Journal of Enzyme Inhibition and Medicinal Chemistry, 2011; 26(3): 359–366

ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.3109/14756366.2010.506874

informa
healthcare

ORIGINAL ARTICLE

Ternary copper(II) complexes of levofloxacin and phenanthroline derivatives: *In-vitro* antibacterial, DNA interactions, and SOD-like activity

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Abstract

A series of ternary copper(II) complexes have been derived using levofloxacin and five phenanthroline derivatives. Complexes were characterized using infrared spectroscopy, Thermogravimetric (TG)-analysis, fast atom bombardment mass spectroscopy and reflectance spectra. Synthesized complexes exhibit the only d-d band at ~ 666 nm points toward a distorted square pyramidal geometry at metal centre with one unpaired electron responsible for paramagnetic behaviour of whole moiety. Binding behaviour of the complexes toward Herring Sperm DNA were determined using ultraviolet-Vis (UV-Vis) absorption titration and viscometric titration experiment, where as the cleavage efficacy of the complexes toward pUC19 DNA was determined by electrophoresis in presence of ethidium bromide. Complexes exhibit superoxide dismutase–like activity with their IC_{50} values ranging from 0.7917 to 1.7432 μM.

Keywords: Ternary copper(II) complexes, phenanthroline derivatives, DNA scissoring, levofloxacin, SOD mimics

Introduction

Quinolones can act as antibacterial drugs that effectively inhibit DNA replication and are widely used in the treatment of many infections. The interaction of metal ions with diverse deprotonated quinolones have been thoroughly studied[1]. The recently released fluoroquinolone levofloxacin (LFLH) possess broad-spectrum antibacterial activity similar to that of earlier quinolones. However, it has enhanced activity against gram-positive and a typical organisms[2,3]. But, the optically active S(–)-isomer, LFLH is 2 fold more potent than the racemate and 8–28 fold more potent than its R(+)-isomer, ofloxacin[4].

The interaction of transition metal complexes with DNA has received considerable attention because they serve as potential models of biological systems[5]. Copper complex derived from 1,10-phenanthroline shows efficient DNA cleavage activity. The chemical attributes of metal complexes of phenanthroline are particularly attractive for developing new diagnostic and therapeutic agents[6]. Among the metal complexes so far investigated, those of polypyridyl phenanthroline bases have attracted great attention by virtue of its binding propensity to nucleic acid under the physiological condition[7–9]. Copper phenanthroline derivatives show an important biological activity. This includes chemical nuclease, antitumoural, antimycobacterial, antifungal, and antimicrobial activity[10].

Copper is a biologically relevant element and many enzymes that depends on copper for their activity have been identified. Copper(II) complexes are known to play a significant role in naturally occurring biological systems like [Cu,Zn–superoxide dismutase (SOD)] SOD. SOD can destroy the superoxide very rapidly, is a nature's gift to organism to get rid from the burden of reactive superoxide radical. In fact a native SOD enzyme is found in many studies to exhibit protection in ani-

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(Received 12 May 2010; revised 03 July 2010; accepted 05 July 2010)

mal models of inflammatory diseases[11]. We present the synthesis and structural characterization of five ternary copper(II) complexes based on LFLH and five phenanthroline derivatives.

Experimental

Materials

Analytical grade of solvents, reagents, and chemicals were used throughout. Bayer AG (Wuppertal, Germany) generously supplied LFLH. Cupric chloride dihydrate was purchased from E. Merck (India) Ltd. Mumbai. 1,10-Phenanthroline, ethidium bromide (EtBr), bromophenol blue, agarose, and Luria Broth were purchased from Himedia (India). 2,9-Dimethyl-1,10-phenanthroline (A^1), 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (A^2), nicotinamide adenine dinucleotide reduced (NADH), nitro blue tetrazolium (NBT) and phenazin methosulphate (PMS) were purchased from Loba Chemie PVT. LTD (India).

