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Structural Characterization, Thermal Analyses, Antiproliferative and Antimicrobial Activity of Cocaine Complexes with Mn(II) and Cu(II)

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REACTION of cocaine (Cn) with Mn(II) and Cu(II) chloride salts afforded complexes of the $[M(Cn)Cl(OH_2)_3]Cl$ type which were structurally characterized by elemental analysis, conductance measurements, spectroscopic methods and mass spectrometry. Their thermal properties were studied. The *in vitro* antitumor activity of the newly synthesized complexes was investigated by MTT assay on MCF-7 and HepG-2 cell lines. Both complexes exhibited promising cytotoxic activity on both cell lines with high safety on normal human cells. Their antifungal activity against *Aspergillus fumigatus* and *Candida albicans* and antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhimurium* and *Escherichia coli* were also included.

Keywords: Cocaine, Transition metal complexes, Thermal analyses, Antiproliferative activity, Antimicrobial activity.

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Introduction

Cancer is a deregulated cell multiplication with consequent abnormal increase in cell numbers in particular organs [1]. Despite the significant progress made in its treatment and prevention, breast cancer is still considered the most abundant type of cancers among women worldwide causing the highest number of cancer-related death cases among them [2]. In Egypt, breast cancer amounted to 18.3 percent of the reported cancer cases in 2016 [3] and the second one for both sexes [4]. On the other hand, globally, liver cancer is the fifth most common malignancy and ranks as the third prevalent cause of cancer-related death cases [5].

Since the discovery of cisplatin, metal-based chemotherapeutics have been extensively studied as antiproliferative agents in the last few decades [6-9]. Moreover, platinum-based anticancer agents are nowadays utilized in approximately seventy percent of all cancer treatments [10].

Transition metal complexes have been also extensively investigated as antimicrobial agents due to their high ability to exert their effect by various mechanisms such as interaction with intracellular biomolecules, enhancing lipophilicity, inhibition of enzymes, alteration of cell membrane functions and arrest of cell cycle [11].

The azabicyclo[3.2.1]octane motif (Fig. 1) constitutes the core structure of many biologically active compounds with analgesic, antimicrobial, anti-inflammatory and anticancer effects and are occasionally utilized in drug molecules [12–15]. Cocaine (Cn) (Fig. 2) is a naturally occurring azabicyclo[3.2.1]octane extracted from the coca bush (*Erythroxylum coca*) leaves [16]. Cn was first reported as a cancer treatment by Gilchrist in 1909 [17]. Additionally, different binary transition metal complexes [18] and heteroleptic lanthanide–metal complexes [19] of Cn have been recently investigated for their anticancer activity.

Herein, Mn(II) and Cu(II) complexes of cocaine were synthesized and fully structurally characterized by means of a variety of physicochemical tools such as elemental analysis, UV-Vis, FT IR, molar conductance, mass spectrometry and thermal analyses techniques. The *in vitro* antiproliferative activity of the newly synthesized complexes were also investigated against human HepG-2 and MCF-7 cancer cells. Further, their antifungal activity against *Aspergillus fumigatus* and *Candida albicans* and antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhimurium* and *Escherichia coli* were also studied.

Experimental

Synthesis of the metal complexes

All chemicals and reagents utilized throughout the present study were of analytical reagent grade (Merck) without further purification. As it is shown in Scheme 1, the solid metal complexes were synthesized by adding a hot methanolic solution (60 °C) of the metal chloride ($MCl_2.2H_2O$) (1.5 mmol; $MnCl_2.2H_2O$, 0.24 g; $CuCl_2.2H_2O$, 0.26 g) dropwisely to a stirred hot methanolic solution (60 °C) of the ligand cocaine (1.5 mmol; 0.51 g). The reaction solution was stirred under reflux for 2–3 h and then cooled down to the room temperature, whereupon the solid complexes were precipitated. The formed solid complexes were filtered off, washed with methanol followed by diethyl ether, and finally dried under vacuum.

$[Mn(Cn)Cl(OH_2)_3]Cl.2H_2O$

Brown; yield 83%; m.p. 137 °C. Anal. Calcd for $C_{17}H_{31}Cl_2NO_9Mn$ (%): C, 39.32; H, 6.02; N, 2.70; Mn, 10.58. Found (%): C, 39.28; H, 5.97; N, 2.65; Mn, 10.53. Conductivity (Ω^{-1} mol^{-1} cm^2) in DMF: 68. FT-IR (ν, cm^{-1}) in KBr: carbonyl (C=OCH_3) 1720sh, carbonyl (C=OPh) 1602sh, (C−N) 1268sh, (O−H) stretching of coordinated water 887w and 827w, (M−O) 566w, (M−O) of coordinated water 509w. UV–Vis (λ_{max}, nm): 270 (π–π*).

