found (calcd)	n[b]	Total mass loss	Assignment	Metallic residue
FEN·HBr	185–500	323	250(−), 280(+), 300(−), 370(+), 400(−), 430(+), 480(−), 600(+), 650(−), 700(+), 800(+)	39.30 (39.80)	1	100.0 (100.0)	Loss of $C_8H_9O_3$	–
	500–815	588		60.70 (60.20)	1		Loss of $C_9H_{13}NOBr$	
$[Cr(FEN)_2(H_2O)_2]Cl·H_2O$	30–120	88	90(+), 230(−), 435(+)	5.99 (5.11)	2	86.74 (85.76)	Loss of H_2O and HCl	$½Cr_2O_3$
	120–600	132, 220		85.76 (86.47)	3		Loss of $C_{34}H_{42}N_2O_{6\ldots5}$ and $2H_2O$	
$[Mn(FEN)_2(H_2O)_2]·2H_2O$	30–200	55,101, 157	50(−), 70(+), 100(−), 150(+), 200(−), 525(+).	4.01 (5.03)	2	92.61 (93.43)	Loss of $2H_2O$	MnO
	200–650			88.60 (88.40)	4		Loss of $C_{34}H_{42}N_2O_7$ and $2H_2O$	
$[Co(FEN)_2(H_2O)_2]·4H_2O$	30–100	63,118, 560, 335	60(−), 100(+), 130(−), 497(+), 510(−), 560(+)	7.95 (7.72)	1	92.55 (91.96)	Loss of $4H_2O$	CoO
	100–650			84.60 (84.24)	2		Loss of $C_{34}H_{42}N_2O_7$ and $2H_2O$	
$[Ni(FEN)_2(H_2O)_2]·4H_2O$	30–120	67, 189, 433, 567	40(+), 72(−), 192(−), 430(+), 600(+), 700(−), 730(+)	7.60 (7.70)	1	92.40 (92.90)	Loss of $4H_2O$	NiO
	120–650			84.80 (85.20)	3		Loss of $C_{34}H_{42}N_2O_7$ and $2H_2O$	
$[Cu(FEN)_2]·2H_2O$	30–270	77, 261	200(+), 270(−), 300(+), 330(−), 460(−), 520(+), 550(−), 620(+)	4.90 (5.10)	2	88.42 (88.73)	Loss of $2H_2O$	CuO
	270–1000	669, 943		83.52 (83.63)	2		Loss of $C_{34}H_{42}N_2O_7$	
$[Zn(FEN)_2(H_2O)_2]$	100–200	175, 317, 453, 538	179(−), 370(−), 434(+), 538(+),	4.10 (5.30)	1	92.60 (91.70)	Loss of $2H_2O$	ZnO
	200–680			86.50(87.40)	3		Loss of $C_{34}H_{42}N_2O_7$	

[a] (+) endothermic, (−) exothermic

[b] n = number of decomposition steps

4.01% (calcd. 5.03%). The subsequent steps correspond to the removal of coordinated water and the residue of the drug molecules with mass loss of 88.60% (calcd. 88.40%). These steps are accompanied by exothermic peaks at 50, 100, and 200 °C. Also these steps are accompanied by endothermic peaks at 70, 150 and 525 °C.

The TG curves of the $[Ni(FEN)_2(H_2O)_2]·4H_2O$ (Fig. 4c), $[Cu(FEN)_2]·2H_2O$, and $[Zn(FEN)_2(H_2O)_2]$ (Fig. 4e) chelates show four stages of decomposition within the temperature range from 30 to 650, 30 to 1000, and 100 to 680 °C, respectively. The first stage corresponds to the loss of water molecules of hydration (in case of Ni(II) and Cu(II) complexes) and the loss of coordinated water molecules (in case of Zn(II) complex). While the subsequent steps involve the loss of organic part of FEN drug molecules. The overall weight losses amount to 92.40% (calcd. 92.90%), 88.42% (calcd. 88.73%), and 92.60% (calcd. 91.70%). The DTA data are listed in Table 4 and represented graphically in Fig. 4c, e. It is clear from these data that these mass losses are accompanied by exothermic and endothermic peaks within the temperature ranges of decomposition.