Physical measurements

Elemental analyses (C, H, and N) of the synthesized complexes were performed with a model 240 Perkin Elmer elemental analyzer (MA, USA). Metallic content of the complex was determined after decomposing it under effect of acid mixture and titrating against EDTA solution volumetrically. Chlorine content of the complexes was carried out by modified Stepanow method. Room temperature magnetic measurement for the complexes was made using Gouy magnetic balance. The Gouy tube was calibrated using mercury(II) tetrathiocyanatocobaltate(II) a calibrant ($\chi_g = 16.44 \times 10^{-6}$ cgs units at 20°C), Mumbai (India)[12]. Thermogravimetric (TG) analyses data were obtained with a model 5000/2960 SDTA, TA instrument New castle (DE, USA). The electronic spectra were recorded on a UV-160A UV-Vis spectrophotometer, Shimadzu Kyoto (Japan). Infrared (IR) spectra were recorded on a Fourier transform–IR Shimadzu spectrophotometer as KBr pellets in the range 4000–400 cm^{-1}. Fast atom bombardment (FAB)-mass spectrometry (MS) were recorded on Jeol SX 102/Da–600 mass spectrophotometer/Data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature (MA, USA). Photo quantization of the gel after electrophoresis was done using AlphaDigiDoc™ RT. Version V.4.0.0 PC–Image software (CA, USA).

Preparation of phenanthroline derivative

4,5-Diazafluoren-9-one (A^3), 1,10-phenanthroline-5,6-dione (A^4) and 5-nitro-1,10-phenanthroline (A^5) were prepared as per reported methods[13–15].

Synthesis of ternary copper(II) complexes

A methanolic solution of $CuCl_2.2H_2O$ (1.5 mmol) was added to a methanolic solution of NN donor ligand (1.5 mmol), followed by addition of a previously prepared solution of LFLH (1.5 mmol) in methanol in presence of CH_3ONa (1.5 mmol). The pH was adjusted to ~ 6.2 using dilute solution of CH_3ONa. The resulting solution was refluxed for 1 h on a steam bath, followed by concentrating it to half of its volume. A fine amorphous product of green colour obtained was washed with ether/hexane and dried in vacuum desiccator.

Synthesized complexes at biological interphase

In-vitro antimicrobial behaviour

In-vitro antimicrobial tests were performed against *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Bacillus subtilis* and *Staphylococcus aureus* using 2-fold serial dilution technique in triplicate[16]. Former three are gram-negative while later two are gram-positive organism. Microbes were subjected to test compounds at various concentration. The lowest concentration which inhibits the growth of microbes incubated at 37 ± 1°C for 24 h is termed as minimum inhibitory concentration (MIC; μM). All these operations were carefully performed under aseptic conditions.

DNA binding study by absorption titration

Hypochromism and bathochromism from intercalation mode of binding[17], is due to strong stacking interaction between an aromatic chromophore and the DNA base pair[18]. Selection of an appropriate absorbance peak was done by performing spectrophotometric wavelength scans of Cu(II) complexes. After addition of equivalent amount of DNA to reference cell, both were kept for incubation of 10 min at room temperature followed by absorption measurement. It was specifically done to enable direct comparison between the assays that was required to interpret the results obtained. The intrinsic binding constant, K_b was determined by making it subject in following equation[19].

$$\frac{[\mathrm{DNA}]}{(\epsilon_a - \epsilon_f)} = \frac{[\mathrm{DNA}]}{(\epsilon_b - \epsilon_f)} + \frac{1}{K_b(\epsilon_b - \epsilon_f)},$$

where [DNA] is the concentration of DNA in base pairs, ε_a the apparent extinction coefficient is obtained by calculating $A_{obs.}$/[complex] and ε_f corresponds to the extinction coefficient of the complex in its free form. The data were fitted to above equation where ε_b refers to the extinction coefficient of the complex in the fully bound form. When each set of data, fitted to the above equation, gave a straight line with a slope of $1/(\varepsilon_a - \varepsilon_f)$ and a *y*–intercept of $1/K_b(\varepsilon_b - \varepsilon_f)$. K_b was determined from the ratio of the slope to Intercept.

DNA binding study by hydrodynamic volume measurement

Ubbelohde viscometer immersed in a thermostatic bath maintained at 27 ± 0.1°C was used to measure the change in hydrodynamic volume with change in complex concentration. Digital stopwatch with least count of 0.01 sec.

was engaged for flow times measurement with accuracy of ± 0.1 sec. Plot of $(\eta/\eta_0)^{1/3}$ versus [complex]/[DNA] is use to study the behaviour of binding, where η is the viscosity of DNA in presence of complex and η_0 is the viscosity of DNA alone. Viscosity values were calculated from the observed flow time of DNA-containing solutions (t) corrected for that of the buffer alone (t_0), $\eta = (t - t_0)$[20].

