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Pyrimido[4,5-b]quinoline-2-thiol/ol: microwave-induced one-pot synthesis, DNA binding and cleavage studies

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This article describes the synthesis of pyrimido[4,5-b]quinoline-2-thiol/ol **(3a/3b)** by microwave irradiation technique. The dynamic interaction of compounds with deoxyribonucleic acid (DNA) was investigated by absorption spectra, viscosity measurements, and thermal denaturation studies. Intrinsic binding constants (K_b) had values 3.1×10^6 for **3a** and 2.3×10^5 for **3b**. The proposed DNA binding mode supports the large enhancement in the relative viscosity of calf thymus (CT-DNA) on binding to compounds. Results suggest that **3a/3b** can bind to CT-DNA by intercalation via the aromatic ring into the base pairs of DNA. Moreover, efficient DNA damage was observed on oxidative cleavage in the presence of **3a/3b**.

Keywords: pyrimidoquinolines; microwave irradiation; CT-DNA binding; oxidative cleavage; viscosity–thermal

1. Introduction

Dihydropyrimidinones (DHPMs) constitute a very important class of organic compounds due to their attractive pharmacological properties, including antiviral, antitumor, and antibacterial activities. The dihydropyrimidinone core is also found in many natural products that explain the important efforts devoted to the synthesis of these heterocycles (*1*). Quinoline alkaloids, such as quinine, chloroquine, mefloquine, and amodiaquine, are used as efficient drugs for the treatment of malaria (*2–6*). Several derivatives of quinoline have been reported to be associated with interesting pharmacological properties like antibacterial, antifungal and antimalerial agents (*7–14*). A literature survey shows that there is evidence that antitumor activity is due to the intercalation of drug between the base pairs of DNA and interferences with the normal functioning of enzyme topoisomerase II which is involved in the breaking and releasing of DNA strands (*15*).

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The antitumor drugs that intercalate DNA are of growing interest in the field of anticancer derivatives. Generally, they are characterized by planar chromospheres, which are often constituted by three or four condensed rings, that can intercalate into base pairs of calf thymus DNA (CT-DNA). Results of these various binding studies have been useful in designing new and promising anticancer agents for clinical use (*16*). DNA binding studies of pyrimidothienoquinolines have been recently reported (*17, 18*).

There are a variety of studies concerning DNA cleavage (*19–23*) by photosensitizers which either initiate a single electron transfer from a base to the triplet state of chromophores, which often leads to a selective cleavage at the 5′-G of GG step in duplex DNA, or generate active oxygen species; but there have been less reports on comparing the cleaving and intercalating activities of compounds with oxo or oxy groups with those of their thiono or thio counterparts.

By consideringthe above facts and in continuation of our work on biologically active quinoline heterocycles (*24*), it has been found that the sulfur-containing molecule has advantages, such as easy preparation and derivatization, and longer-wavelength absorption. Our results showed that DNA photocleavages and intercalations were significantly enhanced in the case of compounds possessing a thiono or thio group compared with oxygen-containing counterparts.

