

Current Trends and Future Perspectives of Hydrogen Sulfide Donors

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Abstract

Hydrogen sulfide (H₂S) gas is included to be the most critical endogenous gasotransmitters that has several pathophysiological effects in many human cells and organ tissues. The synthesis of endogenous H₂S in cells via several pathways. Variant biological effects of H₂S including ion channel regulation, redox regulation of protein, thiols, polysulfides, thiosulfate/sulfite, and anti-oxidant activities affecting many cellular and molecular reactions. Therefore, it is essential to review H₂S chemical biology, methods of detection of H₂S release and its effects on pathological and physiological functions along with their therapeutic uses, including cardiovascular protective activities, anti-inflammatory and anti-tumor activities of the H₂S donors.

Key words

Hydrogen sulfide (H₂S), gasotransmitters, donors, anticancer, hybrids..

Introduction

As nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H₂S) is considered one of the most important gasotransmitter [1–7]. Synthesis of endogenous H₂S in cells of mammals through three enzymes: cystathionine γ -lyase (CSE), cystathionine β -synthase (CBS), and 3-mercaptopyruvate sulfur-transferase (MPST) (**Figure 1**), that also regulate H₂S levels in tissues [8–12].

H₂S has potent reducing properties and is scavenged by endogenous oxidizing molecules including hydrogen peroxide, superoxide and peroxynitrite [14, 15]. Also, H₂S is forming sulfhemoglobin when reacts with methemoglobin [16] and causing protein S-sulfhydration (formation of -S-SH) [17–19]. H₂S can also interact with S-nitrosothiols forming thionitrous acid (HSNO) which is metabolized forming NO, NO⁻, and NO⁺ that are with several physiological activities [17–19].

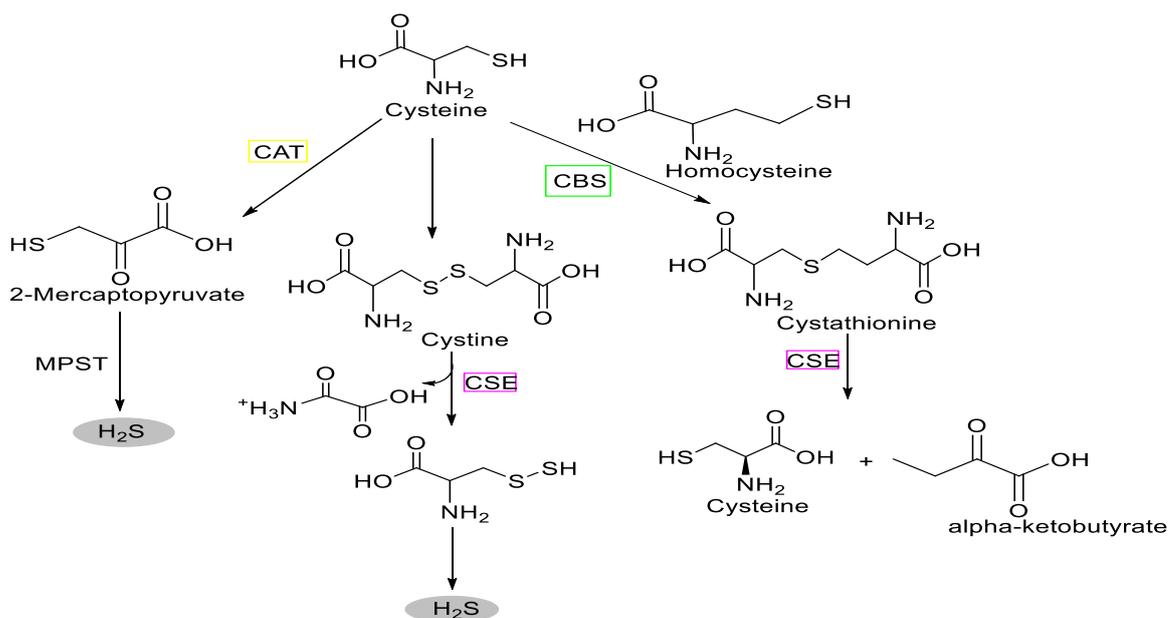


Figure 1. Endogenous Enzymatic Biosynthesis of H₂S [13].

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H₂S exhibits various biological activities at concentrations between 10 and 300 μM [3]. Whereas, it can modulate many physiological responses including reducing oxidative stress [21], anti-inflammatory [20], vasoregulation [23], neuromodulation [22], inhibition of insulin resistance [25] and protection against myocardial ischemia injury [24]. H₂S at concentrations of <100 ppm causes several toxic effects in human such as nausea, dizziness, sore throat, eye irritation, chest tightness and short breath [26, 27]. While severe adverse effects of high exposure to >1000 ppm hydrogen sulfide affecting the central nervous system causing loss of consciousness to death [28] and also affecting the respiratory system causing respiratory paralysis and pulmonary edema [29, 30].

1. Measurement of H₂S release:

Several methods for sulfide detection have been developed ranging from simple spectrophotometric and colorimetric methods to other advanced techniques and methods [31].

1.1. Ion-selective (Sulfide-specific) electrodes (ISEs)

ISEs is usually used for measuring H₂S levels in biological fluids with a range of 1–10 μM. ISEs method detects the sulfide S²⁻ form in an alkaline condition. ISEs is a readily, available and easy method [32, 33].

1.2. Polarographic electrodes

H₂S detection using the polarographic H₂S electrodes for measuring H₂S gas in biological samples, in the nM detection range. However the polarographic H₂S sensor is a very sensitive and accurate method, it can't detect other forms of sulfide [34].

1.3. Chromatographic methods

Chromatographic H₂S detection methods are versatile including ion-exchange chromatography, gas chromatography (GC), and HPLC that can measure volatile sulfur compounds and different sulfide forms in biological samples [35]. RP (reversed-phase)-HPLC is used for measuring methylene blue, zinc acetate that is used to trap H₂S in brain tissue in acidic conditions [36]. The thiol-sensitive fluorescent probe Monobromobimane (MBB) could measure bioavailable H₂S levels, whereas measuring the H₂S/HS⁻ is by HPLC with fluorescence detection [37, 38].

1.4. Fluorescent probes based strategy for H₂S detection

In this strategy measuring H₂S in plasma via evaluating the fluorescence of the formed benzodithiolone [39] [40]. Moreover, a novel dansyl azide (DNS-Az), which is reduction-sensitive, nonfluorescent and upon reacting with sulfide becomes fluorescent [41].

1.5. Methylene blue formation method

It is the usually known chemical method in measuring H₂S as H₂S is firstly trapped with Zn(OAc)₂ forming ZnS. The trapped H₂S is released after Sample acidification, H₂S is reacted with *N,N*-dimethyl-*p*-phenylenediamine **1** in presence of FeCl₃ and forming methylene blue **2** (Figure 2). The absorbance of methylene blue is measured at 670 nm [31, 42].

