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Comparative Studies on DNA Interactions and Biological Activities of Lanthanum (III) Complexes with 2-quinoline terpyridine and 3-quinoline terpyridine

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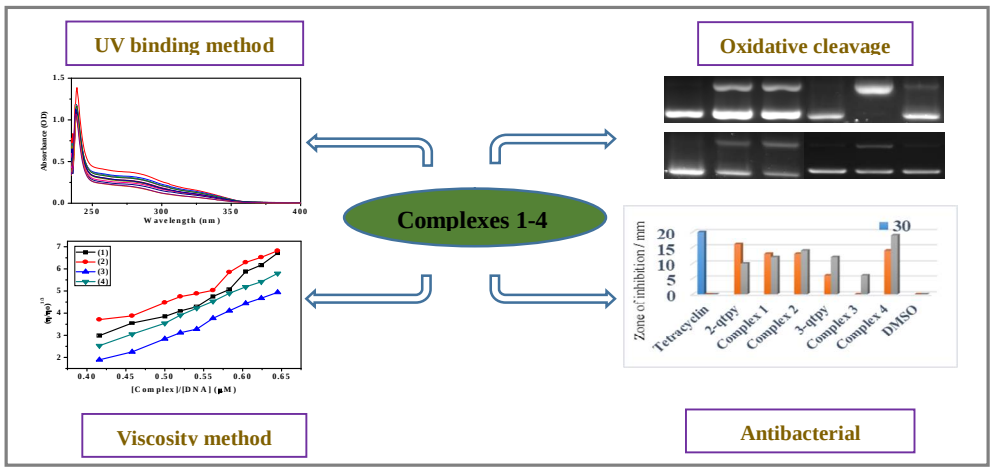
ABSTRACT

*Lanthanum (III) complexes **1–4** were synthesized and studied extensively towards their DNA binding and cleavage properties. Mode of binding of complexes depends on the nature of the ligands and they possess different biological significances. In this regards we have synthesized La(III) complexes with 4'-[(2-quinoline)-2,2';6',2''-terpyridine (2-qtpy), 4'-[(3-quinoline)-2,2';6',2''-terpyridine (3-qtpy) and 1,10-phenanthroline (phen). $[La(2\text{-qtpy})_2(NO_3)_2](NO_3)$ **(1),** $[La(2\text{-qtpy})(phen)_2(NO_3)_2](NO_3)$ **(2),** $[La(3\text{-qtpy})_2(NO_3)_2](NO_3)$ **(3)** and $[La(3\text{-qtpy})(phen)(NO_3)_2](NO_3)$ **(4)**. The newly synthesized complexes were characterized by FT-IR, UV-Vis, ^{1}H-NMR spectroscopic and ESI-mass spectrometric technique and by elemental analysis. The mode of binding of complexes **1–4** towards HS-DNA were examined by UV-Vis absorption spectral studies and viscosity measurements. The chemical nuclease activity of these complexes towards SC pUC 19 DNA was evaluated by agarose gel electrophoresis. The antibacterial activities of the complexes **1−4** were tested against Gram positive and Gram negative bacteria. The cytotoxic activities of 2-qtpy and complex **2** were carried out by MTT assay against HeLa cell lines. The antioxidant activity of 3-qtpy and its complexes were carried out by free radical scavenging and ferrous ion chelating method.*

Graphical Abstract



Keywords: Antibacterial activity, Cytotoxic study, DNA binding and cleavage studies, Lanthanum (III) terpyridine complexes.

INTRODUCTION

The rare earth metal complexes have potential applications in biochemical technology, medicine, catalysis, magnetism, optoelectronic devices and material science [**1, 2**]. They have also been broadly used to study the structure and function of nucleic acids and proteins. Compared to other metal complexes, lanthanides afford a unique environment around the metal centre. Due to their high coordination number they can accommodate multiple ligands, giving rise to intricate coordination compounds [**3**]. Lanthanides and their complexes can proficiently cleave nucleic acids so that they can be used as DNA cleaving agents [**4, 5**]. These ions have high affinity with hard bases such as oxygen or nitrogen atoms [**6**]. Tridentate 2,2'; 6',2''-terpyridine and bidentate 1,10-phenanthroline form stable complexes with La(III), because of suitable structural properties like nature of the donor atoms, structural rigidity and proper spatial position of donating centres they play a very fundamental role in the process of complex formation [**7, 8**]. It is reported that the intercalating ability increases with the planarity of ligands. The coordination geometry and ligand donor atom type also play key roles in determining the binding extent of complexes to DNA [**9**]. Metal complexes of terpyridine can efficiently intercalate into nucleic acid and hence these can be used as potential antitumor agents [**10**]. Cisplatin (cis-$[PtCl_2(NH_3)_2]$) is the first anticancer drug used widely in the world. But its side effects have stimulated the search for other metal-based anticancer drugs. In this regard, studying interaction between small metal complexes and DNA may lead to a new kind of active anticancer drugs [**11-13**]. One approach it should appear as 'one approach to solve this problem' is to identify the new classes of complexes having structural features that differ from those of the existing cisplatin analogues [**14**]. La(III) complex with 1,10-phenanthroline-2,9-bis-α-amino acid and 2-methylene-1,10-phenanthrolin show the promising *in vitro* antitumor activity against a series of cell lines [**15, 16**]. La(III) complex with quercetin play an important role against tumour cells [**17**]. La(III) complex with (N, N'-bis-(1-carboxy-2-methylpropyl)-1,10-phenanthroline-2,9-dimethanamine acts as antitumor agent [**13**].

Oxidative cleavage of DNA generally causes degradation of the sugar and/or base moiety thus making the process suitable for foot-printing and therapeutic applications. Oxidative cleavage of DNA by metal complexes can be achieved in the presence of external reagents [**18**]. Some metal complexes containing 1,10-phenanthroline are also known to bind to DNA by an intercalative mode [**19, 20**]. Some lanthanum(III) complexes play a major part in bioinorganic chemistry because of their biological and pharmaceutical activities, such as antibacterial [**21**], cytotoxic [**17**], antioxidant activities [**22**]. Some Lanthanum(III) complexes possess photophysical properties such as luminescence that can be employed as labelling agents in MRI and immunohybridization techniques [**23**].

In the present work, we report the syntheses and characterization of the La(III) complexes with 2-quinoline terpyridine and 3-quinoline terpyridines. The DNA binding properties of the complexes have been investigated by UV-visible absorption titration and viscosity measurements. The DNA cleavage of the complexes has been investigated by agarose gel electrophoresis method. These complexes exhibit cytotoxic effects against HeLa cell lines and bactericidal action against tested bacteria *E. coli*, *K. pneumonia*, *S. aureus* and *B. subtilis*.

