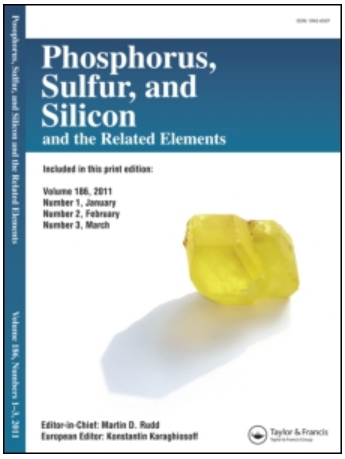


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# Synthesis, DNA Binding, and Antimicrobial Activity of Base-Catalyzed 2-Phenyl-3-pyrido[3,2][1,3,4]thiadiazolo [3,2]quinoline Derivatives

Devappa S. Lamani[a]; K. R. Venugopala Reddy[a]; H. S. Bhojya Naik[a]; Anil B. Naik[b]; Prakash Naik[a]
[a] Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Shankaraghatta, Karnataka, India [b] Department of Physics, Karnataka University, Dharwad, India

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# SYNTHESIS, DNA BINDING, AND ANTIMICROBIAL ACTIVITY OF BASE-CATALYZED 2-PHENYL-3-PYRIDO[3,2][1,3,4]THIADIAZOLO [3,2]QUINOLINE DERIVATIVES

**Devappa S. Lamani,[1] K. R. Venugopala Reddy,[1] H. S. Bhojya Naik,[1] Anil B. Naik,[2] and Prakash Naik[1]**

[1]*Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Shankaraghatta, Karnataka, India*

[2]*Department of Physics, Karnataka University, Dharwad, India*

***A series of novel 3-{[(5-phenyl-1,3,4-thiadiazol-2-yl)imino] methyl}quinoline-2-thione (2a–c) and 2-phenyl-3-pyrido[3,2][1,3,4]thiadiazolo[3,2]quinoline derivatives (3a–c) were prepared by a facile synthetic method using an anhydrous potassium carbonate catalyst. The newly synthesized heterocyles were characterized by elemental analysis, FT-IR, $^1$H-NMR, and mass spectral data. The selected compounds were studied for interaction with calf thymus-DNA(CT-DNA) by electronic spectra and viscosity measurements, as well as thermal denaturation studies. Upon binding to DNA, the absorption spectrum underwent bathochromic and hypochromic shifts. The binding constant ($K_b$) observed value of 8.4 × $10^5$ $M^{-1}$ for (2a) and 8.2 × $10^5$ $M^{-1}$ for (3a) suggested that compound (2a) binds more avidly to CT-DNA than compound (3a). The increasing viscosity of sonicated rod-like DNA fragments and the melting temperature of DNA, in the presence of compound solutions, support the binding mode. The synthesized derivatives have been screened for antibacterial and antifungal activities.***

**Keywords** Anhydrous $K_2CO_3$; anticancer agent; antimicrobial activity; DNA binding; 5-phenyl-1,3,4-thiadiazol-2-amine; quinoline; viscosity measurements



## INTRODUCTION

The pharmacological properties of quinolines and their derivatives has attracted worldwide attention in the last few decades because of their wide occurrence in natural products and drugs.[1,2] A 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 antitumor and anticancer properties,[3–5] and their cyclized products, e.g., triazoles,[6] oxadiazoles,[7] thiazolidinones,[8] thiazoles,[9] and thiadiazoles[10] are also associated with a broad spectrum of biological properties.

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Address correspondence to K. R. Venugopala Reddy, Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Shankaraghatta 577 451, Shimoga District, Karnataka, India. E-mail: venurashmi30@rediffmail.com

