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Review

Research progress of 3-*n*-butylphthalide and its derivatives in combating cerebral ischemia

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ABSTRACT

Ischemic stroke (IS) presents a major threat to human life and health due to its high disability and mortality rates. 3-*n*-Butylphthalide (NBP), derived from celery seeds of the Apiaceae family native to the Mediterranean region, was first introduced in China for acute IS treatment in 2004. NBP demonstrates multiple therapeutic actions, including reconstruction of microcirculation in the cerebral ischemia area, inhibition of platelet aggregation, reduction of cerebral infarction volume, maintenance of blood-brain barrier (BBB) integrity, and enhancement of cerebral blood perfusion. However, its overall efficacy remains moderate, limited by poor water solubility and low bioavailability, which constrains its clinical application. To address these limitations, researchers have actively pursued the development of NBP derivatives and analogs, achieving notable progress. These efforts, including substituent introduction, ring opening derivatization, esterification, and atom substitution, have generated diverse NBP derivatives. Several of these derivatives have advanced to clinical studies. Specifically, potassium 2-(1-hydroxypentyl)-benzoate (PHPB), brozopentyl sodium (BZP), and XY-03-EA (ZONK1103) have reached phase II clinical trials, while (*S*)-2-(1-acetoxypentyl)benzoic acid L-arginine salt (AAPB) has received clinical trial approval for 2024. This review examines the structural modification and optimization of NBP over the past two decades from a medicinal chemistry perspective, aiming to facilitate the development of superior derivatives and advance cerebral ischemia treatment.

1. Introduction

The American Heart Association/American Stroke Association define stroke in the 21st century as a neurological deficit caused by acute focal injury to the central nervous system (CNS), primarily encompassing cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) [1]. World Health Organization (WHO) statistics indicate that approximately 15 million people worldwide experience a stroke annually, with 5 million fatalities and another 5 million suffering permanent disability [2]. Significantly, approximately 85% of strokes result from cerebral arterial embolism or thrombosis, leading to cerebral ischemia [3, 4]. Cerebral ischemia involves reduced cerebral blood flow that initiates complex metabolic and pathological cellular responses, ultimately causing neuronal cell death and cerebral infarction, manifesting clinically as ischemic stroke (IS) [5-7]. Following IS onset, substantial reactive oxygen species (ROS) accumulation occurs in brain tissue, causing oxidative damage to endothelial cells in cerebral microvessels and neurons, triggering inflammatory cascades that further aggravate brain injury [8]. Hydrogen peroxide (H_2O_2), a significant ROS family component, emerges as a potential biomarker for stroke evaluation [9]. Beyond neuronal death, ischemic injury typically involves complex pathophysiological mechanisms, including excitotoxicity, mitochondrial dysfunction, and blood-brain barrier (BBB) impairment [10, 11].

Treatment options for stroke remain limited. Primary interventions include intravenous thrombolysis using tissue plasminogen activator (tPA) and mechanical thrombectomy [12, 13]. However, the narrow therapeutic window limits thrombolysis efficacy. Moreover, while thrombolysis and mechanical thrombectomy prevent ischemic injury, they neither address inflammation-induced damage during reperfusion nor promote lost neuron regeneration [14]. Therefore, developing novel, safe, and effective therapeutic agents for cerebral ischemia, particularly those with neuroprotective properties, remains critically important.

Natural products, characterized by complex organic molecules with unique scaffolds, constitute a valuable resource for drug development [15-17]. These compounds offer numerous advantages, including diverse sources, multi-target effects, low toxicity, and consistent therapeutic efficacy [18, 19]. Consequently, screening active components from natural products represents a

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promising research direction. Notably, numerous natural products demonstrate beneficial effects on stroke. Research into compounds such as 3-*n*-butylphthalide (NBP), ligustrazine (TMP), ferulic acid (FA), and tanshinone IIA has revealed distinct pharmacological properties and biological activities [20-23]. These compounds show significant potential for clinical applications and may provide additional strategies for treating cerebral ischemia.

2. Brief overview of NBP

NBP, a synthetic compound derived from celery seed extract (a native plant of the Apiaceae family originating from the Mediterranean), appears as a colorless or light yellow viscous liquid with a distinctive celery odor (Fig. 1) [24, 25]. Its chemical nomenclature is (±)3-butyl-3*H*-2-benzonfuran-1-one. Classified as a neuroprotective agent and cerebral blood flow enhancer, NBP has attracted considerable interest in the pharmaceutical field and demonstrates beneficial effects across multiple CNS disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and cerebral ischemia [26, 27].

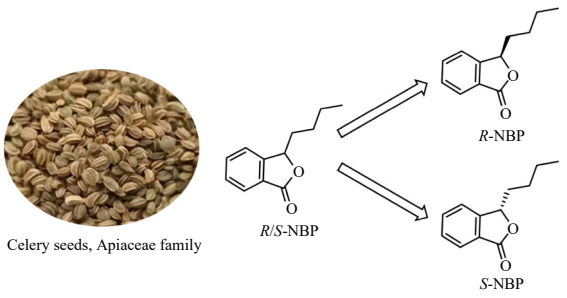


Fig. 1 The chemical structures of NBP and its two enantiomers.