$[Cu(Cn)Cl(OH_2)_3]Cl$

Dark green; yield 91%; m.p. 166 °C. Anal. Calcd for $C_{17}H_{27}Cl_2NO_7Cu$ (%): C, 41.51; H, 5.53; N, 2.85; Cu, 12.92. Found (%): C, 41.45; H, 5.48; N, 2.80; Cu, 12.90. Conductivity (Ω^{-1} mol^{-1} cm^2) in DMF: 75. FT-IR (ν, cm^{-1}) in KBr: carbonyl (C=OCH_3) 1718m, carbonyl (C=OPh) 1601sh, (C−N) 1268sh, (O−H) stretching of coordinated water 881w and 817w, (M−O) 561w, (M−O) of coordinated water 520w. UV–Vis (λ_{max}, nm): 271 (π–π*).

Instruments

The UV-vis measurements were performed using UVmini-1240 UV-vis Shimadzu spectrophotometer with matched 1 cm quartz

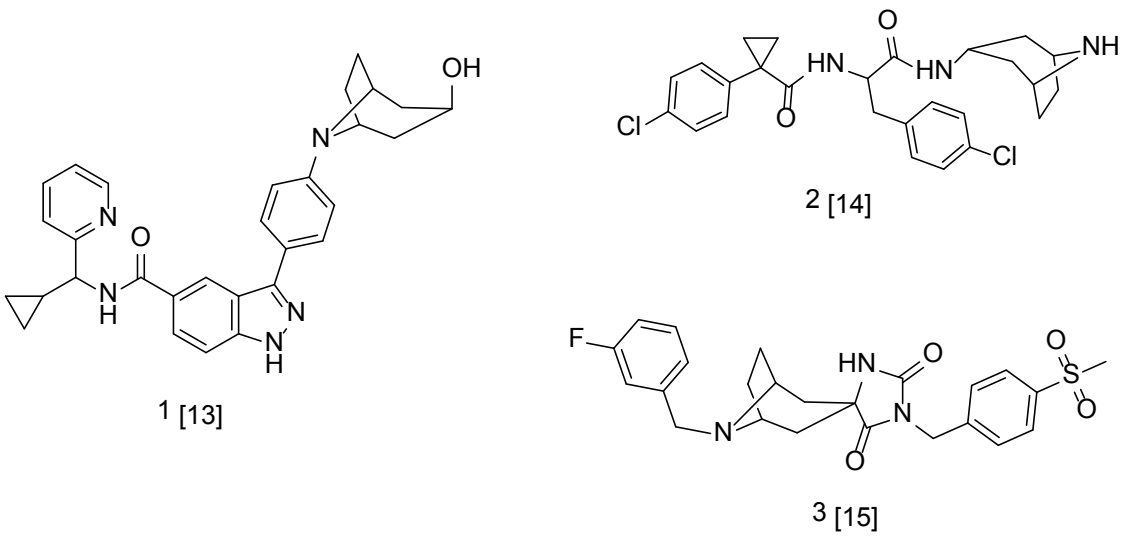


Fig. 1. Reported examples for biologically active azabicyclo[3.2.1]octane–containing compounds.

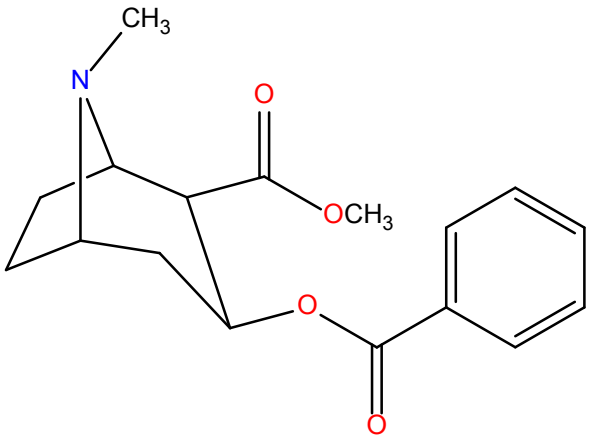


Fig. 2. Chemical structure of cocaine.

