Hydrogen Sulfide (H\textsubscript{2}S) - Poison Gas to Signaling Molecule in Regulation of Human Biology

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\textbf{Abstract}

Hydrogen sulfide is a blossomed exploration of whiff. It is a well known poisonous gas but now serve as a gaseous transmitter which may act as an important signaling mediator in different cellular and physiological processes. It is recently discovered, that H\textsubscript{2}S is generated enzymatically from L-cysteine in various mammalian and human tissues to carry out number of signaling pathways in human biology. It has been revealed that ATP-sensitive K+ (K\textsubscript{ATP}) channel is widely accepted cellular target associated with H\textsubscript{2}S which is responsible for vasorelaxation, cardioprotection, neuroprotection and also in diabetes mellitus. Evidence is accumulating to demonstrate that H\textsubscript{2}S exerts significant effects in different diseases by different mechanisms of action; also this review summarizes a detailed description of current signaling mechanism responsible for various effects in human biology.

\textbf{Keywords:} Hydrogen sulfide (H\textsubscript{2}S); Cystathionine-\textbeta-synthase (CBS); Cystathionine-\gamma-lyase (CSE); 3-mercaptopyruvate sulfurtransferase (3-MST); K\textsubscript{ATP} channel

\textbf{Abbreviations:} H\textsubscript{2}S: Hydrogen Sulfide; CBS: Cystathionine-\textbeta-synthase; CSE: Cystathionine-\gamma-Lyase; CAT: Cysteine Aminotransferase; MST: 3-Mercaptopyruvate Sulfurtransferase; NO: Nitric Oxide; CO: Carbon Monoxide; PKA: Protein Kinase A; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NaHS: Sodium Hydrosulfide; MAPK: Mitogen Activated Protein Kinase; AOA: Aminooxyacetate; ICAM-1: Intercellular Adhesion Molecule; TNF-α: Tumor Necrosis Factor-α; TRPV-1: Transient Receptor Potential Vanilloid-1; ERK: Extracellular Signal Related Kinase; EGFR: Endothelial Growth Factor Receptor; LTP: Long Term Potentiation; ROS: Reactive Oxygen Species; RNS: Reactive Nitrite Species.

\textbf{Introduction}

Hydrogen sulfide is a small gaseous and the diffusible compound with the formula H\textsubscript{2}S that constitute a family of labile gas-transmitters together with Nitric oxide (NO) and Carbon monoxide (CO) \cite{1,2}. Although all three gas-transmitters has the same toxicity status, H\textsubscript{2}S yet has not been awarded the degree of initial skepticism which is associated with other two NO and CO \cite{3}. It is a colorless, flammable gas with the characteristic foul smell of rotten eggs. Often it results from the bacterial decomposition of organic matter in the absence of oxygen. It also occurs in volcanic gases, natural gas, and some well waters. Despite being as environmental pollutant and bio hazardous compound it is widely integrated in various human physiological processes and diseases \cite{4,5}. The main mechanism behind H\textsubscript{2}S toxicity is mitochondrial damage or oxidative damage through blockade of cytochrome-c oxidase \cite{6,7}. Recent studies suggested that H\textsubscript{2}S acts as an important mediator in various signaling pathways of human biology. Endogenously it is produced in various parts of the body like blood vessels \cite{8}, heart \cite{9}, GIT and central nervous system \cite{10}. The present article reviews the prominent role of H\textsubscript{2}S in human biology with special focus on current literature and clinically relevant studies.