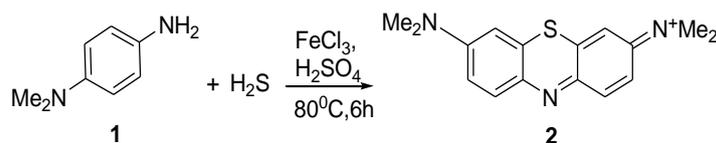


Figure 2. Methylene Blue (2) Formation Method for H₂S Detection.

1.6. Chemical properties based methods

Due to H₂S physicochemical and reactive properties, it was developed new H₂S detection methods can be classified into three types: (1) 1.6.1. Chemical reduction method (2) Nucleophilic Attack method and (3) Methods depend on metal precipitation.

1.6.1. Chemical reduction method

Due to H₂S reducing properties it can reduce azide and nitro groups [14, 15] [43] and this is used for H₂S detection using different fluorescent probes (Figure 3) [44–46].

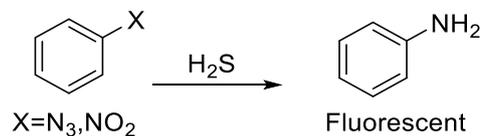


Figure 3. H₂S Reducing Azide and Nitro Groups Forming Fluorescence

1.6.2. Nucleophilic Attack method

H₂S can go two sequential nucleophilic attacks, therefore upon reaction with two equivalents monobromobimane that trapping H₂S forming the fluorescent thioether product (Figure 4) followed by HPLC separation for detection of H₂S [47, 48].

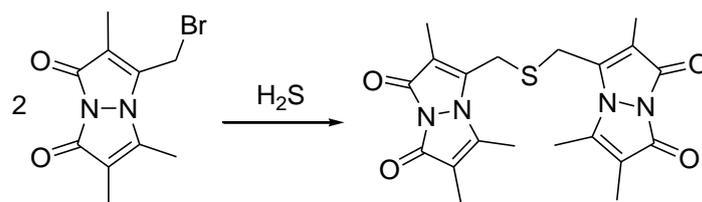


Figure 4. Formation of A Fluorescent Bimane Thioether for H₂S Detection.

1.6.3. Methods depend on metal precipitation

H₂S can precipitate metals including copper, magnesium and zinc, therefore developing H₂S detection method using the Cu(II) gravimetric method in which precipitation of CuS by H₂S and using a fluorescein derivative (dipicolylamine) [49]. When the fluorescein compound is complexed with Cu (II) that causing quenching of the fluorescence. While the fluorescence is restored after precipitation of CuS by the released H₂S in the sample [49] (Figure 5).

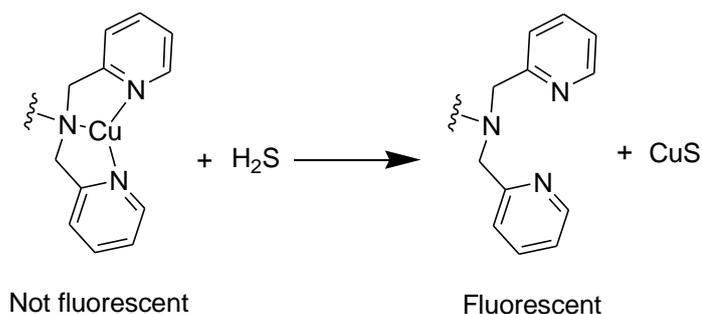


Figure 5. Complexation of Cu (II) With H_2S and Precipitation of CuS Releasing The Fluorescent Compound.

2. Hydrogen sulfide releasing agents (H_2S donors)

However, the endogenous or the exogenous H_2S are showing different useful effects in many pathophysiological conditions [50, 51], H_2S gas can not be considered as an ideal source for H_2S as it is difficult to reach controlled concentrations and release of H_2S and the toxic effects of high H_2S concentrations [52]. Therefore, novel H_2S donors were established that releasing H_2S through different mechanisms such as:

2.1. Inorganic Salts Of Sulfide

Inorganic salts of sulfide are sodium hydrogen sulfide (NaHS) and sodium sulfide (Na_2S) and which are equivalents to H_2S . After the dealings of animal cells and tissues with inorganic salts of sulfide, it could protect against many diseases [20, 53–55]. Na_2S can also diminish ischemia-induced heart failure and decrease cardiac hypertrophy, and improving cardiac function [56]. Na_2S can also reduce oxidative stress-related heart failure [57, 58]. Furthermore, sulfide salts could protect against many diseases including inflammation [59]. Moreover, the release of H_2S release from sulfide salts is rapid but can lead to severe cell and tissue damages [60].

2.2. Garlic and Related Sulfur Compounds

Recent studies revealed that many of the biological effects of garlic were related to H_2S release from garlic active constituents such as Allicin (diallyl thiosulfinate) in aqueous solutions is unstable and is rapidly decomposed to diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) and also in the presence of glutathione (GSH), H_2S is released (**figure 6**), (**Figure 7**) [61]. Also, garlic polysulfide derivatives can produce H_2S by Human blood cells (RBCs) [62].

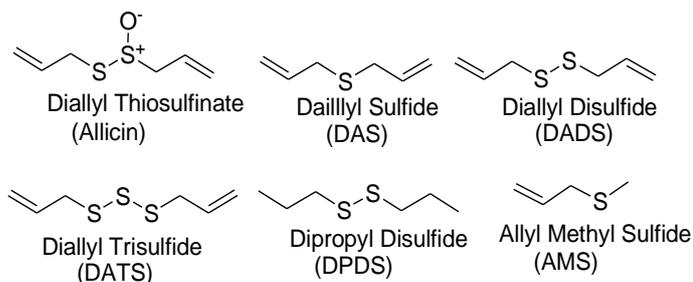


Figure 6. Garlic-Derived Sulfur Compounds.

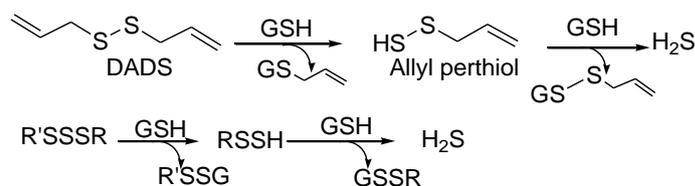
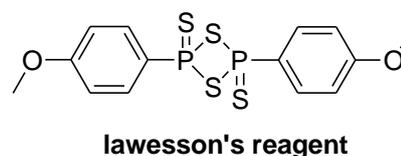


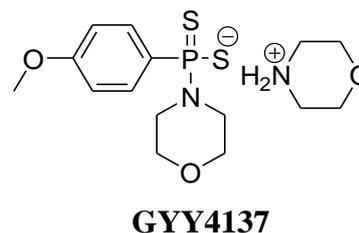
Figure 7. Release of H_2S from Garlic- Sulfur Compounds.