DNA cleavage study by gel electrophoresis

Gel electrophoresis of plasmid DNA (pUC19 DNA) was carried out in Tris-acetate-EDTA (TAE) buffer (0.04 M TAE, pH 8, 0.001 M EDTA). Fifteen microlitre reaction mixture containing plasmid DNA in TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0) and 200 μM complex. Reactions were allowed to proceed for 24 h at 37°C. All reactions were quenched by addition of 5 μL loading buffer (0.25% bromophenol blue, 40% sucrose, 0.25% xylene cyanole, and 200 mM EDTA). The aliquots were loaded directly on to 1% agarose gel and electrophoresed at 50 V in 1X TAE buffer. Gel was stained with 0.5 μg/mL EtBr and was photographed on a UV illuminator. The percentage of each form of DNA was quantities using AlphaDigiDoc™ RT. Version V.4.0.0 PC–Image software.

Enzymatic behaviour

NBT/NADH/PMS system was used to study SOD-like behaviour of the complexes. The superoxide radial produce by 79 μM NADH, 30 μM PMS in phosphate buffer (pH = 7.8) was responsible for reduction of 75 μM NBT in system, and 0.25–3.0 μM tested compound are responsible for retardation in the reduction rate of NBT which was determined spectrophotometrically by monitoring the concentration of blue formazan form which absorbs at 560 nm. All measurements were carried out at room temperature. The % inhibition (η) of NBT reduction was calculated using following equation[21]:

$$\eta(\%\ \text{Inhibition of NBT reduction}) = (1 - k'/k) \times 100\%,$$

where k' and k present the slopes of the straight line of absorbance values as a function of time in presence and absence of SOD mimic or a model compound, respectively. IC_{50} value of the complex was determined by plotting the graph of percentage inhibition of NBT reduction against increase in concentration of the complex. Concentration of the complex which causes 50% inhibition of NBT reduction is reported as IC_{50}.

Results and discussion

Characterization of complexes

Several instrumental techniques like elemental analysis, magnetic measurement, TG-analysis, reflectance, IR, and FAB-MS were used to evaluate structure of the complexes. Figure 1 represents the sketch of proposed structure. Elemental analysis and magnetic moment data are in good agreement with proposed structure (Table 1). (Supplementary Figure S1).

IR spectroscopy

Major changes in IR spectra of ligands on complexation are comprised in Table 2 and some important points are as follows:

- Band at 1634 and 1316 cm^{-1} in case of LFLH corresponds to $\nu(COO)_{assy}$ and $\nu(COO)_{sym}$ respectively, which on complexation with metal ion shifts about 1580 and 1347 cm^{-1} respectively[22].
- Unidentate nature for the carboxylato group of LFLH is proved by frequency of separation ($\Delta\nu = \nu COO_{assy} - \nu COO_{sym}$) which is about 233 cm^{-1} [23].
- Deprotonation of the hydroxyl group of LFLH was confirmed by deduction of band at 3519 cm^{-1} from spectra due to hydrogen bonding[24].
- Coordination via pyridone oxygen atom of LFLH was suggested from the shift of its band from 1728 cm^{-1} to about 1625 cm^{-1} [25], these data are further supported by ν(M–O) which appear at ~ 520 cm^{-1} [26].
- NN donating nature of ligand was confirmed from band appearing at ~ 538 cm^{-1} [27].

Thermogravimetric analyses

TG-analysis data confirms that there are five molecule of water of crystallization which are librated during 75–120°C. No loss in weight during 120–210°C points toward absence of coordinated water molecules. Residue remaining at the end of heating i.e. after 720°C is in full competition with expected weight for metal oxide[28].

Magnetic and electronic behaviour

The magnetic moment measurement was found about 1.79 Bohr Magneton (B.M.) which is very close toward spin only value i.e. 1.73 B.M. expected for one unpaired electron hence it confirms the copper(II) ion in form of d^9 system[29].

