

Review

Research Progress of H₂S Donors Conjugate Drugs Based on ADTOH

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Abstract: H₂S is an endogenous gas signaling molecule and its multiple biological effects have been demonstrated. The abnormal level of H₂S is closely related to the occurrence and development of many diseases, and H₂S donors has important pharmacological implications. In recent years, H₂S donors represented by ADTOH (5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione) are often used to synthesize new ‘conjugate’ compounds that can release H₂S and parent drugs. These hybrids retain the pharmacological activity of the parent drugs and H₂S and have a synergistic effect. ADTOH and parent drug hybrids have become one of the important strategies for the development of H₂S donor conjugate drugs. This review summarizes molecular hybrids between ADTOH and clinical drugs to provide new ideas for the study of H₂S donor drug design.

Keywords: H₂S donors; ADTOH; clinical drugs; conjugate drugs

1. H₂S and H₂S Donors

Hydrogen sulfide (H₂S) is the third endogenous gas signaling molecule discovered after nitric oxide (NO) and carbon monoxide (CO). H₂S plays an important regulatory role in a variety of physiological and pathological processes [1–3]. The reduction of H₂S level in the body would lead to the occurrence and development of hypertension, atherosclerosis, gastrointestinal ulcer, liver cirrhosis, diabetes, inflammation, Alzheimer’s disease, cancer, and other diseases. Therefore, the supply of exogenous H₂S is an effective way to solve the above questions [4–9]. However, the toxicological concentration of H₂S is close to the physiological and pharmacological effective concentration, and the gas is volatile. Considering that, it is difficult to accurately control its effective concentration in vivo, which greatly limits the application of H₂S gas itself as a drug in basic research and clinical trials. Therefore, sustained-release and controllable H₂S donor drugs have not only broad application prospects, but also important significance for further elucidating the biological effect of H₂S [10].

Like other gas signaling molecules, the activity of H₂S is closely related to the site, concentration, and velocity of its release [11]. Therefore, the key problem in the study of H₂S donor drugs is how to improve the selectivity of H₂S donor molecules, release appropriate concentrations of H₂S at the target site (generally the lesion site), play a therapeutic role while limiting its adverse reactions. At present, H₂S donor can be roughly divided into sulfide salt, natural organic sulfur compounds, and synthetic H₂S donors. Among them, many researchers focused on synthetic H₂S donors. According to the different molecular structures and functional group properties, they can be broadly classified into thiophosphate derivatives (GYY4137) [12], aryl thiamides (TBZ) [13], 1,2-dithiole-3-thiones (ADT-OH) [14,15], thiol-activated H₂S donors (NSHDs) [16], etc. (Figure 1).



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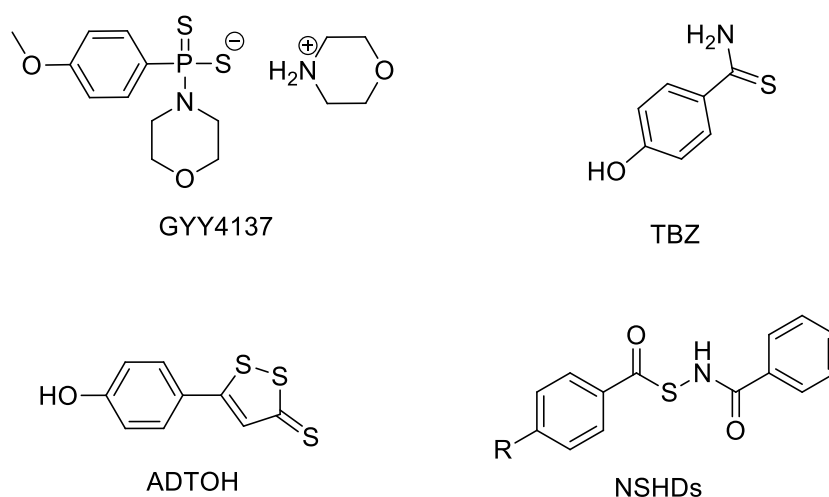


Figure 1. Structures of representative synthetic H₂S donors.

2. ADTOH and Its Conjugates

5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADTOH) is the main metabolite of 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione (ADT). The thione of ADTOH can be transformed into the corresponding ketone by hydrolysis and release H₂S (Figure 2) [17]. In recent years, the research on ADTOH has been boosting. New H₂S donor derivatives represented by ADTOH have been developed and designed widely, especially in some basic experimental studies. ADTOH is often used to synthesize new ‘conjugate’ compounds that can release H₂S and parent drugs. Therefore, this paper reviews the hybrid compounds of ADTOH and parent drugs in order to provide a reference for the study of ADTOH-based donor drug design.

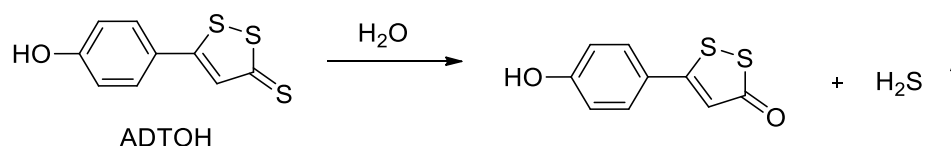


Figure 2. Mechanism of H₂S release from ADTOH.

