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ORIGINAL PAPER

Study on the Synthesis and Spectra of a Novel Kind of Carbozole Benzothiazole Indole Styryl Cyanine Dye with a Carbazole Bridged Chain

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Abstract Based on the frequently-used cyanine dye probe thiazole orange (TO) and Cy3, a novel kind of styryl cyanine dye was designed and synthesized. Carbazole was inserted into the structures of two cyanine dyes, TO and Cy3, to act as a bridge to link the benzothiazole and indole. This modification resulted in a novel kind of carbozole benzothiazole indole cyanine dye with a carbazole-bridged chain. The dyes were characterized by HNMR and MS. The spectra of the novel dyes were also studied and the results showed that the fluorescence wavelength of novel carbazole benzothiazole indole cyanine dye shifted red, the Stokes shift and Fluorescence quantum yields increased and the fluorescence intensity was enhanced compared to that of TO. These results indicated that the novel dye could be used as an excellent fluorescent probe in biological labeling.

Keywords Carbazole bridge chain · Benzothiazole · Indole styryl cyanine dye · Fluorescent spectrum

Introduction

Because of the excellent properties as an electron rich system, carbazole and its derivatives are widely used in the fields of dyes, medicine[1], biology [2, 3], photoelectricity [4, 5] and more others owing to their advantages of possessing a large rigidity plan conjugated system, aromatic structures with strong fluorescence and easily modified by introduction of different kinds of functions.

Thiazole Orange (TO), an embedded cyanine dye, is comprised of a benzothiazole ring covalently linked to a quinoline via a monomethine bridge which has been widely used for labeling nucleic acids for detection of DNA and RNA in gels by flow cytometry or microscopy [6]. Although the fluorescence of free TO is extremely low in aqueous solutions, the viscosity of the dye's local environment is markedly increased when it is bound to nucleic acids, resulting in a dramatic increase in fluorescence intensity [7–10]. The large difference in fluorescence between free dye and nucleic acid-bound dye suggests an excellent way to image, label and detect cancer cells [11–19].

The advantages of the near-IR dyes for bioanalytical applications include their excellent spectral properties in the near-infrared region (700–1,000 nm) with minimal background attributed to biomolecules and high sensitivity. The indole cyanine dye Cy_3, Cy_5 and Cy_7 dyes have been used in the labeling of a variety of biological/biomedical macromolecules and nanoparticles [20–22]. And also other new IR dyes were designed and synthesized by many scientists [23–27].

The fluorescent properties of dyes mainly depend on their chemical structures, such as conjugate system, coplanarity and rigidity. in order to reduce the background disturbances of the fluorescent probe and light scattering, the fluorescent dye should be with longer conjugate system, stronger fluorescence intensity, redshift the fluorescent emission wavelength, bigger Stokes shift and fluorescence quantum yields. However, this reduces photostability [28].

Recently, we studied the synthesis and properties of the cyanine dye TO and its derivatives [29–33].

In order to make the conjugated system lengthen with larger Stokes shift and stronger fluorescence intensity, carbazole was inserted into the methylidyne structure as a bridge to obtain a novel carbazole cyanine dye with a carbazole bridged chain.

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Choosing the benzothiazole of TO and indole of Cy3, carbazole was inserted into the structures of two cyanine dyes, TO and Cy3, as a bridge to link the benzothiazole and indole in order to generate a novel kind of carbozole benzothiazole indole styryl cyanine dye with a carbazole bridged chain. With the introduction of carbazole, the stability of the novel probes increased, fluorescence wavelength shifted red, the Stokes shift and Fluorescence quantum yields increased and the fluorescence intensity was enhanced. The design process of the novel probe was shown in Fig. 1.

Materials and Methods

Materials and Instruments

Fluorescence spectra were scanned on a Cary Eclipse fluorescence spectrophotometer (Varian, USA). The UV–vis spectra were recorded on a Shimazu 2550 spectrophotometer (Japan). American Mass spectral analyses were obtained using an electrospray ionization (ESI) mass spectrometer. ^{1}HNMR spectra were recorded on a Bruker (300 MHz or 400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm) downfield from TMS (tetramethylsilane) using $CDCl_3$ or DMSO-d_6 as a solvent.