There are two possibilities of geometry, if copper(II) ion is surrounded by five donor atoms. First is trigonal bipyramidal, which shows the pattern of λ_{max} > 800 nm along with shoulder at ~ 660 nm[30] and second is square pyramidal, where only a broad band about 660 nm is

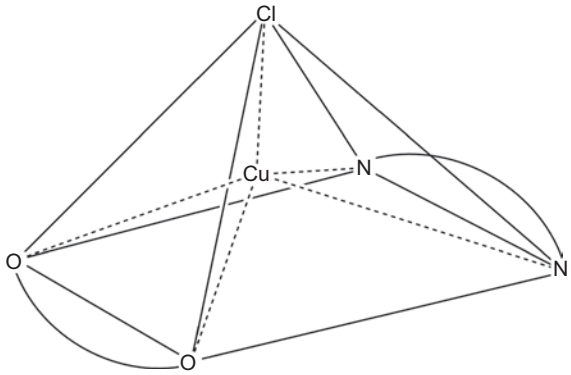

Figure 1. Basic sketch for square pyramidal copper(II) complexes derived from levofloxacin (LFLH); uninegative bidentate OO-donating, and phenanthrolines; neutral bidentate NN- donating ligands.

observed[31] (Supplementary Figure S2). The spectra clearly kick out the first possibility and strongly directs toward distorted square pyramidal geometry for Cu(II)-d^9 system.

FAB-MS

Peaks at 136, 137, 154, 289, and 307 m/z value appearing in the mass spectra are due to *m*-nitro benzyl alcohol. Figure 2 represents the FAB-MS of complex 1, i.e. [Cu(LFL)(A^1)Cl] $5H_2O$. The doublet at 668 and 670 corresponds to (M) and (M + 2) of the complex 1 associated with two protons in absence of crystallization water; which is due to one chlorine and metal. Doublet at 459 and 461 is assigned to fragment with one chloride associated with one proton. Whereas the doublet at 306 and 308 due to fragment with single chlorine atom associated with no proton. Several other fragments at 424, 362, 271, and 209 m/z value are observed, attributed to fragments associated with different numbers of H^+ ions. The proposed fragmentations are shown in Supplementary Figure S3.

Synthesized complexes at biological interphase

In-vitro *antimicrobial behaviour*

Table 3 comprises the data for antibacterial efficacy of complexes, ligands, and LFLH against two gram(+) and three gram(–) microorganisms. It is clear from the data that all complexes are active compare to LFLH and phenanthroline derivatives but complex 5 proved to most active for all the bacterial species employed.

DNA binding studies by absorption titration

It is a general observation that the binding of intercalative molecules to DNA is accompanied by a red shift and hypochromism in the absorption spectra[32]. The extent of spectral change is related to the strength of binding. The absorption spectra of the complex in absence and presence of DNA is illustrated in Figure 3. In order to compare

Table 1. Analytical and physical data of the complexes.

Empirical formula for complexes	Elemental analysis % required (found)					mp (°C)	% Yield	$\mu_{eff.}$ BM	Formula weight (g/mol)
	C	H	N	Cu	Cl				
$C_{32}H_{41}ClCuFN_5O_9$ (1)	50.73 (50.66)	5.45 (5.63)	9.24 (9.17)	8.39 (8.35)	4.68 (4.34)	> 300	64.52	1.83	757.69
$C_{44}H_{49}ClCuFN_5O_9$ (2)	58.08 (58.02)	5.43 (5.37)	7.70 (7.62)	6.98 (6.91)	3.90 (3.98)	245	73.89	1.79	909.89
$C_{30}H_{38}ClCuFN_5O_{10}$ (3)	48.26 (48.30)	5.13 (5.04)	9.38 (9.29)	8.51 (8.44)	4.75 (4.66)	> 300	66.76	1.88	746.65
$C_{30}H_{35}ClCuFN_5O_{11}$ (4)	47.43 (47.36)	4.64 (4.71)	9.22 (9.28)	8.37 (8.43)	4.67 (4.72)	293	54.62	1.82	759.62
$C_{30}H_{36}ClCuFN_6O_{11}$ (5)	46.51 (46.56)	4.68 (4.74)	10.85 (10.88)	8.20 (8.16)	4.58 (4.50)	286	77.82	1.77	774.64

BM, Bohr Magneton.

Table 2. Characteristic IR bands (4000–400 cm^{-1}) of LFLH and their complexes.

Compound	ν(C=O)pyridone	ν(H–O)Carboxyl	$\nu(COO)_{asym}$	$\nu(COO)_{sym}$	$\Delta\nu$	ν(M–N)	ν(M–O)
LFLH	1728	3519	1634	1316	318	—	—
(1)	1628	—	1584	1350	234	534	520
(2)	1627	—	1588	1362	226	533	519
(3)	1624	—	1572	1333	239	544	522
(4)	1621	—	1576	1341	235	537	527
(5)	1626	—	1579	1348	231	542	511

IR, infrared; LFLH, levofloxacin.