2.3. Lawesson's reagent and its analogs

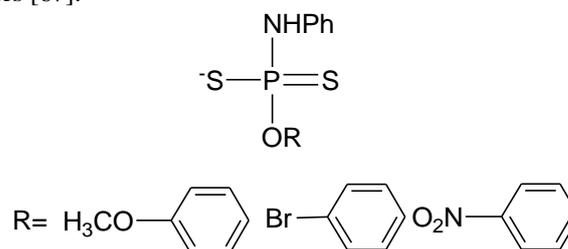
(Lawesson's reagent) is 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide and is considered as sulfurization substance used in synthesis [63]. Many biological activities are related to H_2S release including regulation of ion channels and anti-inflammation showing reduction of ulceration of the colon and reduced the severity of colitis [64].



Furthermore, Compound (GYY4137) is the derivative of Lawesson's reagent which is water-soluble and upon hydrolysis releases H_2S [65]. H_2S released from GYY4137 was much slower than inorganic sulfide salts which are pH- and temperature-dependent [66].



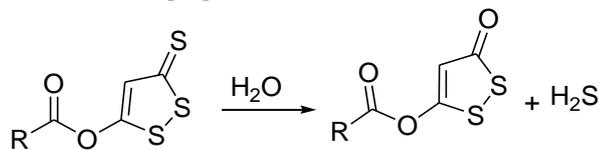
Lately in GYY4137 substituting the phosphorus-carbon with phosphorus-oxygen affording the phosphorodithioate H_2S donors [67].



Moreover, phosphorodithioates hydrolysis is under acidic conditions and releases H_2S [68]. *O*-aryl substituted phosphorodithioates donors exhibited protection against H_2O_2 -induced oxidative damage and marked enhanced cell viability [69],[70]. Moreover, phosphorodithioate oligodeoxycytidine showed activities against the human immunodeficiency virus [71].

2.4. 1, 2-Dithiole-3-Thiones:

H₂S release from 1,2-Dithiole-3-Thiones (DTTs) is in aqueous solutions [72–74] (**Figure 8**), and is measured by a sulfide-sensitive electrode [75].



1,2-Dithiole-3-thiones (DTTs)

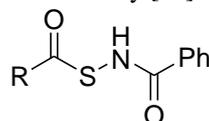
Figure 8. H₂S Release from DTTs.

2.5. Thiol activated H₂S donors:

The release of H₂S from H₂S donors must be slowly and in moderate amounts and stable compounds [76], Therefore it is critical for developing new H₂S donors with the controlled H₂S release and production.

2.5.1. *N*-mercapto-based H₂S donors:

N-mercapto-based H₂S donors were the first thiol-activated donors of controlled release H₂S donors that were stable in aqueous solutions [77]. Many factors controlling H₂S release including pH, biomolecules and light. The thiol-activated *N*-mercapto (*N*-SH) H₂S donors is unstable, however the addition of acyl groups to *N*-mercapto (*N*-SH) for protection of SH groups could improve the stability [77].



N-SH-Based H₂S donors

In the presence of cysteine or GSH, the *N*-mercapto-based donors are decomposed releasing H₂S (**Figure 9**). Moreover, the structure-activity relationship studies revealed that adding of electron-withdrawing groups caused more and rapid release of H₂S while electron-donating groups showed slower release of H₂S [77].

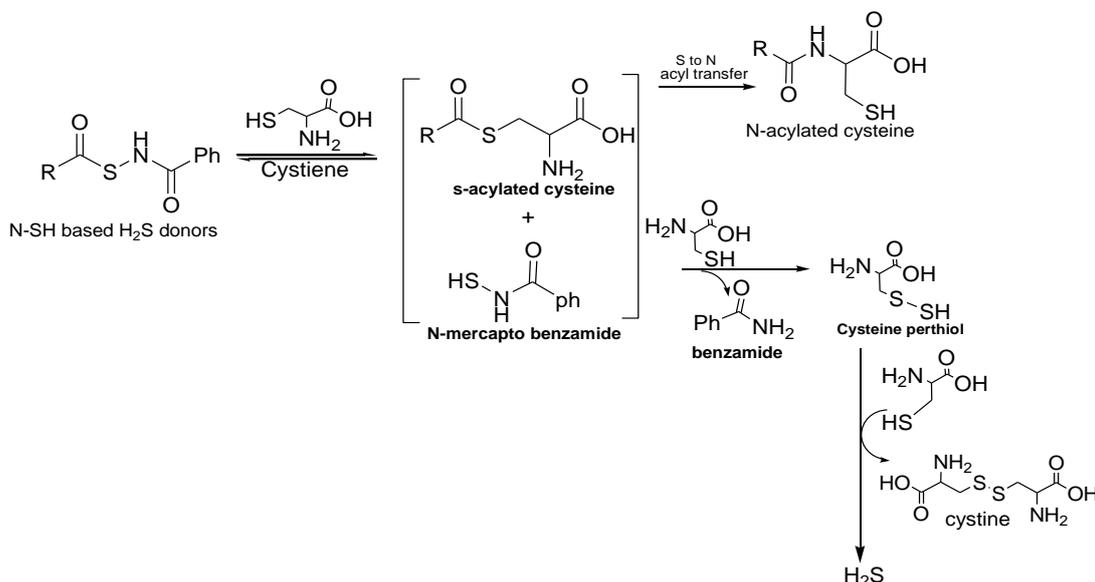


Figure 9. Release of H₂S from *N*-mercapto-based H₂S Donors in The Presence of Cysteine or GSH.

2.5.2 Perthiol-based H₂S donors

Perthiol-based donors which in the presence of thiols (cysteine or GSH) showed H₂S release [78]. (**figure 10**).

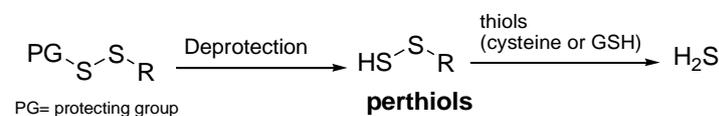
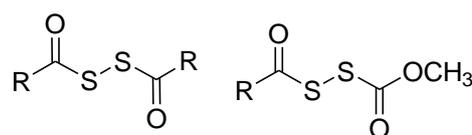


Figure 10. Release of H₂S from Perthiol-Based H₂S Donors.

Primary perthiol-based donors exhibited a marked decrease in H₂S release, The tertiary perthiol-based compounds were more potent H₂S donors. [78] and H₂S release can be controlled as in *N*-SH-based donors by structural modifications, also steric effects exhibited slower or no H₂S release [78]. The perthiol-based donors exhibited H₂S-mediated cardiac protection in MI/R injury [79–81].

2.5.3 Dithioperoxyanhydrides

Dithioperoxyanhydrides release H₂S as perthiol-based donors and *N*-mercapto-based H₂S donors in both buffers and cellular lysates [82].



dithiocarboxyanhydrides

Additionally, $\text{CH}_3\text{C}(\text{O})\text{SSC}(\text{O})\text{CH}_3$ was reported to prompt vasorelaxation of pre-contracted rat aortic rings [82] (**Figure 11**).