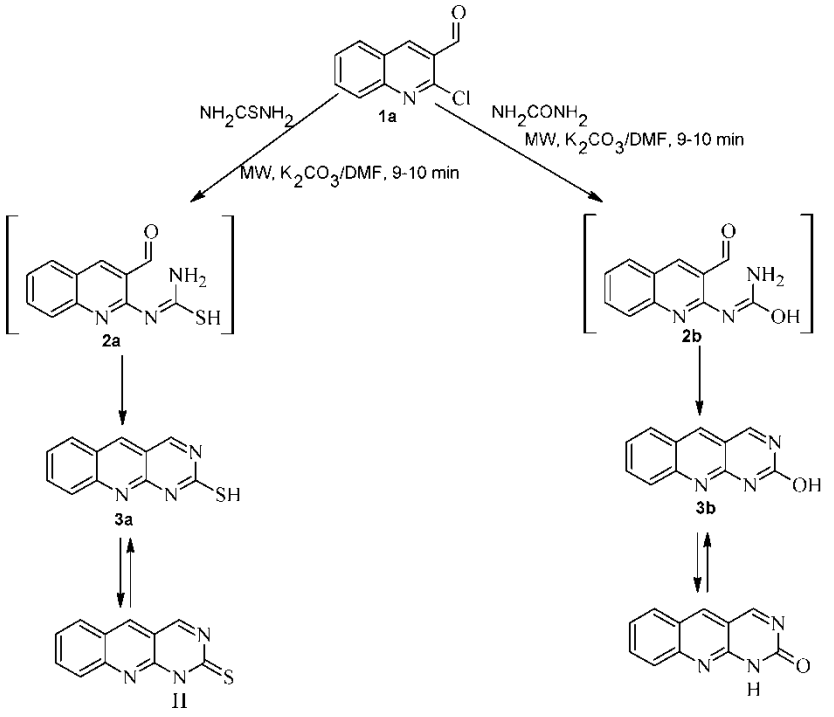
2. Results and discussion

Numerous condensed quinolines have various bioactivities, which render them valuable pharmacological activities as mentioned earlier and, therefore, they are a useful material in drug research. Hence, in continuation of our study in developing condensed quinoline derivatives (*24*) due to their significant biological activates, it appeared expedient to synthesize a series of systematically condensed and appropriately functionalized thiopyrano pyrimido quinolines in the present study.

Access to **3a** and **3b** was via cyclization between 2-chloroquinoline-3-carbaldehyde (**1a**) with urea or thiourea under microwave irradiation in the presence of anhydrous potassium carbonate as catalyst. The expected structures appeared at IR absorption bands of 2593 cm^{-1} (S–H) and 2458 cm^{-1} (O–H) in both **3a** and **3b**. Appearance of singlet in ^{1}H NMR at δ 10.5 (SH) and 11.3 (OH) in **3a, 3b** shows formation of desired compounds. Furthermore, absence of singlet in CHO group in ^{1}H NMR and absorption frequency of NH_2 group IR spectra of urea or thiourea supports the expected compounds. Finally, the structure was confirmed by its mass spectrum through the appearance of molecular ion peak at m/z 214 [M^+] for **3a** and 197 [M^+] for **3b** (Scheme 1).

2.1. *DNA binding studies (absorption spectral part)*

The UV–visible absorption spectra of **3a** and **3b** were characterized by two maxima at 293 and 312 nm. The addition of increasingly higher concentrations of DNA led to bathochromic and hypochromic changes, as shown in Figures 1 and 2, *i.e.* the interaction of **3a** and **3b** with DNA resulted in a strong decrease of the absorption intensity at both peaks, accompanied by a shift towards higher wavelengths. A reduction of 18.3% and 15.2% in absorption was observed at 293 and 312 nm peak-maximum in the presence of excess of DNA at a molar ratio of DNA nucleotide. Two isosbestic points were observed at 302 nm for **3a** and 325.6 nm for **3b**, respectively. Hypochromism was suggested to be due to strong interactions between the electronic states of the intercalating chromophore and that of the DNA base pairs (*25*). The spectral changes that we observed (hypochromicity, red shift, and isosbestic points) were consistent with the intercalation of the chromophore into the stack DNA base pairs (Table 1).



Scheme 1. Synthesis route carried out for the synthesis of targeted molecules **3a** and **3b**.

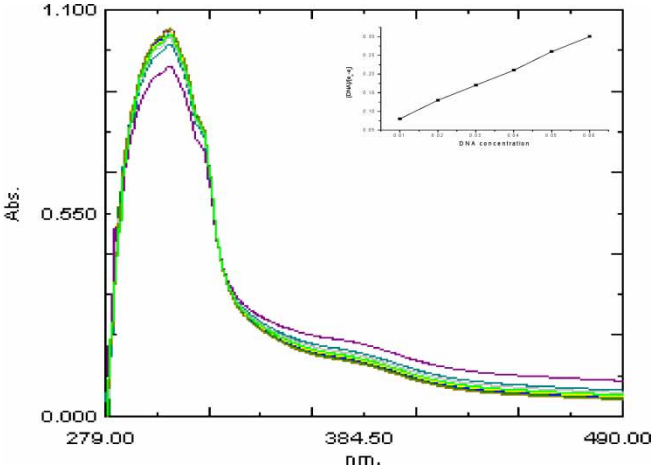


Figure 1. Absorption spectra of complex (**3a**) in Tris–HCl buffer upon addition of DNA: pyrimido[4,5-b]quinoline-2-thiol (**3a**) = 0.5 μM, [DNA] = 0–100 μM. Showing variation in absorption with increase in concentration of [DNA]. Inner plot of [DNA]/($\varepsilon_a - \varepsilon_f$) versus [DNA] for titration of DNA with **3a**.

