



Review

Fluorescent probe for mercury ion imaging analysis: Strategies and applications

Yue Wang^{a,e}, Li Zhang^{a,e}, Xiaoyue Han^a, Liangwei Zhang^{a,d,*}, Xiaoyan Wang^b, Lingxin Chen^{a,b,c,d,*}

^a CAS Key Laboratory of Coastal Environmental Processes and Ecological Remediation, Shandong Key Laboratory of Coastal Environmental Processes, Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, China

^b School of Pharmacy, Binzhou Medical University, Yantai 264003, China

^c Laboratory for Marine Biology and Biotechnology, Pilot National Laboratory for Marine Science and Technology, Qingdao 266237, China

^d Center for Ocean Mega-Science, Chinese Academy of Sciences, Qingdao 266071, China

^e University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

Environmental pollution problem, especially mercury ions (Hg^{2+}) pollution, seriously threatens the organism health. Numerous researches have revealed that even extremely low concentration of Hg^{2+} can severely damage the organisms. Therefore, it is essential for real-time detection of Hg^{2+} . Fluorescent probe technology with great advantages has become the preferred technique for environmental detection and *in vivo* analysis of Hg^{2+} . In recent years, lots of contributions have been committed to designing and synthesizing novel fluorescent probes for environmental pollutant Hg^{2+} analysis. In this feature article, we review the recent advances in fluorescent probes for Hg^{2+} analysis, focusing on probe response modes, including signal-decreased fluorescent probes, signal-enhanced fluorescent probes, ratiometric fluorescent probes as well as fluorescent probes for Hg^{2+} and other species analysis. Moreover, the design strategies, performance and applications of fluorescent probes are summarized in detail. Challenges and prospects for fluorescent probe are proposed, orienting new design strategies and applications expanding.

1. Introduction

Mercury is one of the most toxic metal pollutants, which seriously pollutes environment and threatens the organism health [1,2]. The main sources of mercury pollution include mineral industry production, chemical manufacturing, waste incineration, and fossil fuel combustion [3–5]. In addition, volcanic activity, forest fire, and atmospheric mercury deposition can also lead to mercury pollution. What's worse, mercury pollution cannot be naturally degraded, and it can further cause atmospheric pollution, soil pollution as well as water pollution once exposed into the environment [6–8]. Mercury will accumulate along the food chain and human at the top of food chain suffered the most [9,10]. In this feature article, we focus on the research of mercury ions (Hg^{2+}), the main form of mercury.

Hg^{2+} can be transported throughout the organisms with blood circulation once it enters organisms, causing various diseases with severe toxicity. For example, the horrendous Minamata disease is mainly

caused by consumption of mercury-contaminated food. Mineral leaching and human activities can cause the Hg^{2+} content in water to rise, and Hg^{2+} will accumulate along the food chain. After humans consume contaminated fish and shrimp and other seafood, Hg^{2+} affects human health seriously. In addition, industrial wastes containing Hg^{2+} can also accumulate along crops in terrestrial ecosystems. Hg^{2+} can interact with active species *in vivo*, and induce severe mercury poisoning after entering the organism. Hg^{2+} mainly targets the kidney and brain tissue, and induces kidney tissue damage and neurotoxicity [11–13]. The mechanism of mercury poisoning can be elaborated from three aspects: the electrophilic effect of Hg^{2+} , the “calcium overload” effect caused by Hg^{2+} and the immune damage effect [11–14]. More specifically, Hg^{2+} has a high affinity towards active groups due to its high electrophilic effect, such as mercapto, amino, carbonyl and carboxyl groups [15,16]. These active groups generally play vital roles in the physiological processes. Once reacted with Hg^{2+} , the activity of active groups and the normal physiological processes *in vivo* will be seriously disturbed. For

* Corresponding authors at: Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, China.

E-mail addresses: liangweizhang@yic.ac.cn (L. Zhang), lxchen@yic.ac.cn (L. Chen).

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instance, Hg^{2+} can strongly combine with mercapto groups, which usually acts as the active site to participate in the redox regulation process *in vivo*. Hg^{2+} is also prone to attack DNA strands due to the strong electrophilicity, causing DNA strand breaks and inducing the outbreak of reactive oxygen species [17–20]. Calcium overload caused by Hg^{2+} is another manifestation of mercury poisoning. Calcium ion homeostasis is critical for maintaining normal cell physiological function. Under normal conditions, there is a huge concentration difference between intracellular and extracellular calcium ions. Maintaining such a huge concentration difference requires a series of transport mechanisms. However, Hg^{2+} interferes with the transport mechanism and induces “calcium overload” effect [21,22]. The organism itself has various protective mechanisms to deal with the mercury poisoning [23,24]. Selenium-mercury complexes formed in erythrocyte and plasma belong to first-line protection [15,16]. Glutathione (GSH), which can help the organism relief mercury poisoning by combining Hg^{2+} with the sulfhydryl group, belongs to second-line protection. However, alleviating mercury poisoning by GSH will sacrifice the antioxidant capacity of organism [25–28]. Once Hg^{2+} concentration far exceeds the regulation ability of organism, Hg^{2+} will continue to combine with other biologically active molecules and cause severe damages to organism [29–32]. Based on these facts, real-time and online monitoring the concentration fluctuation of Hg^{2+} in environmental samples and biological samples is crucial to organism health.

Traditional analytical techniques for Hg^{2+} detection, like spectrophotometry, atomic absorption spectroscopy, atomic fluorescence spectroscopy, x-ray absorption spectroscopy, and inductively coupled plasma mass spectrometry cannot achieve real-time and *in situ* monitoring at the expense of time-consuming inspection processes, complex sample pretreatment and destruction of biological samples [33–39]. Fluorescence probe technology has good selectivity, high sensitivity, fast response speed and the capability of real-time online detection, thus it has been widely applied for the detection of ions, molecules as well as other species [40–46]. So far, a variety of fluorescent probes for Hg^{2+} detection have been developed [47–55]. Even though some excellent reviews give the related topic and they focus on the fundamental and design aspects of fluorescent probes for various heavy metal ions [56–59]. Only a few specific reviews have summarized the detection methods for Hg^{2+} [60,61]. However, they merely focus on the details of detection, and do not systematically introduce the design strategies, response modes, challenges and prospects of fluorescent probes, which can provide ideas and opinions for the development of novel fluorescent probes. And the design strategies as well as new mechanisms for construction of Hg^{2+} fluorescent probes have been developed recently. Therefore, specifically review to introduce fluorescent probes for Hg^{2+} analysis is meaningful. In this article, we will summarize the response types, design strategies, performances and applications of the fluorescent probes for Hg^{2+} detection. The fluorescent probes are classified according to the changes in fluorescence signals, including signal-decreased fluorescent probes, signal-enhanced fluorescent probes and ratiometric fluorescent probes (Fig. 1). In addition, multi-responsive fluorescent probes that can simultaneously detect Hg^{2+} and other species are also summarized.

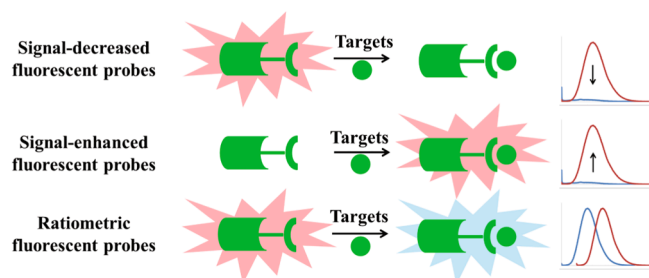


Fig. 1. Typical signal response modes of fluorescent probes.

2. Signal-decreased fluorescent probes for Hg^{2+} analysis

Signal-decreased fluorescent probes are also called on–off type fluorescent probes, namely the fluorescence signals are decreased after reacting with targets. This type of probes is usually applied for Hg^{2+} and Cu^{2+} detection. In this section, we will introduce the signal-decreased fluorescent probes rely on different reaction types, including N-atom complexation, deprotection reaction of dithioacetals and S-atom complexation.

2.1. Fluorescent probes for Hg^{2+} analysis based on N-atom complexation

Ono and co-workers reported an oligodeoxyribonucleotide (ODN)-based probe **1** for Hg^{2+} detection in aqueous solutions [62]. Inspired by the strong binding reaction between Hg^{2+} and thymine-thymine (T-T) base pairs in DNA duplexes, researchers linked ODN with fluorescein fluorophore and dabcyI quencher unit to afford a novel fluorescent probe **1** (Fig. 2). After addition of Hg^{2+} , thymine residues interacted with Hg^{2+} to form a hairpin structure, accompanied by a decrease in fluorescence signal intensity. Probe **1** showed good selectivity and sensitivity towards Hg^{2+} , and the limit of detection (LOD) of probe **1** can reach 40 nM. Later, Wang and co-workers reported a new fluorescent probe **2** for Hg^{2+} detection based on thymine residue (Fig. 2) [63]. And probe **2** displayed superior selectivity towards Hg^{2+} . Probe **2** showed practicality for Hg^{2+} detection in solution, and the LOD of probe **2** was 0.1 μM . Chiang et al. also developed a turn-on fluorescent probe for Hg^{2+} selective detection based on polythymine oligonucleotide [64]. The probe showed practicality for Hg^{2+} detection in pond water and batteries, and the LOD of probe was 0.6 ppb.

Given pyrene unit displayed high fluorescence quantum yield, Banerjee et al. designed and synthesized a novel probe **3** that consisted of pyrene unit and methionine units for Hg^{2+} selectively detection [65]. Initially, probe **3** emitted strong fluorescence signal at 455 nm. After reacting with Hg^{2+} , the fluorescence signal from probe **3** was obviously quenched. Probe **3** showed fairly high binding constant towards Hg^{2+} (7.5630×10^4), and the fluorescence lifetime of the probe as well as its Hg^{2+} -complex were 1.54 ns and 0.72 ns, respectively. Probe **3** was applied for Hg^{2+} determination in industrial wastewater successfully.

Vengaiyan and co-workers reported a fluorescent probe **4** for Hg^{2+} detection based on phenothiazine-diaminomaleonitrile derivative [66]. They chose phenothiazine derivative as fluorescence reporter and probe **4** was synthesized after connecting diaminomaleonitrile as response site (Fig. 3). The nitrile group with strong electron-withdrawing ability can effectively promote the intramolecular charge transfer process. The fluorescence signal decreased significantly after adding Hg^{2+} , however, the fluorescence signal recovered again after adding S^{2-} . Therefore, researchers proposed the concept of turn-off–on logic gate for Hg^{2+} and S^{2-} sensing. Furthermore, the probe exhibited low cell toxicity and was applied for Hg^{2+} imaging in living cells.

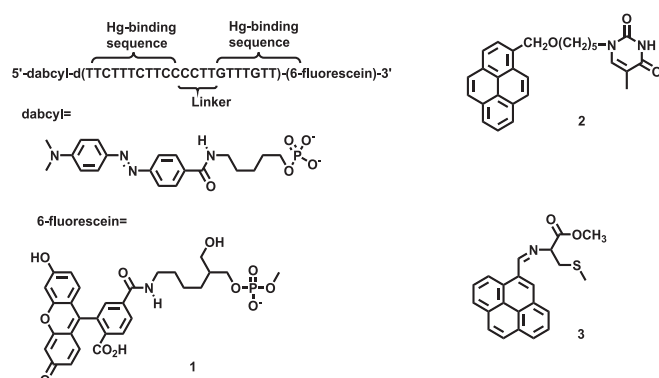


Fig. 2. Structures of 1–3.