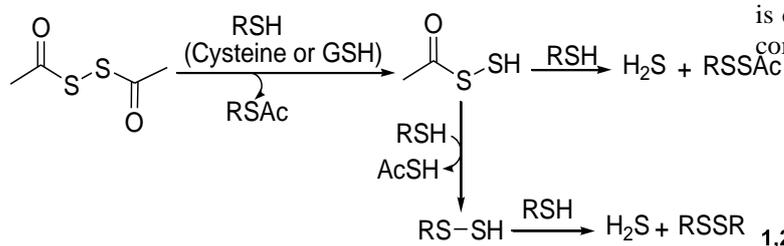


Figure 11. H_2S Release from Dithioperoxyanhydrides.

2.5.4 Arylthioamides

The lead arylthioamide compound (*p*-hydroxybenzothioamide) was followed by more arylthioamide compounds by structural modifications [83] (**Figure 12**). However, arylthioamides release small amounts of H_2S but exhibit (3-21 mM) as maximum concentrations [83].

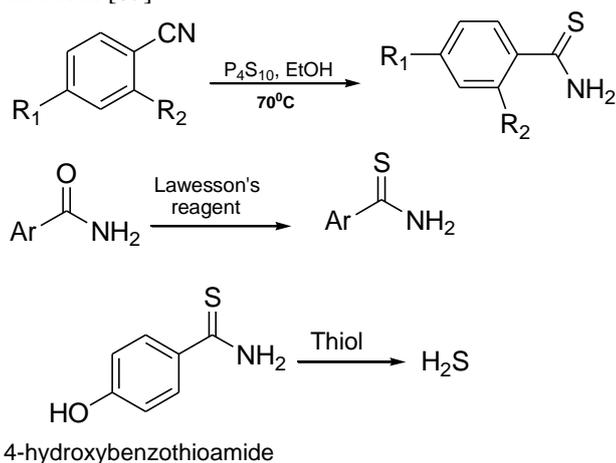
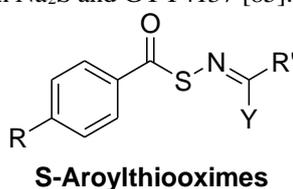


Figure 12. Synthesis and Release of H_2S from *p*-hydroxybenzothioamide.

In absence of cysteine release of H_2S is very weak in buffers, however When 4 mM cysteine or GSH (4 mM) with 1 mM of *p*-hydroxybenzothioamide showed complete inhibition of vasoconstriction and a decrease in blood pressure ($89 \pm 1\%$) [83]

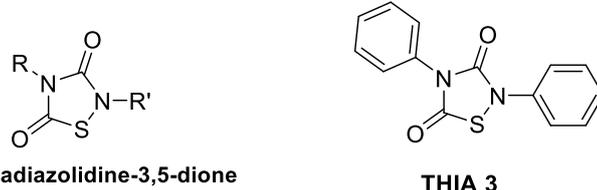
2.5.5 S-Aroylthiooximes (SATOs)

S-Aroylthiooximes (SATOs) are also thiol-triggered donors [84]. Treatment of HCT116 colon cancer cells with 250 μM S-Aroylthiooximes showed a great reduction of colon cancer cell viability more than Na_2S and GYY4137 [85].



2.5.6. 1,2,4-thiadiazolidine-3,5-dione scaffold

1,2,4-thiadiazolidine-3,5-dione are novel thiol-based H_2S donors aiming to obtain with more controllable H_2S release and is detected by an amperometric method. (1 mM). THIA 3 could completely diminish any vasoconstriction ($\text{Emax} > 94\%$) [86].

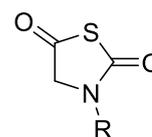


2.6. Dual Carbonyl Sulfide / H_2S Donors

Compounds releasing carbonyl sulfide (COS) can be used as an intermediate to generate H_2S through the action of carbonic anhydrase (CA) [87].

2.6.1. N-Thiocarboxyanhydrides

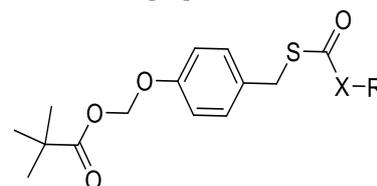
A carbonyl sulfide releasing compounds that in the presence of glycine and carbonic anhydrase CA, convert carbonyl sulfide COS into H_2S that evaluated by the methylene blue method [88].



N-Thiocarboxyanhydrides

2.6.2. Esterase Activated Carbonyl Sulfide/Hydrogen Sulfide (H_2S) Donors

These compounds are triggered by esterase and release carbonyl sulfide (COS) followed by carbonyl sulfide (COS) is hydrolyzed and release H_2S [89].



Esterase Activated Carbonyl Sulfide/Hydrogen Sulfide (H_2S) Donors

2.6.3. Cyclic Sulfenyl Thiocarbamates

These compounds in presence of cellular thiols generate carbonyl sulfide (COS) followed by the release of H_2S by carbonic anhydrase (CA) [90] (**Figure 13**).

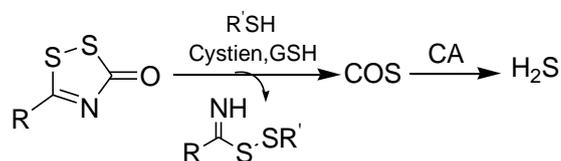


Figure 13. Cyclic Sulfenyl Thiocarbamates Releasing H_2S .

2.7. Photo-Induced H₂S Donors:

2.7.1. Gem-dithiol-based- H₂S Donors:

The stable-dithiol-based- H₂S Donors are obtained by the addition of a photolabile 2-nitrobenzyl group for protection of SH group. Light irradiation liberates the free *gem*-dithiol derivatives that are hydrolyzed to release H₂S [91–93] (**figure 14**).

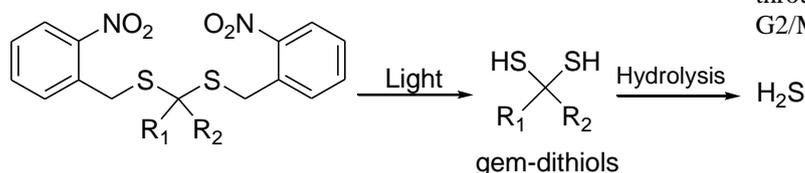


Figure 14. Release of H₂S from *gem*-dithiol-based H₂S Donors.

2.7.2 Ketoprofenate-caged H₂S donors

Lately to develop photolabile H₂S donors, ketoprofenate-caged donors were synthesized and released H₂S after the irradiation at 300–350 nm [94, 95] (**Figure 15**).