2.2. *Viscosity measurements*

The interaction modes of **3a, 3b** with DNA were investigated by viscosity measurements. An increase in viscosity of native DNA is regarded as a diagnostic feature of an intercalation process (*26, 27*). We have measured the viscosity changes in short, rod-like DNA fragments. The relative increase in length (L/L_0) of the complex formed between **3a** and **3b** with DNA is shown

Table 1. DNA binding constant and melting temperature data of compounds **3a** and **3b**.

Compounds	$K_b(M^{-1})$	T_m(°C)
Pyrimido[4,5-b]quinoline-2-thiol (3a)	3.1×10^6	60
Pyrimido[4,5-b]quinolin-2-ol (3b)	2.3×10^5	58

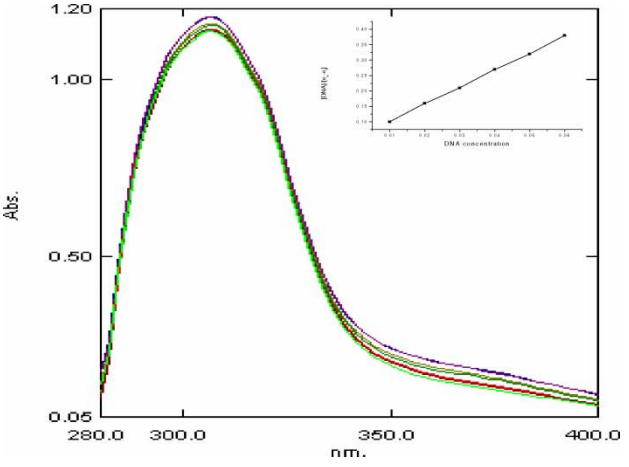


Figure 2. Absorption spectra of compound (**3b**) in Tris–HCl buffer upon addition of DNA: pyrimido[4,5-b]quinolin-2-ol (**3b**) = 0.5 μM, [DNA] = 0–100 μM. Showing variation in absorption with increase in concentration of [DNA]. Inner plot of [DNA]/($\varepsilon_a - \varepsilon_f$) versus [DNA] for titration of DNA with **3b**.

in Figure 3. It is evident that binding of MPTQ increased the viscosity of DNA, corresponding to an increase in the contour length of the DNA fragments. The measured slope of the plot 1.21 ± 0.03 falls within 61% for **3a** and 1.06 ± 0.021 falls within 52% for **3b** in the slope of a theoretical curve for an idealized intercalation process $(1 + 2r)$ (*28, 29*). On this basis we calculate that intercalation of one **3a** molecule caused an increase of 1.9 Å in the contour length of DNA. Since the size of these sonicated fragments was significantly greater than the persistence length, the estimated 1.9 Å lengthening is probably best regarded as a lower limit as shown in Figure 3.

2.3. *Thermal denaturation*

Other strong evidence for the intercalative binding of **3a** and **3b** into the double helix DNA was obtained from DNA melting studies. The intercalation of small molecules into the double helix is known to increase the DNA melting temperature (T_m), at which the double helix denatures into single-stranded DNA, owing to the increased stability of the helix in the presence of an intercalator (*30*). The molar extinction coefficient of DNA bases at 260 nm in the double helical form is much less than that in the single-stranded form; hence, melting of the helix leads to an increase in the absorbance at 260 nm (*31*). Thus, the helix-to-coil transition temperature can be determined by monitoring the absorbance of DNA at 260 nm as a function of temperature. The DNA melting studies were carried out with CT-DNA in the absence and presence of MPTQ [1:5 ratio of **3a** and **3b** to DNA-c(P)]. The T_m for DT-DNA was 60 ± 5 °C in the absence of **3a** and **3b**, but in the presence of **3a** and **3b** the T_m of CT-DNA was increased by 5 °C and 3 °C, respectively. The advantage of this method is that it is much easier to identify when more than one transition occurs (*32*). These various DNA melting experiments strongly supported the intercalation of **3a** and **3b** into the double helix DNA shown in Figure 4.