cells within 200–700 nm wavelength range. Infrared spectra were recorded using JASCO FT/IR-4100 spectrometer in 4000–400 cm^{-1} region as KBr pellets. Elemental analyses (C, H, N, and Cl) were carried out using Thermo Scientific Flash 2000 Organic Elemental Analyzer at the Microanalytical Center, Cairo University. Melting points' values were measured using Stuart SMP30 instrument. Metal contents of the solid complexes were estimated by the dissolution in conc. HNO_3 and dissolving the residue in deionized H_2O. The metal content was performed using inductively coupled plasma atomic absorption spectrometry (ICP□AES), Egyptian Petroleum Research Institute. Molar conductivities of the metal complexes were measured for their DMF solutions (10^{-3} M) at 25 ± 2 °C using Jenway 4010 conductivity meter. Mass spectra were recorded at the Microanalytical Center, National Center for Research, Egypt, by EI ionization mode using MS-5988 GS-MS Hewlett-Packard instrument at 70 eV. Thermal analyses (TG and DTG) were performed using Shimadzu thermal gravimetric analyzer from room temperature to 1000 °C under N_2 atmosphere with heating rate of 10 °C min^{-1}.

Cell culture

Human HepG-2 liver hepatocellular carcinoma, human MCF-7 breast adenocarcinoma, and human normal non-malignant HFB4 melanocytes cell lines were obtained from American Type Culture Collection (ATCC) and routinely cultured in a Dulbecco's modified eagle medium (DMEM, Invitrogen/Life Technologies) supplemented with 10% fetal bovine serum (FBS, Hyclone), 1% penicillin–streptomycin and insulin (10 µg mL^{-1}). All other chemicals and reagents were purchased from Sigma-Aldrich and Invitrogen. All cell lines were grown at 37 °C as adherent monolayers in a humidified atmosphere with 5% CO_2.

Antiproliferative activity

To investigate the cytotoxicity of the newly synthesized complexes, the MTT assay [20] was utilized. The MTT assay is based on the reduction of the soluble 3-(4,5-methyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) into a blue purple formazan product, mainly by mitochondrial reductase activity inside living cells. Cells were seeded in cell culture treated 96-well flat-bottomed plates at a density of 1.2–1.8 × 10^4 cells per well. Before adding the tested compounds, the plates were pre-incubated for 24 h in a drug-free medium at 37 °C and 5% CO_2. Cells were treated with 100 µg mL^{-1} for a compound-exposure period of 48 h. Then, the MTT solution was added to each well and incubated further for 2 h. MTT solubilization solution was added to dissolve the resulting MTT formazan crystals. Cell metabolic activity was estimated spectrophotometrically by measuring the absorbance at 450/690 nm using ROBONIK P2000 Elisa Reader. The results were expressed as growth inhibition percentage.

Antimicrobial activity

Antimicrobial activities were carried out using the agar well-diffusion technique [21,22] with nutrient agar or Sabouraud dextrose agar media for bacteria and fungi, respectively. Dimethyl sulfoxide (DMSO) was used for dissolving the tested compounds and also as a control. Antimicrobial activities were investigated against *Aspergillus fumigatus* (RCMB 002008) and *Candida albicans* (RCMB 005003 (1) ATCC 10231) as fungi, *Staphylococcus aureus* (RCMB 010010) and *Bacillus subtilis* (RCMB 015 (1) NRRL B-543) as Gram positive bacteria and *Salmonella typhimurium* (RCMB 006 (1) ATCC 14028) and *Escherichia coli* (RCMB 010052) ATCC 25955) as Gram negative bacteria.

Results and Discussion

Elemental analysis

Analytical and physical data of the synthesized solid complexes were summarized in Table 1. It is obvious that the elemental analyses (C, H, N, Cl, and M) were in a good agreement with the calculated values for the suggested structures showing that all the formed complexes were of 1:1 metal − ligand stoichiometry of the $[M(Cn)Cl(OH_2)_3]Cl$ type, wherein Cn acted as a neutral bidentate ligand (Scheme 1). All the synthesized complexes were found to be stable in ambient air at room temperature and soluble in DMF, water, ethanol, and methanol.

Molar conductance measurements

The values of the molar conductivities (Λ_m) of the DMF solutions of the prepared complexes (1 × 10^{-3} mol L^{-1}) at 25 ± 2 °C (Table 1) indicated their ionic nature (1:1 electrolytes) as their molar conductance values were 68 and 75 Ω^{-1} mol^{-1} cm^2 for Mn(II) and Cu(II) complexes, respectively [23].

Infrared spectra

The infrared spectra of the formed complexes were inspected along that of the free Cn (Fig. 3) and the major infrared bands were listed in Table 2 in order to corroborate the complexation process and to interpret the sites of coordination.

