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Recent Advances in Fluorescent Probes based on Different Recognition Motifs for Biothiols

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Abstract. Fluorescent probes are useful tools for viewing living biothiols but the structural similarities between Cys, Hcy, and GSH complicate their selective selection. This review presents a systematic overview of fluorescent probes for biothiols organized by chemical recognition motifs used in their design. The probes are classified into three main groups according to the responsive sites: nucleophilic addition sites (acrylates, maleimides and unsaturated ketones), nucleophilic substitution sites (e.g. ester bonds, disulfides and nitrobenzoxadiazole (NBD)) and metal coordination or redox sites (e.g. Cu^{2+}/Hg^{2+} centers and Selenium ethers). Recognition mechanisms (addition-cyclization cascades, SNAr reactions, metal displacement) are summarized. Biomedical applications of these probes (subcellular organelle imaging, in vivo disease monitoring, and theranostic platforms) are summarized. Finally, current challenges and future perspectives, particularly regarding near-infrared II (NIR-II) imaging and artificial intelligence-assisted design, are briefly outlined.

Keywords: fluorescent probes, biothiols, design strategies, recognition mechanisms, theranostics

1. Introduction

GSH, Cys, and Hcy are three sulfur-containing molecules that help cells maintain redox balance, transmit signals, and remove harmful electrophiles [1, 2]. Their levels are closely tied to cancer, liver injury, and cardiovascular disease. Fluorescence imaging is now widely used to track these thiols in live cells and animals. It gives real-time, non-invasive readouts with high sensitivity and spatial resolution [3, 4]. The difficulty is that all three molecules contain a thiol group, and Cys/Hcy also carry a nearby amino group. Most thiol-reactive probes therefore cannot easily tell them apart [5, 6].

Although numerous fluorescent probes for biothiols have been reported and reviewed, a systematic framework for categorizing their recognition mechanisms based on specific functional groups at the molecular level remains highly desirable. Based on the inherent chemical reactivities of biothiols, the responsive sites in probes can be broadly categorized into three main types according to their reaction mechanisms: (i) nucleophilic addition sites (e.g., acrylates, maleimides,

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and α,β-unsaturated ketones); (ii) nucleophilic substitution sites (e.g., nitrobenzoxadiazole (NBD), sulfonyl groups, halogens, and aromatic ethers); and (iii) metal coordination or redox sites (e.g., Cu^{2+}/Hg^{2+} centers, and selenium/tellurium ethers) Figure 1 schematically illustrates this classification.

Specifically, probes based on nucleophilic addition reactions commonly utilize Michael acceptors, where the thiol group attacks the α,β-unsaturated carbonyl to disrupt the probe's conjugation. For instance, Liu et al. developed a dual-acrylate-site probe for the discrimination of Cys from GSH and Hcy via an addition-cyclization cascade, while Li et al. constructed a maleimide-based probe for the highly selective detection of Cys [7, 8]. Probes utilizing nucleophilic substitution reactions enable a fluorescence turn-on by cleaving a leaving group from the fluorophore via SNAr (nucleophilic aromatic substitution) or ester hydrolysis. Dou et al. reported a boron-dipyrromethene (BODIPY) probe for Cys through ester-cleaving. Lang et al. developed coumarin-tetraphenylethylene probe for ratiometric detection of GSH and adenosine triphosphate (ATP) via disulfide bond cleavage. Du et al. developed curcumin probe for Cys, Hcy and GSH by NBD substitution [9-11]. Finally, probes based on coordination or redox reactions exploit the strong chelating ability or reducing power of thiols to displace metal ions from a quenching complex, or trigger selenium/tellurium ether oxidation. Zhao et al. synthesized a coumarin-based probe for the sequential detection of Cu^{2+} and GSH via an on-off-on fluorescence process. Cugnasca et al. synthesized a probe **Seleno-BODIPY** to distinguish Cys and GSH through distinct substitution and rearrangement mechanisms induced by the redox-active selenium center [12, 13]. This review provides a clear guide for the rational design of high-performance fluorescent probes, thereby facilitating their broader applications in biological imaging, disease diagnosis, and theranostics