On the other hand, $[Co(FEN)_2(H_2O)_2]·4H_2O$ chelate exhibits three decomposition steps (Fig. 4d). The first step in the temperature range 30–100 °C in which the complex losses the hydrated water molecules with estimated mass loss = 7.95% (calcd. 7.72%) (Table 4). The total mass losses of the decomposition steps are found to be 92.55% (calcd. 91.96%), leaving CoO as a residue. The DTA data are listed in Table 4 and represented graphically in Fig. 4d. It is clear from these data that these mass losses are accompanied by three exothermic (60, 130, and 510 °C) and three endothermic (100, 497, and 560 °C) peaks.

Calculation of activation thermodynamic parameters

The thermodynamic activation parameters of decomposition processes of dehydrated complexes namely activation energy (E^*), enthalpy (ΔH^*), entropy (ΔS^*), and Gibbs free

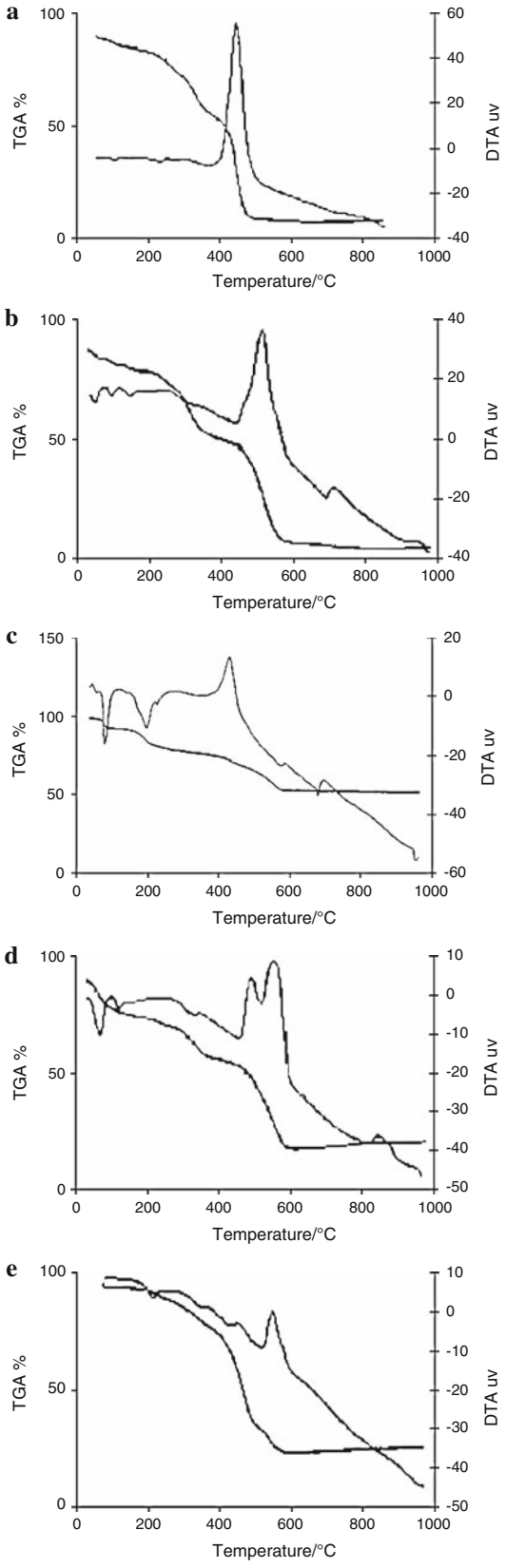


Fig. 4 Thermal analyses (DTA and TGA) of **a** Cr(III), **b** Mn(II), **c** Ni(II), **d** Co(II), and **e** Zn(II)–FEN complexes

energy change of the decomposition (ΔG^*) are evaluated graphically by employing the Coats-Redfern relation [20].