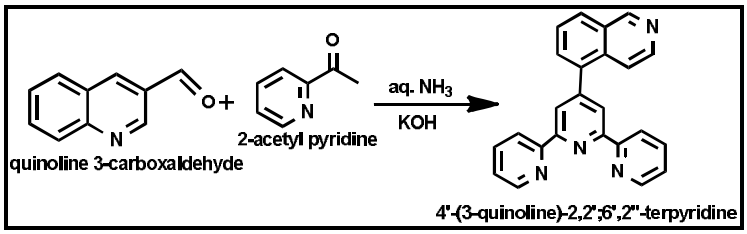
MATERIALS AND METHODS

2-acetyl pyridine, 3-quinoline carbaxaldehyde, 2-quinoline carbaxaldehyde $La(NO_3)_3.6H_2O$, Ethidium bromide (EB), Agarose (molecular biology grade) were purchased from Sigma (USA). HS-DNA (Herring Sperm DNA), Supercoiled (SC) pUC19 DNA (caesium chloride purified), were purchased

from Bangalore Genie (India). Bacterial media was purchased from Himedia. The bacterial strains were purchased from IMTECH, Chandigarh, India. All the cell lines for MTT assay were purchased from ATCC.

The elemental analyses of the newly synthesized complexes were carried out by using Thermo Finnigan FLASH EA 1112 CHNS analyser. The FT-IR spectra were recorded on Perkin Elmer Lambda 35 spectrophotometer in the range 4000-500 cm^{-1}. UV-Visible absorption measurements were recorded on a Shimadzu UV-1800 UV-Visible spectrophotometer (Japan) in the range 200-800 nm. ^{1}H-NMR for the compounds were recorded on 400 MHz liquid state NMR spectrometer, Bruker, in DMSO-d_6 solution using tetramethylsilane (TMS) as internal standard. Mass spectrometry was performed on a Bruker Esquire 6000 (ESI) mass spectrometer. Molar conductivity measurements were carried out by Control Dynamics (India) conductivity meter.

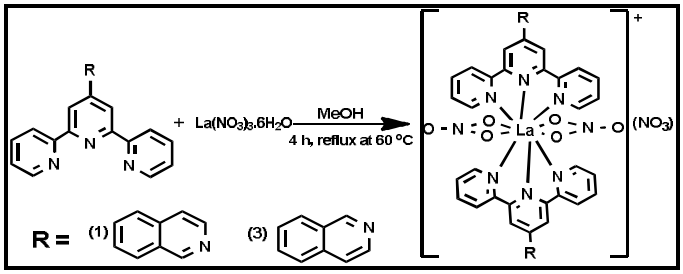
Synthesis of 4'-[(3-quinoline)-2,2';6',2''-terpyridine (3-qtpy): The ligand 3-qtpy was synthesized from modified reported method [24]. 2-acetyl pyridine (0.605 g, 5 mM) was added to the 20 mL ethanolic solution of 3-quinoline carbaxaldehyde 0.392 g, 2.5 mM). KOH pellets (0.364 g, 6.5 mM) and aq. NH_3 were added to the solution then stirred for 24 h at room temperature. An off white precipitate obtained was filtered and washed with water-ethanol (3:1) mixture, dried under vacuum. Residue was recrystallized from chloroform and methanol gives white crystalline solid. They are soluble in MeOH, EtOH, acetone, acetonitrile, DMF and DMSO.



Scheme 1. Synthesis of 3-quinoline terpyridine ligand (3-qtpy).

Spectral data for [4'-(3-quinoline)-2,2';6',2''-terpyridine] (3-qtpy): Analysis (calculated *%)* C, 79.98; H, 4.47; N, 15.55. Found: C, 79.02; H, 4.12; N, 14.78. FT-IR (KBr disc, cm^{-1}): 1582 m, 1491 w, 1468 m, 1349 w, 1075 w, 989 w, 891 w, 786 s, 739 s, 618 m, 558 w (s, strong; m, medium; w, weak). ESI-MS (m/z): 383.0 $[M+Na]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm) 7.379-7.412 (2H, m), 7.636-7.656 (1H, td), 7.794-7.814 (1H, td), 7.896-7.984 (3H, d), 8.194-8.215 (1H, d), 8.676-8.776 (5H, m), 8.880 (2H, s), 9.438-9.444 (1H, d).

Synthesis of complexes 1 $[La(2\text{-qtpy})_2(NO_3)_2](NO_3)$ and 3 $[La(3\text{-qtpy})_2(NO_3)_2](NO_3)$: The complexes were synthesized from modified reported method [25]. Methanolic solution of $La(NO_3)_3.6H_2O$ (0.030 g, 0.69 mM) was added to the methanolic solution of the ligands 2-qtpy **(1)** and 3-qtpy **(3)** (0.050 g, 0.138 mM)**.** The reaction mixture was refluxed for 4 h at 60°C under nitrogen atmosphere with continuous stirring. Then the solution was allowed to dry, yielded an off-white solid. These complexes are soluble in MeOH, DMF and DMSO.

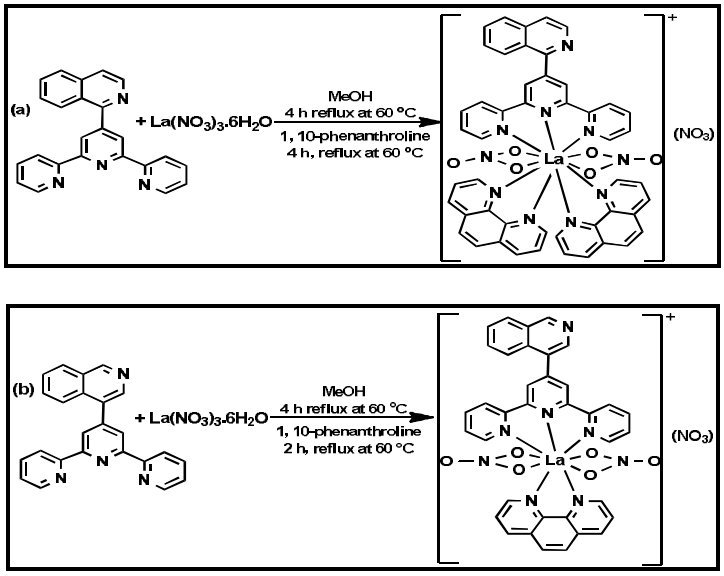


Scheme 2. Synthesis of complexes **1** and **3.**

Spectral data for Bis[4'-(2-quinoline)-2,2';6',2''-terpyridine] bis(nitrato) lanthanum(III) nitrate (1): Analysis (calculated *%)* C, 55.13; H, 3.08; N, 4.73. Found: C, 54.94; H, 2.92; N, 14.52. FT-IR (KBr disc, cm^{-1}): 1588 m, 1540 w, 1456 s, 1396 w, 1289 s, 1018 m, 896 m, 821 w, 781 s, 734 s, 632 w, 542 w (s, strong; m, medium; w, weak). Λ_M ($Scm^2 M^{-1}$) in DMF at 25 ºC 88.6. ESI-MS in methanol (m/z): 982.68 $[M-(NO_3^-)]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm) 7.548–7.581 (4H, td), 7.688–7.725 (2H, t), 7.860–7.901 (2H, td), 8.049–8.100 (4H, m), 8.120 (2H, s), 8.237–8.258 (2H, d), 8.390–8.412 (2H, d), 8.616–8.638 (2H, d), 8.712–8.732 (4H, d), 8.813–8.823 (4H, d), 9.267 (4H, s).