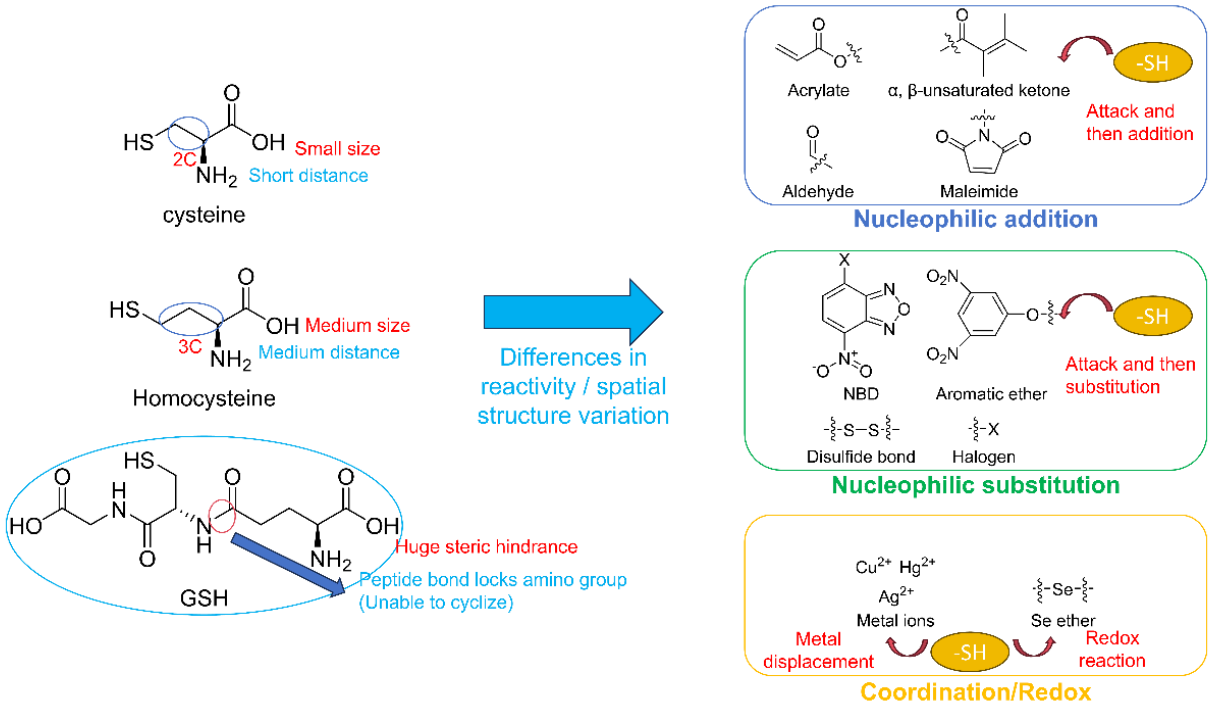


Figure 1. Schematic illustration of structural differences among biothiols (left) and the classification of responsive functional groups based on their reaction mechanisms (right). The right panel is categorized into nucleophilic addition, nucleophilic substitution, and coordination/redox reactions

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2. Design frameworks of differentiation strategies

2.1. Fluorescent probes based on nucleophilic addition reactions

Nucleophilic addition reactions, particularly the Michael addition, represent one of the most extensively employed sensing mechanisms for biothiols. This is achieved by the highly nucleophilic sulfhydryl group (-SH) of biothiols destroying the electron-deficient carbon of α,β-unsaturated carbonyls and producing a distinct fluorescence response. Figure 2 shows representative reactions for this class of compounds.

Acrylates are the most popular because they are highly electrophilic and can induce large Stoke shifts. Liu et al. developed a dual-acrylate fluorescent probe, 1,3-bis(2-pyridylimino)-4,7-phenylene diacrylate isoindole (**BPI-AC**) for Cys detection [7]. After Cys reaction, the probe is nucleophilic added, intramolecular cyclization, released the free fluorophore BPI-OH and produced large fluorescence enhancement at 648 nm (Fig 2(a)). This add-cyclization cascade provides Cys detection from Hcy and GSH. Large Stokes shift (265 nm) of the probes minimize background interference.

Maleimide probes are also widely used. The carbon-carbon double bond in maleimide ring is highly activated by adjacent carbonyl groups, which makes it highly sensitive to nucleophilic attack by thiols. Li et al. construct a fluorescent probe (**TCF-MA**) using 2-(3-cyano-4,5,5-trimethylfuran-2(5*H*)-ylidene) malononitrile (TCF) as the fluorophore and maleimide as the recognition group [8] (Fig 2(b)). This probe is highly selective and sensitive to Cys (Detectivity limit 0.26 μM) which can detect Cys over Hcy and GSH.

