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Review

Review of Hydrogen Sulfide Based on Its Activity Mechanism and Fluorescence Sensing

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Abstract: The significance of hydrogen sulfide (H_2S) in biological research is covered in detail in this work. H_2S is a crucial gas-signaling molecule that is involved in a wide range of illnesses and biological processes. Whether H_2S has a beneficial therapeutic effect or negative pathological toxicity in an organism depends on changes in its concentration. A novel approach to treatment is the regulation of H_2S production by medications or other measures. Furthermore, H_2S is a useful marker for disease assessment because of its dual nature and sensitivity. We can better understand the onset and progression of disease by developing probes to track changes in H_2S concentration based on the nucleophilicity, reducing properties, and metal coordination properties of H_2S. This will aid in diagnosis and treatment. These results demonstrate the enormous potential of H_2S in the detection and management of disease. Future studies should concentrate on clarifying the relationship between diseases and the mechanism of action of H_2S in organisms. Ultimately, this work opens new possibilities for disease diagnosis and treatment while highlighting the significance of H_2S in biological research. Future clinical practice and medical advancements will benefit greatly from our thorough understanding of the mechanism of action and therapeutic applications of H_2S.

Keywords: hydrogen sulfide; gaseous drugs; physiological activity; fluorescent probe; integration of diagnosis and treatment

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1. Introduction

The study of H_2S was first prompted by the irritating effects of sewer gas on the eyes, as described in Bernardino Ramazzini's book "*De Morbis Artificum Diatriba*" [1], an Italian physician from the 18th century known as the "Father of Occupational Medicine". It was not until 1775 that the associated product was identified as H_2S, despite the fact that Carl Wilhelm Scheele initially created H_2S in 1750 by reacting ferrous sulfide with mineral acid [2]. Nonetheless, H_2S has been studied primarily for its toxicity since it was discovered centuries ago when it was thought to be a dangerous gas with a rotten egg odor. The discovery of endogenous H_2S in animal and human brains by Warenycia [3], Goodwin [4], Savage, and Gould [5] did not lead to the widespread acceptance of H_2S as a biological transmitter until the 20th century. H_2S was identified as the third gas signal molecule, after carbon monoxide (CO) and nitric oxide (NO), since the ground-breaking research conducted in the late 1990s by Abe and Kimura, who demonstrated that H_2S can control nerves and relax blood vessels [6]. Many studies on H_2S have advanced quickly in recent years. These studies cover a wide range of topics, such as promoting tissue repair, preventing apoptosis, altering lipid metabolism, stimulating angiogenesis, and inhibiting monocyte adhesion. The pathway of H_2S signaling is connected to the physiological changes mentioned above [7–12].

2. Endogenous H_2S Production

2.1. Enzymatic Pathway

In mammalian tissues, the enzymatic production of endogenous H_2S has been extensively studied and is primarily mediated by the following three enzymes: cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3- MST). Different tissues contain these enzymes, which show different patterns of expression [13]. The liver exhibits the highest level of expression of CSE, which is also highly expressed in the kidneys, neurons, macrophages, and smooth muscle cells [14–18]. The conversion of cysteine into H_2S, pyruvate, and ammonia is catalyzed by the expression of CSE. High concentrations of homocysteine can also produce H_2S under the catalysis of CSE [19–22]. Nonetheless, it is generally accepted that the expression and activity of CSE in the heart and spleen are insignificant [23,24]. CBS is mainly expressed in astrocytes in the pancreas, reproductive organs, and brain [25–29]. Research has demonstrated that there is no discernible decrease in the endogenous H_2S concentration in the liver of CBS-/-mice when compared to mouse tissue of the wild type [30]. Studies have shown that compared with wild-type mouse tissue, the liver of CBS-/-mice does not show a significant reduction in endogenous H_2S concentration [31]. CBS generates H_2S through two catalytic pathways. Under CBS catalysis, cysteine will condense with water to generate H_2S following β-elimination. Cysteine and homocysteine are directly condensed when catalyzed by CBS to generate cystathionine and H_2S [20,32], and 3-MST is mostly present in the cytoplasm and is expressed mainly in the gastrointestinal tract. Additionally, it is expressed in liver, kidney, heart, and brain cells [33,34]. Cysteine and α-ketoglutarate are first catalyzed by cysteine aminotransferase (CAT) into glutamic acid and 3-mercaptopyruvate, and then 3-mercaptopyruvate is converted into H_2S and acetone by 3-MST. In addition, 3-MST can form pyruvate and persulfide MST-SSH through 3-mercaptopyruvic acid, which is then triggered by a thiol-containing reducing agent (R-SH) to release H_2S (Figure 1) [35–37].

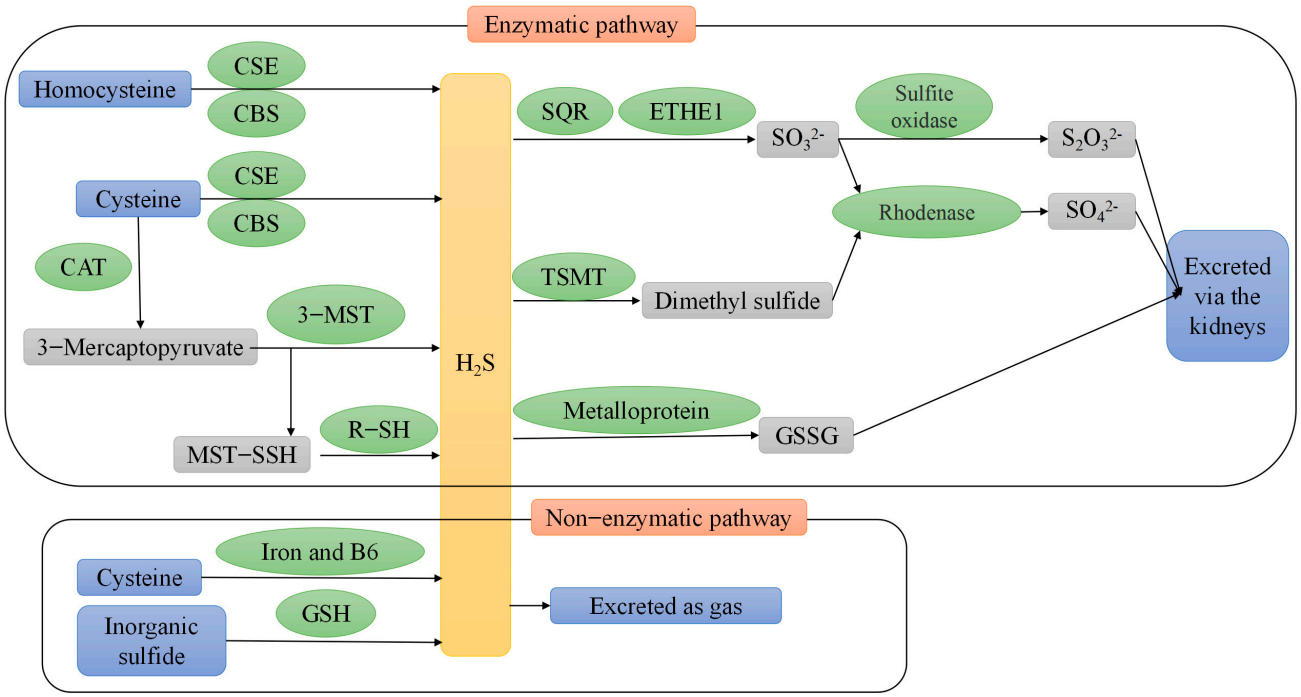


Figure 1. Production and metabolic process of endogenous H_2S.

