

## Advances on Structural Modification and Applications of Heptamethine Cyanine Dyes

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### ABSTRACT

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Heptamethine cyanine dyes (HCDs) feature a large molar extinction coefficient, a high fluorescence quantum yield, and an adjustable structure, with maximum absorption and emission wavelengths located in the near-infrared region. Thanks to these excellent features, the HCDs have been widely used in biological imaging, ion detection, new energy, and many other fields. However, the unique structure of the HCDs brings some defects, such as poor hydrophilicity and low photostability. Many scholars have been striving to expand the application of the HCDs in biological analysis by improving properties like spectral properties, hydrophilicity, photostability, and fluorescence quantum yield. This paper thoroughly reviews the advances of structural modification in the sites of terminal heterocycles (indole, benzothiazole, benzoxazole and benzoselenide) and polymethine chains (straight chain or rigid bridged ring), and introduces the influences of functional materials over the features of the HCDs. Finally, the authors predicted the development trend of the HCDs.

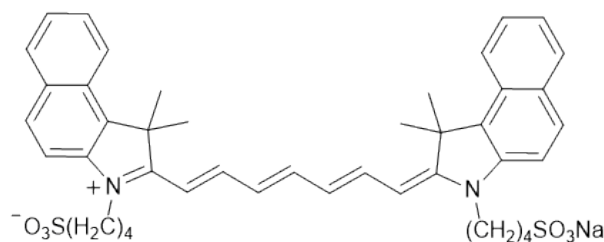
### 1. INTRODUCTION

Fluorescence detection, being a technology with contamination-free, fast responding, highly sensitive, and easily operable technology, has been widely applied in ion detection [1-3], molecular recognition [4-9], cell labeling [10-12], deoxyribonucleic acid (DNA) sequencing [13], and photodynamic therapy [14-16]. Accompanying with the development of life sciences, the fluorescence technology demonstrates incomparable advantages in the analysis and detection of ultra-trace substances in the life process.

Many fluorescent probes have been developed, including porphyrins [17, 18], coumarins [19-21], rhodamines [22, 23], boron dipyrrole methylene (BODIPY) [24-28], and cyanine dyes [29-31]. Among them, cyanine dyes connect the electron donor section (D) and electron acceptor section (A) through a polymethine chain. The absorption and emission spectra, which are affected by the length of the methine chain and the substituents, fully cover the visible light region and the near-infrared region. As a result, cyanine dyes have been widely adopted for biological analysis [32]. In particular, heptamethine cyanine dyes (HCDs), with seven carbon atoms in the polymethine chain, have a maximum emission wavelength in the biological blank window region around 800nm. In biological analysis, the HCDs can effectively avoid the interference of biological background fluorescence, and improve the detection accuracy.

In 2000, the United States Food and Drug Administration (FDA) approved an HCD named indocyanine green (ICG) (Figure 1) for clinical use, kicking off further research on the

HCDs. Nevertheless, the ICG and other HCDs face a poor photostability, because the electron donor section (D) and electron acceptor section (A) are connected via a linear methine chain. However, there are many other problems with the HCDs, including small Stokes shift, low fluorescence quantum yield, and propensity to fluorescence quenching. These problems must be solved urgently for the further application of the HCDs.



**Figure 1.** Structure of the ICG

To make up for the defects of the HCDs in actual applications, this paper probes into the molecular structure of the HCDs, and optimizes molecular properties through structural modification. The research results would provide an important guide for developing cyanine dyes with diverse functions. Structure of the HCDs

The HCDs are prepared through the condensation reaction of basic nitrogen heterocycles (indole, thiazole, oxazole, etc.), which contain active methylene groups, with dialdehydes

compounds. Two basic nitrogen heterocycles are connected by a polymethine chain containing seven carbon atoms, forming a conjugated system with a certain electron push-pull effect (Figure 2). The whole molecule is a larger conjugated system with good coplanarity. That is the reason that the HCDs boast excellent fluorescence properties.

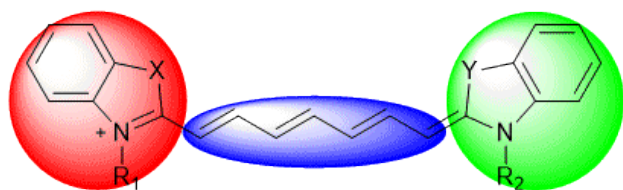


Figure 2. Structure of the HCDs

When the basic nitrogen heterocycles at the end of the molecule have the same structure ( $X=Y$ , and  $R_1=R_2$ ), the molecule is highly symmetric, and the HCDs are symmetric. When the basic nitrogen heterocycles do not have the same structure ( $X\neq Y$ , or  $R_1\neq R_2$ ), the molecule is no longer symmetric, and the HCDs are asymmetric. The electron push-pull effect and electron cloud density of the polymethine chain are greatly affected by the type of nitrogen heterocycles in the molecule, substituents on heterocyclic nitrogen, substituents on benzene rings, types of conjugated chains, and substituents on conjugated chains. They all play important roles in the photostability and spectral properties of the dyes.

