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Communication

The chromogenic and fluorogenic chemosensors for hydrogen sulfide. A comprehensive review of their detection mechanisms since the year 2009

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With the biological importance of hydrogen sulfide(H_2S), the development of probes for hydrogen sulfide has been an active research area in recent years. In this review, we summarize recent exciting reports according to recognition mechanism of hydrogen sulfide and their applications in hydrogen sulfide detection. Several types of recognition mechanisms were classified such as the cleavage of alcoxyl (R-O) bond, the cleavage of S-O bond, reduction of azide, reduction of nitro groups to amine, the replacement of copper complex, and double bond addition reaction. In all cases, the reactions are accompanied with color and/or emission changes. The recognition mechanism is a very important and straightforward procedure for designing highly selective colorimetric or fluorimetric probes for detection of H_2S in living cell.

1. Introduction

Hydrogen sulfide (H_2S) is a colorless gas with a pungent taste. Exposure to this colorless and flammable gas, which gives distinctive otten eggs odor, can trigger eye and respiratory tract irritation.[1] H_2S originates from various industries such as mining, smelting, beet sugar, manufacturing carbon disulfide, organophosphorus pesticides, as well as leather, sulfur dyes, paints, animal glue and so on. Hydrogen sulfide is also emitted from organic corruption places such as swamps, sewers, septic tanks, sewage settling ponds, etc. So, it is inevitable to be poisoned working at these places for a long time.

Once exposed via inhalation, it is rapidly absorbed by the lungs, which could then lead to unconsciousness with attendant neurological sequelae, even to death. It has also been associated with cardiovascular related deaths.[2] More recent studies have challenged this traditional view of H_2S as a toxin and have shown that some animals can also produce H_2S in a controlled fashion,[3] suggesting that this reactive sulfur species is important in maintaining normal physiology.[4] H_2S may arise from non-enzymatic processes, including release from sulfur stores and metabolism of polysulfides.[5, 6]

On the other hand, a variety of disease phenotypes have been associate with inadequate levels of H_2S, including Alzheimer's disease,[7] impaired cognitive ability in CBS-deficient patients,[8] and hypertension in CSE knockout mice,[9] excessive H_2S production in vital organs may be responsible for the pathogenesis of other diseases such as diabetes.[10-12] These seminal studies have patently established H_2S as an essential physiological mediator and cellular signaling species,[13,14] but our understanding of H_2S chemistry and its far-ranging contributions to physiology and pathology is still in its infancy.

The multitude of physiological functions in which H_2S is involved guarantees the development of useful methods for its detection. To date, several detection methods for hydrogen sulfide have been developed, such as gas chromatography,[15,16] electrochemical analysis [17,18], colorimetric and/or fluorescent method,[19-22] metal nanoparticles sensors.[23] These methods are useful to monitor hydrogen sulfide in environmental samples, such as air, water, sediment, and sludge.[24] Among these detection methods, colorimetric and/or fluorescent probes have been developed rapidly due to their excellent properties and simplicity, especially turn-on fluorescent probes not only due to high sensitivity, selectivity, ease of application[25,26] but also ascribe to their specific sensing behavior, high signal-to-noise ratio.[27,28] In addition, their detection process always have fluorescence and ultraviolet change, which can realize "naked-eye" detection. Until now, many graceful fluorescent imaging probes[29-39] for H_2S detection have come into place. All these probes are connected with following mechanism: (1) the cleavage of alcoxyl (R-O) bond, (2) the cleavage of S-O bond, (3) reduction of azides, (4) reduction of nitro groups to amine, (5) the replacement of copper complex, (6) double bond addition reaction.

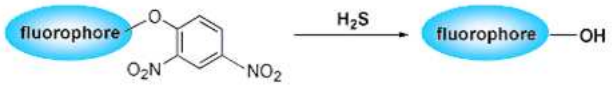
The review of about H_2S gas sensors based on their material type and/or sensing principle was reported by Pandey[2] et al. Lin[5] et al. concluded that fluorescent probes which could be used for imaging of H_2S in biological systems. Recently, Yu et al. wrote a review that addressed the synthesis and design strategies of probes.[40] Different with all these reviews about hydrogen sulfide, this review will focus on discussing the recognition mechanism in their detection process.

2. The recognition mechanisms for Hydrogen sulfide

2.1. The cleavage of alcoxyl(R-O) bond

Representative of the cleavage of R-O bond is the thiolysis of dinitrophenyl ether, which is often used to protect the tyrosine in the synthesis of peptide. The removal of the dinitrophenyl protective group is conducted using thiols as the thioly agents under basic conditions.[41,42] H_2S is a small gas molecule and has a

pKa values about 6.9,[43] while the typical cellular free thiols (i.e. glutathione, cysteine) have higher pKa values around 8.5.[44,45] Thus, based on the significant difference such as size and pKa values at physiological pH, the thiolysis of the dinitrophenyl ether reaction can be used to detect H_2S over biologically abundant glutathione and cysteine. [46] (scheme 1)



Scheme 1. The summary of strategies for the design of fluorescent probes based on cleavage of R-O bond.

Cao et al. [46] designed and synthesized NIR-H_2S probe (1), a unique type of a fluorescent turn-on probe for H_2S based on dinitrophenyl ether chemistry (Fig. 1). Free probe 1 was essentially non-fluorescent in 50 mM PBS buffer (pH 7.0) with 3 mM cetyltrimethylammonium bromide (CTAB) and 10 % ethanol. However, on addition of NaHS (it should be noted NaHS or Na_2S is the source of H_2S afterwards), the fluorescence intensity of the probe increased significantly (18-fold fluorescence enhancement), giving a strong emission at 708 nm which is in the near-infrared (NIR) region, and favorable for fluorescent imaging studies [36]. The detection limit was 5×10^{-8} M (S/N=3), and the authors also used the probe for biological imaging of living cells.

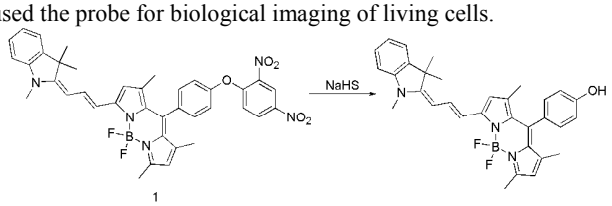
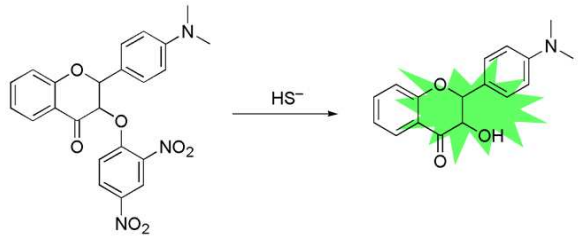


Fig. 1. The reaction of the probe 1 and NaHS.

Liu et al. reported a new 3-hydroxyflavone-based ESIPT probe 2, which is able to rapidly detect H_2S both in aqueous solution and in biological serum samples with high selectivity and sensitivity.[47] The free probe 2 in pH 7.4 PBS buffer (20 μM) is light yellow, and itself was not fluorescent, addition of HS^- led to the emission intensity at 538 nm increased significantly with a color change from light yellow to deep yellow. However, other anions as well as the thiol group did not cause any significant changes in the emission of probe 2. The optical changes of probe 2 in the presence of HS^- suggest that HS^- specifically triggered the thiolysis of dinitrophenyl ether in probe 2 and simultaneously released compound 4′-dimethylamino-3-hydroxyflavone (Fig. 2), which is a known visible light excitable ESIPT dye with high fluorescence quantum yield.



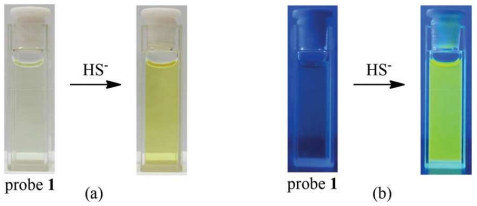


Fig. 2. The reaction of the probe 2 and HS^-. Color changes of the probe 2 (20 μM) solution after addition of NaHS (200 μM). (a) Under room light. (b) Under a 365 nm light. Reprinted with permission from Org. Biomol. Chem., 2014, 12, 438-445. Copyright 2014, Royal Society of Chemistry.

Sameh El Sayed et al. reported the synthesis and sensing features of fluorescent probe 3 (Fig. 3) based on quinoline for hydrogen sulfide detection in water and living cells.[48] Addition of HS^- induced the hydrolysis of the ether with subsequent emission 345-fold enhancement. But the other competitors such as OH^-, F^-, Cl^-, Br^-, I^-, N_3^-, CN^-, SCN^-, AcO^-, CO_3^{2-}, PO_4^{3-},SO_4^{2-}, SO_3^{2-}, $S_2O_3^{2-}$, H_2O_2, Cys, Me-Cys, Hcy, GSH, and lipoic acid, caused no obvious change after their addition into the probe. The selectivity towards HS^- was ascribed to the HS^- induced hydrolysis of the 2,4-dinitrophenyl ether moiety, which yielded the highly fluorescent 8-hydroxyquinoline group.[48-50] Probe 3 is essentially non-toxic which can selectively and sensitively detect HS^- anion in HeLa cells. The well detection limit (60 nM), as well as the excellent solubility in HEPES–DMSO 99 : 1 v/v, indicated 3 was a nice probe for hydrogen sulfide.

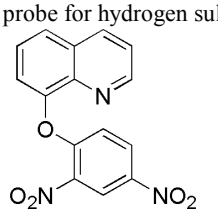


Fig. 3. The structure of probe 3.

Two new colorimetric and fluorescent turn-on probes (4 and 5) were developed by Wei[51] et al., which sensored H_2S based on thiolyling of the NBD ether bond (Fig. 4, Fig. 5). Both 4 and 5 were no obvious fluorescence in PBS buffer (pH = 7.4). Addition of H_2S resulted in the fluorescence enhancement with 1000-fold for 4 and 77-fold for 5. The different fluorescence enhancement level of two probes is related with the molecule structure. The electron-withdrawing oxygen moiety in 4 could enhance the reactivity of electrophilic NBD ether and increase the stability of phenol anions, which result in the H_2S reactivity for 4 is three-fold faster than that for 5 under physiological conditions, accompanied with stronger fluorescence enhancement for 4. The fluorescent turn-on response could be observed by the naked eye under a 365 nm UV lamp. At the same time, the color of the sensor 4 changed from colorless to red at 490 nm, while the sensor 5 got a near-infrared wavelength of 662 nm after reaction with H_2S. The high selectivity to H_2S can help achieve naked eye observation.

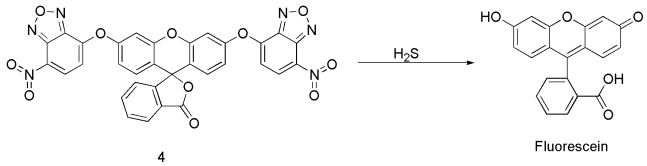


Fig. 4. The reaction of the probe 4 and H_2S.

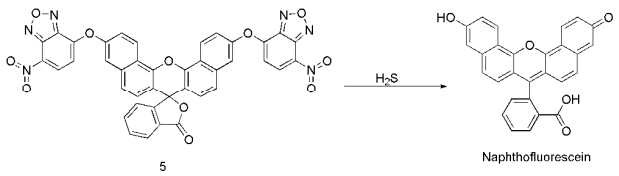
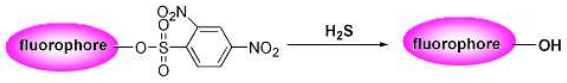


Fig. 5. The reaction of the probe 5 and H_2S.

