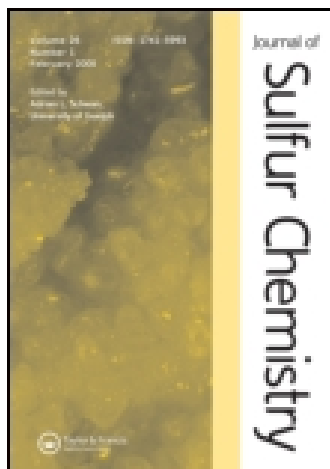


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An efficient carbodiimide-mediated synthesis and DNA-binding studies of novel 2-chloro/mercapto-quinoline-fused 1,3-thiazolidinones via one-pot three-component condensation

Devappa S. Lamani^a, K.R. Venugopala Reddy^{a*}, H.S. Bhojya Naik^a, H.R. Prakash Naik^a and L.R. Naik^b

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A new and efficient method for the preparation of 2-(2-chloroquinolin-3-yl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one derivatives has been assembled by DCC-mediated three-component one-pot reaction of amine, aldehyde, and mercaptoacetic acid. The final compounds were obtained in quantitative yields within 50 min. The synthesized compounds were characterized by elemental analysis, FT-IR, ¹H-NMR, and mass spectral data. The selected compounds were studied for interaction with calf thymus DNA by electronic spectra, viscosity measurements as well as thermal denaturation studies. On binding to DNA, the absorption spectrum underwent bathochromic and hypochromic shifts. The binding constant (K_b) had a value of $5.3 \times 10^5 \text{ M}^{-1}$ for **2a** and $5.8 \times 10^5 \text{ M}^{-1}$ for **3a**. The viscosity measurements indicated that the viscosity of sonicated rod-like DNA fragments increased.

Keywords: quinoline; DCC; thiazolidinones; one-pot synthesis; DNA binding; viscosity measurements; thermal denaturation

1. Introduction

The pharmacological properties of quinoline and their derivatives attracted worldwide attention in the last few decades because of their wide occurrence in natural products and drugs (1). Literature survey revealed that five- to six-membered heterocyclic compounds containing one or two heteroatoms fused to a quinoline ring in a linear fashion were found to possess anti-tumor, anti-cancer, anti-HSV (2), anti-convulsion (3), and anti-inflammatory (4) activities. On the other hand, thiadiazoles, in general, and 1,3-thiadiazoles, in particular, have variety of applications in medicine. The heterocycles have various pharmacological and biological activities, namely COX-1 inhibitors (2), inhibitors of the bacterial enzyme MurB (3), non-nucleoside inhibitors of HIV-RT (4), and anti-histaminic agents (5). Consequently, many different protocols that allow the synthesis of 1,3-thiazolidinones skeletons have been developed.

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These methods employ a one-pot three-component condensation or a two-step synthesis (6). The reaction is believed to proceed via imine formation in the first step followed by an attack of a sulfur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The latter step seems to be critical for obtaining high yields of 2-(2-chloroquinolin-3-yl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one. Therefore, variations have been made in the removal of water during the cyclization. In addition, there are scattered reports of using anhydrous ZnCl_2 or sodium sulfate as a desiccant (7). In all the above-mentioned methods, the reaction requires prolonged heating at a high temperature (90–100 °C) for nearly 12–15 h. In order to circumvent these difficulties, we have chosen a radically different approach to generate 1,3-thiazolidin-4-one scaffolds by simpler methods in quantitative yields. The protocol is ideally suited for the synthesis of a thiazolidinone library (8).

The literature survey reveals that there is evidence to infer that the anti-tumor activity is due to the intercalation 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 (9). The anti-tumor drugs that intercalate DNA are of growing interest in the field of anti-cancer drugs. Particularly, they are characterized by planar chromospheres, which are often constituted by three or four condensed rings, which can intercalate into base pairs. Results of the various binding studies have been useful in designing new and promising anti-cancer agents (10). The DNA-binding studies of pyrimidothienoquinolines have been recently reported (11, 12).