2.2. Non-Enzymatic Pathways

Despite the widespread belief that enzymatic H_2S production is the primary source of endogenous H_2S, Yang and colleagues discovered that non-enzymatic pathways account for the majority of endogenous H_2S production in all human tissues, except for

the liver and kidney [38]. Their study shows that iron and vitamin B6 catalyze the non-enzymatic production of H_2S, with cysteine being the preferred substrate. In addition, thiols or compounds containing thiols can react with other molecules to produce H_2S non-enzymatically. Examples of such reactions include a reduction in dietary inorganic sulfide salts or polysulfides by glutathione (GSH) [39–41]. This non-enzymatic pathway is widespread in mammals, but its mechanism is poorly understood. A better understanding of non-enzymatic pathways is crucial for further investigation of the physiological role of H_2S [42].

3. Metabolism of Endogenous H_2S

Research has indicated that the highest possible concentration of endogenous H_2S in cells is 0.1 mM, whereas the majority of tissues exhibit a steady-state concentration of endogenous H_2S in the nanomolar range [43]. According to kinetic studies, the low steady-state concentration of H_2S in tissues results in a higher rate of H_2S production and metabolism [44]. When administered in large doses, H_2S is rapidly oxidized and excreted as $S_2O_3^{2-}$ and SO_4^{2-} at tissue-specific rates [45,46]. The metabolism of H_2S is mainly carried out through enzymatic pathways. Initially, H_2S undergoes oxidation by sulfide quinone oxidoreductase (SQR) within the mitochondrial matrix, resulting in the production of persulfide. This persulfide is subsequently oxidized by ethylmalonic encephalopathy 1 protein (ETHE1), yielding sulfite. Finally, sulfite is further oxidized by sulfite oxidase or rhodenase into SO_4^{2-} and $S_2O_3^{2-}$ and then excreted in the urine through the kidneys [14].

Unlike enzymatic oxidation, which is a primary mechanism for H_2S metabolism, methylation of H_2S primarily takes place in the cytoplasm of cells [47]. A small amount of H_2S is converted into methylmercaptan and dimethyl sulfide by thiol-S-methyl-transferase (TSMT). Another substrate for rhodanese is dimethyl sulfide, which is oxidized to thiocyanate and SO_4^{2-} before being eliminated in the urine.

H_2S in the blood can be cleared by metalloproteins (such as hemoglobin, myoglobin, neuroglobin, and cytochrome C oxidase) through the formation of sulfoxide products or metal/disulfide-containing molecules (such as L-glutathione oxidized (GSSG)) [47–50]. The substance is ultimately eliminated from the body via the kidneys and intestines within a specified timeframe. Very small amounts of H_2S are excreted directly from the body in the form of gas from the intestines and lungs (Figure 1).

4. Donor Categories of H_2S

The surge of interest in H_2S research has led researchers to explore a multitude of H_2S donors. To investigate the physiological impacts of endogenous H_2S, an appropriate H_2S donor needs to have drug-like properties such as stability, low metabolite toxicity, water solubility, and a well-defined release mechanism. This leads to a summary and classification of H_2S donors from various sources and release mechanisms based on recent research on H_2S donors. By examining these various kinds of H_2S donors, we can broaden our perspectives and offer fresh research approaches. There are still many restrictions that prevent the practical application of different types of H_2S donors, even though they can address some of the issues that arise in the clinical application of H_2S donors. The therapeutic potential of these donors will eventually be realized as H_2S research advances.

4.1. Inorganic H_2S Donors

H_2S gas and sulfide salts (NaHS and Na_2S) are the most common ways to study the properties of H_2S in biology and are the most direct ways to administer H_2S [51,52]. There are still issues with investigating this class of inorganic H_2S donors as possible therapeutic agents, although they are frequently used to assess the therapeutic potential of H_2S in vitro [53]. When sulfide salt is dissolved in water, it will be hydrolyzed into H_2S, HS^-, and S^{2-} very quickly. This dynamic change makes the quantitative release of H_2S from sulfide salts challenging as it lacks targeting capabilities. The most critical issue is that sulfide salts release H_2S too quickly, which will cause the H_2S content in the blood

tissue to rise sharply and then drop rapidly after administration. This is contrary to strictly controlled endogenous H_2S release, resulting in the inability to exert a therapeutic effect. The above shortcomings have prompted researchers to explore quantitatively controllable targeted H_2S donors.

4.2. Naturally Derived H_2S Donors

Garlic has been demonstrated to have positive effects on the cardiovascular system as a naturally occurring product that can release H_2S, including lowering blood pressure, lowering cholesterol, preventing platelet aggregation, and preventing oxidative stress [54]. Among them, garlic extract S-allyl-L-cysteine (L-SAC) is a potential source of H_2S and is the reason why garlic has cardioprotective effects [55–57]. Allicin is also the most common garlic extract, which can be broken down to form diallyl disulfide (DADS), diallyl sulfide (DAS), and diallyl trisulfide (DATS) [58]. Studies have shown that these decomposition products are similar to sulfide salts. In the presence of free sulfhydryl groups, they are released by red blood cells in the blood and release H_2S, which plays a role in relaxing blood vessels [39]. In addition to garlic extract (Figure 2), many natural products are considered to be H_2S-releasing donors, such as sulforaphane and Erucin [59,60]. Extracting potential H_2S donors from natural products is the most attractive method to researchers, not only because such compounds are easy to obtain but, more importantly, because they are easily absorbed by the human body and have low toxicity. Unfortunately, compared with most synthetic H_2S donors, natural H_2S donors are generally structurally unsuitable for modification and have many by-products. These shortcomings limit the use of natural H_2S donors in in vitro and in vivo studies.

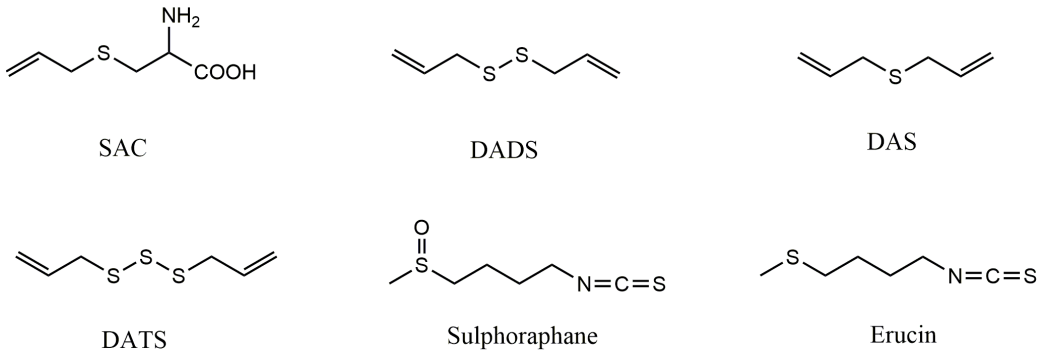


Figure 2. Natural H_2S donors.