2.2. The cleavage of S-O bond

Now available report showed that the fluorescence of the fluorophores can efficiently be quenched, when electron-withdrawing groups such as dinitrobenzenesulfonyl bonded with fluorophores.[52-55] While the cleavage of these groups will release the fluorophores and recover the fluorescence. Using this general approach, a several elegant hydrogen sulfide probes have been found based on the cleavage of dinitrophenyl ether or dinitrobenzenesulfonyl group due to the nucleophilicity of H_2S (scheme 2).



Scheme 2. The summary of strategies for the design of fluorescent probes based on cleavage of S-O bond.

Yang et al. showed a new probe 6 for the sensitive detection of sulfide anion based on its nucleophilicity in aqueous solution.[56] In 25% (v/v) aqueous acetone, the probe itself has an absorption peak at about 453 nm and no obvious fluorescence in emission spectrum. Upon mixing with sulfide anion in 25% (v/v) aqueous acetone, both fluorescence and absorbance of the reaction solution dramatically increased due to the efficient remove of 2,4-dinitrobenzenesulfonyl group of 6 and release of fluorescein (Fig. 6). Based on the obvious color change, the probe also can achieve naked eye detection for sulfide anion.

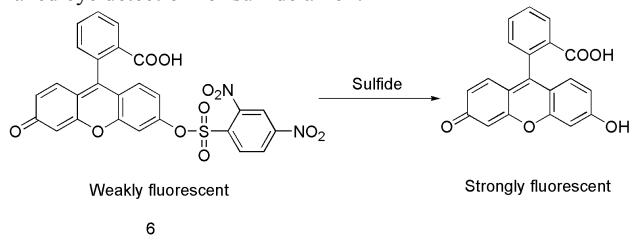


Fig. 6. The reaction of the probe 6 and H_2S.

Fu[57] et al. designed a new probe 7 for sensing HS^-. This probe had a strongly red-emitting styryl-containing BODIPY, and a DNBS (2,4-dinitrobenzenesulfonyl) unit as an electron acceptor known to quench fluorescence by electron transfer.[58-60] The optical response of probe 7 to various species was investigated in acetone (10 μM). Through the UV-vis spectra, about 10 nm red-shift of the absorption band can be seen. Upon the additions of HS^-, probe 7 was cleaved and dinitrobenzenesulfonyl was released, which led to the fluorescence of this system significantly enhanced (Fig. 7). The authors also found probe 7 is cell membrane permeable which could be achieve the detection of HS^- within living cells.

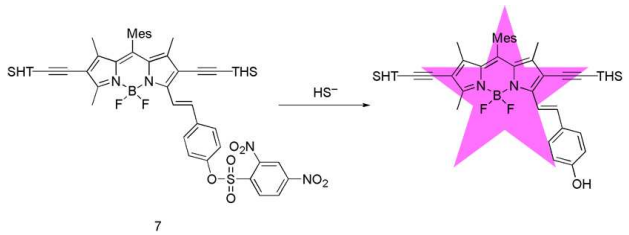


Fig. 7. The reaction of the probe 7 and HS^-.

To selectively detect H_2S, Zheng et al. designed a fluorescent turn-on probe 8, which is based on the nucleophilicity of S^{2-} and low cytotoxicity.[55] The probe had obvious fluorescence in pH 7.4 HEPES buffered water. Among all the competitors (F^-, Cl^-, Br^-, I^-, CO_3^{2-}, NO_3^-, $S_2O_3^{2-}$, SO_3^{2-}, HSO_3^-, SO_4^{2-}), only with the addition of S^{2-}, it will appeared a new peak at 518 nm in the emission spectra, which was enhanced up to 340-fold. The enhancement of the fluorescence was ascribed to the cleavage of the strong electron-withdrawing dinitrobenzenesulfonate ester group from probe 8 and release the fluorescein fluorophore (Fig. 8). The probe is low-cytotoxic and can permeate the cell membrane to realize monitor and image sulfide anion in live cells and real sample.

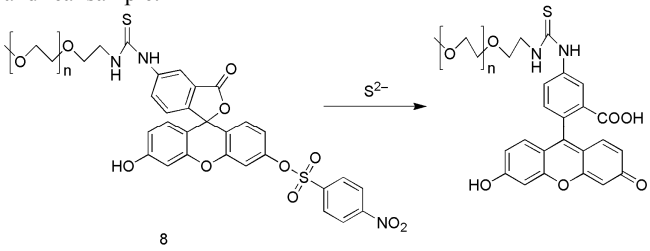
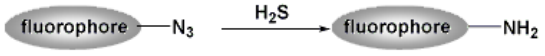


Fig. 8. The reaction of the probe 8 and S^{2-}.

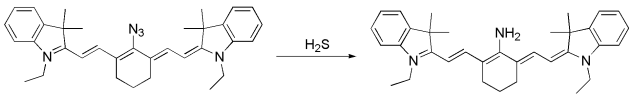
2.3. Reduction of azides

On the basis of the reduction ability of the hydrogen sulfide to azide, it is possible to design and synthesize all kinds of fluorescent probes for biological messenger molecule H_2S based on excited state intramolecular proton transfer (ESIPT) fluorescence control mechanism and ICT-induced blue or red shifts in the emission spectrum[61-63] by controlling electron-donating ability of different substituent groups.



Scheme 3. The summary of strategies for the design of fluorescent probes based on reduction of azides.

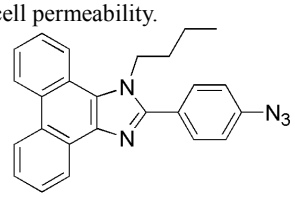
Yu et al. presented a colorimetric and ratiometric fluorescent probe 9 that exhibited a selective response to H_2S.[63] The probe was based on NIR heptamethine cyanine equipped with a chemical responsive azide unit (Cy-N_3). The detection mechanism of the probe was illustrated in Fig. 9. When azides were reduced to amines by H_2S, a NIR fluorescence maximum appeared at 750 nm (F = 0.12) accompanied by color changes from blue to green. Probe 9 had an excellent selectivity for H_2S among a series of anions and its detection limit was 0.08 μM. The probe had a good permeability in cells and was able to sense different intracellular H_2S levels.



9

Fig. 9. The reaction of the probe 9 and H_2S.

Zheng et al. reported PI-N_3 (Fig. 10) as a new fluorescent chemosensor for H_2S based on a phenanthroimidazole dye.[64] The free probe 10 showed a maximal absorption band at 358 nm and relatively weak fluorescence (Φ = 0.030) in pH 7.4, 25 mM PBS buffer–ethanol (7:3, v/v) at ambient temperature. The fluorescence intensity enhancement on addition of NaHS to probe 10 was approximately 20-fold (Fig. 9). Unfortunately, the detection limit for probe 10 was 0.879 μM, which is inferior to other reported probes such as probe 9 (0.08 μM). To examine the specificity of 10 for H_2S, the authors introduced representative species including N_3^-, ClO^-, Cl^-, F^-, H_2O_2, CO_3^{2-}, HCO_3^-, HPO_4^{2-}, NO_2^-, OAc^-, $S_2O_3^{2-}$, SO_4^{2-} and citrate, and found these species nearly no fluorescence response over 5 min. However, cellular abound thiols such as GSH and cysteine have a <8.0 fold fluorescence enhancement which may disturb the detection process of HS^- in a certain extent. The sensing process was confirmed by both NMR spectroscopy and mass spectrometry. It's also suitable for monitoring variations of H_2S levels in living cells because of cell permeability.



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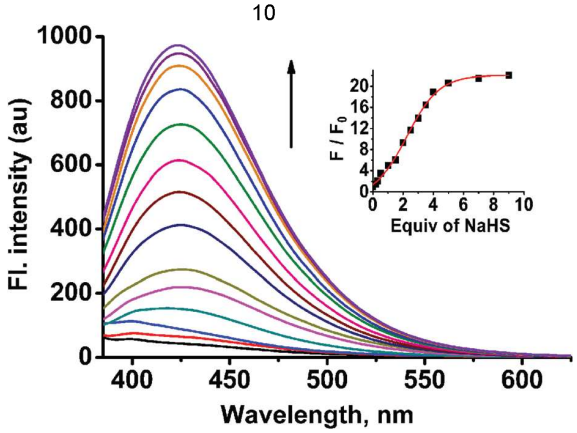
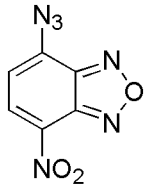


Fig. 10. The structure and fluorescence titration of the probe 10 with sulfide ions. Reprinted with permission from Org. Biomol. Chem., 2012, 10, 9683-9688, Copyright 2012, Royal Society of Chemistry.

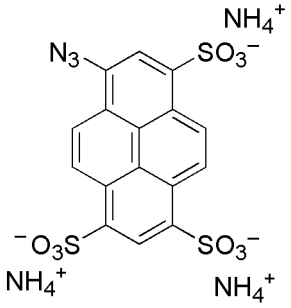
Zhou[24] et al. reported a fluorescent probe 11 (Fig. 11) based on 7-nitrobenz-2-oxa-1,3-diazole (NBD) fluorophore combined with a azide group. The absorption spectrum displayed that the addition of NaHS resulted in a red-shift of absorption peak from 396 nm to 468 nm, which could be produced a colorimetric change from pale-yellow to deep-yellow. The free probe 11 is weak-fluorescent since the quenching effect of azido group, with the addition of NaHS, the increase of the fluorescence intensity was up to 16-fold. MCF-7 cells were incubated with 11 to image H_2S, and the detection limit was 680 nM.



11

Fig. 11. The structure of probe 11.

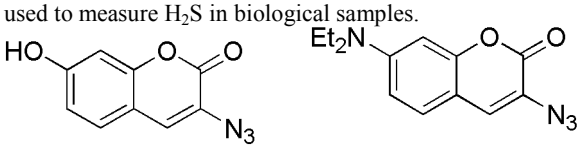
The fluorescence probe 12 (Fig. 12) based on 8-amin opyrene-1,3,6-trisulfonate was designed and used for the detection of H_2S by Matthew[65] et al. The presence of the electron-rich azide dramatically quenches the fluorescence of 12. However, after reduce of azides to amines by H_2S, the fluorescence of solution showed a 7-fold enhancement. The probe could detect H_2S in serum, and HS^- was easily quantifiable by fluorescence when its concentration was between 2 and 100 μM.



12

Fig. 12. The structure of probe 12.

Two coumarin-based probes 13 and 14 (Fig. 13) were designed by Li et al. [66] The optical response of probe 13 and 14 to various species was investigated in 100 mM sodium phosphate buffer (pH 7.4, 0.05% DMF). The free probes have no or very weak fluorescence. Because of the stronger electron-donating ability of $–NEt_2$ than that of –OH, probe 14 showed a larger fluorescence enhancement after reduced by H_2S. Moreover, the quantum yields significantly increased from (0.16±0.013) % and (0.58±0.02) % to (0.66±0.015) % and (10.93±0.15) %, respectively. The authors also proved selectivity of the two probes among species including cysteine, glutathione, thiophenol, 4-chlorophenyl thiophenol, 2-amino thiophenol, NaSCN, $NaHSO_3$. It was also confirmed that the recognition mechanism was reduction of azide to amine controlled by stronger ICT effects. And both 13 and 14 could be used to measure H_2S in biological samples.

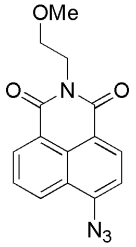


13 14

Fig. 13. The structure of probe 13 and 14.