NBP molecules contain a chiral carbon atom, resulting in two enantiomers, *R*- and *S*-NBP (Fig. 1). Studies demonstrate that both enantiomers and NBP exhibit dose-dependent inhibition of platelet aggregation and experimental thrombosis. Notably, *S*-NBP displays significant biological activity, including suppression of inflammatory response, reduction of cell apoptosis, enhancement of mitochondrial function, protection of brain microcirculation and neuroprotective effects, making it appropriate for acute cerebral ischemia treatment and secondary prevention [28, 29]. At 100 mg·kg^{-1}, *S*-NBP inhibited platelet aggregation induced by adenosine diphosphate (ADP), collagen (COL), and arachidonic acid (AA) by 49%, 67%, and 86%, respectively, while aspirin at equivalent dosage inhibited aggregation by 19%, 48%, and 100%, respectively [30]. The chiral resolution of NBP establishes a foundation for developing its chiral derivatives and analogs with improved activity or water solubility.

2.1. Action targets

Multiple studies confirm that NBP demonstrates beneficial effects on various pathophysiological pathways following stroke, including enhancement of microcirculation, mitochondrial function, and energy metabolism, reduction of oxidative damage and intracellular calcium levels, and inhibition of apoptosis. Notably, NBP demonstrates the ability to inhibit platelet aggregation and reduce thrombus formation [31, 32]. Recent studies have revealed that p53, NQO1, and indoleamine 2,3-dioxygenase may serve as direct binding targets of NBP [33]. However, its precise molecular mechanism requires further investigation.

2.2. Clinical application

Since the late 1980s, NBP research has focused primarily on cerebral ischemia. Decades of comprehensive research have demonstrated the therapeutic efficacy of NBP in treating cerebral ischemia. In 2002, NBP received approval from the National Medical Products Administration (NMPA) for acute IS treatment [34]. In 2010, it was included among the recommended drugs in the China Stroke Management Guidelines. Furthermore, the phase II clinical trial of NBP soft capsules for treating stroke patients received FDA approval in 2017 (NCT02905565), primarily aiming to evaluate NBP treatment safety in patients with mild to moderate acute IS.

2.3. In vivo metabolism

NBP undergoes metabolism by various human P450 enzymes following oral administration [35, 36]. The primary metabolic pathways involve hydroxylation of the alkyl side chains, particularly at the 3-, ω-1-, and ω-carbons, followed by oxidation and conjugation. The predominant circulating metabolites identified are 10-hydroxy-NBP (**1**, 10-OH-NBP) and 3-OH-NBP (Fig. 2), with their area under the concentration-time curve (AUC) being 10.3 and 2.9 times greater than that of NBP, respectively. After normalization for intrinsic abundance in the liver, CYP2E1 emerges as the most active enzyme in **1** formation, followed by CYP2B6 and CYP2C19. Meanwhile, CYP3A4 functions as the principal enzyme responsible for 3-OH-NBP generation, with CYP2E1 and CYP3A5 as secondary contributors. Among these, **1** demonstrates superior BBB penetration compared to 3-OH-NBP. Diao et al. reported that AUC of **1** in rat brain and plasma was 8.47 times and 0.22 times that of 3-OH-NBP, respectively [37].

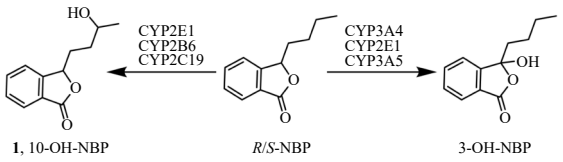


Fig. 2 The two major *in vivo* metabolites of NBP.

2.4. Deficiencies and shortcomings

Although NBP has demonstrated considerable success in treating cerebral ischemia, its effectiveness as a standalone therapy remains suboptimal. Clinical practice often requires combining NBP with antioxidants or antiplatelet agents (such as aspirin and edaravone) to maximize therapeutic outcomes [38, 39]. Furthermore, NBP's limited water solubility and low bioavailability significantly restrict its widespread clinical application in acute cerebral ischemia treatment. The compound's oily characteristics also present challenges in preparation and storage [40].

3. NBP derivatives: research updates

Considering NBP's important role in cerebral ischemia treatment and its inherent limitations, researchers have focused on structural modifications in recent years to enhance its physicochemical properties and therapeutic efficacy. Current modification strategies primarily include substituent introduction, ring opening derivatization, esterification, and atom substitution, yielding several promising NBP derivatives. Notably, among these derivatives, several have shown substantial promise in treating cerebral ischemia (Table S1). Potassium 2-(1-hydroxypentyl)-benzoate (PHPB), brozopentyl sodium (BZP), and XY-03-EA (ZONK1103) have advanced to phase II clinical trials, while (*S*)-2-(1-acetoxypentyl)benzoic acid L-arginine salt (AAPB) has received approval for clinical evaluation in 2024.

Through various structural modification strategies, numer-

ous NBP derivatives have demonstrated enhanced pharmacokinetic (PK) and pharmacodynamic properties. From a medicinal chemistry perspective, these derivatives can be categorized based on their structural differences, including substituted derivatives, ring-opening derivatives, hybrids of ring-opening NBP and active molecules, gas-donating derivatives, and NBP analogues. This review examines their design rationale, strategies, *in vitro* and *in vivo* activities, and potential therapeutic applications.

3.1. Substituted derivatives

Through asymmetric synthesis, Wang et al. developed two optical enantiomers of **1**, compounds **1a** and **1b** [41]. *In vivo* experiments demonstrated that **1b** effectively ameliorated cerebral ischemia symptoms and reduced cerebral infarction volume in ischemic rats, while **1a** showed no such effect. To address the poor water solubility of **1b**, they esterified it with succinic acid and salified the free carboxylic acid to obtain ZONK1103 (**2**) (Fig. 3). When administered *via* injection, **2** significantly reduced cerebral infarction volume with slightly higher activity than **1b**. Notably, compound **2** is currently undergoing phase II clinical trials in China (NCT05515393).

