

Review

Application of Fluorescent Probes for the Detection of Zinc Ions in Cells and Oil Paintings

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Abstract: Zinc is an essential trace metal element in the human body, but it also constitutes a variety of proteins in the body of the important elements necessary; this element plays an important role in physiological metabolism. Disturbances in the metabolism of zinc ions in the body can significantly threaten human health, especially neurological diseases. Therefore, developing a rapid and straightforward method for determining zinc ions is important. Fluorescent probe technology has been widely used for detecting and labeling zinc ions. Among many fluorescent probes, the rhodamine derivative LPDQ fluorescent probe has unique application scenarios, for example, it plays an important role in the detection of zinc white in oil colors, and its advantages are simplicity, rapidity, and real-time operation. This paper introduces the types of fluorescent probes for zinc ions and the three main mechanisms of fluorescent probe detection. The characteristics, design strategies, and application effects of the three fluorescent probes for zinc ions, as well as their advantages and limitations, are reviewed and summarized, which are intended to provide valuable references for the development of new probes for zinc ions detection in the future and for the future direction of research in this field.

Keywords: fluorescent probes; zinc ions; detection; application



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1. Introduction

As the environmental pollution problem is getting more and more attention, the environmental awareness of human beings has gradually improved, and people have begun to pay attention to the harm of metal pollution to human beings [1]. However, some trace metal elements essential to the human body are often overlooked and not given enough attention [2]. For example, metallic elements such as iron, zinc, and copper are essential elements in the human body, but excessive intake can also seriously jeopardize human life and health [3,4].

Zinc is the second most abundant trace metal element in the human body and an important element necessary for the composition of many proteins [5]. Most of the zinc in the body is in the form of zinc ions (Zn^{2+}) and this element plays an important role in physiological metabolism [6,7]. Zinc ions are important cofactors in the catalytic process of constructing many biological enzymes that regulate protein and nucleic acid synthesis, gene expression, cell growth, differentiation, and transmission of neural signals [8,9]. The disturbance of zinc ion metabolism in the body can pose a significant threat to the life and

health of the human body, especially neurological diseases, which can induce Alzheimer's disease, Parkinson's disease, epileptic diseases, etc. [10,11]. Zhang et al. [12] prepared a peptide-based ratiometric fluorescent probe, HcZ9, by solid-phase peptide synthesis for the quantification of zinc ions in biological solutions, which showed promising applications in cellular and human semen studies. Therefore, monitoring the concentration of zinc ions in the body in real-time is of great significance.

The primary detection methods of trace metal elements include electrochemical analysis, atomic spectrometry, isotope mass spectrometry, and chromatography [13–16]. Despite the high sensitivity of these traditional methods, the high requirements for samples, time-consuming operation, reliance on large-scale equipment and professional operators, and unsuitability for on-site rapid detection have primarily limited the application in real life. In recent years, fluorescence detection technology has been widely used in chemistry, medicine, and life sciences. It has been developed considerably because of its advantages of simple sample preparation, fast response, higher sensitivity, better selectivity, and ease of operation [17–19]. Rivera-Fuentes et al. [20] developed the far-red light probe SpiroZin2, which has a nanomolar affinity for zinc ions and is insensitive in the physiological pH range, and can be used for the precise detection and imaging of zinc ions in cells and tissues, providing a reliable tool for the study of zinc dynamics in acidic vesicles and neural synapses. Fluorescence detection techniques have been applied to detect metal ions in the environment and living organisms. In particular, fluorescent probe-targeted detection, labeling, and imaging techniques have received tremendous attention and have become a specialized field of research. In recent years, fluorescent probe detection has been significantly developed, mainly including fluorescent molecular probes for recognizing and detecting relevant metal ions, small molecules, etc. [21,22]. At the same time, the detection target can be labeled and imaged in the cell, which has an important reference significance for the study of related diseases [23]. The coumarin platform is widely used to design and synthesize small-molecule fluorescent probes. The backbone has been used to develop fluorescent chemosensors for various applications in molecular recognition, molecular imaging, bioorganic chemistry, analytical chemistry, materials chemistry, and biological and medical sciences. Goldberg et al. [24] designed a ZP1-based photoactivatable zinc sensor to achieve spatiotemporal control of zinc response to fluorescence through the introduction of a photocleavable protecting group. The sensor restored the metal-binding ability under UV irradiation and was successfully applied to imaging zinc dynamics in living cells and brain slices with high spatiotemporal resolution, providing a novel tool for resolving the transient function of zinc in biological processes such as neural signaling. The Schiff base is a suitable metal ion ligand, its structure contains rich nitrogen oxygen and other electron-rich coordination atoms that can be easily coordinated with metal ions; rhodamine and other organic fluorescent dyes have better light stability, and unique rigid coplanar structure, etc.; it is an ideal probe material, which prepares rhodamine derivatives of fluorescent probes with a strong fluorescence signal during the reaction and good light stability / The prepared rhodamine derivative fluorescent probe has strong fluorescent signal during reaction, good photostability, short detection time, apparent reaction phenomenon, non-toxicity, and other outstanding photophysical properties. Strianese et al. [25] investigated the coordination behavior of complexes formed by phenol-substituted bis(pyrazolyl)methane ligands (L1-H and L2-H) with zinc ions (Zn^{2+}) and their potential for use in the detection of zinc ions by fluorescent probes. The fluorescence intensity of L1-H was shown to be significantly enhanced upon coordination with zinc ions, especially in dichloromethane solution (switching ratio SR = 90%) suggesting that this ligand–metal system has the potential to serve as a fluorescent probe for zinc ions. The quinoline-based macrocyclic receptors and heteroscorpionate ligands share common features in the detection of zinc ions, (1) both contain specific