A naphthalimide derivative as a fluorescent turn-on probe 15 for H_2S detection was reported by Leticiai[67] et al (Fig. 14). 15 is weakly fluorescent in its unreacted state, with addition of H_2S, 15 were converted efficiently to fluorescent amine (Φ = 0.096 ±0.001) fllowing a turn-on fluorescent response. These changes were attributed to the reaction of the reduction of azides to amine, which was confirmed by both NMR spectroscopy and mass spectrometry. To demonstrate the selectivity of 15, other reactive

sulfur, oxygen, and nitrogen species (RSONS) including cysteine, glutathione, a-lipoic acid (ALA), NO, H_2O_2, SO_3^{2-}, and $S_2O_3^{2-}$ was examined. All these species all induced no obvious change in fluorescence spectra under the same conditions. Probe 15 could be used to research the physiological roles of endogenous hydrogen sulfide and the detection limit was 5-10 μM.



15

Fig. 14. The structure of probe 15.

Alexander[68] et al. designed and synthesized two azide-caged rhodamine analogues as fluorescent probes 16 and 17 (Fig. 15) for the sensitive detection of H_2S. The fluorescence properties of these two probes were tested in 20 mM HEPES buffered solutions (pH 7.4). There were no absorption features in the visible region because of closed lactone conformation of the two probes. Upon addition of HS^-, both of two probes would appear new absorption bands in the visible region and there were significant enhancement in fluorescence intensity (Φ = 0.51 and 0.60). The reason of the changes in fluorescence was that the productions of reactions between 16 and 17 with HS^-, and their corresponding rhodamine dyes structures were confirmed by ^1H NMR and LC-MS analyses. These probes were able to sense different H_2S levels in HEK293T cells using confocal microscopy images.

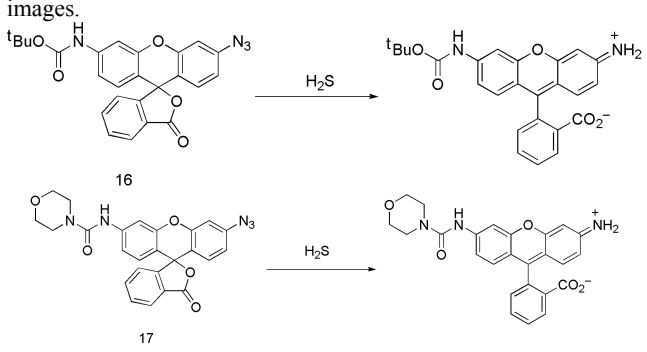
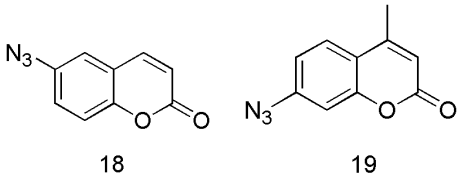


Fig. 15. The reaction of the probes (17 and 16) and H_2S.

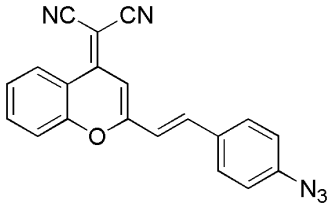
Chen et al. synthesized two chemoprobes for the detection of H_2S based on the coumarinyl moiety, 18 and 19 (Fig. 16).[69] Both of these probes were no fluorescent when they are free. Upon addition of 100 μM NaHS to the solution of 19, it appeared a strong fluorescence enhancement at 445 nm, and would reach up to 40-90-fold after 50 min. 18, unlike 19, has weak response to 100 μM H_2S and has low selectivity over other species, which indicated that 18 was not a good probe for detection of H_2S. The authors evaluated the pH variation of 19, and found it will increased up to 170-fold in the buffer of pH 7.9 after reaction with H_2S. Imaging of H_2S was achieved in the cardiac tissues of normal rats and atherosclerotic rats.



18 19

Fig. 16. The structure of probe 18 and 19.

The benzopyran derivative 20 (Fig. 17) found by Sun et al. was used for fluorescence turn-on detection of H_2S.[70] Upon addition of H_2S, a color change from yellow to orange red was observed as a result of a large red-shift of 90 nm in the absorption band to 505 nm. At the same time, a strong fluorescence enhancement at 670 nm strongly appeared (λ_{ex}=520 nm), which meaned that the azido group of 20 can be reduced into fluorescent 20-amino group. More importantly, the probe 20 was first successfully utilized to realize H_2S imaging in living mice. Besides of the excellent selectivity for H_2S over other relative analytes and a wide pH range of 2.5–10, the water solubility (here was PBS buffer/DMSO 1:1) could be improved to better imaging in living system.



20

Fig. 17. The structure of probe 20.

Bailey et al. reported two reaction-based Chemiluminescent sulfide sensors, 21 and 22, with strong luminescence responses toward H_2S.[71] Both 21 and 22 completely converted each azide to the corresponding amine (Fig. 18) after addition of H_2S, and the products were confirmed by ^1H NMR spectroscopy. The response of 21 and 22 to biologically relevant reactive sulfur, oxygen, and nitrogen species (RSONS) also were tested. 21 and 22 showed a 128-fold and 45-fold respectively, turn on for H_2S and high selectivity for H_2S over oxygen and nitrogen reactive species. However, 21 showed a poor selectivity over cysteine-derived reductants, while 22 has a high selectivity. The authors determined the detection limit was 0.7±0.3× μM and 4.6±2.0 μM, respectively.

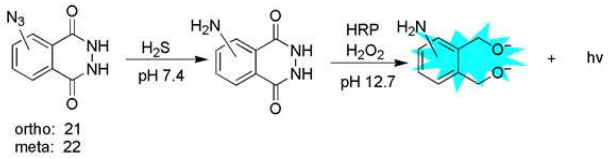


Fig. 18. The reaction of the probes (21,22) and H_2S.

Jiang et al. reported a turn-on fluorescent probe 23 (Fig. 19) for hydrogen sulfide imaging in living cells based on an excited-state intramolecular proton transfer(ESIPT) mechanism.[72] This probe was consist of a *p*-aminobenzyl moiety and 2-(20-hydroxyphenyl)-benzothiazole (HBT). When the azido group was reduced to an amino group, the *p*-aminobenzyl moiety could self-immolate to release the ESIPT chromophore HBT, corresponding an remarkable ratiometric fluorescence signals. Control experiments in the presence of other reactive species revealed that 23 exhibited good selectivity for H_2S. This probe was able to sense H_2S in HeLa cells using confocal fluorescence microscopy

imaging. The detection limit was 2.4 μM under the test conditions.

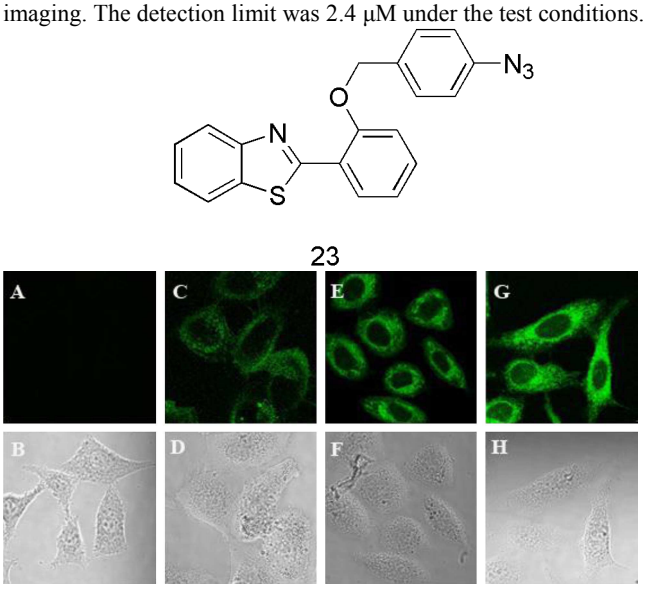
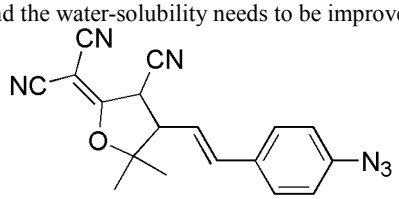


Fig. 19. Above： The structure of probe 23. Bottom： Fluorescence microscopy experiments of imaging H_2S with probe 23 (5 μM) in HeLa cells. (A) Fluorescent image of HeLa cells incubated with probe 1 for 60 min and (B) brightfield image of HeLa cells in(A). Fluorescent images (top) and brightfield images (down) of HeLa cells incubated with probe1for 30 min followed by incubation with different concentrations of NaHS, 20 μM (C and D), 50 μM (EandF), 100 μM (G and H), for another 30min. Ex=330 nm and Em=450–600nm. Reprinted with permission from Talanta, 2014, 12, 1122–126, 2014 Elsevier B.V. All rights reserved.

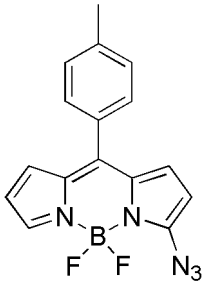
Chen et al. reported a red emission fluorescent probe 24 (Fig. 20) for H_2S based on the reduction reaction of azide with H_2S.[73] Because of its long excitation and emission wavelength, dicyanomethy lenedihydrofuran (DCDHF) was selected as a fluorophore. After incubation with H_2S, azide of this probe was reduced to form a highly fluorescent amine-derived compound. The fluorescence enhancement at 619 nm could up to 55-fold. The sensing mechanism was confirmed by both ^{1}HNMR and ^{13}CNMR. Probe 24 was low toxic toward HUVEC cells and could be used to detect H_2S in living cells. Despite the excellent selectivity, the time-dependent fluorescence responses assay showed that the reaction was complete within 60 min, which is too long. And the water-solubility needs to be improved.



24

Fig. 20. The structure of probe 24.

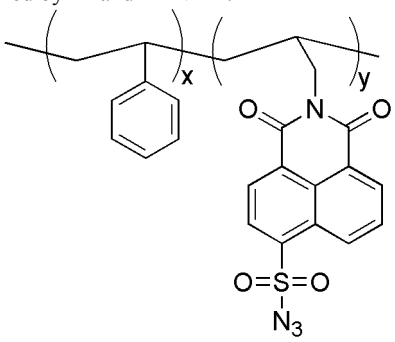
A BODIPY-azide based colorimetric and fluorescence probe 25 (Fig. 21) for selective and sensitive detection of H_2S is reported by Tanmoy Saha[74] et al. This probe was no fluorescence because of quenching effect of the electron-rich azido group. The BODIPY-azide could be reduced to a BODIPY-amide by H_2S with a turn-on fluorescent response. The probe was used to detect H_2S in HeLa cells. The probe had high water solubility, and could measure H_2S in serum with a 28-fold fluorescence increase. The detection limit was 265 nM. Moreover, it was found that 25 could be used to determine the fluctuating concentrations of H_2S in biological systems.



25

Fig. 21. The structure of probe 25.

Sun et al, for the first time, reported a kind of polymeric fluorescent sensor 26 (Fig. 22) for H_2S detection in PBS-CH_3CN (1:1, v/v, pH 7.4).[75] The intensity will increase with increasing Na_2S concentration. Na_2S induced a 3-fold increase in the fluorescence intensity of 26. The probe 26 also showed a selectivity for H_2S among other biologically anions. Furthermore, confocal microscope images of HeLa cells incubated with 26 indicated that the probe could be used for the detection of H_2S in vivo. The mechanism of the response of 26 to H_2S was the reduction of sulfonyl azide to sulfonamide in the presence of Na_2S confirmed by IR and ^{1}H NMR.

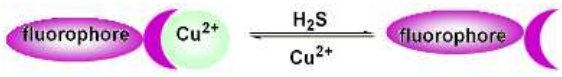


26

Fig. 22. The structure of probe 26.

