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Synthesis and interaction of thiazolo [2, 3-a] isoquinoline analog with DNA

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A reaction between 1-(furan-2-yl)-3,4-dihydroisoquinoline and thioglycolic acid using N,N-Dicyclohexylcarbodiimide at 0−5 °C has given 10b-(furan-2-yl)-5,6-dihydro-2H-thiazolo[2,3-a]isoquinolin-3(10bH)-one [FUIQTGA]. The interaction between FUIQTGA and DNA has been studied using UV-visible spectroscopy, fluorescence and circular dichroism techniques. Static quenching mechanism is observed from fluorescence measurements of interaction between FUIQTGA and DNA. Circular dichroism reveals the minor groove binding mode between FUIQTGA and DNA.

Keywords: N,N-Dicyclohexylcarbodiimide (DCC), Fluorescence, Static quenching, Circular dichroism

A macromolecule which contains genetic information for growth and development of living being is known as deoxyribonucleic acid (DNA)[1]. The interaction of drugs, small molecules with DNA was reported in literature.[2-3] Quinoline derivatives are known to exhibit antiviral activity[4], antimalarial activity[5], and antidengue activity[6]. Thiazolidinones were known to exhibit potential biological activities[7-14]. It was reported earlier[15] the combination of quinoline and thiazolidinone exhibit potential antidengue activity in silico. Development and manufacturing of a new pharmaceutical analog, generally involves determination of binding affinities between the molecule and DNA at many stages during drug development process[16]. Hence a detailed study of the interaction between small molecule and DNA is necessary.

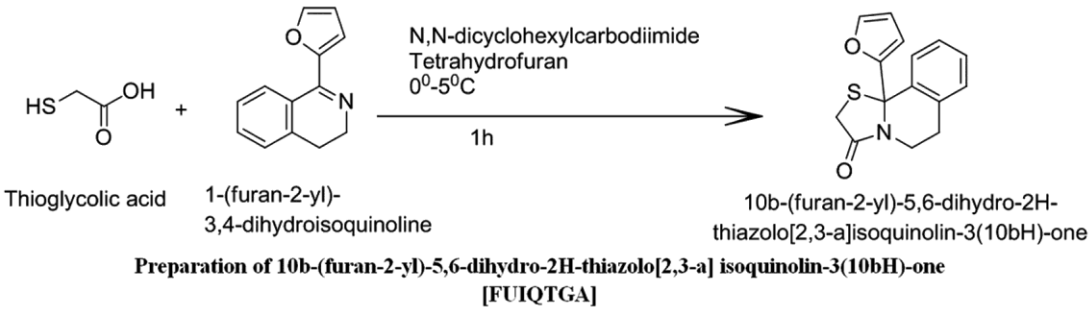
The synthesis of thiazolo [2, 3-a] isoquinolines analogs were reported in literature[17-18]. Synthesis of thiazolidinones were reported by three component condensation using N,N-Dicyclohexylcarbodiimide (DCC)[19]. However, there are no reports on the synthesis of 10b-(furan-2-yl)-5, 6-dihydro-2H-thiazolo [2,3-a]isoquinolin-3(10bH)-one [FUIQTGA] and its binding with DNA. Hence in this article, we report the synthesis of 10b-(furan-2-yl)-5, 6-dihydro-2H-thiazolo [2,3-a]isoquinolin-3(10bH)-one [FUIQTGA] and its interaction with DNA.

Materials and Methods:

Tetrahydrofuran (THF), N,N-Dicyclohexylcarbodiimide (DCC) and Thioglycolic acid was purchased from S. D. Fine Chemicals Ltd India. Hs-DNA and ethidium bromide dye (EB) was purchased from Sigma-Aldrich, India. Double distilled water for making requird solutions and analytical grade chemicals were used throughout the experiments. The detailed synthesis procedure for synthesis of FUIQTGA along with the reaction is shown in Scheme 1.