structures or functional groups capable of liganding with zinc ions. These structures can provide coordination sites for zinc ions, thus realizing the recognition and binding of zinc ions. (2) The formation of stable complexes: After they are combined with zinc ions, they are able to form a more stable complex structure. This stability helps maintain the capture and signal response to zinc ions during the detection process, reducing the loss of zinc ions and interference, and thus improving the accuracy and reliability of the detection. Yu et al. [26] systematically reviewed the research progress of zinc-ion fluorescent probes in the last ten years, focusing on the bioimaging properties of typical fluorophores such as naphthol, naphthalenediimide, pyrene, quinoline, coumarin, and rhodamine. The application potential of the probe in highly selective detection, real-time imaging, and disease diagnosis was analyzed, and theoretical reference was provided for the development of new zinc ion fluorescence probes with a low detection limit and high water solubility. Based on this, this paper describes some fluorescent probes for detecting zinc ions. This paper reviews the relevant literature from 2017 to the present, mentions some important findings dating back to earlier years, and aims to provide a comprehensive overview of the research vein of the field from its early development to the present, and these papers provide important support for understanding the origin of the field and its basic theory.

2. Detection Mechanism of Fluorescent Probes

Alexander Demchenko [27] systematically explained the design principle and detection mechanism of fluorescent probes in his book. The core mechanisms include the following: (1) photoinduced electron transfer (PET) (inhibition of electron transfer to restore fluorescence after the probe binds to the analyte); (2) intramolecular charge transfer (ICT) (liganding or protonation alters the distribution of electrons, resulting in spectral shifts); (3) fluorescence resonance energy transfer (FRET) (ratiometric detection through energy transfer); and (4) aggregation-induced luminescence (AIE) (inhibition of molecular motion to enhance fluorescence). Demchenko emphasized that the probe design needs to balance selectivity with a signal dynamic range and optimize the detection sensitivity and immunity to interference through a modular strategy, providing the basis for molecular tools for disease diagnosis and environmental monitoring. The detection mechanism of fluorescent probes has a wide range of applications in the fields of bioassay, environmental monitoring and medical diagnosis due to its high sensitivity, high selectivity, and real-time monitoring capability. With the continuous development of technology, the design and application of fluorescent probes has been optimized, providing more possibilities for the detection of complex biological systems.

2.1. Light-Induced Electron Transfer

The photoinduced electron transfer (PET) process transfers electrons from an energy donor to an energy acceptor under photochemical action. This transfer occurs only when the donor and the acceptor are in proximity to one another [28,29]. The design of fluorescent probes using the PET mechanism must have the following conditions: (1) a fluorophore with high fluorescence quantum yield; (2) a recognition group with strong electron-donating or electron-acquiring ability; and (3) the highest occupied molecular orbital or the lowest unoccupied molecular orbital of the recognition group is between the highest occupied molecular orbital/lowest unoccupied molecular orbital of the fluorophore [30,31]. The PET system consists of a “fluorophore-spacer group-receptor”. The fluorophore undergoes intramolecular electron transfer with the receptor upon light excitation, resulting in a change in the fluorescence signal. In probes designed based on the PET mechanism, pesticides disrupt the original PET, leading to enhancement, bursting, or changes in the

fluorescence signal, depending on the nature of the donors and acceptors involved in the PET mechanism [32,33].

2.2. Fluorescence Resonance Energy Transfer

Fluorescence resonance energy transfer (FRET) is a process in which an excited fluorophore energy (energy donor) transfers its energy to a neighboring ground state acceptor (energy acceptor) through a relatively long-distance dipole–dipole interaction [34]. Loas et al. [35] synthesized ZBR4 and ZR1, two two-site zinc ion probes based on carnosine, which showed significant fluorescence enhancement in response to zinc ions, and ZBR4 could be localized to the mitochondria, while ZR1 was located in the endoplasmic reticulum. The reversible detection of zinc ions in living cells can be realized, providing a new tool for the study of organelle-specific zinc dynamics, but the solution stability problem needs to be further solved. The key to designing a fluorescent probe based on the FRET mechanism is to ensure an inevitable spectral overlap between the emission spectrum of the energy donor and the absorption spectrum of the acceptor, and that the distance between the donor and the acceptor is less than 10 nm. The practical challenge of FRET-based fluorescent probe design, however, lies in the fact that the substance to be tested may alter the distance between the donor and the acceptor or change the emission or absorption spectra of either the donor or the acceptor, leading to the possibility of observing the emission of an energy donor even in the absence of energy transfer [36,37], thus affecting the sensitivity of the assay. Pesticides usually act as FRET receptors in probes designed based on the FRET mechanism, causing a fluorescence burst when energy is efficiently transferred.

2.3. Intramolecular Charge Transfer

Intramolecular charge transfer (ICT) refers to the fact that the fluorophore backbone of a probe has electron-donating and electron-absorbing groups attached at the ends of the probe, so that the electron-donating group inside the molecule can transfer charge to the electron-absorbing group. The stronger the electron-donating or electron-absorbing ability of the electron-donating or electron-absorbing groups in the probe molecule, the stronger the ICT effect, the longer the wavelength of the ICT peak, and usually the enhanced fluorescence intensity [38]. When a probe is designed based on the ICT mechanism, the binding of a substance to be detected to the probe affects the electron-donating and electron-absorbing abilities of the moiety, resulting in a change in the fluorescence signal and a change in the quantum efficiency of the probe.