In addition, thiadiazoles in general, and 1,3,4-thiadiazoles in particular, have a variety of applications in medicine. Heterocycles having various pharmacological and biological activities such as antimicrobial,[11–14] antitubercular,[15] anti-inflammatory,[16] anticonvulsant,[17] antihypertensive,[19] anesthetic,[20] and anticancer,[21] etc., have attracted the attention of synthetic chemists. They are also well known for their applications in agricultural and material chemistry,[22] There is evidence that the anticancer activity is due to the intercalation between the drug and the base pairs of DNA, and interference with the normal functioning of the enzyme topoisomerase II that is involved in the breaking and releasing of DNA strands.[23] In recent years, various fused systems such as thiophene,[24] furan, and pyridine analogues of ellipticine and benzothiazoloquinoline[25] have been studied for their intercalative properties. Recently, Cao and He studied DNA affinity properties of safranine T, which features a planar phenazine ring, and they showed that electrostatic binding plays an important role in the intercalation of safranine T.[23]

The recent interest in green chemistry has posed a new challenge for organic synthesis, in that new reaction conditions need to be found that reduce the emission of volatile organic solvents and the use of hazardous toxic chemicals. Therefore, variations have been made in the removal of water during the cyclization. There are scattered reports of using bases such as anhydrous AcONa, piperidene, and $Et_3N$[26,27] as desiccants for removal of water. In all the above mentioned methods, the reaction requires prolonged heating at high temperatures (80–90°C) for nearly 15–18 h. In order to circumvent these difficulties, we have chosen a radically different approach to generate new 2-phenyl-3-[1,3,4]thiadiazolo[3,2]quinoline scaffolds by simpler methods in quantitative yields.

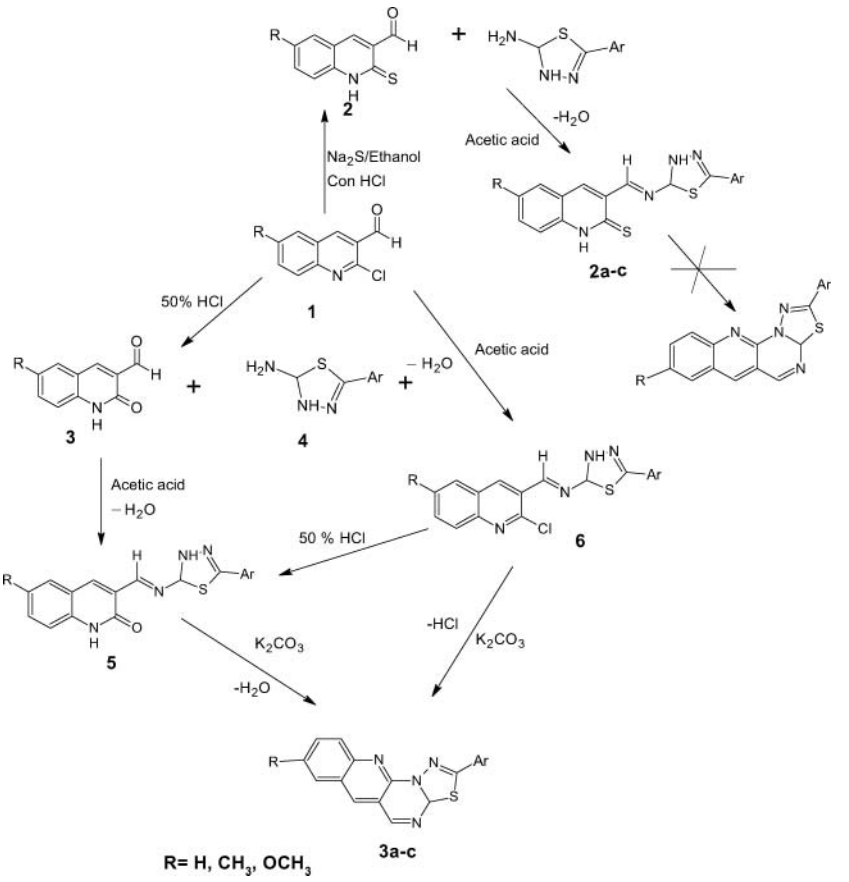
In continuation of our research program[3,4,28,29,34] toward the synthesis of potentially bioactive anticancer agents via a simple and practical approach, herein we report a rapid and efficient method for the synthesis of sulfur-containing quinoline derivatives. The newly synthesized compounds (**2a**) and (**3a**) were studied for their interactions with CT-DNA.