Preparation of FUIQTGA

0.001 mol 1-(furan-2-yl)-3,4-dihydroisoquinoline and 0.001 mol thioglycolic acid were stirred in THF at 0–5 °C. After 5 min 0.003 mol DCC was added to reaction mixture[14]. The reaction mixture then allowed to stir till 1 h. Progress of reaction was monitored on TLC (30:70 Chloroform:Pet Ether). After completion of reaction, the content was filtered through filter paper to remove dicyclohexylurea (DCU). Filtrate was taken in separating funnel and washed with sodium bicarbonate to remove any traces of thioglycolic acid and then extracted by using (2×10 mL) ethyl acetate. The solvent was removed by distillation under reduced pressure to get crude product 10b-(furan-2-yl)-5, 6-dihydro-2H-thiazolo[2,3-a] isoquinolin-3(10bH)-one. The crude product was purified and finally white solid product was obtained. Yield: 76%, M.P.: 94 °C. IR (cm^{-1}): 2982.01, 1682.87, 1394.87, 1257.06, 1022.04, 739.91, 671.42. ^{1}H NMR ($CDCl_3$): 7.26–7.39 (m, 1H, aromatic), 7.16–7.19 (m, 3H, aromatic), 5.89–6.24 (m, 3H aromatic), 2.78–2.86 (ddd, 1H, aliphatic *J*=24 Hz), 3.02–3.08(d, 1H, Aliphatic *J*=18 Hz), 3.67–3.72 (dd, 1H, aliphatic, *J*=15 Hz), 4.09–4.14 (dd, 1H, aliphatic *J*=15 Hz), 4.30–4.37 (ddd, 1H, aliphatic *J*=21 Hz). ^{13}C NMR ($CDCl_3$): 28.02, 34.86, 37.23, 67.26, 109.59, 110.14, 126.74, 126.91, 128.40, 129.23, 132.79, 135.85, 143.40, 155.17, 169.44. MS: M^+ at m/z: 271.02.



Scheme 1 — Preparation of 10b-(furan-2-yl)-5,6-dihydro-2H-thiazolo[2,3-a] isoquinolin-3(10bH)-one [FUIQTGA]

To study the interaction of FUIQTGA with DNA, following procedure was followed. 0.5 mol L^{-1} phosphate buffer solution was prepared and pH was adjusted to 7.0. Hs-DNA was dissolved in buffer solution and stored at 4 °C for 12 h. Its concentration was determined by UV absorption at 260 nm using an extinction coefficient[20] of 13200 M^{-1} cm^{-1}. FUIQTGA stock solution (2.0×10^{-3} mol L^{-1}) was prepared in 10% DMSO. The stock solution (2.0×10^{-3} mol L^{-1}) of EB was prepared by dissolving in phosphate buffer solution.

Characterization technique

SHIMADZU UV-2401 PC spectrophotometer was used for UV absorption spectra measurement of Hs-DNA and the interaction between DNA and FUIQTGA were recorded at 298 K. For recording the fluorescence spectra SHIMADZU RF-5301 PC spectrofluorophotometer was used. The excitation wavelength was set at 526 nm and the emission was recorded in the range of 550-800 nm. The emission was recorded in 1 cm quartz cell for different concentrations of FUIQTGA solution at temperatures of 293, 298 and 310 K. Incubation time of 20 min was kept before each fluorescence measurment. To record the circular dichroism JASCO, J-815 CD spectrometer was used. The CD spectra of interaction between Hs-DNA and FUIQTGA were recorded under N_2 atmosphere.

Results and Discussion

UV absorption spectra analysis

The absorption spectrum of Hs-DNA shows maximum absorption at 260 nm. A gradual addition of FUIQTGA solution with increasing concentration, to DNA solution results in increase in absorption intensity as shown in Fig. 1. The UV spectra indicate the hyperchromism effect which reveals change in a secondary structure of DNA. This may be due to groove binding of FUIQTGA[21].

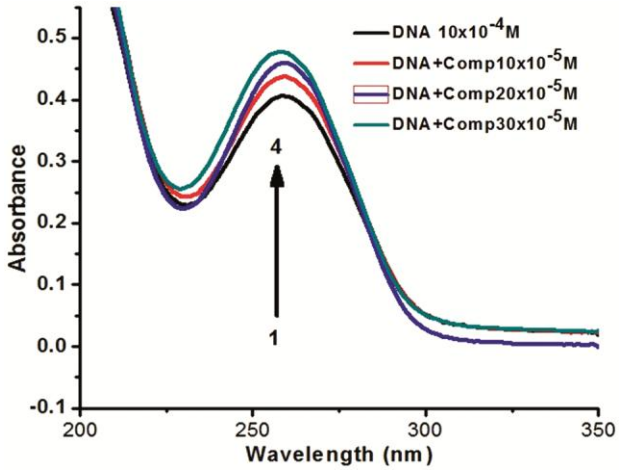


Fig. 1 — UV spectra of DNA and FUIQTGA–DNA systems.