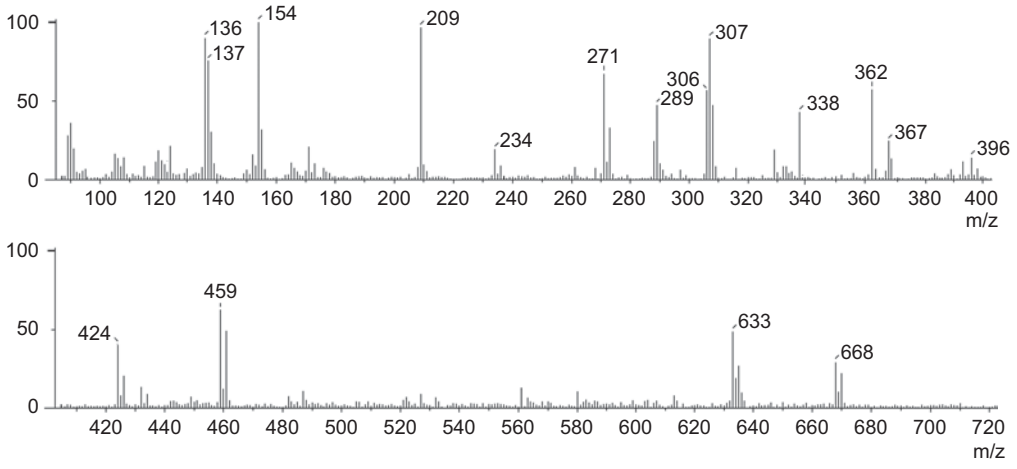

Figure 2. Fast atom bombardment (FAB)-mass spectrum of complex 1, i.e. [Cu(LFL)(A^1)Cl]·$5H_2O$ recorded on Jeol SX 102/Da–600 mass spectrophotometer/Data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas at accelerating voltage of 10 kV.

quantitatively the binding strength of the complexes, the intrinsic binding constant K_b was obtained by monitoring the changes in absorbance for complexes with increasing concentration of DNA. From the K_b value (Table 4) and red shift it is clear that complexes bind via intercalation mode.

DNA binding study by hydrodynamic volume measurement

The binding modes of the Cu(II) complexes were further investigated by viscosity measurements, which are sensitive to DNA length change, regarded as the least ambiguous and the most critical tests of binding in solution. A classical intercalative mode demands that the DNA helix must lengthen as base pairs are separated to accommodate the binding ligand, leads to the increase in DNA viscosity[33]. The effects of complexes, EtBr and LFLH on the viscosity of rod-like DNA are shown in Figure 4. EtBr increases the relative specific viscosity by lengthening the DNA double helix through the intercalation mode. On increasing the amounts of complexes, the relative viscosity of DNA increases steadily, this is similar to the behaviour of EtBr. The increased degree of viscosity, which may depend on its affinity to DNA follows the order of EtBr > 5 > 4 > 3 > 1 > 2. In contrast, LFLH binds via partial, non-classical intercalation of ligand on bending (or kinking) the DNA helix and reduce its effective length and, concomitantly, its viscosity[34].

DNA cleavage study

Agarose gel electrophoresis is used as a base for monitoring plasmid DNA cleavage reaction. Circular plasmid DNA when subjected to electrophoresis, relatively fast migration is observed for the intact supercoil form (SC; Form I). The scission on one strand (nicking) will relax supercoil to generate a slower-moving open circular form (OC; Form II), and if both strands are cleaved, a linear form (LC; Form III) that migrates between Form I and Form II will be generated[35]. Data of the cleavage study obtain from Figure 5 are presented in Table 5. Difference in DNA cleavage efficiency of complexes was due to the difference in binding affinity of complexes to DNA.

Enzymatic behaviour; SOD-like activity

Measured IC_{50} values for SOD-like activity at biological pH ranges from 0.7917 to 1.7432 μM (Table 4) (Supplementary

Table 3. Antimicrobial activities of LFLH, phenanthrolines and their complexes in terms of minimum inhibitory concentration (MIC; μM).