2.4. Other Mechanisms

In addition to the above three common mechanisms, the fluorescent probes work by the inner filter effect (IFE) [39], aggregation-caused quenching (ACQ) [40], aggregation-induced emission (AIE) [41], and so on. (ACQ), aggregation-induced emission (AIE), etc. Molecular IFE, like FRET, requires spectral overlap between the fluorophore and the absorber. However, unlike FRET, IFE is derived from radiative energy transfer, with no distance requirement between the energy donor and the acceptor. This process affects only the fluorescence intensity and wavelength. ACQ is a phenomenon in which a fluorophore luminesces strongly in a dilute solution but weakens or even disappears at high concentrations [42]. The mechanism of ACQ may originate from the accumulation or aggregation of fluorophores at high concentrations or bursting caused by interaction with other molecules. The process of AIE is diametrically opposite to that of ACQ. AIE is a phenomenon in which fluorophores do not emit light in dilute solution but at high concentrations or in the aggregated state. The mechanism of AIE may be because the dynamic molecular internal rotation in a dilute solution dissipates the energy of their excited states. The combined effect of molecular internal rotation limitation in the aggregated state, molecular confor-

mation changes, and changes in electronic states due to the aggregation state give this type of probe optimal luminescence efficiency in the aggregated state [43]. In addition, Wen et al. [44] reviewed the research progress of zinc ion fluorescent probes from 2019 to 2023. The sensing systems based on the photoinduced electron transfer (PET), excited state intramolecular proton transfer (ESIPT), intramolecular charge transfer (ICT), fluorescence resonance energy transfer (FRET), chelate-enhanced fluorescence (CHEF) and aggregation induced luminescence (AIE) are mainly described, and their recognition performance is analyzed in combination with typical cases and theoretical calculations. It provides a reference for the development of new zinc ion detection technology.

3. Fluorescent Probe to Detect Zinc Ions

3.1. Coumarin-Based Fluorescent Probes

Coumarins containing the 1-benzopyran-2-one moiety are a large and widely studied family of compounds. Coumarins and their derivatives occupy an important place in the synthesis of natural products and organic chemistry. The coumarin parent ring emits weak or even no fluorescence. However, some substituted coumarin-like derivatives can produce strong fluorescence in the UV–visible range. Some novel coumarin dyes with improved and extended structures and properties have been designed and synthesized. At present, some novel coumarin dyes with improved and extended structures and properties have been designed and synthesized. Wang's group also designed and synthesized coumarin derivatives based on the C=N rotation mechanism, as shown in Figure 1, which can selectively recognize zinc ions very well [45]. The compound itself fluoresces weakly at 480 nm before binding zinc ions. However, after binding zinc ions, the heteroatoms O, N, and O in the molecular structure are involved in coordination with Zn^{2+} and the C=N rotation is suppressed, resulting in strong fluorescence at 565 nm and a redshift of the emission peak by 85 nm.

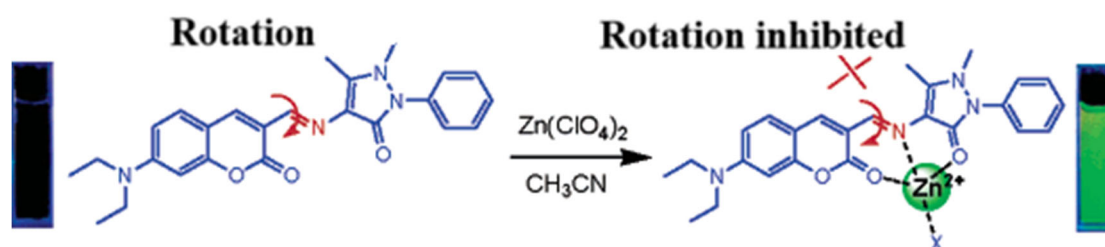


Figure 1. Schematic diagram of C=N heterogeneous fluorescent probes and their recognition of Al^{3+} [45].

Yang's group [46] designed and synthesized a novel coumarin derivative fluorescent probe, FCP, based on the photo-induced electron transfer (PET) mechanism, which can be used for the quantitative detection of Zn^{2+} . The probe FCP has the advantage of good selectivity, high sensitivity, and a broad pH response range and can be used to detect Zn^{2+} in aqueous solutions. Fluorescence enhancement (~ 13 -fold) was observed upon adding Zn^{2+} to the solution. FCP also showed good cell penetration in the HeLa cell model and exhibited very low cytotoxicity in the HEK-293 cell model. Nam's [47] group reported HN1, a Zn^{2+} ratiometric fluorescent probe with a dual fluorophore as a platform. The binding of the probe to Zn^{2+} inhibited the intramolecular phototransfer of the electrons mechanism and facilitated the resonance energy transfer of energy to the receptor. With good selectivity, excellent pH tolerance, and a suitable K value, probe HN1 is suitable for detecting Zn^{2+} in living organisms. Finally, the exogenous Zn^{2+} content can be detected by fluorescence colorimetry in HeLa live cells. The probe can reliably monitor the equilibrium state of zinc ions as they cross the cell membrane. Zastrow et al. [48] designed and