2.1. ADTOH–NSAID Conjugates

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used drugs. NSAIDs generate anti-inflammatory activities by inhibiting cyclooxygenase to reduce the production of inflammatory cytokines such as prostaglandins. However, long-term use of NSAIDs may lead to significant side effects, such as gastrointestinal adverse effects. It has been reported that NO and H₂S could enhance the local defense of gastric mucosa, thus reducing NSAID-induced gastrointestinal disorders and other side effects [18,19]. Therefore, designing hybrids of H₂S donors or NO donors together with NSAIDs to enhance the efficacy and reduce the side effects of NSAIDs is an important strategy of current research.

In recent years, new hybrid compounds linking ADTOH with NSAIDs are the most widely studied category in H₂S research. These ADTOH–NSAID hybrids can release H₂S and exert H₂S activity while exerting the pharmacological effects of NSAIDs. The biggest advantage of these compounds compared with the parent NSAIDs is alleviating the gastrointestinal adverse effects.

NOSH-aspirin is a derivative formed by combining aspirin with ADTOH and NO donors (Figure 3). It has similar antipyretic, analgesic, anti-inflammatory and anti-platelet aggregation effects as aspirin, but has less adverse effects on gastrointestinal bleeding and better tumor prevention effects. In addition, HS-aspirin, a hybrid of aspirin and ADTOH exhibited inhibitory effects in estrogen receptor-negative breast cancer cells and leukemic Jurkat cells [20,21].

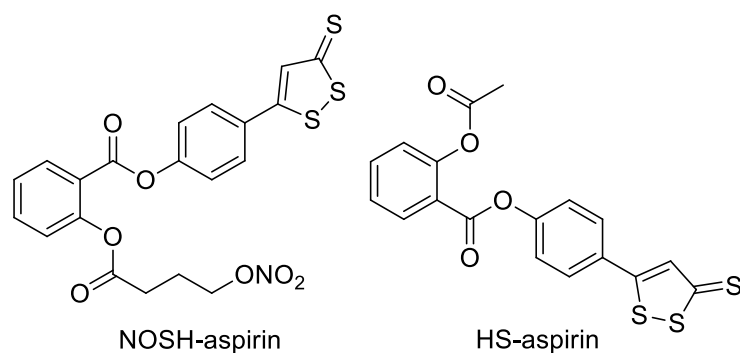


Figure 3. Structures of NOSH-aspirin and HS-aspirin.

ATB-429 is a hybrid of mesalamine and ADTOH, which has improved anti-inflammatory and analgesic activity (Figure 4). ATB-429 significantly reduced gastrointestinal side effects compared to mesalamine, especially in a mouse model of colitis with better anti-inflammatory activity. ATB-429 exerts anti-inflammatory effects in LPS-induced liver injury, lung injury, ulcerative colitis. Additionally, it has anti-inflammatory effects in NSAID-induced gastric mucosal injury. ATB-429 is superior to mesalamine in reducing mucosal damage and disease severity; moreover, it significantly reduces the infiltration of chronic granulocytes and the expression of several important inflammatory cytokines mRNA. ATB-429 has entered Phase III clinical trials with the U.S. FDA [22]. Inspired by the above findings, Wang et al. [23] designed and synthesized a series of ATB-429 derivatives containing NO-releasing moieties, and evaluated its anti-tumor activity. The results showed that the derivatives have strong anti-tumor activity. Among them, compound **1a** ($IC_{50} = 2.677 \mu M$), **1b** ($IC_{50} = 3.051 \mu M$) against MCF-7 cancer cell line and **1a** ($IC_{50} = 1.270 \mu M$) against DU145 cancer cell line are more active than Vandetanib ($IC_{50} = 3.536, 1.974 \mu M$).

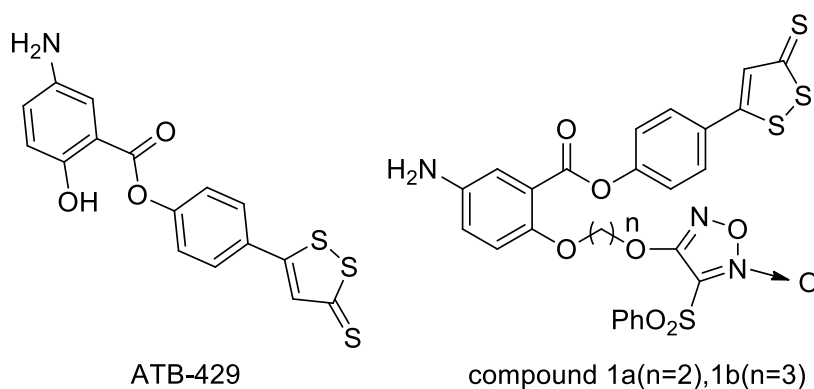


Figure 4. Structures of ATB-429 and compound **1a**, **1b**.

ACS15 is an H_2S donor-type derivative formed by the combination of diclofenac and ADTOH (Figure 5). Compared with diclofenac, it has better anti-inflammatory effects and less gastrointestinal adverse effects. ACS15 can release H_2S in vitro and in vivo, thus not only improving anti-inflammatory activity, but also significantly reducing the lung injury associated with pancreatitis [24]. Another study found that ACS 15 had anti-myocardial ischemia reperfusion injury activity, while diclofenac did not show this activity [25].

ATB-352 is an H_2S donor derivative obtained by the coupling of ketoprofen and ADTOH (Figure 5). Studies demonstrated that ATB-352 not only showed anti-inflammatory activity similar to ketoprofen, but also had almost no side effects on the gastrointestinal tract. It can be used for chemoprevention of tumors [26].