\textbf{Synthesis of Hydrogen Sulfide in Mammalian and Human Tissues}

L-Cysteine (sulfur containing amino acid) is the major substrate for producing H\textsubscript{2}S in mammalian tissues via two pyridoxal-5’-phosphate (PLP) dependant enzymes: cystathionine-\beta-synthase (CBS) and cystathionine-\gamma-lyase (CSE) as well as a PLP independent enzyme 3-mercaptoppyruvate sulfurtransferase (3-MST) \cite{11-14} as depicted in Figure 1. Both CBS and CSE exist in cytosol whereas the 3-MST present mainly
in mitochondria and expressed in vascular endothelium. \( \text{H}_2\text{S} \) formation through biosynthetic pathway is dependent on tissue location [15]. Enzymatically, \( \text{H}_2\text{S} \) is produced in different areas of the human body at a particular concentration [16] as shown in Figure 2. A recent investigation shows that CBS is predominantly found in the brain and nervous tissues whereas CSE is in the vascular system and other organs including GI tract, lungs and kidneys. 3-MST is also present in kidney, liver, lung and heart [17,18] CBS and CSE both can produce \( \text{H}_2\text{S} \) by catalyzing different sulfur containing substrates, L-cysteine that can be derived from alimentary canal and can be liberated from endogenous proteins [19] whereas sulfur transfer reactions from 3-mercaptoppyruvate can only be catalyzed by 3-MST [20]. These sulfur transfer reaction yields hydropersulfide not \( \text{H}_2\text{S} \) directly, further a redox reaction between RSSH and a biological thiol (GSH) is required for releasing \( \text{H}_2\text{S} \). Recently it has been investigated by Kumara et al. [21] that for production of \( \text{H}_2\text{S} \) from 3-mercaptoppyruvate and 3-MST depend on biological dithiol-thioredoxin or dihydrolipoic acid. In tissue homogenates it has been observed that 1-10 pmoles per second per mg protein range of sulfide is produced that can cause low micromolar extracellular concentrations of sulfide [22-25].

**Potential Effects of \( \text{H}_2\text{S} \) in Human Biology**

\( \text{H}_2\text{S} \) together with NO and CO, comes under a family of labile transmitters termed as gas-transmitters. Being a potential endogenous gas-transmitter, \( \text{H}_2\text{S} \) is a highly lipophilic molecule that is rapidly diffusible through the cell membranes without using any specific transporters [26] and it is 5 fold more soluble in lipophilic solvent than aqueous solvent [2,27]. \( \text{H}_2\text{S} \) is weakly acidic in nature (pKa = 6.76 at 37\( ^\circ \)C) in aqueous solution [28].
$\text{H}_2\text{~S}$ dissociate into two dissociation states: HS$^-$ (pKa = 7.04) and S2$^-$ (pKa = 11.96). Approximately 18.5% of total sulfide are present in undissociated form and 81.5% exists as HS$^-$ [28]. Various studies have suggested that $\text{H}_2\text{~S}$ exerts many potential effects on a large number of biological targets and is involved in several physiological and pathological processes (Figures 3 & 4).

**Figure 3:** Potential targets for Hydrogen sulfide ($\text{H}_2\text{~S}$). Various experimental investigations suggest that $\text{H}_2\text{~S}$ plays a prominent role in normal physiology and pathophysiology. Therefore, targets for $\text{H}_2\text{~S}$ therapy includes heart failure, peripheral arterial diseases, acute MI, stroke, atherosclerosis, GI irritation, Alzheimer’s disease, cancer, thrombosis, organ transplantation, diabetes and erectile dysfunction.

**Figure 4:** This figure illustrates the major cardiovascular actions of $\text{H}_2\text{~S}$.

**$\text{H}_2\text{~S}$ and Cardiovascular Effects**

For various important physiological processes $\text{H}_2\text{~S}$ needs to interact with a wide range of ion channels. There are varieties of experimental models, including a canine model of cardiopulmonary bypass with hypothermic cardiac arrest that describes the cardioprotective effects of $\text{H}_2\text{~S}$. Cardioprotective action is through modulation of ATP-sensitive potassium (KATP) current [29] and voltage-gated L-type calcium current [30]. It
has been seen that H$_2$S plays a prominent role in myocardial pre and post conditioning responses [31]. H$_2$S exerts a negative inotropic and chronotropic effects both in-vivo and in-vitro in the heart [32] and protect the heart against injury following coronary artery ligation [33] and ischemia [34]. Recent review suggested that in vasculature, H$_2$S in combination with NO generates nitrosothiol with inotropic properties [129,130].

**Mechanistic Pathways that are Implicated in the Cardioprotective Effect of H$_2$S are**

a) Involvement of ATP sensitive K$^+$ channel and Voltage gated L-type calcium current [29,30]

b) Regulation of mitochondrial respiration [7]

c) Regulation of cytoprotective genes such as Nrf-2 [35]

d) Activation of cardiac extracellular-signal-regulated kinase (ERK) and/or phosphotidyl-inositol 3-kinase (PI3K-Akt) pathway [36].