synthesized a HaloTag-based zinc sensor, fusing ZP1 and HaloTag to achieve intracellular zinc targeting, and then combined with mCherry to achieve ratiometric sensing, which provides a powerful tool for studying the distribution and dynamic changes of zinc ions. Tong [49] group designed and synthesized a novel Zn^{2+} fluorescent probe, T2, using coumarin and quinoline as the detection platform. T showed high affinity for Zn^{2+} . Its K value was 0.98 μM . The limit of detection of Zn^{2+} was estimated to be 48.1 nM. In addition, Probe T showed low cytotoxicity and good cell membrane permeability under physiological conditions for the quantitative determination of Zn^{2+} levels in actual water samples. In this study, we developed a novel Zn^{2+} receptor and successfully realized Zn^{2+} imaging in living cells, which provides a basis for the further qualitative and quantitative detection of Zn^{2+} in living cells. Yang's [50] group designed and synthesized HL, a one- and two-photon probe that is simple for detecting Zn^{2+} . This probe is highly selective for Zn^{2+} and shows a significant enhancement of the fluorescence intensity at 500 nm, which may be attributed to the generation of the 2:1 stoichiometric complex HL–Zn between HL and Zn^{2+} , which results in the blocking of the isomerization of the C=N structure, thus inhibiting the light-induced electron transfer. Furthermore, the HL recognition process's reversibility was achieved by adding the Zn^{2+} scavenger EDTA disodium salt. Dimethylpyridinamine (DPA) is a good zinc ion-recognizing group, and the probe [51] is composed of 7-amino-4-methylcoumarin and dimethylpyridinamine (DPA) linked by chloroacetyl chloride. Probe 1 showed almost no fluorescence in neutral aqueous solution ($\Phi_F = 0.05$) due to the transfer of a lone pair of electrons from the nitrogen atom to coumarin in the excited state (PET effect). When Cd^{2+} was added, the probe produced a strong violet fluorescence ($\Phi = 0.36$) at 386 nm. With the addition of Zn^{2+} , the probe also showed a strong fluorescence emission at 437 nm ($\Phi_F = 0.63$), while other metal ions showed no fluorescence response. IR, NMR, and potentiometric analyses confirmed that Zn^{2+} and Cd^{2+} integrated with N on pyridine, N on the amine group, and O on amide, respectively, and formed a 1:1 complex, which led to the inhibition of PET and the restoration of fluorescence. Although the coumarin probe has achieved excellent results in detecting zinc ions, the parameters of coumarin synthesis, such as reaction time and temperature, may impact on the effect of the coumarin probe on specific analytes. Therefore, the control and optimization of coumarin probe synthesis parameters may be a direction for future attention.

3.2. Schiff Base Fluorescent Probes

Schiff bases are excellent ligands for metal ions, and their structures contain electron-rich coordination atoms such as nitrogen and oxygen, which can be easily coordinated with metal ions. Classical Schiff bases, formed by the condensation of amine and aldehyde groups, have received attention from researchers recently because of their simple and inexpensive synthesis and the fact that they can be easily modified and remodeled. In 2016, Liu et al. [52] synthesized a quinoline fluorescent probe, QLAS, from salicylaldehyde hydrazone and quinacrine chloride, with the structure shown in Figure 2. The probe structure contains phenolic hydroxyl groups, quinoline nitrogen atoms and imine bonds, which can provide ligand sites for zinc ions. The probe triggers a fluorescence-enhanced response after forming a ligand with zinc ions, with reasonable specificity in the response process, resistance to various ionic interferences, and a low detection limit as low as 21 nM. The probe has a low cytotoxicity and a significant Stokes shift and can be used to detect zinc ions in cells. Gandin et al. [53] developed a new, sensitive, selective, and non-invasive Zn^{2+} fluorescence sensor. Zinpyr-1, a Zn^{2+} sensitive probe in a porous membrane, responds quickly and reversibly, detecting 1 μM –1 mM Zn^{2+} in seconds for cell-related studies. Mameli et al. [54] systematically investigated the coordination chemical behaviors of three novel quinoline derivative macrocyclic ligands (L1–L3) with Cu^{2+} , Zn^{2+} , Cd^{2+} , Hg^{2+} , and

Pb^{2+} , and confirmed that the quinoline-based fluorescent probe can modulate the selective recognition of $\text{Zn}^{2+}/\text{Cd}^{2+}$ through steric effect, which provides a theoretical basis for the design of highly selective zinc ion sensors.

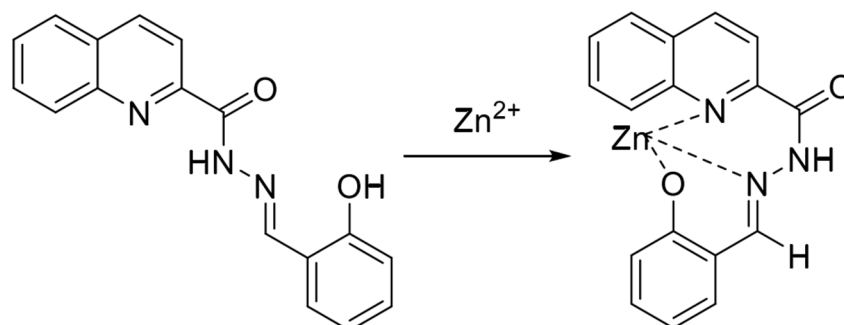


Figure 2. Mode of action of fluorescent probe QLAS with zinc ions [52].

In 2019, Lu et al. [9] synthesized the fluorescent probe P-OH in a one-step process using 2-aminobenzoylhydrazine and 3'-formyl-4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile, and the structure is shown in Figure 3. In the THF/HEPES (4/6, *v/v*) buffer system, the phenolic hydroxyl oxygen in the probe structure, the nitrogen atom in the imine structure and the oxygen atom in the hydrazide structure can be coordinated with zinc ions and the probe and zinc ions form a 2:1 ligand to realize the fluorescence-enhancement response to zinc ions, but cadmium ions also cause a fluorescence-enhancement phenomenon in the detection process. The assay process's short response time and high sensitivity (13 nM), accompanied by visualization, can be used to detect zinc ions in cells and zebrafish.

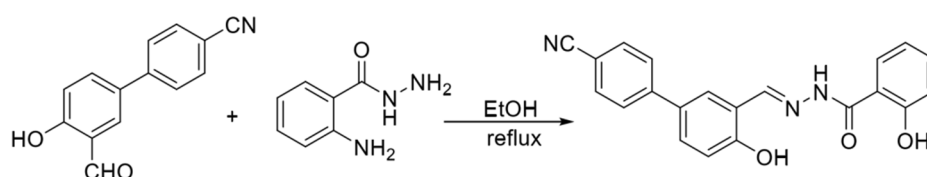


Figure 3. Synthesis route of the probe P-OH [9].