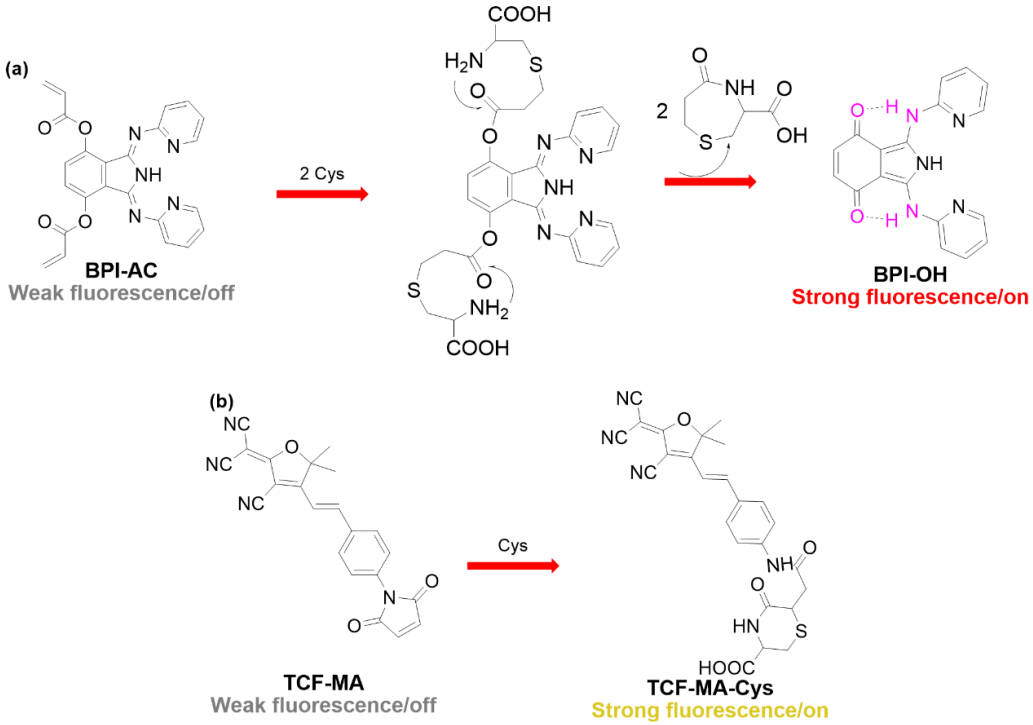


Figure 2. Representative reaction mechanisms of nucleophilic addition probes. (a) The addition-cyclization cascade of **BPI-AC** with Cys to release the fluorophore BPI-OH (b) The Michael addition mechanism of the maleimide-based **TCF-MA** probe with Cys

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2.2. Fluorescent probes based on nucleophilic substitution reactions

The nucleophilic substitution reaction represents another crucial mechanism for biothiol sensing. Usually, this is the attack of thiol group (-SH) on the carbon atom with a leaving group followed by cleavage of the carbon-heteroatom bond. This restores the interrupted intramolecular charge transfer (ICT) or photoinduced electron transfer (PET) process and produces turn-on fluorescence response. Figure 3 shows three examples of this type of substitution. Ester probes are widely used. Dou et al. developed a **BODIPY-A** NIR fluorescent probe for Cys detection [9], using ester group as the reaction site. After reaction with Cys, the nucleophilic substitution releases fluorophore BODIPY-B and produces fluorescence enhancement at 672 nm with detection limit of 0.3 μM (Figure 3(a)). The probe successfully eliminated interference from Hcy and GSH and applied in serum samples.

Disulfide bond cleavage is another classic substitution mechanism. Lang et al. developed a bifunctional coumarin-linked tetraphenylethylene (TPE) probe **P1** for the simultaneous sensing of ATP and GSH [10]. The disulfide bond serves as the recognition site for GSH. The disulfide bond is broken when GSH reacts with it. It disrupts the forster resonance energy transfer (FRET) between coumarin and TPE, and it can be used ratiometrically for GSH detection (Fig 3(b)).

In addition, 7-nitrobenzoxadiazole (NBD) probes are also notable. Du et al. reported curcumin-based probe **FBCN** by introducing NBD-Cl as leaving group [11]. Using SNAr mechanism, Cys, Hcy and GSH can be distinguished at one wavelength, with ratiometric responses Cys/Hcy and turn off response to GSH (Fig 3(c)).