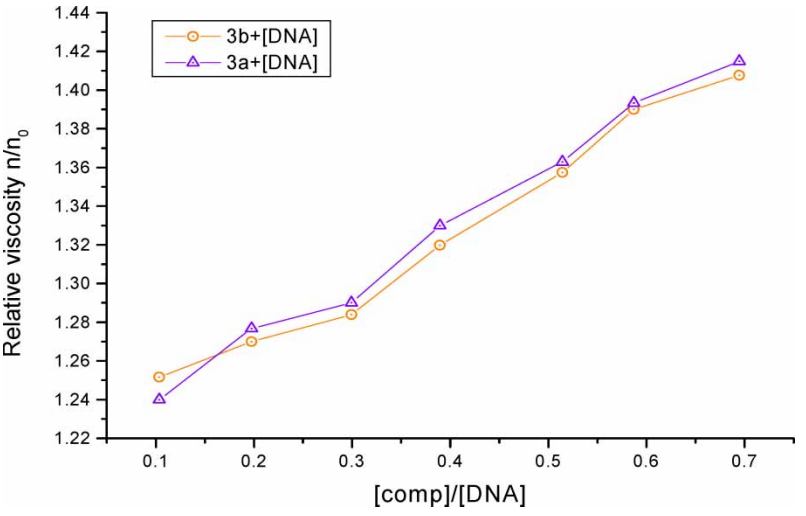


Figure 3. Plot of relative viscosity versus [compound]/[DNA] effect of **3a** and **3b** on the viscosity of CT-DNA at 25 (±0.1 °C): **3a** = 0–100 μM, **3b** = 0–100 μM, and [DNA] = 50 μM.

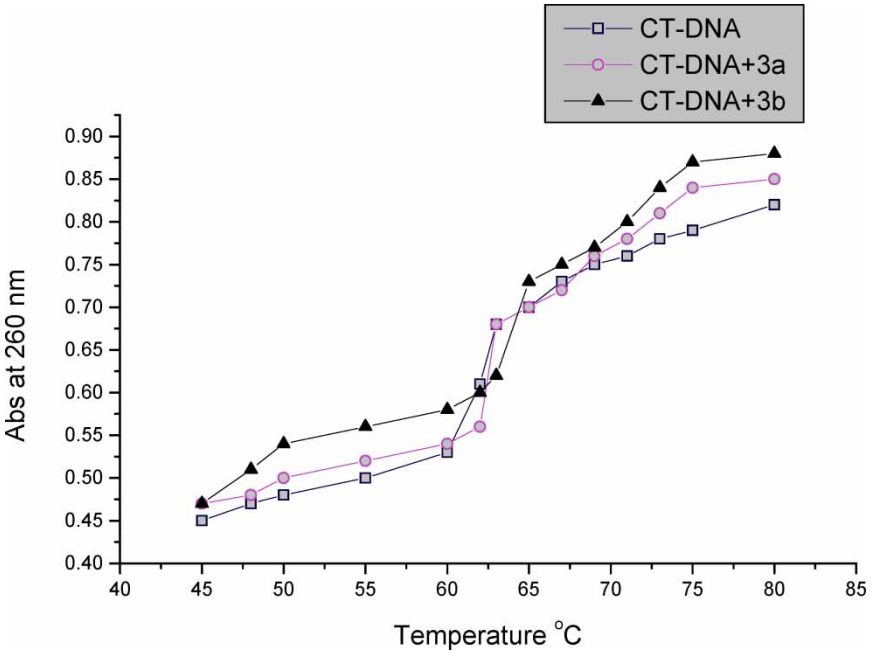


Figure 4. Melting curves of CT-DNA in absence and presence of compounds **3a** and **3b**.

2.4. *Oxidative DNA cleavage studies*

We examine the general situation that thiono or thio groups promote efficient reaction for oxidative cleavage of DNA. Inspection of the data of relative ratios of form I to form II and sulfur to oxygen revealed that DNA cleavages were significantly enhanced in the case of a compound possessing a thiono or thio group (**3a**) compared with their oxygen-containing counterparts (**3b**). Compound **3a** was the most active DNA-nicking agent; one of the reasons for thiono compounds having

high DNA cleaving activity might be that they usually have more efficient intersystem crossing efficiency and much higher photosensitizing activity (*33–35*).

The characterization of DNA recognition by the above synthesized pyrimido quinolines chemistry that is associated with redox activation. DNA cleavage is controlled by relaxation of supercoiled circular form of pUC19 DNA into nicked circular form and linear form. When circular plasmid DNA is conducted by electrophoresis, the fastest migration will be observed for the supercoiled form (form I). If one strand is cleaved, the supercoils will relax to produce a slow-moving open circular form (form II).