In continuation of our research program (3, 13–17) toward the synthesis of potentially bioactive quinoline molecules, we made an attempt to report an efficient method for the synthesis of novel 2-chloro/mercapto-quinoline-fused 1,3-thiazolidinones derivatives, via one-pot three-component condensation. The sulfur-containing molecule has advantages, such as easy preparation derivatization, and biological impotents; the DNA-binding studies indicate compounds **2a** and **3a** when they bind with base pairs of calf thymus DNA (CT-DNA).

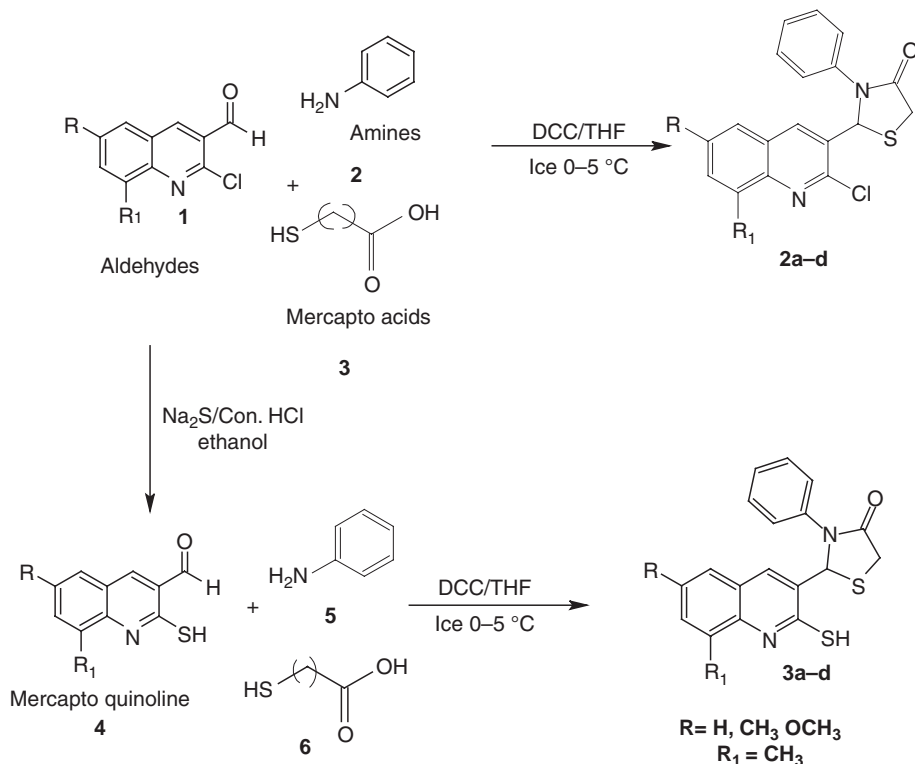
2. Results and discussion

The chemistry using amine, aldehyde, and mercaptoacetic acid proceeded uneventfully and the product was isolated in a quantitative yield after work-up. To optimize the ratio of reactants, experiments were carried out using different proportions of the reactants. It was observed that the ratio of reactants at 1:2:3 for amine, aldehyde, and mercaptoacetic acid, respectively, gave almost quantitative yields. This is in agreement with the earlier observation reported by Homes et al. (18). In a typical experiment, amine and aldehyde were stirred in THF under ice cooling for 15–20 min, followed by the addition of mercaptoacetic acid and DCC and the reaction mixture is stirred for an additional 50–55 min. The DCC, which was precipitated, was removed by filtration and the usual work-up gave the desired products in almost quantitative yields. We have observed that the addition of DCC in ice-cold conditions gives better yields when compared with the reaction carried out at refluxion in a water bath and ambient room temperature.