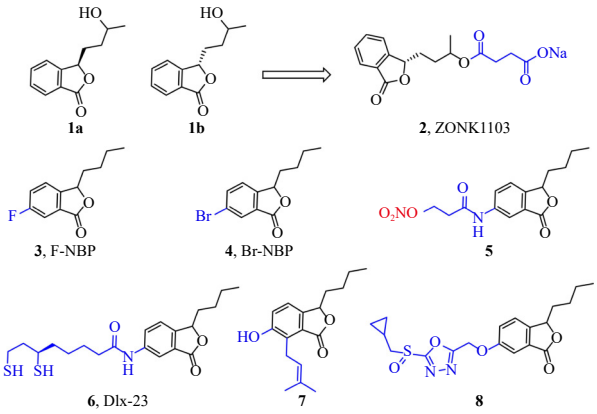


Fig. 3 The chemical structures of NBP derivatives by substituent introduction.

In 2010, Wang et al. synthesized halogenated derivatives by substituting the C-6 position of NBP with fluoride or bromine atom, producing 6-fluorine-NBP (**3**, F-NBP) and 6-bromo-NBP (**4**, Br-NBP) (Fig. 3) [42]. These compounds demonstrated *in vitro* vasodilatory effects in rat thoracic aorta induced by adrenaline in a dose-dependent manner, showing superior efficacy compared to NBP. Acute toxicity experiments revealed that **4** exhibited enhanced biological safety, with a median lethal dosage (LD_{50}) exceeding 1000 mg·kg^{-1}, surpassing both **3** (LD_{50} 750.89 mg·kg^{-1}) and NBP (LD_{50} 592.93 mg·kg^{-1}). That same year, Gao et al. discovered that **4** could ameliorate H_2O_2-induced oxidation and apoptosis in PC12 cells [43]. This protective mechanism involved inhibiting lipid peroxidation and ROS formation, restoring mitochondrial membrane potential, and reducing intracellular calcium ion concentration. Similarly, Xu et al. confirmed that **3** provided protection against H_2O_2-induced cytotoxicity by inhibiting ROS overproduction and reducing nitric oxide (NO) levels and nitric oxide synthase (NOS) activity [44].

NO, an essential endogenous free radical gas, plays a crucial role in modulating physiological functions. Appropriate levels of NO enhance cerebral circulation, dilate blood vessels, and protect nerves. Recent research has identified NO donor-type molecules that mimic endothelial nitric oxide synthase (eNOS)-produced NO as a promising strategy for IS treatment [45, 46]. In 2013, Wang et al. developed NBP derivative **5** by conjugating 6-amino-NBP with an NO donor moiety (Fig. 3) [47]. Notably, **5** demonstrated significantly increased water solubility of 1.18 mmol·L^{-1}, compared to NBP's 0.54 mmol·L^{-1}. *In vitro* studies revealed that **5** (30.42% at 0.1 mmol·L^{-1}) exhibited superior inhibitory effects on ADP-induced platelet aggregation in rabbit platelet-rich plasma (PRP) compared to clinical anti-IS drugs NBP (15.72%) and Ticlid (26.45%) at equivalent concentrations. While 6-amino-NBP (18.43%) and the NO donor fragment (8.32%) showed some antiplatelet activity, their efficacy was lower than **5**, suggesting potential synergistic inhibition. The release of optimal NO levels (12.88 μmol·L^{-1}) by **5** proved crucial for its antiplatelet function, as demonstrated by significant attenuation of its inhibitory effect (from 30.42% to 23.05%) upon treatment with endogenous NO scavenger hemoglobin.

α-Lipoic acid (ALA), a natural antioxidant, has demonstrated neuroprotective effects in both *in vitro* and *in vivo* models [48-50]. In 2020, Uppakara et al. developed a novel bifunctional conjugate, Dlx-23 (**6**), by combining ALA and 6-amino-NBP (Fig. 3) [51]. Compared to the parent compound ALA, **6** showed enhanced neuroprotective effects against H_2O_2-induced cell death. *In vitro*, **6** exhibited significant antioxidant activity, demonstrating a 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging capacity of 91.4% at 200 μmol·L^{-1}, a characteristic not present in ALA. Additionally, **6** strengthened endogenous antioxidant systems by reducing ROS accumulation and protected against oxidative stress-induced neuronal death. The multiple beneficial properties demonstrated by **6** suggest its potential as an antioxidant and indicate promise for development as a novel neuroprotective agent.

Given the notable activities of natural products containing the isopentenylphenol framework in antiplatelet aggregation, antioxidant, and neuroprotective aspects [52], Yu et al. combined isopentenylphenol with NBP to create NBP-isopentenylphenol derivative **7** in 2022 (Fig. 3) [53]. Compared to NBP [half maximal inhibitory concentration (IC_{50}) 318.8 μmol·L^{-1}] and ASP (IC_{50} 75.3 μmol·L^{-1}), compound **7** demonstrated more potent inhibitory effects against AA-induced platelet aggregation (IC_{50} 68.3 μmol·L^{-1}). In the tail thrombosis model, at a dose of 15 mg·kg^{-1}, **7** reduced the length of mouse tail thrombus by 51.4%, exceeding the effect of NBP (78.0%). Furthermore, hematoxylin-eosin (HE) staining revealed that **7** possessed excellent thrombolytic and vasodilatory effects. In a rat model of transient focal cerebral ischemia, **7** significantly reduced infarct size (from 23.6% to 5.9%), demonstrating substantial protective effects against cerebral ischemia-reperfusion. Additional PK analysis indicated that the favorable absorption properties and metabolic stability of **7** contributed to good bioavailability *in vivo*. These findings suggest that **7** represents a promising candidate for cerebral ischemia therapy.