Along with these cardioprotective effects H$_2$S also interacts with those ion channels that are involved in the membrane action potential and may be effective in cardiac arrhythmias [37]. In addition to these effects against collagen, ADP and aggregating agents H$_2$S can inhibit human platelet aggregation *in-vitro* [38]. Furthermore, several studies on vascular tissue have been concluded that H$_2$S is a potent vasodilator and perhaps an EDHF (endothelium derived hyperpolarizing factor) [8,35]. Experimentation in isolated rat aortic and portal vein and using a perfused rat mesenteric showed that H$_2$S dilates only blood vessels [8,39-41] not coronary [39] and vascular beds. The Vasodilatory effect of H$_2$S is independent of guanylyl cyclase/cGMP pathway [42]. However H$_2$S induces vasorelaxation through involvement of cGMP-dependent protein kinase-I. Recently, it was focused on the role of H$_2$S in chronic changes of vasculature. It has been reported that chronic treatment with NaHS can reduce hypertrophy of intramyocardial arterioles and ventricular fibrosis in hypertensive rats [43]. In addition, H$_2$S also inhibits L-type calcium currents in rat cardiomyocytes and the study suggested that if cardiomyocytes were treated with (dithiothreitol) DTT, an H$_2$S donor could change in cardiac function [44]. Wei H et al. [132] reported that H$_2$S could inhibit hyperpolarization of activated inward current and delayed rectifier potassium channels in human cardiomyocytes. These effects could have a significant role in prolongation of the action potential and vasodilatory function of H$_2$S [45].

**H$_2$S and Nervous System**

**Biosynthesis of H$_2$S and its Regulation in CNS**

![Figure 5: Production and Regulation of H$_2$S in central nervous system: when electrical stimulation or neuronal excitation occurs, electrical signals descend to axon terminals and Ca$^{2+}$ enters into the nerve terminal then interact with calmodulin which activates the CBS and the formation of H$_2$S. An influx of Ca$^{2+}$, perhaps triggered by the activation of NMDA receptors by glutamate or via separate channels, binds to calmodulin (CaM), thereby activating CBS. CBS seems to be the main H$_2$S-forming enzyme in the CNS. SAM is an allosteric activator of CBS whereas hydroxylamine and amino-oxyacetate are inhibitors of CBS.](image-url)
In the CNS, H$_2$S is enzymatically produced by three major enzymes- CBS, CSE [11] and 3-MST [46] and there it is usually stored in astrocytes as bound sulfane sulfur and releases free H$_2$S in response to neuronal excitation [47]. The concentration of CBS is highly present in the hippocampus and the cerebellum [48] whereas it is highly localized to microglial cells [49] and astrocytes [50]. Generally, mRNA of CBS is found in the brain especially hippocampus [48]. Lee et al. [51] investigated that H$_2$S is enzymatically produced in astrocytes 7.9 fold greater than in cultured microglial cell and suggest that astrocytes is the largest brain cell for producing H$_2$S [51]. CSE is also the second major enzyme for producing H$_2$S and in CNS; it is highly expressed in the spinal cord [52] and cerebellar granule neurons [53]. In the brain, endogenous H$_2$S is formed from L-cysteine by pyridoxal 5’-phosphate dependent enzyme CBS. CBS activity is enhanced by S-adenosyl-L-methionine (SAM) and pyridoxal 5’-phosphate and mediated by Ca$^{2+}$ and a calmodulin pathway [54, 55] as shown in Figure 5. Longer-term regulation of CBS activity most probably is dependent on SAM whereas hydroxylamine and amino-oxyacetate reverses the activity of CBS. In AD brains, the level of SAM is lower than the brains of normal individuals [56]. It has also been reported that production of H$_2$S is stimulated in response to neuronal excitation as well as electrical stimulation. Furne et al. [57] has investigated the brains of eight mice and estimated free concentration of H$_2$S around 14 ± 3.0 nM [57]. It has been suggested that 50-160µM of H$_2$S in the brain is found for physiological function [58,59].