Spectral data for Tris[4'-(3-quinoline)-2,2';6',2''-terpyridine] bis(nitrato)lanthanum(III) nitrate (3): Analysis (calculated %) C, 55.13; H, 3.08; N, 4.73. Found: C, 54.98; H, 2.98; N, 14.58%. FT-IR (KBr disc, cm^{-1}): 1608 m, 1584 w, 1432 s, 1392 w, 1295 s, 1036 m, 874 m, 788 m, 724 m, 609 m, 528 w (s, strong; m, medium; w, weak). Λ_M ($Scm^2 M^{-1}$) in DMF at 25ºC 112.2. ESI-MS in methanol (m/z): 982.8 $[M-(NO_3^-)]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm) 7.516–7.546 (2H, td), 7.691–7.709 (1H, t), 7.818–7.839 (1H, t), 8.019–8.057 (2H, td), 8.093–8.114 (1H, dt), 8.205–8.225 (1H, dd), 8.675–8.695 (2H, d), 8.764–8.774 (2H, d), 8.873 (2H, 2), 8.998 (1H, d), 9.408 (1H, d).

Synthesis of $[La(2\text{-qtpy})(phen)_2(NO_3)_2](NO_3)$ (2), $[La(3qtpy)(phen)(NO_3)_2]$ (NO_3) (4): The same procedure was followed as mentioned in 2.3 for the synthesis of complexes **2** and **4**. The methanolic solution of $La(NO_3)_3.6H_2O$ (0.060 g, 0.138 mM) was added to the methanolic solution of 2-qtpy **(2)** and 3-qtpy **(4)** (0.050 g, 0.138 mM). The reaction mixture was refluxed for 4 h at 60 °C with stirring under nitrogen atmosphere. After 4 h, methanolic solution of 1,10-phenanthroline (0.012 mg 0.138 mM) was added drop wise to both the complexes and stirred for an additional 2 h. Then the solution was allowed to dryness, yielded off-white solid. The complexes were soluble in MeOH, DMF and DMSO.



Scheme 3. Synthesis of (a) complexes **2** and (b) **4**.

Spectral data for [4'-(2-quinoline)2,2';6',2''-terpyridine]bis(1,10-phenanthroline)-bis (nitrato) lanthanum(III)nitrate (2): Analysis (calculated %) C, 55.13; H, 3.08; N, 14.73. Found: C, 54.96; H, 3.01; N, 14.64. FT-IR (KBr disc, cm^{-1}): 1608 w, 1584 w, 1432 s, 1392 w, 1295 s, 1122 w, 1041 m, 965 w, 885 m, 816 m, 786 m, 734 s, 665 w, 613 m, 536 w (s, strong; m, medium; w, weak). Λ_M ($Scm^2 M^{-1}$) in DMF at 25ºC 78.4. ESI-MS in methanol (m/z): 982.77 $[M-(NO_3^-)]$. ^{1}H-NMR (400MHz, DMSO-d_6, δ ppm) 7.536–7.569 (2H, m), 7.675–7.715 (1H, td), 7.769–7.800 (4H, m), 7.847–7.889 (1H, td) 7.999 (4H, s), 8.037–8.106 (3H, m), 8.224–8.245 (1H, d), 8.365–8.385 (1H, d), 8.496–8.516 (4H, dd), 8.597–8.619 (1H, d), 8.694–8.714 (2H, d), 8.802–8.814 (2H, d), 9.105–9.112 (4H, d), 9.248 (2H, s).

Spectral data for [4'-(3-quinoline)-2,2';6',2''-terpyridine](1,10-phenanthroline)bis (nitrato) lanthanum (III) nitrate (4): Analysis (calculated %) C, 49.96; H, 2.79; N, 14.56%. Found: C, 49.74; H, 2.66; N, 14.46. FT-IR (KBr disc, cm^{-1}): 1604 w, 1544 w, 1440 s, 1378 s, 1282 m, 1032 w, 844 w, 788 m, 729 m, 609 w, 549 w (s, strong; m, medium; w, weak). Λ_M ($Scm^2 M^{-1}$) in DMF at 25 ºC 108.2. ESI-MS in methanol (m/z): 803.6 [M-(NO_3^-)]. ^{1}H-NMR (400MHz, DMSO-d_6, δ ppm) 7.527 (2H, t), 7.687–7.835 (4H, tt), 7.972–8.112 (5H, m), 8.201–8.222 (1H, d) 8.464–8.483 (2H, d), 8.670–8.690 (2H, dd), 8.765 (2H, t), 8.870 (2H, s), 8.992–9.075 (3H, d), 9.405 (1H, t).

DNA binding studies: DNA binding interactions were carried out to examine the binding mode of HS-DNA and binding propensity of the complexes **1**–**4**. By using UV-Visible absorption spectral method and viscosity method mode of binding was determined.

Absorption spectral studies: The binding interactions of complexes **1–4** with HS-DNA were monitored by Tris-HCl/NaCl buffer (5 mM, pH 7.2) using DMF solvent. The changes in the spectral bands of the complexes **1–4** were measured with constant complex concentration (10 µM) with the varying concentration of HS-DNA. Before recording the spectrum, complexes were equilibrated to bind sufficiently with the HS-DNA. From this titration, the intrinsic binding constant *(K_b)* was determined using the equation

$$[DNA]/(\varepsilon_a-\varepsilon_f) = [DNA]/(\varepsilon_b-\varepsilon_f) + 1/K_b(\varepsilon_a-\varepsilon_f)$$

Where, ε_a, ε_f and ε_b corresponds to A_{obsd}/[La], the molar extinction coefficient of free La(III) complex and that of fully bound complex. Plots of [DNA]/ε_a-ε_f vs [DNA] gives K_b as the ratio of slope to the intercept [**26, 27**].

Viscosity measurements: The binding of complexes **1–4** were also confirmed by this method. Viscosity measurements were carried out at 37 (± 0.1) ^oC in a constant temperature bath. The rate of flow of Tris-HCl buffer (5 mM, pH 7.2), HS-DNA and complexes **1–4** with DNA at various concentrations were measured in these experiments. Using the equation $\eta=(t-t_0)/t_0$, η was calculated, where t is the flow time of HS-DNA in the absence and presence of complexes and t_0 is the flow time of buffer alone. A plot of $(\eta/\eta_0)^{1/3}$ vs. [complex]/[DNA] was constructed from viscosity measurements, where η is the viscosity of DNA with the complexes and η_0 is the viscosity of DNA alone [**28**].