In 2023, Yu et al. designed and synthesized hybrid compound **8** by incorporating 1,3,4-oxadia zole and sulfoxide moieties (Fig. 3) [54]. **8** exhibited potent inhibition of AA-induced platelet aggregation, with an IC_{50} of 19.9 μmol·L^{-1}, superior to NBP (IC_{50} 318.8 μmol·L^{-1}) and ASP (IC_{50} 75.3 μmol·L^{-1}). Compared to its precursor NBP, intraperitoneal administration of **8** demonstrated enhanced antithrombotic activity and improved protection against ischemic brain injury. PK, hepatic microsomal stability, and parallel artificial membrane permeability assay for BBB (PAMPA-BBB) assays revealed that **8** possessed high bioavailability, metabolic stability, and BBB permeability. Additionally, molecular docking results indicated that **8** formed strong interactions with key residues of the P2Y12 receptor. These findings highlight the potential of **8** as a promising therapeutic agent for IS.

3.2. Ring-opening derivatives

Due to its hydrophobic properties, NBP is unsuitable for intravenous administration. In 2006, Yang et al. first synthesized HPBA (**9**) and its potassium salt compound PHPB (**10**) by open-

ing the lactone ring of NBP (Fig. 4) [55]. Zhang et al. demonstrated that **10** reduced platelet aggregation induced by ADP, AA, and COL in a dose-dependent manner, with inhibitory effects comparable to NBP or ASP [56]. The inhibition of platelet aggregation peaked at 1 h after oral administration or 30 min following intravenous injection. When introduced into plasma at concentrations of 6, 30, and 60 μg·mL^{-1}, approximately 70% of **10** transformed into *R*/*S*-NBP within 5 min [57]. In a rat model simulating 2-h middle cerebral artery occlusion (MCAO) followed by 24 h reperfusion, **10** (1.3, 3.9, and 12.9 mg·kg^{-1}) significantly reduced infarct volumes dose-dependently, decreasing from 37.4% in controls to 25.4%, 17.4%, and 13.7%, respectively, demonstrating efficacy parallel to NBP. Neurobehavioral tests revealed improved neuronal deficits, with scores decreasing from 3.2 in controls to 2.7, 2.1, and 1.8 with **10** treatment. Additionally, **10** reduced thrombus formation in an *in vivo* arteriovenous shunt model [56]. These findings highlight **10**'s therapeutic potential in stroke management. Currently, it has entered phase II clinical trial (CTR 20181494) in China.

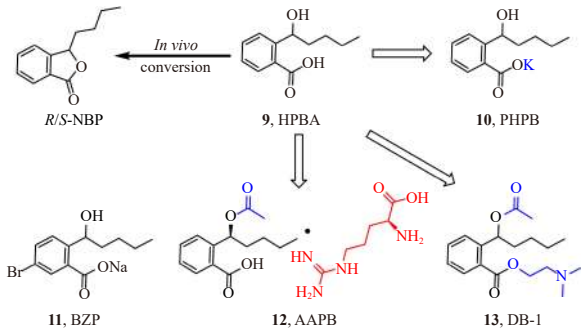


Fig. 4 The chemical structures of NBP ring-opening derivatives.

Considering the notable vasodilatory, antioxidant, and antiapoptotic properties of compound **4** , Tian et al. synthesized its ring-opened product's water-soluble sodium salt (**11**, BZP) to enhance solubility (Fig. 4) [58]. **11** converts to compound **4** both *in vivo* and *in vitro* [59]. Research has shown that **11** demonstrates therapeutic and preventive effects on stroke in Dahl-SS hypertensive rats, likely through antioxidant, antiplatelet aggregation, and antithrombotic mechanisms. Furthermore, **11** exhibited enhanced PK and biosafety compared to compound **4** . Pharmacodynamic studies indicated that **11** protects neurological function post-MCAO in rats *via* the NF-κB pathway and mitochondrial apoptosis pathway, reducing infarct volume dose-dependently. Additionally, **11** significantly improved neurological deficits in rats and demonstrated neuroprotective effects on permanent focal cerebral ischemia [60, 61]. BZP represents a significant advancement in addressing unmet medical needs and has progressed to phase II clinical trial (CTR20192145) in China.

Research indicates that L-arginine (L-Arg) converts to NO through NOS or non-enzymatic pathways *in vivo*, providing protection against cerebral ischemia [62]. Cerebroventricular L-Arg injection significantly reduces neuronal death in rats with ischemia-reperfusion injury (IRI) and promotes functional recovery [63]. Employing a multi-targeted strategy, Zhang et al. isolated the *S*-enantiomer of **9**, esterified its hydroxyl groups, and reacted it with L-Arg to form salts, synthesizing NBP derivative AAPB (**12**) (Fig. 4) [64]. As a prodrug, **12** effectively converts to *S*-NBP and L-Arg *in vivo*, producing synergistic anticerebral ischemia effects. Compared to *S*-NBP, **12** showed significantly improved solubility at 136.17 mg·mL^{-1}. In rat arteriovenous bypass thrombosis models, **12**'s inhibitory effect on thrombosis formation exceeded equivalent doses of aspirin, *S*-NBP and edaravone. Notably, **12**'s inhibitory effects on cerebral infarction and edema, and improvement of neurological function surpassed both combined administration of its components and equivalent doses of *S*-NBP and edaravone. Furthermore, **12** demonstrated excellent PK properties and safety, establishing it as a promising agent against IS. Significantly, **12** for injection has received tacit approval for clinical trials in 2024.