4.3. Hydrolysis-Triggered H_2S Donors

Lawesson's reagent (S-1), a sulfide reagent originally developed as a sulfide reagent, and its derivatives such as GYY4137 (S-2) have been shown to release H_2S in aqueous solutions more slowly than sulfide salts [61,62]. JK series compounds can achieve different rates of H_2S release at different pH values and are also a method for hydrolysis to trigger the release of H_2S [63]. 1,2-dithio-3-thiones (DTTs, S-3) are a class of H_2S donor compounds that are generally considered to be hydrolysis-triggering [64]. Secondly, a derivative of the DTT compound noranitrisulfide (ADT-OH, S-4) is also worth noting [65]. It is biologically active on its own, and the compound is often derivatized and linked to other drugs to create H_2S donor forms of those drugs. At present, according to the activity of ADT and other DTT derivatives that have been studied, the activity of these drugs is closely related to H_2S-releasing ability. In addition to developing organic donors of H_2S released by hydrolysis, the inorganic H_2S donor TTM (S-5) was initially used as a thiol transfer agent in organic synthesis (Figure 3), but under physiological conditions, it can also release H_2S by hydrolysis [66].

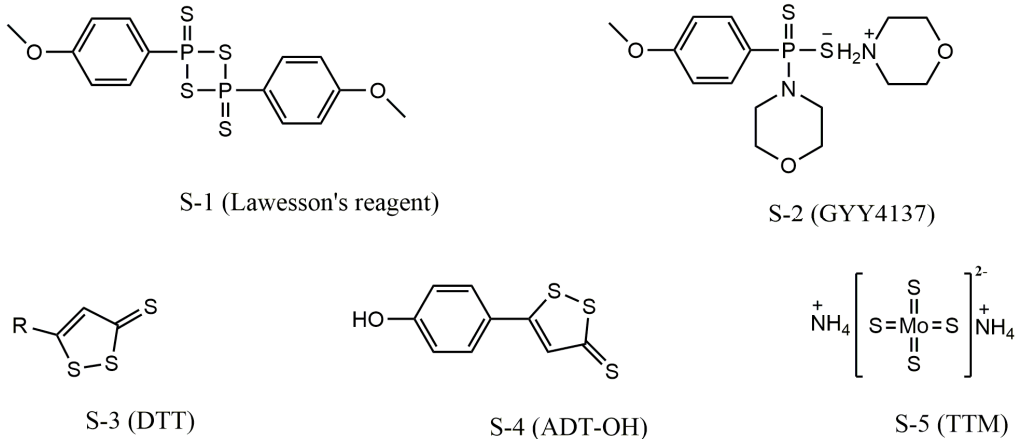


Figure 3. Hydrolysis-triggered H_2S donors.

4.4. Thiol-Triggered H_2S Donors

The most common cause of endogenous H_2S production is cysteine. Two common cellular nucleophiles and reducing agents that are essential for preserving cellular redox homeostasis are cysteine and glutathione. Additionally, they are thought to activate a variety of bioactive substances, including prodrugs and donors of H_2S [67]. Studying these thiol-triggered H_2S donors (S-6–S-12) is useful for creating H_2S-targeted medications since cysteine and glutathione are expressed and enriched in specific tissues under physiological and pathological circumstances (Figure 4) [68–74].

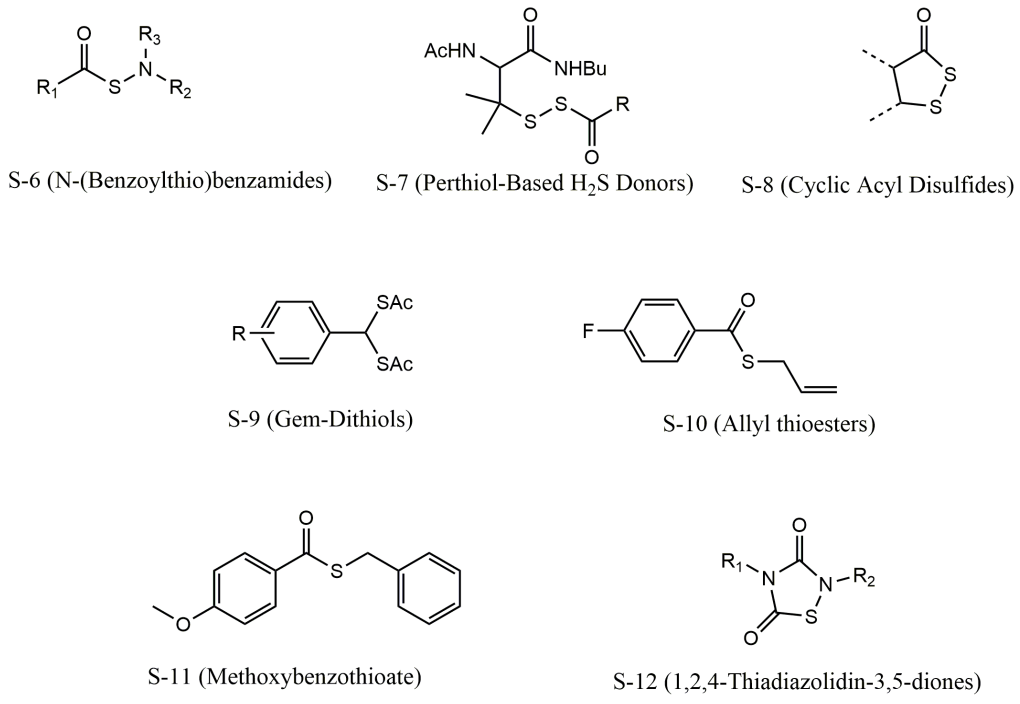
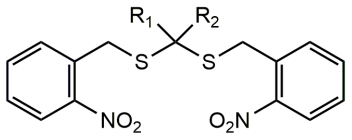


Figure 4. Thiol-triggered H_2S donors.

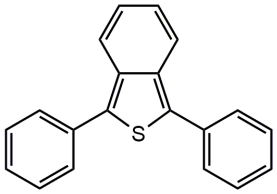
4.5. Light-Triggered H_2S Donors

Compared with other types of H_2S donors, light-triggered donors have "on–off" characteristics that completely rely on external light sources, making them bio-orthogonal, non-invasive, cheap, and practical [75]. As an external stimulus, light irradiation can achieve controllable H_2S release by adjusting relevant parameters. The most critical aspect is that the spatiotemporal control characteristics of release at specific locations can reduce off-target effects during delivery and will not be interfered with by a large number of

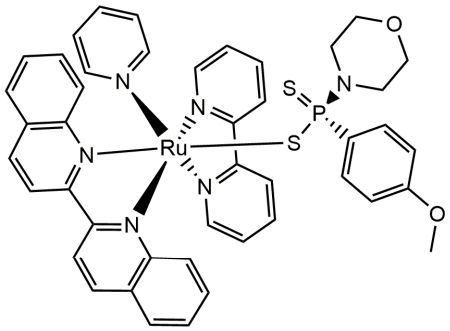
surrounding biologically active substances during the release of H_2S. This delivery method provides an effective avenue for the development of targeted therapies and diagnostic visualization. Because of the potential application prospects of the controlled release of H_2S, the development of photoresponsive H_2S donors (S-13–S-17) has received increasing attention (Figure 5) [76–80]. Although light-triggered H_2S donors provide a convenient method for H_2S release, potential photodamage to tissues also hinders their biological applications.