AVT-219 and AVT-18A (Figure 6) are NOSH drug complexes formed by combining naproxen and sulindac with ADTOH and NO donors [27]. Both AVT-219 and AVT-18A

maintain the anti-inflammatory and anti-platelet aggregation properties of naproxen and sulindac. However, the side effect of naproxen and sulindac on the gastrointestinal tract is reduced. These NOSH compounds also have the ability to inhibit the growth activity of many tumor cells, including colon cancer cells, breast cancer cells, and pancreatic cancer cells [28].

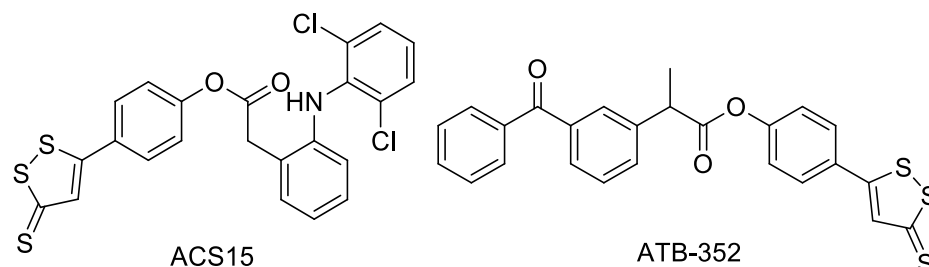


Figure 5. Structures of ACS15 and ATB-352.

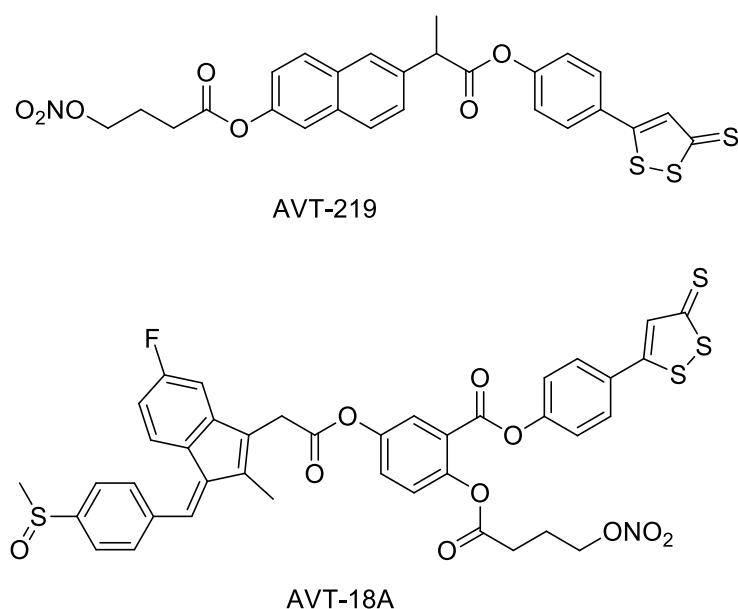


Figure 6. Structures of AVT-219 and AVT-18A.

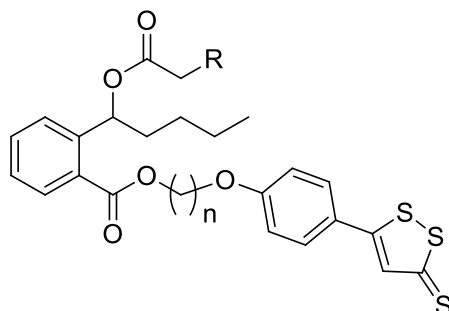
2.2. ADTOH–Butylphthalide Conjugates

Despite the wide range of drugs available for the clinical management of ischemic stroke, none have yet achieved satisfactory results in the treatment of ischemic stroke. Blocking multiple components of the pathophysiological development of cerebral ischemia is the key to treating this type of disease. For ischemic stroke, the appropriate amount of exogenous NO and H₂S supplementation can relax blood vessels, inhibit platelet aggregation, increase cerebral blood flow, and protect neuronal cells. On the other hand, supplementation of NO and H₂S can inhibit the expression of iNOS, which is beneficial for the prevention and treatment of ischaemic brain injury diseases. Therefore, research on NO and H₂S donor in anti-ischemic brain injury is a hot topic of current research [29,30].

Butylphthalide (NBP) is an effective stroke prevention drug. It inhibits platelet aggregation and reduces thrombosis and cerebral infarct volume. NBP can act on multiple pathological aspects of acute ischemic stroke through multiple targets, pathways, and links, and its clinical effects have been confirmed; however, it still has many shortcomings and needs to be developed further [31,32].

Wang et al. [33] synthesized a series of hydrogen sulfide-releasing derivatives by collocating butylphthalide with ADTOH and performed a biological evaluation of them (Figure 7). In vitro experiments, compound **2e** significantly inhibited adenosine diphos-

phate (ADP) and arachidonic acid (AA)-induced platelet aggregation, with better effects than NBP, ticlopidine hydrochloride and aspirin. In addition, **2e** produces moderate levels of H₂S slowly in vitro, which is beneficial for improving cardiovascular circulation. On top of that, **2e** has a protective effect on collagen and epinephrine-induced thrombosis in mice and exhibits stronger antithrombotic activity than NBP and aspirin in rats. In conclusion, **2e** has promising applications in the treatment of thrombosis-related ischemic strokes.