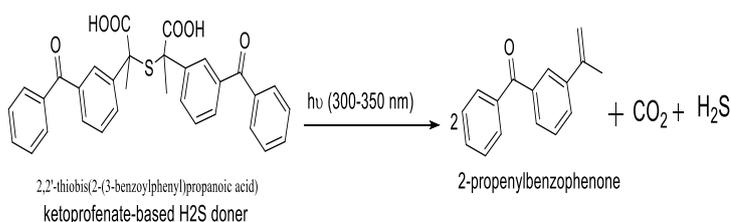


Figure 15. H₂S Release from The Ketoprofenate-Caged Donor.

2.8 Thioamino acids

Thioglycine and thiovaline are thioamino acids that can be converted to their corresponding amino acid *N*-carboxyanhydrides and releasing H₂S in the presence of bicarbonate [96] (**figure 16**). Also, the pharmacological benefits showed a rise in cGMP levels (~ 10-fold increase) and vasorelaxation of precontracted aortic rings [96].

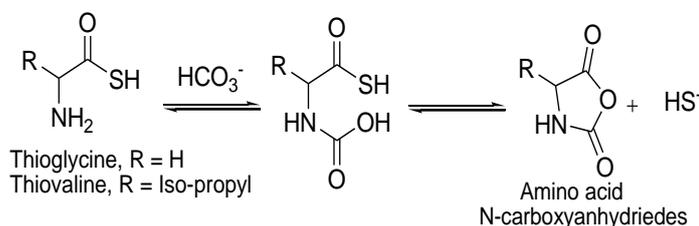
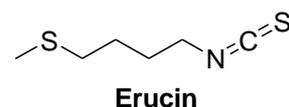


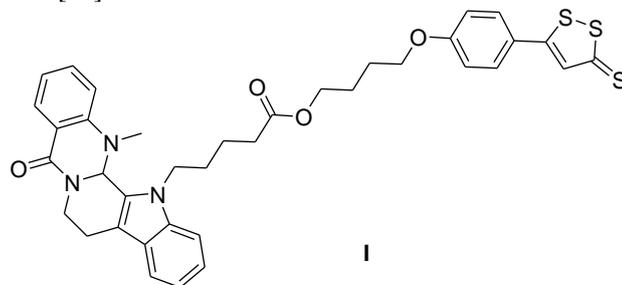
Figure 16. Release of H₂S from Thioamino Acids.

2.9. Other natural H₂S releasing compounds:

Erucin (1-isothiocyanato-4-(methylthio)butane) (ERU), a natural isothiocyanates H₂S-releasing compounds exhibited significant antiproliferative effects and at high concentrations (30–100 μM) could inhibit AsPC-1 cell viability. ERU could also inhibit cell migration and showed proapoptotic effects in pancreatic cancer [97].



Moreover, the hydrogen sulfide releasing evodiamine derivative compound **I** exhibited effective inhibition of human leukemia HL-60 and epithelial colorectal adenocarcinoma Caco-2 cells with IC₅₀ values of 0.58 and 2.02 mM, respectively. Also, Compound **I** showed mitochondrial dysfunction in HL-60 cells through induction of apoptosis and arrest the cell cycle at the G2/M phase [98].



3. Biological activities of Hydrogen sulfide:

H₂S exhibits various biological activities at concentrations between 10 and 300 μM [3]. Whereas, H₂S can modulate many physiological responses including reducing oxidative stress [21], anti-inflammatory [20], neuromodulation [22], protection against myocardial ischemia injury [24], vasoregulation [23] and inhibition of insulin resistance [25].

3.1. Vasodilation and anti-hypertensive effects

Studies reported that H₂S showed relaxation of blood vessels similar to NO by altering K⁺ channel and increased cGMP levels of vascular smooth muscles [99, 100]. It also reported that the H₂S donor (NaHS) causing reduction of hypertension through rapid relaxation of aortic rings smooth muscles due to opening KATP channels [65]. The genetic deletion of cystathionine c-lyase (CSE) the H₂S generating enzyme cause hypertension [99].

3.2. Anti-inflammatory effects

As known that chronic and excessive administration of nonsteroidal anti-inflammatory drugs induce gastroenteropathy, and it was suggested that NSAIDs cause suppression of cystathionine c-lyase (CSE) expression lead to a decrease of endogenous H₂S synthesis in gastric injury [101–103]. Therefore, the administration of exogenous H₂S could reduce gastric injury [104]. Also, the short-term treatment with NaHS down-regulated expression of IL-6 and IL-8 and showed anti-inflammatory effects against osteoarthritis OA [59]. Moreover, GYY4137 could inhibit the production of pro-inflammatory mediators such as nitric oxide, TNF-α, IL-1β, IL-6 and PGE2 and rise the anti-inflammatory IL-10 chemokine levels [75].

3.3. Anti-oxidant effects

As known that H₂S has antioxidant properties via stimulation of glutathione metabolism [105] and increasing the activity of cysteine that increasing substrates for production of glutathione (GSH) [106]. Also, H₂S causes up-regulation of intracellular antioxidants and protection from ischemia-reperfusion (I/R) injury [107]. Moreover, H₂S could reduce mitochondrial ROS production through inhibition of cytochrome C oxidase [109].

3.4. Fibrinolytic activity

Essential oils of garlic showed a significant reduction in the rise in blood coagulation of hypercholesterolemic rabbits [110]. Furthermore, recent studies on garlic showed inhibition of platelet aggregation and increased fibrinolytic activity [111].

3.5. Anti-platelet activation and aggregation effects

Observations indicated that garlic H₂S releasing compounds could be helpful in the prevention of thrombosis [112]. It was found that treatment of rabbits with garlic extract could block synthesis of thromboxane-B₂ (TXB₂) that protects from thrombocytopenia [112]. Moreover, garlic aqueous extract prevents platelet aggregation stimulated by collagen and epinephrine *in vitro* [113]. Moreover, diallyl disulfide and diallyl trisulfide in garlic could inhibit platelet thrombus formation in stenosed coronary arteries [114].

3.6. Pro-angiogenic effects

Angiogenesis is a microvascular growth that revascularizes ischemic tissues and has an important role in modifying and developing chronic inflammation and tumorigenesis [115, 116]. It was reported that low micromolar concentrations of Na₂S or NaHS could modulate angiogenesis by increasing endothelial cell growth and migration [115, 117, 118]. More studies showed that H₂S could improve blood flow and microvascular growth in ischemic organs [119]. Additionally, H₂S regulates angiogenesis with other molecules, such as NO and CO [120] by increasing cGMP in vascular smooth muscle cells that inhibiting phosphodiesterase action [121].

3.7. Cardioprotective effects (MI and I/R)

Many studies showed that H₂S has a cardioprotective effect *in vitro* and *in vivo* [24, 57, 58, 122]. The CSE inhibitor DL-propargylglycine (PAG) inhibiting endogenous H₂S production that inhibits the cardioprotective effect. It has been demonstrated that at elevated plasma H₂S concentrations a decrease of infarct size and mortality after MI, while at decreased H₂S levels in the plasma the infarct size and mortality are increased [123]. Also, H₂S causes opening K-ATP channels that protect the heart during I/R injury [122], [24, 123, 124]. Moreover, H₂S could block cytochrome c oxidase that inhibits cellular respiration and protect against myocardial ischemic injury [125, 126]. H₂S could also suppress Na⁺/H⁺ exchanger and prevent Ca²⁺ overload of the ischemic heart that explains the H₂S cardioprotection effect [127].