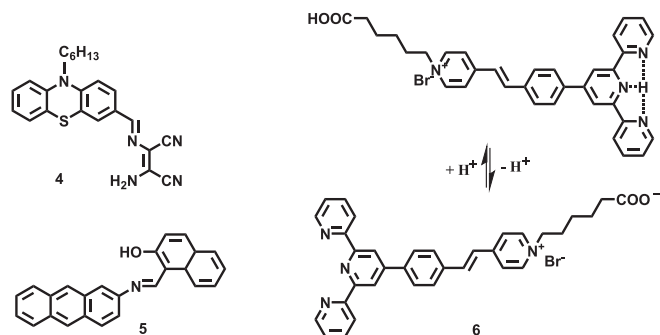


Fig. 3. Structures of 4–6.

Shyamal and co-workers designed a “turn-off” fluorescent probe **5** for Hg^{2+} selective recognition in solution [67]. The probe **5** was synthesized by connecting anthracene with naphthalimide via a Schiff base linker and the introduction of anthracene can increase the hydrophobicity of the probe. Probe **5** showed strong fluorescence signal in the binary solvent mixture (THF/ H_2O , 3:7, v/v). After reacted with Hg^{2+} , the fluorescence signal decreased apparently. Scanning electron microscope analysis, dynamic light scattering analysis, TRPL analysis and optical microscope were used to study the particles size and growth process during aggregation after reacted with Hg^{2+} in different mixture. The applications of probe in test strip provided convenience for Hg^{2+} detection in the actual samples.

Zhou and co-workers reported a terpyridine-based fluorescent probe **6** for Hg^{2+} sensing [68]. Probe **6** was composed of terpyridine and hexanoic acid units. The probe **6** showed good selectivity for Hg^{2+} in acidic environment although Cd^{2+} interfered with the Hg^{2+} detection in neutral aqueous solution. Since probe **6** was aggregated after reacted with Hg^{2+} , the author introduced a procedure for Hg^{2+} removal. Furthermore, the probe **6** can be effectively regenerated and recovered after being treated with H_2S .

2.2. Fluorescent probes for Hg^{2+} analysis based on deprotection of dithioacetals

The deprotection reaction of dithioacetals requires Hg^{2+} . Based on this principle, researchers have designed a series of fluorescent probes for Hg^{2+} detection (Fig. 4). And the fluorescent probes based on deprotection reaction of dithioacetals undergo chemical reaction under test conditions, thus this type of probes is usually irreversible.

Rani synthesized a signal-decreased fluorescent probe **7** for Hg^{2+} sensing (Fig. 5) [14]. Researchers selected pyrene unit as chromophore for its superior spectral performance and they chose mercaptothiadiazole moiety as the recognition unit for Hg^{2+} detection. Probe **7** initially emitted fluorescence signals at 378, 388 and 397 nm. After adding Hg^{2+} , the electrons were transferred from the pyrene unit to metal ion Hg^{2+} , which can promote spin-orbit coupling due to the heavy atom effect, and Hg^{2+} quenched the fluorescence signals of probe **7**. The mechanism of probe **7** for Hg^{2+} detection was confirmed through DFT analysis. The response of probe **7** towards Hg^{2+} was reversible, and the combination of probe **7** and Hg^{2+} can be reversed by cysteine. Probe **7** can be applied for Hg^{2+} detection in water samples and living cells.

Zhao and co-workers developed a fluorescent probe **8** for Hg^{2+} visual detection based on aggregation-induced emission [69]. Probe **8** was synthesized based on tetraphenylethylene derivatives. Researchers

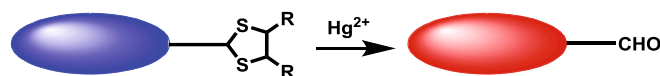


Fig. 4. Summary of strategies for fluorescent probes based on deprotection of dithioacetals.

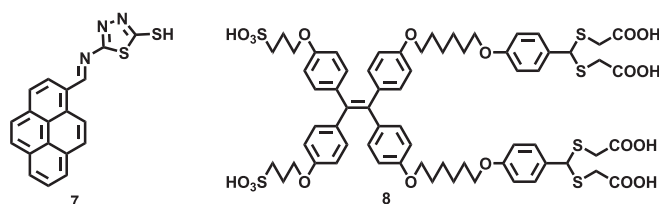


Fig. 5. Structures of 7–8.

introduced sulfonic acid groups to increase the water solubility of probe, and dithioacetal was selected as response sites for Hg^{2+} detection. Furthermore, fibrous strips were decorated with probe **8** for Hg^{2+} detection in actual samples. They attached active carboxyl groups to the probe for inducing condensation reaction with the terminal amino groups on the fiber surface, thereby connecting the probe to the fiber surface for Hg^{2+} sensing. This process was characterized by scanning electron microscope analysis and X-ray photoelectron spectroscopy analysis. Probe **8** cannot move freely after fixed on the fiber surface, thus probe **8** emitted strong fluorescent signals. After reacting with Hg^{2+} , the fiber mat exhibited a significant decrease in fluorescence signal. The loading device with fluorescent probe **8** fixed on the test paper provided convenience for on-line detection compared with the Hg^{2+} detection in solutions.

2.3. Fluorescent probes for Hg^{2+} analysis based on S-atom complexation

Based on Hg^{2+} has strong sulfur affinity, researchers constructed a series of fluorescent probes by adopting S atom, azathiocrown ether and thioether-rich crown as response unit to achieve Hg^{2+} analysis (Fig. 6).

To overcome the poor water solubility of fluorescent probes, Descalzo and co-workers constructed a fluorescent probe **9** for Hg^{2+} detection (Fig. 7) [70]. They used the phenoxazinone unit as fluorophore to guarantee sufficient water solubility, and phenoxazinone can emit intense fluorescence signals in the visible spectral region. In order to improve the selectivity of probes for Hg^{2+} detection, researchers chose dithia-dioxo-monoaza crown unit as the response group. The fluorescence signals were reduced after reacted with Hg^{2+} , and probe **9** exhibited high selectivity for Hg^{2+} with a LOD of 10^{-7} M in solution.

Koteeswari and co-workers reported a series of fluorescent probes **10a–e** based on acridinedione derivatives linked with amidothiourea for Hg^{2+} detection [71]. Probes can be excited by one-photon and two-photon microscope for Hg^{2+} analysis. Probe **10a** showed a 92-fold fluorescence quenching after reacted with Hg^{2+} , and it can be

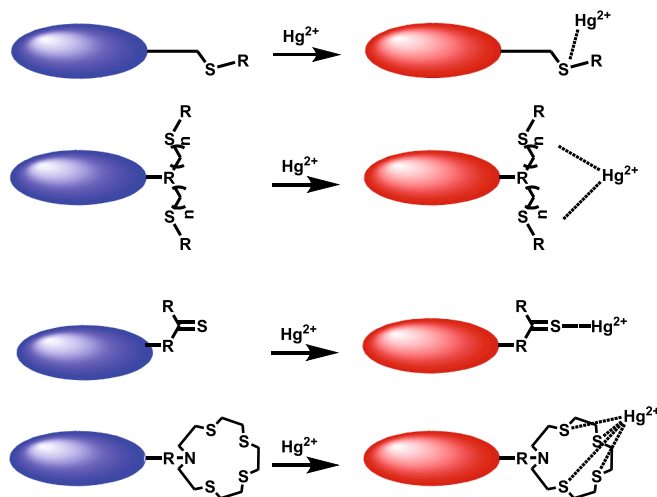


Fig. 6. Summary of strategies for fluorescent probes based on S-atom complexation.

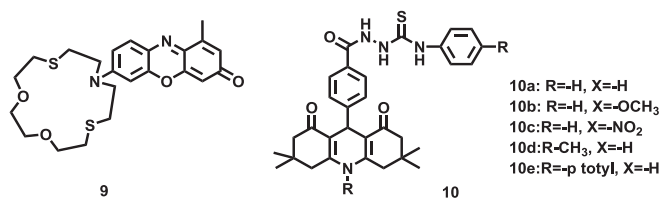


Fig. 7. Structures of 9–10.

employed for Hg^{2+} rapid detection in cells with a LOD of 2 nM.

For Hg^{2+} fluorescent probes with fluorescence signal decrease, researchers should pay attention to the false positives experimental results that fluorescence quenching caused by external environmental factors when applying this type of probes for analysis. In addition, the high background signals from probes limit the improvement of probe sensitivity, which poses a great challenge for low-level targets detection. Thus, these limitations of this type of probes in analysis field should be improved.

3. Signal-enhanced fluorescent probes for Hg^{2+} analysis

Hg^{2+} is usually considered as a fluorescence quencher which can reduce fluorescence signal output. Therefore, it is valuable to obtain signal-enhanced fluorescent probes. The signal-enhanced fluorescent probes can be called off-on type fluorescent probes, and the fluorescence signals from which are increased after reacting with analytes. The initial fluorescence signal values from the signal-enhanced fluorescent probes are low, that is, the background signals are low. After reacting with analytes, the fluorescence signals from probes are significantly enhanced. Compared with the signal-decreased fluorescent probes, the signal-enhanced fluorescent probes have higher sensitivity and are more suitable for qualitative analysis. In this section, we will introduce the signal-enhanced fluorescent probes according to different reaction mechanisms: rhodamine ring-opening reaction, deprotection reaction of dithioacetals, S-atom complexation and N-atom complexation.

3.1. Fluorescent probes for Hg^{2+} analysis based on rhodamine ring-opening reaction

Hg^{2+} has strong sulfur affinity, and the reactions based on Hg^{2+} -promoted desulfurization reactions, including ring-opening and elimination reaction of the rhodamine structure, cyclization as well as hydrolysis, are employed to construct fluorescent probes for Hg^{2+} detection [71]. Rhodamine dyes have been widely used in the field of biological imaging due to its high molar absorption coefficient, superior fluorescence quantum yield as well as long emission wavelength. Generally, rhodamine dyes in the form of spirocyclic rings have no fluorescent signals. After reacting with the targets, the spirocyclic ring opens accompanied by emitting strong fluorescent signals from rhodamine dyes. So far, the Hg^{2+} fluorescent probes designed based on the rhodamine skeleton have two main mechanisms: 1) Hg^{2+} promotes cyclization by desulfurization, in which process the carbonyl group of spirocyclic lactone acts as reaction site, leading to ring opening; 2) The coordination between Hg^{2+} and receptors, in which process the carbonyl group of spirocyclic lactone plays a complexing role, leading to ring opening [72]. In the first case, the ring-opening reaction of rhodamine is irreversible because it produces a new molecule. In the latter case, the ring-opening reaction of rhodamine is reversible because it is based on Hg^{2+} complexes.