## RESULTS AND DISCUSSION

Novel condensed heterocyclics such as 2-phenyl-3-[1,3,4]thiadiazolo[3,2]quinoline derivatives (**3a–c**) can be conceivably synthesized by two pathways as shown in Scheme 1. In the first step, various aldehydes react with 5-phenyl-1,3,4-thiadiazol-2-amine (**4**) using acetic acid, which affords Schiff bases. In the second, the cyclization is achieved when the Schiff base is refluxed with a base catalyst to yield the title compound in quantitative yield. The desired compounds (**3a–c**) are obtained with high yield and short time when they have been cyclized from compound (**6**) rather than from compound (**5**).

Our mechanistic investigations using spectral studies gave proof of cyclized and uncyclized products. IR spectra of compounds (**2a**) and (**3a**) show the absence of an aldehyde carbonyl stretching frequency instead it gave a band at 1657–1720 $cm^{-1}$, and sharp bands in the region of 755–760 $cm^{-1}$, 1562–1567 $cm^{-1}$, and 3256–3252 $cm^{-1}$ corresponding to (C=S), (−C=N−), and (−NH−) groups, respectively.[28] The $^1H$ NMR spectra (**2a**) show signals corresponding to (-SH- mercapto), and appeared at $\delta$ 14.05, revealing the formation of an uncyclized product. Further, the assigned structure was confirmed by its mass spectra with a molecular ion peak at m/z = 350 [$M^+$]. On the other hand the IR spectra of compound (**3a**) shows an absence of -OH in the region of 3462–3458 $cm^{-1}$, and the reappearance of a sharp band at 1056–1054 $cm^{-1}$ (−N−N−) confirmed that cyclization had occurred. The $^1H$ NMR spectra prompted us to confirm the subsequent




**Scheme 1** Synthesis of 2-phenyl-3-[1,3,4]thiadiazolo[3,2]quinazoline derivatives.

cyclization due to the absence of aromatic −OH− and a halogen group present at the two position of the quinoline nucleus.[29,30] The structure assigned was confirmed by its mass spectrum. It gave a molecular ion peak at m/z = 317 [M+H]. The spectral details of all other compounds are given in the Experimental section.

## DNA Binding Studies

The application of electronic absorption spectroscopy in CT-DNA binding studies is a very important technique.[31] The addition of increasingly higher concentrations of DNA led to hypochromic and bathochromic (red shift) changes in its visible absorption spectra as a result of the formation of more stable complexes (Figures 1 and 2). The interaction of compounds (**2a**) and (**3a**) with CT-DNA resulted in a strong decrease of absorption intensity accompanied by a shift towards higher wavelengths (∼3 and 5 nm). Around 15% to 20%, reduction of absorption was observed at 330 nm (**2a**) and 300 nm for (**3a**) peak maximum in the presence of an excess of calf thymus DNA. The binding of the molecules to DNA has been well characterized by the large hypochromism. After intercalation, the $\pi^*$ orbital of compounds could couple with $\pi$ orbital of base pairs, thus decreasing the