3.8. Metabolic suppression

Literature reported that after administration of H₂S the metabolic oxygen demand is reduced through inhibition of the cellular oxygen receptors [128–130]. Also, the metabolic rate is reduced reversibly with decreased cardiovascular function without affecting blood pressure in mice [131].

3.9. Anticancer activity

As reported that H₂S could affect cell transporters [132] and ion channels causing down-regulation of cellular activities [133, 134]. Also after the treatment of HEK293 cells with NaHS

caused inhibition of voltage-gated T-type Cav3.2 channels [135] and increased anticancer effects and enhanced sensitivity of cancer cells to drugs [136, 137]. Moreover, DAS and DATS caused a decrease in tumor growth due to increased expressions of heme oxygenase-1 (HO-1) [140, 141]. Also, NaHS treatment enhances the release of NO and increased cytoprotective effects in L1210 leukemia cells [142].

H₂S Cancer suppressing activities:

3.9.1. H₂S donor regulates immune responses

Treatment of glomerulus cells with NaHS could protect against antibody-induced cell lysis and reducing antibody binding ability lead to a reduction of apoptosis [143].

3.9.2. H₂S donors regulating many transcription factors

H₂S can affect various transcription factors including STAT-3 [139], NF-κB [144] and Nrf-2 [145] which are included in apoptosis and inflammation. NaHS and GYY4137 showed protection from inflammatory and apoptotic reactions through sulfurating the p65 subunit of NF-κB at Cys-38 in monocyte/macrophage [146, 147]. Moreover, the treatment with NaHS, GYY4137 or DATS could enhance Nrf-2 antioxidant pathway that improves antioxidant status [148].

3.9.3. H₂S donor blocks cell cycle

It was reported that GYY4137 could induce arrest of cell cycle at G1/S in HCC cells [139], and S-G2/M phases in colorectal cancer [149] and breast cancer cells [66]. Also, NaHS could trigger G0/G1 arrest that prevents cell cycle progression in breast cancer [150]. Moreover, DATS could induce DNA damage and arrest G2/M phase in thyroid and bladder cancer [151, 152], and in prostate cancer [153]. Also, DATS enhanced the intercellular cyclins (A2 and B1) expression, and increased levels of apoptotic markers (Bax, p53, cleaved caspase 8, 9, and cytochrome c) and phosphorylation of histone 3 in gastric cancer [154, 155]. Additionally, DADS could induce arrest of G2/M phase in pancreatic [156] and ovarian cancer [157].

3.9.4. H₂S donor modulating cell proliferation and viability

H₂S could interact with the cell cycle regulators that control cell proliferation and viability by [155, 158]. As GYY4137 could enhance cell cycle arrest and apoptosis that showed pro-proliferation activities in colon and breast cancer [66, 149]. Moreover, DATS could decrease cell proliferation and viability in gastric cancer [155], osteosarcoma [158]. Also, NaHS could inhibit the growth of HepG2 cells [159] and breast cancer MCF-7 cells [150].

3.9.5. H₂S donor inhibiting cell migration and invasion

NaHS (600-1000 μM) could inhibit migration and invasion of tumor cells due to regulation of EGFR/ERK/MMP-2 and PTEN/AKT pathways in HCC cells [160]. Moreover, 200 μM NaHS caused deactivation of the MAPK and PI3K/AKT/mTOR pathways that inhibited migration activities in thyroid cancer cells [161]. However, treatment of colon cancer HT29 cells with DATS could decrease vascular endothelial growth factor, focal adhesion kinase and inhibiting p38, MAPK and JNK signaling cascades that prevented angiogenesis and migration [162].

3.9.6. H₂S donor induces apoptosis

H₂S could interact with numerous apoptosis-inducing pathways that cause the regulation of apoptosis [149, 163]. GYY4137 could increase the apoptotic markers caspase-9 expressions in breast cancer MCF-7 cells, colorectal cancer Caco-2 cells [149], and ovarian cancer A2780 cells [164], without affecting normal cell lines [66]. Moreover, GYY4137 showed a significant increase in apoptotic activities in HCC cells through the prevention of phosphorylation of STAT-3 prompted by interleukin-6 and JAK-2 [139]. In addition, NaHS causes upregulation of apoptosis- genes caspase-3 expressions and suppression of anti-apoptotic marker Bcl-2 through modulation of p38, MAPK and p53 pathways [165]. Also, DATS could induce apoptosis by enhancing mitochondria-mediated DNA damage [151]. Moreover, DADS could suppress cancer progression by enhancing DNA damage [156]. Furthermore, HA-ADT (a hybrid formed from ADT-OH and hyaluronic acid) showed a very great apoptotic index in breast cancer cells compared to NaHS and GYY4137 [166].

3.9.7. H₂S donor increase the sensitivity of cancer cells to anticancer drug

In addition to H₂S exhibited anti-cancer activities even in drug-resistant cancer cells including cisplatin-resistant cells [167], H₂S donors could also increase the sensitivity and decrease the resistance of cancer cells to anti-cancer agents [155, 168]. Treatment with DATS could improve the sensitivity of cancer cells to docetaxel (anticancer drug) the anti-cancer drug and increased the survival of gastric cancer patients through elevation of the mRNA and MT2A protein levels [168]. Moreover, treatment of osteosarcoma cells with DATS could suppress multidrug resistance protein 1 (P-gp1) and reduce drug resistance [169]. Furthermore, treatment of breast cancer cells with NaHS could increase tumor oxygen levels and enhance radiosensitivity [170]. In addition, NaHS could decrease the methotrexate (MTX) induced hepatotoxicity [171].

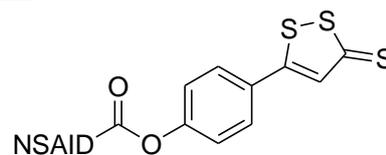
3.9.8. H₂S donor decreasing *in vivo* tumor growth

The treatment of leukemia model with 100-300 mg/kg GYY4137 showed a decrease in cancer growth and size [66]. It was reported that (50 mg/kg/day) GYY4137 decreased subcutaneous HepG2 cancer growth and size through regulation of STAT-3 pathway [139]. Moreover, DADS/DATS cause inhibition of cancer growth, size and weight [172]. Similarly, treatment of HCC mice model with NaHS(0.8-1 mM) leads to suppression of cancer growth and development [160].

4. H₂S donors hybrids:

As known that molecular hybridization is commonly used in drug design and development depending on binding two or more pharmacophoric groups having more biological activities to obtain a novel hybrid with enhanced affinity, efficacy and/or decreased side effects compared to the parent drugs[173]. Such a strategy was used in many studies gathering an H₂S donor pharmacophore with another pharmacologically active moiety. NSAIDs were the most used drug moieties in the design of such hybrids.