Given the strong thiophilic affinity of Hg^{2+} , Tae group coupled the rhodamine cyclization process with Hg^{2+} -promoted reaction of thiosemicarbazides to design a novel probe **11** for Hg^{2+} detection (Fig. 8) [73]. Originally, probe existed in the spirocyclic form. After adding Hg^{2+} , it would promote thiosemicarbazides to form 1,3,4-oxadiazoles accompanied by emitting strong yellow fluorescence signals. This

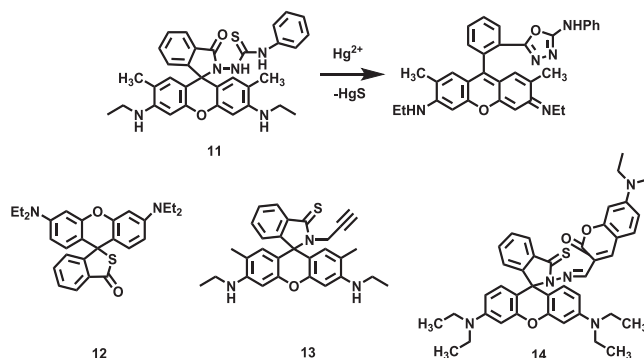


Fig. 8. Structures of 11–14.

reaction did not require high temperature and it can be conducted at room temperature in a 1:1 stoichiometric manner for Hg^{2+} detection, in addition, the LOD of probe **11** for Hg^{2+} analysis was below 2 ppb. Later, the same group applied probe **11** for Hg^{2+} imaging analysis *in vivo* for the first time [74]. They investigated the selectivity, reaction kinetics and pH application range of the probe, and the results demonstrated that probe **11** was suitable for Hg^{2+} detection *in vivo*. Probe **11** can achieve Hg^{2+} selective detection within 1 min, and it was stable in the pH range of 4–14. Probe **11** was successfully applied for Hg^{2+} detection in cells, organs and zebrafish, and the experimental results of Hg^{2+} detection in vertebrate zebrafish exhibited the potential application of probe *in vivo*. They pioneered the application of fluorescent probe to *in vivo* analysis.

After replacing the nitrogen atom in rhodamine spirocyclic lactone with sulfur atom, Zhan and co-workers obtained a monothiospirolactone-based rhodamine derivative **12**, which had better pH stability [75]. After replacement, the thiol atom can be served as an active site for Hg^{2+} detection, and probe **12** was stable in the pH range of 1–11. The reaction between probe **12** and Hg^{2+} was reversible, and the Hg^{2+} detection by probe **12** can be naked-eye observed in the solution.

Lin group reported a turn-on fluorescent probe **13** for Hg^{2+} detection by a novel sensing strategy. Probe **13** consisted of a rhodamine reporter unit, an alkyne unit, and an S atom response site [76]. Alkyne unit and S atom were selected as response sites due to the thiophilic and π -philic nature of Hg^{2+} . Probe **13** in spirocyclic form had no fluorescence signal, and it would convert into an open-ring product with strong fluorescence signal after reacted with Hg^{2+} . The probe can selectively respond to Hg^{2+} within 3 min without interference from other species. Probe **13** was cell membrane permeable and it can be used for intracellular Hg^{2+} detection with a LOD of 39 nM. The new design strategy can be used for constructing novel fluorescent probes for targets detection.

Based on rhodamine ring-opening reaction, Ma and co-workers reported a turn-on fluorescent probe **14** for Hg^{2+} selective detection [77]. Probe **14** consisted of rhodamine and coumarin dyes, and the LOD of probe **14** can reach 4.0×10^{-8} M. The fluorescence signals of probe **14** was significantly enhanced about 24-fold after reacted with Hg^{2+} in 50% water/ethanol buffer (pH 7.4), in addition, probe **14** and Hg^{2+} can form a 1:1 complex. The fluorescence response of probe **14** towards Hg^{2+} was reversible, and the probe can be utilized for Hg^{2+} detection in actual samples including tap water and river water.

Mandal and co-workers also reported a signal-enhanced fluorescent probe **15** for Hg^{2+} detection based on rhodamine ring-opening mechanism (Fig. 9) [78]. Rhodamine dye was selected as fluorescence reporter, and a new probe **15** was obtained for Hg^{2+} sensing after being linked to thiophene. The synthesis procedure of the probe was simple, and the structure of probe **15** was characterized by ^1H NMR, mass spectra as well as FTIR, and the purity of the probe was detected by elemental analysis. After reacted with Hg^{2+} , the fluorescence signals from probe **15** were enhanced significantly and the naked-eye color of probe **15** changed from colorless to red. The LOD of probe **15** was as low as 1.0×10^{-9} M, and the probe can be applied for Hg^{2+} detection in allamanda puberula,

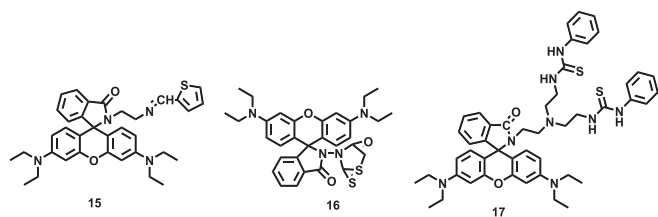


Fig. 9. Structures of 15–17.

Candida albicans and cells.

Bera and co-workers reported a turn-on fluorescent probe **16** for Hg^{2+} selective detection [79]. They selected rhodamine as fluorophore and introduced 3-aminorhodamine receptor to increase the affinity of probe towards Hg^{2+} . After reacted with Hg^{2+} , probe **16** in benzenoid form converted to quinonoid form with increased fluorescence signals. The reaction between probe **16** and Hg^{2+} was irreversible, and probe can be applied in a wide pH range (pH 5–10). Probe **16** can react with Hg^{2+} quickly within 3 min and it can be applied for Hg^{2+} detection at nanomolar level. Researchers applied probe **16** for Hg^{2+} detection in living cells and zebrafish, and time evolution of inorganic mercury distribution in zebrafish can be obtained using the probe **16**. However, the detection of Hg^{2+} by probe **16** was hindered in pure acetonitrile medium.

To improve the binding capacity of fluorescent probe towards Hg^{2+} , Hong and co-workers introduced a phenyl isothiocyanate unit into the rhodamine fluorophore to afford probe **17** [80]. After addition of Hg^{2+} , probe **17** strongly complexed with sulfur atoms and a desulfurization reaction occurred simultaneously that further resulted in the ring opening of rhodamine spirolactam. The stoichiometry of probe and Hg^{2+} was 1:2, and the binding constant was $2.89 \times 10^8 \text{ M}^{-2}$. After probe **17** reacted with Hg^{2+} , Hg^{2+} induced an intramolecular charge transfer process accompanied by the turning on of fluorescence. The new sensing mechanism proposed by Hong et al. was confirmed by LC-MS spectra, IR spectra and ^1H NMR spectra. The probe exhibited good selectivity and binding capacity for Hg^{2+} , and it can be applied for Hg^{2+} detection in cells. In addition, the probe-containing cellulose disc produced by researchers can be applied for Hg^{2+} determination via naked eye, which revealed the promising prospect of probe **17** in the portable onsite detection of Hg^{2+} .

Based on ring-opening reaction of rhodamine, Hu and co-workers reported a reversible fluorescent probe **18** for Hg^{2+} selective detection (Fig. 10) [72]. After adding Hg^{2+} , the fluorescent signals from probe **18** were increased approximately 105 times. The binding and dissociation constants of probe **18** for Hg^{2+} were $0.22 \times 10^5 \text{ M}^{-1}$ and $25.2 \text{ }\mu\text{M}$ respectively, and the binding stoichiometry was 1:1. Using S^{2-} and I^- ,

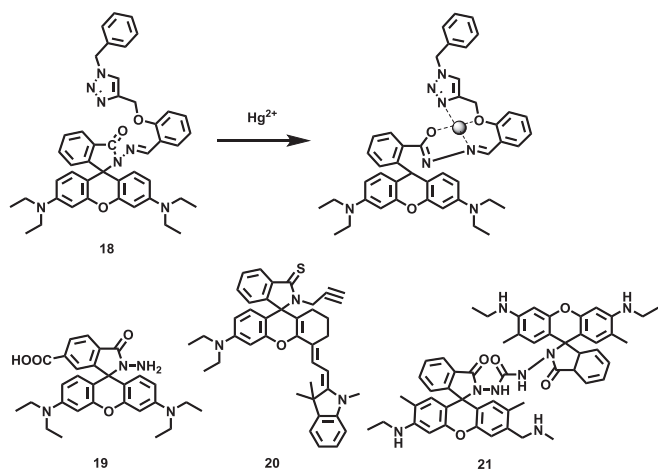


Fig. 10. Structures of 18–21.

researchers showed a new idea of reversible logic gates based on the reversible Hg^{2+} recognition. In addition, probe **18** can be utilized for Hg^{2+} detection in actual samples of lake and rain water, and it can be employed for intracellular Hg^{2+} imaging.

Li and co-workers reported a turn-on fluorescent probe **19** for Hg^{2+} detection based on irreversible ring-opening reaction of rhodamine [81]. To improve the water solubility of probe, researchers introduced a hydrophilic carboxylic acid unit into the probe structure. After the addition of 1 equiv. Hg^{2+} , a 42-fold increase in fluorescence signal can be observed within 3 min. Probe **19** showed good spectral performances for Hg^{2+} analysis, and it can be adopted for Hg^{2+} selective detection in actual water samples as well as living cells.

Considering that the near-infrared fluorescence signal has unique advantages in biological imaging, including less light damage to tissues and deep penetration depth, Wang and co-workers designed a near-infrared fluorescent probe **20** for Hg^{2+} detection [82]. Researchers connected semi-cyanine with rhodamine to obtain a fluorescent reporter with a larger conjugated system, which emitted near-infrared fluorescence signal at 760 nm. After the fluorescent reporter reacted with prop-2-yn-1-amine, probe **20** was synthesized. The ring-opening reaction of rhodamine caused by Hg^{2+} occurred and the fluorescence signal at 760 nm was significantly enhanced once addition of Hg^{2+} . The reaction mechanism of probe **20** was confirmed by ^1H NMR analysis, DFT analysis and MS analysis. In addition, probe **20** can be applied for Hg^{2+} imaging in living cells and mice owing to the near-infrared fluorescence signals from probe **20**.

Based on rhodamine ring-opening mechanism, Yang and co-workers developed a turn-on fluorescent probe **21** for Hg^{2+} selective sensing [83]. Probe **21** was composed of a rhodamine dimer, and probe **21** in the spirocyclic form had no fluorescent signal. After reacting with Hg^{2+} , rhodamine structure in probe **21** turned to the ring-opened form and engendered a 478-fold fluorescent signal enhancement at 561 nm. The sensing mechanism was verified by IR spectra and ^1H NMR titration analysis. The stoichiometry between probe **21** and Hg^{2+} was 1:2, and the LOD of probe **21** can reach 1.3 ppb. Furthermore, probe **21** can be employed for Hg^{2+} imaging in living cells and tissues.

Fluorescent probes based on rhodamine ring-opening reaction are usually complex with Hg^{2+} using N atom. Other groups, for instance carbonyl, alkynyl and S atom can promote rhodamine ring-opening reaction. Whether the ring-opening reaction is reversible needs to be analyzed according to the actual situation.

3.2. Fluorescent probes for Hg^{2+} analysis based on deprotection of dithioacetals

Hg^{2+} -induced conversion of 1,3-dithiane to carbaldehyde is an efficient umpolung reaction, which can favor the formation of intramolecular charge transfer (ICT) mechanism in compounds. Based on this principle, Guo group reported a turn-on fluorescent probe **22** for Hg^{2+} selective detection based on benzoxadiazole derived dithiane (Fig. 11) [84]. After addition of Hg^{2+} , an aldehyde recovery reaction occurred, accompanied by an increase in the fluorescent signal. Probe **22** was non-fluorescence because of the weak electron withdrawing ability of 7-(1',3'-dithiane). After Hg^{2+} -triggered aldehyde recovery reaction occurred, the strong electron-withdrawing properties of 7-aldehyde were conducive to the ICT effect of the product and induced strong fluorescence emission. The fluorescence signals can reach equilibrium quickly within 3 min, and probe **22** can be utilized for detecting Hg^{2+} in zebrafish.