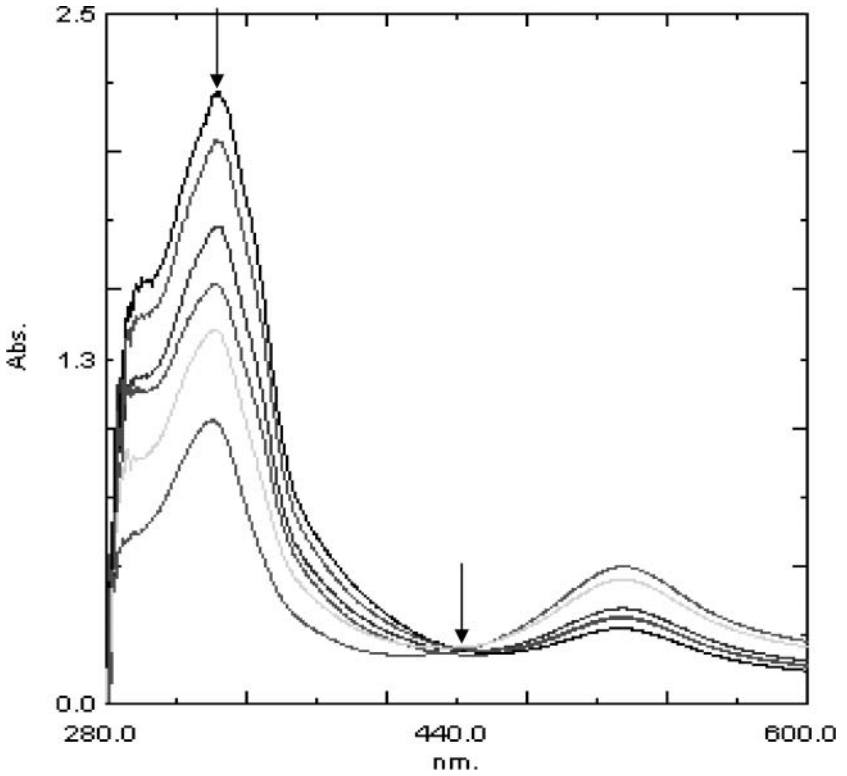



**Figure 1** UV absorption spectra in Tris-HCl buffer upon addition of CT-DNA (**2a**). [DNA] = 0.5 $\mu$m, 10 $\mu$m, drug, 20 $\mu$m; 30 $\mu$m; 40 $\mu$m; 50 $\mu$m. The arrow shows the absorbance changing upon the increase of DNA concentration.



$\pi^*$–$\pi$ transition energy and further resulting bathochromism. The change in the absorbance values (including red shift, hypochromicity, and isosbestic point) was used to evaluate the intrinsic binding constants ($K_b$). The values $8.4 \times 10^5\ M^{-1}$ for (**2a**) and $8.2 \times 10^5\ M^{-1}$ for (**3a**) were observed. The spectral results indicate that compound (**2a**) binds more strongly than (**3a**) (Table I).

## Viscosity Measurements

To further clarify the interaction modes of (**2a**) and (**3a**) with DNA, viscosity measurements were investigated. As optical phatophysical probes provide necessary but not sufficient clues to support a binding mode, viscosity experiments are considered as one of the least ambiguous and the most critical tests of a binding mode in solution in the absence of crystallographic structure data. An increase in the viscosity of native DNA is regarded as a diagnostic feature of an intercalation process.[35,36] We have measured the viscosity changes in short, rod-like DNA fragments. The relative length increase ($L/L_0$) of the complex formed between the compounds 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