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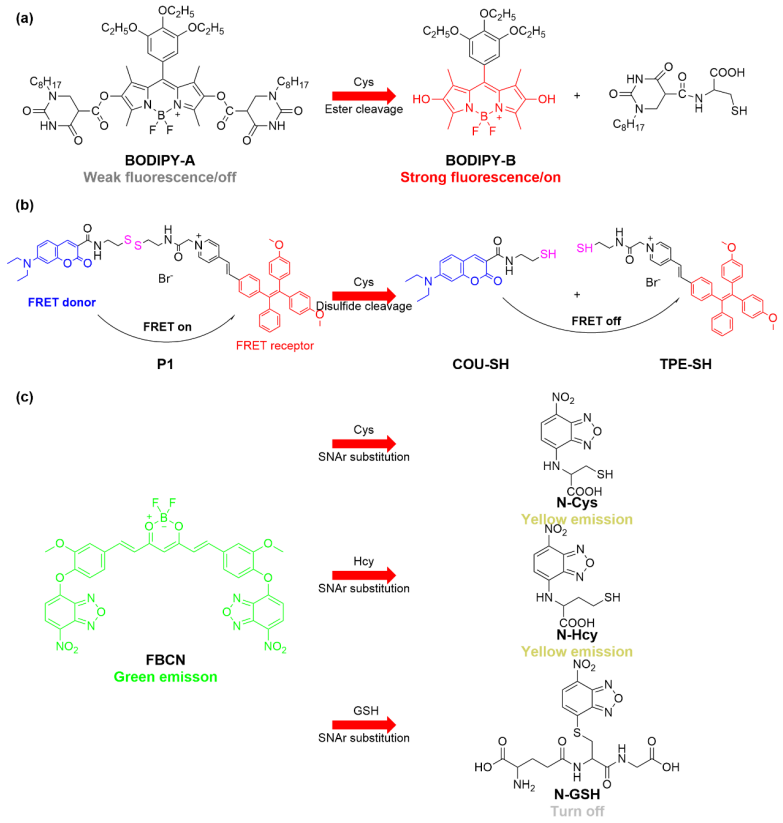


Figure 3. Representative reaction mechanisms of nucleophilic substitution probes. (a) The ester cleavage-based sensing mechanism of **BODIPY-A** for Cys (b) The disulfide bond cleavage mechanism of the coumarin-TPE probe **P1** for ratiometric sensing of GSH (c) The SNAr substitution mechanism of the curcumin-NBD probe **FBCN** for the discrimination of Cys, Hcy, and GSH

2.3. Fluorescent probes based on coordination or redox reactions

In contrast to covalent bond-forming addition or substitution reactions, probes based on coordination or redox mechanisms rely on the strong binding affinity or reducing ability of biothiols toward specific metal ions or redox-active centers. These strategies provide alternative means of highly selective detection, especially in complex biological environments. Figure 4 shows the method of coordination and redox-based probes. Metal coordination-displacement is common. Fluorophore-metal complexes are first quashing, biothiols addition causes metal displacement, fluorescence is re-energized competitively. Zhao et al. built a coumarin-based Schiff base probe (**X4**) for sequential Cu^{2+} and GSH detection [12]. By binding Cu^{2+} to **X4**, the fluorescence was quenched by PET effect. Then GSH removed Cu^{2+} from complex due to its stronger chelating ability and gave "turn-on" response for GSH with detection limit of 4.30 10^{-7} M (Fig 4(a)).

Redox mechanism is another important strategy. Cugnasca et al. reported **Seleno-BODIPY** probe for differential Cys detection [13], where selenium atom is not only fluorescence quencher but also redox-active site. Reaction with Cys give fast SNAr-rearrangement resulted in amino-substituted BODIPY (green) fluorescence, while GSH reacts with probe to form thio-substituted product (redshift) fluorescence). This distinct mechanism enabled the simultaneous and highly selective detection of both analytes with low detection limits (61.18 nM for Cys; 1.66μM for GSH)