## 2. MODIFICATIONS OF HCDs ON THE TERMINAL POSITIONS AND THEIR APPLICATIONS

### 2.1 Effects of the heterocycle type to the characteristics of HCDs

With the increasing basicity of the terminal nitrogen heterocycle, the absorption spectra of the HCDs will be red-shifted. For instance, Yao et al. [33] developed the HCDs whose terminal heterocycles are oxazole, indole, thiazole, and selenazole, respectively (Figure 3). In ethanol solution, the maximum absorption wavelengths ( $\lambda_{ab}$ ) of the four types of HCDs are 734.4 nm, 789.8 nm, 803.6 nm and 809.4 nm ( $R=H$ ), respectively. In addition, the introduction of a heteroatom at the X position causes the two methyl groups on the original carbon atoms to be replaced, thereby reducing intermolecular hydrogen bonds. Then, the aggregation of dye molecules in protic solvents is weakened, which reduces the fluorescence quenching caused by molecular aggregation, and increases the fluorescence quantum yield of the molecule.

Nevertheless, the introduction of the heteroatom X in the molecular terminal heterocycle dampens the photostability of the dye. The greater the radius of the substituted heteroatom X, the worse the photostability of the dye. Through comparison, Yao et al. [33], Liu and Bao [34] agreed that, the best photostability is achieved with indole as the terminal nitrogen heterocycle ( $X=C$ ) when the HCDs have the same polymethine chain structure. After the introduction of the substituted heteroatom into the heterocycle, the dyes can be ranked in descending order of photostability as oxazocyanines ( $X=O$ ) > thiazocyanines ( $X=S$ ) > selenazocyanines ( $X=Se$ ). As a result, heptamethine

indocyanine dyes are frequently studied in the follow-up research. There are occasional reports on heptamethine oxazocyanines and heptamethine thiazocyanines. For example, Vus et al. [35] and Zhytniakivska et al. [36] applied heptamethine thiazocyanines for the diagnosis of Alzheimer's disease and other illnesses. However, selenazole HCDs are rarely reported.

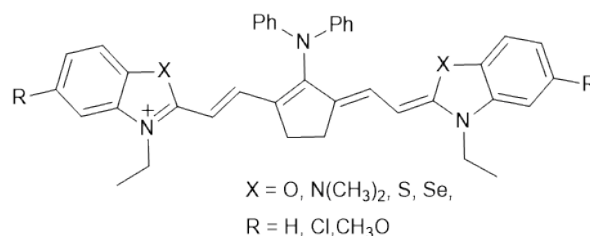


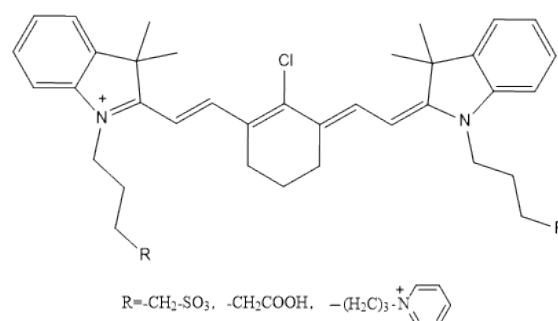
Figure 3. HCDs with different terminal heterocycles

### 2.2 Effects of the substituent on the N of heterocycle to the characteristics of HCDs

The N of the heterocyclic ring is generally connected to the corresponding substituent via a methylene group. Since the substituent is not directly connected to the heptamethine conjugated chain of the molecule, the substituent at this position does not significantly affect the spectral properties of the molecule. The limited effect is primarily the impacts on molecular stability and aggregation, which arise from electronic effect and spatial effect.

The introduction of substituents at this position can expand the application field of the molecule. For example, the introduction of hydrophilic substituents like  $-\text{COOH}$  [37], and  $-\text{SO}_3\text{H}$  [38, 39] on the N of heterocycle (Figure 4) can greatly enhance the water solubility and fluorescence quantum yield of the dye [40], facilitating the application of the HCDs in biological analysis.

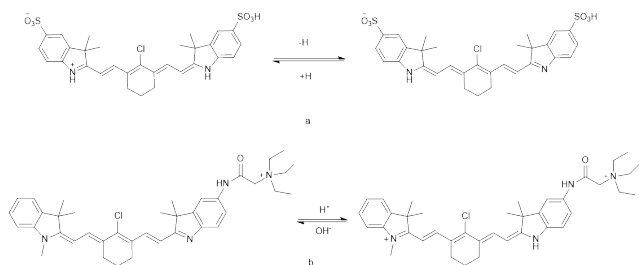
Ryu's research team [41] introduced a pyridyl group on the N of heterocycle (Figure 4), which enhances the water solubility of the molecule, improves the generation efficiency of singlet oxygen  $\text{O}^{\cdot-}$ , and elevates the efficiency of dyes in photodynamic therapy. Chen et al. [42] found that the dye has a good photostability, when the substituent on N of heterocycle is a sterically hindered benzyl group. Chen et al. [43] introduced six substituents (carboxypentyl, benzyl, 4-methylbenzyl, 4-fluorobenzyl, 4-carboxybenzyl, and 4-nitrobenzyl) with different electron donating abilities to the N of heterocycle of heptamethine indocyanine, and discovered that: their  $\lambda_{ab}$  values were all around 770 nm, and the photostability of the dye increased with the electron donating ability of the N substituent on the indole ring.