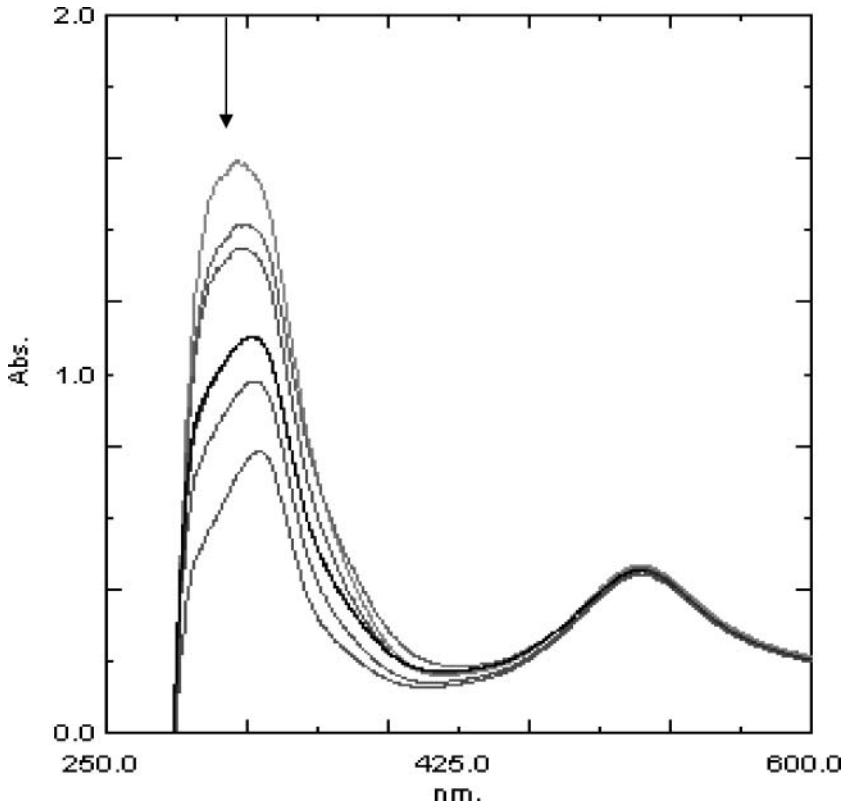



**Figure 2** UV absorption spectra in Tris-HCl buffer upon addition CT-DNA (**3a**). [DNA] = 0.5 $\mu$m, = 10$\mu$m, drug, 20 $\mu$m; 30 $\mu$m; 40 $\mu$m; 50 $\mu$m. The arrow shows the absorbance changing upon the increase of DNA concentration.



by varying the concentration of added compound. The effects of the compounds on the viscosity of rod-like DNA were shown (Figure 3). The presence of the compounds had an obvious effect on relative viscosity of CT-DNA with an increase in concentration of the added compounds.[37]

## Thermal Denaturation Studies

Thermal denaturation studies of CT-DNA are useful in determining the ability of the present compounds to stabilize the double-stranded DNA. The intercalation of small molecules into the double helix was known to increase the DNA melting temperature ($T_m$). The melting temperature $T_m$ of DNA characterizes the transition from double-stranded to

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

| Compound | $\lambda_{max}$ (nm) | $K_b$ ($M^{-1}$) | $T_m$ (°C) |
|---|---|---|---|
| **2a** | 330 | $8.4 \times 10^5$ | 62 |
| **3a** | 300 | $8.2 \times 10^5$ | 68 |

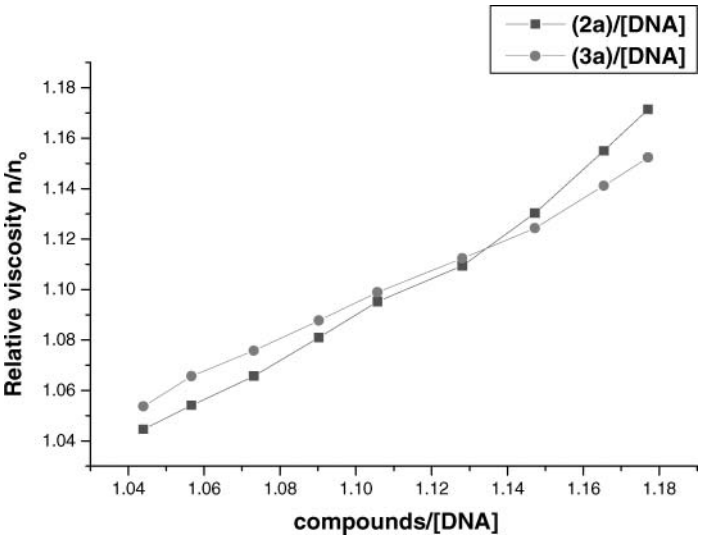



**Figure 3** Effect of increasing amount of the compounds (**2a**) and (**3a**) on the relative viscosities of CT-DNA, at 25°C.



single-stranded nucleic acid.[38,39] The DNA melting studies were carried out with CT-DNA in the absence and presence of the compounds. The melting profiles ($T_m$) for CT-DNA in the absence of the compounds had the value 60 ± 5°C. Under the same experimental conditions, the presence of the compounds increased the melting temperature ($T_m$) about 62°C for (**2a**) and 68°C for (**3a**) (Figure 4). Likewise the various DNA melting experiments strongly supported the stabilized double-stranded calf thymus DNA.[34]

