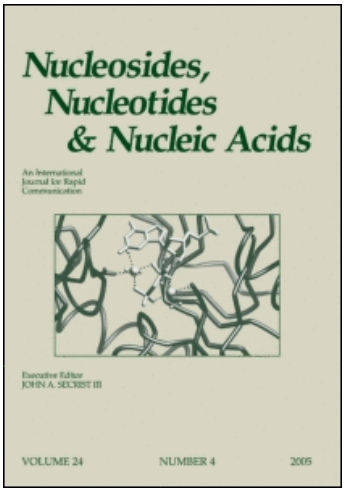


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and DNA Binding Studies of Novel Heterocyclic Substituted Quinoline Schiff Bases: A Potent Antimicrobial Agent

Devappa. S. Lamani[a]; Kallam. R. Venugopala Reddy[a]; H.S. Bhojya Naik[a]; A. Savyasachi[a]; H. Raja. Naik[b]
[a] Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Karnataka, India [b] Department of P. G. Studies and Research in Biotechnology, Kuvempu University, Karnataka, India

To cite this Article Lamani, Devappa. S. , Venugopala Reddy, Kallam. R. , Bhojya Naik, H.S. , Savyasachi, A. and Naik, H. Raja.(2008) 'Synthesis and DNA Binding Studies of Novel Heterocyclic Substituted Quinoline Schiff Bases: A Potent Antimicrobial Agent', Nucleosides, Nucleotides and Nucleic Acids, 27: 10, 1197 — 1210
To link to this Article: DOI: 10.1080/15257770802400081
URL: http://dx.doi.org/10.1080/15257770802400081

Nucleosides, Nucleotides and Nucleic Acids, 27:1197–1210, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802400081

Taylor & Francis
Taylor & Francis Group

SYNTHESIS AND DNA BINDING STUDIES OF NOVEL HETEROCYCLIC SUBSTITUTED QUINOLINE SCHIFF BASES: A POTENT ANTIMICROBIAL AGENT

Devappa. S. Lamani,[1] Kallam. R. Venugopala Reddy,[1] H. S. Bhojya Naik,[1] A. Savyasachi,[1] and H. Raja. Naik[2]

[1]Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Karnataka, India
[2]Department of P. G. Studies and Research in Biotechnology, Kuvempu University, Karnataka, India

□ *The present article deals with the synthesis of 2-chloroquinoline-3-carbaldehyde [(2-hydroxy-1-naphthyl) methylene] hydrazone (CQCMH) (**2a-c**) and 2-chloroquinoline-3-carbaldehyde [4-(dimethylamino) benzylidene] hydrazone (CQCDBH) (**3a-c**) from quinoline derivatives under suitable experimental conditions. The synthesized compounds were characterized by elemental analysis, FTIR, ^{1}HNMR, and mass spectral data. The selected compounds were studied for interaction with calf thymus-DNA (CT-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 value of 2.3×10^3 M^{-1} for (**2a**) and 2.5×10^4 M^{-1} for (**3a**). The viscosity measurements indicated that the viscosity of sonicated rod like DNA fragments increased. The synthesized derivatives have been screened for antibacterial and antifungal activities.*

Keywords Quinoline; Schiff bases; DNA binding; viscosity measurement; antimicrobial anticancer agents

INTRODUCTION

Schiff-bases are currently being extensively studied for biological and anticancer activities.[1–5] The pharmacological properties of quinoline and their derivatives attracted worldwide attention in the last few decades

Received 9 June 2008; accepted 30 July 2008.
D. S. L. thanks the Indian Institute of Science Bangalore, Karnataka University Dharwad for providing spectral data and Kuvempu University for awarding Research Fellowship.
Address correspondence to K. R. V. Reddy, Department of Studies in Industrial Chemistry, Jnana Sahyadri Kuvempu University, Shankaraghatta-577 451, Shimoga District, Karnataka, India. E-mail: venurashmi30@gmail.com

because of their wide occurrence in natural products, and drugs.[6,7] Literature Survey revealed that five to six membered heterocyclic compounds containing one or two heteroatoms fused to a quinoline ring in linear fashion were found to possess antitumor and anticancer properties.[8–10] On the other hand hydrazones possessing an azamethine −NHN=CH- proton constitute an important class of compound for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities.[11] These observations have been guiding for the development of new quinoline containing hydrazones that possess varied biological activities.

There is evidence that anticancer activity was due to the intercalation between the drug and the base pairs of DNA and interference with normal functioning of the enzyme topoisomerase II that was involved in the breaking and releasing of DNA strands.[12] In recent years various fused systems such as thiophene,[13] furan and pyridine analogues of ellipticine[14] and benzothiazoloquinoline,[15] 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 have shown that the electrostatic binding plays an important role in the intercalation of safranine T.[13] The results of these various binding studies have been useful in designing new and promising anticancer agents for clinical use.[16–18] In addition to these, they are also known to exhibit antiallergenic[19] antifungal[20] hypocholesterolemic, hypolemic,[21] antibacterial,[22] and antiviral[23] properties. This finding has stimulated researchers to find new antitumour drugs containing planar fused ring system.