Our mechanistic investigations using spectral studies gave proof of cyclized products. IR spectra of the compound **2a/3a** showed the carbonyl stretching frequency at $1625\text{--}1660\text{ cm}^{-1}$. This confirms the subsequent cyclization of compound **1**, by removal of CHO present at the 3-position of the quinoline nucleus. Further, the structure assigned was confirmed by $^1\text{H-NMR}$ spectra that show doublet peak at 3.72–3.76 ppm due to fused 1,3-thiazolidinones ($-\text{S}-\text{CH}_2$) (**2a**)/(**3a**). The resonate singlet at 12.26–12.24 ppm corresponds to tautomeric form of SH proton of compound **3a**, signal exhibits multiplets at 7.13–7.78 ppm for aromatic protons. The mass spectral results show molecular ion peak at $m/z = 339[\text{M}^+]$ for **2a** and $338[\text{M} + \text{H}]$ for **3a**, respectively (Table 1, Scheme 1) (13, 19–22).

Table 1. Physical and analytical data of 2-(2-chloro/mercapto-quinolin-3-yl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one derivatives.

| Compound | Color | Yield (%) | m.p. (°C) | Crystal solvent | Molecular formula (mol/wt) | Analysis calculated (found) (%) | | | |
|-----------|------------------|-----------|-----------|-----------------|---|---------------------------------|-------------|-------------|---------------|
| | | | | | | C | H | N | S |
| 2a | Yellowish | 79 | 215–217 | Ethanol | C ₁₈ H ₁₃ ClN ₂ OS (340.8) | 63.43 (63.53) | 3.84 (3.74) | 8.22 (8.28) | 9.41 (9.49) |
| 2b | Yellowish orange | 89 | 198–200 | Ethanol | C ₁₉ H ₁₅ ClN ₂ OS (354.8) | 64.31 (64.23) | 4.26 (4.32) | 7.89 (7.78) | 9.04 (9.09) |
| 2c | Yellowish | 82 | 225–227 | Ethanol | C ₁₉ H ₁₅ ClN ₂ O ₂ S, (370.8) | 64.31 (64.23) | 4.26 (4.32) | 7.89 (7.78) | 9.04 (9.09) |
| 2d | Yellowish orange | 84 | 192–194 | Ethanol | C ₁₉ H ₁₅ ClN ₂ OS, (354.8) | 61.53 (61.46) | 4.08 (4.02) | 7.55 (7.58) | 8.65 (8.72) |
| 3a | Orange solid | 79 | 232–236 | Ethyl acetate | C ₁₈ H ₁₃ N ₂ OS ₂ , (338.4) | 63.83 (63.77) | 4.17 (4.21) | 8.28 (8.22) | 18.95 (18.90) |
| 3b | Yellowish orange | 69 | 210–213 | Ethyl acetate | C ₁₉ H ₁₆ N ₂ OS ₂ , (352.47) | 64.74 (64.70) | 4.58 (4.61) | 7.95 (7.89) | 18.19 (18.24) |
| 3c | Yellowish orange | 74 | 225–227 | Ethanol | C ₁₉ H ₁₆ N ₂ O ₂ S ₂ , (368.47) | 61.93 (61.87) | 4.38 (4.44) | 7.60 (7.55) | 17.40 (17.34) |
| 3d | Orange solid | 67 | 205–208 | Ethyl acetate | C ₁₉ H ₁₆ N ₂ OS ₂ , (352.47) | 64.74 (64.70) | 4.58 (4.61) | 7.95 (7.89) | 18.19 (18.24) |



Scheme 1. Synthesis of 2-(2-chloro/mercapto-quinolin-3-yl)-3-(4-methylphenyl)-1,3-thiazolidin-4-one derivatives.

2.1. DNA-binding studies (absorption spectral studies)

The application of electronic absorption spectroscopy in CT-DNA-binding studies is one of the most important techniques (13). The binding of the molecules to DNA has been well characterized by the large hypochromism. After intercalation, the π^* orbital of compounds could couple with π orbital of base pairs, thus decreasing the $\pi^* \rightarrow \pi$ transition of energy and resulting bathochromism. Hence, the decrease in the absorption intensity and significant red shift due to stacking interaction between drug and CT-DNA (14). The DNA-binding studies were characterized by absorbance maximum at 298 nm for **2a** and 302 nm for **3a**. The addition of increasing higher concentration of DNA led to hypochromic and bathochromic (red shift) changes in its visible absorption spectra as a result of formation of more stable complexes (Figures 1 and 2). The interaction of **2a** and **3a** with CT-DNA resulted in the decrease of absorption intensity accompanied by a shift toward higher wavelengths (~ 3 and 5 nm). Around 12–9% reduction intensity of absorption was observed at 298 and 302 nm peak maximum in the presence of an excess of CT-DNA. The lowest value observed in spectral changes (including red shift and hypochromicity) was used to evaluate intrinsic binding constant (K_b); its observed value of $5.3 \times 10^5 \text{ M}^{-1}$ for **2a** and $5.8 \times 10^5 \text{ M}^{-1}$ for **3a** from the spectral result suggested that compound **2a** binds more strongly with base pairs than **2d** (Table 2) (15, 16, 23–26).