The determination of total mercury content was readily and can be done by specific techniques. However, detection of different forms of mercury poses a huge challenge to existing analysis techniques, for example, detection of MeHg^+ and Hg^{2+} separately. Based on covalent assembly, Zhang and co-workers achieved differentiated detection of Hg^{2+} and MeHg^+ in solution by multiplexing in the time domain with a single fluorescent probe **23** [85]. For MeHg^+ and Hg^{2+} separate

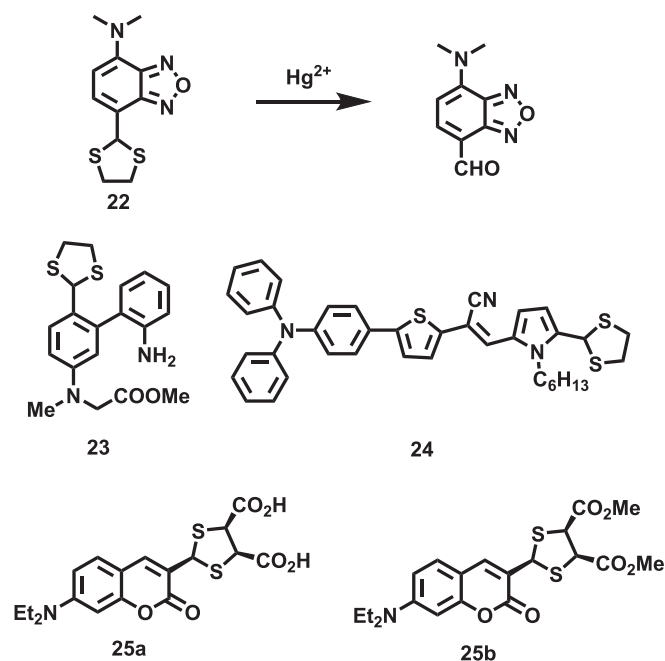


Fig. 11. Structures of 22–25.

detection, there were several considerations: a) the probe should have appropriate reaction kinetics for Hg^{2+} detection, not only to achieve the purpose of distinguishing monitoring, but also to complete the measurement within a reasonable time range; b) the probe should be applicable in aqueous solutions. Based on these considerations, they designed and synthesized a desirable probe **23**, in which the 2-amino-phenyl group can promote the detection of Hg^{2+} , and the methyl ester unit can increase the water solubility of probe. After addition of Hg^{2+} , 1,3-dithiolane was desulfurized to form a formyl unit, which then underwent a condensation reaction with nearby amino groups ($-\text{NH}_2$) to form phenanthridine. The polycyclic aromatic hydrocarbon had a greater degree of binding than the biphenyl precursor. They proved that Hg^{2+} and MeHg^+ can be detected separately by a single kinetic curve through experiments, and the LOD can reach 4.6 pM and 160 pM for Hg^{2+} and MeHg^+ respectively. The strategy researchers proposed may be applicable to the differential detection of other substrate pairs, such as cysteine and homocysteine.

Based on the deprotection of dithioacetal induced by Hg^{2+} , Ding and co-workers reported a turn-on fluorescent probe **24** for Hg^{2+} selectively detection [2]. Probe **24** was synthesized through Wittig reaction, Suzuki coupling reaction and Knoevenagel condensation reaction. Cyano group was introduced to decrease the electron transition energy from the ground state to excited state, and it was favor to the intramolecular charge transfer process. FTIR analysis and ^1H NMR analysis were conducted to confirm the sensing mechanism of Hg^{2+} -induced deprotection reaction. The LOD of probe **24** for Hg^{2+} was as low as 8×10^{-7} M and the probe showed powerful imaging potential in test strips detection and cell imaging.

Similarly, Song and co-workers reported two fluorescent probes **25a** and **25b** based on the deprotection of dithioacetal for Hg^{2+} sensing [86]. 7-N-diethyl coumarin was selected as fluorescence reporter and 2, 3-dimercaptosuccinic acid was chosen as recognition unit, the two components were connected by a dithioacetal linker. After reacted with Hg^{2+} , strong fluorescence emission at 502 nm can be observed. However, the detection for Hg^{2+} was disturbed by Ag^+ and Au^+ . Even so, researchers provided a concept of fluorescent theranostic agent for Hg^{2+} detection and detoxification treatment based on the deprotection of dithioacetal, which was deserved further exploration.

3.3. Fluorescent probes for Hg^{2+} analysis based on S-atom complexation

Hennrich et al. designed and synthesized a redox switchable fluorescent probe system **26** for Hg^{2+} detection (Fig. 12) [87]. Interestingly, the two compounds exhibited different cation selectivities. **26a** (oxidized form of probe **26**) showed good selectivity for Hg^{2+} with chelation-enhanced fluorescence signal, and **26b** (reduced form of probe **26**) exhibited spectral response mainly to Cd^{2+} and Zn^{2+} . Probe **26a** can achieve Hg^{2+} selective analysis with turn-on fluorescence signals in a wide concentration range.

Lippard group reported a novel fluorescent probe **27** for Hg^{2+} detection with satisfactory water compatibility [88]. They chose seminaaphthofluorescein as a fluorescence reporter, and thioether-rich metal-binding unit as a response site. Probe **27** can be used for Hg^{2+} reversible detection with a LOD of 50 nM, and it can also be employed for Hg^{2+} detection in natural water samples.

To improve the hydrophilicity of fluorescent probe, li and co-workers introduced hydrophilic amino acids dansyl-L-tryptophan methyl ester and constructed a signal-enhanced fluorescent probe **28** for Hg^{2+} selective detection [89]. Initially, probe **28** showed weak fluorescence emission peak at 550 nm; upon addition of Hg^{2+} , a strong fluorescence signal enhancement appeared at 487 nm with the solution color changed from red to green. Probe **28** displayed a low LOD of 5 nM for Hg^{2+} , and the probe had been successfully applied for Hg^{2+} detection in living cells, which exhibited the potential in biological applications.

Xu and co-workers designed and synthesized a signal-enhanced fluorescent probe **29** for Hg^{2+} detection based on desulfurization and cyclization reaction induced by Hg^{2+} (Fig. 13) [90]. After reacting with Hg^{2+} , the fluorescence signal from probe **29** was significantly enhanced, accompanied by an increase in quantum yield from 0.05 to 0.37. Hg^{2+} can induce more efficient intramolecular charge transfer from the electron-donating diethylamino group to the electron-withdrawing 1,3,4-oxadiazole group. Probe **29** can achieve Hg^{2+} selective detection with desirable spectral performance in solution, mammalian cells and bacteria.

Duan and co-workers developed a far-red fluorescent probe **30** for Hg^{2+} sensing [91]. Researchers selected seminaaphthorhodafluor dye as fluorescence reporter based on its superior spectral performance, and carbonothioate unit was selected as the recognition site. Hg^{2+} can promote the desulfurization of carbonothioate unit and probe was hydrolyzed to release oxygen anions, which caused the intramolecular charge transfer and emitted strong fluorescence at 625 nm with a large Stokes shift of 105 nm. Furthermore, probe **30** with a LOD of 3.6 nM can be applied for Hg^{2+} recognition in real water samples and living cells.

In order to improve the water solubility of fluorescent probe, Haldar

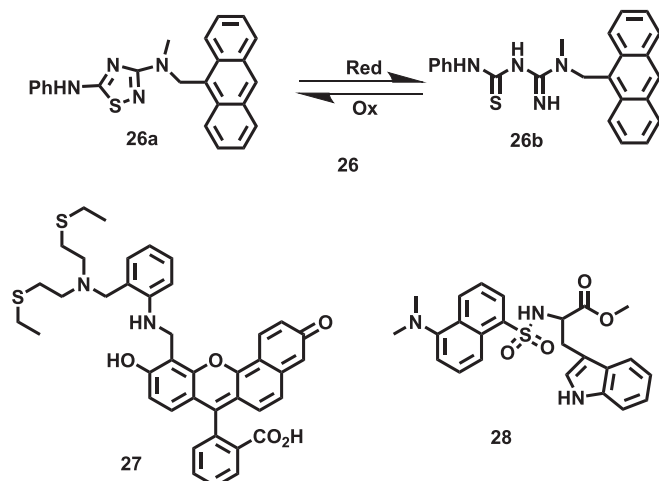


Fig. 12. Structures of 26–28.

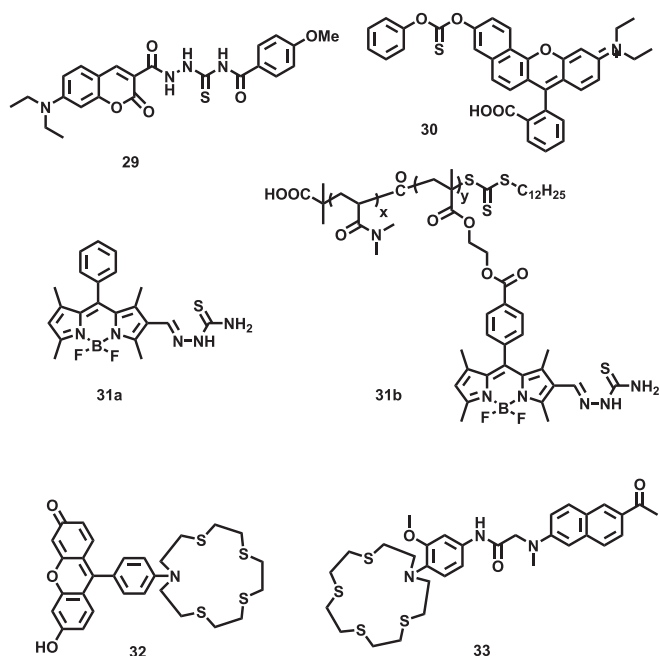


Fig. 13. Structures of 29–33.

and co-workers developed probe **31a** based on the BODIPY fluorophore and thiosemicarbazide was introduced as response group [92]. Probe **31a** had no fluorescence emission due to the non-radiative inactivation process of the excited state caused by C = N isomerization. After reacted with Hg^{2+} , the C = N isomerization in the probe was blocked, and probe **31a** emitted bright fluorescent signal. However, the hydrolytic stability of the probe was disappointing. Thus to overcome this problem, researchers integrated the BODIPY fluorophore and semicarbazone units into the backbone of the water-soluble polymer N,N'-Dimethylacrylamide. After reacting with thiourea, the desired polymer probe **31b** was obtained. Compared with the small molecule probe **31a**, the polymer probe **31b** showed excellent hydrolytic stability. **31b** can test and remove highly toxic Hg^{2+} from other potential competing metal ions by precipitation (86%), which expanded the application range of **31b** in the field of environmental remediation and pollution control.

Later, Yoon and co-workers designed and synthesized a fluorescent probe **32** for Hg^{2+} selective detection [93]. The probe contained a fluorescein reporter with desirable water solubility and a thioether-rich crown response unit for Hg^{2+} recognition. After reacted with Hg^{2+} , there was a 170-fold increase in fluorescence intensity, and probe **32** can be applied for Hg^{2+} detection in fish within the safe edible limit.

Two-photon microscopy using two near infrared photons as excitation source has great advantages of longer observation time, deeper penetration depth and less light tissue damage. Given the advantages of two-photon fluorescent probe, Lim and co-workers reported a novel two-photon fluorescent probe **33** for Hg^{2+} selectively detection [94]. They used 6-dimethylamino-2-acetylnaphthalene as a fluorescence reporter and azathiocrown ether as the response site. The probe showed a large two photon action cross section of 110 GM at 780 nm, and it can respond to Hg^{2+} selectively with a dissociation constant of $0.45 \pm 0.01 \mu\text{M}$. Furthermore, the probe can be applied for Hg^{2+} detection using two-photon microscopy in living cells and organs at 80–150 μm depth.