			ADP	AA
2a	R=H	n=2	IC ₅₀ =0.23± 0.09mM	0.15± 0.05mM
2b	R=H	n=3	IC ₅₀ =0.20± 0.11mM	0.14± 0.06mM
2c	R=H	n=4	IC ₅₀ =0.18± 0.10mM	0.14± 0.08mM
2d	R=H	n=5	IC ₅₀ =0.17± 0.13mM	0.15± 0.07mM
2e	R=H	n=6	IC ₅₀ =0.14± 0.06mM	0.09± 0.01mM
2f	R=H	n=8	IC ₅₀ =0.19± 0.14mM	0.16± 0.05mM
2g	R=H	n=12	IC ₅₀ =0.24± 0.12mM	0.20± 0.06mM
2h	R=di ethyl ami no	n=4	IC ₅₀ =0.23± 0.14mM	0.18± 0.03mM
2i	R=di ethyl a i no	n=5	IC ₅₀ =0.21± 0.13mM	0.17± 0.04mM
2g	R=di ethyl amno	n=6	IC ₅₀ =0.19± 0.11mM	0.15± 0.06mM
2k	R=N- met hyl pi perazi no	n=4	IC ₅₀ =0.71± 0.19mM	0.37± 0.10mM
2l	R=N- met hyl pi perazi no	n=5	IC ₅₀ =0.52± 0.17mM	0.23± 0.09mM
2m	R=N- met hyl pi perazi no	n=6	IC ₅₀ =0.49± 0.14mM	0.23± 0.08mM

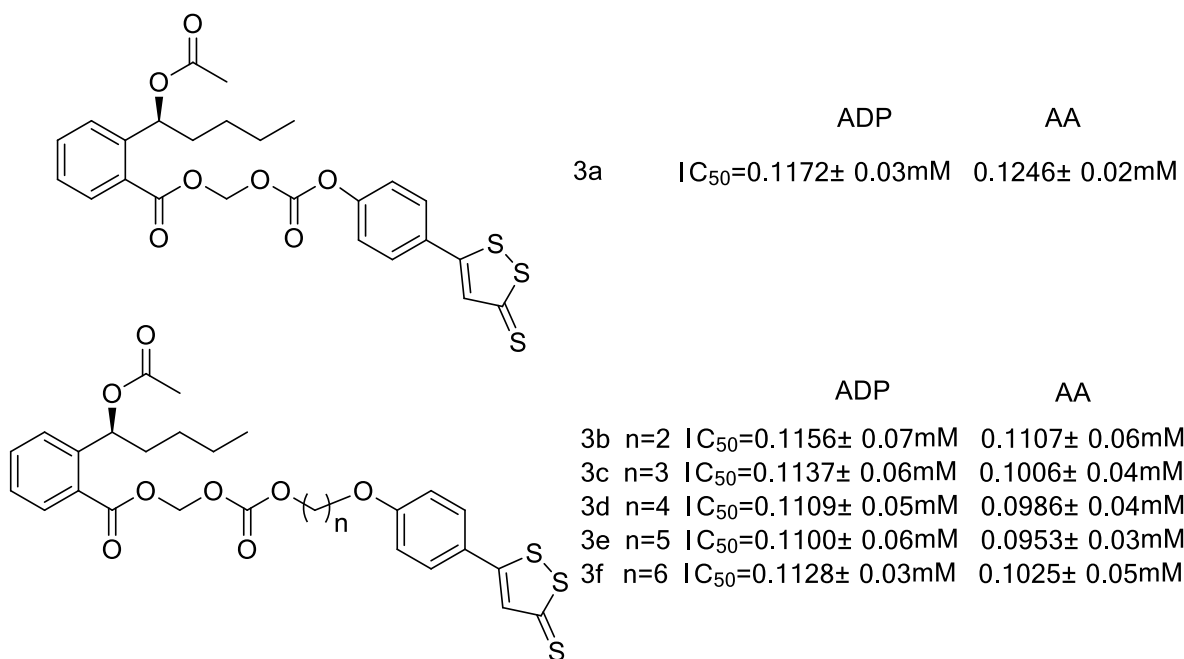


Figure 7. Structures of ADTOH–NBP conjugates.

Inspired by the above findings, Wang et al. [34] designed and synthesized a series of ADTOH-butylphthalide derivatives (Figure 7) by combining the ring-opening derivative of butylphthalide with ADTOH. Among them, compound 3e showed significantly better inhibitory activity than butylphthalide against platelet aggregation induced by adenosine diphosphate and arachidonic acid.

Additionally, Wang et al. [35,36] also synthesized a series of new NOSH-type compounds by combining butylphthalide with NO donors and ADTOH (Figure 8). Compared to butylphthalide parent, compound NOSH-NBP-5 has stronger anti-platelet aggregation activity and is capable of releasing both NO and H₂S, exerting a protective effect on cardiovascular and cerebral circulation.