Fluorescence Quantum Yields

Fluorescence quantum yields (Φ_f) were determined by comparison with a standard solution with the following equation to calculate relative fluorescence quantum yields [34].

$$\phi_X = \phi_S \cdot \left(\frac{n_X}{n_S}\right)^2 \cdot \frac{A_S}{A_X} \cdot \frac{F_X}{F_S} \quad (1)$$

where n_X and n_S are the refractive indexes of the sample and reference, F_X and F_S are the integrated fluorescence spectra for the sample and reference respectively, and A_x and A_S are the absorbance for the sample and reference at the excitation wavelength, respectively. The standard used in this study is rhodamine B of 5 μg/mL in absolute ethanol with a known fluorescence quantum yield of 0.97 in this condition [35].

Synthesis

Synthesis of 3-Benzothiazole-6-Formyl Carbazole(4)

3-benzothiazole-6-formyl carbazole was synthesized by alkylation, formylation, ring closing reaction and formylation from carbazole. The compound 4 was synthesized according to the literature method [30].

Synthesis of N- Propionic Acid-2,3,3-Trimethyl-3H-Indole

Derivatives of N-propionic acid-2,3,3-trimethyl-3H-indole (6a–6c) were synthesized and the synthetic route was depicted in Scheme 1.

1 mol Phenylhydrazinium chloride and 150 mL glacial acetic acid were added to a flask-3-neck under a flow of nitrogen. The solution was stirred and refluxed in the dark and 44 mL 3-methyl-2-butanone was added to be refluxed for another 8 h. After the solvent was removed using a rotary evaporator, the residue was washed with saturated sodium bicarbonate solution to adjust the pH value to a final pH of about 7. The crude product was extracted with chloroform. The organic layer was then dried with anhydrous magnesium sulfate overnight. After the solvent was evaporated, the remaining solid was purified by column chromatography with eluent of dichloromethane/petroleum ether=1:3 (v/v) to afford product.

The intermediates 6a-6c were synthesized according to the procedure as follows.

2, 3, 3-trimethylindole derivative 5a-5c (0.02 mol) and 3-bromopropanoic acid (0.03 mol) were refluxed in 1,2-dichlorobenzene for 12 h. The mixture was cooled to room temperature and poured into ethyl acetate. The precipitate was collected by filtration, washed with acetone and dried under vacuum to yield compound 6.

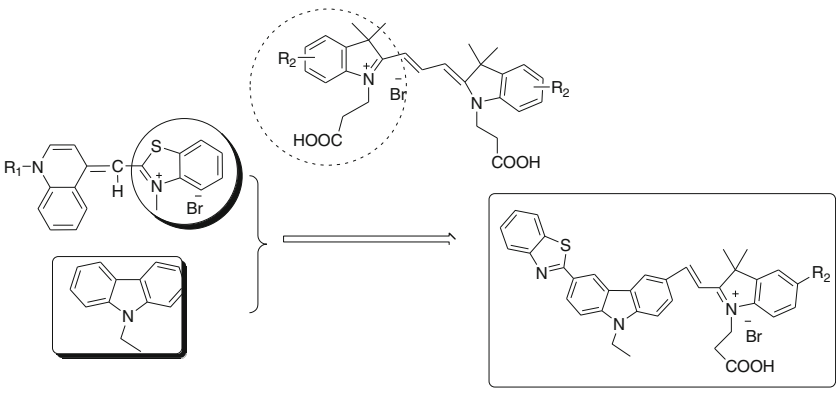
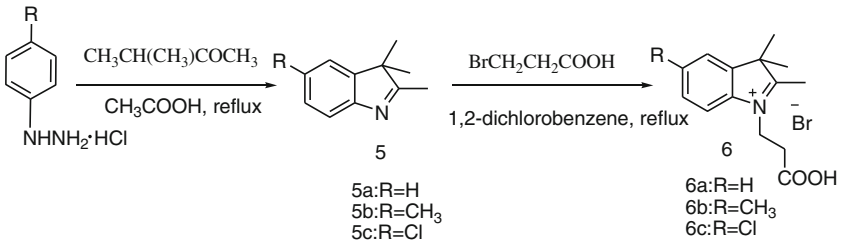