$$\log\left[\frac{\log\{W_f/(W_f - W)\}}{T^2}\right] = \log\left[\frac{AR}{\theta E^*}\left(1 - \frac{2RT}{E^*}\right)\right] - \frac{E^*}{2.303\,RT} \quad (1)$$

where W_f is the mass loss at the completion of the reaction, W is the mass loss up to temperature T, R is the gas constant, E^* is the activation energy in kJ mol^{-1}, θ is the heating rate, and $(1 - (2RT/E^*)) \cong 1$. A plot of the left-hand side of Eq. 1 against $1/T$ gives a slope from which E^* was calculated and A (Arrhenius factor) was determined from the intercept. The entropy of activation (ΔS^*), enthalpy of activation (ΔH^*), and the free energy change of activation (ΔG^*) are calculated using the following equations:

$$\Delta S^* = 2.303[\log(Ah/kT)]R \quad (2)$$

$$\Delta H^* = E^* - RT \quad (3)$$

$$\Delta G^* = \Delta H^* - T\Delta S^* \quad (4)$$

The data are summarized in Table 5. The activation energies of decomposition were found to be in the range 11.20–26.90 kJ mol^{-1}. The entropy of activation is found to have negative values in all the complexes which indicate that the decomposition reactions proceed with a lower rate than the normal ones.

Structural interpretation

The structures of the complexes of FEN drug with metals are confirmed by the elemental analyses, ^{1}H NMR, IR, molar conductance, magnetic and thermal analyses data. The structures proposed for the complexes are given as shown below in Fig. 5.

Biological activity

The main aim of the production and synthesis of any antimicrobial compound is to inhibit the causal microbe without any side effects on the patients. In addition, it is worthy to stress here on the basic idea of applying any chemotherapeutic agent which depends essentially on the specific control of only one biological function and not multiple ones. The chemotherapeutic agent affecting only one function has a highly sounding application in the field of treatment by anticancer, since most anticancers used in the present time affect both cancerous diseased cells and healthy ones which in turn affect the general health of the patients. Therefore, there is a real need for having a chemotherapeutic agent which controls only one function. In testing the antibacterial activity of FEN drug and its metal complexes, more than one test organism are used to

Table 5 Thermodynamic data of the thermal decomposition of FEN and its metal complexes

Compounds	Decomp. temp/°C	E^*/kJ mol^{-1}	A/s^{-1}	ΔS^*/J K^{-1} mol^{-1}	ΔH^*/kJ mol^{-1}	ΔG^*/kJ mol^{-1}
FEN·HBr	185–500	26.90	2.5×10^{-3}	−101.9	24.70	51.40
	500–815					
$[Ni(FEN)_2(H_2O)_2]\cdot 4H_2O$	30–120	15.30	4.6×10^{-3}	−134.0	12.60	56.00
	120–650					
$[Cu(FEN)_2]\cdot 2H_2O]$	30–270	11.20	7.2×10^{-3}	−157.1	65.10	95.40
	270–1000					

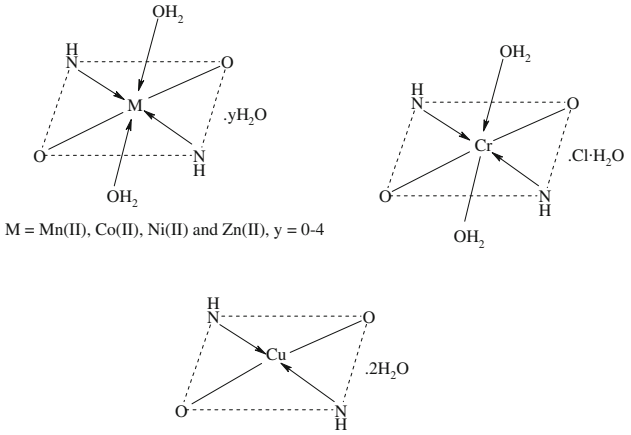


Fig. 5 Structure of metal complexes of FEN drug

increase the chance of detecting antibiotic principles in tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents is determined by the assay plates which are incubated at 37 °C for 2 days for bacteria. All the tested compounds show a remarkable biological activity against different types of Gram-positive (G^+) bacteria, Gram-negative (G^-) bacteria, yeast, and fungi. The data are listed in Table 6. The data show that FEN drug is under investigation and its metal complexes have the capacity of inhibiting the metabolic growth of the investigated bacteria and fungi to different extent. The size of the inhibition zone depends upon the culture medium, incubation conditions, rate of diffusion, and the concentration of the antibacterial agent. The activities of all the tested complexes may be explained on the basis of chelation theory; chelation reduces the polarity of the metal atom mainly because of partial sharing of its positive charge with the donor groups and possible π electron delocalization within the whole chelate ring. Also, chelation increases the lipophilic nature of the central atom which subsequently favors its permeation through the lipid layer of the cell membrane [21].