From Table 2, it is obvious that the sharp band at 1272 cm^{-1} in the free Cn spectrum which was assigned to ν(C−N) [24] did not display any significant shift upon chelation which indicates that N atom did not act as a coordination site. The frequency for the C=O stretching vibration of the carbonyl group attached to the methoxy group which located at 1732 cm^{-1} in the free Cn, shifted to lower wavenumbers (1720 and 1718 cm^{-1}) for Mn(II) and Cu(II) complexes, respectively, with decreasing in its intensity which suggests its participation in chelation. The appearance of ν(C=O) mode of the carbonyl group attached to the phenyl ring at slightly lower wavenumbers, 1602 and 1601 cm^{-1} for Mn(II) and Cu(II) complexes, respectively, instead of 1610 cm^{-1} for free Cn, was due to the involvement of its neighbouring etheric oxygen in the complex formation.

The new bands observed in the range of 509–566 cm^{-1} in the infrared spectra of the complexes were attributed to the formation of the M–O bonds [25, 26]. In addition, the new bands arose at 817–887 cm^{-1} can be assigned to the coordinated water molecules [26] which were strongly confirmed by studying the thermal analysis of these complexes.

Therefore, it was concluded from the analysis of IR spectra that cocaine behaved as a neutral bidentate ligand and coordinated to the metal centers via the carbonyl oxygen of the (−$COOCH_3$) ester and the etheric oxygen bonded to the bi-cycloalkane.

Mass spectrometry

The electron impact mass spectra of the formed complexes were recorded at 70 eV. These spectra exhibited a weak molecular ion peaks, M^+ at *m/z* 520 and 492 amu for Mn(II) and Cu(II) complexes, respectively, confirming the complex formation. The complexes underwent successive fragmentations resulted in the appearance of various peaks at different *m/z* values. The molecular peak relative to the free ligand, Cn, was detected at *m/z* 303.62 amu. The molecular ion peaks were in a good accordance with the suggested molecular formulas indicated from elemental and thermal analyses.

Thermal analyses

The TG and DTG analyses of the formed Mn(II) and Cu(II) complexes (Fig. 4) were measured in the 30–1000 °C temperature range to investigate their thermal stabilities and also to investigate the nature of water molecules in the synthesized complexes. The obtained results were collected and tabulated in Table 3.

For $[Mn(Cn)Cl(OH_2)_3]Cl.2H_2O$ complex, its thermal decomposition passed through four steps, the first step (55–115 °C) with a DTG_{max} of 88 °C and corresponded to the elimination of the two hydrated water molecules with a mass loss of 6.86% (calcd. 6.93%). The last three steps (115–885 °C) involved a 79.41% mass loss due to the releasing of one mole of Cl_2 gas and the three coordinated H_2O molecules and the decomposition of $C_{17}H_{21}NO_3$ molecule (calcd. 79.38%) leaving MnO as the final residue with overall mass loss amounting to 86.27% (calcd. 86.31%).

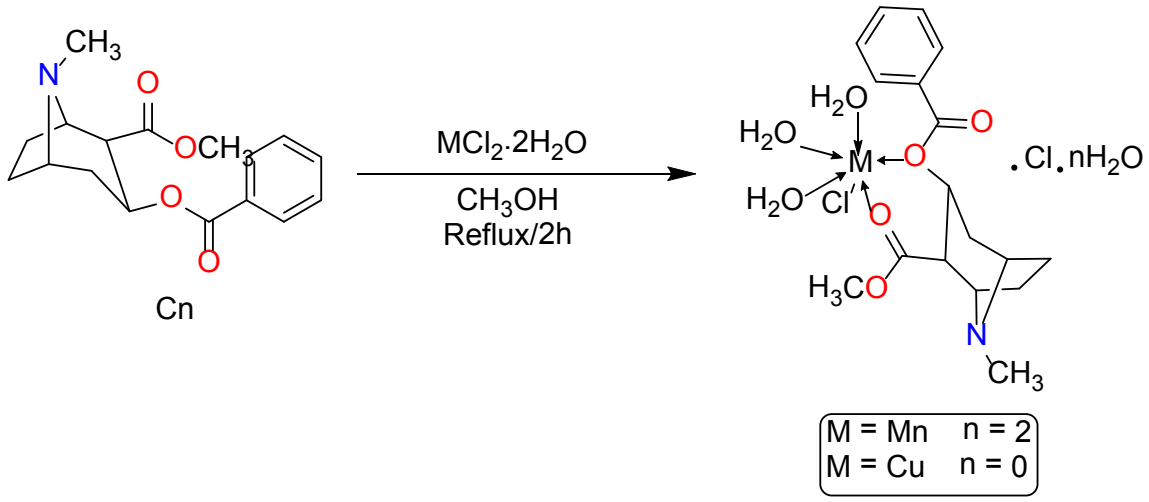
The TG/DTG curves of $[Cu(Cn)Cl(OH_2)_3]Cl$ complex exhibited four decomposition steps with DTG_{max} of 221, 357, 601 and 845. The first two step was from 45 to 435 °C and corresponded to the releasing of one mole of Cl_2 gas and the three coordinated H_2O molecules with an 25.54% mass loss (calcd. 25.42%). The last two steps (435–870 °C) involved a 58.51% mass loss due to the decomposition of $C_{17}H_{21}NO_3$ molecule (calcd. 58.43%) leaving CuO as a final residue with overall mass loss amounting to 84.05% (calcd. 83.85%).