In view of the growing interest in the field of anticancer agents, we made an attempt to report an efficient method for the synthesis of new series of quinoline containing hydrazone derivatives, and DNA binding studies, indicate compounds (**2a**) and (**3a**) when it binds with base pairs of calf thymus-DNA.

EXPERIMENTAL SECTION

Materials and Methods

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 Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra was recorded on Jeol spectrometer (400 MHz), and chemical shifts (δ) given in ppm relative to the TMS in $CDCl_3$ solvent. Mass spectra were recorded by electron ionization (EI) on a finnigan MAT 312 spectrometer. C, H, and N analysis were performed at Cochin University, Sophisticated

Test & Instrumentation Center, Kochi, Kerala, India. Ammonium hexaflurophosphate (NH_4PF_6) 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.

UV-Visible Absorption Studies

The concentration of CT-DNA per nucleotide [C(p)] was measured using its known extinction coefficient at 260 nm ($6600 M^{-1}cm^{-1}$).[24] 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 μM) and maintaining the compound concentration constant (30 μM). Absorption spectra were recorded after each successive addition of DNA and equilibration (approximately 10 minutes). For both the compound (**2a**) and (**3a**) observed data were then fit into (1) in order to obtain the intrinsic binding constant, K_b.[25]

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

Where $\varepsilon_a, \varepsilon_f$, and ε_b are the apparent, free, and bound compound extinction coefficients at 422 nm, (**2a**) and 340 nm (**3a**), respectively. A plot of $[\text{DNA}]/(\varepsilon_a - \varepsilon_f)$ 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. 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. Melting studies were carried out by monitoring the absorption of CT-DNA (50 μM) at 260 nm at various temperatures in the presence (5–10 μM) 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 (σT), the temperature range between 10% and 90% noticed absorption increases occurred and calculated as reported.[26,27]

General Syntheses

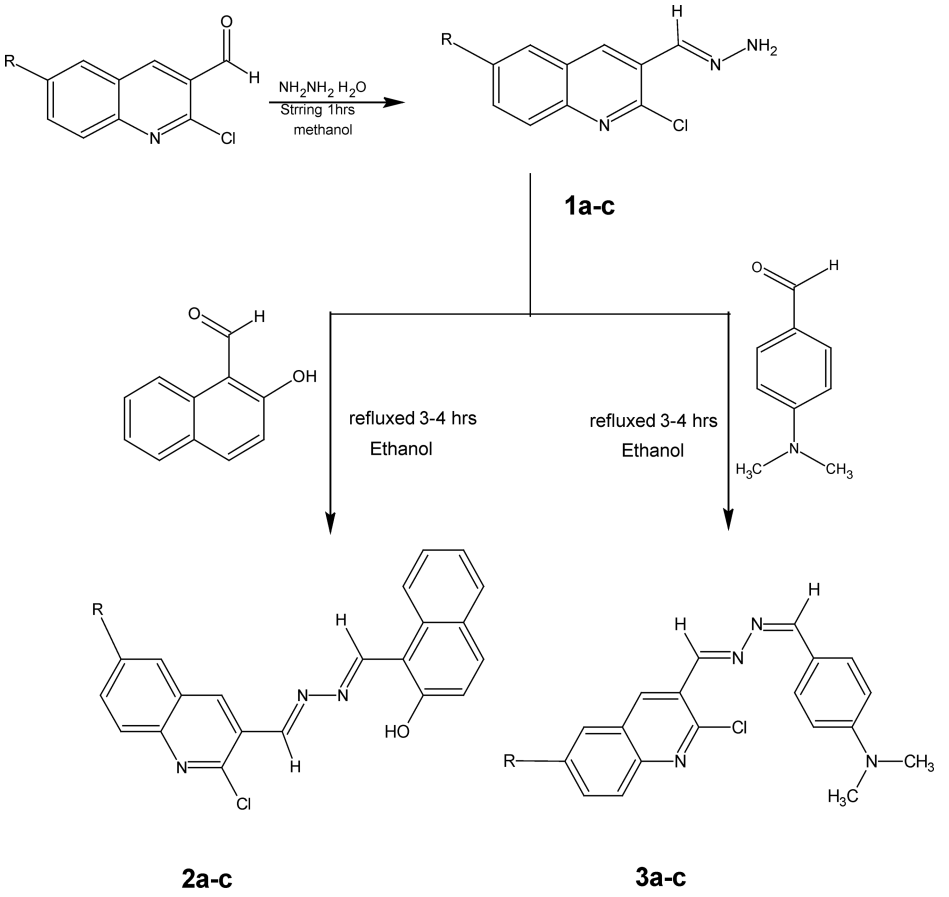
Synthesis of 2-chloroquinoline-3-carbaldehyde hydrazone (1a-c). Methanolic solution of 2-chloro-3-formylquinoline (9.55 g, 0.049 mol) was added to hydrazine hydrate 98% (2.5mL 0.05mol) dropwise at room temperature and stirred for 1 hour. The reaction mixture was poured on ice-cold water; a whitish solid was collected by filtration and dried under vacuum. The compounds (**1a–c**) were recrystallized using ethanol.