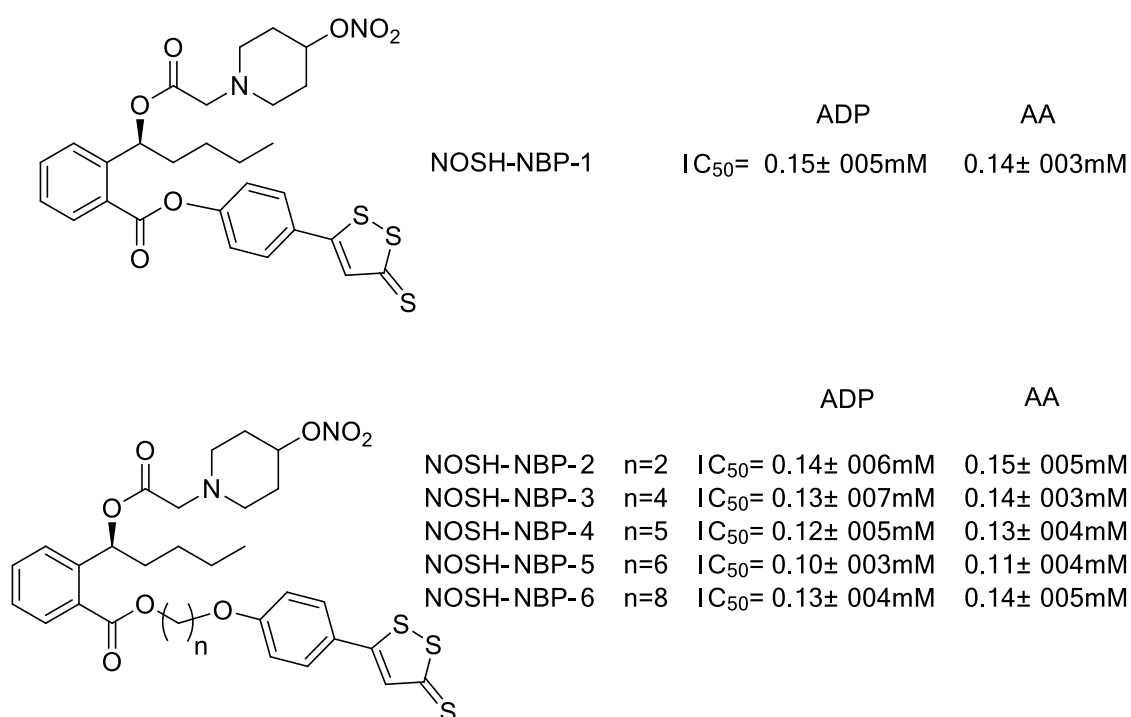


Figure 8. Structures of NOSH–NBP conjugates.

2.3. ADTOH–Niacin Conjugates

Niacin is known to be involved in lipid metabolism in the body, reducing plasma triglyceride and very low-density lipoprotein concentrations and increasing high density lipoprotein levels [37]. In addition, niacin has a vasodilating effect and is therefore commonly used clinically to treat hyperlipidemia, headaches, venous migraines, and cerebral artery thrombosis. Recent studies have shown that niacin can act as a neuroprotective agent in the treatment of stroke [38]. Therefore, the development of H₂S donor-nicotinic acid hybrids designed to exert a synergistic neuroprotective effect is considered as a potential therapeutic strategy for ischemic brain injury.

Sun et al. [39] synthesized a range of derivatives by combining nicotinic acid with ADTOH. Most of the compounds were found to exhibit significant neuroprotective effects. Among them, compound 4f (Figure 9) can significantly reduce the volume of cerebral infarction in the pMCAO model. The results suggest that such compounds have promising applications in the interventional treatment of cerebral ischemic injury.

2.4. ADTOH–Levodopa Conjugates

Levodopa (L-DOPA) is currently an important drug in the treatment of Parkinson's syndrome, but it only replenishes dopamine levels in the brain and does not inhibit the progression of the disease. Lee et al. [14] have combined L-DOPA with ADTOH to obtain a series of H₂S-releasing derivatives (compounds ACS83 to ACS86, Figure 10). These

derivatives not only can release dopamine but also protect nerves, and have antioxidant effects. Research has shown that ACS84 can avoid β -amyloid-induced neuronal cell damage through anti-inflammatory effects, and protect mitochondrial in p38- and JNK-mediated stress responses. Thus, ACS84 has the potential to treat neurodegenerative diseases [40].

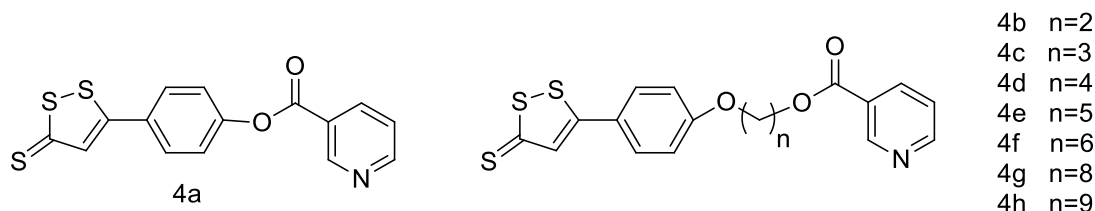


Figure 9. Structures of ADTOH–niacin conjugates.