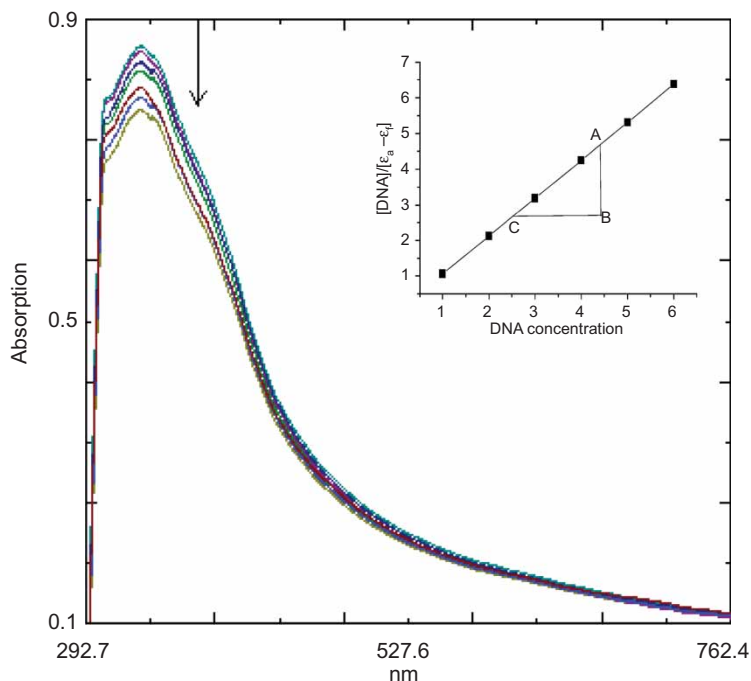


Figure 1. UV-absorption spectra in Tris-HCl buffer upon addition of CT-DNA (**2a**) [DNA] = 0.5 and 10 μM, drug, 20, 30, 40, and 50 μM. Arrow shows the absorbance changing upon the increase of DNA concentration.