2-chloroquinoline-3-carbaldehyde [(2-hydroxy-1-naphthyl) methylene] hydrazone (**2a-c**). An ethanolic mixture of (**1a–c**) (6.15 g, 0.029 mol) and 2-hydroxy-1-napthtaldehyde (5.14 g, 0.029 mol) was refluxed for 3–4 hours. The yellow solid formed was then collected by the filtration, and recrystallized using chloroform/ethanol. The same procedure was followed for the synthesis of (**2b–c**) and (**3a–c**).

RESULTS AND DISCUSSION

The target compound (**2a–c**) and (**3a–c**) were synthesized by two pathways. In the first step the substituted 2-chloroquinoline-3-carbaldehyde reacted with hydrazine hydrate results in NH_2 functionalized compounds (**1a–c**). In the second step the resulted NH_2 functionalized compound react with different aldehydes to yield (**2a–c**) and (**3a–c**) as per the (Scheme 1). The established structure was characterized by various physico-chemical methods.

IR spectra of the compound (**1a–c**) showed the absence of aldehyde carbonyl stretching frequency, instead it gave a band at 1657–1720 cm^{-1} and two sharp bands in the region of 3233–3435 cm^{-1} due to −NH & $-NH_2$ groups. This confirms subsequent substitution by removing (CHO) present at the 3- position of the quinoline nucleus (**1a–c**). IR spectra of the compound (**2a–c**) and (**3a–c**) showed the absence of $-NH_2-$ stretching frequency at 3435 cm^{-1} and generation of new sharp bands at 1052–1023 cm^{-1} corresponding to (−N−N−) stretching. Further structure (**2a–c**) was confirmed by ^{1}H-NMR spectra shows a broad peak at 13.22–13.24 ppm due to phenolic −OH− present at second position of (**2a–c**) and resonate doublets at 9.16–9.82 ppm, corresponds to the −CH=N− adjacent to aromatic protons, and signal exhibits multiplets at 7.21–8.29 ppm for aromatic protons and a molecular ion peak at m/z = 359[$M^{\pm}$]. Similarly for compounds (**3a–c**), ^{1}H-NMR spectra shows doublets at 8.88–9.12 due to −CH=N− and multiplets at 6.77–8.65 ppm (m, Ar-H). In addition to this a sharp signal exhibits 3.50–3.52 ppm that corresponds to −N− $(CH_3)_2$ dimethylamin (s, 6H). Further structure was confirmed by its mass spectra having molecular ion peak at m/z = 336 [$M^{\pm}$]. The obtained elemental analysis values stands in good agreement with theoretical data (Table 1). Hence we synthesized six more title compounds, which exhibited similar spectral data



R = H, CH_3, OCH_3

SCHEME 1 The general synthetic procedure for 2-chloroquinoline-3-carbaldehyde hydrazone derivatives (**2a–c**) and (**3a–c**).

summarized in (Table 2). All the established derivatives have been screened for antimicrobial activity some of its derivatives exhibited significant antibacterial and antifungal activities and obtained protocols were summarized in (Table 3).

DNA Binding Studies

The DNA binding studies were characterized by absorbance maximum at 298, 342, and 422 nm for (**2a**) and 340, 403 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 DNA resulted in

TABLE 1 IR, ^{1}H-NMR, and mass characterization of the synthesized compounds

Compd	IR cm^{-1} (KBr)	^{1}H-NMR, ($CDCl_3$) δ :(ppm) (400 MHz,), Mass, m/z
2a	3233; (N—H); 1643;(C═N); 1050 (—N—N—); 3536 (O—H)	13.24 (s, 1H, —OH), 9.16 (d, 1H, —CH═N—); 9.80 (d, 1H, —CH═N—); 7.21–8.21 (m, 11H, Ar-H), m/z = 359[$M^{\pm}$]
2b	3236 (N—H); 1050 (N—N); 1653 (C═N); 3526 (O—H)	13.22 (s, 1H, —OH), 9.15 (d, 1H, —CH═N—); 9.82 (d, 1H, —CH═N—); 7.21–8.29 (m, 10H,Ar-H), 2.58 (s, 3H, OCH_3); m/z = 390 [M+H]
2c	3235 (N—H); 1052 (—N—N—); 1653(C═N); 3529 (O—H)	13.23 (s, 1H, —OH), 9.16 (d, 1H, —CH═N—); 9.82 (d, 1H, —CH═N—); 7.20–8.29 (m, 10H, Ar-H), 2.19 (s, 3H, CH_3) m/z = 373[$M^{\pm}$]
3a	3213 (N—H); 1023 (—N—N—); 1653 (C═N);	6.7–8.65 (m, 9H, Ar-H), 9.12 (d, 1H, —CH═N—); 8.88 (d, 1H, —CH═N—); 3.50 (s,6H, N—$(CH_3)_2$); m/z = 336[$M^{\pm}$]
3b	3218 (N—H); 1650 (C═N); 1023 (—N—N—);	6.72–8.65 (m, 8H, Ar-H), 2.56 (s, OCH_3); 9.14 (s, 1H, —CH═N—); 8.89 (s, 1H, —CH═N—); 3.52 (s, 6H, N—$(CH_3)_2$); m/z = 367 [$M^{\pm}$]
3c	3216 cm^{-1} (N—H); 1025 (—N—N—); 1643 (C═N);	6.71–8.65 (m, 8H, Ar-H), 3.98 (s, CH_3); 9.13 (d, 1H, —CH═N—); 8.89 (d, 1H, —CH═N—); 3.52 (s, 6H, N—$(CH_3)_2$). m/z = 351[M+H]