**Effect of H$_2$S in Regulation of Intracellular Signaling Pathways in CNS**

Brain function is regulated by phosphorylation of intracellular proteins and Ca$^{2+}$ release. These both processes are regulated by activation of protein kinase-A (PKA). Maintenance of long term potentiation (LTP) requires activation of PKA that may phosphorylate NMDA receptors and can enhance permeability of Ca$^{2+}$ [60,61]. Kimura et al. [17] found that NaHS, an H$_2$S donor enhances cAMP production in cerebral cortex and cerebellum neuron culture which activates protein kinase-A [62]. Another one is tyrosine kinase which is present on the surface of cell receptor; where H$_2$S activates receptor tyrosine kinase and protect neurons against oxidative stress [63]. H$_2$S also activates endothelial growth factor receptor (EGFR) and EGFR activation can modulate signaling of NMDA receptors and LTP [48]. Whiteman et al. [64] suggests that H$_2$S may work as an antioxidant because it potentially inhibits intracellular nitration of proteins and oxidation of proteins in human neuroblastoma cells with inhibition of peroxynitrite induced cytotoxicity and presumably increases GSH production [64] and additionally this can enhance glutamate uptake [65]. Kimura and Kimura [66] reported that increased GSH level can increase neuroprotection using immature cortical neurons culture and HT22 cells that depends on extracellular cysteine [66]. Taking together, these effects of H$_2$S can regulate intracellular signaling in CNS i.e. oriented towards neuroprotection and other CNS diseases.

**Role of H$_2$S in Neuronal Diseases with their Mechanism**

Various recent studies suggested that H$_2$S has played a prominent role as an antioxidant, antiapoptotic in neurons and glial cells [66,67]. Additionally, H$_2$S may also have anti-inflammatory activity because it induces alteration in Ca$^{2+}$ in astrocytes and microglial cells [68,69]. H$_2$S seem to have multiple roles as it can enhance NMDA receptor mediated responses and facilitate long term potentiation in hippocampus but it can block excitatory postsynaptic potentials (EPSPs) (inhibit synaptic transmission). Literature findings also suggested that H$_2$S enhances NO-induced relaxation of smooth muscles [70] and decreases corticotrophin secretion from hypothalamus [71]. Therefore Kimura et al. [17] demonstrated the function of H$_2$S as a neuromodulator in the brain. It was reported that H$_2$S is abundantly found in cerebrospinal fluid of patients with Down syndrome because of chromosome 21 which encodes CBS [72]. Neurodegenerative diseases of the CNS such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and Amyotrophic lateral sclerosis (ALS) are strongly associated with oxidative stress causing neuronal cell death [73]. Endogenous H$_2$S can activate protective signaling pathways that are processed through antioxidant enzymes such as SOD, GSH and heme-oxygenase-1 (HO-1) and further their expression is regulated by transcriptional factors like NfF2, NrF2 and PGC-1a [74,75]. H$_2$S may protect neuronal damage from oxidative stress via increasing levels of GSH or redistributing GSH into mitochondrial localization [76]. It was also investigated that in AD, NaSH attenuated lipopolysaccharide-induced cognitive defects [77] and inhibited Aβ induced cellular injury or death in rats [78]. H$_2$S may also reduce amyloid-β plaques in AD [79], can prevent neurodegeneration in mouse models of PD [80] and can enhance analgesia via µ-opioid receptor interaction [81]. In ischemia/reperfusion, mitochondria are the major part of cell which is affected and enhances the production of ROS with depolarizing the mitochondrial membrane. H$_2$S scavenges the free radicals and decreases the generation of ROS [82,83]. During ischemia, mitochondrial cytochrome oxidase activity was enhanced that can generate ROS. H$_2$S decrease the level of ROS and imparting cytoprotection, also inactivates the activity of mitochondrial cytochrome oxidase and stimulate SOD to lower the level of ROS [84].

**Mechanistic role of H$_2$S in CNS –**

(a) It increases cAMP levels in neuronal and glial cell lines and primary neuron cultures

(b) It hyperpolarizes CA1 and dorsal raphe neurons by activating KATP channels [85, 62]

(c) Increasing the sensitivity of NMDA receptors following a rise in intracellular cAMP facilitates hippocampal LTP and increase H$_2$S production and NaHS (H$_2$S donor) with direct electrical stimulation and glutamate application. H$_2$S promotes glutamate mediated neurotransmission via NMDA receptors (Figure 6a).
It scavenges ROS and RNS (free radicals) directly or indirectly via enhancing GSH production and enhances mitochondrial protection (Figure 6b).