Figures 5 and 6 illustrate the gel electrophoretic separations showing the cleavage of plasmid pUC19 DNA induced by the two pyrimidoquinolines under aerobic conditions. With the increase of **3a** and **3b**, the circular supercoiled DNA is converted into nicked DNA via single-strand cleavage (lanes 2–7). By comparing Figures 5 and 6, we can estimate that **3a** exhibits a more significant nuclease activity than **3b**. Similarly, Figure 6 also shows the conversion from SC

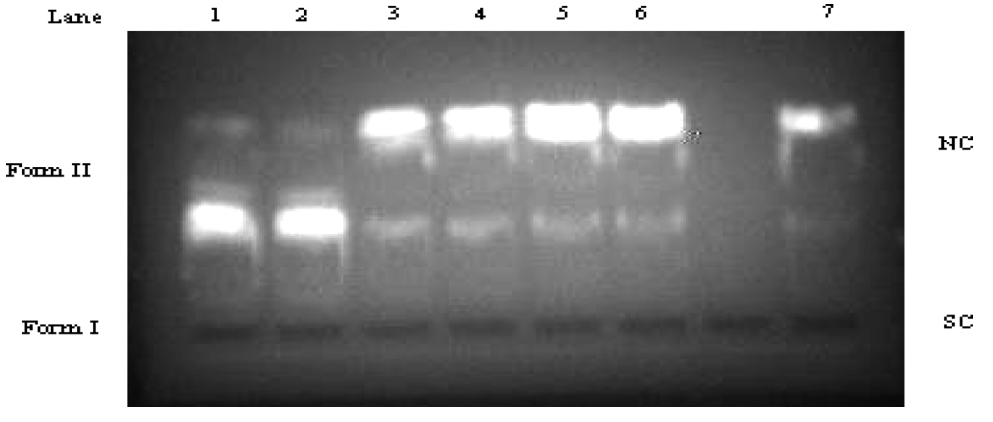


Figure 5. Cleavage of supercoiled pUC19 DNA (0.5 μg) by the compound **3a** in a buffer containing 50 mM Tris–HCl and 50 mM NaCl at 37 °C: lane 1, DNA alone; lane 2, DNA + 10 μM of compound (**3a**); lane 3, DNA + 20 μM of compound (**3a**); lane 4, DNA + 30 μM of compound (**3a**); lane 5, DNA + 40 μM of compound (**3a**); lane 6, DNA + 50 μM of compound (**3a**); lane 7, DNA + 60 μM of compound (**3a**). Forms I and II are supercoiled, nicked circular DNA, respectively.

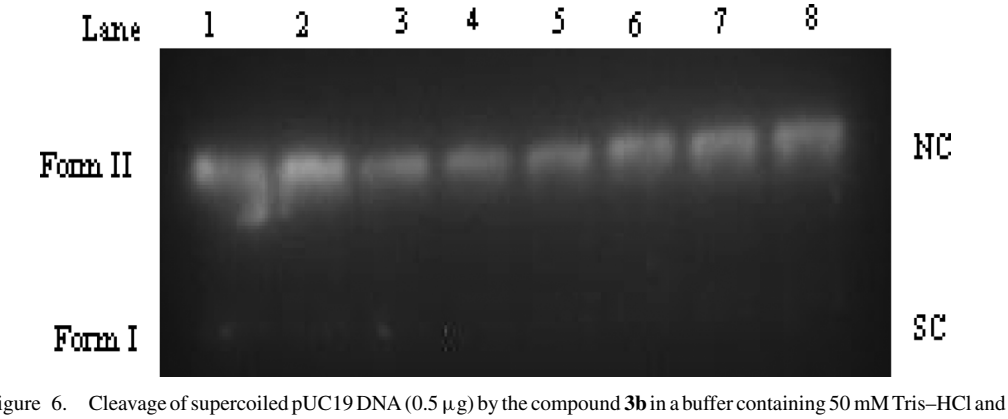


Figure 6. Cleavage of supercoiled pUC19 DNA (0.5 μg) by the compound **3b** in a buffer containing 50 mM Tris–HCl and 50 mM NaCl at 37 °C: lane 1, DNA alone; lane 2, DNA +10 μM of compound (**3b**); lane 3, DNA + 20 μM of compound (**3b**); lane 4, DNA + 30 μM of compound (**3b**); lane 5, DNA + 40 μM of compound (**3b**); lane 6, DNA + 50 μM of compound (**3b**); lane 7, DNA + 60 μM; lane 8, DNA + 70 μM of compound (**3b**). Forms I and II are supercoiled, nicked circular DNA, respectively.