Fig. 1 Design of novel styryl cyanine dye with carbazole on the methylidyne bridge chain

Scheme 1 Synthesis of N-Hexanoic acid-2,3,3–trimethyl-3H-indole



6a (300 MHz, DMSO-d_6) δ: 1.53(s, 6H), 2.95(s, 3H), 2.95–3.00(t, J=6.9 Hz, 2H), 4.62–4.66(t, J=6.9 Hz, 2H), 7.58–7.61(m, 2H), 7.80–7.83(m, 1H), 7.95–7.98(m, 1H). ESI-MS(m/z): 232.1[M^+] , 233.2 [M^++1].

6b (300 MHz, DMSO-d_6) δ: 1.50(s, 6H), 2.50(s, 3H), 2.81 (s, 3H), 2.93–2.97(t, J=7.0 Hz, 2H), 4.58–4.63(t, J=6.9 Hz, 2H), 7.40(d, J=8.4 Hz, 1H), 7.62(s, 1H), 7.84(d, J=8.4 Hz, 1H). ESI-MS(m/z): 246.0[M^+], 247.1 [M^++1].

6c (300 MHz, DMSO-d_6) δ: 1.53(s, 6H), 2.84(s, 3H), 2.93–2.97(t, J=6.7 Hz, 2H), 4.60–4.64(t, J=6.7 Hz, 2H), 7.67–7.71(m, 1H), 8.00–8.04(m, 2H). ESI-MS(m/z): 266.0[M^+], 268.1 [M^++2].

Synthesis of Carbozole Benzothiazole Indole Cyanine Dye 7a–7c

The compounds 7a–7c were obtained by Knoecenaget condensation (Scheme 2).

The typical procedure for 7a–7c was: aldehyde 4 (0.10 g, 0.28 mmol) in 30 mL CH_3CH_2OH and salt 6 (0.13 g, 0.42 mmol) in 20 mL CH_3CH_2OH were added to a 100 mL flask, followed by catalytic piperdine (1–3 drop). The resulting mixture was allowed to be refluxed and stirred for 12 h. When it was cooled to room temperature, CH_3COOH was added and the mixture was stirred for an additional 2 h. Finally, ether was added to generate a red solid, which was then filtered, washed by ether and water to yield compound 7.

7a (300 MHz, $CDCl_3$) δ: 0.85–0.87(t, J=6.00Hz, 3H), 1.53(s, 6H), 2.67(d, 2H), 4.19–4.37(m, 4H), 7.32–7.40(m, 2H), 7.46–7.54(m, 5H), 7.89 (d, J=7.5 Hz, 2H), 8.05(t, J=6.9 Hz, 2H), 8.21(s, 1H), 8.40(s, 1H), 8.85(d,J=11.1Hz, 1H), 10.10(s, 1H). ESI-MS(m/z): 570.4[M^+], 571.4[M^++1].

7b (300 MHz, $CDCl_3$) δ: 0.85–0.88(t, J=7.20Hz, 3H),1.72(s, 6H), 2.43(s, 3H), 3.01–3.04(m, 2H), 4.31–4.34(m, 2H), 4.89–4.92(m, 2H), 7.33–7.56 (m, 6H), 7.69–7.71(m, 1H), 7.82–7.94(m, 2H), 8.02–8.20(m, 4H), 8.74(s, 1H), 8.88(s, 1H), 10.11(s, 1H). ESI-MS(m/z): 584[M^+], 585[M^++1].