**Figure 4.** Substituents on the N of terminal heterocycle

Liu et al. [44] and Shi et al. [45] introduced glycine or carboxyl group on the N of heterocycle of heptamethine indocyanine, respectively, and managed to boost the cell permeability, strengthen the binding ability to cancer cells, and lower the biological toxicity of the dye. Khairutdinov and Serpone [46] demonstrated that, with the growing length of the substituted alkyl chain on the N of heterocycle of the HCDs, the molecular aggregation weakened, and the fluorescence quantum yield gradually increased. Yadav et al. [47] also found that, the molecule had the best cancer cell penetration ability, when there were six carbon atoms in the alkyl chain of the substituent on the N of heterocycle of heptamethine indocyanine.

Achilefu's research team [48] developed an unsubstituted pH probe at the N of the indole ring, drawing on the effect of the protonation of the N atom of the indole ring on the push-pull of the polymethine chain (Figure 5a). The probe has no fluorescence in neutral and alkaline environments, but emits a strong fluorescence after contacting  $H^+$  in the weakly acidic environment of pH 4.00-6.00. After binding to cRGD, the probe can be used for early diagnosis of various cancers (e.g., breast cancer). Following this principle, Hou et al. [49] designed a water-soluble fluorescence-enhanced probe containing quaternary ammonium salts (Figure 5b) for pH detection in a weakly acidic environment. To generate molecular fluorescence, the probe uses  $H^+$  in the environment to positively charge the N of heterocycle of the dye, and enhance the push-pull of the polymethine chain. This generation method has been widely adopted to develop weakly acidic fluorescent probes.



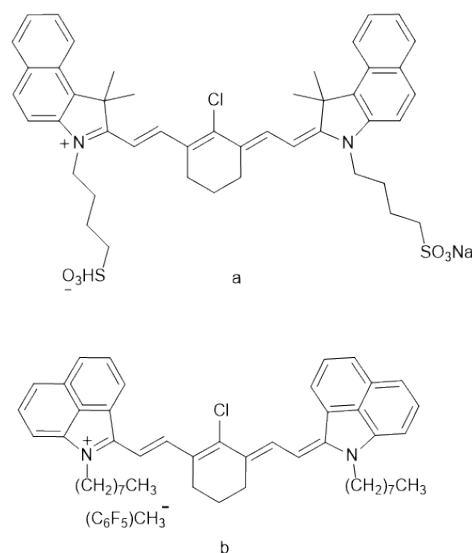
**Figure 5.** The HCDs with different substituents on the N of heterocycle and their applications as pH probes

### 2.3 Effects of the substituents on the terminal benzene to the characteristics of HCDs

The substituents on the benzene ring, which are not directly connected to the polymethine chain of the molecule, do not significantly affect the spectral properties of the molecule, and are mostly adopted to expand the application field of cyanine dyes. For instance, Hubner et al. [50] introduced a carboxyl group ( $-COOH$ ) at the 5 and 5' positions of the heptamethine cyanine indole ring, respectively, and realized the quantitative fluorescent labeling of dye molecules in the field of biological analysis through the amide condensation of the carboxyl group and the amine group. Zheng et al. research team [51] increased the water solubility of the dye by introducing sulfonic acid groups ( $-SO_3H$ ) at the 5 and 5' positions of heptamethine

indocyanine, which greatly simplified the operation of the HCDs in biological analysis.

The substituents on the benzene ring do not directly participate in the conjugation of the molecule. But they can cause the red shift of the absorption spectrum of the dye, by regulating the degree of conjugation of the polymethine chain through lone pair electrons or  $\sigma$  electrons. The electron withdrawing group can decrease the electron cloud density of the conjugated system, thus enhancing the photostability of the dye. By contrast, the electron donating group can increase electron cloud density of the conjugated system, thus reducing the photostability of the dye. For example, after  $-Cl$  and  $-OCH_3$  were introduced on the terminal benzene ring of the HCDs (Figure 3), the  $\lambda_{ab}$  values in ethanol solvent was red-shifted from 803.6 nm to 810 nm or 823 nm, respectively. The introduction of  $-Cl$  enhanced the photostability of the dye, while the introduction of  $-OCH_3$  reduced the photostability of the dye [33]. Wang et al. [40] further investigated the effect of substituents on the benzene ring on the fluorescence properties of the dye, and discovered that the introduction of  $-Cl$  on the benzene ring could reduce the fluorescence quantum yield of the dye from 6.5 to 1.2, owing to the heavy atom effect. Since the electron-withdrawing effect of the benzene ring can effectively improve the photostability of the dye, the HCDs (Figure 6) with a dibenzindole structure at the terminal position have also been well developed [52-54].