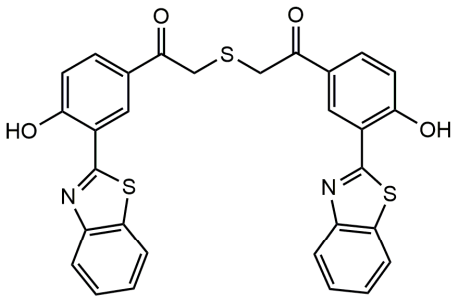
S-13 (Caged gem-Dithiols)



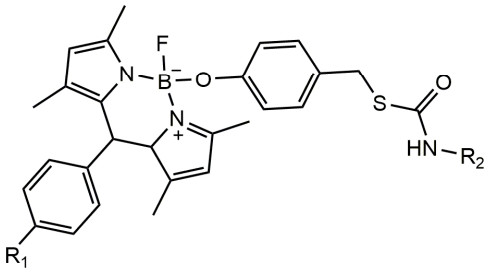
S-14 (1,3-diarylisobenzothiophene)



S-15 (Ruthenium(II) Complex)



S-16 (p-hydroxyphenacyl)



S-17 (Uncaging of Carbonyl Sulfide)

Figure 5. Light-triggered H_2S donors.

4.6. Enzyme-Triggered H_2S Donors

Enzymes are a vital class of biological catalysts that are produced by cells and found in many different parts of living things. Because of their high specificity and catalytic properties, enzymes facilitate chemical reactions within organisms with remarkable efficiency and precision under exceedingly mild conditions. Enzyme specificity can be used to target H_2S release because particular enzymes can act on structurally similar substrates and are found in particular tissues. Moreover, abnormal up-regulation of specific enzymes is a common accompanying feature of many diseases, supporting the selectivity of enzyme-triggered donors for specific diseases. In other words, an enzyme-triggered H_2S donor can precisely release H_2S in targeted tissues. Above all, using an enzyme activation strategy does not cause cellular thiols—which are essential for preserving intracellular redox balance—to be depleted. The targeted delivery of H_2S (S-18–S-22) through enzyme triggering is therefore a reasonable and practical strategy (Figure 6) [81–85].

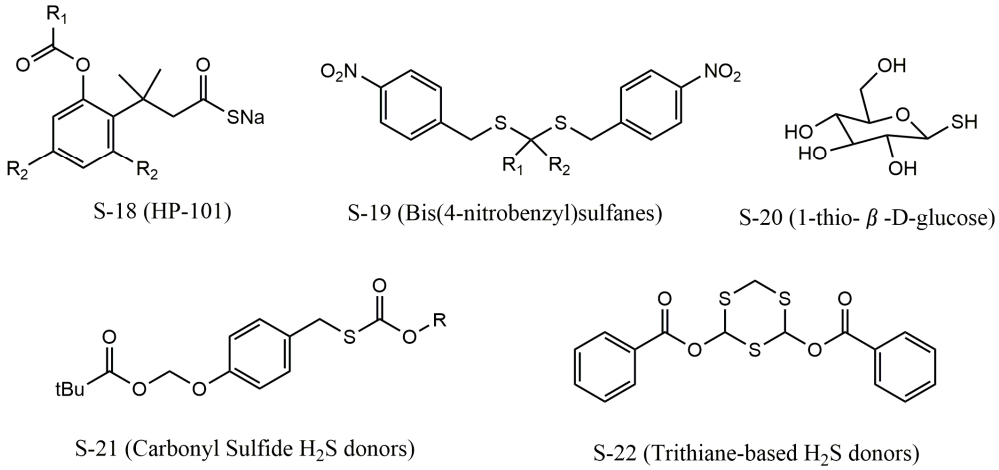


Figure 6. Enzyme-triggered H_2S donors.

4.7. Reactive Oxygen Species-Triggered H_2S Donor

Reactive oxygen species (ROS) can influence different signaling pathways within organisms; however, an overabundance of ROS can result in oxidative damage, which can cause cell dysfunction or even death [86]. Numerous illnesses, including cancer, diabetes, cardiovascular disease, neurodegenerative diseases, and aging, are strongly linked to oxidative stress brought on by ROS [87–89]. On the other hand, diseases associated with oxidative damage mediated by ROS can be fought off by the reduction protection mechanism of H_2S [90–92]. The generation of H_2S donors in response to ROS has the dual potential to both lower ROS concentration and enhance H_2S's antioxidant properties, ultimately serving to protect cells. Despite this, there are currently very few ROS-triggered H_2S donors available, and cell-level research is the only area of study. On the other hand, it is somewhat anticipated that the creation of ROS-triggered H_2S donors (S-23, S-24) will offer a new approach to diagnosis and treatment for a variety of illnesses (Figure 7) [93–98].

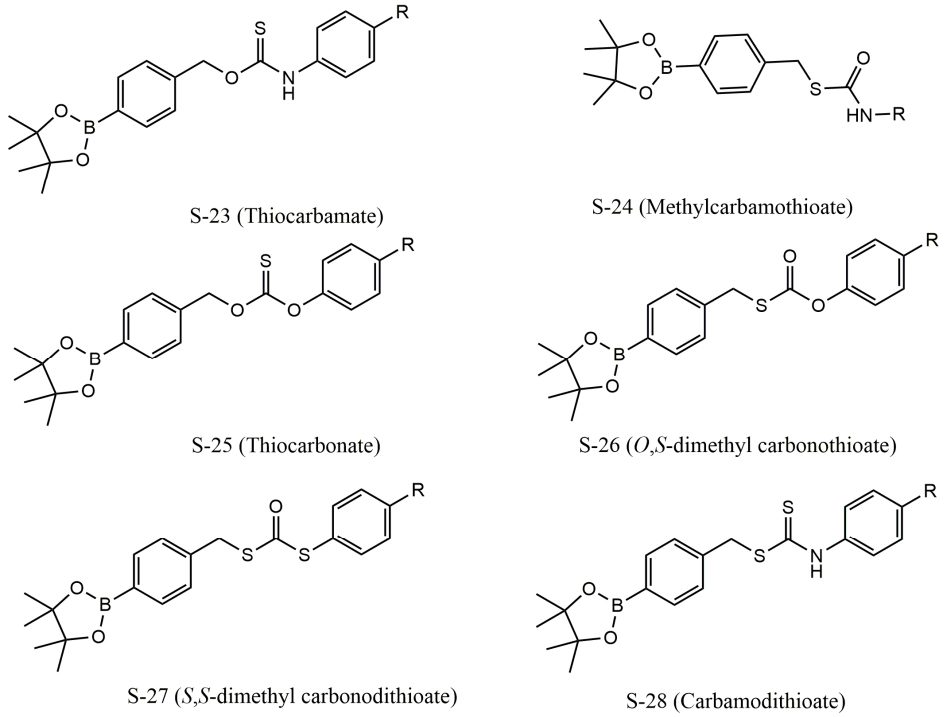


Figure 7. H_2S donors triggered by ROS.