2.4. The replacement of copper complex

In recent years, the complex of dye and metal(s) has also been designed for sensing anions, as the metal(s) coordinated could strongly interact with anionic analytes to attain recognizing purpose.[76-80] It was reported that copper complex sensitively senses thiols, such as cysteine and glutatione, over other amino acids in aqueous media.[81-83] The recognition mechanism was based on the metal-anion affinity, which had been also utilized as another method of sensing anions.[84–88] Here we will focus on the copper complex sensitively senses H_2S, which will release of copper when H_2S binds to the Cu^{2+} center (scheme 4).



Scheme 4. The summary of strategies for the design of fluorescent probes based on replacement of copper complex.

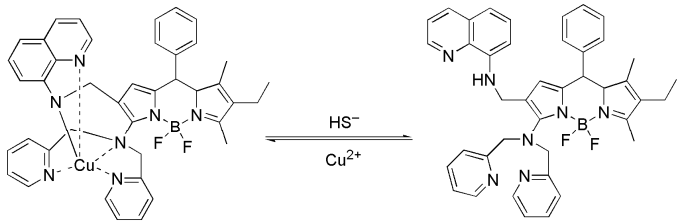


Fig. 23. The reaction of the probe 27 and H_2S.

Boron-dipyrromethene-Cu^{2+} 27 has been proved to be a suitable probe for H_2S in the solution of HEPES buffer (50 mM, pH 7.4, containing 5% DMSO).[83] After hydrogen sulfide was added, the solution color of the 27 turned from orange to pink. This indicates the capability of 27 for detecting HS^- by the release of Cu^{2+} and the formation of compound 27_1 in aqueous solution (Fig. 23). The detection limit for HS^- was 1.67×10^{-7} M under the same experimental conditions. 27 did not show any significant changes in the absorption spectra on addition of excess other anions such as F^-, Cl^-, Br^-, I^-, SO_4^{2-}, SO_3^{2-}, NO_3^-, HCO_3^-, $H_2PO_4^-$, N_3^-, NO_2^-, SCN$^-$ and CN$^-$, that indicate the excellent selectivity of 27 over other competitive anions. Unfortunately, probe 27 has almost no fluorescence response to HS^-, which hinder the application of the probe in vivo system.

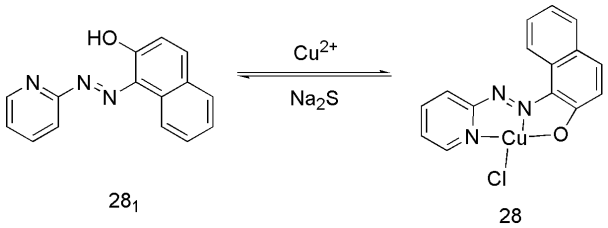


Fig. 24. The reaction of the probe 28 and Na_2S.

Zhang[89] et al. reported another copper complex of azo-dye 28 for the detection for H_2S based on the displacement method. The association constant between compound 28_1 and Cu^{2+} (K_{ass} = 1.82×10^4) was much smaller than that of Cu^{2+} and S^{2-} (K_{ass} = 7.87×10^{35}), thus, the Cu^{2+} was easily captured by S^{2-}, and free compound 28_1 was released from the complex. When Cu^{2+} was grabbed by $S^{2-}$from 28, the color of solution changed from pink to yellow. Probe 28 could still retain the sensing response to H_2S in the presence of most competing anions. The ^{1}HNMR signal and the data of absorption spectrum indicated the displacement reaction mechanism (Fig. 24).

A benzimidazole based tripodal fluorescence derivative 29_1 can capture Cu^{2+} to form complex 29, which was used to detect H_2S.[90] Probe 29 was consist of a benzimidazole based tripodal ligand binding with Cu^{2+} ions induced quenching of the fluorophore. It is worth mentioning that copper complex 29 will release Cu^{2+} after reaction with S^{2-} result in both of the absorption and fluorescence spectroscopy revived to the formers. These elucidated that copper complex 29 could be used to detect hydrogen sulfide. Thus copper complex 29 could be a retrievable fluorescence sensor for H_2S (Fig. 25).

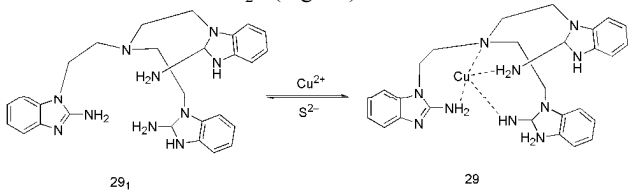


Fig. 25. The reaction of the probe 29 and S^{2-}.

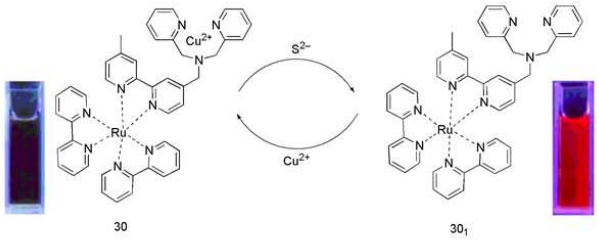


Fig. 26. The reaction of the probe 30 and S^{2-}.

A heterobimetallic Ru (II)-Cu (II) complex 30, reported by zhang et al. could be used for the detection of H_2S.[91] Compound 30_1 is a highly luminescent Ru (II)-bipyridine complex, which has a strong fluorescence (λ_{ex} = 456 nm, λ_{em} = 612 nm). The fluorescence of 30_1 could be 99% quenched after response with 1.0 molar equiv of Cu^{2+} ions through an electron transfer or energy transfer mechanism and form Ru (II)-Cu (II) complex 30. What's interesting is that complex 30 has a dramatically high sensitivity for the sense of sulfide in 100% aqueous solutions. Upon addition of S^{2-}, the fluorescence intensity of the system could gradually increase until fully revive due to the formation of stable CuS species (Fig. 26). The probe 30 was applied to detect H_2S in various wastewater samples.

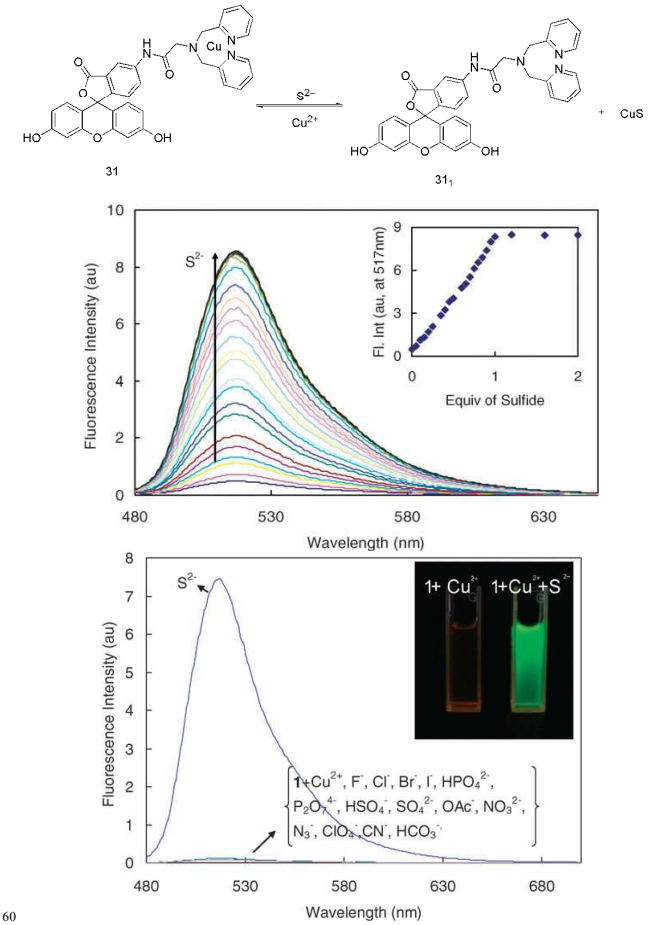


Fig. 27. Above: Reaction of the probe 33 and S^{2-}. Bottom: Fluorescence titration (left) of the compound 33_1 with sulfide ions and emission spectra (right) of probe 33 with different species. Reprinted with permission from

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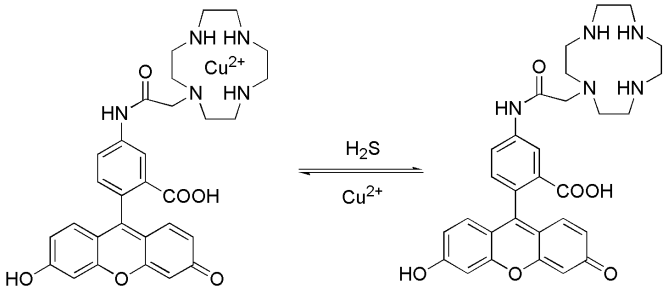
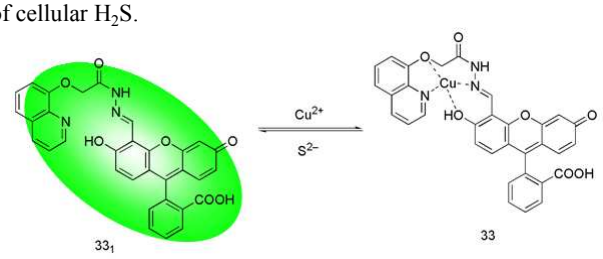
A new sulfide-selective chemosignaling system based on a Cu^{2+} complex of fluorescein derivative was reported by Choi et al.[92] Probe 31 was no fluorescence attributed to the effective binding of Cu^{2+} in the three nitrogen coordination pocket of compound 31_1 which induces the strong communication between Cu^{2+} and that of dipicolylamine (DPA) binding moiety. Upon addition of S^{2-}, the emission intensity of 31 at 517 nm increased quickly with increasing amounts of S^{2-} as a result of the release of free compound 31_1 (Fig. 27). The detection limit was 420 nM in 100% water solution. In combination with photochemical properties, perfect water solubility, nice detection limit and excellent selectivity allow this probe an effective tool for the sensing of sulfides.



32 32_1

Fig. 28. The reaction of the probe 32 and H_2S.

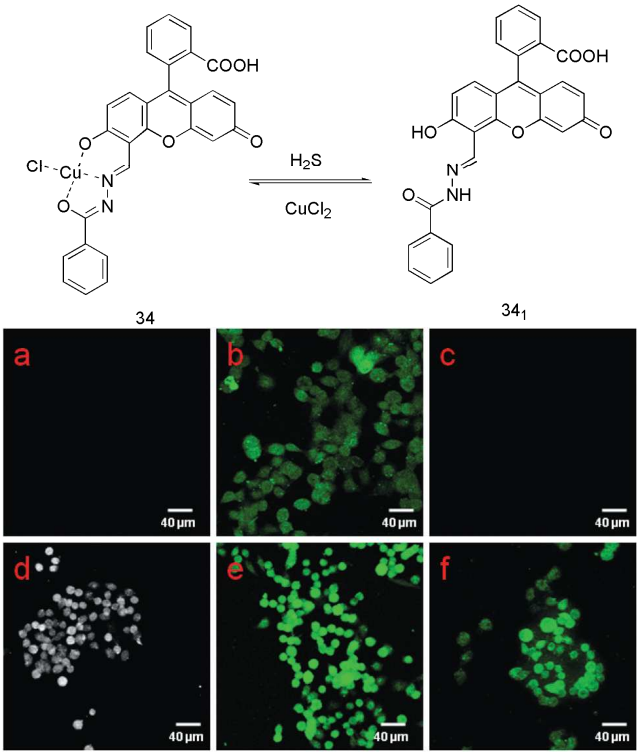
Another copper complex fluorescence sensor 32 (Fig. 28) was reported by Kiyoshi [93] et al. for the selective detection of H_2S. The reason why probe 32 was no fluorescence is the paramagnetic Cu^{2+} center has a significant quenching effect on fluorophores. Cu^{2+} would be captured by S^{2-} from the azamacrocyclic ring when H_2S binds to the Cu^{2+} center, resulting in 50-fold fluorescence enhancement. The probe 32 has a fast response to H_2S within seconds and exhibited high selectivity over other species in the detection of H_2S. It's also confirmed that the copper complex 32 were appropriate for fluorescence imaging of cellular H_2S.