3.4. Fluorescent probes for Hg^{2+} analysis based on N-atom complexation

Srivastava and co-workers reported a turn-on fluorescent probe **34** for Hg^{2+} selective detection based on photoinduced electron transfer mechanism (Fig. 14) [95]. They used anthracene core as the fluorescence signal reporter and two benzhydryl moieties were incorporated

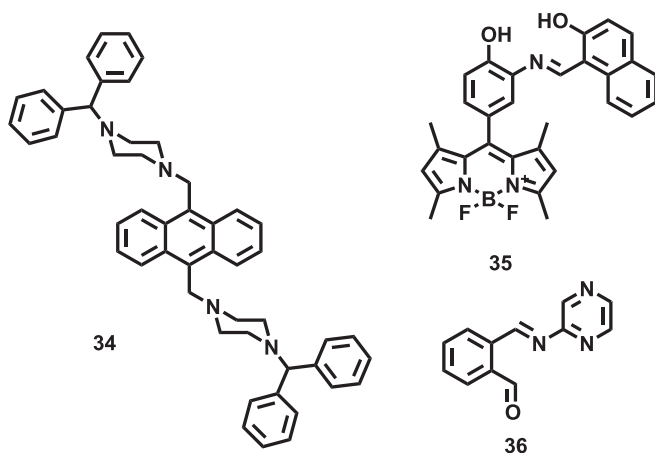


Fig. 14. Structures of 34–36.

into the anthracene core through piperazine bridge units for Hg^{2+} detection. An obvious fluorescence enhance (10 times) can be observed after addition of Hg^{2+} , and probe **34** can be used for Hg^{2+} reversible detection in ACN- H_2O and HEPES buffer. The stoichiometry of probe towards Hg^{2+} was 1:2, and the detection limit was 2 ppb. They further applied probe **34** for Hg^{2+} detection in actual mercury-contaminated water samples, cellulose paper tape, protein medium (such as BSA) and living cells. Furthermore, they utilized probe **34** for producing a reusable combinational logic circuit. Regrettably, the detection for Hg^{2+} can be disturbed by PO_4^{3-} .

Xiao and co-workers reported a turn-on fluorescent probe **35** based on BODIPY fluorophore [96]. The probe showed a strong binding capacity for Hg^{2+} , and the association constant was determined to be $9.43 \times 10^4 \text{ M}^{-1}$. The probe also displayed good imaging capabilities in living cells, zebrafish and nude mouse with LOD of 1.73 nM. Unfortunately, Al^{3+} caused slight interference with Hg^{2+} detection.

Gangatharan and co-workers reported a fluorescent probe **36** for Hg^{2+} sensing based on N-atom complexation reaction [97]. Probe **36** was synthesized from 2-amino pyrazine and phthalaldehyde, and it achieved Hg^{2+} detection by chelation-induced fluorescence signal changes with a stoichiometry of 1:1. After adding Hg^{2+} , probe **36** formed a stable chelate complex with Hg^{2+} , which had a larger conjugated structure. Hg^{2+} limited the C = N isomerization of probe **36**, thereby the fluorescence signal of probe **36** at 437 nm was enhanced. Based on molecular logic circuits, researchers applied the probe to molecular-level sequential logic gates containing a memory function. Furthermore, researchers produced test kits using probe **36** for actual samples detection.

3.5. Fluorescent probes for Hg^{2+} analysis based on other mechanism

Fluorescent probes can also be designed for Hg^{2+} sensing based on the reaction between Hg^{2+} and vinyl ether, arylboronic acid.

Ando and co-workers designed and synthesized a novel strategy for Hg^{2+} detection in environmental samples based on vinyl ether oxymercuration [98]. The first generation probe **37a** they designed can be applied for Hg^{2+} detection at a 1 ppb level in river water and dental samples (Fig. 15). However, the detection conditions of probe **37a** were harsh, and the probe needed to work in the acidic pH range of 3–4. And the Hg^{2+} detection by probe **37a** was interfered by Cl^- , and it was necessary to add silver nitrate to eliminate the interference from Cl^- . In order to overcome the above shortcomings, researchers optimized the probe structure with vinyl ether and probe **37b** was obtained. After optimization, the interference of Cl^- on the probe was reduced, and the reactivity of probe **37b** towards Hg^{2+} was increased. Probe **37b** exhibited desirable performance for Hg^{2+} detection with a LOD of 1 ppb.

Wu and co-workers reported a turn-on fluorescent probe **38** for Hg^{2+}

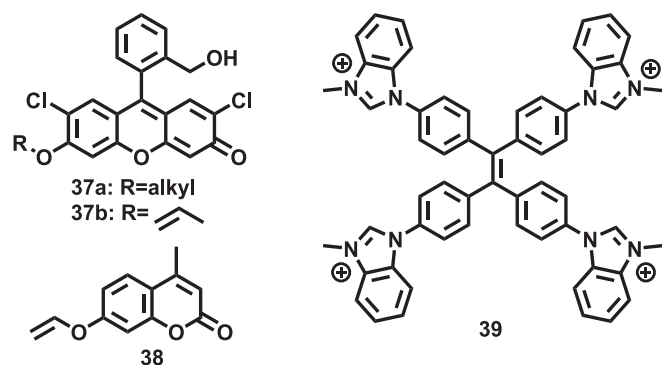


Fig. 15. Structures of 37–39.

sensing [99]. Coumarin was chosen as a fluorescence reporter, and vinyl ether unit was selected as a recognition site. Probe **38** exhibited no fluorescence signals in buffer solution. After adding Hg^{2+} , it can promote the irreversible hydrolysis of vinyl ether, accompanied by fluorescence signal increased at 450 nm. The sensing mechanism was verified by ^1H NMR analysis and MS analysis. The probe showed good water solubility, and the LOD of probe **38** can reach $0.12\ \mu\text{M}$. The probe also exhibited potential application value in water quality detection.

Yuan and co-workers developed a turn-on fluorescent probe **39** for Hg^{2+} sensing based on aggregation-induced emission [100]. They introduced four positively charged methylenated benzimidazole units into the styrene structure to increase the water solubility of probe. The rotation of the C–C bond between benzene ring, between benzene ring and benzimidazole, as well as the C–N bond between benzimidazole not only reduced the planarity of the probe structure, but also increased the possibility of non-radiative transitions. Therefore, probe **39** had no fluorescence emission signals. Probe **39** can coordinate with Hg^{2+} or organic mercury, and mercury-mediated chelate ring formation as well as subsequent aggregation made probe **39** more rigid, accompanied by strong fluorescence signal emission. The complexing mechanism was verified by transmission electron microscopy, dynamic light scattering and resonance light scattering. The probe was further applied for Hg^{2+} selective sensing in living cells.

Based on the displacement reaction between arylboronic acid and Hg^{2+} , Neupane and co-workers synthesized a new fluorescent probe **40** with enhanced fluorescence signal for Hg^{2+} detection (Fig. 16) [101]. They used dansyl as fluorophore, and probe **40** was synthesized after connected dansyl with phenylboronic acid through sulfonamide group. Researchers reported that the exchange reaction between boric acid and Hg^{2+} may enhance intramolecular charge transfer within the probe molecule, accompanied by an increase in fluorescence signal at 500 nm. They explored the reaction mechanism through spectral testing, HPLC analysis, HPLC-MS analysis and ^1H NMR analysis. The probe showed desirable sensing performance, such as good selectivity, high sensitivity, fast response and low detection limit, which exhibited good application potential in Hg^{2+} analysis.

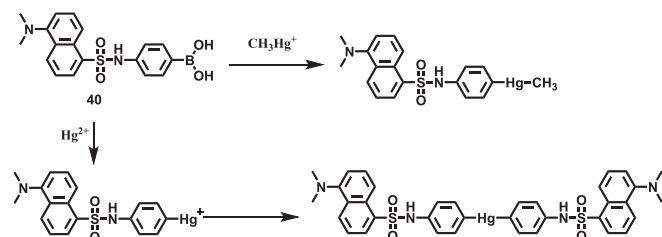


Fig. 16. The response mechanism of probe 40.

4. Ratiometric fluorescent probes for Hg^{2+} analysis

The fluorescence wavelength of ratiometric fluorescent probes will be red-shifted or blue-shifted after reacting with targets. Ratio determination of analyte can be achieved by calculating the ratio of signals at different fluorescence wavelengths. Ratiometric fluorescent probes have the following advantages: it can achieve self-correction and reduce the interference from various environmental factors such as photo-bleaching and instrument efficiency changes. Thus, the ratiometric fluorescent probes have high sensitivity. However, the acquisition operation of ratio fluorescence signals and the data processing operations are cumbersome. In addition, the fluorescence wavelength of ratiometric fluorescent probes should possess a large Stokes shift to reduce the fluorescence spectrum overlap and improve the sensitivity of the probe. In this section, we will introduce the ratiometric fluorescent probes based on the following reaction mechanisms: S-atom complexation, deprotection reaction of dithioacetals, rhodamine ring-opening reaction and N-atom complexation.

4.1. Fluorescent probes for Hg^{2+} analysis based on S-atom complexation

Most of the developed fluorescent probes for Hg^{2+} detection were based on the increase or decrease in fluorescence signals. Tian group reported a ratiometric fluorescent probe **41** for Hg^{2+} selective detection (Fig. 17) [102]. They used benzoyl thiourea unit as response site, and probe **41** with yellow-green fluorescence emission was obtained after connected benzoyl thiourea unit to fluorophore 4-amino-1,8-naphthalimide through ethylene. Hg^{2+} can trigger intramolecular cyclization by reacting with thiourea, accompanied by the change in fluorescence emission wavelength from 530 nm to 475 nm.

Tian and co-workers reported a ratiometric fluorescent probe **42** for Hg^{2+} selective detection with excellent water solubility [103]. They selected 9-amino-substituted acridizinium derivatives as fluorophore and 1,4-dioxo-7,13-dithia-10-azacyclopentadecane unit as response site to afford probe **42**. The probe can be applied for Hg^{2+} detection in pure water without the requirement of organic cosolvent. However, the fluorescence quantum yield of probe **42** was reduced after reacted with Hg^{2+} , and Ag^{+} also caused interference during Hg^{2+} detection, which limited the practical applications of the probe.

Given the advantages of ratiometric fluorescent probe, Xuan and co-workers designed and synthesized a ratiometric fluorescent probe **43** for Hg^{2+} selective detection (Fig. 18) [104]. They used coumarin as the fluorophore based on the desirable stability and optical properties of coumarin. In order to expand the conjugate system of the probe **43** and obtain a larger spectral separation, they introduced a thioether functional group at the 3rd position of the coumarin framework. Hg^{2+} can induce desulfurization and elimination reactions after reacted with probe **43**, and subsequently, an electron-withdrawing α , β -unsaturated ketone was produced. The conjugate system was expanded and the fluorescence emission spectrum was red-shifted. Probe **43** can be employed for Hg^{2+} selective detection, and the reaction stoichiometry of probe **43** to Hg^{2+} was 2:1. The colorimetric changes caused by probe structure change can be visually observed, and the probe can be applied for Hg^{2+} detection in living cells.