To enhance the BBB penetration ability of NBP, Xiang et al. synthesized its prodrug (**13**, DB-1) by esterifying the hydroxyl group of **9** and introducing *N*,*N*-dimethylethanolamine at the carboxyl group in 2021 (Fig. 4) [65]. **13** demonstrated significantly enhanced solubility and cellular uptake, potentially mediated by the pyridineamine cation transporter. Compared to unmodified NBP, intravenous administration of **13** achieved a notable 10.9-fold increase in brain accumulation in mice within 5 min, suggesting improved brain bioavailability facilitated by the added amino group. **13** exhibited superior anti-ischemic and neuroprotective effects compared to equivalent concentrations of NBP. In the MCAO surgical rat model, **13** extended the survival time, with median survival reaching 8 d versus 5.5 d for NBP, while significantly reducing cerebral infarction area and brain water content. This prodrug shows promise as a candidate for IS treatment, and this modification approach may be applicable to other CNS diseases.

3.3. Hybrids of ring-opening NBP and active molecules

Given the complex pathophysiology of IS, monotherapy often encounters limitations such as insufficient efficacy or drug resistance [66]. Therefore, hybrid multitargeting prodrugs combining mechanisms of multiple drugs can address the limitations of conventional single-drug approaches. This strategy enables more effective management of the complex pathophysiological processes in cerebral ischemia, leading to improved therapeutic outcomes for IS.

As a novel antioxidant, edaravone received approval from the Japanese Ministry of Health for IS treatment in 2001. It reduces oxidative damage to brain, endothelial, and neuronal cells by scavenging free radicals and inhibiting lipid peroxidation, thereby decreasing brain ischemia and edema [67-69]. In 2015, Sheng et al. developed and synthesized hybrid (**14**, FMPB) by combining NBP and edaravone analogues (Fig. 5) [70]. **14** demonstrated inhibition rates of 31.80% and 59.87% against ADP- and AA-induced platelet aggregation, respectively, exceeding the combined effects of NBP and edaravone (28.06% and 42.45%). Furthermore, **14** exhibited free radical scavenging activity, effectively inhibiting H_2O_2-mediated apoptosis of PC12 neuronal cells, with enhanced cell survival (93.33%), surpassing NBP (71.01%), edaravone (76.89%), and their combination (76.60%). These results indicate that the inhibition of ADP- or AA-induced platelet ag-

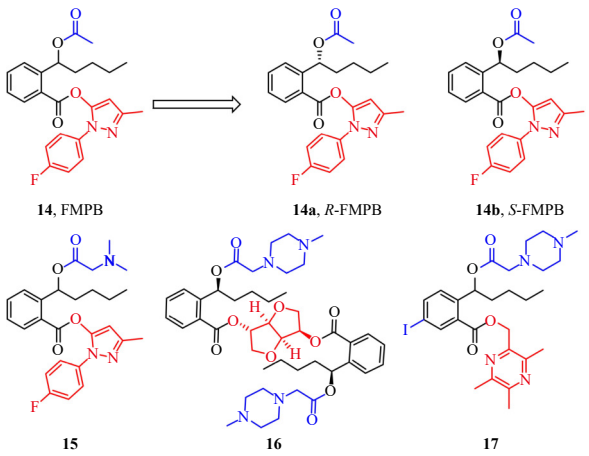


Fig. 5 The chemical structures of ring-opening NBP hybrids.

gregation *ex vivo* and protection against H_2O_2-induced cellular damage may result from synergistic effects of its components. **14** represents a promising intervention for IS, establishing a novel class of therapeutic candidates based on hybrid molecules derived from edaravone and ring-opening NBP.

In 2022, Jia et al. synthesized two optical enantiomers (**14a** and **14b**) of **14** (Fig. 5) [71]. Notably, **14b** showed significant reduction of tMCAO-induced cerebral infarction, achieving an inhibition rate of 77.85%, exceeding **14** (66.89%) and **14a** (67.56%). The therapeutic efficacy of **14b** substantially surpassed that of its individual components used alone or in combination (68.37%). Moreover, **14b** effectively reduced brain edema with an inhibition rate of 13.96%. In rat plasma or hepatic microsomes, **14b** exhibited moderate degradation, with respective half-time of approximately 17 h and 50 min, indicating relative stability *in vitro*.

To enhance the BBB penetration ability of **14**, Li et al. developed NBP derivative **15** by incorporating dimethylamine into the side chain of the open-ring NBP in 2021 (Fig. 5) [72]. **15** demonstrated significant protective activity against damage induced by oxygen and glucose deprivation (OGD) and H_2O_2 in SH-SY5Y cells. The platelet aggregation inhibitory effect of **15** (43.03%) exceeded that of edaravone (21.13%) and NBP (23.53%), suggesting **15** may inhibit ADP-induced platelet aggregation through synergistic effects of the edaravone analogue and NBP. Additionally, **15** prevented ROS accumulation and inhibited OGD-induced apoptosis in SH-SY5Y cells. Further analysis indicated that **15** may mitigate oxidative damage in SH-SY5Y cells through regulation of the Nrf2 pathway.