7c (300 MHz, $CDCl_3$) δ: 1.43–1.48(t, J=6.9 Hz, 3H), 1.56(s, 6H), 2.86(s, 2H), 4.31–4.38(q, J=6.7 Hz, 2H), 4.44–4.54(m, 2H), 7.21(s,1H), 7.30–7.55(m, 7H), 7.74 (d, J=12.30Hz, 1H), 7.84–7.91(m, 2H),8.01(d, J=7.80Hz, 1H), 8.18(d, J=8.4 Hz, 1H), 8.68–8.70(d, J=7.20Hz, 1H), 8.86(s, 1H), 10.10(s, 1H). ESI-MS(m/z): 604.4[M^+], 605.4.4[M^++1].

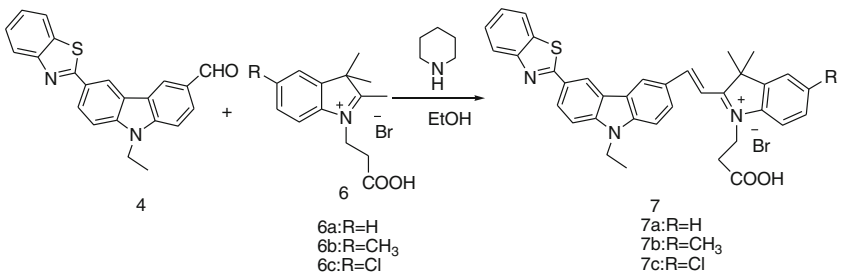
Results and Discussion

Synthesis

In order to enhance the fluorescence intensity, Stokes shift and the stability of TO, carbazole was inserted into the methylidyne structure of TO and Cy3 as a bridge to generate a novel carbozole benzothiazole indole cyanine dye with a carbazole bridged chain. First, 3-substituted of carbazole was formoxylated, reacted with aminothiopheno to afford 3-benzothiazoleN-ethyl carbazole, which was further formoxylated to prepare 3-benzothiazole-6- formoxyl-N-ethyl carbazole.

During the process of formoxylation, $POCl_3$ should be reacted completely. However, a residual amount remained that could not be reacted. The workup should be performed carefully. The reaction mixture should be poured into ice water slowly and stirred.

Scheme 2 Benzothiazole indole styryl cyanine dyes with carbazole on the methylidyne bridge chain



The formoxyl reacted with the active methylene compounds by Knoecenaget condensation to afford C=C and the title compound with the carbazole bridged chain could be obtained.

Spectral Properties of Carbozole Benzothiazole Indole Cyanine Dye with Carbazole Bridged Chain

Effect of the Substitutional Groups of the Quinoline Side Chain on the Fluorescent Properties of Carbozole Benzothiazole Indole

Fluorescent properties of carbozole benzothiazole indole with a carbazole bridged chain could be affected by substitutional groups on the quinoline side chain. In this paper, the fluorescent spectra of 7a, 7b, 7c at the same concentration (0.002 mmol/L) in CH_3OH were scaned at 490 nm and the results were shown in Fig. 2

The Φ_f of 7a-7c was 0.039, 0.041 and 0.023 respectively. The emission bands of compounds 7a, 7b and 7c were similar in shape but with a slight different maximmu emission wavelength in the range of 607–617 nm. The maximum emission wavelengths of 7c with a -Cl group on the quinoline side chain was red-shifted of 9 nm compared to that of 7b. The fluorescence intensity and Φ_f of 7b were the strongest while those of 7c were the weakest. The effect of substitutional groups on fluorescent properties was accordance with the reference [36]. Regarding the compounds with similar structure, those with electron-donating groups exhibited stronger fluorescence intensity than those containing electron-withdrawing groups. The nonbonding electron n on electron-donating groups -CH_3 was parallel to the π orbital of aromatic ring, which produces the n-π conjugation and enhances the conjugation degree, resulting in the enhancement of fluorescence intensity. There were also a nonbonding electron n on the electron-withdrawing group -Cl, but the n electron was not parallel to the π orbital of the aromatic ring and the n-π conjugation did not exit. The n-π^* transition was a kind of forbidden transition, whose molar absorptivity was low, leading to the fluorescence intensity decreased.