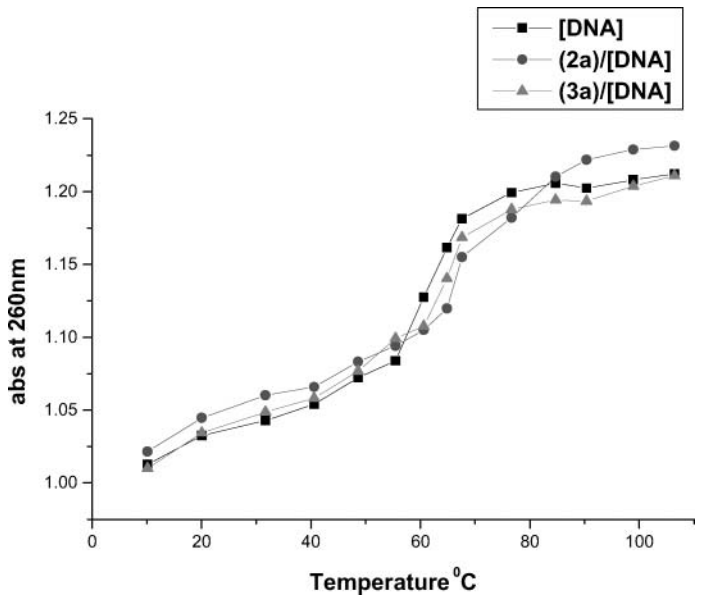



**Figure 4** Melting cures of CT-DNA in the presence and absence of (**2a**) and (**3a**).

## EXPERIMENTAL

All organic solvents used for the synthesis were of analytical grade. The 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 a Perkin-Elmer 1430 spectrometer. $^1$H NMR spectra were recorded on a JEOL spectrometer (400 MHz), and chemical shifts ($\delta$) given in ppm relative to the TMS in $CDCl_3$ solvent. Mass spectra were calculated on a JEOL JMS-D 300 mass spectrometer operating at 70 eV. C, H, and N analyses were performed at Cochin University, Sophisticated Test & Instrumentation Center, Kochi, Kerala, India. Ammonium hexaflurophosphate ($NH_4PF_6$) 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. Calf thymus DNA (CT-DNA) was purchased from Bangalore Gene, Bangalore, India. Ultraviolet-visible absorption spectra were determined in a Perkin-Elmer model 554 UV-Vis recording spectrophotometer using quartz cuvettes of 10 mm path-light. 3-Formyl-2-cholroquinolines, 2-hydroxyquinoline-3-carbaldehyde, and 3-formyl-2-mercaptoquinolines were synthesized using reported methods.[28,35]



### UV-Visible Absorption Studies

The concentration of CT-DNA per nucleotide [C(p)] was measured using its known extinction coefficient at 260 nm (6600 $M^{-1}$ $cm^{-1}$).[40] The absorbance at 260 nm ($A_{260}$) and at 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. 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 DNA concentration (0–100 $\mu$M) and maintaining the compound concentration constant (30 $\mu$M). 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, $K_b$

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

where $\varepsilon_a$, $\varepsilon$, and $\varepsilon_b$ are the apparent, free, and bound compound extinction coefficients at 330 nm (**2a**) and 300 nm (**3a**), respectively. A plot of $[DNA]/(\varepsilon_a - \varepsilon_b)$ versus [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 $y$.[41]

### 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 $(\eta/\eta_o)$ versus binding ratio, where $\eta$ is the viscosity of DNA in the presence of complex and $\eta_o$ is the viscosity of DNA alone.[42]

### Thermal Denaturation

Melting studies were carried out by monitoring the absorption of CT-DNA (50 $\mu$M) at 260 nm at various temperatures in the presence (5–10 $\mu$M) and the absence of each

complex. The melting temperature ($T_m$), at which 50% of double-stranded DNA becomes single-stranded and the curve width ($\sigma T$), in the temperature range between 10% and 90%, absorption increases occurred and were calculated as reported.[43]