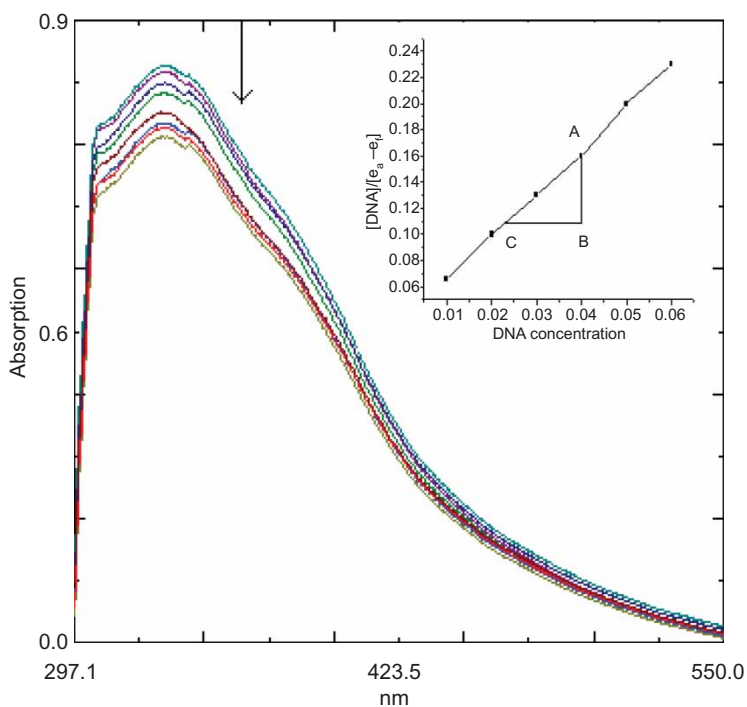
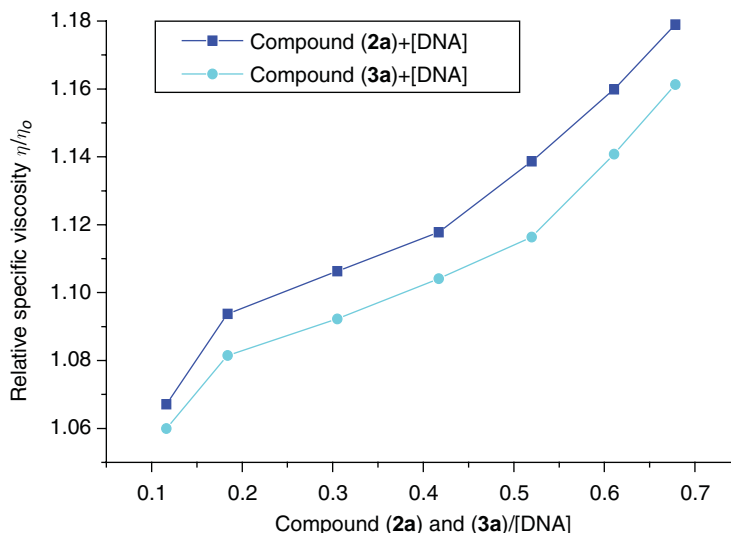


Figure 2. UV-absorption spectra in Tris-HCl buffer upon addition of CT-DNA (**3a**) [DNA] = 0.5 and 10 μM, drug, 20, 30, 40, and 50 μM. Arrow shows the absorbance changing upon the increase of DNA concentration.

Table 2. Absorption spectral properties of compounds **2a** and **3a** bound to CT-DNA.

| Compound | λ_{max} (nm) | K_b (M^{-1}) | T_m ($^{\circ}\text{C}$) |
|-----------|-----------------------------|---------------------------|------------------------------|
| 2a | 298 | 5.3×10^5 | 69 |
| 3a | 302 | 5.8×10^5 | 65 |

Figure 3. Effect of increasing amount of **2a** and **3a** on the relative viscosities of CT-DNA at 25 $^{\circ}\text{C}$.

2.2. Viscosity measurements

For further clarification, the interaction modes of **2a** and **3a** with DNA were investigated by viscosity measurements. An increase in the viscosity of native DNA is regarded as a diagnostic feature of an intercalation process (17, 24). We have measured the viscosity changes in short, rod-like DNA fragments. The relative length increase (L/L_0) of the complex formed between **2a**, **3a** and DNA is shown in Figure 3. It is evident that the binding of **2a** and **3a** increased the viscosity of DNA corresponding to an increase in the contour length of the DNA fragments. In order to elucidate the binding mode of the present compound, the viscosity measurements were carried out on CT-DNA by varying the concentration of added compounds. The effects of the compounds on the viscosity of rod-like DNA were shown (Figure 3). The presence of compound had an obvious effect on the relative viscosity of CT-DNA with an increase in concentration of the added compounds (17).

2.3. Thermal denaturation

Other strong evidence for the intercalative binding of **2a** and **3a** 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 a single-stranded DNA, owing to the increased stability of the helix in the presence of an intercalator (13). The molar extinction coefficient of DNA bases at 260 nm in the double helical form is much less than the single-stranded form; hence, melting of the helix leads to an increase in the absorbance at 260 nm. The DNA melting studies were carried out with CT-DNA in the absence