the decrease of absorption intensity accompanied by a shift towards higher wavelengths (~3 and 5 nm). Around 7–9% reduction (hypochromism) of absorption was observed at 422 nm, 340 nm peak maximum in the presence of an excess of calf thymus DNA. One isosbestic point was observed at 408 nm for (**2a**).[28] The lowest observation value observed in spectral changes (including red shift, hypochromicity and isosbestic points) were used to evaluate intrinsic binding constant (K_b), it observed $\mathbf{2.3\times10^3\ M^{-1}}$ for (**2a**) and $\mathbf{2.5\times10^4\ M^{-1}}$ for (**3a**) which are consistent with the intercalation of (**2a**) and (**3a**) into DNA base pairs.[29–31]

Viscosity Measurements

The binding modes of (**2a**) and (**3a**) with CT-DNA, was further confirmed by viscosity measurements. Hydrodynamic measurements that are sensitive to length change (e.g., viscosity, sedimentation) are regarded as the most critical test for binding in solution, in the absence of crystallographic structural data.[32] A classical intercalative mode causes a significant increase in viscosity of DNA solution due to an increase in separation of base pairs at intercalation sites, hence, an increase in overall DNA length. By contrast, the compounds (**2a**) and (**3a**) that bind exclusively in the DNA grooves by partial and/nonclassical intercalation, under the same conditions, typically cause negative or no change in DNA solution viscosity.[33,34] 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

TABLE 2 Physical and analytical data of synthesized quinoline derivatives

Compd	Color	Yield%	m.p. °C	Cryst solvent	Molecular Formula mol/wt	Analysis Calcd (Found) %		
						C	H	N
2a	Yellowish	73	250–252	Chloroform/Ethanol	$C_{21}H_{14}ClN_3O$ (359.80)	70.10 (70.08)	3.91 (3.90)	11.68 (11.61)
2b	Yellowish	75	154–156	Chloroform	$C_{22}H_{16}ClN_3O_2$ (389.83)	67.78 (67.72)	4.14 (4.15)	10.78 (10.72)
2c	Greenish yellow	89	130–132	Chloroform	$C_{23}H_{16}ClN_3O$ (373.83)	70.68 (70.61)	4.31 (4.26)	11.24 (11.30)
3a	Reddish Orange	93	126–128	Ethanol	$C_{19}H_{17}ClN_4$ (336.81)	67.71 (67.75)	5.09 (5.04)	16.63 (16.61)
3b	Yellowish Orange	83	168–170	Ethanol	$C_{20}H_{19}ClN_4O$ (366.84)	65.48 (65.51)	5.22 (5.16)	15.27 (15.23)
3c	Reddish Orange	90	156–158	Ethanol	$C_{20}H_{19}ClN_4$ (350.84)	68.47 (68.52)	5.46 (5.50)	15.97 (15.92)

TABLE 3 Evaluation of antimicrobial activity of quinoline derivatives

	Antibacterial activity Zone of inhibition in mm		Antifungal activity Zone of inhibition in mm	
Compd.	*P. aerugenosa*	*S. aureus*	*A. niger*	*C. albicans*
2a	17	16	13	12
2b	14	12	15	17
2c	18	—	—	13
3a	14	16	16	15
3b	—	15	17	—
3c	15	18		16
Chloramphenicol	22	24	—	—
Flucanazole	—	—	25	26