	Gram-positive		Gram-negative.		
Compounds	*S. aureus*	*B. subtilis*	*S. marcescens*	*P. aeruginosa*	*E. coli*
$CuCl_2$ $2H_2O$	2698.00	2815.00	2756.00	2404.00	3402.00
LFLH	1.70	2.20	1.70	1.70	1.00
A^1	130.00	250.00	506.00	154.00	129.00
A^2	194.00	169.00	272.00	255.00	278.00
A^3	631.00	670.00	604.00	725.00	758.00
A^4	829.00	733.00	771.00	738.00	762.00
A^5	578.00	631.00	609.00	658.00	591.00
(1)	0.68	0.66	0.43	0.73	0.48
(2)	0.88	0.44	0.44	0.88	0.83
(3)	0.63	0.54	0.40	0.58	0.45
(4)	0.35	0.46	0.38	0.33	0.40
(5)	0.33	0.40	0.32	0.61	0.37

LFLH, levofloxacin.

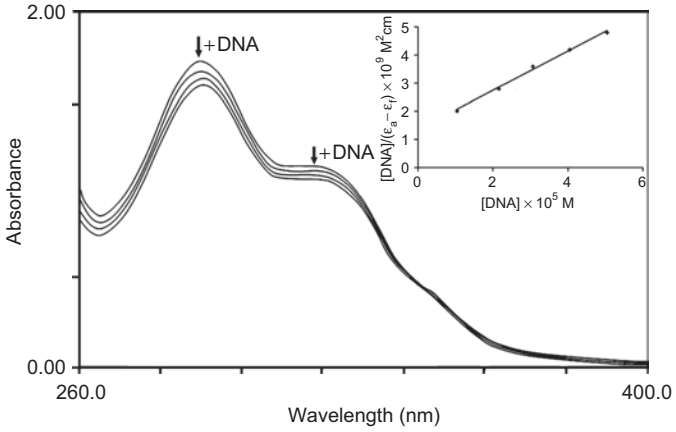

Figure 3. Absorption spectral traces on addition of Herring Sperm DNA to the solution of complex 1 after incubating it for 10 min at room temperature in phosphate buffer at 7.2 pH. (shown by arrow). Inset: plot of [DNA]/(ε_a-ε_f) versus [DNA] for absorption titration of Herring Sperm DNA with complex 1.

Figure S4). The complexes show different extent of superoxide scavenging ability. The higher IC_{50} can be accredited to the vacant coordination site facilitating the binding of superoxide anion, electrons of aromatic ligands that stabilize Cu–O_2^- interaction and not only to the partial dissociation of complex in solution. Difference in electron withdrawing group on phenanthroline can also be taken under consideration for difference in affinity of complexes toward reactive specie. Cotton and Wilkinson suggested the mechanism for scavenging of superoxide radical which move forward via unstable octahedral

Table 4. Binding constant (K_b) and 50% inhibitory concentration (IC_{50}) values of the complexes.

Complexes	K_b (M^{-1})	IC_{50} (μM)
(1)	0.613×10^4	1.5000
(2)	0.584×10^4	1.7432
(3)	0.767×10^4	1.1154
(4)	0.823×10^4	0.9795
(5)	1.123×10^4	0.7917

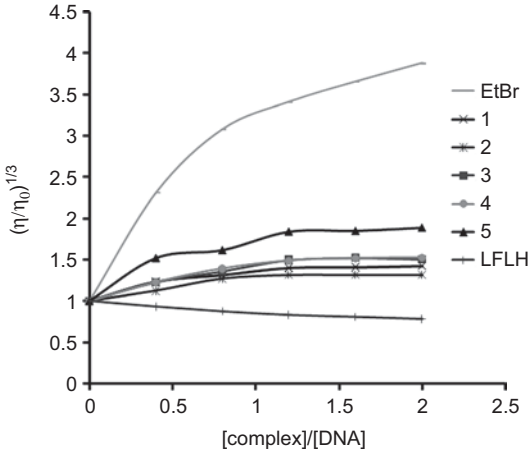

Figure 4. Effect of increasing amount of ethidium bromide (EtBr), levofloxacin (LFLH) and complexes on the relative viscosity of Herring Sperm DNA at 27 ± 0.1°C.

Table 5. Percentage of all the three forms of plasmid separated on agarose gel, when subjection to different synthesized complexes at 200 μM concentration.

Lane No.	Compounds	Form I (SC)	Form II (OC)	Form III (LC)
1	Control	89	11	—
2	$CuCl_2{\cdot}2H_2O$	84	16	—
3	Levofloxacin	38	51	11
4	(1)	32	44	24
5	(2)	38	40	22
6	(3)	29	49	22
7	(4)	25	42	33
8	(5)	16	58	26

SC, Super coiled; OC, Open Circular; LC, Linear.

