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DNA CLEAVAGE STUDIES OF SOME COMPLEXES OF SCHIFF BASE PYRIMIDINE ONE DERIVATIVES

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ABSTRACT: A series of metal complexes, namely, Ni (II), Zn (II), Cu (II) and Pt (II), have been synthesized with newly prepared biologically active ligands. These ligands and their functional groups were carefully designed and selected to display DNA cleavage effect. Schiff base compoundof 2 - methyl - 3 - aminobenzopyrimidine - 4 - one (L_1) was prepared by condensation of an equimolar mixture of 2-methyl-3-aminobenzopyrimidine-4-one (0.01 mole) and 2-hydroxybenzaldehyde (0.01 mole) in ethanol (25 ml). Schiff base (L_2) compound was prepared by condensation of a mixture of Schiff base (1) (0.02 mole) and o-phenylenediamine (0.01 mole) in ethanol (25 ml) and a catalytic amount of KOH. The mixture was refluxed for 36 hrs. Ligand L_2 (1 mmole) was dissolved in hot methanol. The metal chloride (1 mmole) was then added and the mixture was stirred under reflux for 24 h. The structures of ligands and their complexes have been confirmed by spectroscopic data *i.e.* IR, 1HNMR, MS, electronic and elemental (CHN) analysis. All Compounds were screened for DNA cleavage and showed complete cleavage of CT-DNA.

INTRODUCTION: Schiff bases play an important role in development of coordination chemistry. Many coordination compounds of biologically active ligands have been synthesized and received much attention [1-3]. Chelation causes drastic change in the biological properties same applies to ligands and metal moieties [4]. Azomethines exhibit a wide range of pharmacological activities like anti-microbial [5], anti-parasitic [6], anti-inflammatory [7] and anticancer [8]. Pyrimidines and their derivatives possess several interesting biological activities such as anti-microbial and antitumor [9-15].

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In this work, Schiff base ligands were prepared by condensation of a mixture (0.02 mole) of Schiff base (1) and o-phenylenediamine (0.01 mole). The metal chloride (1 mmole) was then added and the mixture was stirred under reflux for 24 h. Characterization, electronic properties, biological activities and DNA cleavage effects were reported.

EXPERIMENTAL:

Chemicals: Anthranilic acid, hydrazine hydrate, 2-hydroxybenzaldehyde and 1, 2- phenylenediamine were obtained commercially from BDH chemicals. The anhydrous metal chlorides of (Cu (II), Zn (II)), K_2PtCl_4, $FeCl_3.6H_2O$ and Ni (II).$6H_2O$ (BDH) were used as received. The solvents were reagent grade and were used as received: acetic anhydride, dry absolute ethanol, butanol and diethyl ether.

Instrumental: Melting points were measured on an electro-thermal melting point apparatus and were not corrected. FTIR spectra were recorded using the KBr disc technique on a JASCO 410 FTIR spectrophotometer. Elemental (CHN) analysis was reported using an Exeter CE-440 elemental analyzer. UV-vis absorption spectra were measured in DMF ($\approx 10^{-5}$ mole^{-1}) on a Pye-Unicam 8800a UV-vis automatic scanning spectrophotometer. Molar Conductivity was measured on a systronic conductivity bridge with a dip-type cell, in 1×10^{-3} M solution of complexes in DMF. ^{1}HNMR spectra of ligands and their complexes were recorded on a Varian Gemini-200 spectrometer (200 MHZ) and (300 MHZ) in presence of DMSO-*d*$_6$ as solvent and TMS as internal reference. Mass spectra were measured on a Shimadzu Qp-2010 plus mass spectrometer. Microbiological analysis was carried out at the Microanalytical Center, Faculty of Science, Sana'a University, Yemen.

Synthesis of Schiff Base of 2-Methyl-3-Amino-Benzopyrimidine-4-one (L$_1$): The Schiff base compound was prepared by condensation of an equimolar mixture (0.01 mole) of 2-methyl-3-aminobenzopyrimidine - 4 - one and 2-hydroxybenzaldehyde (0.01 mole) in ethanol (25 ml). The mixture was refluxed for 24 h under nitrogen atmosphere. The Schiff base compound formed was filtered, washed and recrystallized from ethanol.