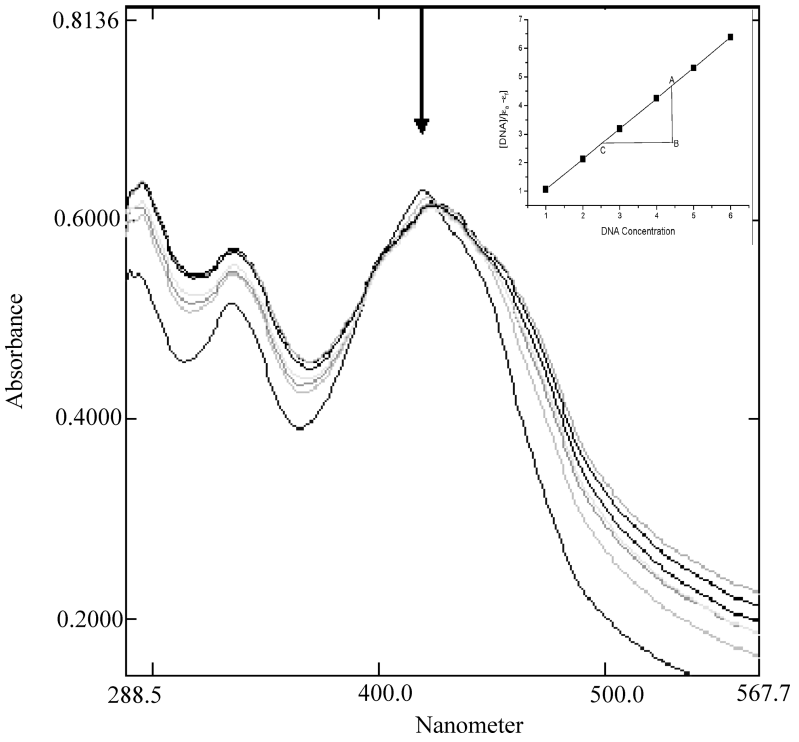


FIGURE 1 UV- absorption spectra in Tris-HCl Buffer upon addition CT- DNA (**2a**) [DNA] = 0.5 μm, = 10 μm, drug, 20 μm; 30 μm; 40 μm; 50 μm; Arrow shows the absorbance changing upon the increase of DNA concentration.

compound. 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 relative viscosity of CT-DNA with an increase in concentration of the added compounds.

Thermal Denaturing Studies

Additional information on the DNA binding properties of (**2a**) and (**3a**) into the double helix DNA was obtained from melting studies. The intercalation of small molecules into the double helix was known to increase the DNA melting temperature(T_m).[35,36] The DNA melting studies were carried out with CT-DNA in absence and presence of compound. The melting profiles (T_m) for CT-DNA in absence of compound had the value 59 ± 1°C. Under the same experimental conditions the presence of compounds increased the melting temperature (T_m) about 70°C for (**2a**) and 68°C for (**3a**) (Figure 4). Likewise the various DNA melting experiments strongly supported the stabilized double strand calf thymus DNA.[37–39]

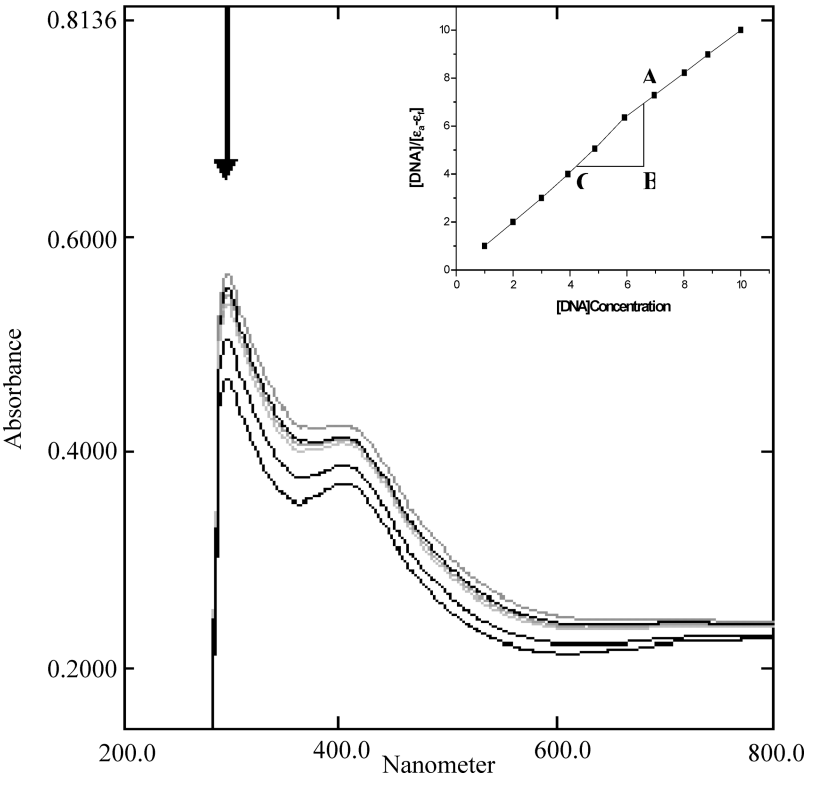


FIGURE 2 UV- absorption spectra in Tris-HCl Buffer upon addition CT- DNA (**3a**) [DNA] = 0.5 μm, = 10 μm, drug, 20 μm; 30 μm; 40 μm; 50 μm; Arrow shows the absorbance changing upon the increase of DNA concentration.

EVALUATION OF ANTIMICROBIAL ACTIVITY

The in vitro antimicrobial activity was carried out against 24-hour old cultures of two bacteria and two fungi by cup-plate method.[40] Compounds have been 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 solution 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 concentration. 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 hours for bacteria at 28°C and 48 hours for fungus at 35°C. Each experiment was repeated thrice and the average of the three independent