33_1 33

Fig. 29. Reaction of the probe 33 and S^{2-}.

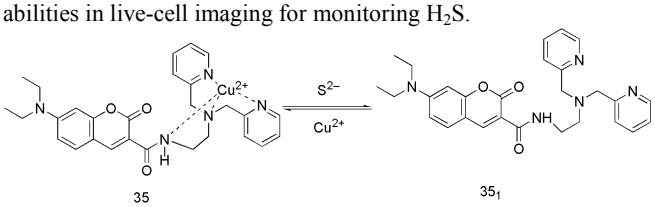
The probe 33 was designed by Hou et al. as a probe for hydrogen sulfide in PBS/CH_3CN (1:1, v/v) at pH = 7.2.[94] The addition of Cu^{2+} would lead to compound 33_1 a visible pink-to-yellow color change and green fluorescence quenching. Density functional theory (DFT) and ESI-MS analysis proved the formation of copper complex 33 in a 1:1 stoichiometry (Fig. 29). What's really valuable is 33 has a highly selective for detection of H_2S. When add S^{2-} to solution of 33, the fluorescence of the system revived on the basis of forming CuS. The chemosensor 33 has the ability of imaging in Hela cells.



34 34_1

Fig. 30. Above: The reaction of the probes 34 and H_2S. Bottom: Confocal fluorescence images in HepG2 cells (Zeiss LSM 510META confocal microscope, 40× objective lens). (a) HepG2 cells without adding indicator. (b) Fluorescence image of HepG2 cells incubated with 34_1 (10 μM). (c) Darkfield and (d) brightfield of cells supplemented with 10 μM 34_1 in the growth media for 60 min at 37 °C and then incubated with 15 μM $CuCl_2$ for 30 min at 37 °C. Cells incubated with 34_1 and $CuCl_2$ and (e) 200 μM, (f) 400 μM NaHS for another 30 min. Reprinted with permission from Dalton Trans., 2012, 41, 5799–5804. Copyright 2012, Royal Society of Chemistry.

Hou[95] et al. reported a probe 34 based on fluorescein for recognition of hydrogen sulfide. Upon addition of Cu (II), fluorescence intensity of 34_1 has a 28-fold quenching with a tiny blue shift of the absorption band. The formation of 34 in 1:1 stoichiometry was confirmed by DFT calculations. It's a remarkable fact that the copper complex 34 has a high selectivity and specificity for recognition of hydrogen sulfide. With increasing addition of H_2S to 34, fluorescence intensity of the system enhance gradually (25-30 fold) untill to recovere to the formers. All these phenomenons ascribe to the release of Cu^{2+} from 34 and the formation of CuS (Fig. 30). 34 also had the abilities in live-cell imaging for monitoring H_2S.

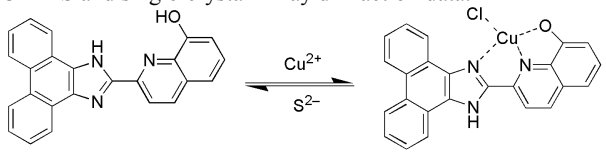


35 35_1

Fig. 31. The reaction of the probe 35 and S^{2-}.

A regenerable and highly selective fluorescent probe 35 for the detection of sulfide was reported by Wu et al.[96] With addition of Cu^{2+}, fluorescence of compound 35_1 was gradually quenched until completely quenched ($(I_o - I)/I_o \times 100\% = 98\%$) due to the produce of a non-fluorescent stable copper complex 35. Adding S^{2-} to the solution of 35, the compound 35_1 will totally

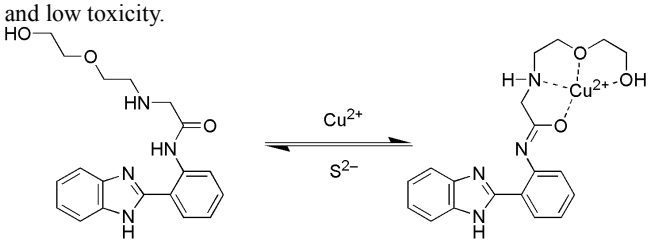
regenerated with fluorescence revive (both intensity and maximum emission peak) of the system (Fig. 31). The non-fluorescent stable copper complex 35 is highly reactive to sulfide and has a high selectivity for S^{2-} in aqueous solution. The mechanism was the copper ions were captured by S^{2-}, resulting in the revival of compound 35_1 confirmed by ^{1}HNMR, MALDI-TOF-MS and single-crystal X-ray diffraction data.



36_1 36

Fig. 32. Reaction of the probe 36 and S^{2-}.

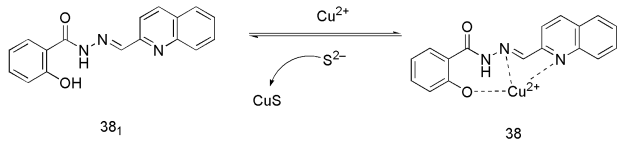
A displacement method of detecting hydrogen sulfide in aqueous media based on copper complex 36 is reported by Wang et al.[97] The fluorescence of compound 36_1 can be efficiently quenched by paramagnetic Cu^{2+} due to complexation with a large red shift (80 nm) in the absorption from 360 to 440 nm which indicating that compound 36_1 binds with Cu^{2+}. What's interesting is that addition of sulfide induced a significant fluorescence enhancement (20-fold) at 445 nm, ascribe to the release of the free compound 36_1 (Fig. 32). To investigate the selectivity of copper complex 35 to sulfide, the authors introduced representative species including anions Cl^-, Br^-, I^-, AcO^-, N_3^-, CO_3^{2-}, NO_2^-, H_2O_2, ClO^-, NO, $S_2O_3^{2-}$, SO_3^{2-}, and ascorbic acid, and found these species did not generate the same response. Therefore, copper complex 36 can be a highly selective probe for detection of S^{2-}. What's more, 36 also could be used to sense sulfide in living cells due to the cell membrane permeabilization and low toxicity.



37_1 37

Fig. 33. The reaction of the probe 37 and S^{2-}.

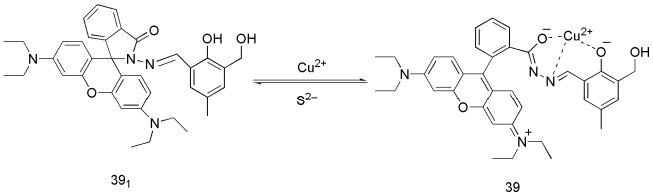
Tang et al. reported a novel benzimidazole derivative which exhibited highly selective and successive recognition of Cu^{2+} and sulfide anion in 100 % water solution.[98] Compound 37_1 has a strong fluorescence emission (λ_{ex}=338 nm, λ_{em}= 475nm) in water solution at pH 6.0, while addition of appropriate amount of Cu^{2+} will cause a complete fluorescence quenching (($I_0 - I)/I_0 \times 100$ = 99%). The TOFESI high resolution mass spectrum and IR spectra indicates the stoichiometric ratio is 1:1 to form the copper complex 37. It's worth noting that addition on f 1.0 equiv of S^{2-} to the solution of 37, fluorescence of the system completely revived at 475 nm both in intense and shape due to the release of Cu^{2+} (Fig. 33). This probe has an excellent selectivity toward S^{2-} in aqueous solution and is highly reactive to sulfide, with a fast response (30 s). The probe 36 could be used for the detection of S^{2-} in real water samples.



38_1 38

Fig. 34. The reaction of the probe 38 and S^{2-}.

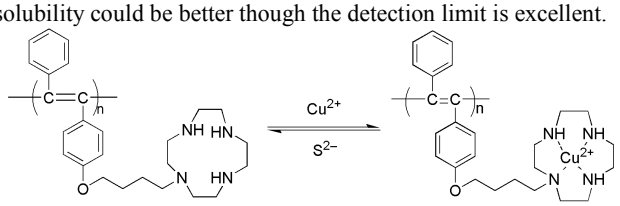
A new selective fluorescent sensor S^{2-}, based on 2-methylquinoline derivative has been designed by Gao et al.[99] The compound 38_1 could bind with Cu^{2+} along with a significant fluorescence quench (Φ = 0.059) and a color change from colorless to yellow. These changes attributed to the formation of copper complex 38 confirmed by DFT calculations. Particularly, the addition of S^{2-} would lead to fluorescence and color change totally revived. This indicated that Cu^{2+} was released from 38 ascertained by the XRD measurement and ESI-MS analysis (Fig. 34). However, other anions and various forms of sulfate did not generate the same changes. Therefore, 38 could be a retrievable and highly selective fluorescent sensor for detecting sulfide. The detection limit of this probe for S^{2-} was determined to be 9.49×10^{-7} M.



39_1 39

Fig. 35. The reaction of the probe39 and S^{2-}.

Guo et al. also reported a selective fluorescent chemosensor 39 based on rhodamine B derivative.[100] In the presence of Cu^{2+}, the spirocycle structure of compound 39_1 would open and bind with Cu^{2+} to form 39 resulted in a color change from colorless to clear pink and a 7-fold fluorescence enhancement response. Interestingly, adding S^{2-} to the solution of 39, the compound 39_1 will totally regenerated with fluorescence quenched and the color of the system revived (Fig. 35). This phenomenon showed that Cu^{2+} released from complex 39 was captured by S^{2-} to produce CuS. Control experiments in the presence of other common amino acids revealed that 39 exhibited good selectivity for S^{2-}. The detection limit of this probe for S^{2-} was 2.43×10^{-8} M. This probe realizes "naked-eye" detection due to the color change and turn-on fluorescence response. The deficiency is the water-solubility could be better though the detection limit is excellent.



40_1 40

Fig. 36. Reaction of the probe 40 and S^{2-}.

The chemosensor 40 was reported by Huang et al. as a suitable probe for H_2S.[101] Compound 40_1 showed a strong fluorescence (λ_{ex}=360nm) due to a disubstituted polyacetylene (P2) bearing cyclen moieties in the side chains, while addition of Cu^{2+} lead to the fluorescence of the compound quenched completely attributed to the formation of copper complex 40 (Fig. 36). What's more important is that the quenched fluorescence could recover to more than 62 % of the original intensity of free 40_1 after addition

increasing concentration of sulfide anion to solution of 40. No fluorescence change could be observed upon the addition of other anions. The result indicated that 40 had a high selectivity to sense sulfide anion. Probe 40 could be used for detection of S^{2-} in real water samples and the detection limit was 2.0×10^{-7}M.

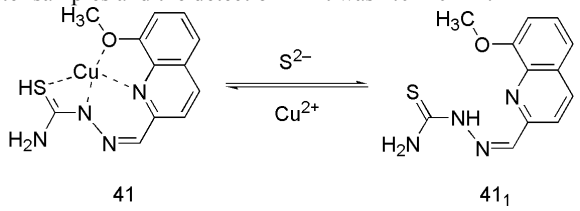


Fig. 37. Reaction of the probe 41 and S^{2-}

Tang et al. reported a simple quinoline derivatized thiosemicarbazone as a colorimetric and fluorescent sensor for relay recognition of Cu^{2+} and sulfide in aqueous solution.[102] The compound 41_1 could tightly bind to Cu^{2+} through 1:1 interaction with a deprotonation process with a color change from colorless to yellow. Fluorescence of compound 41_1 quenched after bind to Cu^{2+} duo to the formation of copper complex 41 (Fig. 37). Subsequently, addition of S^{2-} to the solution of 41, fluorescence of the system enhanced and restored to the initial emission property of free 41_1, concomitantly, absorption spectrum also revival. Competition experimental results reveal that only S^{2-} can lead to the regeneration of free compound 41_1. The detection limit of this probe for S^{2-} was 7.2×10^{-7} M.