Isosorbide serves not only as a diuretic used in conditions such as hydrocephalus and glaucoma but also as a versatile scaffold for developing derivatives with potent vasodilatory and anti-inflammatory properties [73, 74]. Wang et al. developed a novel hybrid compound (**16**) of ring-opening NBP and isosorbide through the introduction of substituted amine in 2013 (Fig. 5) [75]. **16** exhibited IC_{50} values that were 8.4 to 33.6 times lower than those of *S*-NBP and ticlid against ADP- and AA-induced platelet aggregation. Additionally, **16** demonstrated a lower log *D* value (log $D_{3.6}$ 1.87) compared to *S*-NBP (log $D_{7.0}$ 3.19), and its water solubility (11.2 mg·mL^{-1}) exceeded that of *S*-NBP (0.53 mg·mL^{-1}). In *in vitro* studies, **16** showed significantly stronger inhibitory activity against ADP-induced platelet aggregation at 0.1 mmol·L^{-1} than the combined administration of *S*-NBP (0.2 mmol·L^{-1}) and isosorbide (0.1 mmol·L^{-1}), demonstrating its synergistic effect. Oral administration of **16** provided protection against acute thrombus formation and reduced ischemia/reperfusion-related brain injury in animal models, indicating promising potential for **16** in IS management.

TMP, an essential bioactive component extracted from the Chinese herbal medicine *Ligusticum chuanxiong*, demonstrates functions including vasodilation promotion, neuronal protection, and inflammation inhibition [76, 77]. Despite these advantages, TMP faces limitations including poor water solubility, short half-life, and low bioavailability [78]. Through molecular hybridization, Jia et al. developed hybrid compound **17** by combining TMP with NBP to enhance therapeutic efficacy in 2023 (Fig. 5) [79]. At 6.25 μmol·L^{-1}, **17** exhibited no cytotoxicity towards normal SH-SY5Y cells and demonstrated significant neuroprotective effects in the oxygen and glucose deprivation/reperfusion (OGD/R) model, with a protection rate of 90.2%, exceeding NBP (69.2%). Additionally, **17** effectively reduced ROS generation and decreased mitochondrial damage within cells. Mechanistically, **17** protected against ischemic injury by modulating the caspase 3/Bcl-2/Bax signaling pathway. *In vivo*, **17** showed favorable PK properties and BBB permeability, significantly reducing infarct volume in the middle cerebral artery occlusion and reperfusion (MCAO/R) model within 7 d. These results establish **17** as a promising neuroprotective agent for IS treatment.

3.4. NO-releasing NBP derivatives

Considering NO's beneficial role in cerebral ischemia treatment as described above, Wang et al. innovatively synthesized NO-releasing derivative (**18**, ZJM-289) of NBP in 2011, utilizing FA as a linker between NO donor and 2-(1-hydroxypentyl) benzoic acid (Fig. 6) [80]. **18** demonstrated exceptional potency in inhibiting *ex vivo* platelet aggregation induced by ADP and TH, with IC_{50} values of 0.24 and 0.41 mmol·L^{-1}, respectively, surpassing NBP and aspirin. At 0.2 mmol·L^{-1}, **18** inhibited ADP-induced platelet aggregation by 51.1%, exceeding the individual effects of its components: NBP precursor (36.3%), butyl ferulate (32.5%), and organic nitrate (16.0%), indicating synergistic inhibitory interactions. **18** also showed significantly enhanced water solubility, reaching a saturation concentration of 0.98 mmol·L^{-1}, surpassing that of NBP (0.53 mmol·L^{-1}). Furthermore, **18** demonstrated superior antithrombotic efficacy in rats compared to NBP and aspirin, and exhibited protective effects against COL and adrenaline-induced thrombus formation in mice.

In 2012, Wang et al. synthesized and evaluated two enantiomers (**18a** and **18b**) of **18** for their biological activities (Fig. 6) [81]. **18b** demonstrated comparable efficacy to **18** in inhibiting ADP- and TH-induced platelet aggregation. For AA-induced platelet aggregation, **18b** (IC_{50} 0.09 mmol·L^{-1}) exhibited substantially higher potency than **18a** (IC_{50} 0.34 mmol·L^{-1}) and **18** (IC_{50} 0.16 mmol·L^{-1}). Both enantiomers and **18** showed similar antithrombotic activity in rat models. Three-day oral administration of the enantiomers or **18** significantly reduced infarct area, brain edema, and neurological deficits following cerebral ischemia-reperfusion in rats. **18b** demonstrated superior performance compared to **18a** in certain aspects, potentially due to subtle differences in metabolism and PK properties, though the exact mechanisms require additional investigation.

In 2011, Li et al. employed HPBA as the lead compound and linked nitrate ester NO donors with HPBA *via* amide bonds using FA as the connecting group to synthesize NBP derivatives **19** and **20** (Fig. 6) [82]. At 1 mmol·L^{-1}, compounds **19** and **20** exhibited markedly enhanced antiplatelet activity compared to NBP (67.8%) and aspirin (68.5%), achieving 83.0% inhibition against ADP-induced platelet aggregation, with IC_{50} values of 54.44 and 39.40 μmol·L^{-1}, respectively. Furthermore, **19** and **20** released NO, contributing to improved cardiovascular and cerebral circulation. Treatment with an endogenous NO scavenger (20 μmol·L^{-1} hemoglobin) significantly reduced the antiplatelet effect of **19**, decreasing inhibition from 81.2% to 54.4%. These findings substantiate the essential role of NO release in the antiplatelet activity of these derivatives.