DNA cleavage experiments: The agarose gel electrophoresis of SC pUC 19 DNA was carried out by using Tris-HCl buffer (50 mM, pH 7.2). The extent of cleavage of SC pUC 19 DNA into nick circular form by the ligands and complexes at 10 µM concentration in the presence and absence of H_2O_2 and MPA was studied. Agarose gel 0.8 % was prepared by using 0.25 g in 25 mL 1xTAE buffer and 1.0 mg mL^{-1} EB. The samples were incubated for 1 h 30 min. The samples were loaded to the gel using loading dye, and the experiments were carried out in dark for 1 h 30 m in TAE buffer and finally photographed [**29, 30**]. The extent of cleavage of SC pUC 19 DNA was determined by measuring the intensities of the bands using a UVITECH Gel Documentation system. Due corrections were made for the low level of NC form present in the original SC-DNA sample and for the low affinity of EB binding to SC compared to NC and linear form of DNA. For the complex **2** concentration dependent experiment at 5 and 7 µM was also done. Mechanistic studies were also carried out with different additives such as DMSO (hydroxyl radical quencher), NaN_3 (singlet oxygen quencher) and with the methyl green (major groove binder) [**31**].

Antibacterial activity: The antibacterial activity of ligands 2-qtpy and its complexes **1**, **2**, 3-qtpy and its complexes **3** and **4** were done by disc diffusion method [**32**] against Gram positive *(Bacillus subtilis MTCC 645, Staphylococcus aureus MTCC 3160)* and Gram negative (*Escherichia coli ATCC 25922, Klebsiella pneumoniae MTCC 109)* bacteria as test organisms. About 50 and 100 µg of the sample permeated in Whatman filter paper discs were used to determine antibacterial activity. All the

plates were incubated at 37°C for 24 h. DMSO is used as a solvent for the bacterial activity. Zones of inhibition were measured after 24 h. The control discs contained DMSO as negative control and tetracyclin as positive control.

Cytotoxic studies: To evaluate the influence of complex on the cell growth, the cytotoxic studies of 2-qtpy and complex **2** were tested against HeLa (human cervical carcinoma) cell lines determined by using MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay. The assay was carried out by the modified reported method [**33, 34**], with the concentration range of 10–320 μg mL^{-1}. 96 well plate was used for the assay, 100 μL of the diluted cell suspension (2,000 cells/well) was seeded using RPMI-1640 medium containing10% FBS (Fetal bovine serum). Different concentration of test drugs (100 μL) were added after 24 h. At 37°C, the plates were incubated in 5% CO_2 atomsphere for 24 h. For each well, after 24 h the test solution was discarded and 100 mL of MTT was added (6 mg 10 mL^{-1} of MTT in PBS [Phosphate bovine serum]). The well plates were again incubated for additional 4 h. The supernatant was removed and 100 μL of DMSO was added and the plates were gently shaken to solubilize the formed formazan. At the wavelength of 500 nm, the absorbance of each well was measured using a microplate reader. Using the given formula, the percentage growth inhibition was calculated.

$$\% \text{ Inhibition} = 100\text{-(OD of sample/OD of Control)} \times 100.$$

The IC_{50} (concentration of test drugs needed to inhibit cell growth by 50 %) values were generated from the dose-response curves for cell lines.

Antioxidant activity: The antioxidant activities of 3-qtpy and its complexes **3** and **4** were evaluated by DPPH free radical scavenging method and ferrous ion chelating method.

Free radical scavenging method: This is the most commonly used method to evaluate the antioxidant activity. The antioxidant activity of samples was determined by modified reported method [**35**]. The stock solution of 1 mg mL^{-1} 3-qtpy and its complexes **3** and **4** were prepared in DMF. Test solutions of different concentrations (10-70 μg mL^{-1}) were taken in a 96-well plate, using 5 mM Tris-HCl buffer (pH=7.4) solutions were made up to 200 μL. 500 mM ethanolic DPPH solution was added to each well. Then the well plates were incubated in the dark for 30 min. For the base line correction blank solution (without test sample) was used. BHT (Butylated hydroxy toluene) and ascorbic acids were used as a positive control. At the wavelength of 517 nm, absorbance was measured for both blank solution and all the test samples. The decrease in the absorbance values indicated that complexes have free radical scavenging activity. The free radical scavenging activity was calculated by the equation:

$$\text{Free radical scavenging activity (\%)} = [(A_c - A_s)/A_c] \times 100$$

Where, A_c is the absorbance of control in the absence of 3-qtpy and its complexes, A_s is the absorbance of 3-qtpy and its complexes.

Ferrous ion chelating method: The ligand 3-qtpy and its complexes **3** and **4** were assessed for ferric ion reducing antioxidant activity, determined by modified reported method [**36**]. In this method, the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ion takes place in the presence of antioxidants. The stock solution of samples 1 mg mL^{-1} solution was prepared in DMF. Test solutions of different concentrations (10-70 μg mL^{-1}) were taken in a 96-well plate, using distilled water made up to 150 μL. 2 mM $FeCl_2$ solution (20 μL) to each well was added. The reaction was initiated by adding 5 mM Ferrozine (30 μL) to each well and shaken vigorously. After that, the well plates were incubated for 10 min at room temperature. Absorbance of each well was measured at 562 nm against the blank (without test sample). EDTA-Na_2 was used as standard. The % inhibition of Ferrozine-Fe^{2+} was calculated by the formula:

Ferrous ion chelating ability (%) = $[1\text{-}A_s/A_o] \times 100$

Where, A_s and A_o are the absorbance in the presence and the absence of the test samples respectively. A graph was plotted using % inhibition of ferrozine-Fe^{2+} complex formation vs. concentration of sample.

RESULTS AND DISCUSSION

Synthesis and characterization: The ligand 3-quinoline terpyridine was synthesized by using 3-quinoline carbaxaldehyde and 2-acetyl pyridine as shown in scheme 1. The complexes **1**−**3** were synthesized and characterized by elemental and spectral analysis. The coordinating atom of the complexes was evaluated by using FT-IR spectra. The stretching vibration of ν(C=N) band of the ligand 2-qtpy was shown at 1580 cm^{-1} and is shifted to 1588 and 1585 cm^{-1} in the complexes **1** and **2**. In the ligand 3-qtpy the stretching vibration of ν(C=N) band is 1582 cm^{-1} and is shifted to 1608 and 1604 cm^{-1} in the complexes **3** and **4**. This shift of higher wavenumber suggest that the coordination of nitrogen atom [37]. In all the complexes, the two asymmetric stretching bands are shown around 1432–1462 cm^{-1} and 1287–1314 cm^{-1}, indicates the coordination of bidentate nitrate [38]. A band appears around 1372–1396 cm^{-1} indicates the presence of ionic nitrate in all the complexes [39] which is also confirmed by the conductivity measurements.