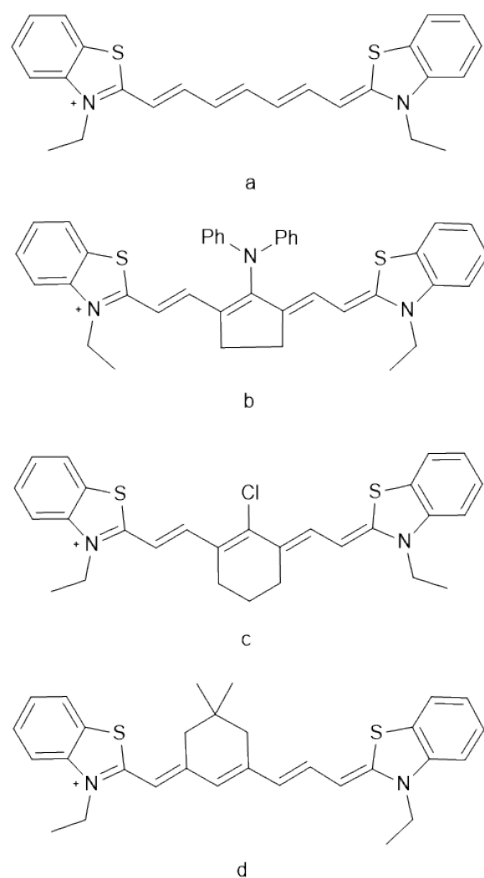
**Figure 6.** Structure of the HCDs with a dibenzindole structure at the terminal positions

### 3. MODIFICATIONS OF HCDs ON THE POLYMETHINE LINE AND THEIR APPLICATIONS

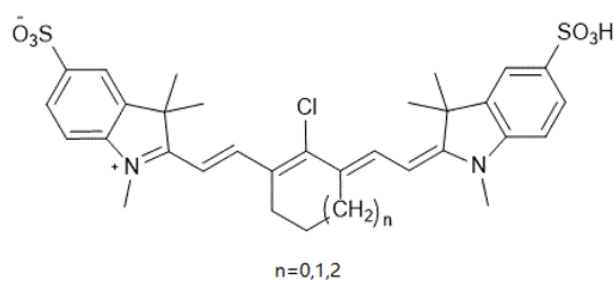
The poor photostability of the HCDs is attributable to the fact that the long polymethine chains loss much energy in chemical bond rotation, and are easily attacked by oxygen or reactive radicals. The photostability is mostly improved through the direct modification of the polymethine chains of HCDs. The specific measures are changing the electron cloud density, increasing molecular rigidity, and adjusting steric hindrance. These structural modifications have a great impact on Stokes shift, fluorescence quantum yield, and application fields.

### 3.1 Effects of rigid bridge ring to the characteristics of HCDs

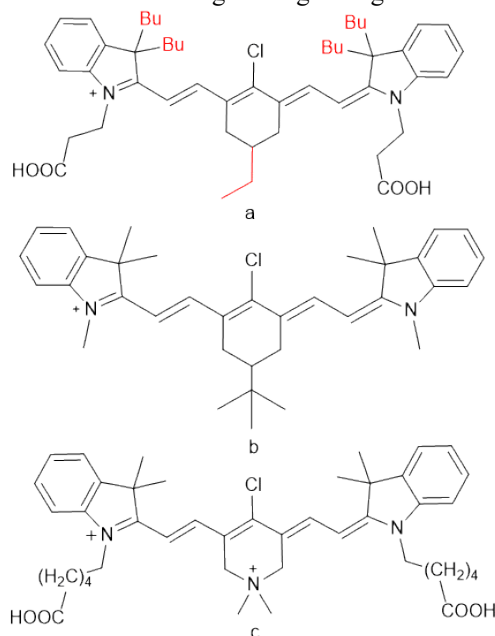
The introduction of a rigid bridged ring at the mid-position of the HCD molecule can enhance the coplanarity of the molecule, reduce the energy loss due to chemical bond rotation, lower the energy required for electronic transitions, and red-shift the molecular absorption spectrum. In addition, the molecular photostability can be improved at the expense of the fluorescence quantum yield of the dye molecule. When the mid-bridged ring is a five-membered ring, the red-shift of the absorption spectrum and the photostability of the molecule are better than those of the six-membered ring, thanks to the limited loss of energy. Yao et al. [55] prepared the HCDs with different polymethine chains (Figure 7), and measured the  $\lambda_{ab}$  values of A, B, C, and D in ethanol as 760 nm, 803.6 nm, 799.8 nm (methanol) and 763.4 nm (methanol), respectively. Further investigation shows that C is more stable than A, while D is slightly less stable than A. Li et al. [56] also found through experiments that the photostability of the dye was greatly improved after the introduction of a chlorine-containing rigid bridged ring on the polymethine chain of the heptamethine indocyanine molecule.