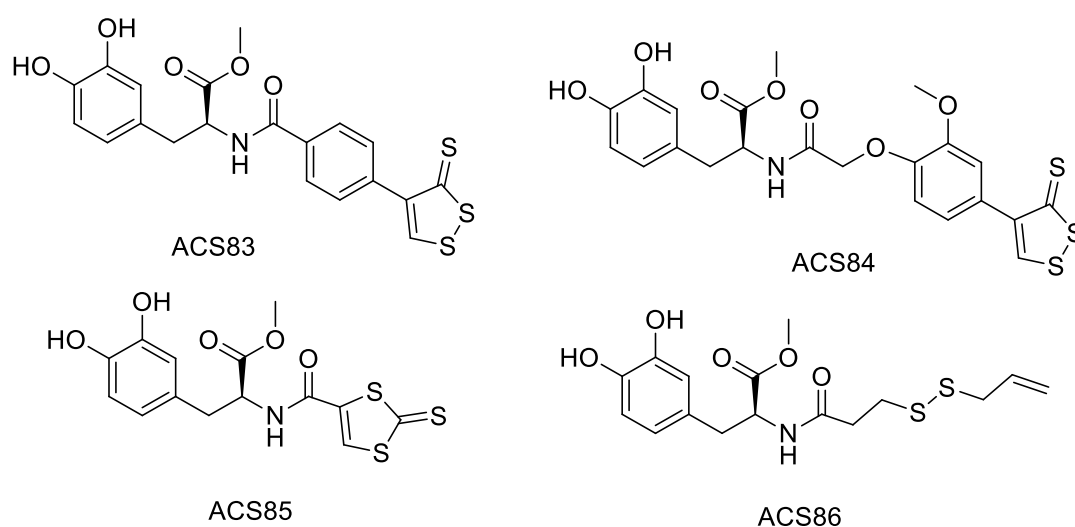


Figure 10. Structures of ADTOH–levodopa conjugates.

2.5. ADTOH–Doxorubicin Conjugates

Doxorubicin is one of the most clinically effective antitumor agents, but cardiotoxicity and drug resistance limit its clinical use. In order to design doxorubicin derivatives with low cardiotoxicity and resistance, Chegaev et al. [41] used doxorubicin as a parent for conjugating with different hydrogen sulfide donors to obtain a series of compounds that can release hydrogen sulfide (compound **5b** and **5d**, Figure 11). It was found that all of these compounds reduced oxidative stress in cardiomyocytes, and some of them showed stronger activity in sarcoma cell lines. Unlike doxorubicin, most of the products are non-toxic to H9c2 cells at 5 μ M concentration and have potential for further research and development.

2.6. ADTOH–Latanoprost Conjugate

Latanoprost (Xalatan) is an inactive but rapidly penetrating substance in the cornea, which can be hydrolyzed to active free acid in the cornea and plasma, increasing the outflow of atrial water through the corneal layer and having a good IOP lowering effect. Perrino et al. [42] designed and synthesized a hybrid (ACS 67, Figure 12) by combining latanoprost acid with ADTOH. Experimental data showed that this compound could increase the production of glutathione in the atrial fluid of rabbit eyes, antagonize the oxidative damage of hydrogen peroxide on the neuronal cells in the fundus, and thus alleviate the retinal ischemic damage, with significant optic neuroprotective effect. It has a significant effect on the treatment of glaucoma [43]. In addition, it has been found that ACS67 can inhibit L-type Ca^{2+} channels and reduce L-type voltage-dependent Ca^{2+} channel currents in pancreatic β -cells, thereby inhibiting insulin secretion, but the inhibitory effect is lower than that of NaHS [44].

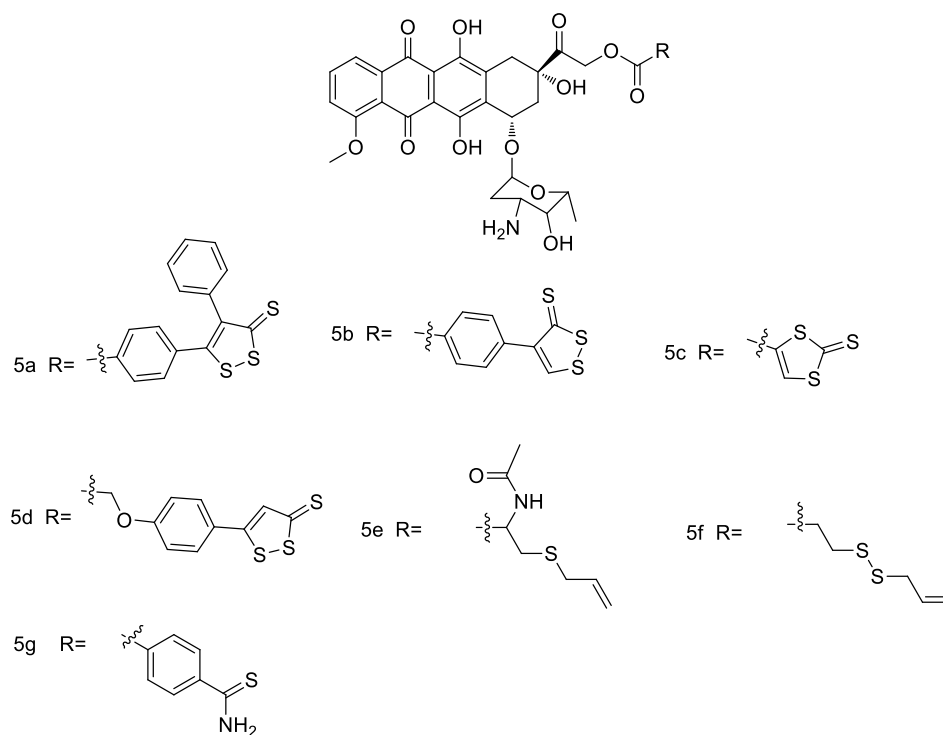


Figure 11. Structures of ADTOH–doxorubicin conjugates.

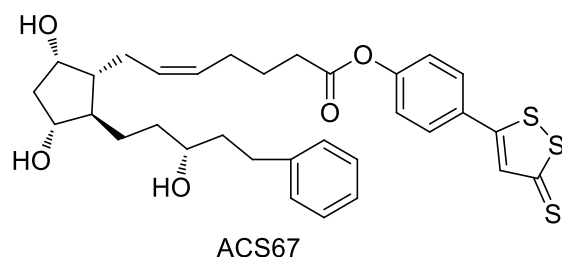


Figure 12. Structure of ACS67.