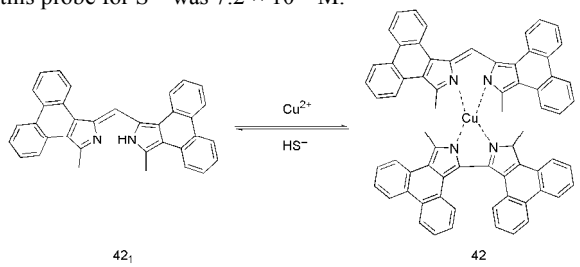
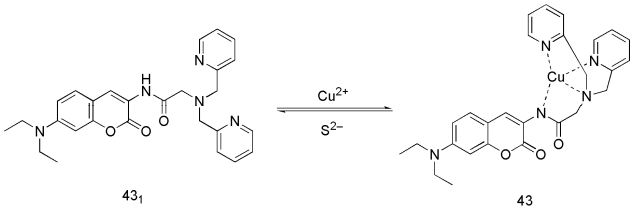


Fig. 38. The reaction of the probe 42 and HS^-.

Qu et al. reported a red fluorescent turn-on probe for hydrogen sulfide.[103] The compound 42_1, containing phenanthrene-fused dipyrromethene structure, had a fluorescence emission at 600 nm. After binding with Cu^{2+}, a red shifted and a fluorescence quench (75 % quenching, $\Phi = 0.002$) were observed, due to the formation of copper complex 42 (Fig. 38). These changes were mainly associated with the compound 42_1 to Cu^{2+} charge transfer transitions associated with the Cu^{2+} center. As expected, Cu-42 solution had very weak fluorescence, upon addition of HS^- to the solution of 42, the fluorescence intensity of the mixture increased dramatically, until the intensity and shape of the emission band totally revived. It had changed little in the fluorescence intensity of 42 after the addition of excess common inorganic anions and other biothiols. 42 is cell-permeable and can respond to intracellular HS^- anions.



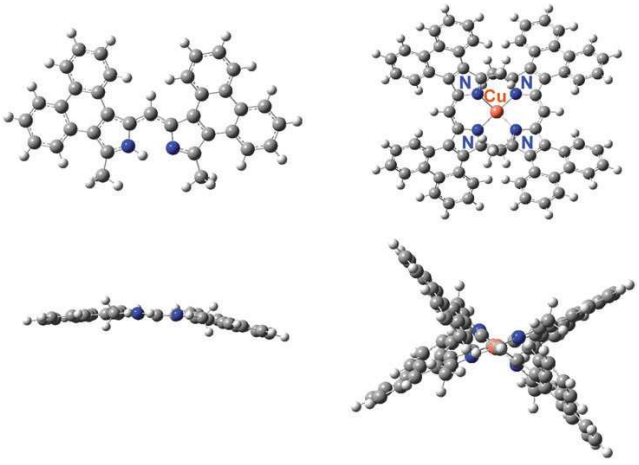


Fig. 39. Above: The reaction of the probe 43 and S^{2-}. Bottom: The calculated energy-minimized structures of 43_1 (left) and 43 (right). Reprinted with permission from Chem. Commun., 2013, 49, 7510-7512. Copyright 2013, Royal Society of Chemistry.

Coumarin derivative 43_1 containing a di-2-picolylamine (DPA) moiety were developed as a probe for Cu^{2+} and S^{2-} reported by Hou et al.[104] On addition of Cu^{2+}, the fluorescence of Compound 43_1 at 500 nm completely quenched because of the formation of 43 (Fig. 39). Due to the low solubility product constant $k_{sp} = 6.3\times10^{-36}$ of CuS, it will release free 43_1 aftre addition S^{2-} to the solution of 43 resulting in a dramatic fluorescence enhancement. However, almost no change was observed in the fluorescence intensity of 43 after the addition of excess competing anions. What's more, this probe was able to sense different H_2S levels in HeLa cells using confocal microscopy imaging. The detection limit was 1.3×10^{-7}M.

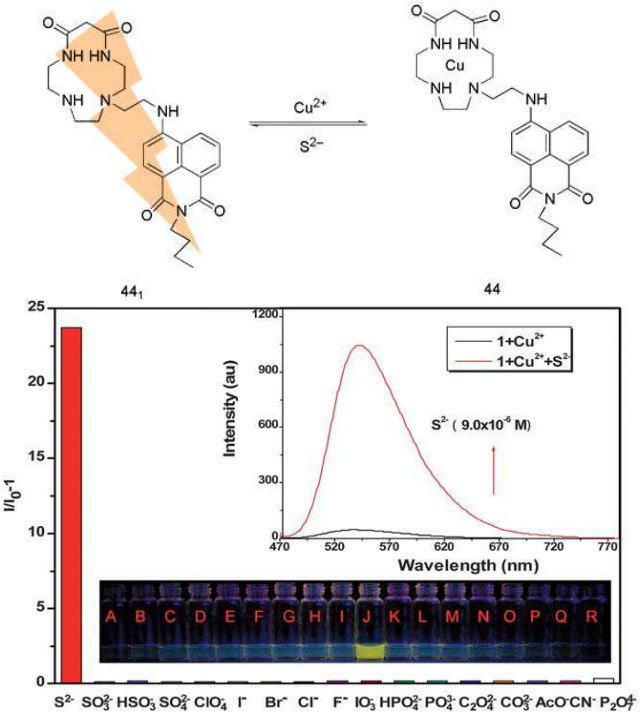


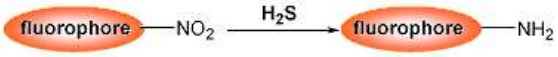
Fig. 40. Above: The reaction of the probe 44 and S^{2-}. Bottom: Fluorescence emission response profiles of $44_1 + Cu^{2+}$. Inset: fluorescence emission spectra of 44_1 (5 μM) in H_2O–CH_3OH (3 : 1, v/v, Britton–Robinson buffer, pH =7.1)

after addition of Cu^{2+} (2.7×10^{-6} mol/L), and turned on by S^{2-} (9.0×10^{-6} mol/L, photo J). The concentrations of different anions were 9.0×10^{-5} mol/L. Excitation wavelength (nm): 451. Reprinted with permission from Analyst, 2011, 136, 684-687, Copyright 2011, Royal Society of Chemistry.

Lou et al. reported a displacement-based sensing method by using Cu^{2+}-based receptors for sulfide anion recognition.[105] After binding with Cu^{2+}, the strong fluorescence of compound 44_1 completely quenched with a color change from yellow-green to almost colorless due to the formation of copper complex 44. Subsequently, addition of S^{2-} to the solution of 44, the fluorescence of 44_1 was fully revived because of the release of free 44_1 and the formation of CuS (Fig. 40). The fluorescent intensity could recover to more than 73% of the original intensity of 44_1. The probe 44 has a high selectivity for S^{2-} over the other anions.

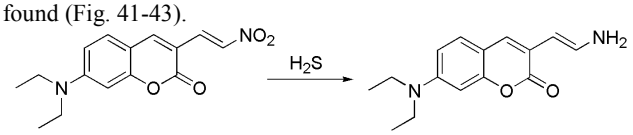
2.5. Reduction of nitro groups

The nitro group has been considered to be a strong quencher of fluorophores, and nitro group can be reduced by Na_2S to produce the corresponding amino group which provides a way to the design and synthesis of new types of fluorescent probe for H_2S detection [36] (Scheme 5).



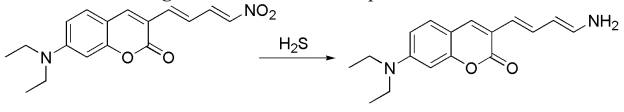
Scheme 5. The summary of strategies for the design of fluorescent probes based on reduction of nitro group.

Wu et al. reported colorimetric and ratiometric fluorescent probes 45-47 based on an ICT strategy for the detection of H_2S.[106] Reaction of probe 45 with H_2S at DMF triggered the chemoselective reduction of nitro to amine with a color change from red to green. However, on addition of H_2S, the fluorescence intensity of the probe decreased at 602 nm and a concomitant increase at 482 nm (λ_{ex}= 397 nm) with a blue shift of 120 nm was observed. Probe 45 has an excellent selectivity compared with other species. And the H_2S detection limit was 2.5 μM. With one more double bond compared with probe 45, probe 46 shows similar ultraviolet and fluorescent properties. There is an excellent selectivity of probe 46 for H_2S over other reactive sulfur, oxygen, nitrogen species (RSONS) and anions, but more equivalents of H_2S was needed to establish the reaction. Probe 47 could not react with H_2S, and almost no fluorescence change was found (Fig. 41-43).



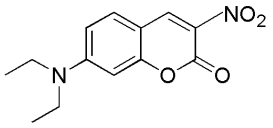
45

Fig. 41. The reaction of the probe 45 and S^{2-}.



46

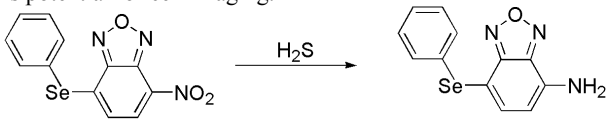
Fig. 42. The reaction of the probe 46 and S^{2-}.



47

Fig. 43. The structure of probe 47.

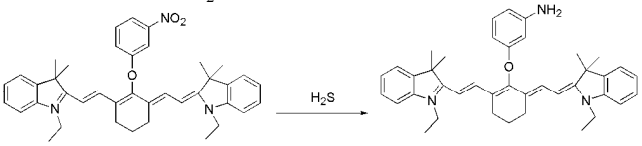
Bae et al. reported a phenylseleno-nitrobenzoxadiazole derivative 48 for the colorimetric signaling of hydrogen sulfide.[107] Reduction of the nitro group of a nitrobenzoxadiazole framework to an amino group by H_2S resulted in pronounced a color change from yellow to pink. The mechanism of this reaction was the reduction of nitro group to amine (Fig. 44), which is confirmed by ^1H NMR spectroscopy. It was proved that the probe 48 has an excellent selectivity compared with other species. Application in tap water and simulated wastewater was rather rare, but the detection limit of 48 in 50 % aqueous DMSO solution was determined to be 2.1×10^{-6} M. If the water-solubility and detection limit could be better, it will be a nice probe which is potential for cell imaging.



48

Fig. 44. The reaction of the probe 48 and H_2S.

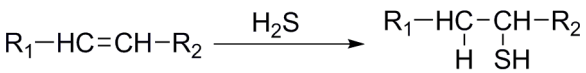
Wang et al. designed a turn-on near-infrared fluorescent probe 49 (Fig. 45) based on nitro group reduction for intracellular H_2S detection.[108] Heptamethine cyanine dye equipped with *m*-nitrophenol, the fluorescence of the cyanine platform was quenched by the electron transfer process between the modulator and the fluorophore. After the nitro group was reduced to the amino group by H_2S, probe 49 showed an increase in the fluorescence intensity with a slight blue shift. This probe also showed remarkable turn-on fluorescence for H_2S in the presence of other biologically relevant species. Probe 49 could be used to detect intracellular H_2S in RAW264.7 cells.



49

Fig. 45. The reaction of the probe 49 and H_2S.