Chen and co-workers synthesized a two-photon ratiometric fluorescent probe **44** for Hg^{2+} recognition [105]. Probe **44** contained a

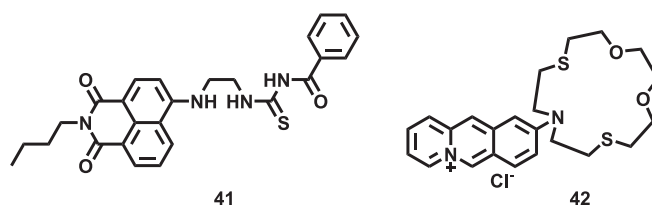


Fig. 17. Structures of 41 and 42.

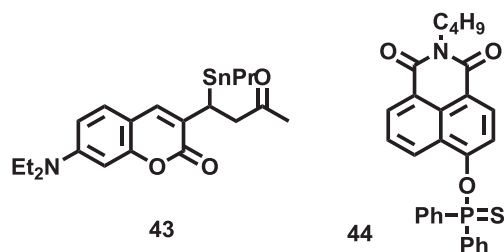


Fig. 18. Structures of 43 and 44.

naphthalimide fluorophore and a diphenylphosphinothioyl response unit. Hg^{2+} can promote to crack the P-O bond of thiophosphinate in the probe, releasing product NAP-O with effective intramolecular charge transfer from the electron-donating oxy-anion site to the strong electron-withdrawing naphthalimide unit. And the recognition mechanism was confirmed by HRMS. In addition, probe 44 was applied for Hg^{2+} imaging in HeLa cells and rat liver tissues.

4.2. Fluorescent probes for Hg^{2+} analysis based on deprotection of dithioacetals

The aldehyde group protected by mercapto can only be converted to previous aldehyde unit again in the presence of Hg^{2+} . Based on this principle, Cheng and co-workers designed and synthesized two fluorescent probes 45 (45a and 45b) for Hg^{2+} detection (Fig. 19) [106]. Probes 45 were obtained through the protection reaction of thiols on aldehydes. And the Hg^{2+} selective detection can be achieved through Hg^{2+} -promoted deprotection reaction of thioacetals. Probes 45 can quickly respond to Hg^{2+} , and probe 45a can be made into test strips which were easily used for actual samples detection. However, the probes had poor water solubility and the Hg^{2+} detection was interfered by Ag^+ , which limited the practical application of probe 45. Anyway, the design strategy of probes provided researchers with new ideas.

Zhou and co-workers synthesized a ratiometric fluorescent probe 46

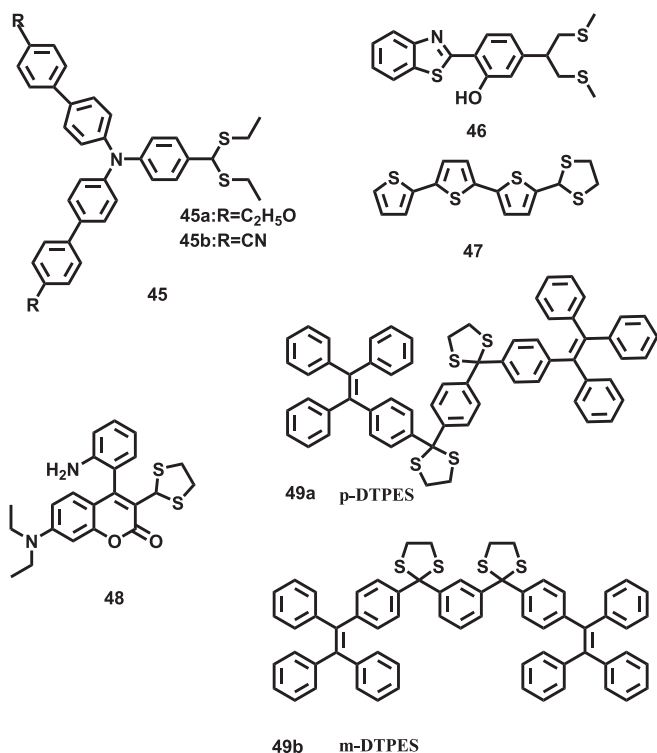


Fig. 19. Structures of 45–49.

for Hg^{2+} detection based excited-state intramolecular proton transfer/intramolecular charge transfer modulation [107]. They selected 2-(2-hydroxyphenyl)benzothiazole as the excited state intramolecular proton transfer (ESIPT) dyes skeleton and thioacetals as the recognition site. After addition of Hg^{2+} , the electron-rich disulfide acetal unit was removed by Hg^{2+} and it converted into an electron-deficient aldehyde group. At the same time, the ICT process from benzothiazole (electron donor) to aldehyde (electron acceptor) caused a significant red shift in the fluorescence wavelength and provided ratiometric fluorescence signals. The response mechanism of probe 46 was confirmed by HRMS and ^1H NMR analysis. The probe exhibited excellent spectral performance and the LOD of probe 46 was as low as 5.8 nM.

Lan and co-workers reported a ratiometric fluorescent probe 47 for Hg^{2+} sensing based on deprotection reaction of thioacetals [108]. Probe 47 5-(1,3-dithiolan-2-yl)-2,2':5',2''-terthiophene was synthesized by Kumada coupling reaction and Vilsmeier reaction. After adding Hg^{2+} , it triggered the deprotection reaction of acetal, and the dithioacetal group converted to aldehyde, accompanying the fluorescence signal at 450 nm decreased as well as fluorescence signal at 550 nm increased. The response mechanism was confirmed by ^1H NMR analysis, FT-IR analysis as well as spectrum analysis, and probe 47 was applied for Hg^{2+} detection in real water samples, shrimp, and fish.

Pan and co-workers developed a reaction-based ratiometric fluorescent probe 48 for Hg^{2+} determination via a "covalent assembly" strategy [109]. The pivotal design idea for probe 48 was to connect the Hg^{2+} response group 1,3-dithiolane unit into the *ortho* position of 2-aminophenyl unit, which would induce fluorescence signal changes of coumarin derivatives via the ICT mechanism. After addition of Hg^{2+} , 1,3-dithiolane was transformed to formyl via desulfurization reaction, and it would condense with nearby amino groups ($-\text{NH}_2$) to produce the product c-ql. $-\text{NH}_2$ can coordinate with Hg^{2+} and brought it closer to 1,3-dithiolane, which was beneficial to the intramolecular ring condensation reaction, and the product c-ql was a heterocyclic aromatic compound with a larger conjugate plane than the probe 48. The reaction mechanism was verified by HRMS and ^1H NMR analysis. The theoretical detection limits of the probe for Hg^{2+} and MeHg^+ were 27 nM and 5.8 μM , respectively.

Ruan and co-workers reported two ratiometric fluorescent probes 49 (49a and 49b) based on aggregation-induced emission for Hg^{2+} sensing [110]. The probe 49 contained tetraphenylethene fluorophore and two thioketal moieties. Hg^{2+} can promote the deprotection reaction of thioketal and produced ratio fluorescent signals changes that visually observable from sky blue to yellow-green, thus probe 49 can achieve the Hg^{2+} selective detection. The probes can be manufactured test strips, and provided convenience for Hg^{2+} on-site real-time detection.

4.3. Fluorescent probes for Hg^{2+} analysis based on rhodamine ring-opening reaction

Ratiometric fluorescent probes with effective internal calibration can reduce interferences from the instrument and other external factors. Qian group designed and synthesized a ratiometric fluorescent probe 50 for Hg^{2+} selective detection by connected BODIPY dye with rhodamine dye using a rigid and conjugated phenyl-ethynyl-phenyl spacer (Fig. 20) [111]. BODIPY with lipophilicity was selected as energy donor, and rhodamine with hydrophilicity was chosen as energy acceptor. The fluorescence spectrum of BODIPY matched well with the absorption spectrum of rhodamine, and they were linked through a phenyl-ethynyl-phenyl spacer, which can promote the through-bond energy transfer process. Initially, probe 50 showed the maximum absorption peak at 488 nm and the maximum emission peak at 514 nm. After reacted with Hg^{2+} , the emission peak of probe 50 at 514 nm was decreased while a new emission peak at 589 nm was increased. The probe showed excellent selectivity towards Hg^{2+} , and it can be applied for Hg^{2+} detection under physiological condition on the ppb scale.

Ge and co-workers designed and synthesized a FRET ratiometric

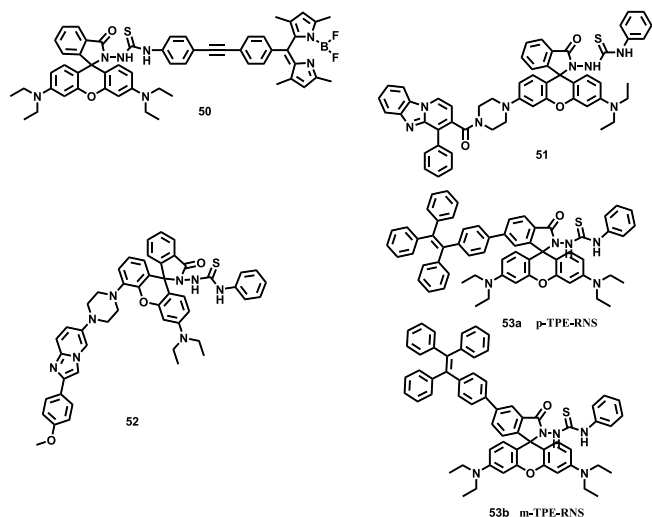


Fig. 20. Structures of 50–53.

fluorescent probe **51** for Hg^{2+} detection based on pyrido[1,2-a]benzimidazole-rhodamine system [112]. In the molecular structure of probe **51**, leuco-rhodamine derivative was selected as energy acceptor, and pyrido[1,2-a]benzimidazole was used as energy donor. The FRET efficiency calculated by donor fluorescence intensity detection was 87.3% in the presence or absence of the acceptor. Probe **51** had a large Stokes shift (204 nm), which can avoid interferences from spectral overlap. The LOD of probe **51** can reach 18.8 nM and it can be used for Hg^{2+} detection in the pH range of 5–10.

Li and co-workers developed a ratiometric fluorescent probe **52** for Hg^{2+} selective sensing based on rhodamine open-ring [113]. They chose rhodamine as energy acceptor and imidazo[1,2-a]pyridine as energy donor because the emission spectrum of imidazo [1,2-a] pyridine overlapped with the absorption spectrum of rhodamine. Probe **52** without FRET mechanism displayed absorption and emission maximum at 370 nm and 436 nm. After reacting with Hg^{2+} , rhodamine underwent a ring-opening reaction and the FRET mechanism turned on, while the fluorescence signal at 436 nm was decreased and the fluorescence signal at 590 nm was enhanced. The probe showed a large Stokes shift of about 220 nm, which can avoid fluorescence self-quenching effectively. The LOD of probe **52** was as low as 9.1 nM, and probe with superior spectral performance was applied for Hg^{2+} imaging in living cells.