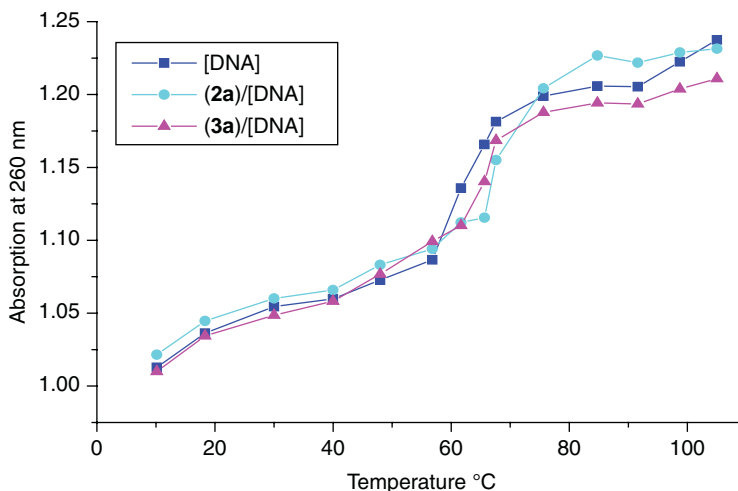


Figure 4. Melting curves of CT-DNA in the presence and absence of **2a** and **3a**.

and presence of **2a** and **3a**. T_m (melting temperature) for CT-DNA was $60 \pm 5^\circ\text{C}$ in the absence of compounds, but in the presence of **2a** and **3a**, the T_m of CT-DNA increased by $7\text{--}10^\circ\text{C}$ (Table 1). These variations in DNA melting temperature strongly supported the intercalation of compounds into the double-helix DNA (Figure 4) (16, 26).

3. General synthesis

3.1. Synthesis of 2-(2-chloroquinolin-3-yl)-3-phenyl-1, 3-thiazolidin-4-one (**2a**)

The appropriate amine (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF under ice-cold conditions for 15 min, followed by an addition of mercaptoacetic acid (3.0 mmol). After 5 min DCC (1.2 mmol) was added to the reaction mixture at $0\text{--}5^\circ\text{C}$ and the reaction mixture stirred for an additional 50 min at room temperature. DCC was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 15% aq. acetic acid, water, 12% aq. sodium hydrogen carbonate, and then finally with brine. The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using ethyl acetate- CHCl_3 as an eluent. Similarly, the same procedure was used for all the quinoline derivatives. This compound was obtained as a yellowish solid in 79% yield; IR cm^{-1} (KBr) 2931 (Ar-CH), 1660 (C=O), 1399, 1291, 1158, 894, 747, 687. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 6.39 (s, 1H, thiazolidin ring -CH), 3.72–3.76 (d, $J = 9.65\text{ Hz}$, -S- CH_2), 7.13–7.45 (m, 5H, Ar-CH, quinoline), 7.61–7.83 (m, 5H, Ar-CH, phenyl ring). FAB mass $m/z = 339(\text{M}^+)$.

3.2. Synthesis of 2-(2-chloro-6-methylquinolin-3-yl)-3-phenyl-1, 3-thiazolidin-4-one (**2b**)

This compound was obtained as a yellowish orange solid in 89% yield; IR cm^{-1} (KBr) 2932 (Ar-CH), 1662 (C=O), 1397, 1293, 1158, 894, 745, 686. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 6.40 (s, 1H, thiazolidin ring -CH), 3.72–3.76 (d, $J = 9.64\text{ Hz}$, -S- CH_2), 2.34 (s, 3H, CH_3), 7.13–7.45 (m, 4H, Ar-CH, quinoline), 7.61–7.83 (m, 5H, Ar-CH, phenyl ring). FAB mass $m/z = 355[\text{M} + \text{H}]$.

3.3. Synthesis of 2-(2-chloro-6-methoxyquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (2c)

This compound was obtained as an yellowish solid in 82% yield; IR cm^{-1} (KBr) 2932 (Ar—CH), 1662 (C=O), 1398, 1293, 1155, 893, 747, 686. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 6.40 (s, 1H, thiazolidin ring —CH), 3.72–3.74 (d, $J = 9.64$ Hz, —S—CH₂), 3.98 (s, 3H, OCH₃), 7.13–7.44 (m, 4H, Ar—CH, quinoline), 7.61–7.84 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 370[\text{M}^+]$.