On comparing the biological activity of the FEN drug and its metal complexes, the following results are obtained:

(1) Biological activity against *Gram-positive bacteria* follow the order: FEN = $[Zn(FEN)_2(H_2O)_2]$ > $[Mn(FEN)_2(H_2O)_2]\cdot 2H_2O$ = $[Co(FEN)_2(H_2O)_2]\cdot 4H_2O$ = $[Ni(FEN)_2(H_2O)_2]\cdot 4H_2O$ = $[Cu(FEN)_2]\cdot 2H_2O$ > $[Cr(FEN)_2(H_2O)_2]Cl\cdot H_2O$. It is obvious that the biological activity of the metal complexes are more or less comparable with the parent FEN drug which means that the complexes can have the same action like the parent drug.

(2) Biological activity against *Gram-negative bacteria* follow the order: $[Co(FEN)_2(H_2O)_2]\cdot 4H_2O$ = $[Zn(FEN)_2(H_2O)_2]$ > FEN = $[Mn(FEN)_2(H_2O)_2]\cdot 2H_2O$ =

Table 6 The antibacterial and antifungal activity of FEN drug and its metal complexes

Complexes	Biological agent							
	Bacteria (G^+)		Bacteria (G^-)		Fungi		Yeast	
	S. aures	*B. subtilis*	*E. coli*	*S. typhi*	*A. niger*	*A. flavas*	*S. cervisiae*	*C. albicans*
FEN·Hbr	++	++	++	+	+	−	+	+
$[Cr(FEN)_2(H_2O)_2]Cl\cdot H_2O$	+	+	+	+	−	+	−	−
$[Mn(FEN)_2(H_2O)_2]\cdot 2H_2O$	+	++	+	++	+	−	−	+
$[Co(FEN)_2(H_2O)_2]\cdot 4H_2O$	++	+	++	++	−	+	+	−
$[Ni(FEN)_2(H_2O)_2]\cdot 4H_2O$	++	+	++	+	+	−	+	+
$[Cu(FEN)_2]\cdot 2H_2O$	++	+	++	+	−	+	−	−
$[Zn(FEN)_2(H_2O)_2]$	++	++	++	++	+	−	+	+

+ Inhibition values up to 10 mm, ++ inhibition values = 11–15 mm, +++ inhibition values = 16–22 mm, ++++ inhibition values more than 23 mm

$[Ni(FEN)_2(H_2O)_2]\cdot 4H_2O = [Cu(FEN)_2]\cdot 2H_2O > [Cr(FEN)_2(H_2O)_2]Cl\cdot H_2O$.

(3) The complexes also show antifungal and anti-yeast activities which are comparative to the parent FEN drug which shows such activity which make these complexes of interest.

Also the data listed in Table 6 shows that *E. coli* is inhibited by Co(II), Ni(II), Cu(II), and Zn(II) complexes. The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by *E. Coli* e.g., septicemia, gastroenteritis, urinary tract infections, and hospital-acquired infections [22, 23].