5. Physiological Activity of Endogenous H_2S

5.1. Antioxidative Stress

Oxidative stress is defined as cellular or molecular damage brought on by ROS-related enzyme deficiencies and a deficiency in antioxidants [99]. Overproduction of reactive oxygen species (ROS) in cells and tissues can cause misfolded proteins, organelle damage, DNA damage, and dysfunction of neuronal synapses [100,101]. H_2S safeguards cells from oxidative stress-induced damage via two distinct mechanisms. Most importantly, it can indirectly mitigate oxidative stress by controlling pathways linked to antioxidants, in addition to its inherent reducing abilities that can eliminate excess ROS [102–105].

Nrf2 (nuclear factor E2-related factor-2) is a member of the NF-E2 family of transcription factors, playing a crucial role in the regulation of gene expression for various enzymes. This includes its function in mitigating oxidative stress [106]. Nrf2 serves a pivotal function in the oxidative stress response in mammals [107]. This regulation is facilitated by the binding of Nrf2 to antioxidant response elements, cis-regulatory elements, or enhancer sequences. These elements are situated in the promoter regions of specific genes, such as heme oxygenase-1 (HO-1), thioredoxin (Trx), glutathione S-transferase (GST), glutathione passase oxidase (GPx), trioxiredoxin reductase (TrxR) and catalase, etc. [108,109]. Calvert et al. showed that H_2S donors can play an anti-oxidative stress role by activating the Nrf2-ROS-AMPK signaling pathway and up-regulating endogenous antioxidants (such as glutathione (GSH)) [110]. SR-A is expressed on the plasma membrane and Golgi apparatus of macrophages and is a clearance receptor for type A macrophages. This process enhances the host's innate immune response by modulating the direct phagocytosis of pathogenic bacteria and recognizing a variety of pathogen-related molecular patterns [111]. The primary significance of SR-A is its potential as a cytokine that modulates oxidative stress and the associated inflammation [112,113]. Kobayashi et al. reported that the expression of SR-A in the lungs can inhibit the production of pro-inflammatory cytokines to reduce macrophage activation and prevent oxidative stress [114]. Glutathione is the main antioxidant that defends cells against oxidative stress. H_2S can increase the production of intracellular glutathione to improve cell vitality [115,116]. Within this context, it is important to note that H_2S does not impede the transport of GSH from the cytoplasm to mitochondria. However, it can effectively reallocate GSH to these organelles. Additionally, reactive oxygen species (ROS) are primarily generated within mitochondria. This H_2S promotes an increase in GSH in mitochondria and may protect cells from oxidative stress [105].

5.2. Anti-Inflammatory

As an important component of inflammation, excessive accumulation of ROS has always existed in inflammatory tissues within the body [117]. The resulting oxidative stress is also one of the important ways in which inflammation causes damage to tissues and organs. Nitric oxide synthase (iNOS) increases NO content in the early stages of inflammation due to oxidative stress, which, in turn, stimulates the production of NADPH oxidase by phagocytes and superoxide (O^{2-}) by endothelial cells. This promotes the interaction between NO and O^{2-} to form peroxynitrite ($ONOO^-$), and catalyzes hydrogen peroxide (H_2O_2) to produce hypochlorous acid (HOCl) by myeloperoxidase (MPO) in neutrophils. These reactive intermediates not only destroy cells but also damage surrounding tissues and cause more severe inflammatory reactions. In vitro experiments have shown that exogenous H_2S-releasing molecules (Na_2S and NaSH) can significantly inhibit intracellular HOCl-induced protein oxidation and thereby inhibit cell damage [52,118]. It has been reported that NaSH can scavenge and degrade lipid peroxides [119,120] and significantly inhibit the expression and activity of NADPH oxidase [121,122]. By directly scavenging a range of ROS and indirectly suppressing the expression of associated enzymes, endogenous H_2S can prevent the occurrence of oxidative stress and may even have anti-inflammatory properties.

By regulating inflammation-related cytokines, H_2S not only reduces inflammation brought on by oxidative stress but also suppresses the inflammatory response in mammals.

Pro-inflammatory cytokines initiate and exacerbate inflammation during the body's inflammatory response, whereas anti-inflammatory cytokines can prevent inflammation from occurring. Studies have shown that endogenous H_2S can significantly reduce the content of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) in plasma interleukin-1 (IL-1) and increase the content of the anti-inflammatory cytokine plasma interleukin-10 (IL-10) in the inflammatory response, thereby producing an anti-inflammatory effect [123]. Lipopolysaccharides (LPSs) induce a significant build-up of neutrophils in tissues during the inflammatory response in the body. According to research, endogenous H_2S can significantly reduce the accumulation of neutrophils in tissues (lung and liver), thereby inhibiting the occurrence of inflammatory responses. It is noteworthy that the majority of inflammatory responses involve leukocyte adhesion as a critical component. However, studies have found that endogenous H_2S can suppress leukocyte adhesion during the inflammatory response in a concentration-dependent manner, as well as suppress the expression of adhesion factors on leukocytes and endothelial cells [124]. A suitable concentration of exogenous H_2S administered to rats in a foot swelling model has been shown to lessen the degree of foot swelling significantly in rats, and it has also been discovered that exogenous H_2S donors can significantly inhibit leukocyte adhesion at the inflammatory site [125].

5.3. Protection against Myocardial Damage

Studies reveal that the excessive production of ROS is the primary cause of myocardial injury following ischemic reperfusion. Oxidative stress can cause DNA strand breaks, oxidize proteins to an inactive state, and stimulate lipid peroxidation [126]. The capacity of cardiomyocytes to activate and induce protective enzymes is a prerequisite for maintaining homeostatic characteristics during oxidative stress [127]. H_2S has been found to inhibit the production of reactive oxygen species (ROS), the activation of nuclear factor kappa B (NF-kB), the elevation in the expression of cell adhesion factors, and the induction of apoptosis. These are all significant contributors to myocardial injury [97,128]. This may also be a potential mechanism by which H_2S reduces arterial plaque and attenuates atherosclerotic damage. Studies have shown that exogenous H_2S can exert a cardioprotective effect by increasing cell viability [129]. More specifically, H_2S enhances the signaling of Nrf2 and promotes the phosphorylation of both signal transducer and activator of transcription 3 (STAT-3) and protein kinase C epsilon (PKCe). Furthermore, H_2S stimulates the expression of heme oxygenase-1 (HO-1), thioredoxin-1 (trx-1), Bcl-2, Bcl-xL, and cyclooxygenase-2 (COX-2) [110]. In cultured cardiomyocytes, NaHS has been observed to exert a concentration-dependent inhibitory effect on apoptosis induced by hypoxia/reoxygenation [130]. Furthermore, NaHS significantly enhances cell viability, increases the proportion of rod cells, and improves myocyte contractility [131]. All of the above indicate that H_2S can exert myocardial protection through different pathways.