The ^{1}HNMR spectra of the ligand 2-qtpy, the chemical shift value of all the aromatic protons ranging from 7.55-8.82, where as in the complexes **1** and **2**, the chemical shift values of the aromatic protons ranging from 7.548–9.267 ppm and 7.536–9.248 ppm respectively. In the ligand 3-qtpy, the chemical shift values of aromatic proton ranging from 7.379–9.444 ppm, in the complexes **3** and **4** the chemical shift values of aromatic protons are observed in the range 7.516–9.408 ppm and 7.527–9.406 ppm respectively. All the expected protons are observed in the complexes **1**–**4** confirms the formation of complexes [40].

The molecular weight of the ligands and the complexes are confirmed by the ESI-MS spectrometry. All the spectra of the complexes are measured in positive ion mode. In the ligand 3-qtpy the molecular ion peak is observed at 383.0 m/z value. In all the complexes the molecular ion peak corresponds to $[M\text{-}(NO_3)]^+$ as shown [17]. The ESI-mass spectral data is completely correlated with the simulated mass.

DNA binding studies

UV-Visible absorption titration: DNA binding experiments were done by UV-Visible experiment and viscosity measurements, to determine the mode of binding of the complexes with HS-DNA. UV-Visible absorption method is an effective method to determine the mode of binding complexes with HS-DNA. The spectral titration of the 15 μM complexes in the absence and incremental addition of HS-DNA were recorded and shown in figure 1. From the spectra, with the increasing concentration of HS-DNA, the absorption bands of HS-DNA have shown hypochromism and slight bathochromic shift indicates the intercalative mode of binding of the complexes [41]. The hypochromicity of the complexes **1**–**4** are in the range 31.1–48.8 and slight red shift can be seen in the spectra. This is due to the strong $\pi \rightarrow \pi^*$ coupling between an aromatic chromophore of the complexes and the HS-DNA base pairs [42]. The order of binding strength of the complexes shows **2** > **4** > **1** > **3**, the K_b values are in the range 10^5-10^6 M^{-1}. The K_b values are tabulated in the table 1. Among all the complexes, complexes **2** and **4** have higher K_b value than the others.

Viscosity measurements: Viscosity experiment is the most convincing technique to specify the mode of binding of La(III) complexes to HS-DNA in the absence of crystallographic data [43]. To examine the mode of binding of complexes viscosity experiments were carried out with the solution, HS-DNA with the complexes and are incubated at 37°C. The viscosity measurements on DNA solution is

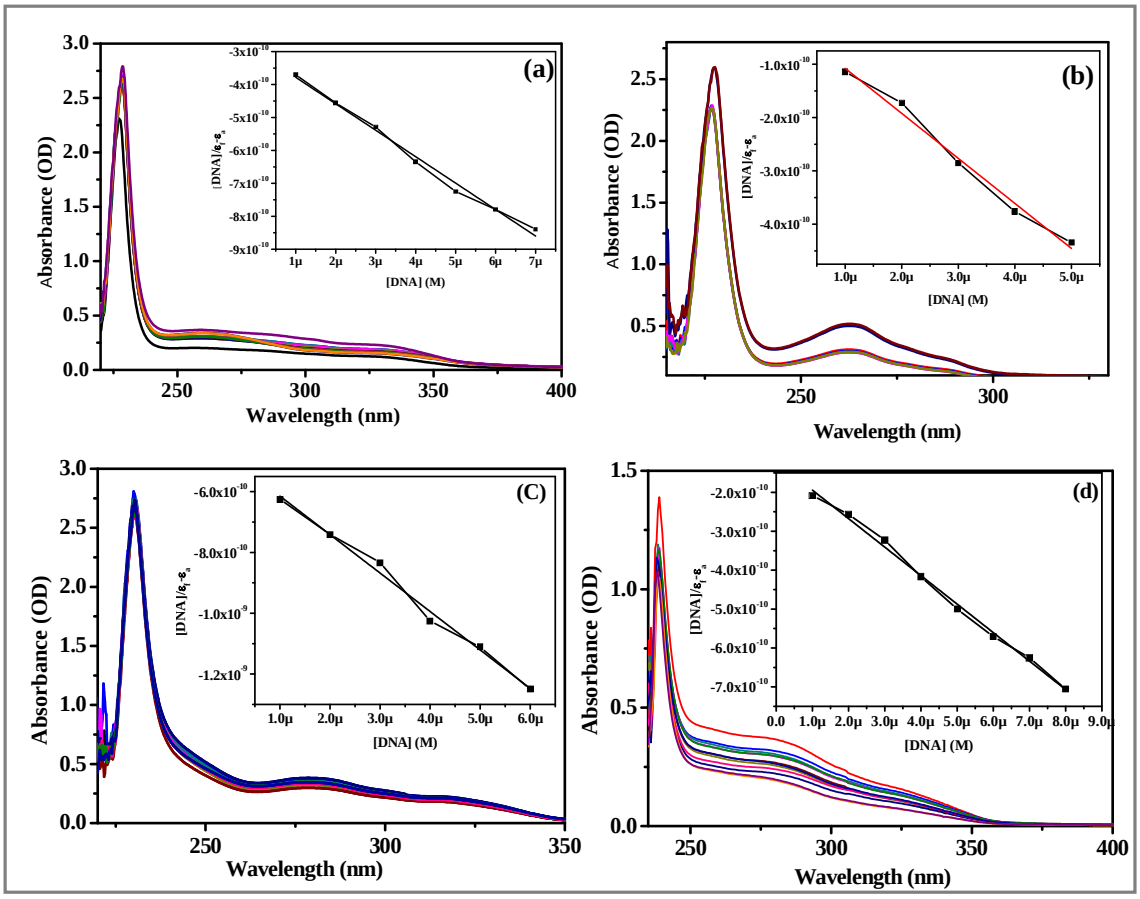


Figure 1. UV-Visible absorption spectra of complexes **1** (a), **2** (b), **3** (c), **4** (d) in the absence and presence HS-DNA in 5 mM Tris-HCl/50 mM NaCl buffer (pH 7.2) at 25 ^{o}C. The inset shows the plot of [DNA] vs. [DNA]/ ε_a-ε_f.