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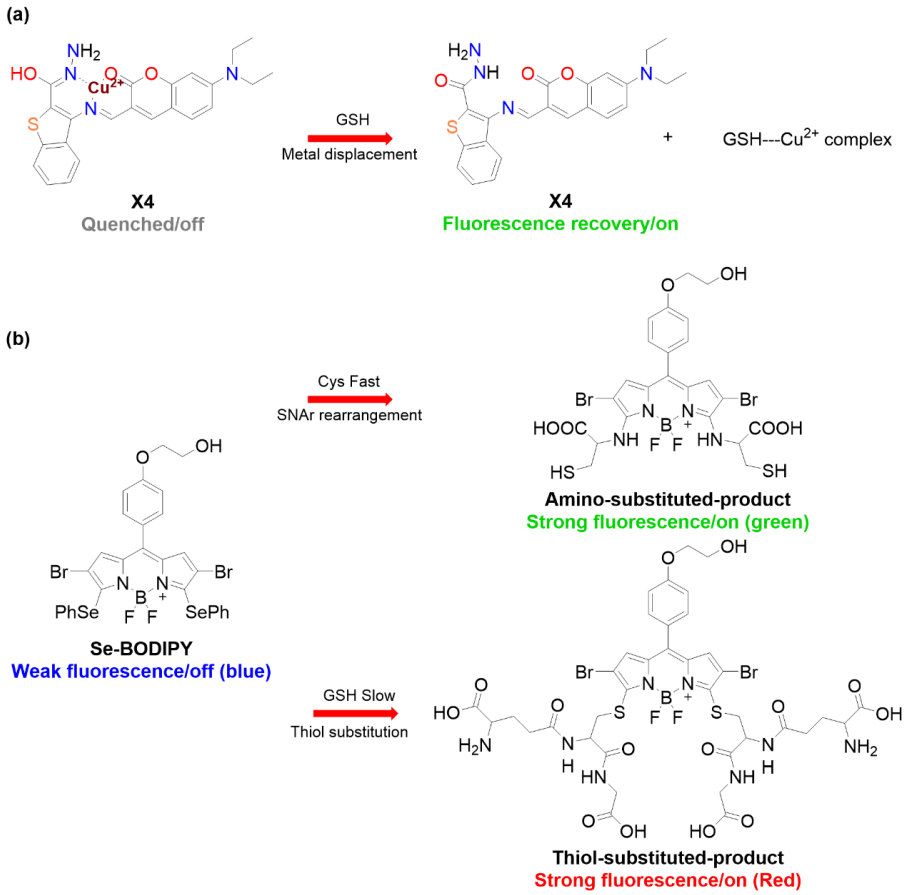


Figure 4. Representative reaction mechanisms of coordination and redox-based probes. (a) The Cu2+ coordination-displacement mechanism of probe **X4** for the sequential detection of GSH (b) The differential SNAr-rearrangement and thiol substitution mechanisms of the **Seleno-BODIPY** probe for distinguishing Cys and GSH via green and red fluorescence signals

3. Biomedical applications

3.1. Cell and subcellular organelle imaging

As a core application of thiol-responsive fluorescent probes, living cell imaging allows for the non-destructive and real-time visualization of intracellular biothiols. With excellent membrane permeability, these probes readily cross the cell membrane and specifically recognize endogenous Cys, Hcy, and GSH through distinct fluorescence variations. The spatiotemporal resolution and real time feedback provide a significant improvement over the off-line detection methods that capture in situ dynamic information for complex processes in cells [14]. To gain more detailed biological information, targeting moieties have been introduced to anchor probes in specific subcellular compartments. For example, probes targeting mitochondria have been used to monitor the oxidative stress-induced protein modifications (protein sulfenic acids) directly in living cells [15], while lysosome-targeted probes have been developed to track cysteine changes during mitophagy, reflecting the dynamic processes in organelle interactions [16]. Structural modifications such as extended emission to near-infrared region and large Stokes shifts have reduced background autofluorescence and improved image quality for real-time monitoring small molecules thiols in living cells [17].

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3.2. In vivo imaging and disease model monitoring

In addition to cell studies, in vivo imaging is needed to translate thiol probes into preclinical applications. Near-infrared probes with large Stokes shifts are preferred because deep tissues are penetration sensitive and background autofluorescence less dense. This is essential for detecting signals accurately in living organisms [18]. Dual-locked probes have been developed to minimize false positive signals for diagnostics. For instance, a dual-biomarker activated NIR probe triggered by glutathione (GSH) and tyrosinase allows to visualize melanoma in vivo and significantly increase signal-to-noise ratio compared to single-locked probes [19]. NIR probes can also be used to monitor dynamic Cys fluctuations in organ-level oxidative stress models. In a renal ischemia-reperfusion injury model, a turn-on probe detected elevated Cys levels during injury, which provided direct evidence for oxidative stress [20], and a 210 nm Stokes shift probe showed biphasic Cys changes (e.g. increase during ischemia and decrease after reperfusion) in hepatic ischemia-reperfusion injury [21]. These probes also play important roles in tumor diagnosis. For instance, a GSH-activated NIR-II probe was used to visualize high GSH levels in tumor microenvironment and showed deep tissue penetration and high sensitivity [22], and a water-soluble cyanine probe showed its ability to image cervical cancer tumor imaging in vivo [23]. A GSH-activated probe with large Stokes shift was used to dynamically monitor GSH fluctuations during ferroptosis in 4T1 tumors for ferroptosis induction efficiency [24]. Overall, these advances in in vivo imaging provide powerful tools for real-time disease diagnosis and therapeutic evaluation directly address limitations of ex vivo analysis.