Synthesis of Schiff Base (L$_2$): This Schiff base (L$_2$) compound was prepared by condensation of a mixture (0.02 mole) of Schiff base (L$_1$) and o-phenylendiamine (0.01 mole) in ethanol (25 ml) in presence of a catalytic amount of KOH. The mixture was refluxed for 36 hrs. The solvent was evaporated and the precipitate was filtrated, washed and purified from ethanol.

Synthesis of Schiff base (L$_2$) Metal Complexes (M+2) (Cu, Zn, Ni) (1:1 L: M): A typical procedure was followed: the ligand L (1 mmol) was dissolved in hot methanol. The metal chloride (1 mmol) was then added and the mixture was stirred under reflux for 24 h. Complexes were filtrated, washed several times with methanol and then dried in air.

Synthesis of Schiff base (L$_2$) Pt Complexes K$_2$PtCl$_4$ (1:1 L: M): The Schiff base ligand L$_2$ (0.0003 mole) was dissolved in hot methanol. K_2PtCl_4 (0.0003 mole) was dissolved in 10 ml methanol and 5 ml de-ionized water. K_2PtCl_4 was then added to Schiff base (L$_2$) and the mixture was stirred under reflux for 24 h. The complex was then filtered and washed with methanol and then dried in air.

Gel Electrophoresis: DNA cleavage experiment was conducted using CT-DNA by gel electrophoresis with the ligand and metal complex in the absence and presence of H_2O_2 as an oxidant. The reaction mixture was incubated before electrophoresis experiment at 37 °C for 2 h as follows: CT-DNA 30 μM, 50 μM, each complex and 500 μM H_2O_2 in 50 mMTris-HCl buffer (7.1). The samples were electrophoresed for 2 h at 50 V on 1% agarose gel using tris-acetic acid-EDTA buffer at pH 8.3. After electrophoresis, the gel was stained using 3 μLethidium bromide (EB) and photographed under UV light using a digital camera [16].

RESULTS AND DISCUSSION:

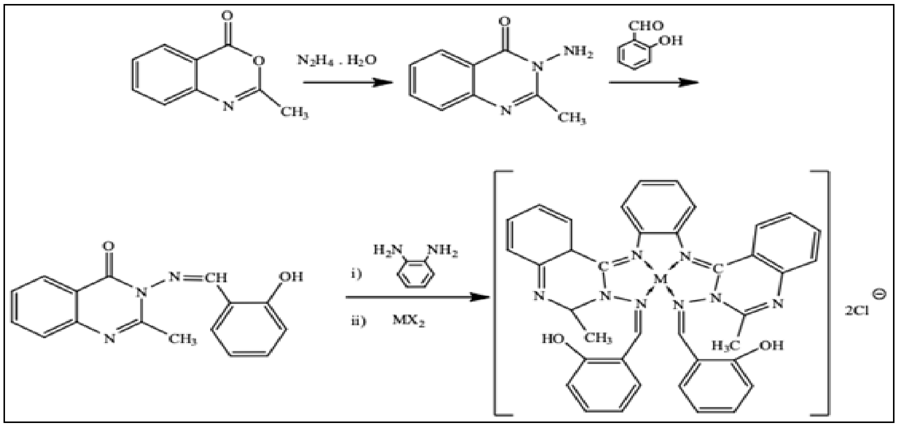
Synthesis and Characterization: Schiff base compound L$_1$ was prepared by condensation of an equimolar mixture (0.01 mole) of 2-methyl-3-amino benzopyrimidine-4-one (17-18) and 2-hydroxybenzaldehyde (0.01 mole) in ethanol (25 ml). The mixture was refluxed for 24 hrs under nitrogen atmosphere. Schiff base (L$_2$) compound was prepared by condensation of a mixture (0.02 mole) of Schiff base (1) and o-phenylenediamine (0.01 mole) in ethanol (25 ml) and a small amount of KOH. The mixture was refluxed for 36 h. Ligand L$_2$ (1 mmole) was dissolved in hot methanol. The metal chloride (1 mmole) was then added and the mixture was stirred under reflux for 24 h. These complexes were filtered, washed several times with methanol and then dried in air (Scheme 1). **Table 1** summarizes the physical properties (melting point, color, percentage yield, molar conductance and elemental analysis) of Schiff bases and their complexes.