Based on dark through-bond energy transfer, Tang group designed and synthesized ratiometric fluorescent probes **53** for Hg^{2+} sensing [114]. Obtaining large pseudo-Stokes shift may reduce the spectral overlap between donor emission and acceptor absorption, which can result in a decrease in FRET efficiency and donor energy leakage. A new design strategy, the through-bond energy transfer (TBET) mechanism, can be used as a desirable method to settle this contradiction. There was a torsion angle between the donor and acceptor, avoiding being regarded as a fluorophore. Compared with the traditional FRET system, the energy transfer rate of TBET can be 2 orders of magnitude faster, thereby reducing the dependence on spectral overlap. Therefore, even if there was a small spectral overlap, researchers can easily realize high energy transfer efficiency and analyze targets through the TBET mechanism, which was beneficial for producing large pseudo Stokes shift. Tetraphenylethene (TPE) had less fluorescence emission because the rapid non-radiative decay in solution, TPE was also easy to modify and TPE derivatives usually had big Stokes shifts. After suppressing non-radiation decay, TPE derivatives had higher signal emission in the aggregate state, thus researchers chose TPE as the dark donor. Rhodamine B derivatives with high quantum yield and large molar absorbance coefficient had been developed for designing various fluorescent probes, thus rhodamine B derivative was selected as acceptors. Researchers designed two

probes used thiosemicarbazides for Hg^{2+} high specifically recognition. Probes with hydrophobicity tended to form aggregates in solution. Rhodamine existed in the form of spironolactone, thus the probes emitted blue fluorescence of the TPE backbone. After addition of Hg^{2+} , the solubility of positively charged rhodamine in solution was increased. Due to the dark through-bond energy transfer process as well as non-radiative decay, the fluorescence of TPE cannot be observed, and the strong fluorescence signal from rhodamine can be observed. This reasonable design strategy can achieve ratiometric Hg^{2+} measurement. Probe had great pseudo Stokes shifts more than 280 nm and 240 for **53a** and **53b** respectively, which was favorable for imaging analysis. After adding Hg^{2+} , the signal was enhanced more than 6000 times, and the LOD can reach 0.3 ppb. This research provides a novel strategy for the design of Hg^{2+} fluorescent probes.

4.4. Fluorescent probes for Hg^{2+} analysis based on N-atom complexation

To solve the problem of spectral overlap, Zhang group designed and synthesized a novel ratiometric fluorescent probe **54** for Hg^{2+} selective detection with excellent spectral separation (Fig. 21) [115]. They selected naphthalimide derivative as chromophore due to its superior quantum yield and stability, porphyrin was chosen as response site for seizing Hg^{2+} . After linked naphthalimide derivative with porphyrin, probe **54** was obtained and it had two well-separated fluorescence peaks with a 125 nm difference (from 650 nm blue-shifted to 525 nm). The probe displayed reversible fluorescence response towards Hg^{2+} , and it can be applied for Hg^{2+} detection in living cells.

Jiang and co-workers reported a ratiometric fluorescent probe **55** based ICT mechanism for Hg^{2+} analysis [116]. They selected 4-amino-naphthalimide as the fluorescence reporter for its outstanding photo-physical properties, and a vinyl enol ether subunit was chosen as response unit for its desirable selectivity for Hg^{2+} detection, and they were connected using a carbamate group. Probe **55** exhibited superior selectivity towards organic mercury and inorganic mercury without interference from other ions. The probe was stable in the pH range of 2.17–11.13, and it can be used for Hg^{2+} detection in living cells.

Jiao and co-workers reported a ratiometric fluorescent probe **56** based on schiff-base for Hg^{2+} sensing [117]. Probe **56** contained a coumarin dye and a 5-aminoisophthalic acid methyl ester chromophore, and the schiff-base C = N site was used for Hg^{2+} response. Probe **56** emitted weak fluorescence signal because of the photoinduced electron transfer process. After addition of Hg^{2+} , the C = N bond hydrolysis reaction occurred and strong fluorescence signal was emitted. The probe showed good spectral response and can be utilized for intracellular Hg^{2+}

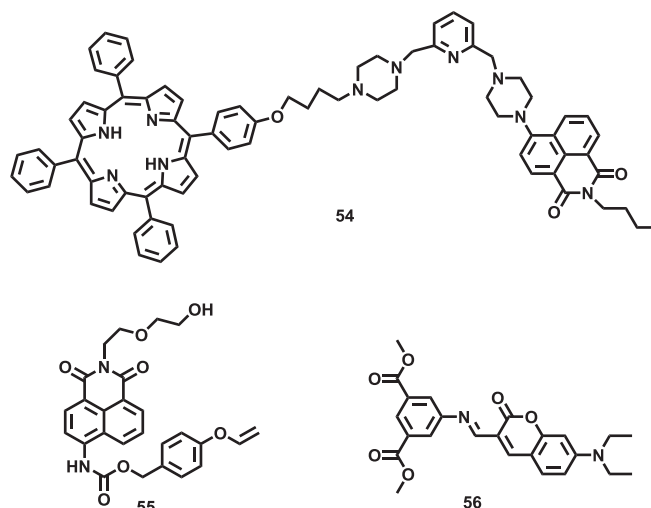


Fig. 21. Structures of 54–56.

detection.

5. Fluorescent probes for Hg²⁺ and other species analysis

Designing fluorescent probes for selectively analyzing individual species is relatively simple. However, multiple species may participate and act in a complex physiological process in environment and organisms. Therefore, multi-responsive fluorescent probes for two or more species detection are valuable, which also poses challenges for probe design. In this section, we will introduce fluorescent probes that are applied for Hg²⁺ and other species analysis.

The BODIPY unit and porphyrin unit showed effective energy transfer characteristics, and the stoke shift between BODIPY unit and porphyrin unit in the maximum fluorescence emission peak was large enough, thus they had great potential in designing FRET ratiometric probes. Chen and co-workers reported a versatile fluorescent probe **57** for Hg²⁺ and Fe²⁺ detection (Fig. 22) [118]. They connected BODIPY unit with porphyrin unit to afforded probe **57**. Hg²⁺ can reduce the ratio fluorescence signals of probe **57**, while Fe²⁺ increased the ratio fluorescence signals of the probe. The association constants of probe towards Hg²⁺ and Fe²⁺ were 3.5×10^6 and 2.2×10^6 respectively, which showed practical application potential of the probe for environmental samples.

Shen et al. reported a triphenylamine-BODIPY based Schiff base fluorescent probe **58** for Hg²⁺ and Fe³⁺ detection [119]. The introduction of 4-hydroxystyrene at the 3,5-positions of the triphenylamine-BODIPY core can expand the conjugate system of probe to achieve near infrared fluorescence emission, while Schiff base was also introduced to afforded a new probe **58** for Hg²⁺ and Fe³⁺ detection. Due to the non-radiative attenuation caused by C = N isomerization and rotation, probe **58** showed weak fluorescence signals. After addition of Hg²⁺ or Fe³⁺, the Schiff base underwent hydrolysis which further resulted in the conversion of C = N group to the formyl group, and the fluorescence

signal from probe **58** was enhanced. The stoichiometry between probe **58** and Fe³⁺/Hg²⁺ were 1: 3 and 1: 2, and the LOD of probe **58** were 5.15×10^{-7} M and 6.81×10^{-7} M respectively. The probe had great application potential in the field of ion detection and biomedicine after encapsulated as nanoparticles, and the probe can be employed for Hg²⁺ and Fe³⁺ detection in solution and living cells.

Gao et al. reported a fluorescent probe **59** based on Schiff-base for Hg²⁺ and Cu²⁺ sensing (Fig. 23) [120]. Probe **59** was synthesized using benzimidazole and coumarin fluorophores. After addition of Hg²⁺, the C = N bond was broken and hydrolyzed, and the new compound coumarin derivative and benzimidazole-Hg complex were finally formed. However, Cu²⁺ can complex with probe **59** to quench the fluorescence signals from probe **59**. Therefore, probe **59** can effectively distinguish Hg²⁺ and Cu²⁺, and it can be used for intracellular imaging.

Gu and co-workers reported a fluorescent probe **60** based on benzothiazole for distinguishing Hg²⁺ and Cu²⁺ [121]. Probe **60** contained two different recognition sites. The thioacetal unit was used for Hg²⁺ detection based Hg²⁺-induced dithioacetal deprotection, the O and N atoms in benzothiazole group was applied for Cu²⁺ sensing. Probe **60** emitted strong green fluorescent signals at 530 nm. After reacted with Hg²⁺, the fluorescence signal at 530 nm decreased and a new fluorescence peak at 545 nm increased gradually. However, the quenching reaction occurred after the addition of Cu²⁺. The reaction mechanism of probe **60** was verified by the spectra analysis, MS analysis and ¹H NMR titration analysis.

For O₂^{•−} and Hg²⁺ detection, Chen group designed two fluorescent probes (**61** and **62**) based on cyanine fluorophore for O₂^{•−} and Hg²⁺ associated-detection via three-channel fluorescence signals (Fig. 24) [15,16]. Probe **61** contained cyanine fluorophore and selenol group. After reacted with NaBH₄, the conjugated system of the cyanine fluorophore was interrupted, therefore probe **61** didn't emit fluorescence signals. The fluorescence signal from probe **61** can be selectively turned on by O₂^{•−}, thereby probe **61** can be applied for O₂^{•−} selective detection. Then, selenol-responsive unit can further achieve Hg²⁺ detection via selenium-mercury antagonism reaction. Probe **61** can be employed for associated-detection of O₂^{•−} and Hg²⁺ in living cells and model mice. Next, to improve the stability of the probe structure, they changed the response group, selenol group, to a more stable thiol unit to afforded probe **62**. The stability of probe **62** was improved, and it can be applied for O₂^{•−} and Hg²⁺ selective detection. Furthermore, probe **62** can be applied for O₂^{•−} and Hg²⁺ detection in living cells, and it can be employed for comparative studies of acute mercury poisoning and chronic mercury poisoning in mice models.

Hu and co-workers reported a turn-on fluorescent probe **63** for Hg²⁺ and Pb²⁺ detection based on a rhodamine-phenylurea conjugate (Fig. 25) [122]. The probe can achieve Pb²⁺ detection in CH₃CN and Hg²⁺ detection in aqueous media. Probe had good selectivity and high sensitivity towards Pb²⁺ and Hg²⁺, and the LOD of probe **63** for Pb²⁺ and Hg²⁺ were 7×10^{-9} as well as 3.5×10^{-8} M, respectively.

Based on desulfurization reaction, researchers have designed some desirable fluorescent probes for Hg²⁺ analysis. Tsukamoto and co-workers provided a novel concept that improved desulfurization susceptibility of 7-hydroxy-3-thioureidocoumarin by proper substituent

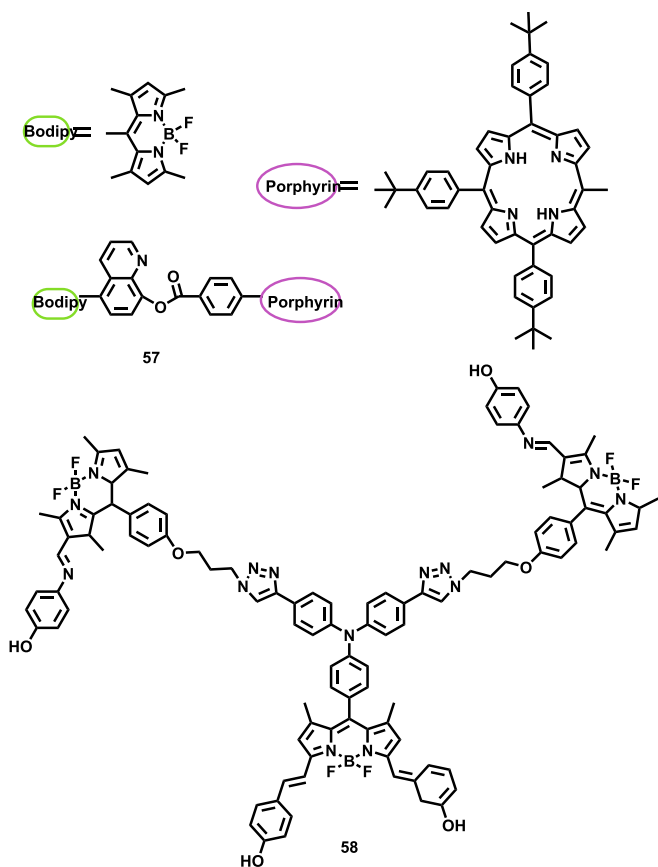


Fig. 22. The structures of probe **57** and **58**.