3.4. Synthesis of 2-(2-chloro-8-methylquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (2d)

This compound was obtained as an yellowish orange solid in 89% yield; IR cm^{-1} (KBr) 2931 (Ar—CH), 1660 (C=O), 1399, 1291, 1158, 894, 747, 687. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 6.36 (s, 1H, thiazolidin ring —CH), 3.71–3.73 (d, $J = 9.64$ Hz, —S—CH₂), 7.18–7.45 (m, 4H, Ar—CH, quinoline), 7.62–7.88 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 355[\text{M} + \text{H}]$.

3.5. Synthesis of 2-(2-mercaptoquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (3a)

This compound was obtained as orange solid in 79% yield; IR cm^{-1} (KBr) 2926 (Ar—CH), 2756 (—SH—), 1626 (C=O), 1399, 1290, 1158, 894, 743, 686. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 12.22 (s, 1H, SH), 6.32 (s, 1H, thiazolidin ring —CH), 3.63–3.70 (d, $J = 9.64$ Hz, —S—CH₂), 7.19–7.44 (m, 5H, Ar—CH, quinoline), 7.53–7.74 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 339[\text{M} + \text{H}]$.

3.6. Synthesis of 2-(2-mercapto-6-methylquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (3b)

This compound was obtained as an yellowish orange solid in 69% yield; IR cm^{-1} (KBr) 2922 (Ar—CH), 2752 (—SH—), 1626 (C=O), 1399, 1290, 1156, 895, 747, 684. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 12.22 (s, 1H, SH), 6.33 (s, 1H, thiazolidin ring —CH), 3.62–3.69 (d, $J = 9.65$ Hz, —S—CH₂), 7.19–7.44 (m, 4H, Ar—CH, quinoline), 2.42 (s, 3H, CH₃), 7.53–7.74 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 353[\text{M} + \text{H}]$.

3.7. Synthesis of 2-(2-mercapto-6-methoxyquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (3c)

This compound was obtained as an yellowish orange solid in 74% yield; IR cm^{-1} (KBr) 2926 (Ar—CH), 2756 (—SH—), 1626 (C=O), 1398, 1291, 1158, 894, 748, 687. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 12.21 (s, 1H, SH), 6.33 (s, 1H, thiazolidin ring —CH), 3.63–3.69 (d, $J = 9.65$ Hz, —S—CH₂), 7.19–7.44 (m, 4H, Ar—CH, quinoline), 3.06 (s, 3H, OCH₃), 7.53–7.74 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 368[\text{M}^+]$.

3.8. Synthesis of 2-(2-mercapto-8-methylquinolin-3-yl)-3-phenyl-1,3-thiazolidin-4-one (3d)

This compound was obtained as orange solid in 69% yield; m.p, 205–208°C; IR cm^{-1} (KBr) 2926 (Ar—CH), 2756 (—SH—), 1626 (C=O), 1398, 1292, 1158, 893, 747, 688. $^1\text{H-NMR}$ (400 MHz, CDCl_3) 12.22 (s, 1H, SH), 6.32 (s, 1H, thiazolidin ring —CH), 3.63–3.70 (d, $J = 9.65$ Hz, —S—CH₂), 7.18–7.42 (m, 4H, Ar—CH, quinoline), 2.34 (s, 3H, CH₃), 7.51–7.74 (m, 5H, Ar—CH, phenyl ring). FAB mass $m/z = 353[\text{M} + \text{H}]$.

4. Conclusion

The synthetic route adopted for the synthesis of quinoline derivatives (**2a/3a**) was very efficient and gave a good yield. The efficient and simple methodology was based on the DCC-catalyzed synthesis, and the efficiency of the employed methodology can be explained by the fact that energy required is probably much less than the activation energy necessary for each reaction, so that the reaction rate is increased. DNA-binding studies indicate hypochromicity and bathochromic shifts of compounds **2a** and **3a** when they bind with base pairs of CT-DNA. The binding constant values of $5.3 \times 10^5 \text{ M}^{-1}$ for **2a** and $5.8 \times 10^5 \text{ M}^{-1}$ for **3a** suggested that the compound **3a** bind more avidly with CT-DNA than **2a**.