Conductance Measurements: All complexes (Ni to Pt) were electrolytes as shown by their molar conductivity ($\wedge_M$) measurements in DMF, 54.3 and 94.4 Scm^2 mol^{-1}, respectively.

IR Spectra: In the absence of a powerful technique such as X-ray crystallography, IR spectroscopy has proven to be a suitable technique to elucidate the method of bonding of the ligand to the metal ion. Determination of coordinating atoms is made by comparison of IR spectra of ligand and complexes, as shown in **Fig 1**. The significant data is given in **Table 2.** IR spectrum of ligand L_1 shows the absence of a band at 3535, 3301 cm^{-1} due to (NH_2) group of 2-methyl-3-aminobenzopyrimidine-4-one and (HC=O) group of aldehyde. Instead, a new strong band at 1655 cm^{-1} due to azomethine stretching vibration (C=N) appears in the L_1. In the ligand, L_2 shows the absence of the band at 1679 cm^{-1} due to the carbonyl group of the amide, instead a new strong band at 1630 cm^{-1} due to azomethine stretching vibration (C=N) appeared. On complexation, (C=N) shifts to higher frequencies and new bands appears in the range 1661-1671cm^{-1} indicating the coordination of azomethine nitrogen atom to the metal ion.

3.4 ^{1}HNMR: ^{1}HNMR spectrum of the Schiff base L_1 showed OH proton of at 10.56 ppm (s, 1H); azomethine proton noted at 9.10 ppm (s, 1H). The multiple signals around 6.96-8.15 ppm (m, 8H) were ascribed to aromatic protons; CH_3 of methyl pyrimidine-one was noted at 3.34 ppm (s, 3H). ^{1}HNMR spectrum of the Schiff base L_2 showed azomthine proton noted at 8.61 ppm (s, 2H). The multiple signals around 6.85-8.10 ppm (m, 20H) were ascribed to aromatic protons; CH_3 of methyl pyrimidine was noted at 3.33 ppm (s, 6H) as shown in **Fig. 2** and **3**.

^{1}HNMR spectrum of the Schiff base L_2 Ni complex showed azomthine proton at 8.89 ppm (s, 2H). The multiple signals around 6.90-8.47 ppm (m, 20H) were ascribed to aromatic protons; CH_3 of methyl pyrimidine was noted at 3.42 ppm (m, 3H), 3.56 ppm (m, 3H). ^{1}HNMR spectrum of Schiff base L_2Pt complex showed azomthine proton noted at 8.90 ppm (s, 2H). The multiple signals around 6.90-8.61 ppm (m, 20H) were ascribed to aromatic protons; CH_3 of methyl pyrimidine was noted at 3.37 ppm (m, 6 h).



SCHEME 1: SYNTHESIS OF SCHIFF BASE PYRIMIDIN-ONE L_1, L_2 AND THEIR COMPLEXES

TABLE 1: PHYSICAL PROPERTIES OF SCHIFF BASES AND THEIR COMPLEXES

No	Color	CHN cal/f	F. wt.	M.p.	Yield	Molar conductivity $\wedge_M$ [$Smol^{-1}cm^2$]
L_1	Yellow	68.8/68.5, 4.6/3.7, 15.00/14.8	279	168-169	65%	-
L_2	Brown	ESI Mass: 630	630	120-123	41%	-
Ni complex. $2H_2O$	Reddish/brown	57.30/57.46, 3.7/3.01, 14.07/13.1	795.69	>250	66%	92.6
Cu complex	Olive green	59.6/58.9, 3.9/2.9, 14.6/13.8	764.5	220 decomp.	66.6%	68.8
Zn complex	Brown	59.5/59.9, 3.9/4.2, 14.6/12.8	766.38	190	56%	94.4
Pt complex	Black	50.8/50.2, 3.3/2.2, 12.5/13.1	896	220	83%	54.3

TABLE 2: MAIN IR ABSORPTION BANDS OF SCHIFF BASES AND THEIR COMPLEXES

Comp.	OH	C=N Schiff base	C=N ring
L_1	3294	1655	1601
L_2	3412	1655, 1630	1598
Ni complex	3415	1661	1606
Cu complex	3411	1669, 1644	1599
Zn complex	3422	1665, 1631	1598
Pt complex	3414	1671, 1644	1610