Biological activity

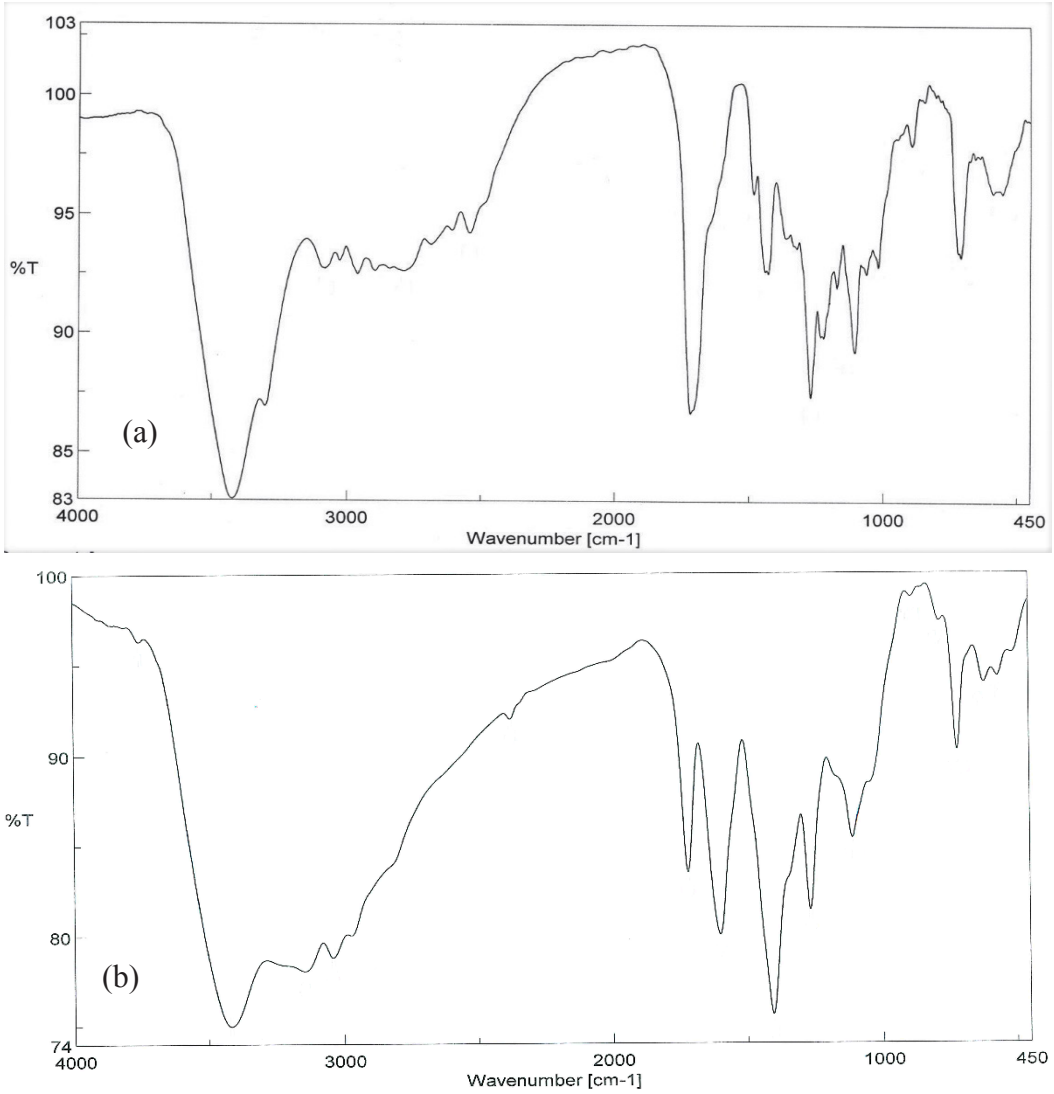
In vitro antiproliferative activity

The antiproliferative activity of the studied complexes was estimated by carrying out single dose growth inhibitory activity (100 μg mL^{-1} for each) on the cell lines MCF-7 and HepG-2 using MTT assay. The results were compared to the growth of untreated cells.

