Coumarin-derivatives for detection of biological important species

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Abstract
Coumarin has been extensively in photovoltaic and chemosensing application as it has high absorption and fluorescence quantum yields. In this write-up, salient features of coumarin based chemosensors have been reviewed.

Introduction
Coumarins have been extensively investigated with regard to their outstanding optical properties, and therefore they are a powerful tool for the study of simple molecules in complex biological systems. They are effective fluorophores characterized by high fluorescence quantum yields. Undeniably they constitute the largest class of fluorescent dyes and are widely used as emission layers in organic light-emitting diodes (OLED), optical brighteners, nonlinear optical chromophores, fluorescent whiteners, and fluorescent labels as well as probes for physiological measurement. Recently, coumarins have found wide applications in labeling and caging. Moreover, compounds of this family likewise show numerous and remarkable biological activity. Due to their analytical and biological uses[1-6], photophysical and spectroscopic properties can be readily modified by the introduction of substituents into the coumarin ring, giving them more flexibility to fit well into various applications. Coumarins, with the structure of benzopyrone, have many advantages including high fluorescence quantum yield, large Stokes shift, excellent light stability, and less toxicity. Therefore coumarins have been widely used in the fields of biology, medicine, perfumes, cosmetics, and fluorescent dyes[7-9]. By far coumarin derivatives have been used as fluorescent probes of pH, for detection of nitric oxide, nitrooxide, and hydrogen peroxide. Moreover, coumarin derivatives have served as good chemosensors of anions, cations and reactive oxygen species[10-15].

Structural characteristics of coumarin
The fusion of a pyrone ring with a benzene ring gives rise to a class of heterocyclic compounds known as benzopyrones, of which two distinct types are recognized[16-21], namely
benzo-α-pyrones, commonly called coumarins, and benzo-γ-pyrones[22-26], called chromones, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring as shown in Fig. 1. It is well known that stilbene with a trans conformation is highly fluorescent. From the viewpoint of molecular structure, coumarins bear a carbon-carbon double bond which is fixed as trans conformation as in trans-stilbene through a lactone structure[27-31]. This can help to avoid the trans-cis transformation of the double bond under ultraviolet (UV) irradiation as observed in stilbene compounds and results in strong fluorescence and high fluorescence quantum yield and photostability in most of coumarin derivatives[32-35].

Figure 1 Coumarin structure

It was showed in the late 1950s that substitutions on the coumarin structure shifted the fluorescence band. For instance[36-41], adding a methyl group to the 4-position of 7-hydroxy- or 7-Methoxy coumarin red shifts the fluorescence spectra. Addition of electron-repelling groups in the 4-, 6-, or 7-position or electron-attracting groups in the 3-position all shifts the fluorescence band to longer wavelengths. When the carbonyl is substituted with a thione, the absorbance was red shifted and the fluorescence was quenched[1]. The reduction of the acceptor strength of the substituent at the 3-position, as in a 7-diethylaminocoumarin dye 1 (the structure of which is shown in Fig. 1) does not always result in sustained fluorescence in polar, aprotic solvents. Thus 7-diethylamino-3-styrylcoumarin dyes are not technically important as laser dyes; however, the extreme sensitivity of coumarin 1 to the medium polarity could provide an opportunity to probe the microenvironment experienced by the molecule[2]. Changing the solvent or the solution pH also affected the fluorescence spectra[42-45]. Study on the effect of solution pH on 7-hydroxy-4-methylcoumarin showed that increasing the solution pH raised the fluorescence intensity. Studies on the effect of changing the solvent polarity on coumarin derivatives revealed that increasing solvent polarity red shifted the absorbance as well as red shifted and broadened the emission of the coumarins due to increased hydrogen bonding. Studies
on the excited-state properties of 4- and 7-substituted coumarin derivatives revealed that solvent polarity shifted both the emission and absorption peaks, with a greater shift observed in the emission spectra, indicating that the excited-state dipole moment of the solute molecule was greater than the ground-state dipole moment.