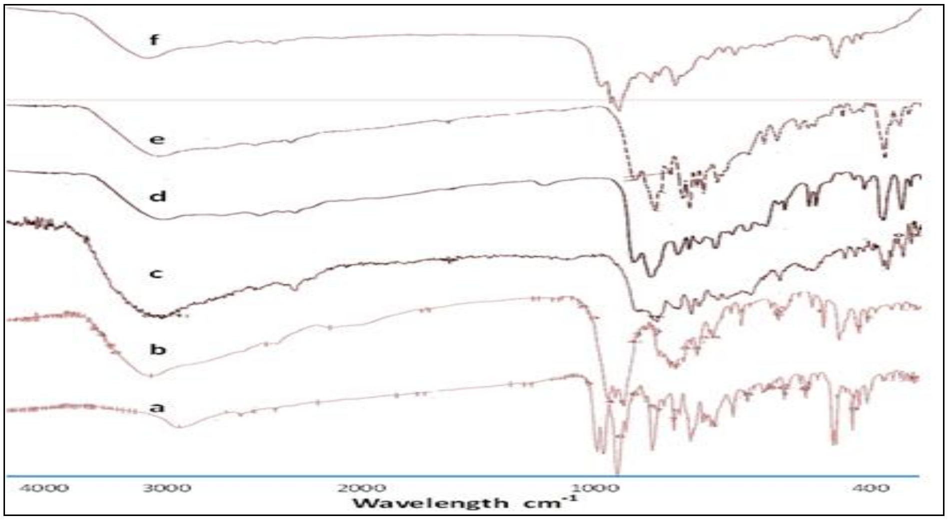


FIG. 1: IR SPECTRA OF L_1, L_2 AND THEIR COMPLEXES

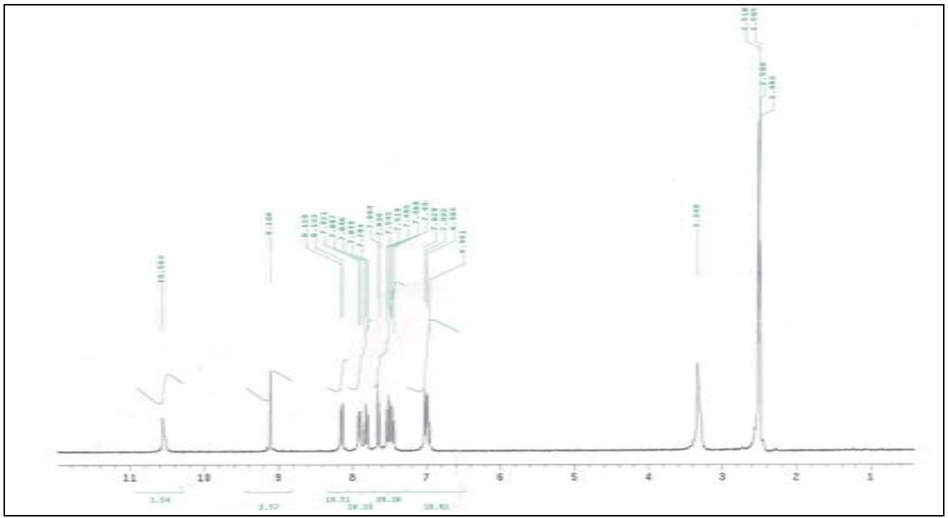


FIG. 2: ^{1}HNMR OF SCHIFF BASE L_1

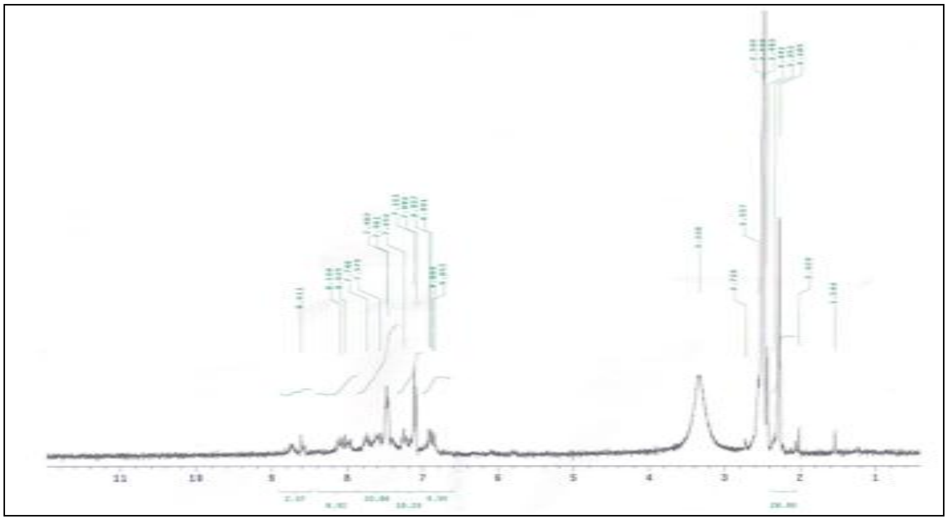


FIG. 3: ^{1}HNMR SPECTRUM OF L_2

Electronic Spectra: The main electronic absorptions are summarized in Table-3 and shown in **Fig. 4**. UV-Vis spectra of the ligands and their complexes were measured in the range of 200-800 nm. The lower wavelength in the range 200-400 nm is specific for the electronic intra-ligand transitions. The spectra of complexes generally show the characteristic band of the free ligands with some changes both in wavelengths (λmax) and intensity together with appearances of new bands at longer wavelengths. The spectra of the ligands and their complexes exhibit bands in the regions 213-215, 268-292 and 343-414 nm, which may be due to σ-σ*, π-π*, n-π* transitions, respectively. **Fig. 5** illustrates the mass spectrum of L_2.

TABLE 3: MAIN ELECTRONIC ABSORPTIONS OF THE SCHIFF BASES AND THEIR COMPLEXES

No	σ-σ* nm, (cm^{-1})	π-π* nm, (cm^{-1})	n- π* nm, (cm^{-1})
L_2	221 (45248.8)	280 (35714.3)	326 (30674.8) 341 (29325.5) 360 (27777.7)
Ni	215 (46512)	233 (42918.4)	272 (36764.7) 300 (33333.3) 414 (24154.5)
Zn	215 (46512)	234 (42735.0)	271 (36900.3) 325 (30769.2) 405 (24691.3)
Cu	213 (46729)	231 (43290)	324 (30864.2) 367 (27247.9) 407 (24570)
Pt	213 (46729)	232 (43103.4)	313 (31948.8) 358 (27932.9) 419 (23866)