(form I) to NC (form II) almost in the same manner. The different DNA-cleavage efficiency of **3a** and **3b** were due to the different binding affinity of the **3a**, **3b** to DNA, which has been observed in other cases (*36–38*). This suggested the possible generation of oxygen-based radicals mediated by the pyrimidoquinolines **3a** and **3b** complex resulting in DNA cleavage. Further studies are currently underway to clarify the cleavage mechanism.

It is shown that the concentrations of 20, 30, 40, and 50 μM of **3a** could convert 52%, 65%, 71% and 79% of the initial supercoiled (SC) form (form I) to nicked circular (NC) form (form II), respectively (lane 1–7). However, **3b** at the same concentration could convert only 34%, 49% and 62% of the initial supercoiled (SC) form (form I) to nicked circular (NC) form (form II), respectively.

3. Experimental

Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using petroleum ether (ethyl acetate solvent). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr pellets on Perkin–Elmer 157 IR spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on EM-390 (300 MHz) NMR spectrometer, mass spectra were recorded on MASPEC low-resolution instrument operating at 70 eV, and UV–visible absorption spectra were recorded using Shimadzu model. All reagents and solvents were AR grade, purchased commercially. All solvents were purified and used; CT-DNA and pUC 19 DNA were purchased from Bangalore Gene, Bangalore, India. Tris–HCl buffer (5 mM Tris–HCl, 50 M NaCl, pH = 7.2, Tris = Tris(hydroxymethyl)aminomethane) solution was prepared using deionized, double-distilled water.

3.1. *General procedure for the synthesis of pyrimido[4,5-b]quinoline-2-thiol (3a), pyrimido[4,5-b]quinolin-2-ol (***3b***)*

A mixture of 2-chloroquinoline-3-carbaldehyde (**1a**) (0.955 g, 0.005 mol), urea (0.3 g, 0.005 mol), thiourea (0.38 g, 0.005 mol), and anhydrous potassium carbonate (1.38 g, 0.01 mol) was taken in a beaker containing 10 ml of DMF and irradiated in a microwave oven for about 9–10 min in an interval of 10 s at 160 W. The progress of the reaction was monitored by TLC; the obtained product was poured into ice-cold water, stirred well, acidified with dilute HCl. The solid separated out was filtered, washed with water, and dried and recrystalized from methanol.

3.1.1. *Pyrimido[4,5-b]quinoline-2-thiol (***3a***)*

Yield 73%; m.p.167–169 °C; IR (KBr) cm^{-1}; 3020 (C–H, Ar−H); 1590 (C=N); 2593 (S–H); ^{1}H NMR; δ 8.48 (d, 1H, Ar-H, J = 8.0 Hz), 7.83 (d, 1H, Ar–H, J = 8.0 Hz), 7.56 (d, 1H, Ar–H, J = 7.6 Hz), 7.52 (d, 1H, Ar–H, J = 7.6 Hz), 7.50 (d, 1H, Ar–H, J = 7.5 Hz), 7.20 (d, 1H, Ar–H, J = 7.5 Hz), 4.15 (s, 1H, N–H, J = 4.0 Hz), MS: m/z 214 [M]$^+$; Anal. Calcd. for ($C_{11}H_7N_3S$)%: C, 61.95; H, 3.31; N, 19.70. Found: C, 61.94; H, 3.32; N, 19.72.

3.1.2. *Pyrimido[4,5-b]quinolin-2-ol (***3b***)*

Yield 75%; m.p.178–181 °C; IR (KBr) cm^{-1}; 3025 (C–H, Ar–H); 1591 (C=N); 2458 (O–H); ^{1}H NMR; δ 8.52 (d, 1H, Ar–H, J = 8.0 Hz), 7.85 (d, 1H, Ar–H, J = 8.0 Hz), 7.58 (d, 1H, Ar–H, J = 7.6 Hz), 7.54 (d, 1H, Ar–H, J = 7.6 Hz), 7.48 (d, 1H, Ar–H, J = 7.4 Hz), 7.25

(d, 1H, Ar–H, $J = 7.4$ Hz), 4.52 (s, 1H, N–H, $J = 4.08$ Hz), MS: m/z 197 $[M]^+$; Anal. Calcd. for ($C_{11}H_7N_3O$)%: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.01; H, 3.57; N, 21.32.