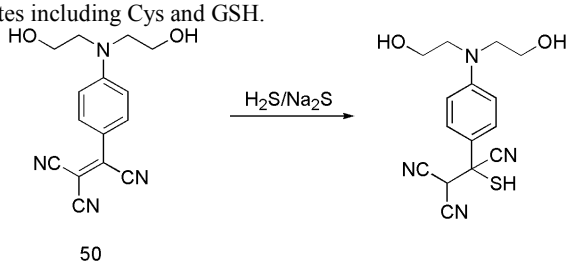
2.6. double bond addition reaction



Scheme 6. The summary of strategies for the design of fluorescent probes based on double bond addition reaction.

It was found that the nucleophilic HS^- adds faster to an electron-poor C=C double bond (Scheme 6). Zhao et al. published a highly selective colorimetric probe 50 (Fig. 46) for fast and quantitative detection of hydrogen sulfide.[109] The probe 50 itself has the absorption band at 527 nm in simulated physiological conditions (20 mM PBS, pH 7.4). However, when Na_2S was gradually added to the solution of 50, the absorption intensity decreased significantly, and the color of the solution turned from red to colorless. To investigate the selectivity, probe

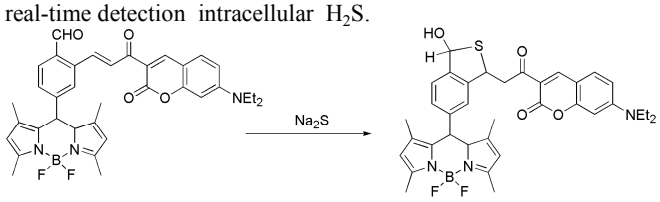
50 was incubated with various bio-species. The results show probe 50 has an excellent selectivity for H_2S over other analytes including Cys and GSH.



50

Fig. 46. The reaction of the probe 50 and H_2S.

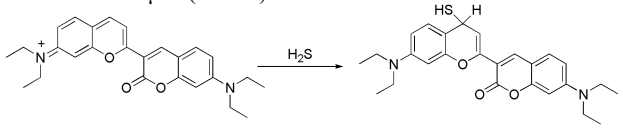
Qian et al. reported a sensitive and selective fluorescent probe 51 (Fig. 47) for hydrogen sulfide detection based on BODIPY-coumarin platform.[110] The free 51 has a very weak fluorescence at 512 nm (λ_{ex}=458 nm). After incubation with H_2S for 20 min, probe 51 displayed significant fluorescence enhancement at 512 nm (ε = 1.69×104 $M^{-1}cm^{-1}$, Φ = 0.19, >26-fold), whereas other representative biological thiols and amino acids in the PBS buffer induced negligible optical changes in 51 under similar conditions. The sensing mechanism was confirmed by high resolution mass spectrometry. This probe could be used to detect H_2S in fresh mouse blood plasma and could be used for imaging H_2S in live cells. The fluorescence response will be completed within 20 min which need to be improved to actually realize fast, accurate, and real-time detection intracellular H_2S.



51

Fig. 47. The reaction of the probe 51 and Na_2S.

Liu et al. reported a fluorescent probe 52 (Fig. 48) for the detection of H_2S based on a flavylium derivative.[111] The free probe 52 has an NIR emission peak at 690 nm. Addition of H_2S to the solution of 52 would lead to fluorescence decrease based on the selective nucleophilic attack of H_2S on the electrically positive benzopyr-ylium moiety. It was proved that 52 has an excellent selectivity for H_2S over other analytes. This probe could detect H_2S in HeLa cells and in human serum by preliminary confocal laser scanning microscopy and the detection limit was 0.14 μM (S/N=3).



52

Fig. 48. The reaction of the probe 52 and H_2S.

3. Conclusion

In this review, we have summarized recent exciting reports regarding recognition mechanism of hydrogen sulfide and their applications in hydrogen sulfide detection. The examples reported can be classified into several types according to their mechanisms (Table 1) such as the cleavage of alcoxyl (R-O) bond, the cleavage of S-O bond, reduction of azides, reduction of nitro groups, the replacement of copper complex, and double bond addition reaction. The cleavage of alcoxyl (R-O) occurs with probes containing bonddinitrophenyl ether. The cleavage of S-O bond takes place mainly with probes containing electron-withdrawing groups such as dinitrobenzenesulfonyl. Reduction of azides and nitro groups to amines is based on the reduction ability of the hydrogen sulfide. The replacement of copper complex based on the higher stability of CuS than that of the copper complex. Double bond addition reaction is mainly about the fast H_2S nucleophilic addition to the double bond in a medium of nearly neutral pH. Moreover many examples be used for cell imaging due to its cell permeability and low toxicity.[24, 46, 57, 64, 66-70, 73-75, 93-95, 97, 103, 104, 108, 111] The recognition process of many probes accompany with color changes which could be monitored by the naked eye. [24, 47, 51, 56, 63, 68, 70, 74, 83, 89, 90, 94, 95, 97, 99, 100, 102, 105-107, 109, 111] We hope that this review will help to design highly selective simple colorimetric or fluorimetric turn-on probes for detection of H_2S in living cell.

Table 1. The recognition mechanism of hydrogen sulfide.

Type of reaction	Cell imaging	Chromogenic	Fluorogenic
The cleavage of alcoxyl (R-O) bond	46	47,51	46-51
The cleavage of S-O bond	57	56	55-57
Reduction of azide	24,64,66-70,73-75	24,63,68,70,74	24,63-75
The replacement of copper complex	93-95,97,103,104	83,89,90,94,95,97,99,100,102,105	90-105
Reduction of nitro groups to amine	108	106,107	106-108
Double bond addition reaction	111	109,111	109-111

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Notes and references

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1. C. L. Evans, *J. Exp. Physiol.*, 1967, **52**, 231-248.
2. S. K. Pandey, K. H. Kim and K. T. Tang, *Trac Trend. Anal. Chem.*, 2012, **32**, 87-99.
3. P. Kamoun, *Amino Acids*, 2004, **26**, 243-254.
4. C. Szabo, *Nat. Rev. Drug. Discov.*, 2007, **6**, 917-935.
5. V. S. Lin and C. J. Chang, *Curr. Opin. Chem. Biol.*, 2012, **16**, 595-601.
6. G. A. Benavides, G. L. Squadrito, R. W. Mills, H. D. Patel, T. S. Isbell, R. P. Patel, V. M. Darley-Usmar, J. E. Doeller and D. W. Kraus, *Proc. Natl. Acad. Sci. U.S.A.*, 2007, **104**, 17977-17982.
7. K. Eto, T. Asada, K. Arima, T. Makifuchi and H. Kimura, *Biochem. Biophys. Res. Commun.*, 2002, **293**, 1485-1488.
8. R. S. Beard Jr and S. E. Bearden, *Am. J. Physiol. Heart Circ. Physiol.*, 2011, **300**, H13-H26.
9. G. Yang, L. Wu, B. Jiang, W. Yang, J. Qi, K. Cao, Q. Meng, A. K. Mustafa, W. Mu, S. Zhang, S. H. Snyder and R. Wang, *Science*, 2008, **322**, 587-590.
10. Y. Kaneko, Y. Kimura, H. Kimura and I. Niki, *Diabetes*, 2006, **55**, 1391-1397.
11. L. Wu, W. Yang, X. Jia, G. Yang, D. Duridanova, K. Cao and R. Wang, *Lab. Invest.*, 2009, **89**, 59-67.
12. X. Feng, Y. Chen, J. Zhao, C. Tang, Z. Jiang and B. Geng, *Biochem. Biophys. Res. Commun.*, 2009, **380**, 153-159.
13. N. Krishnan, C. Fu, D.J. Pappin and N. K. Tonks, *Sci. signal.*, 2011, **4**, ra86(1-12).
14. L. Li, P. Rose and P. K. Moore, *Annu. Rev. Pharmacool. Toxicol.*, 2011, **51**, 169-187.
15. J. Radford-Knoery and G. A. Cutter, *Anal. Chem.*, 1993, **65**, 976-982.
16. P. R. Brub, P. D. Parkinson and E. R. Hall, *J. Chromatogr. A*, 1999, **830**, 485-489.
17. N. S. Lawrence, J. Davis, L. Jiang, T. G. J. Jones, S. N. Davies and R. G. Compton, Electroanalysis, 2000, **12**, 1453-1460.
18. B. Spilker, J. Randhahn, H. Grabow, H. Beikirch and P. Jeroschewski, *J. Electroanal. Chem.*, 2008, **612**, 121-130.
19. E. Fischer, *Chem. Ber.*, 1883, **16**, 2234-2236.
20. M. M. F. Choi, *Analyst*, 1998, **123**, 1631-1634.
21. L. M. Siegel, *Anal. Biochem.*, 1965, **11**, 126-132.
22. T. K. J. Edison, M. P. Y. Cristiana, B. R. Arlete, S. M. Itamar and T. F. Telma, *Polym. Int.*, 2011, **60**, 951-956.
23. N. Mahapatra, S. Datta and M. Halder, *J. Photochem. Photobiol. A*, 2014, **275**, 72-80
24. G. D. Zhou, H. L. Wang, Y. Ma and X. Q. Chen, *Tetrahedron*, 2013, **69**, 867-870.
25. Y. S. Xie, P. C. Wei, X. Li, T. Hong, K. Zhang and H. Furuta, *J. Am. Chem. Soc.*, 2013, **135**, 19119−19122.
26. Y. S. Xie, Y. B. Ding, X. Li, C. Wang, J. P. Hill, K. Ariga, W. B. Zhang and W. H. Zhu, *Chem. Commun.*, 2012, **48**, 11513–11515.
27. Y. B. Ding, X. Li, T. Li, W. H. Zhu and Y. S. Xie, *J. Org. Chem.*, 2013, **78**, 5328−5338.
28. B. Chen, Y. B. Ding, X. Li, W. H. Zhu, J. P. Hill, K. Ariga and Y. S. Xie, *Chem. Commun.*, 2013, **49**, 10136–10138.
29. W. Xuan, C. Q. Sheng, Y. Cao, W. He and W. Wang, *Angew. Chem. Int. Ed.*, 2012, **51**, 2282-2284.
30. B. H. Zhang, F. Y. Wu, Y. M. Wu and X. S. Zhan, *J. Fluoresc.*, 2010, **20**, 243-250.
31. H. J. Peng, Y. F. Cheng, C. F. Dai, A. L. King, B. L. Predmore, D. J. Lefer and B. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 9672-9675.
32. S. K. Das, C. S. Lim, S. Y. Yang, J. H. Han and B. R. Cho, *Chem. Commun.*, 2012, **48**, 8395-8397.
33. C. R. Liu, J. Pan, S. Li, Y. Zhao, L. Y. Wu, C. E. Berkman, A. R. Whorton and M. Xian, *Angew. Chem. Int. Ed.*, 2011, **50**, 10327-10329.
34. C. R. Liu, B. Peng, S. Li, C.M. Park, A. R. Whorton and M. Xian, *Org. Lett.*, 2012, **14**, 2184-2187.
35. Y. Qian, J. Karpus, O. Kabil, S. Zhang, H. Zhu, R. Banerjee, J. Zhao and C. He, *Nat. Commun.*, 2011, **2**, 495-501.
36. S. Chen, Z. J. Chen, W. Ren and H. W. Ai, *J. Am. Chem. Soc.*, 2012, **134**, 9589-9592.
37. A. R. Lippert, G. C. Van de Bittner and C.J. Chang, *Accounts Chem. Res.*, 2011, **44**, 793-804.
38. M. C. Y. Chang, A. Pralle, E. Y. Isacoff and C. J. Chang, *J. Am. Chem. Soc.*, 2004, **126**, 15392-15393.
39. B. C. Dickinson and C. J. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9638-9639.
40. F. B. Yu, X. Y. Han and L. X. Chen, *Chem. Commun.*, 2014, **50**, 12234-12249
41. T. Y. Liu, Z. C. Xu, D. R. Spring and J. N. Cui, *Org. Lett.*, 2013, **15**, 2310-2313.
42. J. L. Wang and W. Y. Lin, *Biomaterials*, 2013, **34**, 7429-7436.
43. J. C. Mathai, A. Missner, P. Ku¨gler, S. M. Saparov, M. L. Zeidel, J. K. Lee and P. Pohl, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 16633-16638.
44. M. P. Lutolf, N. Tirelli, S. Cerritelli, L. Cavalli and J. A. Hubbell, *Bioconjugate Chem.*, 2001, **12**, 1051-1056.
45. C. N. Salinas and K. S. Anseth, *Macromolecules*, 2008, **41**, 6019-6026.
46. X. W. Cao, W. Y. Lin, K. B. Zheng and L. W. He, *Chem. Commun.*, 2012, **48**, 10529-10531.
47. Y. Liu and G. Q. Feng, *Org. Biomol. Chem.*, 2014, **12**, 438-445.
48. S. E. Sayed, C. de la Torre, L. E. Santos-Figueroa, E. Pérez-Payá, R. Martínez-Máñez, F. Sancenón, A. M. Costero, M. Parraae and S. Gilae,, *RSC Adv.*, 2013, **3**, 25690-25693.
49. S. Shaltiel, *Biochem. Biophys, Res. Commun.*, 1967, **29**, 178-183.
50. R. Philosof-Oppenheimer, I. Pechtz and M. Fridkin, *Int. J. Pept. Protein Res.*, 1995, **45**, 116-121.
51. C. Wei, Q. Zhu, W. W. Liu, W. B. Chen, Z. Xi and L. Yi, *Org. Biomol. Chem.*, 2014, **12**, 479-485.
52. W. Y. Lin, L. L. Long and W. Tan, *Chem. Commun.*, 2010, **46**,1503-1505.
53. W. Jiang, Q. Q. Fu, H. Y. Fan, J. Ho and W. Wang, *Angew. Chem. Int. Ed.*, 2007, **46**, 8445-8448.
54. W. Jiang, Y. T. Cao, Y. Liu and W. Wang, *Chem. Commun.*, 2010, **46**, 1944-1946.
55. F. Y. Zheng, M. Wen, F. Zeng and S. Z. Wu, *Polymer*, 2013, **54**, 5691-5697.
56. X. F. Yang, L. Wang, H. M. Xu and M. L. Zhao, *Anal. Chim. Acta*, 2009, **631**, 91-95.
57. L. Fu, F. F. Tian, L. Lai, Y. Liu, P. D. Harvey and F. L. Jiang, *Sens. Actuators B*, 2014, **193**, 701-707.
58. X. D. Jiang, J. Zhang, X. Shao and W. Zhao, *Org. Biomol. Chem.*, 2012, **10**, 1966-1968.
59. J. Shao, H. Sun, H. Guo, S. Ji, J. Zhao, W. Wu, X. Yuan, C. Zhang and T. D. James, *Chem. Sci.*, 2012, **3**, 1049-1061.
60. Y. Tang, H. R. Yang, H. B. Sun, S.J. Liu, J. X. Wang, Q. Zhao, X. M. Liu, W. J. Xu, S. B. Li and W. Huang, *Chem. Eur. J.*, 2013, **19**, 1311-1319.
61. A. P. de Silva, H. Q. Gunaratne, T. Gunnlaugsson, A. J. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515-1566.
62. Z. R. Grabowski, K. Rotkiewicz and W. Rettig, *Chem. Rev.*, 2003, **103**, 3899-4032.
63. F. Yu, P. Li, P. Song, B. S. Wang, J. Z. Zhao and K. Han, *Chem. Commun.*, 2012, **48**, 2852-2854.
64. K. B. Zheng, W. Y. Lin and L. Tan, *Org. Biomol. Chem.*, 2012, **10**, 9683-9688.
65. M. C. T. Hartman and M. M. Dcona, *Analyst*, 2012, **137**, 4910-4912.
66. W. H. Li, W. Sun, X. Q. Yu, L. P. Du and M. Y. Li, *J. Fluoresc*, 2013, **23**, 181-186.
67. L. A. Montoya and M. D. Pluth, *Chem. Commun.*, 2012, **48**, 4767-4769.
68. A. R. Lippert, E. J. New and C. J. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 10078-10080.
69. B. F. Chen, W. Li, C. Lv, M. M. Zhao, H. W. Jin, H. F. Jin, J. B. Du, L. R. Zhang and X. J. Tang, *Analyst*, 2013, **138**, 946-951.
70. W. Sun, J. L. Fan, C. Hu, J. F. Cao, H. Zhang, X. Q. Xiong, J. Y. Wang, S.Cui, S. G. Sun and X. J. Peng, *Chem. Commun.*, 2013, **49**, 3890-3892.
71. T. S. Bailey and M.D. Pluth, *J. Am. Chem. Soc.*, 2013, **135**, 16697-16704.
72. Y. Jiang , Q. Wu and X. J. Chang, *Talanta*, 2014, **121**, 122-126.
73. T. Chen, Y. Zheng, Z. C. Xu, M. Zhao, Y. N. Xu and J. N. Cui, *Tetrahedron Lett.*, 2013, **54**, 2980-2982.
74. T. Saha, D. Kand and P. Talukdar, *Org. Biomol. Chem.*, 2013, **11**, 8166-8170.