5.4. Related to Liver Disease

The liver is widely recognized for its pivotal role in the synthesis and clearance of H_2S, as well as in the metabolism of carbohydrates and fats. Additionally, it plays a significant part in the excretion of xenobiotics and the host's defense against harmful microbes. Thus, it is extremely important from a pathological standpoint to investigate how H_2S contributes to the onset of liver diseases [132–135]. H_2S production and signaling in the liver are altered in several liver diseases, including liver ischemia/reperfusion (I/R) injury [136], non-alcoholic steatohepatitis (NASH) [137], liver fibrosis [138], and liver cancer [139]. However, the cellular and molecular mechanisms of H_2S-mediated liver function have not been fully elucidated. Insufficient endogenous H_2S production is closely related to NASH and liver fibrosis, and the role of H_2S in liver I/R injury is still controversial. Furthermore, endogenous H_2S production or lower exogenous H_2S may contribute to the development of liver cancer, while exposure to high amounts of H_2S may exhibit anticancer properties. Studies in recent years have shown that H_2S plays a key role in glucose and lipid metabolism, circadian rhythm, cell differentiation, and mitochondrial function in the

liver [140,141]. A detailed understanding of the exact role and mechanisms of H_2S in liver health will greatly advance new potential therapeutic applications of H_2S in preclinical and clinical research.

5.5. Related to Cancer

H_2S exerts cancer-promoting effects by stimulating mitochondria, promoting angiogenesis, activating anti-apoptotic pathways, and accelerating the cell cycle. In addition, oversulfation of H_2S-related proteins is associated with various types of cancer. Three H_2S-producing enzymes (CSE, CBS, and 3-MST) were found to be highly expressed [142–144]. Among them, CBS can show anti-tumor activity when inhibited, especially in colon cancer, ovarian cancer, and breast cancer; however, whether CSE or 3-MST can produce anti-tumor activity after being inhibited has not been widely studied [8,145,146]. Interestingly, H_2S can also induce apoptosis in cancer cells when administered at high concentrations or for long periods in vitro and in vivo without affecting non-cancerous fibroblasts [147]. Consequently, a bell-shaped model can elucidate the role of H_2S in cancer development. Specifically, endogenous H_2S or relatively low levels of exogenous H_2S can manifest carcinogenic effects, whereas high concentrations or prolonged exposure to H_2S can induce cancer cell death [148,149]. This observation underscores the fact that inhibiting H_2S biosynthesis and supplementing H_2S represent two distinctly different therapeutic approaches to cancer. The paradoxical impact of H_2S has invigorated interest in the creation of innovative CBS inhibitors, H_2S donors, and systems integrating H_2S with drugs.

6. Fluorescent Probes for Detecting H_2S

Endogenous H_2S is a representative material of active sulfur in organisms, and its monitoring is crucial for understanding pathological processes and illness prediction. Many techniques for the in vitro detection of H_2S have been developed after years of work, such as gas chromatography, the sulfide ion selective electrode method, electrochemical analysis, and methylene blue spectrophotometry [150]. However, these methods are unsuitable for in vivo detection, which necessitates immediacy, non-invasiveness, and convenience. Fortunately, the H_2S fluorescent probe designed in this manner can be extensively utilized in complex and diverse biological environments because of the reducibility, nucleophilicity, and metal coordination chemical properties of H_2S [151]. The imaging capabilities of fluorescent probes enable the detection of H_2S in organisms, unaffected by physiological tissues and environmental interference. The progression from initial ultraviolet–visible (UV-vis) fluorescence imaging to near-infrared (NIR) fluorescence imaging, and now to the current second region near-infrared fluorescence imaging, has been facilitated by a variety of fluorophores and design strategies. These have ensured sensitivity, accuracy, and detection efficiency. The advancement of microscopy imaging technology has facilitated the progression of H_2S detection from a cellular level to an in vivo level, thereby offering a broader scope for exploring the biological functions of H_2S. H_2S probes are categorized based on their characteristics, which can be encapsulated into several mechanisms such as reduction, nucleophilicity, and metal sulfide.

6.1. Based on Reducibility

As the smallest thiol molecule in biological systems, H_2S possesses potent reducing properties. It can effectively reduce chemical groups such as azide, hydroxylamine, and nitro to amino groups. By altering the photoelectric characteristics of the probe, fluorescent probes built in this manner can be used to achieve targeted detection. In chemical biology, organic azides have been extensively employed as bioorthogonal functional groups [152]. Upon the attachment of the potent electron-withdrawing azide moiety to the fluorophore in a conjugated manner, the resultant structure adopts an "A-π-A" electronic configuration, characterized by diminished fluorescence emission [153]. Upon reduction of the azide moiety to an amine by H_2S, the electron-withdrawing group is transformed into an electron-donating moiety. This transformation leads to the formation of a "D-π-A"

electronic structure, which in turn induces an intramolecular charge transfer (ICT) effect (P-1). Consequently, there is a marked enhancement in the fluorescence emission [154].

In addition to the strategy of introducing the reducing properties of H_2S into azide-amines, another "turn-on" probe (P-2) based on the reducing properties of H_2S was also developed. This type of probe generally has a two-step sensing mechanism. With the reduction of the disulfide by H_2S, a new disulfide is generated. This newly formed disulfide then undergoes partial cyclization with benzoic acid. The resultant cyclized benzoic acid-disulfide structure acts as a self-sacrificial unit, detaching from the overall probe structure. This detachment leads to the restoration of its original fluorescence [155].

In mild conditions, the nitro group can be reduced to the amino group (P-3) by H_2S. This principle forms the basis for loading nitro groups onto fluorophores, which significantly quenches fluorescence because of the photoinduced electron transfer (PET) process. However, when H_2S reduces the nitro group to the amino group, thereby destroying its electron-withdrawing ability, the PET process is interrupted and fluorescence is restored. This restoration facilitates detection [156].

In addition to the nitro group, the sulfonyl group is also capable of undergoing reduction by H_2S (P-4). These sulfonyl groups serve as electron-withdrawing elements within PET systems (Figure 8). Upon reduction of the sulfonyl group to a thiol by H_2S, the electron-withdrawing element is transformed into an electron-donating element, leading to a significant enhancement in fluorescence [157].