Fluorescence quenching

Small molecular interaction with DNA can be studied easily using fluorescence technique. Individually DNA and ethidium bromide (EB) have no fluorescence. Combination of DNA with EB shows fluorescence around 600 nm. Hence ethidium bromide can be used as fluorescent probe to measure the change in fluorescence of DNA-EB-FUIQTGA. The fluorescence emission spectrum between DNA-EB and FUIQTGA is shown in Fig. 2. Gradual addition of FUIQTGA in DNA-EB solution results in decrease in fluorescent intensity of DNA-EB system. The decrease in fluorescence is due to FUIQTGA-DNA-EB complex formation.[22-23]

Binding constant for DNA-FUIQTGA-EB system was found to be 3.915×10^{3} mol L^{-1} and that of DNA-EB[24] is 5.16×10^{5} mol L^{-1}. This results reveals FUIQTGA interacts with DNA-EB complex via groove binding or electrostatic interactions[20,25].

Dynamic or static mechanisms mainly responsible for fluorescence quenching can be studied by Stern-Volmer plot. By using Stern-Volmer equation[26], at 293, 298 and 310 K, fluorescence quenching

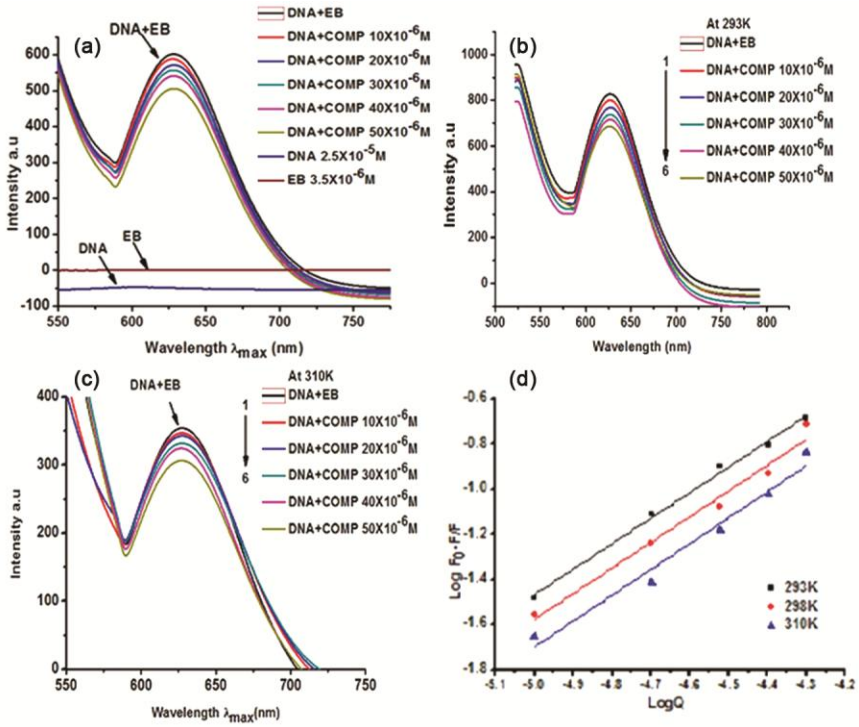


Fig. 2 — Fluorescence of FUIQTGA–DNA system at (a) 298 K, (b) 293 K and (c) 310 K with (d) showing the Stern-Volmer plots for the system at all three temperatures.

mechanism can be found out for DNA-FUIQTGA system.

$$\frac{F_0}{F} = 1 + K_{SV}[Q] = 1 + Kq.\tau_0[Q] \quad \ldots (1)$$

Where the fluorescence intensities for Hs-DNA in absence and presence of FUIQTGA can be denoted by F_0 and F. Sterm-Volmer quenching constant denoted by K_{sv}, concentration of the compound FUIQTGA denoted by [Q], K_q is the biomolecular quenching rate constant, τ_0 is the average lifetime of the molecule without the quencher which is equal[27] to 10^{-8} s.