75. K. Sun, X. L. Liu, Y. Y. Wang and Z. Q. Wu, *RSC Adv.*, 2013, **3**, 14543-14548.
76. Z. Q. Guo, W. H. Zhu and H. Tian, *Macromolecules*, 2010, **43**, 739-744.
77. S. K. Kim, D. H. Lee, J. I. Hong and J. Yoon, *J. Accounts Chem. Res.*, 2009, **42**, 23-31.
78. X.D. Lou, Y. Zhang, Q.Q. Li, J.G. Qin and Z. Li, *Chem. Commun.*, 2011, **47**, 3189-3191.
79. R. Martinez-Manez and F. Sancenon, *Chem. Rev.*, 2003, **103**, 4419-4476.
80. M. E. Moragues, R. Martinez-Manez and F. Sancenon, *Chem. Soc. Rev.*, 2011, **40**, 2593-2643.
81. H. S. Jung, J. H. Han, Y. Habata, C. Kang and J. S. Kim, *Chem. Commun.*, 2011, **47**, 5142-5144.
82. C. C. Zhao, Y. Zhou, Q. N. Lin, L. Y. Zhu, P. Feng, Y. L. Zhang and J.A. Cao, *J. Phys. Chem. B*, 2011, **115**, 642-647.
83. X. F. Gu, C. H. Liu, Y. C. Zhu and Y. Z. Zhu, *Tetrahedron Lett.*, 2011, **52**, 5000-5003.
84. X. D. Lou, J. G. Qin and Z. Li, *Analyst*, 2009, **134**, 2071-2075.
85. S. Rochat and K. Severin, *Chem. Commun.*, 2011, **47**, 4391-4393.
86. J. S. Wu, R. L. Sheng, W. M. Liu, P. F. Wang, J. J. Ma, H. Y. Zhang and X. Q. Zhuang, *Inorg. Chem.*, 2011, **50**, 6543-6551.
87. L. Zhang, X. Lou, Y. Yu, J. Qin and Z. Li, *Macromolecules*, 2011, **44**, 5186-5193.
88. D. P. Pluth, M. R. Chan, L. E. McQuade and S. J. Lippard, *Inorg. Chem.*, 2011, **50**, 9385-9392.
89. D. Q. Zhang and W. S. Jin, *Spectrochim. Acta Part A*, 2012, **90**, 35-39.
90. C. Kar and G. Das, *J. Photochem. Photobiol. A*, 2013, **251**, 128-133.
91. R. Zhang, X. J. Yu, Y. J. Yin, Z. Q. Ye, G. L. Wang and J. L. Yuan, *Anal. Chim. Acta*, 2011, **691**, 83-88.
92. M. G. Choi, S. Cha, H. Lee, H. L. Jeon and S. K. Chang, *Chem. Commun.*, 2009, **47**, 7390-7392.
93. K. Sasakura, K. Hanaoka, N. Shibuya, Y. Mikami, Y. Kimura, T. Komatsu, T. Ueno, T.Terai, H. Kimura and T. Nagano, *J. Am. Chem. Soc.*, 2011, **133**, 18003-18005.
94. F. P. Hou, L. Huang, P. X. Xi, J. Cheng, X. F. Zhao, G. Q. Xie, Y. J. Shi, F. J. Cheng, X. J. Yao, D. C. Bai and Z. Z. Zeng, *Inorg. Chem*., 2012, **51**, 2454-2460.
95. F. P. Hou, J. Cheng, P. X. Xi, F. J. Chen, L. Huang, G. Q. Xie, Y. J. Shi, H. Y. Liu, D. C. Bai and Z. Z. Zeng, *Dalton Trans*., 2012, **41**, 5799-5804.
96. X. J. Wu, H. D Li, Y. H. Kan and B. Z. Yin, *Dalton Trans.*, 2013, **42**, 16302-16310.
97. J. L. Wang, L. P. Long, D. Xie and Y. W. Zhan, *J. Lumin.*, 2013, **139**, 40-46.
98. L. J. Tang, M. J. Cai, Z. L. Huang, K. L. Zhong, S. H. Hou, Y. J. Bian and R. J. Nandhakumar, *Sens. Actuators B*, 2013, **185**, 188-194.
99. C. J. Gao, X. Liu, X. J. Jin, J. Wu, Y. J. Xie, W. S. Liu, X. J. Yao and Y. Tang, *Sens. Actuators B*, 2013, **185**, 125-131.
100. D. Guo, Z. P. Dong, C. Luo, W. Y. Zan, S. Q. Yan and X. J. Yao, *RSC Adv.*, 2014, **4**, 5718-5725.
101. Y. F. Huang, D. X. Ou, C. Wang, C. Huang, Q. Q. Li and Z. Li, *Polym. Chem.*, 2014, **5**, 2041-2049.
102. L. J. Tang, P. Zhou, Q. Zhang, Z. L. Huang, J. Zhao and M. J. Cai, *Inorg. Chem. Commun.*, 2013, **36**, 100-104.
103. X. Y. Qu, C. J. Li, H. C. Chen, J. Mack, Z. J. Guo and Z. Shen, *Chem. Commun.*, 2013, **49**, 7510-7512.
104. J. T. Hou, B. Y. Liu, K. Li, K. K. Yu, M. B. Wu and X. Q. Yu, *Talanta*, 2013, **116**, 434-440.
105. X. D. Lou, H. L. Mu, R. Gong, E. Q. Fu, J. G. Qin and Z. Li, *Analyst*, 2011,**136**, 684-687.
106. M. Y. Wu, K. Li, J. T. Hou, Z. Huang and X. Q. Yu, *Org. Biomol. Chem.*, 2012, **10**, 8342-8347.
107. J. Bae, M. G. Choi, J. Choi and S. K. Chang, *Dyes Pigments*, 2013, **99**, 748-752.
108. R. Wang, F. B. Yu, L. X. Chen, H. Chen, L. J. Wang and W. W. Zhang, *Chem. Commun.*, 2012, **48**, 11757-11759.
109. Y. Z. Zhao, X. H. Zhu, H. Kan, W. Z. Wang, B. C. Zhu, B. Du and X. L. Zhang, *Analyst*, 2012, **137**, 5576-5580.
110. Y. Qian, B. Y. Yang, Y. N. Shen, Q. R. Du, L. Lin, J. Lin and H. L. Zhu, *Sens. Actuators B*, 2013, **182**, 498-503.
111. J. Liu, Y. Q. Sun, J. Y. Zhang, T. Yang, J. B. Cao, L. S. Zhang and W. Guo, *Chem. Eur. J.*, 2013, **19**, 4717-4722.