Table 1. Selected physicochemical data and DNA binding parameters of La (III) complexes **(1-4)**

Comp.	IR[a] /cm^{-1}			Λ_M[c] / Scm^2 M^{-1}	K_b, (M^{-1})[d]	H (%)[e]
	ν(C=N)	ν(NO_3)	ν(NO_3)$^-$			
	(coordinated)	(ionic)				
1	1588	1456, 1289	1396	88.6	(2.69 ± 0.2) x 10^5	45.0
2	1585	1462, 1287	1388	112.2	(3.64 ± 0.2) x 10^6	48.0
3	1608	1432, 1295	1392	78.4	(2.59 ± 0.2) x 10^5	31.1
4	1504	1440, 1314	1378	108.0	(6.02 ± 0.2) x 10^6	48.8

[a]In KBr phase, [b]absorption in DMF, [c]Λ_M, Molar conductivity in DMF at 25 ^{o}C, [d]K_b, HS-DNA binding constant, H[e] = $[(A_{free}-A_{bound})/A_{free}] \times 1$

sensitive towards the complexes and organic drug molecules bound by intercalation. With the successive addition of compounds to DNA, we examined the effect of specific viscosity of DNA. With the increase in concentration of complexes thereby increase in the specific viscosity thus we observed changes in the length of DNA (Figure 2). In classical intercalators like EtBr, it causes a significant increase in the specific viscosity of DNA solutions, where as in partial/non-classical intercalators the complexes bend or kink the DNA there by decrease in the length of DNA [41]. The increase in the specific viscosity of DNA suggests that complexes bind to DNA through intercalative mode. From the figure 2, it is clear that, the 2-qtpy complexes **2** and **1** have shown higher relative viscosity than the complexes of 3-qtpy suggesting the 2-qtpy complexes bind strongly than the 3-qtpy complexes.

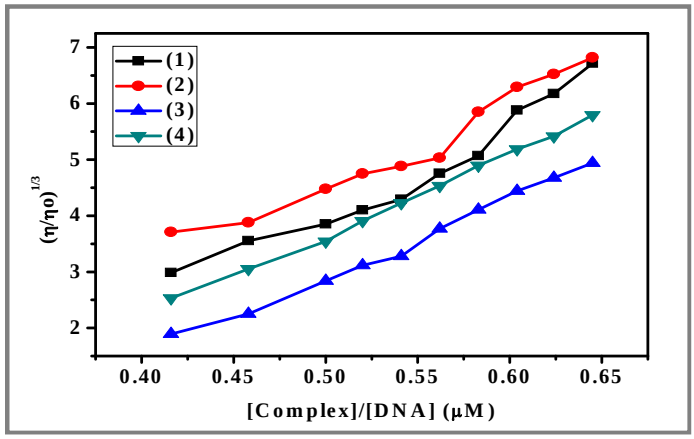


Figure 2. Change in the relative specific viscosity of the HS-DNA with the successive addition of complexes **1–4** in 5 mM Tris-HCl buffer at 37 °C, pH 7.2.

Chemical nuclease activity: The DNA cleavage activity of the complexes **1–4** were studied by agarose gel electrophoresis using pUC 19 DNA in the presence of H_2O_2 as oxidising agent and MPA as reducing agent. The efficiency of DNA cleavage of complexes **1–4** can be known by conversion of SC DNA into its nicked form and its linear form. Figure 3 shows the electrophoretic arrangement of plasmid DNA with ligands and their complexes. The results shows that, the control experiments using H_2O_2 and MPA alone (lanes 1–3) did not show any cleavage activity. Complexes **1** (lanes 7–9) and **3** (Lanes 16–18) have shows moderate cleavage activity in the presence of both H_2O_2 and MPA (Tabel 2) [**44, 45**]. Complex **2** shows maximum activity (lanes 10–12) in the presence of H_2O_2. Complex **4** shows moderate cleavage activity in the presence of H_2O_2. For complex **2**, we have done the cleavage activity at 5 and 7 µM concentrations (Figure 4, lane 4–9). From this, we observed that with the increase in concentration of complexes the rate of extent of cleavage also increases. At 10 µM (lanes 10–12) concentration complex **2** shows maximum cleavage activity than other concentrations (Table 3). The mechanistic aspects of oxidative cleavage were studied for the complexes **1–4** using DMSO (hydroxyl radical quencher, NaN_3 (singlet oxygen quencher) and methyl green (major groove intercalator). Hydroxyl radical scavenger DMSO and major groove intercalator methyl green causes the inhibition of DNA cleavage. Thus, it is clear that oxidative cleavage is mediated by the generation of hydroxyl radicals. This shows that complex **2** is a major groove intercalator [**31**].

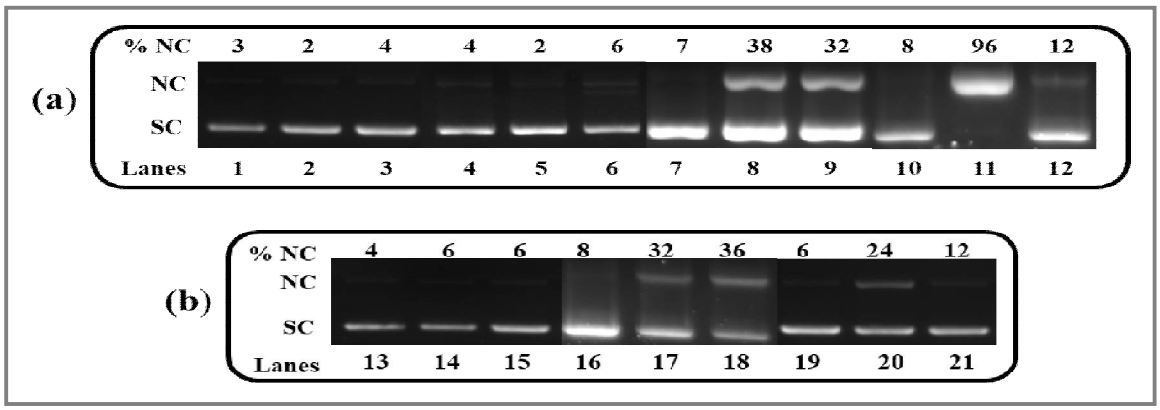


Figure 3. Cleavage of pUC 19 DNA (a) by 2-qtpy and its complexes **1** and **2** (lanes 4–12), (b) 3-qtpy and its complexes **3** and **4** (lanes 13–21) at 10 µM concentration in the presence of H_2O_2 and MPA in 50 mM Tris-HCl/NaCl buffer (pH=7.2) at 37°C.