**Coumarin-derived fluorescent chemosensors for metal ions**

The recognition mechanisms of these chemosensors mainly involve photoinduced electron transfer (PET), intramolecular charge transfer (ICT), fluorescence resonance energy transfer (FRET), coordination, and desulfurization. For instance, the fluorescence detection of 2 upon Hg$^{2+}$ addition is promoted by a Hg$^{2+}$-induced desulfurization of the thiourea moiety, leading to a decrease in an ICT character of the excited-state coumarin moiety. Coumarin-thiazolobenzo-crown ether based chemosensor 3 has been developed for Hg(II) ions that utilizes the strong coordination of Hg(II) ions on the crown oxygen and thiazole nitrogen. The complexation of Hg(II) disrupts the ICT from the oxygen donor to the coumarin fluorophore resulting in blue-shift in absorption and quenching of the fluorescence.

**Figure 2. Hg$^{2+}$ sensors**

Detection of trace amount of Cu$^{2+}$ is important not only for environmental applications, but also for toxicity determination in living organs. Coumarin 4 is a highly effective turn-on fluorescent sensor that is catalytically hydrolyzed by Cu$^{2+}$ leading to a large increase in the fluorescence intensity. Biscoumarin 5 linked by a C=N double bond is highly sensitive and selective to Cu$^{2+}$ and the fluorescent sensing mechanism is based on C=N isomerization.

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Figure 3. Cu\textsuperscript{2+} sensors

Study on the sensory capabilities of two novel di(2-picoly)amine (DPA)-substituted coumarins shows that the variation of the point of attachment of the DPA group to the coumarin framework controls their sensing behavior: the 4-substituted system is a chelation-enhanced fluorescence (CHEF)-type sensor which shows a significant increase in fluorescence intensity upon Zn\textsuperscript{2+} binding. A series of coumarin-based fluorescent probes for detecting Zn\textsuperscript{2+} with high affinities show the ratiometric fluorescent properties.

Figure 4 Zn\textsuperscript{2+} sensors

Coumarin-derived fluorescent chemosensors for anions

Development of highly efficient chemosensors for cyanide is of extreme significance due to the detrimental aspect of cyanide. Much attention has been paid to the utilization of fluorescent methods for the detection of cyanide. Several coumarin-derived fluorescent chemosensors for CN– have been reported, the structures of which are shown in Fig. 5. Doubly activated coumarin acts as a colorimetric and fluorescent chemodosimeter for cyanide. A simple aldehyde-functionalized coumarin has been utilized as a doubly activated Michael acceptor for cyanide.

Figure 5 Cyanide sensors
Coumarin derivative 10 has been developed as a fluorescent probe for detection of F– ion in water and bioimaging in A549 human lung carcinoma cells10. Coumarin 11 is a simple, highly selective, and sensitive chemosensor for fluoride anions in organic and aqueous media based on the specific affinity of fluoride anion to silicon11.

Figure 6 Fluoride sensors

Coumarin-derived fluorescent chemosensors for \( \text{H}_2\text{O}_2 \), and \( \text{O}_2 \)

Water-soluble umbelliferone-based fluorescent probe 12 shows very large increase in fluorescent intensity upon reaction with hydrogen peroxide, and good selectivity over other reactive oxygen species12. Another water-soluble fluorescent hydrogenperoxide probe 13 based on a ‘click’ modified coumarin fluorophore shows significant intensity increases in near-green fluorescence upon reaction with \( \text{H}_2\text{O}_2 \), and good selectivity over other reactive oxygen species13. More recently a simple and highly sensitive fluorometric method was proposed for the determination of \( \text{H}_2\text{O}_2 \) in milk samples. In this method, nonfluorescent coumarin was oxidized to highly fluorescent 7-hydroxyl coumarin by hydroxyl radicals generated in a Fenton reaction, and the oxidation product had strong fluorescence with a maximum intensity at 456 nm and could be used as a fluorescent probe for \( \text{H}_2\text{O}_2 \)14. Thiazo-coumarin ligand directly cyclometallated Pt(II) complex 14 has been used for luminescent \( \text{O}_2 \) sensing15.

Figure 7 ROS sensors

Coumarin-derived fluorescent chemosensors for proteins, DNA, and RNA
A novel coumarin C-riboside 15 is designed and synthesized based on the well-known photoprobe Coumarin 102. The coumarin C-glycoside 15 has been incorporated synthetically into DNA oligomers, and has been used to probe ultrafast dynamics of duplex DNA using time-resolved Stokes shift methods. A simple coumarin derivative 7-diethylaminocoumarin-3-carboxylic acid 16 has been used as an acceptor to construct a useful and effective FRET system for detection of RNA-small molecule binding.

Figure 8 Sensors for biomolecules

References