## General Syntheses

**Part A: Syntheses of 3-{[(5-phenyl-1,3,4-thiadiazol-2-yl)imino]methyl} quinoline-2-thione (2a–c).** 3-Formy-2-mercaptoquinoline (9.55 g, 0.049 mol) was reacted with 5-phenyl-1,3,4-thiadiazol-2-amine (8.89g 0.05mol) in 80 mL acetic acid, and was stirred for 3–4 h at room temperature. The reaction mixture was poured onto ice-cold water. A yellowish solid was collected by filtration and dried under vacuum and recrystallized from ethanol. The same procedure was followed for the synthesis of reported compounds. Yield 83%, mp 123–125°C, IR (KBr): 3256, (−NH−), 2988, (Ar−CH stretching), 1568 (C=N), 755 (C=S tautomaresed). $^1$H NMR (400 MHz, $CDCl_3$) 14.05 (br.s, 1H, SH), 12.22 (br.s, 1H, NH), 10.93 (s, 1H, −CH =N−), 10.23 (s, 1H, N−CH-$_S$), 7.18–8.60 (m, 10H, Ar−H). Mass spectra m/z = 350[$M^{\pm}$], Anal. (%) for $C_{18}H_{14}N_4S_2$ (350), Calcd. C, 61.69; H, 4.03; N, 15.99; S, 18.30, Found: C, 61.74; H, 4.00; N, 15.88. S,18.26.

*Syntheses of 6-methyl-3-{[(5-phenyl-1,3,4-thiadiazol-2-yl)imino]methyl} quinoline-2-thione (2b).* Yellow solid with yield 77%, mp 140–142°C, IR (KBr): 3254, (−NH−), 2989, (Ar−CH stretching), 1566 (C=N), 756 (C=S); $^1$H NMR (400 MHz, $CDCl_3$) 14.06 (br, s, 1H, SH), 12.22 (br.s, 1H, NH), 10.93(s, 1H, −CH =N−), 10.23 (s, 1H, N−CH−S), 2.63 (s, 3H, $CH_3$), 7.18–8.60 (m, 9H, Ar−H). Mass spectra m/z = 365[M+H], Anal. (%) for $C_{19}H_{16}N_4S_2$ (364.4), Calcd. C, 62.61; H, 4.42 N, 15.37; S, 17.59, Found: C, 62.74; H, 4.36; N, 15.39. S, 17.56.

*Syntheses of 6-methoxy-3-{[(5-phenyl-1,3,4-thiadiazol-2-yl)imino]methyl} quinoline-2-thione(2c).* Greenish yellow solid with yield 73%, mp 155–156°C, IR (KBr): 3254, (−NH−), 2988, (Ar−CH stretching), 1567 (C=N), $^1$H NMR (400 MHz, $CDCl_3$) 14.06 (br, s, 1H, SH), 12.22 (br.s, 1H, NH), 10.93 (s, 1H,−CH =N−), 10.23 (s, 1H, N−CH−S), 2.19 (s, 3H, $OCH_3$) 7.18–8.60 (m, 9H, Ar−H). Mass spectra m/z = 380 [$M^+$], Anal. (%) for $C_{19}H_{16}N_4OS_2$ (380.48), Calcd. C, 59.98; H, 4.24; N, 14.73; S, 16.85, Found: C, 59.93; H, 4.18; N, 14.88. S, 16.91.

*Part B: Syntheses of 2-phenyl-3-[1,3,4] thiadiazolo [3,2] quinoline (3a).* A 50 mL ethanolic mixture of (**5**) (6.15 g, 0.029 mol) was refluxed in anhydrous potassium carbonate (1.25 g, 0.02 mol) for 5–7 h. The yellowish brown solid that formed was then collected by filtration, recrystallized using ethanol, and purified by column chromatography using pet ether:ethyl acetate (8:3). The same procedure was followed for the synthesis of (**3b–c**). Yield 73%, mp: 225–227°C, IR (KBr): 2988, (Ar-CH stretching), 1056 (N−N), 1562 (C=N), $^1$H NMR (400 MHz, $CDCl_3$) 11.05 (s, 1H, −CH=N−), 10.33 (s, 1H, N−CH−S), 7.20–8.71 (m, 10H, Ar−H). Mass spectra m/z = 317 [M+H], Anal. (%) for $C_{18}H_{12}N_4S$ (316.3), Calcd. C, 68.33; H, 3.82; N, 17.71; S, 10.13, Found: C, 68.39; H, 3.78; N, 17.66. S, 10.16.