References

1. Beigi F, Bertucci C, Zhu W, Chakir K, Wainer IW, Xiao RP, et al. Enantioselective separation and online affinity chromatographic characterization of R,R- and S,S-fenoterol. Chirality. 2006;18:822–7.
2. Jźwiak K, Khalid C, Tanga MJ, Berzetei-Gurske I, Jimenez L, Kozocas JA, et al. Comparative molecular field analysis of the binding of the stereoisomers of fenoterol and fenoterol derivatives to the beta-2-adrenergic receptor. J Med Chem. 2007;50:2903–15.
3. Wilson AA, Wang J, Koch P, Walle T. Stereoselective sulphate conjugation of fenoterol by human phenolsulphotransferases. Xenobiotica. 1997;27:1147–54.
4. Rominger KL, Mentrup A, Stiasni M. Radioimmunological determination of fenoterol. Part II: antiserum and tracer for the determination of fenoterol. Arzneimittelforschung. 1990;40:887–95.
5. Haasnoot W, Stouten P, Lommen A, Cazemier G, Hooijerink D, Schilt R. Determination of fenoterol and ractopamine in urine by enzyme immunoassay. Analyst. 1994;119:2675–80.
6. Damasceno L, Ventura R, Cardoso J, Segura J. Diagnostic evidence for the presence of β-agonists using two consecutive derivatization procedures and gas chromatography–mass spectrometric analysis. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;780:61–71.
7. Couper FJ, Drummer OH. Gas-chromatograpic-mass-spectrometric detractions of beta-2-agonists in post mortem blood. J Chromatogr B Biomed Appl. 1996;685:265–72.
8. Doerge DR, Bajic S, Blankenship LR, Preece SW, Churchwell MI. Determination of β-agonist residues in human plasma using liquid chromatography/atmospheric pressure chemical ionization mass spectrometry and tandem mass spectrometry. J Mass Spectrom. 1995;30:911–6.
9. Kramer S, Blaschke G. High-performance liquid chromatographic determination of the b2-selective adrenergic agonist fenoterol in human plasma after fluorescence derivatization. J Chromatogr B Biomed Sci Appl. 2001;751:169–75.
10. Grayer RJ, Harbone JB. A survey of antifungal compounds from higher plants. Phytochemistry. 1994;37:19–42.
11. Salama F, El-Abasawy N, Abdel Razeq SA, Ismail MMF, Fouad MM. Validation of the spectrophotometric determination of omeprazole and pantoprazole sodium via their metal chelates. J Pharm Biomed Anal. 2003;33:411–21.
12. Mohamed GG, Nour El-Dien FA, Khalil SM, Mohammad AS. Metal complexes of omeprazole. Preparation, spectroscopic and thermal characterization and biological activity. J Coord Chem. 2009;62:645–54.
13. Icbudak H, Heren Z, Köse DA, Necefoglu H. bis (nicotinamide) and bis (N, N-diethyl nicotinamide) p-hydroxybenzoate complexes of Ni(II), Cu(II) AND Zn(II). J Therm Anal Calorim. 2004;76:837–51.
14. Köse DA, Necefoğlu H. Synthesis and characterization of *bis* (nicotinamide) *m*-hydroxy-benzoate complexes of Co(II), Ni(II), Cu(II) and Zn(II). J Therm Anal Calorim. 2008;93:509–14.
15. Köse DA, Gökçe G, Gökçe S, Uzun I. bis (N, N-diethylnicotinamide) p-chlorobenzoate complexes of Ni(II), Zn(II) and Cd(II). Synthesis and characterization. J Therm Anal Calorim. 2009;95:247–51.
16. Santos AFO, Basílio ID, de Souza FS, Medeiros AFD, Pinto MF, de Santana DP, et al. Application of thermal analysis in study of binary mixtures with metformin. J Therm Anal Calorim. 2008;93:361–4.
17. Cotton FA, Wilkinson G, Murillo CA, Bochmann M. Advanced inorganic chemistry. 6th ed. New York: Wiley; 1999.
18. Zayed MA, Nour El-Dien FA, Mohamed GG, El-Gamel NEA. FT-IR, magnetic, mass spectra, XRD and thermal studies of metal chelates of tenoxicam. J Mol Struct. 2007;841:41–50.
19. Mohamed GG. New cyclodiphosph(V)azane complexes of Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and UO_2(II): preparation, characterization and biological studies. Phosphorus Sulfur Silicon Relat Elem. 2005;180:1569–84.
20. Coats AW, Redfern JP. Kinetic parameters from thermogravimetric data. Nature. 1964;20:68–79.
21. Caudhary A, Singh RV. Synthetic, structural and biological studies on divalent tin complexes of sixteen to twenty-four membered tetraaza macrocycles. Phosphorus Sulfur Silicon Relat Elem. 2003;178:603–13.
22. Jawetz E, Melnick JL, Adelberg EA. Review of medical microbiology. 16th ed. Los Anglos, CA: Lang Medical Publications; 1979.
23. Hughes WH, Stewart HC. Concise antibiotic treatment. London: Butter Worth; 1970.