5. Experimental

All organic solvents used for the synthesis were of analytical grade. The thin-layer chromatography (TLC) was performed on Baker-Flex silica gel 1B-F (1.55) plates using ethyl acetate and petroleum ether (1:8). Melting points were determined on a Mel-Temp apparatus and were uncorrected. IR spectra were recorded in the matrix of KBr with Perkin-Elmer 1430 spectrometer. $^1\text{H-NMR}$ spectra were recorded on Jeol spectrometer (400 MHz), and chemical shifts (δ) given in ppm relative to the trimethylsilyl or tetramethylsilane (TMS) in CDCl_3 solvent. Mass spectra were recorded by electron ionization on a Finnigan MAT 312 spectrometer. C, H, and N analyses were performed at Cochin University, Sophisticated Test & Instrumentation Center, Kochi, Kerala, India. Ammonium hexafluorophosphate (NH_4PF_6) was purchased from Qualigens (India). Tris-HCl buffer (5 mM Tris-HCl, 50 mM NaCl, pH 7.2, Tris=Tris(hydroxymethyl) amino methane) solution was prepared using deionized double distilled water. CT-DNA was purchased from Bangalore Gene, Bangalore, India. Ultraviolet-visible (UV-VIS) absorption spectra were determined in a Perkin-Elmer model 554 and UV-VIS recording spectrophotometer using quartz cuvettes of 10 mm path light.

5.1. UV-VIS absorption studies

The concentration of CT-DNA per nucleotide $[\text{C(p)}]$ was measured using its known extinction coefficient at 260 nm ($6600 \text{ M}^{-1} \text{ cm}^{-1}$) (27). The absorbance at 260 nm (A_{260}) and 280 nm (A_{280}) for CT-DNA was measured to check purity. The ratio A_{260}/A_{280} was found to be 1.8:1.9, indicating that CT-DNA was satisfactorily free from protein. A buffer (5 mM *tris*(hydroxymethyl) aminomethane, pH 7.2, 50 mM NaCl) was used for the absorption, viscosity, and thermal denaturation experiments.

Absorption titration experiments were carried out by varying the DNA concentration (0–100 μM) and maintaining the compound concentration constant (30 μM). Absorption spectra were recorded after each successive addition of DNA and equilibration (approximately 10 min). For both the compounds **2a** and **3a**, observed data were then fit into Equation (1) in order to obtain the intrinsic binding constant, K_b (28):

$$\frac{[\text{DNA}]}{(\varepsilon_a - \varepsilon_f)} = \frac{[\text{DNA}]}{(\varepsilon_b - \varepsilon_f)} + \frac{1}{K_b(\varepsilon_a - \varepsilon_f)}, \quad (1)$$

where ε_a , ε_f , and ε_b are the apparent, free, and bound compound extinction coefficients at 298 nm (**2a**) and 302 nm (**3a**), respectively. A plot of $[\text{DNA}]/(\varepsilon_a - \varepsilon_f)$ versus $[\text{DNA}]$ gave a slope of

$1/(\varepsilon_b - \varepsilon_f)$ and an intercept y equal to $1/K_b(\varepsilon_b - \varepsilon_f)$, where K_b is the ratio of the slope to the intercept y .

5.2. Viscosity measurements

Viscosity measurements were carried out using a semimicro-dilution capillary viscometer at room temperature. Each experiment was performed three times and an average flow time was calculated. Data were presented as (η/η_o) versus binding ratio, where η is the viscosity of DNA in the presence of complex and η_o is the viscosity of DNA alone (29).

5.3. Thermal denaturation

Melting studies were carried out by monitoring the absorption of CT-DNA (50 μ M) at 260 nm at various temperatures in the presence (5–10 μ M) and absence of each complex. The melting temperature (T_m) at which 50% of the double-stranded DNA becomes single-stranded and the curve width (σT), the temperature range between 10% and 90% noticed absorption increases occurred and calculated as reported (30).

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