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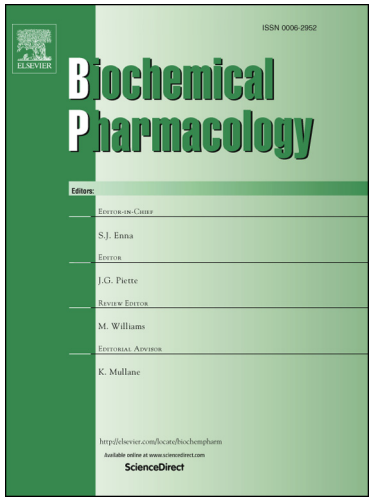


Review

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# A Review of Hydrogen Sulfide ($H_2S$) Donors: Chemistry and Potential Therapeutic Applications

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## Abstract

Hydrogen sulfide ($H_2S$) is a ubiquitous small gaseous signaling molecule, playing an important role in many physiological processes and joining nitric oxide and carbon monoxide in the group of signaling agents termed gasotransmitters. Endogenous concentrations of $H_2S$ are generally low, making it difficult to discern precise biological functions. As such, probing the physiological roles of $H_2S$ is aided by exogenous delivery of the gas in cell and animal studies. This need for an exogenous source of $H_2S$ provides a unique challenge for chemists to develop chemical tools that facilitate the study of $H_2S$ under biological conditions. Compounds that degrade in response to a specific trigger to release $H_2S$, termed $H_2S$ donors, include a wide variety of functional groups and delivery systems, some of which mimic the tightly controlled endogenous production in response to specific, biologically relevant conditions. This review examines a variety of $H_2S$ donor systems classified by their $H_2S$-releasing trigger as well as their $H_2S$ release profiles, byproducts, and potential therapeutic applications.

Keywords: Gasotransmitter, self-immolation, carbonyl sulfide, perthiols, cell signaling

## 1. Introduction

Hydrogen sulfide ($H_2S$) has long been known as a foul smelling, toxic gas. Much of the early literature on $H_2S$ focused on its removal from petroleum and pulp products, concerns due in large part to its noxious odor. The presence of $H_2S$ in mammalian tissue has been known for decades, but it was not until the landmark paper by Abe and Kimura in 1996 that the endogenous production and signaling capacity of $H_2S$ was elucidated.[1] Clarification of the cellular signaling mechanisms and biodistribution of its constitutive enzymes led to the induction of $H_2S$ into a family of small signaling molecules known as gasotransmitters. The term gasotransmitter, coined by Wang in 2002, refers to the gaseous nature of these compounds at standard temperature and pressure in the bulk.[2] There are currently three accepted gasotransmitters: carbon monoxide (CO), nitric oxide (NO), and, most recently, $H_2S$. For a molecule to be considered a gasotransmitter, specific criteria must be met, including: regulated endogenous production, the ability to freely permeate cell membranes, and specific signaling function with specific cellular and molecular targets.[2] The acknowledgement of $H_2S$ as a gasotransmitter has led to a renewed interest in this gas over the past two decades, with a focus on creating chemical tools to probe $H_2S$ physiology, determining its signaling roles in various organs and systems across the plant and animal kingdoms, and exploiting its biological signaling capacity for therapeutic benefits.