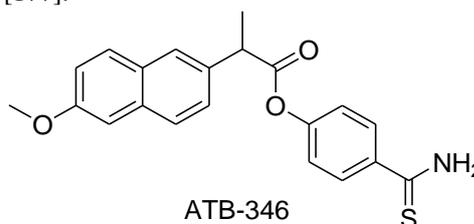
4.1. HS/NSAIDs



HS/NSAIDs

NSAIDs were coupled with 1,2-Dithiole-3-thiones DTTs giving HS-hybrid NSAIDs (HS-NSAIDs) exhibited a decrease of gastrointestinal injury caused by the corresponding NSAIDs [74, 174, 175] (**Table 1**). In addition, HS-SUL, HS-IBU, HS-ASA and HS-NAP showed significant inhibition of several human cancer cell growth such as leukemia, colon, breast, lung, prostate and pancreas cancer cells [176].

ATB-346 a naproxen-hydroxybenzothioamide hybrid that exhibited to promote apoptosis in melanoma cells [177]. **ATB-346** when compared to naproxen showed a decrease in gastrointestinal tract damage with anticancer activity against colorectal cancer [178]. **ATB-346** could also induce cell death through suppression of AKT and NF-κB signaling and reduction of cyclooxygenase-2 (COX-2) effects in human melanoma cells [177].



Moreover, the dual nitric oxide and hydrogen sulfide-releasing hybrid **NOSH-aspirin (NBS-1120)**, showed significant anticancer activity with IC₅₀s of 45.5 ± 2.5, 19.7 ± 3.3, and 7.7 ± 2.2 nM at 24, 48, and 72 h, respectively against HT-29 colon cancer cells. Also, NOSH-aspirin could block G0/G1 cell cycle, induced apoptosis and inhibit cell proliferation, [179]. NOSH-aspirin exhibited anti-inflammatory by the decrease of the interleukin-1 beta (IL-1b) production in carrageenan-induced paw inflammation and reduced prostaglandin E₂-induced hyperalgesia and more potency than aspirin and reduced inflammatory pain [180].

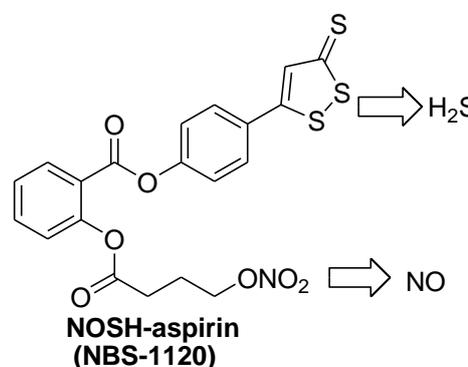
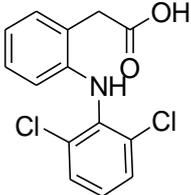
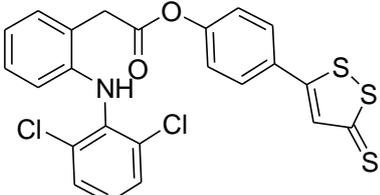
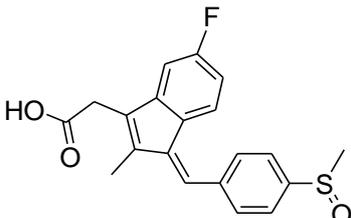
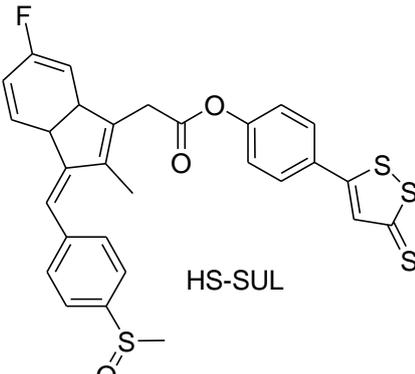
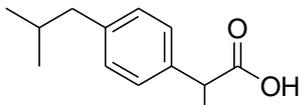
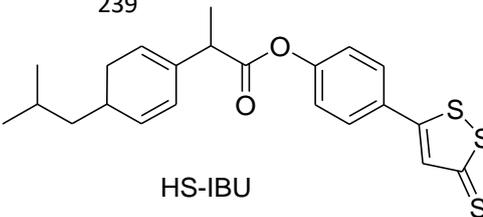
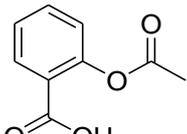
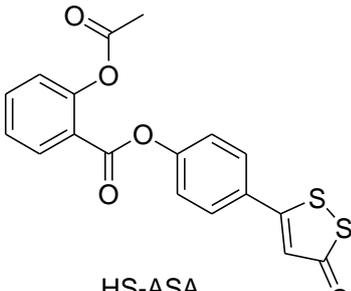
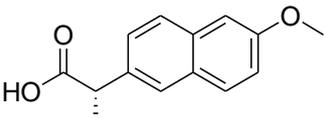
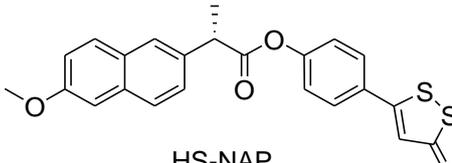
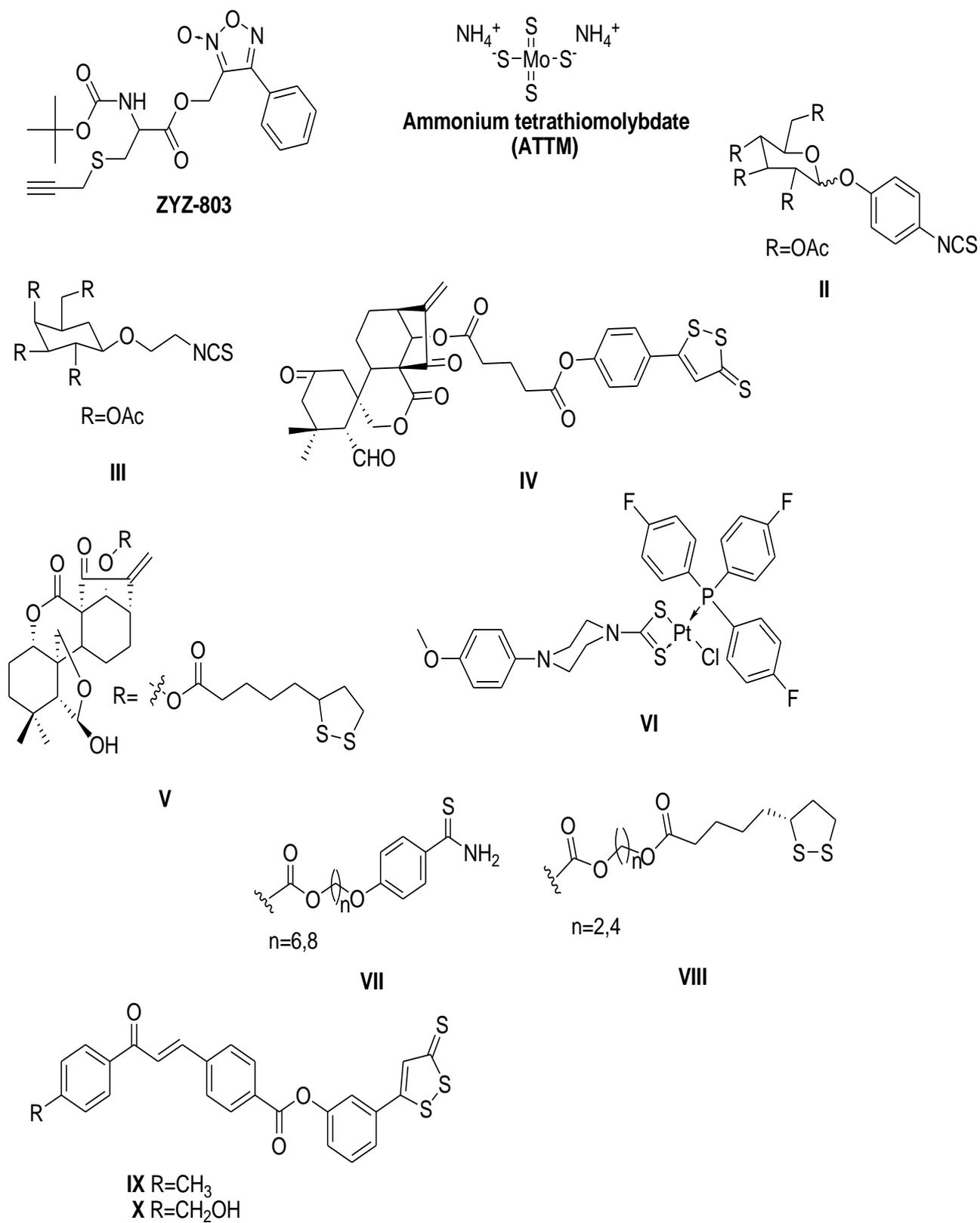