In 2020, Xiao et al. [55] synthesized a terpyridine-based fluorescent probe QTPY with 2-acetylpyridine and quinoline-2-carbaldehyde as raw materials. The probe utilizes the coordination of nitrogen atoms in the pyridine ring to form a 2:1 ligand with ions to achieve the fluorescence enhancement of zinc and cadmium ions simultaneously. However, copper ions will produce serious interference in the detection process. The probe has been applied to detect ions in water. In 2021, based on the PET detection mechanism, Mu et al. [56] synthesized a naphthalene-based Schiff base fluorescent probe based on 2-hydroxy-1-naphthaldehyde and furan-2-carbohydrazide, and the structure is shown in Figure 4. In the neutral system acetonitrile/HEPES (1/1, *v/v*), the phenolic hydroxyl oxygen atom, imine nitrogen atom and furan oxygen atom in the probe structure can bind to zinc ions and form a ligand in the ratio of 1:1, which leads to the inhibition of the PET process to show a strong fluorescence-enhancement effect, which can realize the real-time response to the zinc ions, high sensitivity (118 nM), and the reproducibility of the detection. However, the cadmium ions will also be part of the fluorescence-enhancement effect in the detection process. However, cadmium ions also show partial fluorescence enhancement during the detection process. The probe can be used to detect zinc ions in water and cells.

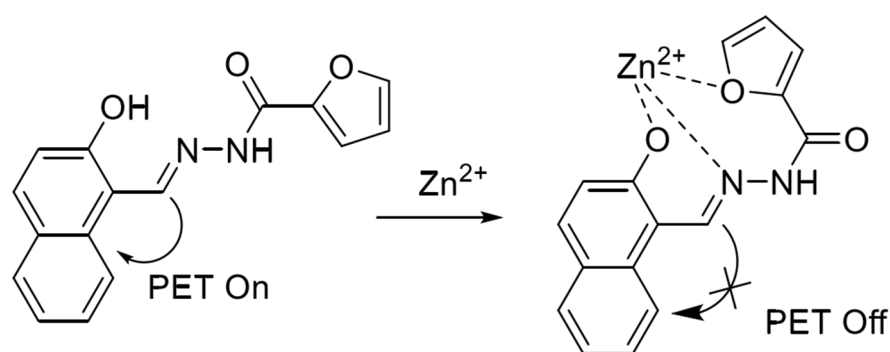


Figure 4. Mode of action of naphthalene-based fluorescent probes with zinc ions [56].

In 2022, Wu et al. [57] synthesized a near-infrared fluorescent probe NIRF by introducing multiple nitrogen and oxygen atoms, the structure of which is shown in Figure 5. It was shown that the probe NIRF utilized the phenolic hydroxyl oxygen atoms, imine nitrogen atoms, and oxygen atoms in the acetylhydrazone in its structure to coordinate with zinc ions to form a 1:1 ligand to achieve a fluorescence-enhanced response to zinc ions. At the same time, the detection limit was 46.1 nM. The experiments also found that the ligand between the probe NIRF and zinc ions could continue to be used as a fluorescent probe to achieve a fluorescence-quenching detection of CN^- , and the detection limit was reasonable, with a detection limit of 790 nM. The probe can detect zinc and cyanogen ions in organisms, with a detection limit of 790 nM. 2016 Hu et al. [58] prepared the fluorescent probe J from 2-amino benzothiazole, as shown in Figures 1–11. It was found that in the neutral system DMSO/HEPES (4/1, v/v), the thiazole ring nitrogen atoms, phenol hydroxyl oxygen atoms and imine bond nitrogen atoms in the structure of the probe can be coordinated with zinc ions and form a 1:1 ligand, which leads to the fluorescence effect enhancement enabling the detection of zinc ions. The detection process has the advantages of good selectivity and reproducibility, and the detection limit is 16.4 nM. The probe can be prepared on test paper for zinc ion detection. In 2021, Wu et al. [59] designed and synthesized a benzothiazole derivative BTT with the structure shown in Figure 7. The probe HBT in Tris/MeOH (2/3, v/v) buffer can utilize the nitrogen, oxygen and sulfur atoms in the structure to form a 1:1 ligand with zinc ions, which leads to the blocked proton transfer (ESIPT) of the excited state within the molecule to produce chelated fluorescence enhancement (CHEF) to achieve the detection of zinc ions. The detection process is accompanied by an apparent color change from orange to green and the detection limit is reduced to 37.7 nM. However, mercury and copper ions can interfere with the detection process. The probe can be used to detect zinc ions in cells. Ling-Yi Shen designed a novel fluorescent probe L to enable the selective detection of Zn^{2+} ions [59]. Spectroscopic and single-crystal x-ray diffraction analyses revealed an asymmetric Schiff base probe structure, and the fluorescence of the probe's fluorescence was significantly enhanced at 475 nm after adding zinc ions. The probe L can form a 1:1 complex with Zn^{2+} ions.

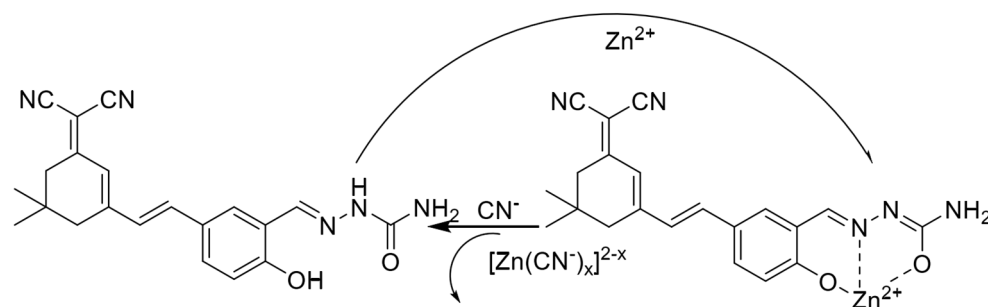


Figure 5. The mechanisms of the probe NIRF recognizing Zn^{2+} and CN^- [57].