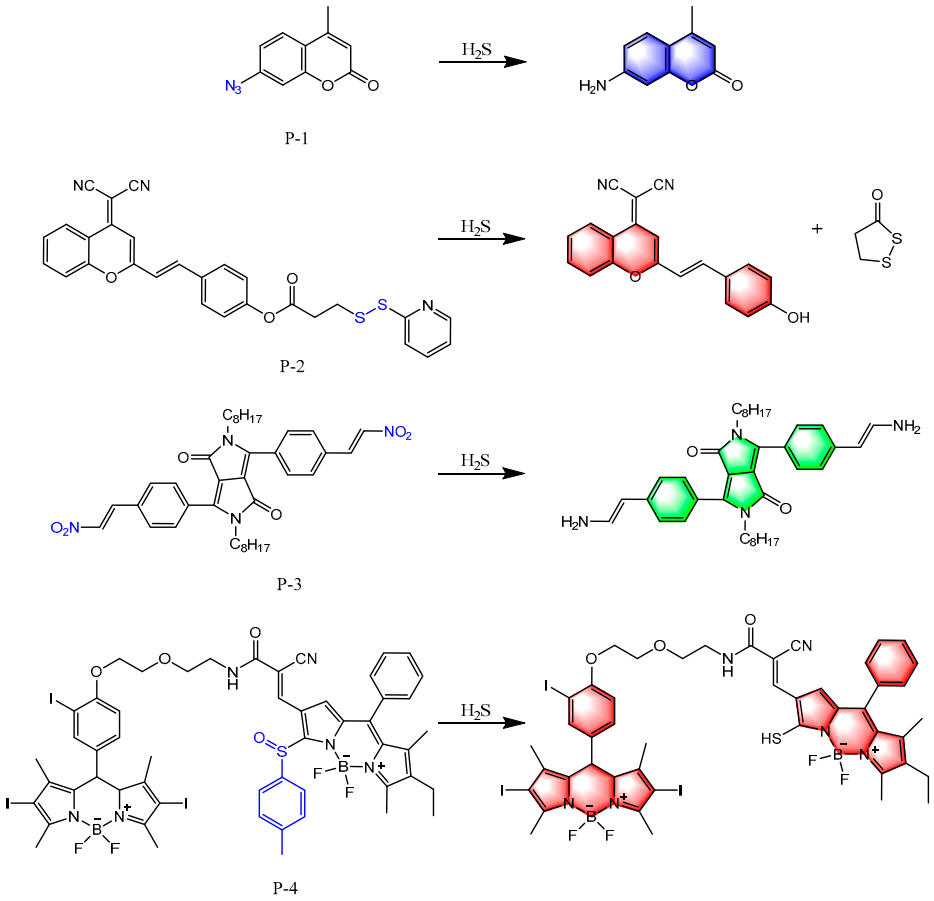


Figure 8. Fluorescent probes related to H_2S (1).

6.2. Based on Nucleophilicity

H_2S is a strong nucleophile and exists mainly in the HS form under physiological conditions at pH, thus exhibiting higher nucleophilicity than many other thiols found in living cells [158]. Taking advantage of the characteristics of this nucleophilic reaction,

various types of H_2S probes have been developed. These probes are usually designed by incorporating electrophilic functions and converting in the presence of H_2S to achieve detection purposes. Two main types of nucleophilic strategy H_2S probes were developed in recent years, including nucleophilic substitution and nucleophilic addition.

Similar to m-nitrophenol, the 2,4-dinitrophenyl structure acts as an electron-withdrawing group in the PET system and can also cause fluorescence quenching (P-5). The difference is that the 2,4-dinitrophenyl structure is nucleophilically substituted by H_2S rather than reduced to the amino group. The most critical aspect is that the nucleophilic substitution selectivity of H_2S on 2,4-dinitrophenyl is preferential to other biothiols. H_2S cleaves the linkage between 2,4-dinitrophenyl and the fluorophore via a nucleophilic substitution reaction, thereby liberating the fluorophore. This process enables the fluorescence detection of H_2S [159].

The 7-Nitro-1,2,3-benzoxadiazole (NBD) structure is a frequently employed H_2S nucleophilically substituted electron-withdrawing group. It shares a similar H_2S reaction mechanism to that of 2,4-dinitrophenyl (P-6). However, unlike the PET mechanism utilized by 2,4-dinitrophenyl, NBD quenches fluorescence via the FRET effect. The NBD structure is linked to the fluorophore via a piperazine bond, allowing the initial absorption of fluorescence by the NBD structure. In the presence of H_2S, the NBD structure is cleaved, and FRET cannot be performed beyond the distance from the fluorophore, resulting in fluorescence recovery [160–162].

The halogen, as an electron-withdrawing group, can be directly connected to the conjugated skeleton of the fluorophore. When H_2S is present, the electron-withdrawing halogen is replaced and destroys the conjugated ICT system, ultimately leading to fluorescence enhancement and redshift (P-7). This detection mechanism is mainly used in cyanine- or BODIPY-based H_2S probes [163].

As a nucleophile, H_2S can not only achieve nucleophilic substitution but also nucleophilically add to electrophilic groups, such as alkenyl and aldehyde groups (P-8, P-9) (Figure 9). Based on this chemical reaction, numerous research groups have documented the development of H_2S probes utilizing various fluorophores [164,165].

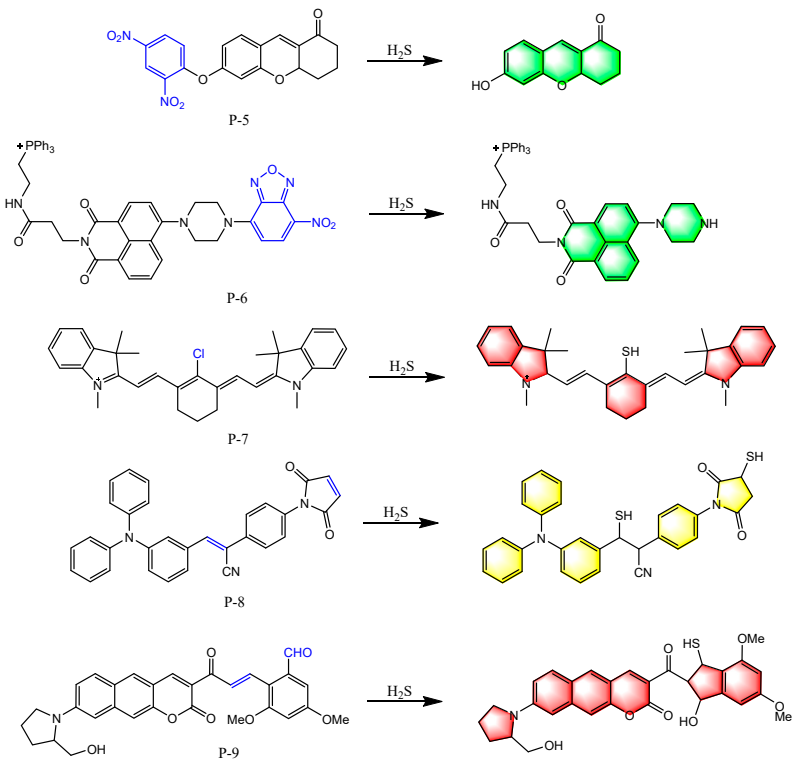


Figure 9. Fluorescent probes related to H_2S (2).

6.3. Based on Metal Coordination

In addition to the H_2S probes designed based on chemical reactions, the detection of H_2S can also be achieved through the demetallization reaction of metal complexes induced by H_2S (P-10). Cu^{2+} is a fluorescence quencher. In the presence of H_2S, it decomplexes from the probe to form CuS, which restores the fluorescence of the probe to achieve the purpose of detection (Figure 10) [166]

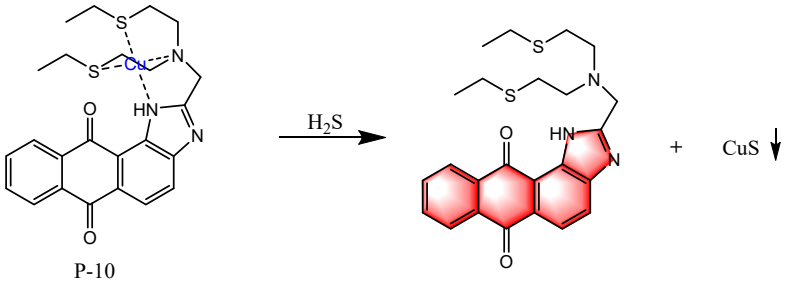


Figure 10. Fluorescent probes related to H_2S (3).