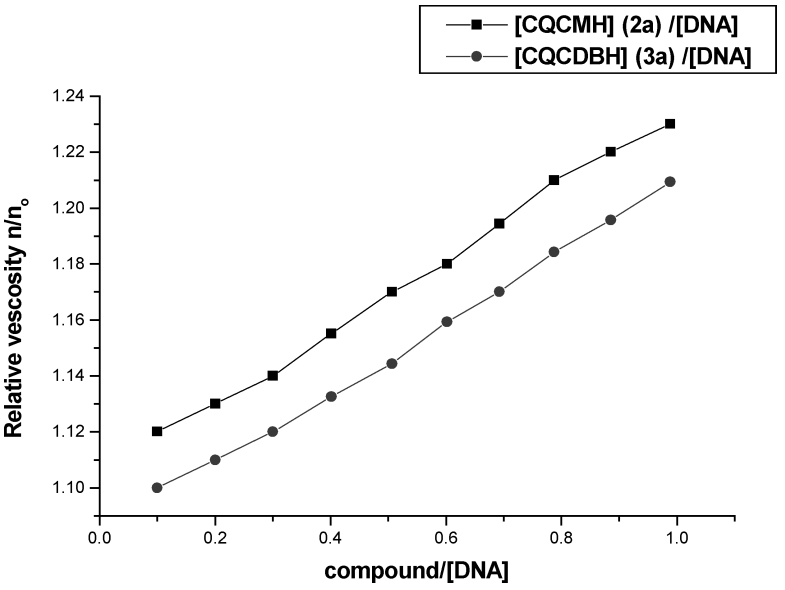


FIGURE 3 Effect of increasing amount of the (**2a**) and (**3a**) on the relative viscosities of CT-DNA, at 25°C.

determinations were recorded. The synthesized derivatives exhibit significant activity, and the resulted protocols were summarized in Table 3. The compounds **2c** and **2a** were found to be more active against *P. aerugenosa* and the compounds **2a, 2c,** and **3a** were found to exhibit more activity

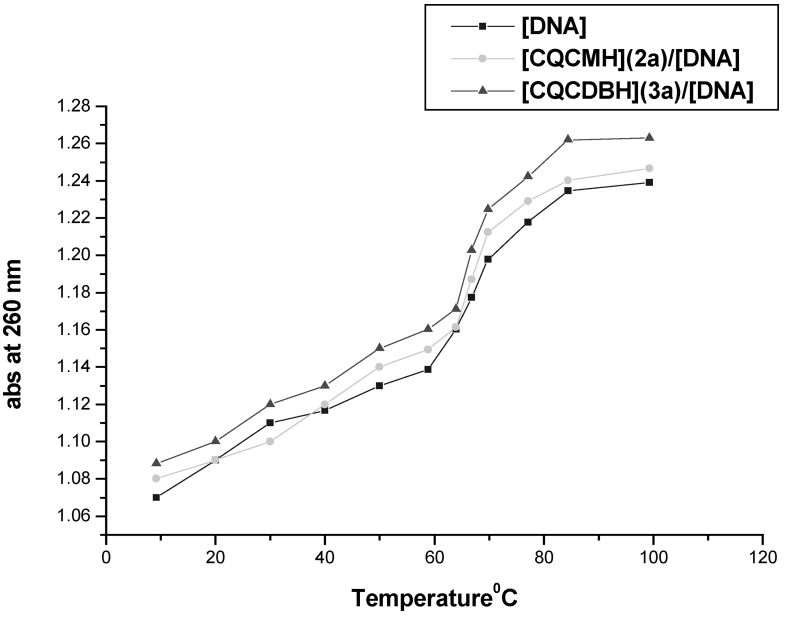


FIGURE 4 Melting cures of CT-DNA in the presence and absences of (**2a**) and (**3a**).

against *S. aureus*. The compounds **3a** and **3b** against *A. niger* and compounds **2b, 3c,** and **3a** against *C. albicans* exhibited significant antifungal activity.

Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity respectively: control (DMF) (-)-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).

CONCLUSIONS

The synthetic route adopted for synthesis of quinoline derivatives (**2a–c**) and (**3a–c**) was very simple and yielded good yield. In DNA binding studies, indicate hypochromicity and bathochromic shifts of the compounds (**2a**) and (**3a**) when it binds with base pairs of calf thymus DNA. The binding constant values of $\mathbf{2.3\times10^3\ M^{-1}}$ for (**2a**) and $\mathbf{2.5\times10^4\ M^{-1}}$ for (**3a**) suggested that the compound (**3a**) bind more avidly to CT-DNA than the (**2a**). In addition, increasing viscosity of sonicated rod-like DNA fragments and the melting temperature of DNA, in the presence of compound solutions supports the binding mode. The antimicrobial activity exhibited significant inhibitory activity.