**Figure 7.** The HCDs with different polymethine chains



**Figure 8.** The HCDs with different number of carbon atoms on the rigid bridged ring



**Figure 9.** The HCDs with substituents on the para-methylene group

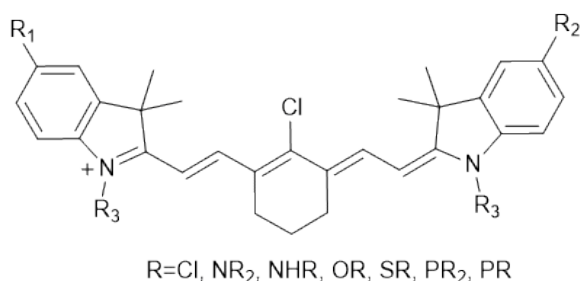
Henry's research team [57] synthesized rigid bridged cyclic cyanine dyes with different number of carbon atoms in the polymethine chain (Figure 8). It is also found that, when the rigid bridged ring is a five-membered ring, the dye absorption wavelength is the largest (803 nm), the molar absorptivity is the greatest, and the photostability is the best; when the rigid bridged ring is a six-membered ring or a seven-membered ring, the maximum absorption wavelengths of the dye are basically the same ( $\lambda_{ab}$  = 780 nm or 781 nm). Moreover, when the bridged ring is a seven-membered ring, the dye has no fluorescence, the molar absorption coefficient is the lowest, and the photostability is the worst.

Apart from the rigid bridged ring, the introduction of substituents on the para-methylene group of the bridged ring will also affect the properties of the dye. If an alkyl chain is introduced at this position, the aggregation degree of the dye in solution will be reduced due to the large steric hindrance, yet enhanced in aqueous solution under the action of hydrogen bonding. Otsuka et al. [58] discovered that the aggregation degree of dye molecules can be effectively suppressed by introducing alkyl chains on the heterocyclic and bridged rings of the HCDs (Figure 9a). Henry's research team [57] noticed that the introduction of a tert-butyl group on the para-methylene group of the six-membered ring would increase the dye aggregation degree in the phosphate-buffered saline (PBS) buffer solution, and lower the

fluorescence quantum yield. Thavornpradit [59] used dimethylamine to replace the para-methylene group on the six-membered ring (Figure 9c), which increases the molar absorption and fluorescence quantum yield of the dye by 1.7 and 3 times, respectively, compared with ICG. The replacement also enhances the photostability of dye molecules and their solubility in aqueous solutions, reducing their biological toxicity.

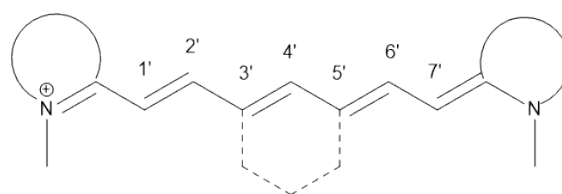
### 3.2 Effects of meso-substituents to the characteristics of HCDs

After the rigid bridged ring was introduced into the HCD molecule, a new functional group was added to allow further structural modifications. For example, chlorine or bromine can be incorporated to the middle position of the molecule, while the six-membered rigid bridged ring is introduced. The new element is easily substituted by nucleophilic reagents like amine, thiol, phenol, phosphide, and carbonyl, to form corresponding derivatives [60, 61] (Figure 10). The C-C bonds (hydrocarbyl or phenyl) can also be introduced into the middle position of polymethine chains by palladium-catalyzed Suzuki coupling or cross-coupling reaction [62-66]. The introduction of new functional groups on the substituents, coupled with the further derivatization of functional groups, greatly expands the application field of the dye.



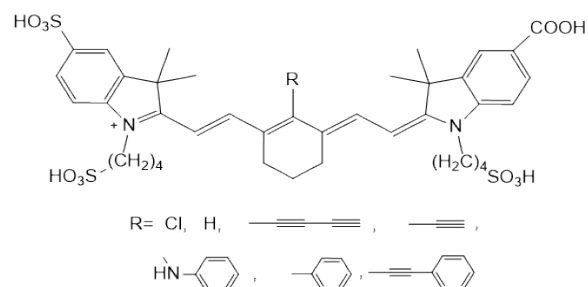
**Figure 10.** The HCDs with different substituents at the middle position

The median substituent of the polymethine chain, which is directly connected with the conjugated system of the dye, directly affects the spectral properties, photostability, and fluorescence quantum yield of the dye. Stackova et al. [67] examined the influence of substituents on the methine chain over dye properties. When the substituents are at the middle position C4' (Figure 11), the electron-withdrawing and electron-donating groups cause the absorption spectrum of the dye molecule to redshift and blueshift, respectively. As the electron-withdrawing ability of the substituents weakens, the red-shift of the dye absorption spectrum becomes larger. As the electron-donating ability of the substituents enhances, the blue-shift of the dye absorption spectrum becomes larger. Lei et al. [68] also believed that the 1'-position substitution with either electron drawing group or electron donating group can cause the red shift of the absorption peak of dye molecules, without exerting much effect on the spectrum.