Both complexes displayed promising growth inhibitory activity against the two tested cell lines. Mn(II) complex displayed 71% growth inhibition on MCF-7 cell line and 63% growth inhibition on HepG-2 cell line. On the other hand, Cu(II) complex showed 76% and 82% growth inhibition



Scheme 1. Synthesis of the studied complexes.



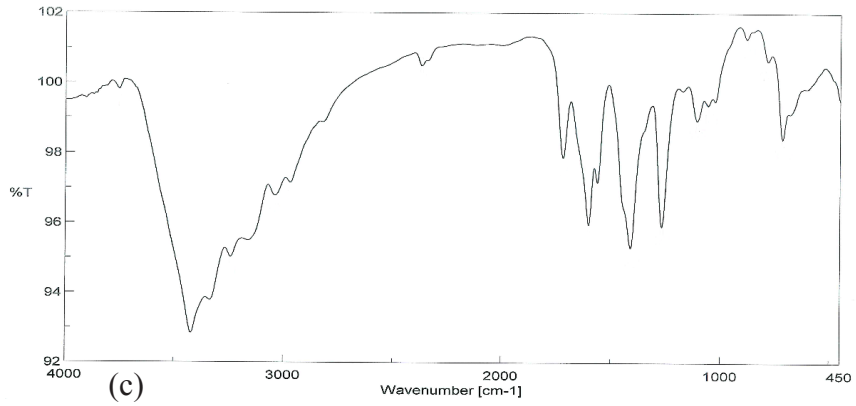


Fig. 3. FT−IR spectra of (a) cocaine and its (b) Mn(II) and (c) Cu(II) complexes

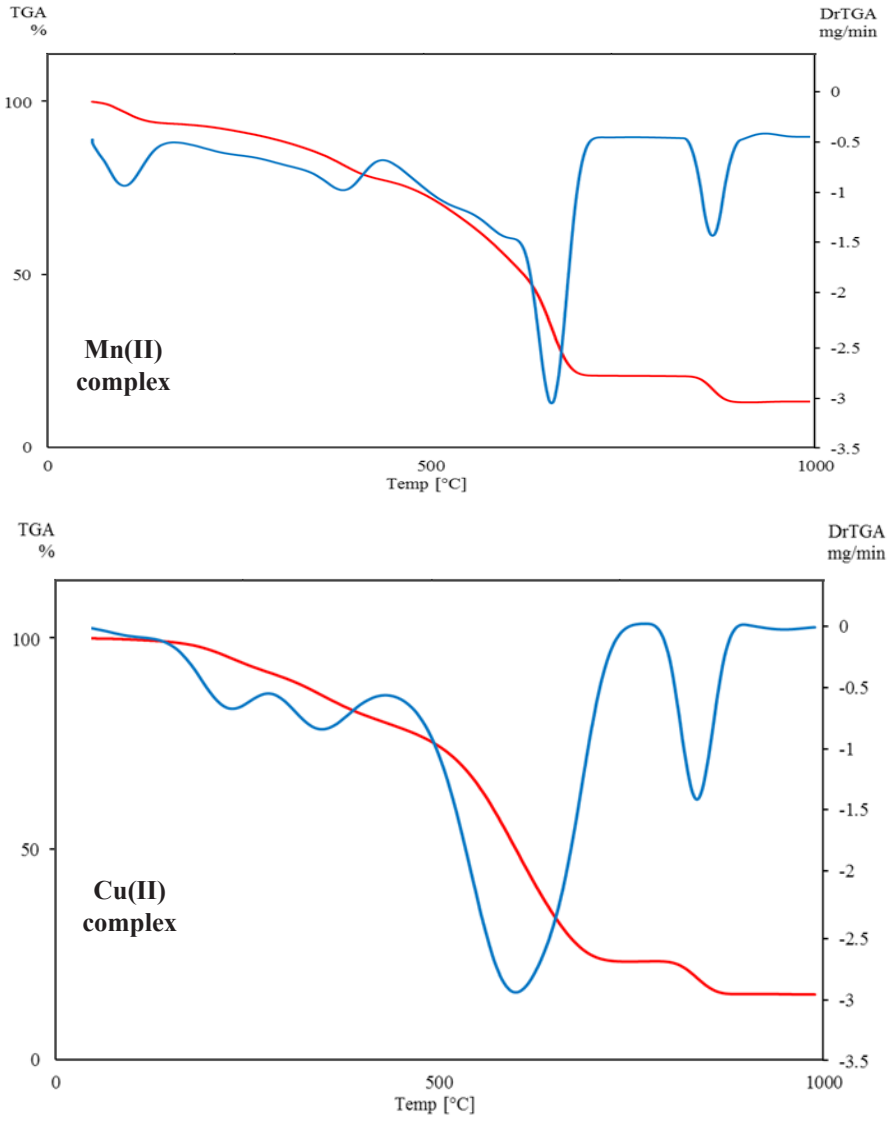


Fig. 4. TG and DTG curves of the formed complexes.