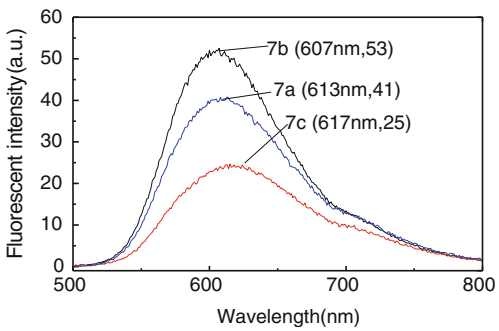


Fig. 2 Fluorescent spectra of benzothiazole indole styryl cyanine dye bearing different substitutional groups on indole. (c=7×10^{-6} mol/L)

Effect of the Substitutional Groups of the Quinoline Side Chain on the UV–vis Absorption Properties of Carbozole Benzothiazole Indole

UV–vis absorption properties of carbozole benzothiazole indole with a carbazole bridged chain could be affected by substitutional groups on the quinoline side chain. In this paper, the fluorescent spectra of 7a, 7b and 7c with the same concentration(0.0035mmoL/L) in CH_3OH were obtained and presented in Fig. 3

There were two peaks at 310 nm and 500 nm respectively in the UV–vis absorption figures. Due to various vibrational and rotational states, these molecules have broad absorption peaks [37]. Compounds 7a-7c with carbazole structure have maximum absorption at ca. 500 nm, which was in the range of TO and its deviratives [38]. The maximum absorption wavelength of 7c with the -Cl group was the longest while that of 7b with the -CH_3 group was the shortest. The order of the maximum wavelength was the same as that of maximum emission wavelengths. Additionally, the absorption intensity of 7a was the strongest and that of 7b was the weakest, and the molar absorption values of the compounds 7a–7c were 1.50×10^5 mol·L^{-1}·cm^{-1}, 1.08×10^5 mol·L^{-1}·cm^{-1} and 1.99×10^5 mol·L^{-1}·cm^{-1} respectively.

Effect of Concentration on the Fluorescence of 7a

Concentration was another factor that affected fluorescence. In this paper, the fluorescent spectra of 7a samples with the concentrations from 0.17×10^{-5} mol/L to 20×10^{-5} mol/L in CH_3OH were excitated at 490 nm and the results were shown in Fig. 4.

The fluorescent spectra were shown in Fig. 4. Peak characteristics of fluorescence and the maximum emission wavelength of samples with different concentrations revealed little difference. The florescence intensity increased with the increasing of concentration between 0.17×10^{-5} mol/L and 2.5×10^{-5} mol/L, but decreased when the concentration exceeded 2.5×10^{-5} mol/L. With the increasing of the concentration, the absorbent excited quantum number increased while the emissive quantum number was also raised, leading to the enhancement of the

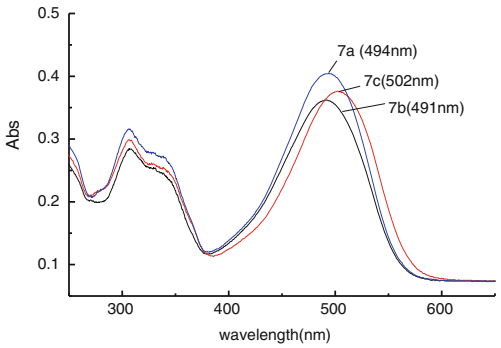


Fig. 3 UV–vis spectra of benzothiazole indole styryl cyanine dye bearing different substitutional groups on indole. (c=7×10^{-6} mol/L)

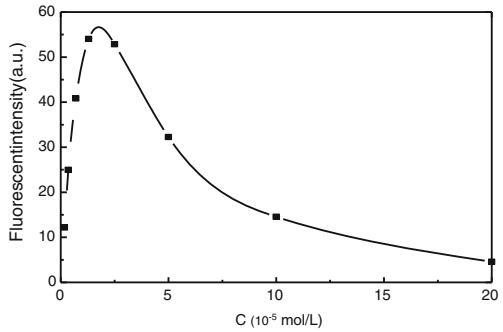


Fig. 4 Fluorescent spectra and tendency chart of 7a with different concentrations in CH_3OH

fluorescence intensity of the fluorescent compound. When the fluorescence intensity was enhanced to its maximum, it then decreased possibly due to fluorescence self-quenching.