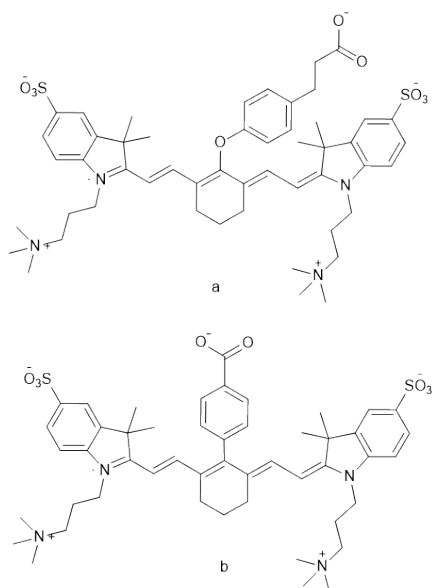


**Figure 11.** Number of carbon atoms in the polymethine chain of the HCDs

König and Krämer [65] introduced a C-C bond to the heptamethine indocyanine molecule through a coupling reaction, and obtained multiple fluorescent probes for HeLa cell labeling. The test results show that, compared with the case of no substituent at the middle position (R=H), the absorption spectrum of the molecule is red-shifted when the middle position substituent is an electron withdrawing group like alkynyl, chlorine, and phenyl; that spectrum is blue-shifted when the middle position substituent is an anilino group. Among all the middle position substitution derivatives, the molecule whose middle position is substituted with phenyl boasts the highest fluorescence quantum yield and the best photostability. But the values are lower than those of the molecule with no substituent at the middle position (R=H) (Figure 12). Su et al. [69] compared the effects of middle position phenoxy (Figure 13a) and phenyl (Figure 13b) substitutions on molecular properties, revealing that molecule 13b has better photostability and fluorescence quantum yield than molecule 13a, due to its relatively good coplanarity. The fluorescence quantum yield of molecule 13b is about 3.4 times higher than that of ICG.

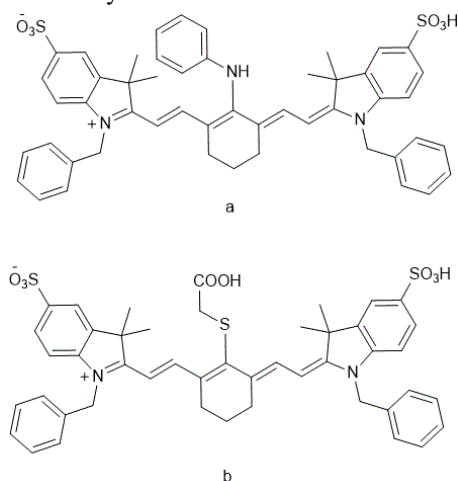


**Figure 12.** The HCDs with different substituents at the middle position



**Figure 13.** The HCDs with phenyl and phenoxy substituents at the middle position

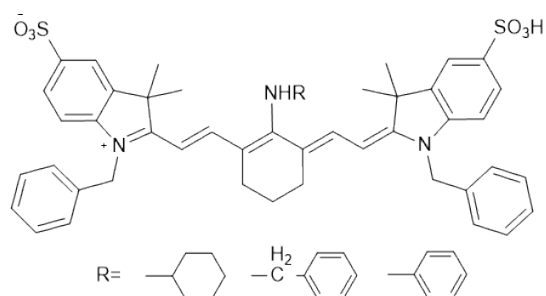
Peng et al. [70] and Song et al. [71] research team prepared heptamethine indocyanine derivatives substituted with sulfur and secondary amine at the middle position (Figure 14), and made the following conclusions: The sulfur substituent at the middle position causes photo-induced electron transfer (PET) of heptamethine indocyanine. It not only red-shifts the  $\lambda_{ab}$  and  $\lambda_{em}$  of the dye, but also greatly reduces the fluorescence quantum yield of the dye. The middle position substitution of secondary amine causes intramolecular electron transfer (ICT) of heptamethine indocyanine. It not only largely blue-shifts the  $\lambda_{ab}$  and  $\lambda_{em}$  of the dye, but also boosts the Stokes shift of the molecule (greater than 140 nm), compared with the parent molecule. These findings lay the basis for developing bioluminescence probes with low self-absorption and high sensitivity.