Table 2. SC pUC 19 DNA cleavage data of 2-qtpy and its complexes **1, 2** and 3-qtpy and its complexes **3, 4**

Lane No.	Conditions	% SC	% NC
1	DNA + NaCl + Tris HCl	97	3
2	DNA + NaCl + Tris HCl + H_2O_2	98	2
3	DNA + NaCl + Tris HCl + MPA	96	4
4	DNA + NaCl + Tris HCl + **2-qtpy**	96	4
5	DNA + NaCl + Tris HCl + H_2O_2 +**2-qtpy**	98	2
6	DNA + NaCl + Tris HCl + MPA +**2-qtpy**	94	6
7	DNA + NaCl + Tris HCl + **1**	93	7
8	DNA + NaCl + Tris HCl + H_2O_2 + **1**	72	38
9	DNA + NaCl + Tris HCl + MPA + **1**	78	32
10	DNA + NaCl + Tris HCl + **2**	92	8
11	DNA + NaCl + Tris HCl + H_2O_2 + **2**	4	96
12	DNA + NaCl + Tris HCl + MPA + **2**	88	12
13	DNA + NaCl + Tris HCl + **3-qtpy**	96	4
14	DNA + NaCl + Tris HCl + H_2O_2 +**3-qtpy**	94	6
15	DNA + NaCl + Tris HCl + MPA +**3-qtpy**	94	6
16	DNA + NaCl + Tris HCl + **3**	92	8
17	DNA + NaCl + Tris HCl + H_2O_2 + **3**	68	32
18	DNA + NaCl + Tris HCl + MPA + **3**	64	36
19	DNA + NaCl + Tris HCl + **4**	94	6
21	DNA + NaCl + Tris HCl + H_2O_2 + **4**	76	24
21	DNA + NaCl + Tris HCl + MPA + **4**	88	12

[NaCl] = 50 mM; [Tris-HCl] = 50 mM; [H_2O_2] = 200 µM; [MPA] = 500 µM; [Complex] = 10 µM.

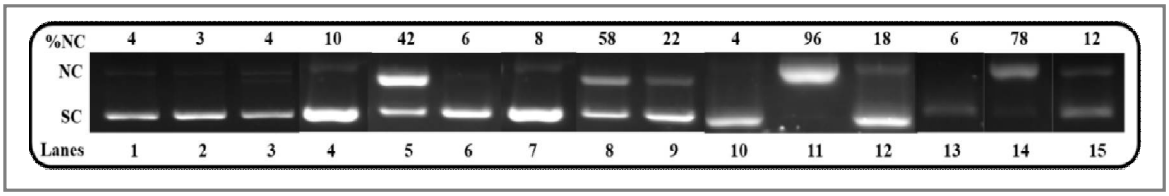


Figure 4. Cleavage of SC pUC 19 DNA by [La(2-qtpy)(phen)$_2$(NO$_3$)$_2$](NO$_3$) **(2)** at 5, 7 and 9 µM concentration (lanes 4–12) in the presence of H_2O_2 and MPA in 50 mM Tris-HCl/NaCl buffer (pH 7.2) at 37^{o}C.

Table 3. Concentration dependent SC pUC 19 DNA cleavage data of [La(2-qtpy)(phen)$_2$(NO$_3$)$_2$](NO$_3$) (3)

Lane No.	Condition	% SC	% NC
1	DNA + NaCl + Tris HCl	96	4
2	DNA + NaCl + Tris HCl + H_2O_2	97	3
3	DNA + NaCl + Tris HCl + MPA	96	4
4	DNA + NaCl + Tris HCl + 5 µM	92	10
5	DNA + NaCl + Tris HCl + H_2O_2 + 5 µM	64	42
6	DNA + NaCl + Tris HCl + MPA + 5 µM	88	6
7	DNA + NaCl + Tris HCl + 7 µM	90	8
8	DNA + NaCl + Tris HCl + H_2O_2 + 7 µM	38	58
9	DNA + NaCl + Tris HCl + MPA + 7 µM	84	22
10	DNA + NaCl + Tris HCl + 10 µM	96	4
11	DNA + NaCl + Tris HCl + H_2O_2 + 10 µM	6	96
12	DNA + NaCl + Tris HCl + MPA + 10 µM	92	18
13	DNA + NaCl + Tris HCl + H_2O_2 + DMSO + **2**	96	6
14	DNA + NaCl + Tris HCl + H2O2 + NaN_3 + **2**	82	78
15	DNA + NaCl + Tris HCl + H2O2 + MG + **2**	88	12

[NaCl] = 50 mM; [Tris-HCl] = 50 mM; [H_2O_2] = 200 µM; [MPA] = 500µM; [Complex] = 10 µM

Antibacterial activity: The antibacterial activities of the ligands 2-qtpy and 3-qtpy as well as their complexes **1–4** were evaluated against Gram positive *B. subtilis* and *S. aureus* and Gram negative bacteria by Agar disc diffusion method [19]. Figure 5 show that the ligand 2-qtpy and complex **1** shows moderate activity against all the bacteria in both 50 and 100 µM concentration. Complex **2** shows moderate activity at 100 mM concentration against *B. subtillis* pathogen. Complex **3** show minimum activity against all the pathogen and complex **4** shows moderate activity against *K. pneumonia* and maximum activity against all other pathogens. All the tested compounds show significant activity against all the bacteria.

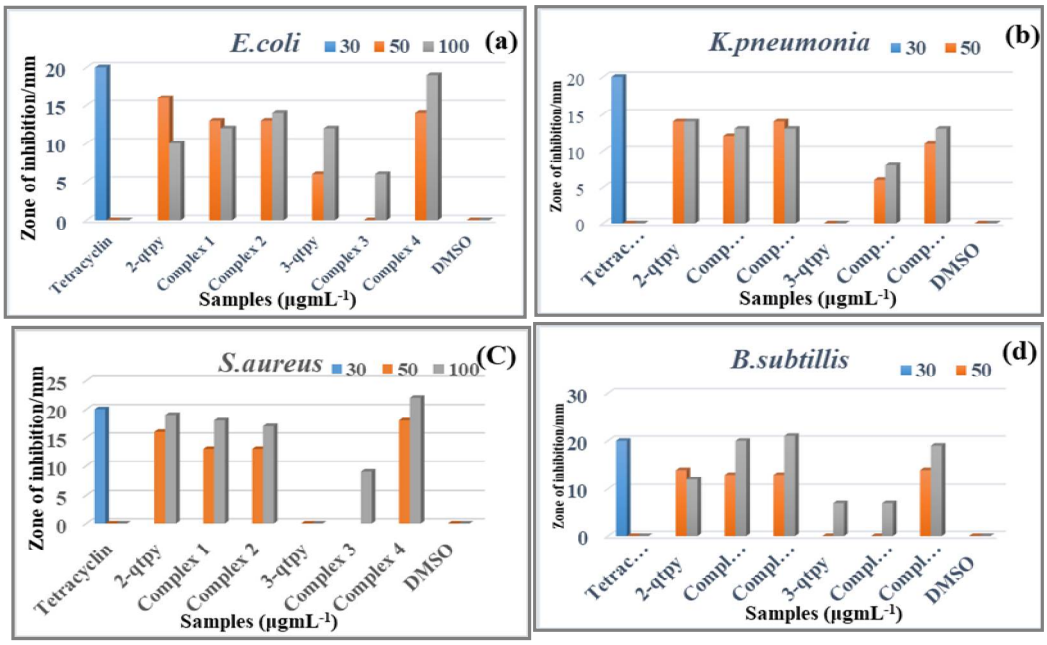


Figure 5. The antibacterial activity of ligands and its complexes **1–4** against Gram positive and Gram negative bacteria at concentration of 50 and 100 µg mL^{-1}.