### H$_2$S and inflammation

The contribution of H$_2$S in inflammation is becoming clearer. A hallmark of inflammation is that H$_2$S has capability to relax vascular smooth muscles [51,86]. There are various animal models like carrageenan induced monoarthritis [87] and synovitis [88] in rats, ischemia-reperfusion injury [89] and tobacco-smoke induced lung inflammation [90,91] in mice that describes the role of H$_2$S in inflammation. Some key effects of H$_2$S that influences inflammation and injury are illustrated in Figure 7. H$_2$S donors or Sulfide salt donors are capable to decrease infiltration of neutrophils and lymphocytes [88,92] which is practically proved by the concussion of H$_2$S in suppression of leukocyte adhesion to the vascular endothelium, inhibit migration of leukocytes into sub endothelial space and the subsequent extravasation of leukocytes [92]. H$_2$S can also inhibit the ability to suppress activation of nuclear transcription factor (NF-κB and P38 MAPK) [93,94,95] with reduction of many proinflammatory cytokines, chemokines and enzyme expression like [iNOS] [88,96-98]. Another anti-inflammatory effect of H$_2$S is through inhibition of enzyme phosphodiesterase and thus elevating cGMP and cAMP levels [99]. In acute and chronic rat models of paw edema, it has been reported that H$_2$S enhances the edema reducing effects from NSAIDS releasing H$_2$S and therefore can reduce plasma exudation [100,101]. Recently it has been reported by Whitteman et al. [98] that H$_2$S is also present in patients with rheumatoid arthritis and osteoarthritis [102].

#### H$_2$S and GI tract:

Due to its anti-inflammatory action H$_2$S is gaining important therapeutic value in the GI tract. It is synthesized from two important enzymes CSE and CBS in many parts of GI tract like stomach ileum, jejunum, and colon. CSE is predominantly found throughout the whole GI tract because of its association with vascular whereas CBS is restricted to some parts like muscular mucosa, lamina and propria [107]. Recently various studies suggested that H$_2$S exerts several actions including relaxation of smooth muscles of the intestine [108], stomach [109] and colon [110] via different mechanisms with anti-inflammatory [96] and anti-nociceptive effects [52].

#### Mechanistic Action of H$_2$S in Different Parts of GI Tract

a) In stomach- H$_2$S activates myosin light chain phosphatase and relaxes smooth muscles.

b) In ileum- H$_2$S relaxation is independent of NO, KATP and Ca$^{2+}$ channels.

c) In colon- The effect of H$_2$S is not involved major known K$^+$ channel, activation of MLCP or rho-kinase.

d) In intestine- H$_2$S stimulates chloride secretion via excitation of secreto motor neurons and through targeting on vanilloid receptors (TRPV1) which is found in afferent nerves of guinea pig and human colon [111].
Various early studies investigated that concentration of $\text{H}_2\text{S}$ is relatively high in the lumen of the gut because human GIT is a home of various bacterial species that are capable of producing $\text{H}_2\text{S}$, but most is bound to fecal material. Therefore it cannot diffuse through the epithelium, only a small amount (i.e. Micromolar concentrations) is free to diffuse across the epithelium that is absorbed and primarily metabolized via mitochondrial sulfide quinine reductase (SQR) to thiiosulfate and produces ATP. Thus $\text{H}_2\text{S}$ is an important energy source for colonocytes and protects gastric mucosa from injury [112].

Moreover, it is known that $\text{H}_2\text{S}$ has dual nature, both anti-inflammatory and inflammatory effects in the GI tract. Anti-inflammatory activity and ulcer healing activity by $\text{H}_2\text{S}$ both are independent of major known $\text{K}^+$ channel and NO synthase [112] and in an experimental model of colitis $\text{H}_2\text{S}$ protects and promotes resolution against colitis [113]. Whereas $\text{H}_2\text{S}$ can modulate cell cycle progression via expression their genes and can cause colorectal cancer through inflammatory and DNA repair processes [114]. In caerulein induced pancreatitis model, $\text{H}_2\text{S}$ acts like inflammatory signaling molecule [115-117]. $\text{H}_2\text{S}$ enhances intracellular adhesion molecule-1 (ICAM-1) expression and through NF-κB stimulates neutrophil adhesion [118]. However, it is also investigating that $\text{H}_2\text{S}$ protects the pancreas from oxidative damage [119-130].