3.5. H_2S-releasing NBP derivatives

Recent research has identified hydrogen sulfide (H_2S) as an endogenous gasotransmitter, following NO and carbon monoxide (CO), demonstrating diverse biological effects. H_2S has proven to be an effective protective agent against cerebral ischemia-reperfusion injury (CIRI). It induces vasodilation, enhancing cerebral blood flow and protecting neurons. Additionally, increased H_2S levels inhibit ROS generation, protecting neurons from oxidative stress [83-85]. Consequently, researchers have developed numerous compounds designed for H_2S delivery *in vivo*, which are currently under extensive investigation.

In 2014, Wang et al. amalgamated HPBA with the H_2S donor 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADTOH) and successfully synthesized the NBP derivative **21** (Fig. 6) [86]. This compound demonstrated potent *in vitro* antiplatelet aggregation activity, with notably lower IC_{50} values for ADP-induced (0.14 mmol·L^{-1}) and AA-induced (0.09 mmol·L^{-1}) platelet aggregation compared to NBP and ticlid. The enhanced activity significantly

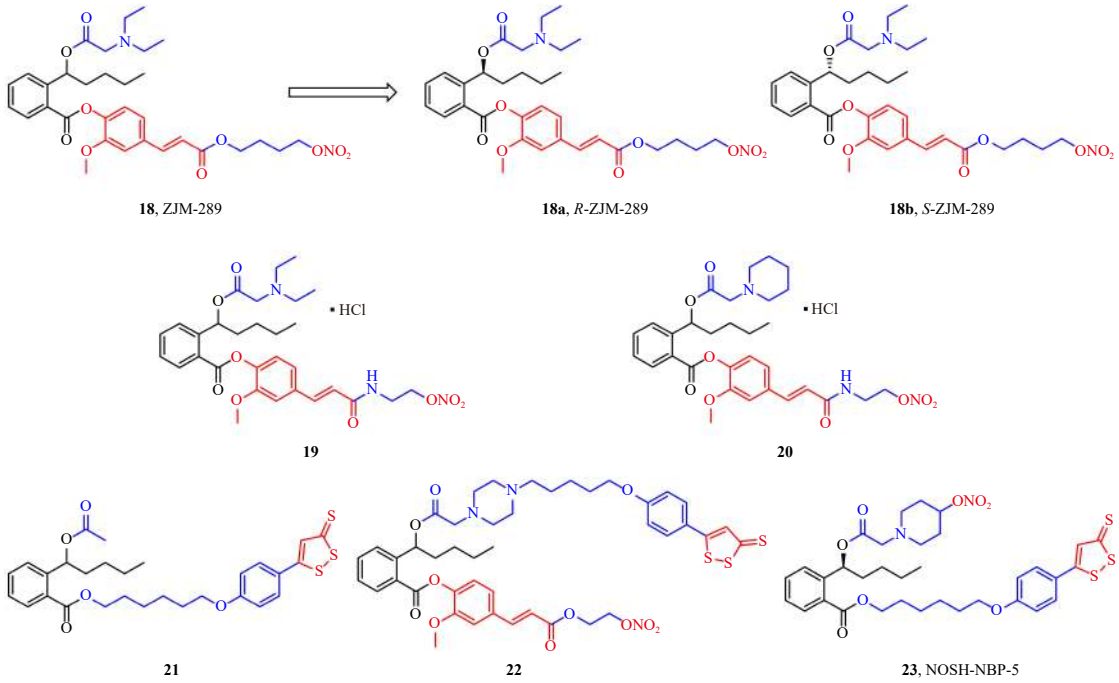


Fig. 6 The chemical structures of NO/H_2S-releasing NBP derivatives.

exceeded that of its constituent fragments administered individually or combined, indicating synergistic effects. **21** demonstrated gradual release of moderate H_2S levels *in vitro*, potentially benefiting cardiovascular and cerebral circulation. In inhibiting arteriovenous bypass thrombosis and pulmonary embolism, **21** showed superior activity compared to NBP and aspirin. In 2018, Wang et al. evaluated **21**'s efficacy against brain damage and the phosphatidylinositol 3-kinase γ (PI3Kγ) signaling pathway following cerebral ischemic injury (CIR) [87]. Results showed that **21** downregulated nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) subunit p47phox and p-p47phox expression, along with upstream PI3Kγ/protein kinase B (AKT) signaling. It reduced superoxide release in the rat brain penumbra and OGD-challenged primary cultured astrocytes. Through modulation of the PI3Kγ/AKT/NOX2 pathway in activated astrocytes, **21** prevented neuronal death in adjacent neurons. These findings indicate **21**'s potential as a candidate drug for IS treatment.