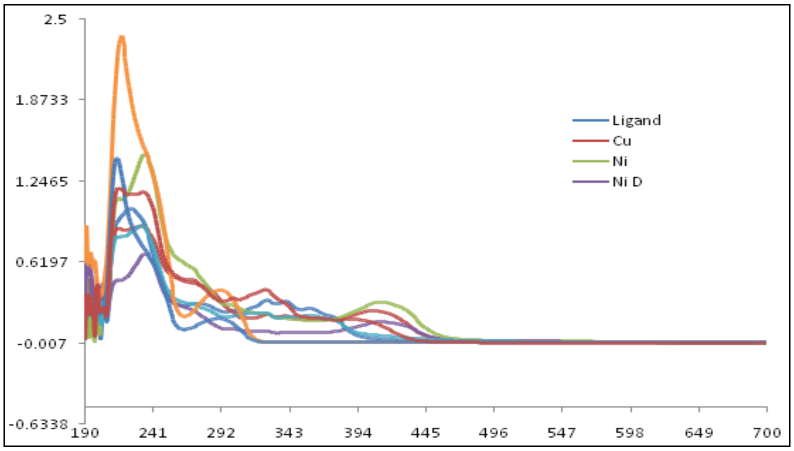


FIG. 4: UV-SPECTRA OF L_2 AND ITS COMPLEXES

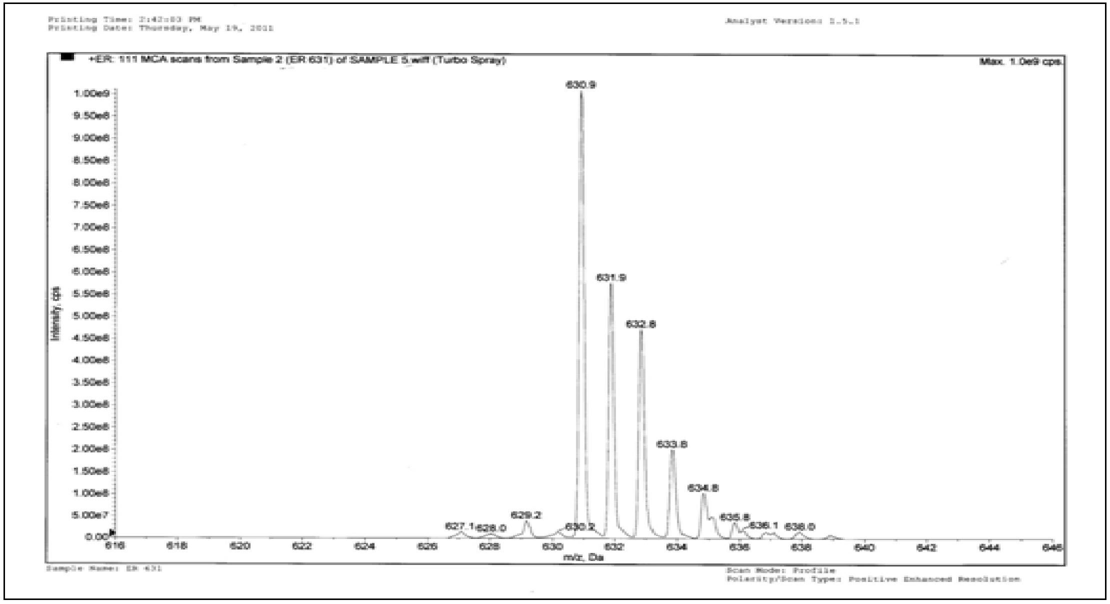


FIG. 5: MASS SPECTRUM OF L_2

DNA Cleavage Studies: The cleavage efficiency of the complexes compared to that of control is due to their efficient DNA-binding ability. The metal complexes were able to convert supercoiled DNA into open circular DNA. The proposed general oxidative mechanisms and account of DNA cleavage by hydroxyl radicals via abstraction of a hydrogen atom from sugar units that predict the release of specific residues arising from transformed sugars, depending on the position from which the hydrogen atom is removed. Cleavage is inhibited by free radical scavengers. This implies that hydroxyl radical or peroxy derivatives mediate the cleavage reaction. The reaction is modulated by metallo complexes bound hydroxyl radical or a peroxo species generated from H_2O_2.

Currently, the CT-DNA gel electrophoresis experiment was conducted at 35 °C using the synthesized complexes in presence of H_2O_2 as an oxidant. As can be seen from the results illustrated in **Fig. 6**, at very low concentrations, all ligands and their complexes exhibited nuclease activity in the presence of H_2O_2.

Control-1 experiment, using DNA alone (line 1) does not show any significant cleavage of CT-DNA even on a longer exposure time. Control-2, using DNA + H_2O_2 (line 2) does not show any significant cleavage of CT-DNA. From the observed results, it can be concluded that the ligand (line 3) and their complexes (lines 4, 5 and 6) show complete cleavage of CT-DNA. The platinum complex showed complete cleavage without H_2O_2.

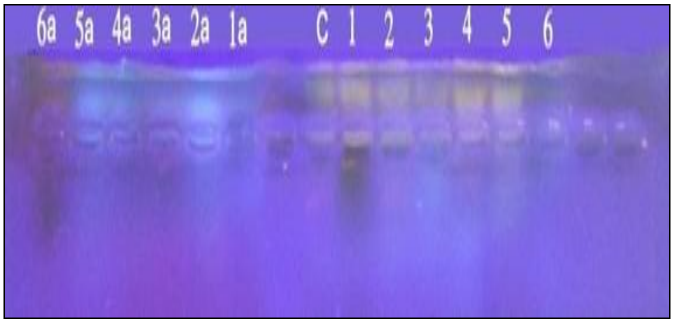


FIG. 6: CHANGES IN THE AGAROSE GEL ELECTROPHORETIC PATTERN OF CT-DNA INDUCED BY H_2O_2 (1A-6A), WITHOUT H_2O_2 (1-6) AND METAL COMPLEXES

CONCLUSION: This work describes the synthesis and DNA cleavage of Schiff base and their complexes.

Most of the tested complexes compounds exhibit complete cleavage with H_2O_2 except the platinum complex showed complete cleavage with and without H_2O_2.

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CONFLICTS OF INTEREST: Authors have no conflict of interest regarding this article.

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