**$\text{H}_2\text{S}$ and Respiratory System**

It has been proposed that $\text{H}_2\text{S}$ produce its effect on lung and showed action on pulmonary blood flow and pulmonary vascular resistance [131]. It was also observed that $\text{H}_2\text{S}$ production decreases during chronic hypoxia and pulmonary hypertension in rats [132,133]. Exogenous $\text{H}_2\text{S}$ or sulfide salt donors attenuate pulmonary arterial pressure and tissue GSSG whereas $\text{H}_2\text{S}$ enhances the total antioxidant capacity [133]. It also relaxes pre contracted bronchial smooth muscles of mouse [134]. It was also reported that $\text{H}_2\text{S}$ attenuates oleic acid induced lung injury [135] and ovalbumin induced lung asthma and generates anti-inflammatory action whereas exogenous $\text{H}_2\text{S}$ enhances inflammation and attenuates iNOS activation.

**Mechanistic Action of $\text{H}_2\text{S}$ on Respiratory System**

a) It relaxes bronchial smooth muscles i.e., independent of KATP channel, cyclooxygenase-1 & 2 and guanylyl cyclase [134].

b) It reduces tissue GSSG [132].

**$\text{H}_2\text{S}$ and Diabetes Mellitus**

Diabetes mellitus and its complications depend on the enhanced generation of ROS. Many substances such as hormones, neurotransmitters and nutrients can control pancreatic-$\beta$ cells to release insulin. Furthermore, experimental studies have been reported that $\text{H}_2\text{S}$ may inhibit the release of insulin via opening of KATP channel. However, it was also explained that this mechanism is independent of the opening of KATP. $\text{H}_2\text{S}$ has dual effects on cell survival/death of pancreatic-$\beta$ cells. Yang et al [123] investigated that $\text{H}_2\text{S}$ and over expressive CSE activates mitogen activated protein kinase (P-38 MAPK) and induce apoptosis in rat insulinoma INS-1E cells, whereas, $\text{H}_2\text{S}$ may also protect intact mouse islets and MIN 6 cells against high glucose, fatty acids or cytokines induced cytotoxicity .

**Mechanistic Actions of $\text{H}_2\text{S}$ to Protect Pancreatic-$\beta$ Cells and in Diabetes are:**

a) $\text{H}_2\text{S}$ donor, NaHS or L-cysteine scavenges ROS via increasing content of glutathione.

b) In MIN-6 cells, $\text{H}_2\text{S}$ stimulates Akt phosphorylation (important for $\beta$-cell survival).
H₂S and Reproductive System/Erectile Dysfunction (ED)

It has been investigated that CBS and CSE were found in the Leydig, Sertoli and germ cells of rat testis [125] as well as in intrauterine tissues and human placenta [126]. Although H₂S relaxes vas deferens smooth muscle and showed vasodilatory properties in the corpus cavernosum [127]. Therefore, H₂S is an effective therapy for ED. The study explores the mechanism that H₂S enhances the NO production via expression of constitutive nitric oxide synthase (NOS) isoforms i.e. endothelial NOS (eNOS) and neuronal NOS (nNOS) in rat corpus cavernosum and states that exogenously applied NaHS enhances eNOS but not nNOS. This can cure inherited erectile impairment which happens due to attenuation of endothelial NO formation in cavernosum [128]. However, per se effect of H₂S in reproduction is still under investigation.

Conclusion

During the past decade, several researches have been focused on H₂S. This review has centered the role of H₂S in human biology. Indeed, efforts are going on to investigate the therapeutic potential of H₂S in human diseases. It was discovered that H₂S is continuously produced enzymatically in mammals and regulates the vast array of physiological processes. Now recently it is considered as a new gaseous signaling molecule that effect on all organ systems and in various pathological states. Accumulating evidence suggests that H₂S have been implicated in neurotransmission via various pathways. It acts as a physiologic vasodilator and plays a prominent role in cardioprotection, pro and anti-inflammatory processes and several metabolic disorders such as diabetes, obesity, gut. Nevertheless, our understanding of mechanistic action is still fragmentary. Since it has a diverse biological profile to treat a number of diseases, H₂S has come under a promising research to develop H₂S-releasing prodrugs. It might be possible that H₂S prodrugs can enhance H₂S bioavailability and be efficacious in physiological processes.

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