REFERENCES

1. Ali, M.A.; Mirza, A.H.; Butcher, R.J.; Tarafder, T.B.; Ali, A.M.; Biological activity of palladium (II) and platinum (II) complexes of the acetone Schiff bases of S-methyl- and S- benzyldithiocarbazate and the X-ray crystal structure of the [Pd (asme)2] (asme = anionic form of the acetone Schiff base of S-methyldithiocarbazate complex). *J. Inorg. Biochem.* **2002**, 92, 141–148.
2. Tai, X.; Yin, X.; Chen, Q.; Tan, M. Synthesis of some transition metal complexes of a novel schiff base ligand derived from 2, 2′-bis(p-methoxyphenylamine) and salicylicaldehyde. *Molecules* **2003**, 8, 439–443.
3. Cozzi, P.G. Metal-Salen Schiff base complexes in catalysis: Practical aspects. *Chem. Soc. Rev.* **2004**, 33, 410–421.
4. Naik, A.D.; Annigeri, S.M.; Gangadharmath, U.B.; Revankar, V.K.; Mahale, V.B. Bimetallic complexes of a potentially pentadentate, acyclic, symmetrical compartmental Schiff base ligand that provides suitable topology for an exogenous bridge. *Trans. Met. Chem.* **2002**, 27, 333–336.
5. Motevalli, M.; Parkin, B.C.; Ramnauth, R.; Sullivan, A.C. The first bis (imido) transition metal Schiff-base complexes. *J. Chem. Soc. Dalton. Trans.* **2000**, 2661–2662.
6. Selvi, S.T.; Mohan, P.S. Structural elucidationof naphthacridones and 1-phenylacridones by ^{1}H-NMR, MASS, and IR spectroscopy. *Spectroscopic. Lett.* **2002**, 35, 439–445.
7. Toth, J.; Blasko, G.; Dancso, A.; Toke, L.; Nyerges, M. Synthesis of new quinoline erivatives. *Synth. Commun.* **2006**, 36, 3581–3589.
8. Raghavendra, M.; Bhojya Naik, H.S.; Sherigara, B.S. One pot synthesis of some new 2-hydrazino-[1,3,4]thiadiazepino[7,6-*b*]quinolines under microwave irradiation conditions. *Arkivoc.* **2006**, 153–159.
9. Gopal, M.; Veeranna, S.; Doddamani, L.S. Intercalation Binding of 4 butylaminopyri mido[4′,5′:4,5′ selenolo(2,3-b)quinoline to DNA: relationship with in vitro ytotoxicity. *Spectroscopic. Lett.* **2004**, 37, 347–366.

10. Loaiza-Rodriguez, P.; Quintero, A.; Rodríguez-Sotres, R.; Solano, J.D.; Lira-Rocha, A. Synthesis and evaluation of 9-anilinothiazolo[5,4-b]quinoline derivatives as potential antitumorals. *Eur. J. Med. Chem.* **2004**, 39, 5–10.
11. Rollas, S.; Guniz Kucukguzel, S. Biological activities of hydrazone derivatives. *Molecules* **2007**, 12, 1910–1939.
12. Gatto, B.; Capranico, G.; Palumbo, M. *Current. Pharacol. Design* **1999**, 5, 195–215.
13. Cao, Y.; He, W.X. Studies of interaction between safranine T and double helix DNA by spectral methods. *Spectrochimica. Acta* **1998**, 54, 883–892.
14. Singh, M.P.; Joseph, T.; Kumar, S.; Lown, J.W. *Chem. Res. Toxicol.* **1992**, 5597.
15. Baez, A.; Gonzalez, F.A.; Vazquez, D.; Waring, M. Interaction between a 3-nitrobenzothioazole[3, 2-a] quinolinium antitumor drug. *Biochem. Pharm.* **1983**, 32, 2089–2094.
16. Tilak Raj, T.; Ambekar, S.Y. Synthesis of 4-amino pyrimido [4′,5′:4,5] thieno (2,3b) quinoline-4(3H)-ones. *J. Chem. Res.* **1988**, 50, 537–551.
17. Nandeshwarappa, B.P.; Arun Kumar, D.B.; Bhojya Naik, H.S.; Mahadevan, K.M. An efficient microwave-assisted synthesis of thieno[2,3-*b*]quinolines under solvent-free conditions. *J. Sulfur. Chem.* **2005**, 26, 373–379.
18. Nandeshwarappa, B.P.; Arun Kumar, D.B.; Kumaraswamy, M.N.; Ravi Kumar, Y.S.; Bhojya Naik, H.S.; Mahadevan, K.M. A fast and large-scale synthesis of 3-formyl-2-mercaptoquinolines. *Phosphorus. Sulfu. Silicon. Relat. Elem.* **2006**, 181, 1545–1556.
19. Althuis, T.H.; Khadin S.B.; Czuba, L.J.; Moore P.F.; Hess, H.J. Structure-activity relationships in a series of novel 3,4-dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylic acid antiallergy agents. *J. Med. Chem.* **1980**, 23, 262–269.
20. Jiang, J.B.; Isaacson, D. 5H-Pyrano[2,3-d: 6,5-d′]dipyrimidine derivatives having an antibacterial, antiviral and immuno-modulating activity. U.S. Pat. No. **1987**, 4656274.
21. Khalil, M.A.; Habib, N.S.; Farghaly, A.M.; El-Sayed, O.A. Synthesis, antimicrobial, inotropic, and chronotropic activities of novel 1,2,4-triazolo[4,3-*a*]quinolines. *Archiv der Phamazie* **2006**, 324(4), 249–253.
22. Wall, M.E.; Wani, M.C.; Nicholas, A.W.; Manikumar, G.; Tele, C.; Moore, A.; Truesdale, D.; Leitner, P.; Besterman, J.M. Plant antitumor agents. 30.l8pb synthesis and structure activity of novel camptothecin analogs. *J. Med. Chem.* **1993**, 36, 2689–2700.
23. Sainsburry, M. The synthesis of 6H-pyrido[4,3-b] carbazoles. *Synthesis.* **1977**, 7, 437–448.
24. Reichmann, M.E.; Rice, S.A.; Thomas, C.A.; Doty, P. A further examination of the molecular weight and size of deoxy pentose nucleic acid. *J. Am. Chem. Soc.* **1954**, 76, 3047–3053.
25. Wolfe, A.; Shimer, G.H.; Meehan, T. Polycyclic aromatic hydrocarbons physically intercalate into duplex regions of denatured DNA. *Biochemistry* **1987**, 26, 6392–6396.
26. Raja, A.; Rajendiran, V.; Maheswari, P.U. Copper(II) complexes of tridentate pyridylmethylethylene-diamines: role of ligand steric hindrance on DNA binding and cleavage. *J. Inorg. Biochem.* **2005**, 99, 1717–1732.
27. Zhang, H.; Liu, C.S.; Bu, X.H.; Yang, M. Synthesis, crystal structure, cytotoxic activity and DNA-binding properties of the copper (II) and zinc (II) complexes with 1-[3-(2-pyridyl)pyrazol-1-ylmethyl]naphthalene. *J. Inorg. Biochem.* **2005**, 99, 1119–1125.
28. Li, G.G.; Wang, H.M.; Li, A.Z. Molecular biophysical chemistry. *Eds Beijing: Higher Education Publisher* **1992**, 276–328.
29. Fairley, T.A.; Tidwell, R.R.; Donkor, I.; Naiman, N.A.; Ohemeng, K.A.; Lombardy, R.J.; Bentley, J.A.; Cory, M.J. Structure, DNA minor groove binding, and base pair specificity of alkyl- and aryl-linked bis(amidinobenzimidazo1es) and bis(amidinoindo1es). *J. Med. Chem.* **1993**, 36, 1746–1753.
30. Gopal, M.; Shahabuddin, M.S.; Sanjeev, R.I. Interaction between an 8- methoxypyrimido[4′,5′:4,5′ thieno (2,3-*b*)quinoline-4(3H)one antitumor drug and deoxyribonucleic acid. *Indian Acad. Sci. (Chem. Sci.)* **2002**, 114, 687–696.
31. Ravikumar Naik, T.R.; Bhojya Naik, H.S.; Raghavendra, M.; Gopalkrishna Naik, S. Synthesis of thieno[2,3-*b*]benzo[1,8]naphthyridine-2-carboxylic acids under microwave irradiation and interaction with DNA studies. *Arkivoc* **2006**, 84–94.
32. Satyanarayana, S.; Dabrowiak, J.C.; Chaires, J.B. Tris(phenanthroline)ruthenium(II) enantiomer interactions with DNA: mode and specificity of binding. *Biochemistry* **1992**, 31, 9319–9324.
33. Haq Suh, I.; Lincolin, D.; Norden, B.; Chowdhry, B.Z.; Chaires, J.B. Interaction of **A-** and A-[Ru(phen)2DPPZI2 +with DNA: A calorimetric and equilibrium binding study. *J. Am. Chem. Soc.* **1995**, 117, 4788–4796.