Solvent Effect on the Fluorescent Spectra of 7a

Solution obviously affects the fluorescent properties. The fluorescent spectra of 7a in different solutions were shown in Fig. 5.

The fluorescence intensity of 7a was the strongest in $CHCl_3$ and weakest in acetone , being about 2.5 times higher in $CHCl_3$ than in acetone. In aprotic polar solvents, the maximum fluorescent emission wavelength was red-shifted with the solvent polarity increased, which is accordance with the squarylium indocyanine dyes [39].

The maximal emission wavelength in DMSO was at 622 nm, which was shifted 9 nm, 4 nm and 17 nm compared to those in CH_3OH, CH_3COCH_3 and $CHCl_3$, respectively. The reason may be that when the dye molecule is excited, the electronic excited state has a greater polarity than the ground state. The increased polarity makes the electronic excited states much more stable than the ground states [40], resulting in the red shift of wavelength.

Properties Compared with TO

The novel carbazole dyes have better fluorescent properties compared to those of TO. The fluorescent data were shown in Table 1.

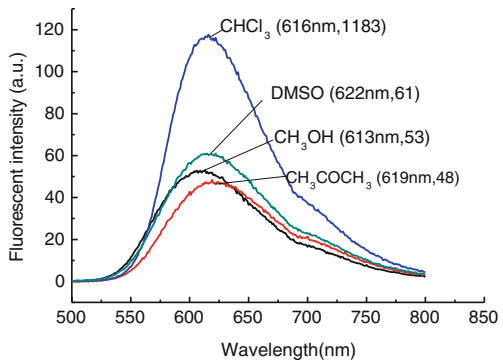


Fig. 5 Fluorescent spectra of 7a in different solvents. ($c=2.5\times10^{-5}$ mol/L)

Table 1 The fluorescent data of 7a compared with TO

Dyes	Emission wavelength (nm)	Stocks shift (nm)	Intensity (a.u.)	Fluorescence quantum yields (Φ_f)
TO	530	29 [38]	7	0.003
7a	615	119	98	0.039

The fluorescent emission wavelength of the novel compound 7a was at 615 nm, which had a shift of 85 nm [41] and fluorescence intensity was enhanced about 14 fold compared to that of TO. The Stokes shift increased about 100 nm compared to that of TO and the fluorescence quantum yields increased about 10 times and Cy3 [42].

In comparison with the structure of TO, the novel carbozole benzothiazole indole has an extended conjugated system. The π electrons are more easily excited, resulting in enhanced fluorescence intensity and red-shifted wavelength. The novel carbazole benzothiazole indole also has a large rigidity plan, which makes the reciprocity and conjugation of π electrons increase. Consequently, the wavelength of the novel carbazole carbozole benzothiazole indole was red-shifted to be near the near-infrared region, the fluorescence intensity was enhanced and the Stokes shift also increased. The novel dyes displayed a better performance than TO, which can be used as an excellent cyanine dye probe in biological labeling.

Conclusion

In summary, we showed the synthesis of a novel kind of carbozole benzothiazole indole styryl cyanine dye with a carbazole bridged chain, based on the structures and properties of the two excellent nucleic acid molecular marker cyanine dye probes, TO and Cy3. The compounds were characterized by ^{1}HNMR and MS.

The novel carbazole benzothiazole indole styryl cyanine dye displayed excellent fluorescent properties. Fluorescent results showed that the fluorescence wavelength of the novel carbazole benzothiazole indole cyanine dye was red-shifted ca. 85 nm compared to that of TO, the Stokes shift was increased ca. 100 nm, and the fluorescence intensity was enhanced 15 fold and the fluorescence quantum yields increased about 10 fold. The novel carbozole benzothiazole indole maintained the same conjugated plane structure as its TO precursor but possessed a better fluorescence performance than TO. Therefore it can be used as an excellent cyanine dye probe in biological labeling. The possible application in biology of this dye is ongoing.

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