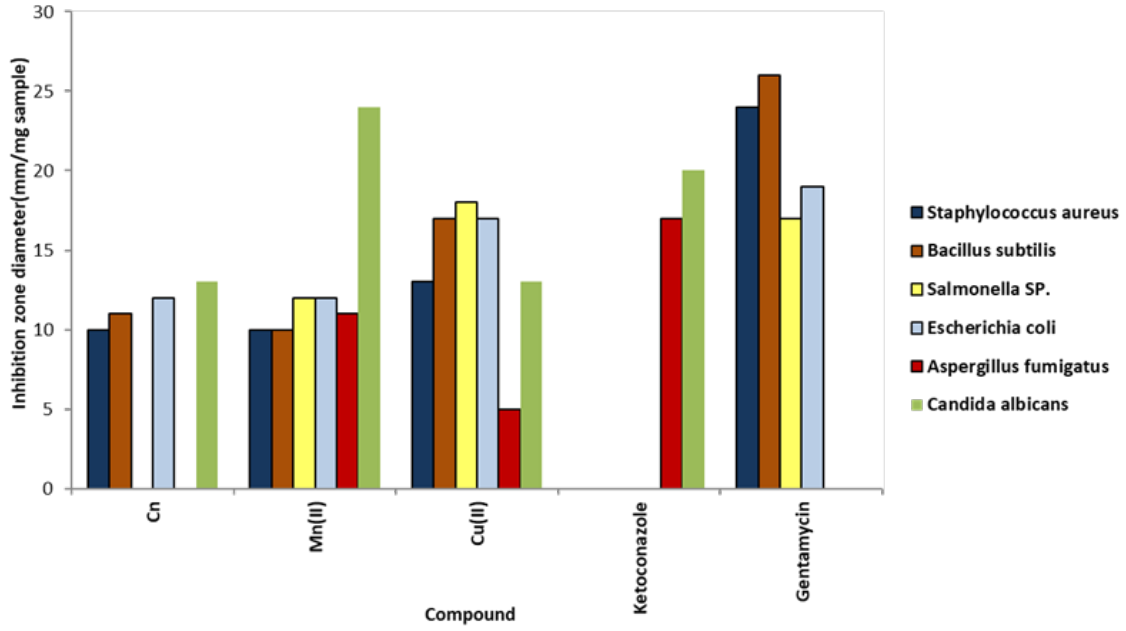


Fig. 5. Antimicrobial activity of Cn and its formed complexes.

TABLE 1. Analytical and physical data of the studied complexes.

MF (M_{wt})	Color	Yield %	M.P. (°C)	Elemental analyses, % Found (% Calcd.)					Λ_m $\Omega^{-1}mol^{-1}cm^2$
				C	H	N	Cl	M	
$[Mn(Cn)Cl(OH_2)_3]Cl.2H_2O$; $C_{17}H_{31}Cl_2NO_9Mn$ (519.19 g mol^{-1})	brown	83	137	39.28 (39.32)	5.97 (6.02)	2.65 (2.70)	13.61 (13.65)	10.53 (10.58)	68
$[Cu(Cn)Cl(OH_2)_3]$ Cl;$C_{17}H_{27}Cl_2NO_7Cu$ (491.80 g mol^{-1})	dark green	91	166	41.45 (41.51)	5.48 (5.53)	2.80 (2.85)	14.39 (14.41)	12.90 (12.92)	75

TABLE 2. Infrared spectra bands (4000–400 cm^{-1}) of Cn and its metal complexes of Mn(II) and Cu(II).

Cn	$[Mn(Cn)Cl(OH_2)_3]Cl.2H_2O$	$[Cu(Cn)Cl(OH_2)_3]Cl$	Assignment
1732sh	1720sh	1718m	ν(C=O)
			($CO-CH_3$)
1610w	1602sh	1601sh	ν(C=O)
			(CO–phenyl ring)
1272sh	1268sh	1268sh	ν(C–N)
			(tertiary amine)
-----	887w, 827w	881w, 817w	ν(O–H)
			(coordinated H_2O)
-----	566w	561w	ν(M–O)
-----	509w	520w	ν(M–O)
			(coordinated H_2O)

sh, sharp; w, weak; s, small; m, medium.