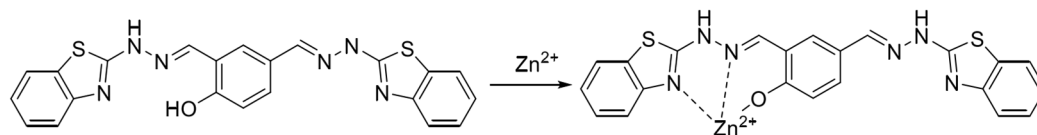


Figure 6. Mechanism of interaction of fluorescent probes with zinc ions [58].

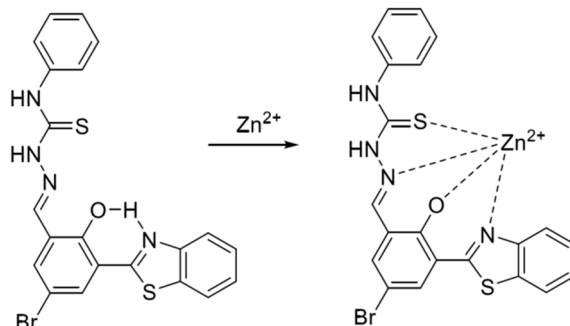


Figure 7. Formulation of benzazole derivative BTT with zinc ions [59].

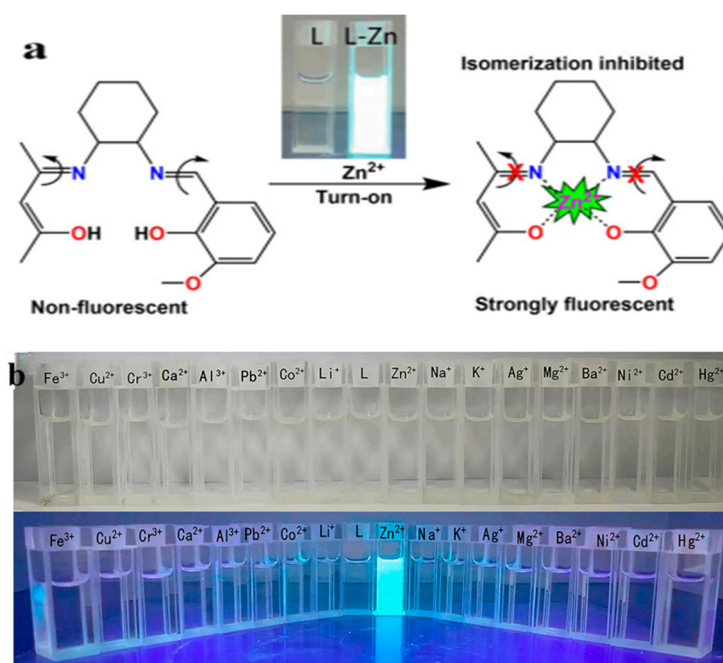


Figure 8. (a) Schematic representation of the response of probe L to zinc ions. (b) Fluorescence response of probe L with the addition of different metal ions [60].

Wanying Li et al. reported that a two-photon probe TEO-MPVQ based on intramolecular charge transfer can be used for scale imaging and biosensing of Zn^{2+} ions. The chelation of the probe TEO-MPVQ with Zn^{2+} ions resulted in a redshift of the fluorescence emission peak by about 60 nm and an increase in the spectral emission intensity [61], which enabled the fluorescence ratiometric recognition of Zn^{2+} ions. The probe has high sensitivity, selectivity, good biocompatibility, high spatial resolution, and profound tissue penetration ability to tracer endogenous Zn^{2+} ions in neuronal cells. It has been applied to imaging Zn^{2+} ions in zebrafish. The probe [62] is a three-legged fluorescent probe synthesized based on terpyridine, which has a strong fluorescence emission at 412 nm in DMSO. With increasing water content in the solvent, the fluorescence intensity decreases and redshifts to 479 nm, which is attributed to the H-aggregation of the ligand with the increase of undesirable solvents, which leads to fluorescence bursts. In contrast, by adding Zn^{2+} , the tertiary pyridyl group forms a coordination bond with Zn^{2+} , which induces the complexes to come

together to inhibit the rotation of the intramolecular chemical bonds of the tripyridine, which reduces the loss of energy due to the non-radiative mode of the probe 53, resulting in a robust fluorescence. It was also shown that the detection limit of this probe for Zn^{2+} was up to 1.1 nM. The probe [63] is a Schiff base obtained by a simple condensation reaction of a diamine with salicylaldehyde, whose mechanism of aggregation-induced luminescence (AIE) is thought to be related to restricted intramolecular rotation (RIR). The ligand has irreversible mechanoluminescent (ML) properties, and upon milling, the solid color changes from blue to green (445 nm–512 nm). However, applying pressure axially (using a hydraulic press) underwent a reversible transformation with the exact color change (blue—green). The probe also showed the good recognition of Zn^{2+} due to the coordination of Zn^{2+} with the ligand to form a 1:1 complex. The complex's aggregation effect restricts the rotation of the intramolecular bonds, resulting in strong fluorescence emission. In addition, the detection limit of the probe was 0.064 ppm for Zn^{2+} . Although the Schiff base fluorescent probe has strong specificity and high sensitivity for the detection of zinc ions, the specific binding of the probe to the target ions needs to be solved in the complex detection environment, especially in the presence of substances with the same functional group as that of the target zinc ions.