6.4. Based on Self-Immolation Reaction

In the latest research, the self-immolation reaction is considered a new method to achieve the functional detection of H_2S (P-11) [167]. During this reaction, the self-immolation spacer group is cleaved into carbonyl sulfide, which can then be catalyzed by carbonic anhydrase in the body to generate H_2S. Based on previous research, our research group first designed and synthesized a new water-soluble near-infrared fluorescent probe for detecting H_2S (P-12) [168]. The design based on the self-immolation structure could more accurately evaluate the process of cell self-repair in pathological processes with the advantage of low toxicity. Then, we synthesized a compensatory fluorescent probe that detects intracellular H_2S without consuming H_2S through the self-immolation structure, which greatly reduced the toxicity of the probe without affecting its detection performance (P-13) [169]. In addition, we also used self-immolating spacer groups that can release H_2S to synthesize new near-infrared fluorescent diagnostic and therapeutic agents and achieved real-time monitoring of the anticancer effect of H_2S in vivo through NTR (nitroreductase) activation, clarifying the complex relationship between H_2S and cancer (P-14) (Figure 11) [170].

In living systems, hydrogen sulfide (H_2S) is intricately linked to a range of sulfur-containing active substances, including homocysteine (Hcy), cysteine (Cys), and glutathione (GSH). These elements form an interconnected network within the body. Hcy serves as an intermediate in the metabolism of methionine to produce Cys, while Cys is the primary substance for aerobic metabolism to generate H_2S; GSH is the central substance of cellular sulfur metabolism. For the detection of H_2S, it is crucial to achieve specific detection and monitoring of related metabolic transformations. However, multiple molecular events often occur simultaneously during the signal transduction process in living systems. In theory, the use of multiple probes can enable simultaneous visual tracking of these events. However, the introduction of multiple probes can lead to negative factors such as spectral overlap and reaction cross-reaction. Therefore, a single fluorescent probe with superior functions remains the most effective tool for addressing these issues. During the probe-target reaction process, new reaction sites can be constructed simultaneously to distinguish the target further or detect its metabolites, thereby enabling simultaneous visual tracing of multiple metabolic pathways [158,171–173].

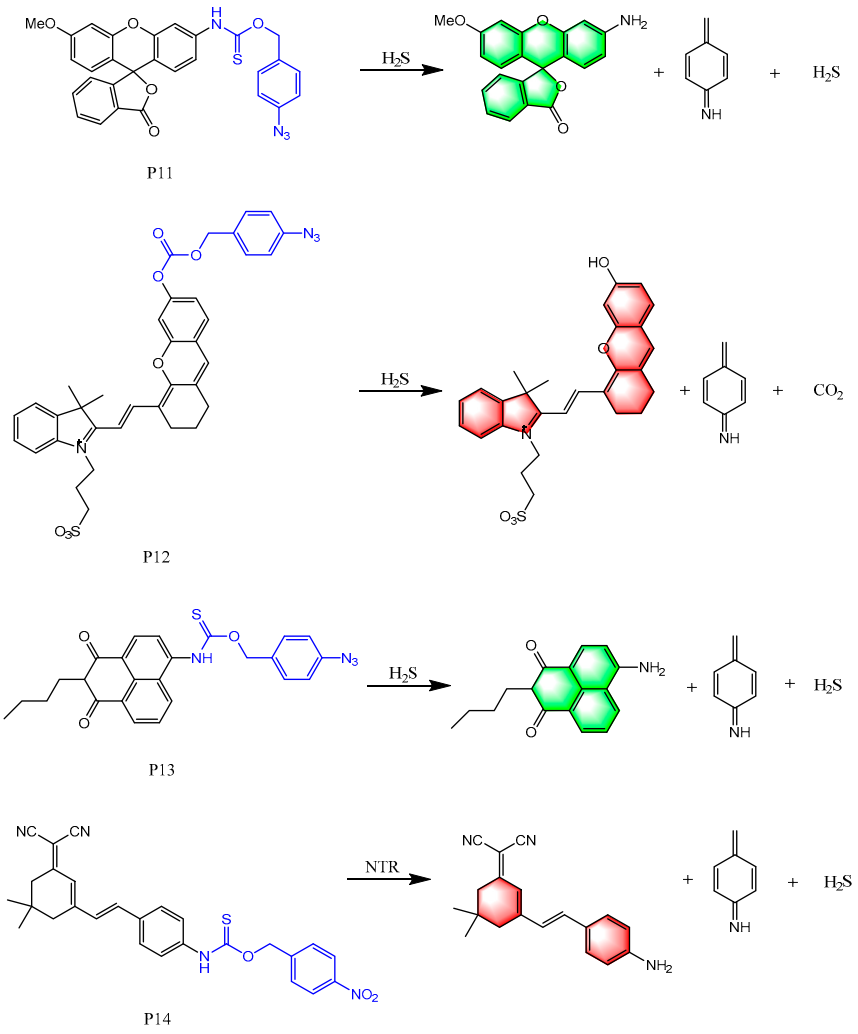


Figure 11. Fluorescent probes related to H_2S (4).

7. H_2S Scavenging Agents

As a gaseous signaling molecule, both up-regulation and down-regulation of H_2S will bring about specific biological consequences. However, in recent years, researchers have focused on developing methods to up-regulate H_2S in the body and have made great progress, but there have been few attempts to down-regulate H_2S in the body. The reason is the lack of effective/specific inhibitors for H_2S-generating enzymes. Ming et al. proposed another solution, which is to develop specific scavengers for H_2S. In their study, sulfonyl azide-based scavengers were effective in in vitro and in vivo experiments [174]. This type of H_2S scavenger will not only become a useful tool for elucidating the biological effects of H_2S but also a potential antidote for H_2S poisoning.

8. Conclusions and Outlook

This study reviews the importance of H_2S in biological research. As a gas signaling molecule, it is involved in the development of various biological processes and diseases. We found that the concentration changes in H_2S are closely related to its biological activity. Moderate H_2S concentrations can exhibit positive therapeutic activities, such as antioxidant, anti-inflammatory, and cytoprotective effects, which have potential in the treatment of various diseases such as cardiovascular diseases, neurological diseases, and inflammatory diseases. However, we also found that H_2S concentrations that are too high or too low may cause negative pathotoxicity and cause damage to cells and tissues. Therefore, regulating H_2S concentration has become an important strategy for treating diseases. We

can increase or decrease the production of H_2S through drugs or other interventions to achieve therapeutic effects. This external intervention provides a new approach to disease treatment. At the same time, we also found that the sensitivity and dual nature of H_2S make it an important marker to evaluate disease. We can use the nucleophilicity, reducing property, and metal coordination characteristics of H_2S to design probes to monitor changes in H_2S concentration. In addition, the synthesis of H_2S-related self-immolation structure compounds and the exploration of H_2S scavengers provide new research methods for studying the relationship between H_2S and diseases and also provide relevant guidance for diagnosing and treating diseases.

Based on these findings, we recognize that H_2S has great potential in the diagnosis and treatment of diseases. In the future, we can further explore the mechanism of action of H_2S in organisms and gain a deeper understanding of its relationship with diseases. At the same time, we can work on developing more effective treatments involving innovations in drug development, biotechnology, and treatment strategies to achieve more precise and personalized treatment plans and bring greater benefits to patient health. In summary, this study reveals the importance of H_2S in biological research and provides new methods and possibilities for the diagnosis and treatment of diseases. Our in-depth research on the mechanism of action and therapeutic applications of H_2S provides important guidance and reference for future medical progress and clinical practice.

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