**Figure 14.** The HCDs with sulfur or secondary amine at the middle position

Further research found that the conjugation effect between the middle position substituent and the molecular polymethine chain also affects the molecular properties. The stronger the conjugation effect, the greater the red-shift of the absorption spectrum. For example, Song et al. [71]

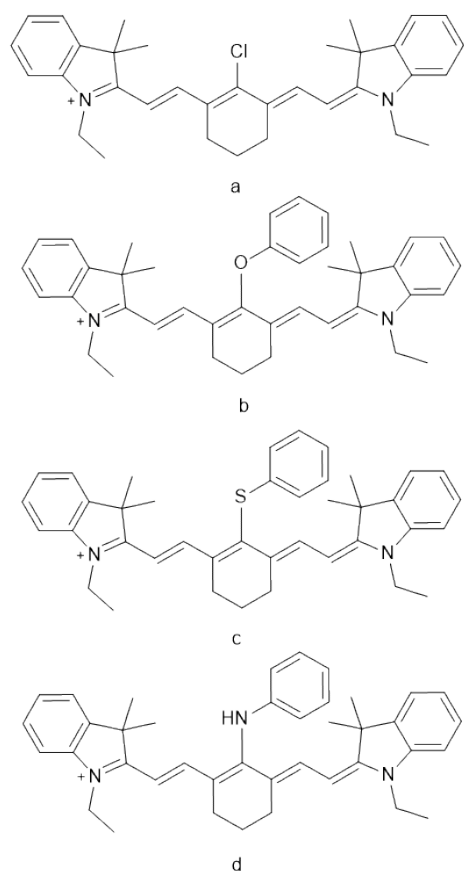
discovered that, when the middle position substituents of the heptamethine indocyanine molecule were cyclohexylamino, benzylamino and aniline (Figure 15), the  $\lambda_{ab}$  values in aqueous solution were 602 nm, 617 nm, and 713nm, respectively.



**Figure 15.** The HCDs with different conjugating substituents at the middle position

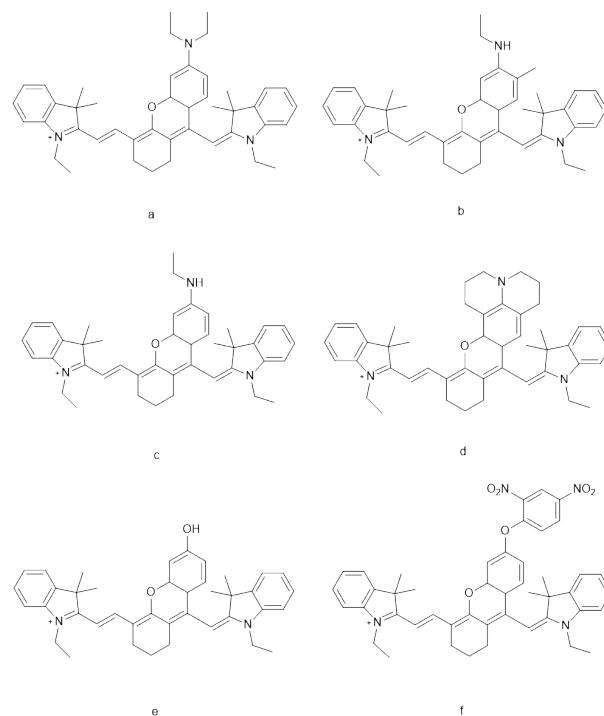
Nano's research team developed a series of fluorescent probes for middle position-substituted heptamethine indocyanines, and analyzed their properties. The experimental results show that, when the middle position substituent is phenoxy (Figure 16b), the photostability and fluorescence quantum yield of the heptamethine indocyanine molecule are greater than those of the parent molecule; when the middle position substituent is thiophenyl (Figure 16c) or anilino (Figure 16d), the photostability and fluorescence quantum yield of the heptamethine indocyanine molecule are smaller than those of the parent molecule. Drawing on the influence of the middle position substituents, the research team developed the fluorescence probes for detecting  $H^+$  in the environment (Figure 17).

Levitz et al. [57] synthesized heptamethine indocyanines with bromine, chlorine, methyl, and phenyl as the middle position substituents, and measured the maximum absorption wavelengths  $\lambda_{ab}$ : 781nm, 780nm, 768nm, and 759nm. Pascal et al. [72] combined the time-dependent density functional theory (TD-DFT) with experiments to analyze the influence of the substituents on the six-membered bridged ring on the absorption spectra of dyes, and made the following discovery: With the growing electron-donating ability of the substituents, the charge distribution on the polymethine chain gradually moves from uniform state to centralized state. By the  $\lambda_{ab}$  value, the HCDs with different middle position substituents can be ranked as  $C-S > C-Cl > C-OR > C-H > C-NHPh > C-NR_2 > C-NHR > C=CR_2 > C=O > C=NPh > C=NR$  (Figure 18).