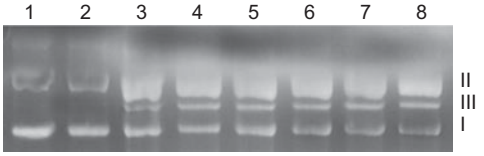

Figure 5. Gel electrophoresis diagram showing the cleavage of SC pUC19 DNA(300 μg/mL) with as series of copper(II) complex (200 μM) in a final volume of 15 μL, incubated at 37°C, using 1% agarose gel, at 50 mV for 1.5 h. Lane 1, DNA control; Lane 2, DNA + $CuCl_2{\cdot}2H_2O$; Lane 3, DNA + LFLH; Lane 4, DNA + $[Cu(LFL)(A^1)Cl].5H_2O$; Lane 5, DNA + $[Cu(LFL)(A^2)Cl].5H_2O$; Lane 6, DNA + $[Cu(LFL)(A^3)Cl].5H_2O$; Lane 7, DNA + $[Cu(LFL)(A^4)Cl].5H_2O$; Lane 8, DNA + $[Cu(LFL)(A^5)Cl].5H_2O$.

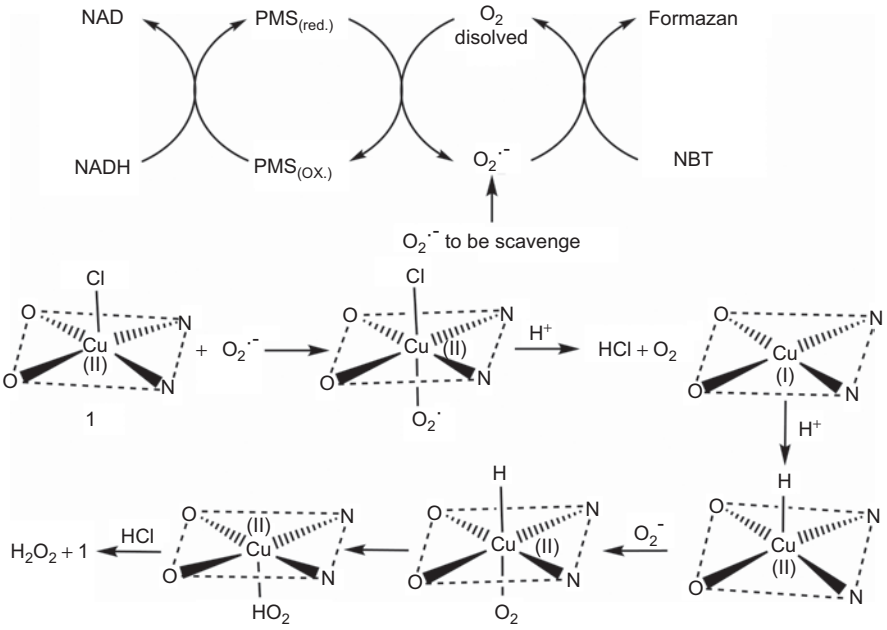

Figure 6. Oxygen radical production by NBT/NADH/PMS system and its scavenging; Proposed mechanism for superoxide dismutase-like activity of complex checked in NBT/NADH/PMS system.

adduct under influence of Jahn–Teller effect[36–38], and there is a possibility of rapid interconversion between Cu(II) and Cu(I) via electron transfer between copper and reactive oxygen radical anion following the principle of electroneutrality[39]. The proposed mechanism for generation of reactive oxygen species and its dismutation is shown in Figure 6

Conclusion

Data of magnetic behaviour and electronic spectral measurement points towards the d^9 system with distorted square pyramidal geometry. Taking a while toward the data from MIC, absorption titration, viscosity measurement, DNA cleavage, and SOD; increasing order of the activity of the synthesized complexes is 2 < 1 < 3 < 4 < 5. MIC values of complexes are much better compare to ligands, drug, and metal salt, which can be studied under chelation theory. From the absorption titration and viscosity data intercalative mode of binding of complexes is proved. Also the antioxidant activity of complex 5 is found to be the highest among all.

Declaration of interest

Authors thank The Head, Department of Chemistry, Sardar Patel University, India for making it convenient to work in laboratory and U.G.C. for providing financial support under 'UGC Research Fellowship in Science for Meritorious Students' scheme.

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