*Syntheses of 7-Methyl-2-phenyl-3-pyrido[3,2][1,3,4]thiadiazolo[3,2]quinoline(3b).* Brown solid with yield 68%, mp 233–235°C, IR (KBr): 2989, (Ar−CH stretching),1054 (N−N), 1569 (C=N), $^1$H NMR (400 MHz, $CDCl_3$) 11.05 (s, 1H, −CH =N−), 10.34 (s, 1H, N−CH−S), 2.68 (s, 3H, $CH_3$) 7.20–8.70 (m, 9H, Ar−H). Mass spectra m/z = 330 [$M^+$], Anal. (%) for $C_{19}H_{14}N_4S$ (330.4), Calcd. C, 69.07; H, 4.27; N, 16.96; S, 9.70, Found: C, 69.10; H, 4.31; N, 16.88. S, 9.67.

*Syntheses of 7-Methoxy-2-phenyl-3-pyrido[3,2][1,3,4]thiadiazolo[3,2] quinoline (3c).* Yellowish brown solid with yield 79%, mp 240–242°C, IR (KBr): 2989, (Ar—CH stretching), 1054 (N—N), 1568 (C=N), $^1$H NMR (400 MHz, $CDCl_3$) 11.05 (s, 1H, -CH =N—), 10.34 (s, 1H, N—CH—S), 1.99 (s, 3H, $OCH_3$) 7.18–8.70 (m, 9H, Ar—H). Mass spectra m/z = 346 [$M^+$], Anal. (%) for $C_{19}H_{14}N_4OS$ (346.4), Calcd. C, 65.88; H, 4.07; N, 16.17; S, 9.26, Found: C, 65.82; H, 4.12; N, 16.22. S, 9.32.

## Evaluation of Antimicrobial Activity

The in vitro antimicrobial activity was carried out against 24-h old cultures of two bacteria and two fungi by the cup-plate method.[44] Compounds were tested for their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans.* Nutrient agar and potatodextrose agars were used to culture the bacteria and fungus respectively. The compounds were tested at a concentration of 0.005 mol/mL in DMSO solution. The solutions of Chloramphenicol (2 mg/mL) and Flucanazole (2 mg/mL) were prepared in sterilized water and used as standards for comparison of antibacterial and antifungal activities, respectively. The compounds were tested at varied concentrations. The minimum inhibition concentration was found to be 0.001 mol/mL in DMSO against all organisms. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 hr fo bacteria at 28°C and 48 h for fungus at 35°C. Each experiment was repeated thrice, and the average of the three independent determinations was recorded. The synthesized derivatives exhibit significant activity, and resulting protocols are summarized in Table II. The compounds **2a**, **2b**, and **2c** were found to be more active against *P. aerugenosa*, and the compounds **2b** and **2c** were found to exhibit more activity against *S. aureus*. The compounds **2c**, **3b**, and **3c** against *A. niger* and compounds **3b**, **3c**, and **2a** against *C. albicans* exhibited significant antifungal activity. From the results, it is evident that the uncyclized sulfur compounds (**3a–c**) exhibit maximum antifungal activity compared to that of compound (**2a–c**), whereas cyclized compounds (**2a–c**) gave more antibacterial activity than that of (**3a–c**).[45]

Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity, respectively: Control (DMSO) (—)—no activity; highly active (inhibition zone > 12 mm); moderately active (inhibition zone 9–12 mm); slightly active (inhibition zone 6–9 mm); inactive—inhibition zone < 6 mm.

**Table II** Evaluation of antimicrobial activity of 2-phenyl-3-[1,3,4]thiadiazolo[3,2] quinoline derivatives

| | Antibacterial activity Zone of inhibition in mm | | Antifungal activity Zone of inhibition in mm | |
|---|---|---|---|---|
| Compd. | *P. aerugenos* | *S. aureus* | *A. niger* | *C. albicans* |
| **2a** | 21 | 18 | 17 | 18 |
| **2b** | 20 | 19 | 15 | 17 |
| **2c** | 21 | 20 | 18 | 15 |
| **3a** | 16 | 17 | 16 | 18 |
| **3b** | 16 | 15 | 22 | 21 |
| **3c** | 18 | 14 | 20 | 19 |
| Chloramphenicol | 22 | 24 | — | — |
| Flucanazole | — | — | 25 | 26 |

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