2.7. ADTOH–Monastrol Conjugate

Monastrol, a mitotic kinesin inhibitor with potent and cell-permeable properties, was reported as an anti-cancer inhibitor back in the 1990s. Recent studies have shown that monastrol also has calcium channel blocker effects. Considering that H₂S also has some calcium channel blocking effect, Braga et al. [45] designed and synthesized a Monastrol–ADTOH hybrid (MADTOH, Figure 13) using a conjugate strategy. Compared to monastrol, this compound was effective in reducing the overall calcium transient amplitude in cardiac myocytes via L-type calcium channels. Most notably, the intermediates ADTOH and monastrol were less effective than the hybrid MADTOH in controlling Ca²⁺ homeostasis. Overall, ADTOH hybridized with calcium channel blockers has a wide range of applications in the discovery of suitable calcium channel blockers.

2.8. ADTOH–Proglumide Conjugate

Atherosclerosis is a common cardiovascular disease. H₂S has important physiological functions in atherosclerotic lesions, and many H₂S donors have been synthesized to study atherosclerosis diseases. Proglumide can reduce the release of cytokines and inflammatory mediators in acute pancreatitis by inhibiting the activation of the NF-κB pathway. Considering that one of the etiologies of atherosclerotic disease is related to inflammation, Ou et al. [46] combined Proglumide with ADTOH to create a hybrid PA (Figure 14). Studies demonstrated that PA is a novel slow-releasing H₂S donor and shows anti-atherosclerotic

positive effect on this disease. Considering that an improved pharmacological activity and a reduced toxicity can be obtained through hybridization, Giordano et al. [50] designed and synthesized novel betamethasone and triamcinolone hybrids with H₂S-donors (Figure 16). These synthesized compounds have potential H₂S-releasing characteristics both in a cell-free environment and into the cytosol of BSMCs (bronchial smooth muscle cells). Among them, the most promising derivatives 6b and 6f have significant inhibitory effect on mast cell degranulation, resulting in a reduction of β -hexosaminidase release more efficiently than the corresponding parent drugs.

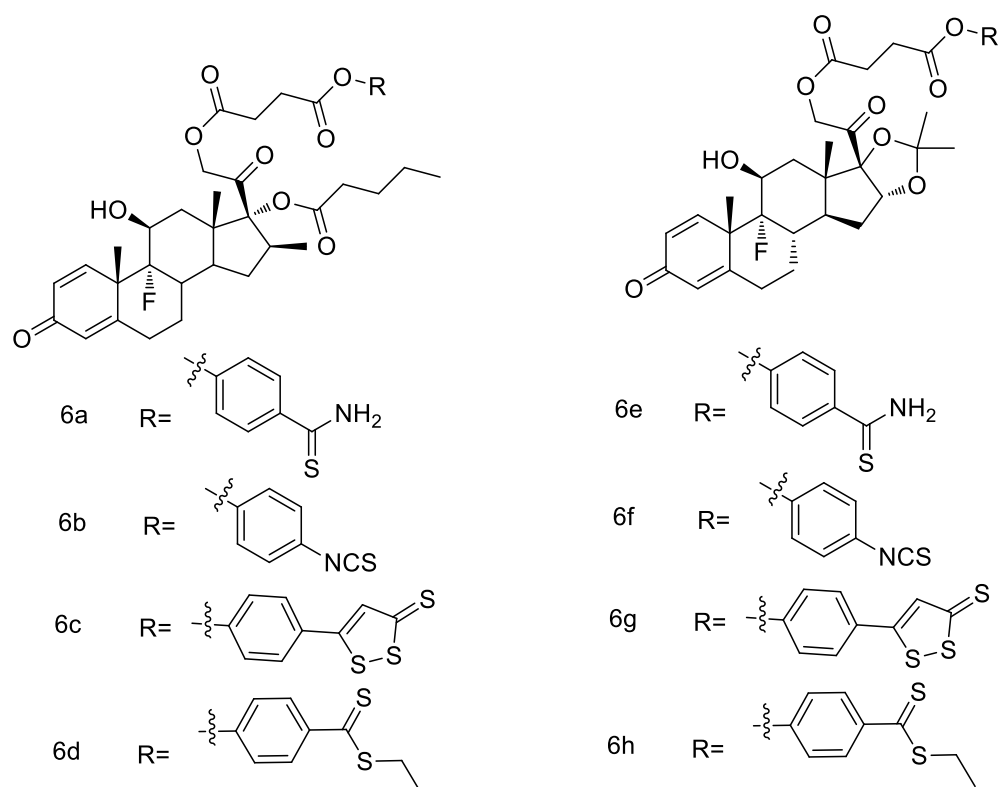


Figure 16. Structures of betamethasone and triamcinolone conjugates.

Additionally, Corvino et al. [51] also synthesized a series of novel prednisone and dexamethasone hybrids with two H₂S-donors (Figure 17). The chemical stability of the synthesized hybrids has been investigated at differing pH values and in human serum. The results show that these hybrids have a prolonged chemical stability both at acidic and physiological pH. Among them, compound 7c was more effective than prednisone in inhibiting mast cell degranulation and in promoting BSMCs membrane hyperpolarization. Due to the protective effect on airway remodeling, compound 7c can be a potentially useful therapeutic option for allergic asthma treatment.

Compound 8, a hybrid of dexamethasone and H₂S-donor moiety [52], is used to treat ocular diseases (Figure 18). Compound 8 has the ability to completely inhibit oxidative stress-induced glutathione depletion. This design not only eliminated the side effects associated with the parent compound, but also improved pharmacological effects.