3.2. *DNA interaction experiment (spectral measurements)*

UV–visible absorption spectra were determined in a SHIMADZU, UV-1650 PC recording spectrophotometer using quartz cuvettes of 10 mm light-path. The parameters of interaction between **3a** and **3b** with CT-DNA were determined spectrophotometrically using a Beckman 25 double-beam spectrophotometer. Aliquots of a concentrated DNA solution (0.18–1.125 mM) were added to a cuvette filled with **3a** and **3b** solution (12–25 μM) and thoroughly mixed. Extreme care was taken to ensure that optical reference solutions were prepared in an identical manner.

The binding data were expressed in the form of a Scatchard plot (*39*). The variables r (moles of ligand bound/mole of nucleotides) and C (the molar concentration of free drug) were calculated from the absorption measurements according to the method of Peacocke and Skerrett (*40*). The intrinsic binding constant K_b and the maximum number of available binding sites/nucleotide (n) were deduced from Scatchard plot.

Absorption:

$$(\text{DNA})/(\varepsilon_a - \varepsilon_f) = (\text{DNA})/(\varepsilon_b - \varepsilon_f) + 1/(\varepsilon_a - \varepsilon_f), \quad (1)$$

where ε_a, ε_f and ε_b are the apparent, free, and bound **3a, 3b** extinction coefficients at 285 nm for **3a** and 328 nm for **3b**, respectively. A plot of $[\text{DNA}]/(\varepsilon_b - \varepsilon_f)$ versus [DNA] gave a slope of $1/(\varepsilon_b - \varepsilon_f)$ and a γ intercept equal to $1/K_b(\varepsilon_b - \varepsilon_f)$, where K_b is the ratio of the slope to the γ intercept.

3.3. *Viscosity measurements*

Viscosity measurements were made according to published procedures using a semimicro dilution capillary viscometer (Viscomatic Fica MgW) with a thermostated bath D40S at 20 °C. The flow time for water was 71.1 s. For the viscosity experiments samples of CT-DNA were sonicated (*41*) to fragments having an estimated molecular weight of approximately 500,000 (*42, 43*).

3.4. *Thermal denaturation experiments*

The DNA melting studies were carried out by controlling the temperature of the sample cell with a Shimadzu (SHIMADZU, UV-1650 PC) circulating bath while monitoring the absorbance at 260 nm. The temperature of the solution was continuously monitored with a thermo-couple attached to the sample holder.

3.5. *DNA cleavage studies by chemical oxidation*

The gel electrophoresis experiments were performed by incubation at 35 °C for 1.5 h as follows: pUC19 DNA 10, 20, 30, 40, 50 μM on compounds **3a** and **3b**, 500 μM H_2O_2 and/or 500 lM ascorbic acid in 50 mM Tris–HCl/18 mM NaCl buffer (pH = 7.2). The samples were electrophoresed for 4 h at 40 V on 1% agarose gel using Tris–boric acid–EDTA buffer (pH = 8.3). After electrophoresis, the gel was stained using 1 g cm^{-3} Ethidium Bromide (EB) and photographed under UV light.

4. Conclusion

We developed a versatile and useful access to different scaffold of biologically important pyrimido[4,5-b]quinoline-2-thiol **(3a)**, pyrimido[4,5-b]quinolin-2-ol **(3b)** using an efficient and simple methodology based on the microwave irradiation technique. The efficiency of the employed methodology can be explained by the fact that microwave energy is probably much higher than the activation energy necessary for each reaction, so that the reaction rate is increased and yields are higher. The DNA binding properties of these two newly synthesized **3a, 3b** were studied by using absorption spectra, viscosity, and thermal denaturation experiments. The results show that the sulfur-containing **3a** has more interaction with CT-DNA as compared to **3b**. We also carried out the DNA cleavage by oxidative method. The cleavage study results show that the sulfur-containing **3a** is more nuclease than **3b**.

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