Table 1. Structures of HS-NSAIDs and Their Corresponding NSAIDs.

NSAIDs	HS/NSAIDs Hybrid
	
diclofenac	ATB-337
	
sulindac	HS-SUL
	
Ibuprofen	HS-IBU
	
aspirin	HS-ASA
	
naproxen	HS-NAP

4.2. Other synthetic H₂S hybridsFigure 17. Structures of Some Synthetic H₂S Hybrids.

The novel hydrogen sulfide-nitric oxide donor hybrid **ZYZ-803** could stimulate STAT3/CaMKII pathway in angiogenesis through H₂S/NO-mediated mechanisms [181]. Moreover, **HA-ADT** a novel hydrogen sulfide-releasing donor caused inhibition of the Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways that decreased the breast cancer cells growth. Results showed that HA-ADT could suppress breast cancer cells growth, migration and invasion. Also, HA-ADT increased the apoptotic index of breast cancer cells [166].

Compounds (**II and III**) are H₂S-Releasing Glycoconjugates showed anticancer activities of pancreas adenocarcinoma metastasis AsPC-1 and are effective in decreasing cell viability. These compounds (**II and III**) produce H₂S inside the AsPC-1 cells that modify the basal cell cycle [182].

A new series of hydrogen sulfide donating ent-kaurane and spiro lactone-type 6,7- seco-ent-kaurane derivatives with anticancer activity against four human cancer cell lines (K562, Bel-7402, SGC-7901 and A549) and two normal cell lines (L-02 and PBMC) specially compound **IV** that was the most potent with IC₅₀ values of 1.01, 0.88, 4.36 and 5.21 mM, respectively [183]. The antiproliferative activity of **IV** was through Bel-7402 cell cycle arrest at G1 phase and induction of apoptosis by enhancing the Bax, cleaved caspase-3 and cytochrome c expression and inhibition of procaspase-3, Bcl-2 and PARP [184]. Furthermore, compound **V** one of enmein- diterpenoid H₂S releasing hybrids showed the most potent antiproliferative activity and release of hydrogen sulfide due to α -thioctic acid moiety and could induce apoptosis through mitochondria-related pathways with anticancer activities against Bel-7402, SGC-7901 and A549 cancer cells with IC₅₀ of 2.16, 5.07 and 6.98 μ M respectively. However, having little activity on normal cell lines L-02 and PBMC with IC₅₀ of 15.81 μ M and 14.15 μ M respectively [185].

Ammonium tetrathiomolybdate (ATTM) is releasing H₂S and is commonly used for chelation of copper. As high levels of copper stimulate tumor and cancer growth, it was found that at high concentrations of ATTM cell growth was inhibited while at low concentrations cell growth is enhanced in three lung adenocarcinoma cell lines (A549, HCC827, and PC9). Conversely, triethylenetetramine another chelator of copper not producing H₂S does not promote cell growth [186].

Furthermore, Platinum(II) dithiocarbamate H₂S releasing compound [Pt(S₂CNR₂)Cl(PAr₃)] **VI** showed potent anticancer activities which could cleave DNA double-helical structure that inhibits tumor cells replication and growth [187].

The hydrogen sulfide donor oleanolic acid/ursolic acid/glycyrrhetic acid- and their 25-pentacyclic triterpene hybrids showed anti-tumor activity especially **VII** and **VIII** hybrids that revealed anticancer activity against K562 cell line. [188].

The novel nitric oxide-hydrogen sulfide donor Chalcone hybrids especially compound **IX** and **X** exhibited vasorelaxation in Isolated Rat Aorta with pEC₅₀ of 3.716 and 3.789 M, respectively and produced significant activation and release of cGMP [189].

Conclusion:

H₂S releasing agents showing several biological activities with many physiological effects. Besides the anti-inflammatory and anti-cancer activities, H₂S releasing agents also showed antioxidant effects and regulation of cardiovascular functions via ion channel alteration. Inorganic salts of sulfide are helpful to study H₂S biological importance, but the acute and rapid rate of

H₂S release makes them not ideal H₂S donors. Natural H₂S releasing agents are potent antioxidant, anti-inflammatory and anti-tumor compounds. Based on the scope of H₂S donors, several new synthetic H₂S releasing compounds with effective moieties such as polysulfide, thioamide, disulfide and anethole trithione have been evaluated for different pathophysiological effects. These agents can be combined with specific scaffolds for targeted therapy. Finally, it is critical for developing novel H₂S releasing drugs with a slow and consistent rate of H₂S and improved efficacy and decreased undesired side or toxic effects. In addition, the solubility of these agents must be controlled to obtain a good pharmacokinetic profile and the donor must be with good aqueous stability. Finally, the importance of the synthesis and development of H₂S releasing agents with enhanced properties will support moving these agents in the direction of clinical trials.

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