**Figure 16.** The HCDs with different substituents at the middle position

Compared with that of the parent molecule, the absorption spectrum of this molecule has a blue shift of about 60-80 nm, with a small shoulder peak at 500-600 nm, and a significant improvement of photostability and fluorescence quantum yield. In addition, Chen et al. [73] derived a H<sub>2</sub>S fluorescence-enhanced fluorescent probe from 19e (19f).



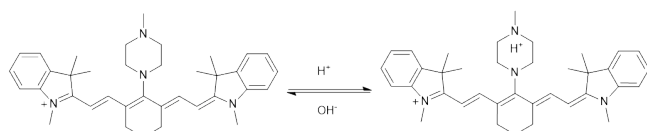
**Figure 19.** The HCDs with the structure "xanthene-cyanine"

Since the middle position substitution has a major impact on HCD molecules, and plays an important role in expanding molecular applications, the derivatization of dye molecules by middle position substitution can realize the fluorescence detection for small molecules and ions like hypochlorous acid, palladium, and promote the application of the HCDs in biological analysis. Liu et al. research team [77] introduced an acyl group to the middle carbonyl of the polymethine chain, and managed to determine the mitophagy in biological cells. Zhao et al. [78] introduced tetraphenylene at the middle position of heptamethine indocyanine, which successfully transforms heptamethine molecules as photothermal conversion materials in cancer treatment, for the introduction effectively avoids the aggregated fluorescence quenching of dye molecules, and improves the photothermal conversion efficiency.

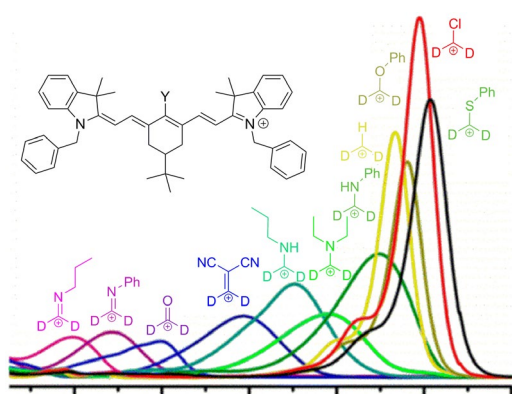
#### 4. CONJUNCTION OF THE HCDS WITH FUNCTIONAL MATERIALS

The application of the HCDs is limited by their water solubility, photostability, and fluorescence quantum yield. To expand the application scope, it is necessary to improve the aggregation degree, fluorescence properties and photostability by combining the HCDs with functional materials (such as metal oxide sols, polymers, surfactants, etc.).

Zheng et al. research team [79] combined cyanine dyes with metal oxides (TiO<sub>2</sub>, and SiO<sub>2</sub>) or cetrimonium bromide



**Figure 17.** The HCDs as pH sensor



**Figure 18.** Relationship of middle position substituents with absorption spectra of the HCDs [72]

The middle position substituents not only directly affect the properties of HCD molecules, but also regulate their photostability and fluorescence properties by combining with the conjugated chains. Chen et al. [73] used phenolic hydroxyl to replace the middle position chlorine of heptamethine indocyanine, and obtained several fluorescent probes of the structure "xanthene-cyanine" (Figure 19a-e).

(CTAB), and observed a large increase in the photostability of the dyes, as well as an increment of the pH response range, compared with the pure dye solutions. Their research sheds new light on how to expand the use scope and application of the dyes.

The HCDs are also complexed with polyethylene glycol (PEG) to increase their water solubility, and then applied to the photodynamic therapy of cancer cells [80, 81]. Pais-Silva et al. [82] loaded IR780 into PEG-succinate vitamin E micelles, which increases its solubility in water by nearly 10 times, reduces its aggregation in aqueous solution, and greatly lowers the clinical dose for cancer cell removal. Zhang et al. [83] and St-Lorenz et al. [84] loaded the HCDs onto nanoparticles like SiO<sub>2</sub>, and PEG-polycaprolactone (PCL), and observed marked improvements to dispersibility, photostability and photothermal conversion efficiency. The combined materials can be used clinically as photothermal conversion materials in cancer therapy.

## 5. CONCLUSIONS

Since the approval of the ICG by the FDA, more and more researchers turned their attention to the application of the HCDs in biological analysis. There is ample room to improve the HCD performance, owing to their defects in water solubility, photostability, and fluorescence quantum yield, as well as the many modifiable sites. In the field of biological analysis, several HCDs with excellent performance have been developed for biological imaging, photothermal conversion, and photoacoustic conversion, thanks to the HCDs' low biological toxicity, lack of obvious side effects, and good targeting and clearing ability of cancer cells. In addition, the HCDs have been applied to photoelectric conversion tasks (e.g., Dye-Sensitized Solar Cells), because their wavelength is adjustable.

The further research on the structural modification of the HCDs will surely make up for their structural defects, and the modified HCDs will achieve better application results in biological analysis, photoelectric conversion, and other fields.

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