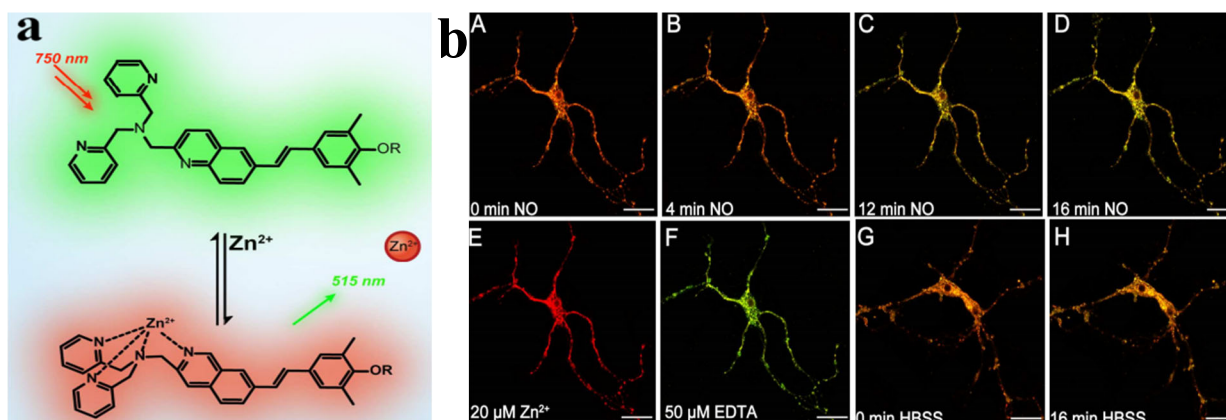


Figure 9. (a) Schematic of the response mechanism of probe TEO-MPVQ to Zn^{2+} ; (b) The fluorescence changes of 5 μM TEO-MPVQ in NO-induced neurons. In TEO-MPVQ, the fluorescence images of NO at different time points before incubation (A) and after incubation were: (B) 4 min, (C) 12 min, (D) 16 min. The image after 10 μM Zn^{2+} /pyrithione (1:2) processing is (E), and the image after 20 μM EDTA processing is (F). HBSS processed fluorescence images of neurons at 0 min (G) and 16 min (H) [61].

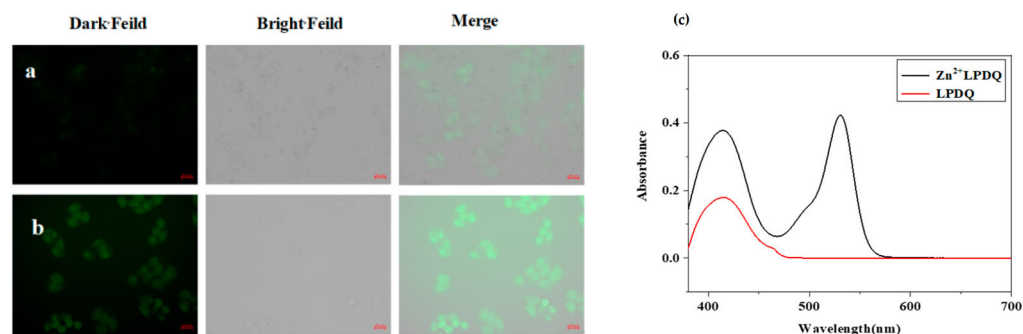


Figure 10. LPDQ cell imaging. (a) HeLa cells incubated with the LPDQ probe. (b) HeLa cells incubated with the LPDQ probe and Zn^{2+} . (c) LPDQ cell imaging, UV–Vis absorption spectrum after the reaction of LPDQ and Zn^{2+} [64].

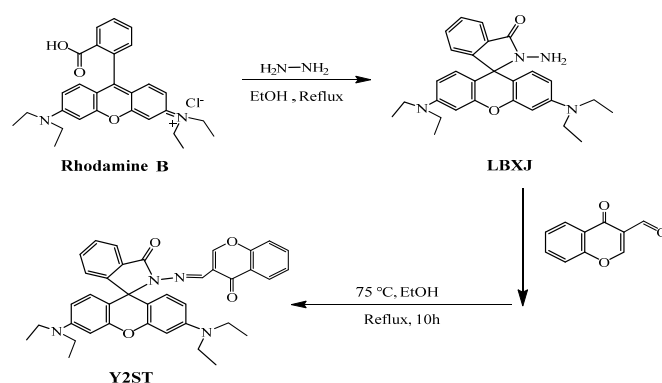


Figure 11. Structure of LBXJ and Y2ST [65].

3.3. Rhodamine Fluorescent Probes

Rhodamine fluorescein-like derivatives belong to the xanthene class of basic dyes and represent a typical organic fluorescent dye with a xanthene structure. The fluorescent material exists an oxygen bridge between benzene rings, which makes this class of molecular materials characterized by rigid coplanarity, manifesting itself as a significant enhancement of the stability of the molecular structure. The material's structure will be transformed into an open ring state, and through the action of excitation light, it will emit strong fluorescence. Its maximum emission wavelength range is between 500 and 700 nm, which is located in the red visible region, and the fluorescence in this range can effectively avoid the background fluorescence range of the biological system, which significantly improves the probe's sensitivity and the fluorescent probe with rhodamine fluorescent derivative as the material has attracted the attention of many researchers and scholars. The fluorescent probes using rhodamine fluorescent derivatives as materials have attracted the attention of many scientific research scholars. They are often used in the design of fluorescent probes in biological analysis and have high application value and research prospects. Wang et al. [64] synthesized an “on-off” rhodamine fluorescent probe LPDQ with a new structure by modifying the structure of pyridoxal phosphate, which can be used for the detection of Zn^{2+} in water and oil paintings, and the probe LPDQ can be applied to cellular imaging studies of Zn^{2+} . Jin et al. [65] prepared the intermediate LBXJ from rhodamine B, hydrazine hydrate, and HCl, and then prepared a Y2ST probe using LBXJ, chromone-3-carbaldehyde, and anhydrous ethanol. It was used for the detection of Zn^{2+} in zinc gluconate. Serkan et al. successfully designed and synthesized a novel dual-channel probe based on bisphenol A-rhodamine (BAR) with high selectivity and sensitivity to Zn^{2+} ions. In pure MeCN and MeCN- H_2O ($v/v = 8/2$, 5 mM, HEPES, pH 7.0), BAR showed adequate selectivity and sensitivity to Zn^{2+} ions through two different mechanisms (i.e., ESIPT and FRET). The detection limit of Zn^{2+} was $2.21\text{ }\mu\text{M}$, which provides a good reference for synthesizing such probe derivatives [66]. Yang et al. synthesized a novel molecular probe for detecting Zn by modifying the intermediate of rhodamine and hydrazine hydrate with chlorsalicylaldehyde. The probe can detect changes in Zn with the naked eye and has a detection sensitivity limit of $3.6\text{ }\mu\text{mol/L}$. When the concentration range of Zn is $10\text{--}250\text{ }\mu\text{mol/L}$, there is a good linear relationship, which can be used for detecting trace amounts of zinc [67]. Tomat E. et al. used the condensation reaction of rhodamine with xanthene to produce a fluorescent probe that can be coordinated with Zn, which is an “on-off” type probe that can be coordinated with Zn in neutral aqueous solution for the detection of Zn [68]. The probe [69] was composed of acridine-dione as a fluorophore. In acetonitrile and aqueous solution (80:20, v/v), the fluorescence of the probe was burst due to the lone-pair electron transfer of N on the DPA, and the fluorescence of the probe at 426 nm was enhanced by a factor of 4.5 when Zn^{2+} was added. The probe [70], which