The Stern-Volmer plot between F_0/F vs. [Q] at 293, 298 and 310 K is shown in Fig. 2d. At 293, 298 and 310] [K, the values of K_q were found. The K_q values are comparatively higher than maximum scattering collision quenching constant value reported in literature. Therefore it can be concluded that static quenching mechanism occurs between Hs DNA and FUIQTGA.[28]

Number of binding sites and binding constant of FUIQTGA-hs DNA complex

The relation between number of binding sites (n) and binding constant (K) can be given[29] by equation below:

$$log\frac{F_0 - F}{F} = logK + nlog[Q] \quad \ldots (2)$$

The plot of log [(F_0–F)/F)] vs log [Q] shown in Fig. 2. The binding constant (K) and number of binding sites (n) were calculated as shown in table. As temperature increases binding constant (K) decreases. The value of binding sites (n) is almost unity. This concludes the formation of unstable complex between Hs DNA and FUIQTGA.

Mode of binding

DNA, enzymes or proteins generally binds with small molecules by weak forces such as, van der Waals forces of interaction, hydrophobic interaction or hydrogen bonding etc.[30]

The enthalpy change (ΔH^0) and entropy change (ΔS^0) was calculated using van't Hoff equation[31] as shown below:

$$\ln K = \frac{-\Delta H^0}{RT} + \frac{\Delta S^0}{R} \quad \ldots (3)$$

Where R is the gas constant, K is the binding constant and T is the temperature.

From the values of enthalpy change and entropy change, change in Gibbs free energy can be calculated using following equation:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 = -RT\ln K \quad \ldots (4)$$

Table 1 — Synthesis and interaction of thiazolo [2, 3-a] isoquinoline analog with DNA

No.	Temp (K)	K_{sv}	K_q	n
1	293	4.257×10^3	4.257×10^{11}	0.99
2	298	3.915×10^3	3.915×10^{11}	0.97
3	310	3.260×10^3	3.260×10^{11}	0.97

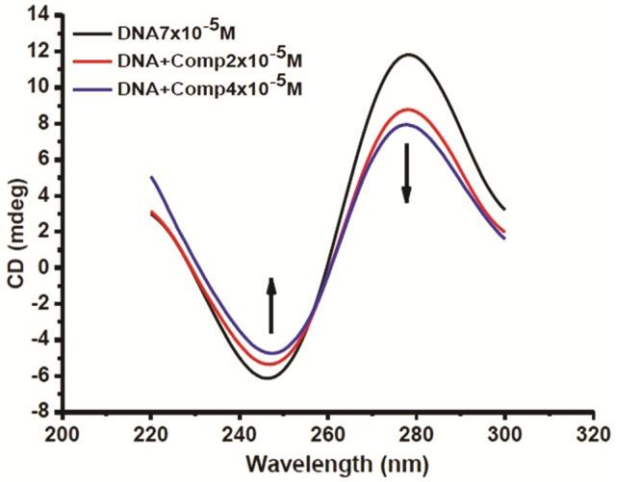


Fig. 3 — CD spectra showing the interaction between FUIQTGA and DNA at different concentrations of FUIQTGA.

From the plot of ln K vs 1/T change in entropy and enthalpy can be calculated. The values of (ΔG^0), (ΔS^0), and (ΔH^0) are summarizes in Table 1. From the values summarized in table it can be concluded that van der Waals' interactions and hydrogen bonding play the important role in the binding of FUIQTGA with DNA[31]. Negative value of change in Gibbs free energy confirms the binding between FUIQTGA and Hs DNA is spontaneous.

Circular dichroism (CD) spectroscopy

The CD spectra of free Hs-DNA and with different FUIQTGA concentrations are shown in Fig. 3. Due to base stacking free Hs DNA exhibits a positive band at 275 nm and polynucleotide helicity results in negative band around 245 nm[31]. From the CD spectra it can be concluded the minor groove binding occurs between FUIQTGA and Hs-DNA[32]

Conclusions

A new thiazolo[2,3-a] isoquinoline analog using DCC was synthesized and its interaction with DNA was studied. A static quenching mechanism was involved in binding between FUIQTGA and DNA as confirmed by the fluorescence quenching studies. Minor groove binding between the two components was revealed from absorption studies which are further confirmed from CD spectral measurements. These results can be used for a better understanding of the pharmaceutical molecules with DNA during drug development process.

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