TABLE 3. TG and DTG analyses of the studied complexes.

Compound	TG range (°C)	n*	DTG_{max} (°C)	Mass loss, % found (calcd.)	Assignment	Residue, % found (calcd.)	Total mass loss, % found (calcd.)
$[Mn(Cn)Cl(OH_2)_3]Cl.2H_2O$	55−115	1	88	6.86 (6.93)	−Loss of $2H_2O$	MnO	86.27 (86.31)
$(C_{17}H_{31}Cl_2NO_9Mn)$	115−885	3	340, 622, 870	79.41 (79.38)	−Loss of $3H_2O$, Cl_2, and $C_{17}H_{21}NO_3$	13.73 (13.69)	
$[Cu(Cn)Cl(OH_2)_3]Cl$	45−435	2	221, 357	25.54 (25.42)	−Loss of $3H_2O$, and Cl_2	CuO	84.05 (83.85)
$(C_{17}H_{27}Cl_2NO_7Cu)$	435−870	2	601, 845	58.51 (58.43)	−Loss of $C_{17}H_{21}N_O3$	15.95 (16.15)	

* n = number of decomposition steps.

TABLE 4. Antimicrobial activity of Cn and its Mn(II) and Cu(II) complexes.

Compound	Inhibition zone diameter (mm/mg)					
	Fungi		Gram +ve bacteria		Gram -ve bacteria	
	Aspergillus fumigatus	*Candida albicans*	*Staphylococcus aureus*	*Bacillus subtilis*	*Salmonella typhimurium*	*Escherichia coli*
Ketoconazole (standard)	17	20	------	-----	-----	-----
Gentamycin (standard)	-----	-----	24	26	17	19
Cn (ligand)	-----	13	10	11	-----	12
Mn(II) complex	11	24	10	10	12	12
Cu(II) complex	5	13	13	17	18	17

on MCF-7 and HepG-2 cell lines, respectively. This data indicated the efficacy of the both complexes as antiproliferative agents on MCF-7 and HepG-2 cell lines.

Antimicrobial activity

Antimicrobial activities of the free ligand cocaine and its Mn(II) and Cu(II) metal complexes were studied in terms of their antibacterial activities against *Staphylococcus aureus* (RCMB 010010) and *Bacillus subtilis* (RCMB 015 (1) NRRL B-543) as Gram positive bacteria and *Salmonella typhimurium* (RCMB 006 (1) ATCC 14028) and *Escherichia coli* (RCMB 010052) ATCC 25955) as Gram negative bacteria comparing to gentamycin and their antifungal activities towards *Aspergillus fumigatus* (RCMB 002008) and *Candida albicans* (RCMB 005003 (1) ATCC 10231) comparing to ketoconazole using the agar well-diffusion technique and the screening data were statistically represented in Fig. 5. The formed complexes have inhibitory action against all microorganisms, whereas free ligand Cn have no inhibitory activity against *Salmonella typhimurium* and *Aspergillus fumigatus* (Table 4).

Mn(II) complex showed remarkable fungal growth inhibition against *Candida albicans* indicated by the diameter of its inhibition zone comparing to that of the standard ketoconazole (Table 4).

Cu(II) complex exhibited antibacterial activity against *Salmonella typhimurium* slightly higher than that of the standard gentamycin (Table 4).

Conclusion

Reaction of cocaine (Cn) with Mn(II) and Cu(II) chloride salts afforded complexes of the $[M(Cn)Cl(OH_2)_3]Cl$ type which were structurally characterized by elemental analysis, conductance measurements, spectroscopic methods and mass spectrometry. Their thermal properties were also studied. The two formed complexes adopted octahedral structures of 1:1 metal−ligand stoichiometry where Cn acted as a neutral bidentate ligand. IR data revealed that Cn chelated to the metal centers through the etheric oxygen adjacent to the azabicyclo[3.2.1]octane ring and the carbonyl oxygen of the ($-COOCH_3$) ester. Both complexes displayed promising growth inhibitory activity against the two tested cell lines. Mn(II) complex displayed 71% growth inhibition on MCF-7 cell line and 63% growth inhibition on HepG-2 cell line and Cu(II) complex showed 76% and 82% growth inhibition on MCF-7 and HepG-2 cell lines, respectively. Mn(II) complex showed remarkable fungal growth inhibition against *Candida albicans* whereas, Cu(II) complex exhibited antibacterial activity against *Salmonella typhimurium*.

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