3.3. Theranostic applications

Besides detection, the integration of diagnosis and therapy has emerged as a major trend in biothiol-based fluorescent probes. Because of high GSH levels in tumor microenvironment (TME), GSH-responsive probes can be rationally designed as activating theranostic platforms which can be used for imaging and therapeutic interacting. The principle relies on GSH as a dual trigger, which activates the imaging signal and also the release of therapeutic agents or photosensitizers to provide exact tumor targeted treatment with minimal nonspecific side effects. For instance, a dual-modal nanoplatform (Ce6@CDP) was constructed that combined GSH depletion with near-infrared (NIR) triggered cascade-amplified phototherapy [25]. This system utilized a disulfide bond-containing polymer to deplete intracellular GSH, thereby amplifying oxidative stress, while concurrently enhancing both photothermal (PTT) and photodynamic (PDT) efficacy. Similarly, a ratiometric theranostic nanoplatform was developed to achieve acid-triggered drug release and GSH-activated fluorescence turn-on, enabling simultaneous tracking of nanocarrier localization and drug activation, as validated in zebrafish xenograft models [26]. Furthermore, a GSH-activable probe conjugated with a kinase inhibitor (NC-G) enabled selective imaging of tumor cells while synergistically exerting high toxicity through GSH depletion and SO_2 release [27]. To broaden the therapeutic modality, a GSH-responsive molecularly imprinted polymer (ML@MIP) was designed for precision delivery of lonidamine (LND), combining anti-metabolism therapy with chemodynamic therapy (CDT) in a single platform [28]. Moreover, a biotin-targeted dual-modal imaging probe (Cy-Bio-GSH) was synthesized, offering NIR fluorescence (NIRF) and photoacoustic (PA) imaging capabilities, along with enhanced PDT/PTT synergistic therapy and tumor ablation in vivo [29]. Additionally, a GSH-activatable pro-drug-photosensitizer (LMB-S-CPT) was reported, which employed a disulfide linkage to deliver camptothecin (CPT) for chemotherapy and methylene blue (MB) for PDT, achieving tumor-selective combination therapy with negligible toxicity [30].

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Collectively, these advances underscore the versatility of GSH-responsive theranostic probes, providing powerful platforms for precise cancer diagnosis and synergistic treatment.

4. Conclusion and outlook

This review summarizes recent developments in fluorescent probes for biothiols that target Cys, Hcy and GSH selectively. Based on the chemical reactivity of biothiols, the responsive sites in probes were classified into nucleophilic addition sites, nucleophilic substitution sites and metal coordination or redox sites, examples showing reactions and applications to biological imaging. It also summarized biomedical applications of the probes including cell and subcellular imaging, in vitro disease monitoring, theranostic applications and cancer diagnosis and treatment.

No single thiol sensing strategy is suitable for all cases. Each reactive group has its strengths and weaknesses. Selecting the best activity-based sensing property depends on imaging biomarkers and optical properties. Different activity-based sensing property can be chosen depending on imaging biomarkers and optical properties. Even though Cys, Hcy, and GSH are still difficult to separate from each other. Since they are similar structures, probes must be designed with proper control over sterics, kinetics and reaction selectivity. Moving probes from cells to animals is still limited by poor tissue penetration, photobleaching and safety concerns. Small molecules probes can be controllable and designable structures. Nanomaterial platforms such as quantum dots and polymers further enrich sensing approaches [31-33]. NIR-II fluorescent probes offer solutions to the penetration depth limitation. NIR-II imaging provides deeper tissue penetration, lower autofluorescence and better signal-to-noise ratio [31, 32]. AI will accelerate probe discovery [34, 35], predicting probe structures with desired properties. Imaging with therapeutic techniques (theranostics) will continue to be a major trend. Expecting these developments will broaden applications of biothiol fluorescent probes in basic research and clinical translation.

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