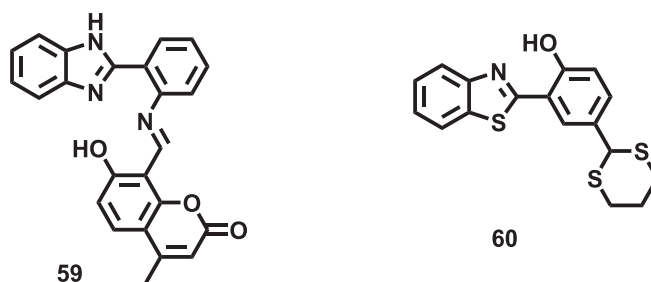


Fig. 23. Structures of **59–60**.

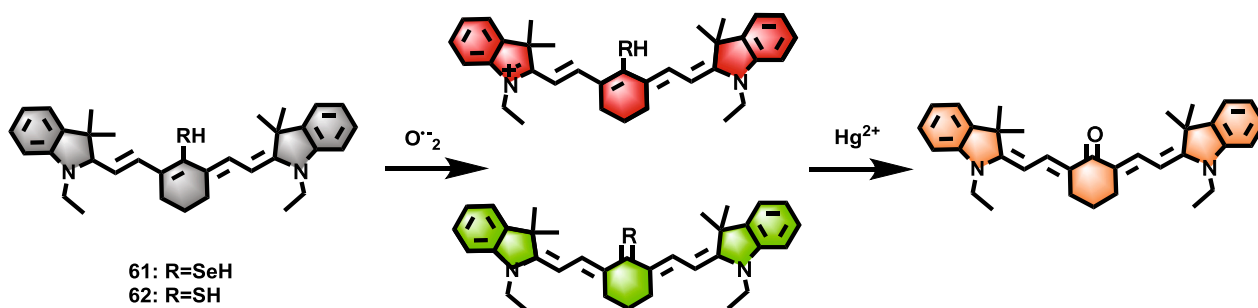
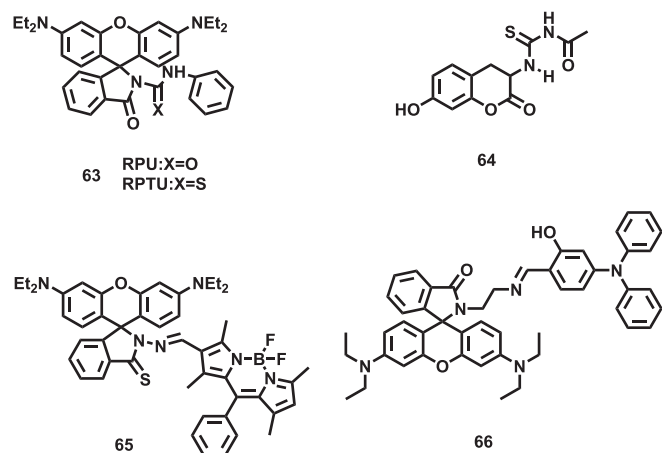
Fig. 24. The response mechanism of probe 61 and 62 for $O_2^{\bullet-}$ and Hg^{2+} sensing.

Fig. 25. Structures of 63–66.

[123]. They selected coumarin as fluorescence reporter and N'-acetylthioureido group as response site to construct probe 64 for Hg^{2+} and Ag^+ analysis. The hydrogen bond formed in the probe between the N-hydrogen and the acetyl O atom can effectively increase the susceptibility of desulfurization between probe and Hg^{2+} as well as Ag^+ . The high susceptibility of desulfurization by Hg^{2+} was confirmed by X-Ray crystallography and 1H NMR analysis. At first, no fluorescence signal was emitted from probe 64. After addition of Hg^{2+} , strong fluorescence signals from probe 64 were emitted and the fluorescence signals can quickly reach saturation within 2 min. Similarly, probe 64 can quickly respond to Ag^+ with fluorescence increase. The LOD of probe 64 for Hg^{2+} and Ag^+ were 2 ppb and 1 ppb, respectively. In addition, the authors proposed two methods to distinguish Hg^{2+} from Ag^+ . One way was to control the pH value, and the other way was to add Cl^- .

Karakus and co-workers reported a rhodamine/BODIPY-based fluorescent probe 65 for Hg^{2+} and Au^{3+} detection [124]. Initially, the rhodamine structure in the probe existed in the closed-ring form, and the probe didn't emit fluorescent signals. The reason can be attributed to the rapid isomerization of C=N group in BODIPY core, which may reduce the fluorescence emission of BODIPY due to the non-radiative deactivation process. After addition of Hg^{2+} , rhodamine existed in the ring-opened isomeric form and it emitted strong fluorescence signals at 585 nm. In addition, probe can achieve Au^{3+} detection based on the hydrolysis reaction. The probe possessed good cell membrane compatibility and it can be used for cell imaging analysis.

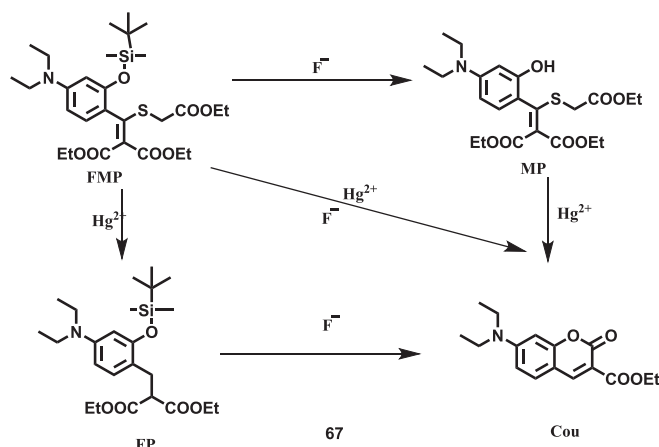
For Hg^{2+} and Al^{3+} sensing, Erdemir reported a new probe 66 based on the connection of aldehyde derivative of triphenylamine and rhodamine [125]. Probe 66 can realize Al^{3+} and Hg^{2+} detection through "PET-off" and "FRET-on" mechanisms, respectively. The LOD of probe 66 towards Al^{3+} and Hg^{2+} were 71.8 nM and 0.48 μM , respectively. To facilitate detection, the authors produced test strips using probe 66, and it can achieve Hg^{2+} and Al^{3+} detection conveniently.

Hu and co-workers designed and synthesized three fluorescent probes 67 (MP, FP, and FMP) for Hg^{2+} and F^- detection (Fig. 26) [126]. Among the three probes, probe MP can realize Hg^{2+} selective sensing based on Hg^{2+} -promoted desulfurization, and probe FP can realize F^- selective detection based on F^- -triggered desilylation, while probe FMP emitted strong fluorescence signal after reacted with Hg^{2+} and F^- . The LOD of probes 67 towards Hg^{2+} and F^- were 4.0×10^{-8} M and 1.14×10^{-6} M, respectively. Researchers considered that the "AND" logic gate of FMP may have potential applications in molecular device development. Furthermore, the probe was applied for cell imaging successfully.

6. Challenges and prospects

In this feature article, we summarized the design strategies, performance and applications of the recent developed fluorescent probes for Hg^{2+} detection. Probes for Hg^{2+} detection are assorted by fluorescence signal response types: signal-decreased fluorescent probes, signal-enhanced fluorescent probes and ratiometric fluorescent probes. Moreover, multi-responsive fluorescent probes that can simultaneously detect Hg^{2+} and other species are also summarized. In each section, fluorescent probes are introduced according to design strategies, for example Hg^{2+} -promoted rhodamine ring-opening reaction, deprotection reaction of dithioacetals, desulfurization reaction, sulfur-complex reaction and nitrogen-complex reaction.

Recently, the development of fluorescent probes for Hg^{2+} detection significantly promoted fluorescence imaging analysis technology. Compared with the traditional analysis technology, Hg^{2+} detection based on fluorescent probes have distinct advantages, such as simple test steps, real-time online monitoring and less interference from environment or organisms. Despite the developed fluorescent probes providing convenience for Hg^{2+} detection in environmental samples and biological samples, several obstacles for fluorescent probes in selectivity, sensitivity and applications need to be overcome. Now the majority of

Fig. 26. The response mechanism of probe 67 for Hg^{2+} and F^- sensing.

fluorescent probes for Hg^{2+} detection are based on the response between sulfur, nitrogen, or oxygen atoms and Hg^{2+} . However, these atoms usually interact with other species that may interfere with Hg^{2+} detection. Therefore, specific fluorescent probes for Hg^{2+} selective detection should be ingeniously designed. Additionally, fluorescent probes should have appropriate hydrophilicity and lipophilicity considering the complexity of the actual application environment. For Hg^{2+} sensing in organisms, probes attached with targeting functions groups are more valuable for exploring the distribution of Hg^{2+} *in vivo*. Moreover, distinguishing inorganic mercury ions (Hg^{2+}) and organic mercury is meaningful and challenging.

Considering the complexity of environmental conditions and organism milieu, developing novel fluorescent probe for Hg^{2+} selectively detection suffer from challenges, such as perturbation from endogenous active species, cell leakage and photostability. Fluorescent probe usually synthesized from organic molecule skeletons, which may suffer poor stability. Therefore it's urgent to improve the stability of fluorescent probes, including photon-stability and hydrolytic stability. Improving specific selectivity for Hg^{2+} detection and decreasing the interference from other species are meaningful. There are various forms of mercury, and it is also valuable for distinguishing determination of mercury with different forms, such as Hg^{2+} and methylmercury. Furthermore, multi-response probes are attractive though they require ingenious probe design. Hg^{2+} as toxic heavy metal ion seriously interferes with normal physiological activities in organism, and designing powerful probe tools is of great significance for studying the effects of Hg^{2+} on organism health. The convenient probe test strips for environmental samples detection have drawn lots of attention and little progress in this field means a lot. In short, there are many interesting things worthy to do in the field of mercury imaging analysis.

Overall, mastering basic concepts and design strategies is necessary for developing superior fluorescent probes. A superior fluorophore should possess the following features: 1) good biocompatibility; 2) superior stability; 3) high quantum yield; 4) suitable emission spectrum wavelength range; 5) favorable chemical modifiability, etc. The response groups should specifically recognize targets and then show the detection signals through fluorophore. During responsive groups screening, selectivity and sensitivity are important considerations. The response units should not only exclusively respond to the target analytes without being influenced by potential interferes, but also have high sensitivity for low-level targets analysis. Moreover, the positioning groups can realize the targets analysis at specific sites through targeting specific organ or subcellular organelle. The applications of fluorescent probes, especially in environmental samples and biological imaging analysis, are the ultimate goal.

7. Summary

Fluorescent probe analysis technology with superior selectivity and high sensitivity has unique advantages for ions and molecules *in situ* real-time analysis. In this feature article, we summarize the fluorescent probes for Hg^{2+} detection, and they are classified according to the response modes of probe signals. We focus on probe design strategies, performance and applications of the fluorescent probes. Fluorescent probes exhibited superior performance for Hg^{2+} detection in complex aqueous medium, and they also can achieve rapid *in situ* detection in cells and *in vivo*. Differentiated detection of various forms of mercury is challenging but meaningful. The production of portable test strips is an extremely promising practical application of fluorescent probes. We strongly believe that the application range of fluorescent probes will be further expanded by drawing on the research results of Hg^{2+} fluorescent probes and combining with the new probe design strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors declare no competing financial interest.

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