2.11. ADTOH–Atorvastatin Conjugates

Atorvastatin is an HMG-CoA reductase inhibitor that reduces plasma cholesterol and lipoprotein levels. Tong et al. [53] designed and synthesized a series of atorvastatin–ADTOH hybrids (Figure 19). Compared with the parent drug atorvastatin, these compounds showed good activity of regulating blood lipids and anti-inflammatory and antioxidant properties. The results showed that these compounds have high application value in regulating blood lipids and vascular protection.

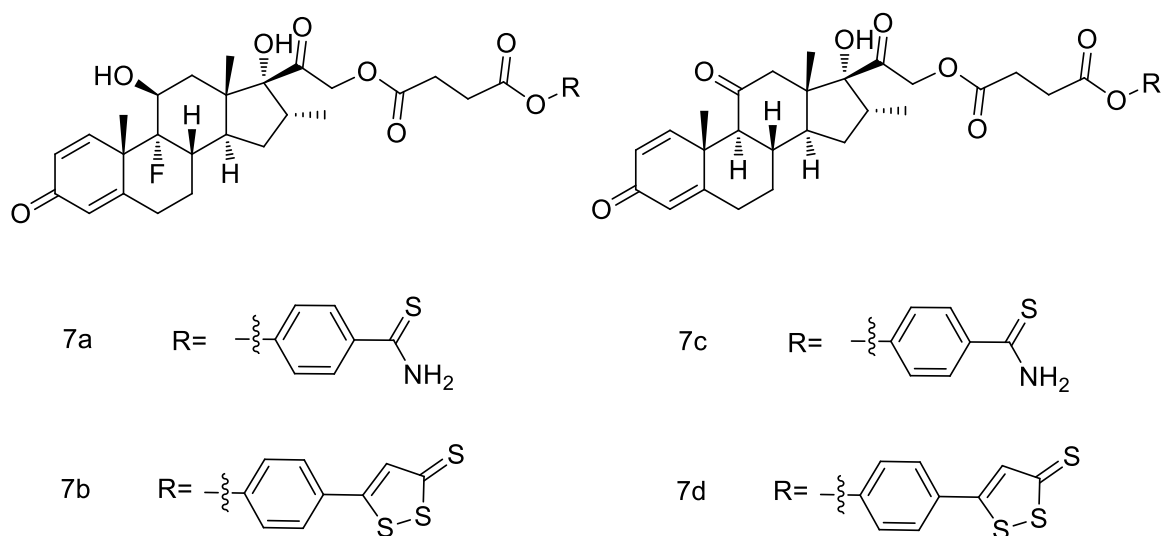


Figure 17. Structures of prednisone and dexamethasone conjugates.

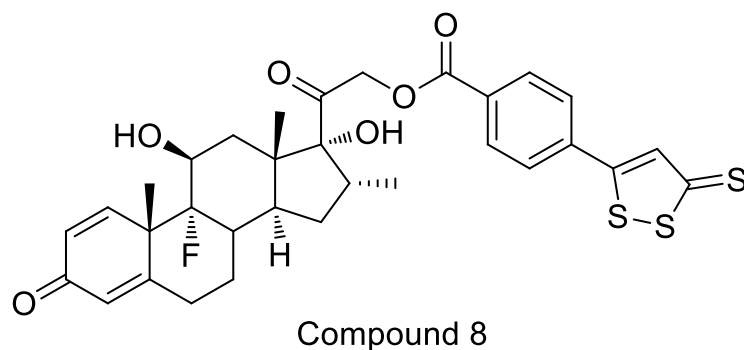


Figure 18. Structure of compound 8.

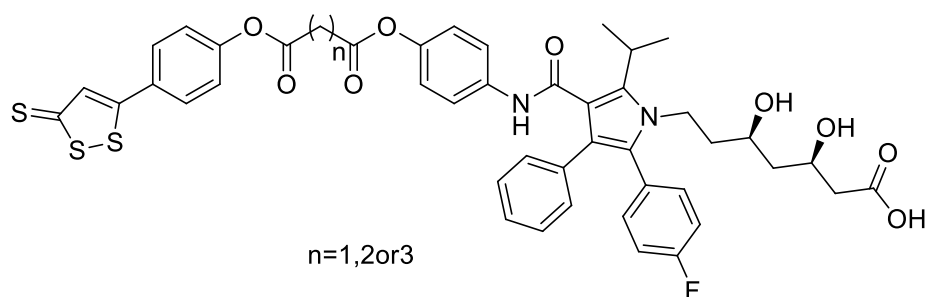


Figure 19. Structures of ADTOH–atorvastatin conjugates.

2.12. ADTOH–Pentacyclic Triterpene Conjugates

Oleanolic acid, ursolic acid, and glycyrrhetic acid are the active ingredients of herbal medicines, belonging to pentacyclic triterpenes, which have been deeply researched for their various biological activities. Sheng et al. [54] attached the hydrogen sulfide donors to oleanolic acid, ursolic acid, and glycyrrhetic acid to afford series of pentacyclic triterpenes- H_2S donor hybrids (Figure 20). The anti-proliferation activity of these hybrids on the tested cell lines was evaluated by MTT assay. The results showed that most of these pentacyclic triterpenes- H_2S donor hybrids exhibited no anti-proliferation activity against tested cell lines. Therefore, it is not suitable to hybridize hydrogen sulfide donors with oleanolic acid, ursolic acid, and glycyrrhetic acid in anti-tumor applications.

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