***In vitro* cytotoxic activity:** In the development of effective anticancer agents, evaluation of cytotoxic activity against cancerous cell lines is of great importance. The cytotoxicity of 2-qtpy and its complex **2** were tested against HeLa (human cervical carcinoma) cell lines by MTT assay [46]. Figure 6 shows that increase in the concentration of samples increases the percentage of inhibition. The complex **2** shows moderate *in vitro* cytotoxicity against HeLa cell lines with an IC_{50} value of 78.84 µM. The biological activity of the complexes was greatly influenced by the aromatic substituents in the terpyridine ligand.

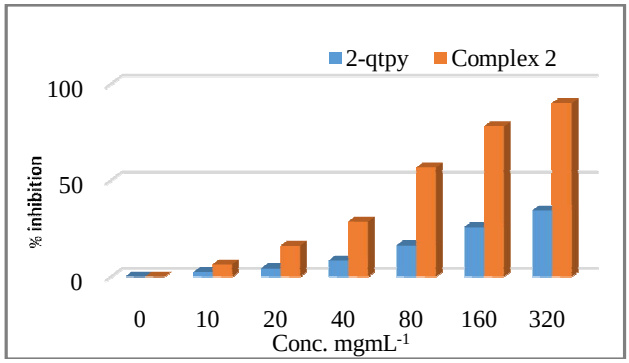


Figure 6. The percentage inhibition of 2-qtpy and its complex **2** at varying complex concentration against HeLa cell lines.

Antioxidant activity: The antioxidant activity of La(III) complexes were carried out by DPPH scavenging method in comparison with the ascorbic acid (natural antioxidant), also with BHT (synthetic antioxidant) and ferrous ion chelating method in comparison with EDTA-Na_2. From the figure 7 and 8, the results show that the complexes do not show any appreciable antioxidant activity [47].

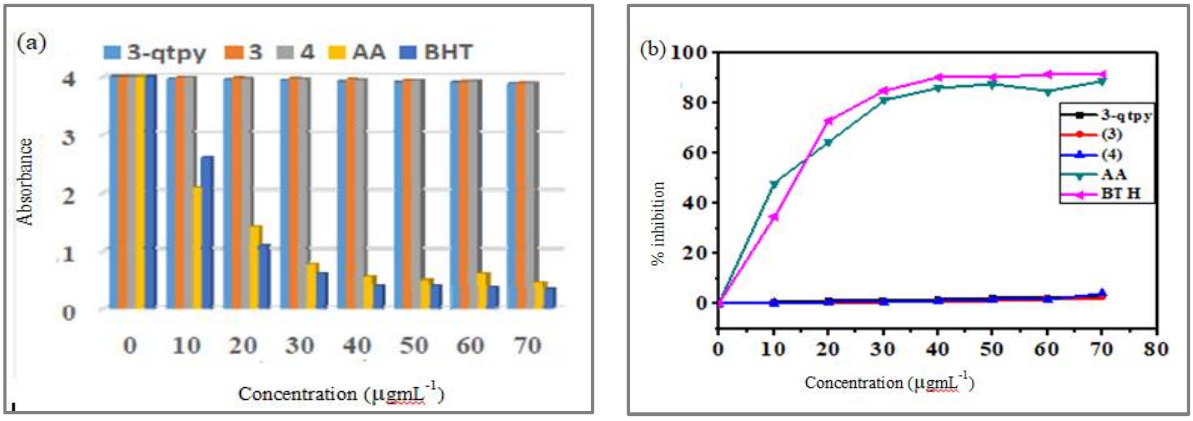


Figure 7. (a) Bar diagram of DPPH radical scavenging ability of 3-qtpy and complexes **3** and **4** in comparison with BHT and ascorbic acid (AA). (b) A plot of % inhibition of formation of DPPH radicals vs. concentration of samples with its standards.

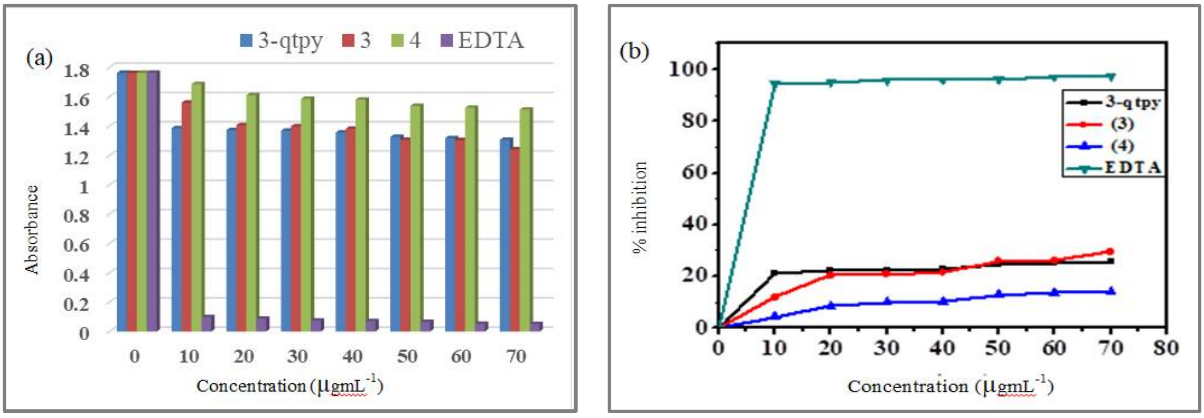


Figure 8. (a) Bar diagram of ferrous ion chelating ability of 3-qtpy and complexes **3** and **4** in comparison with EDTA. (b) A plot of % inhibition of ferrous ion radicals vs. concentration of samples with its standards.

APPLICATION

The lanthanum(III) complexes with aromatic planar phenanthroline in addition to terpyridine ligand can be used as DNA nicking agents under both oxidizing and reducing condition. These complexes can be used as antitumor agents against HeLa cell lines. Because of presence of N, N-heterocyclic bases (terpyridine and 1,10-phenanthroline) they act as antibacterial agents against Gram negative *(E. coli)* and Gram positive bacteria *(B. subtillis)*.

CONCLUSION

In this work, we have synthesized 2-qtpy and its complexes **1** and **2**, 3-qtpy and its complexes **3** and **4**. The complexes **1** and **3** exhibit the coordination number 10, the complex **2** has the coordination number 11 and complex **4** has the coordination number 9. The spectral data confirmed the presence of both coordinated and ionic nitrate in the complexes. The complex $[La(2\text{-qtpy})_2\ (phen)_2(NO_3)_2](NO_3)$ **(2)** and $[La(3\text{-qtpy})(phen)(NO_3)_2](NO_3)$ **(4)** show very good binding and cleavage activities and

antibacterial activity against all the tested bacterial strains. The complex **2** also shows cytotoxicity against HeLa cell lines. Other two complexes 1 and **3** were show moderate binding, cleavage and antibacterial activity.

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