uses a fluorescein backbone as a fluorophore, showed no fluorescence emission or weak fluorescence under physiological conditions (pH = 7.0), also due to the PET process caused by the lone pair of electrons of N on DPA, which was inhibited by the addition of Zn^{2+} coordinated to DPA, thus showing a strong fluorescence emission. The probe [71] was based on BODIPY as a fluorophore, and again the ligand did not fluoresce due to the presence of the PET effect, and the addition of Zn^{2+} increased its fluorescence intensity by a factor of 7, with a quantum yield of 0.857. The Zn^{2+} fluorescent probes are summarized in Table 1.

Table 1. Names of zinc ion fluorescent probes, wavelengths of incidence and excitation, detection limits, etc.

Probe Name	$\lambda_{\text{ex}}/\lambda_{\text{em}}$	LOD	Mechanism	F/F0	Ref.
L_2	400 nm/480 nm	84 nM	Formation of bis-terpyridine zinc complexes ($\text{L}_2\text{-Zn}^{2+}$)	Increase significantly	[19]
Probe 1	482 nm/653 nm	15.3 nM	PET, ICT	Increase significantly	[72]
QCPC	375 nm/484 nm	72 nM	CHEF, PET	Increase significantly (101 times)	[73]
NIR-Zn	481 nm/660 nm	4.8 nM	PET	Increase significantly	[74]
TZn	580 nm/652 nm	0.31 μM	Chelation	Increase significantly	[75]
DCP5	420 nm/580 nm	1.36 nM	PET	Increase significantly	[76]
QSP-H/ QSP-Cl	385 nm/499.5 nm 388 nm/500 nm	71 nM/ 67 nM	Chelation	Increase significantly	[77]
P2	352 nm/462 nm	0.63 μM	PET, ESIPT, Synergistic effects of E/Z isomerization	Increase significantly (7 times)	[78]
Probe 1/ Probe 2	490 nm/670 nm 520 nm/670 nm	1.59 nM/ 2.7 nM	PET	Increase significantly	[79]
Py-Ph/Py-Nap	355 nm/469 nm 355 nm/502 nm	29.2 nM/ 24.6 nM	1:1 complexation	Increase significantly	[80]
BSA-AgNPs	389 nm/502 nm	100 μM	Zn^{2+} leads to some degree of aggregation of BSA-AgNPs	Increase significantly (42.1%)	[81]
Probe for zinc ions detection	406 nm/490 nm	5.8 nM	PET	Increase significantly (65 times)	[82]
Compound 6	360 nm/460 nm	$1.26 \times 10^{-6} \text{ M}$	ESIPT	Increase significantly	[83]
H2L	430 nm/509 nm	$8.6 \times 10^{-9} \text{ M}$	Inhibition of C=N bond isomerization	Increase significantly (54 times)	[84]
DCDs	400 nm/655 nm	$1.2 \mu\text{mol}\cdot\text{L}^{-1}$	Zn^{2+} interaction with DCDs	Increase significantly	[6]
C4P	365 nm/440 nm	0.108 μM	PET	Increase significantly (120 times)	[85]
DCQO	320 nm/470 nm	0.40 μM	ICT	Increase significantly (7.9 times)	[86]
2-HPTP	425 nm/510 nm	$3.48 \times 10^{-7} \text{ M}$	1:1 compatibilizer	Increase significantly (135 times)	[87]
YPT	502 nm/670 nm	12 nM	PET	Increase significantly	[88]
L	330 nm/515 nm	4.9 nM	PET	Increase significantly (5 times)	[89]
F-PNPs	445 nm/502 nm	$2.75 \times 10^{-8} \text{ M/L}$	Zn^{2+} coordination with substances, F-PNPs- Zn^{2+} complexes	Increase significantly	[90]

4. Conclusions

Compared with non-detection problems, fast detection, and the inaccuracy of traditional zinc ion residue detection methods, fluorescent probes have achieved good zinc ion residue detection results. This paper reviewed the mechanism of zinc ion detection by fluorescent probes. This paper refers to the relevant literature since 2017, and cites several earlier studies, which is of great value in building basic knowledge in this field. The characteristics, detection strategies, and applications of different probes were introduced. The fluorescent probe methods have the advantages of rapidity, sensitivity, and easy operation. In summary, given the characteristics of various types of fluorescent materials, attempts can be made to synthesize the advantages of each to achieve accurate detection, multiple detection, and anti-interference detection to meet the realistic needs of ion detection. This review will provide a valuable reference for developing more cost-effective and widely applicable methods for detecting zinc ions in the future.

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