34. Cohen, G.; Eisenberg, H. Viscosity and sedimentation study of sonicated DNA-proflavin complexes. *Biopolymers* **1969**, 8, 45–55.
35. Prabhakara, M.C.; Basavaraju, B.; Bhojya Naik, H.S. Co(III) and Ni(II) complexes containing bioactive ligands: Synthesis, DNA binding, and photocleavage studies. *Bioinorg. Chem. Appl.* **2007**, 7, 3649.
36. Prabhakara, M.C.; Bhojya Naik, H.S.; Krishna, V.; Kumaraswamy, H.M. Binding and oxidative cleavage studies of DNA by mixed ligand Co(III) and Ni(II) complexes of quinolo[3,2-b]benzodiazapine and 1,10-phenanthroline. *Nucleosides Nucleotides Nucleic Acids* **2007**, 26, 459–471.
37. Shahabuddin, S.; Gopal, M.; Sathees, M.; Raghavan, C. Intercalating and antitumour activity of 4-oxopyrimido[4',5':4,5]thieno(2,3-b)quinoline-4(3H)-one. *J. Cancer Mol.* **2007**, 3, 139–146.
38. Gopal, M.; Shenoy, S.; Doddamani, L.S. 4-Anilinopyrimido[4′,5′:4,5]selenolo(2,3-*b*)quinoline and 4-piperazino pyrimido[4′,5′:4,5]selenolo(2,3-*b*)quinoline: New DNA intercalating chromophores with antiproliferative activity. *J. Photochem. Photobiol.* **2003**, 72, 69–78.
39. Kikuta, E.; Katsube, N.; Kimura, E. Natural and synthetic double-stranded DNA binding studies of macrocyclic tetraamine zinc(II) complexes appended with polyaromatic group. *J. Bio. Inorg. Chem.* **1999**, 4, 431–440.
40. Sandane, A.R.; Rudresh, K.; Satyanarayan, N.D.; Hiremath, S.P. Pharmacological screening of 6H, 11H-indolo [3, 2-c] isoquinolin-5-ones and their derivatives. *Indian J. Pharm. Sci.* **1998**, 60, 379–383.