3.6. Double-donor NBP derivatives

To develop more effective anticerebral ischemia agents compared to NBP, Yin et al. synthesized a novel NO/H_2S dual donor NBP derivative **22**, utilizing HPBA as a coupling scaffold for NO and H_2S donors, and evaluated its biological activities in 2016 (Fig. 6) [88]. Nitrate served as the NO-donating fragment and was linked to HPBA through FA. Furthermore, H_2S donor ADTOH was attached to the side chain of HPBA *via* a substituted acetate bond. **22** demonstrated significant inhibitory activity against ADP-induced platelet aggregation with an IC_{50} of 0.14 mmol·L^{-1}, which is 5.2 times more potent than NBP (IC_{50} 0.74 mmol·L^{-1}). This inhibitory effect was substantially superior to that of corresponding H_2S-donor and NO-donor NBP derivatives, suggesting a potential synergistic effect. Additionally, **22** exhibited moderate NO and H_2S release *in vitro*, with the respective scavengers significantly reducing its activity, highlighting the importance of both gases. Notably, **22** significantly decreased cerebral infarct volume and brain edema, and showed enhanced protective effects against ischemia and reperfusion (I/R)-induced brain injury compared to NBP. Overall, **22** demonstrates considerable promise as a neuroprotective agent for cerebral ischemia treatment.

In 2016, Wang et al. incorporated piperidine as a substitute for the acetate bond in the side chain of *S*-HPBA, thereby developing another novel NO/H_2S dual donor NBP derivative, NOSH-NBP-5 (**23**) (Fig. 6) [89]. It demonstrated significant inhibition of AA or ADP-induced platelet aggregation, with IC_{50} values of 0.11 and 0.10 mmol·L^{-1}, respectively, exhibiting 3.8-fold and 7.0-fold greater potency compared to *S*-NBP. Furthermore, **23** alone showed superior antiplatelet aggregation activity compared to the combination of its corresponding parts, indicating a potential synergistic effect.

3.7. NBP analogues

Isoindoline derivatives share structural similarities with NBP and demonstrate efficacy in treating CNS diseases [90]. Their amide bond exhibits greater stability in the gastrointestinal tract compared to the ester bond of NBP, potentially resulting in enhanced anti-IS activity. In 2015, Lan et al. designed and synthesized compound **24** by substituting the oxygen atom in the lactone ring of NBP with a nitrogen atom (Fig. 7) [91]. It exhibited potent antiplatelet aggregation activity against both ADP- and AA-induced platelet aggregation, with IC_{50} values of 1.38 and 1.01 mmol·L^{-1} respectively, surpassing those of NBP (1.79 and 1.10 mmol·L^{-1}). **24** (50 mg·kg^{-1}) significantly reduced the infarct area in permanent middle cerebral artery occlusion (pMCAO) rats and demonstrated greater efficacy than NBP (50 mg·kg^{-1}) and edaravone (3 mg·kg^{-1}). **24** functioned as a free radical scavenger, protecting

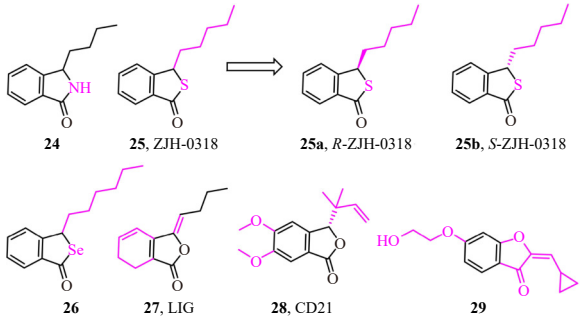


Fig. 7 The chemical structures of NBP analogues.

HT22 cells from H_2O_2-induced cytotoxic damage and significantly reducing oxidative stress caused by cerebral I/R in rats. Importantly, treatment with **24** resulted in substantial reductions in infarct volume and marked improvements in neurobehavioral deficits across both transient and permanent MCAO models. Additionally, **24** demonstrated significant advantages in bioavailability and brain tissue distribution, indicating promising potential for IS treatment.

Based on the significant role of sulfur-containing drugs in antioxidant, free radical scavenging, and neuroprotective effects [92, 93], Wu et al. strategically replaced the oxygen atom in the lactone ring of NBP with a sulfur atom and introduced a pentane side chain at C-3 position, yielding the sulfur-containing NBP analogue ZJH-0318 (**25**) in 2012 (Fig. 7) [94]. The compound demonstrated effective inhibition of ADP- and AA-induced platelet aggregation with IC_{50} values of 0.42 and 0.21 mmol·L^{-1}, respectively, substantially lower than NBP (> 1 and 0.48 mmol·L^{-1}). In the rat arteriovenous shunt model, administration of 30 mg·kg^{-1} of **25** effectively reduced the thrombus dry weight by 32.85% (from 9.74 to 6.54 mg), demonstrating potent antithrombotic activity. Notably, **25** enhanced the neurobehavioral function of MCAO rats, decreased the infarcted brain area, brain water content, and brain damage. Furthermore, **25** significantly mitigated cerebral I/R-related oxidative stress by increasing brain antioxidants superoxide dismutase (SOD) and glutathione (GSH) levels. Its neuroprotective effect may involve enhanced casein kinase 2 (CK2) activity, inhibition of NOX, and reduction of ROS formation [95]. In 2016, Jian et al. proceeded to synthesize its two optical enantiomers, **25a** and **25b**, and examined their biological activities [28]. Both compounds effectively attenuated H_2O_2-induced damage in PC12 cells and exhibited excellent inhibitory effects on platelet aggregation and cerebral infarction. **25a** demonstrated marginally superior efficacy compared to **25** and **25b** in repairing I/R-related cerebral cortical tissue damage in rats, while maintaining comparable efficacy in other aspects.

Given that selenium and sulfur both belong to Group VIA elements and exhibit similar antioxidant and antiinflammatory properties, Fang et al. substituted the oxygen atom in the NBP lactone ring with a selenium atom and introduced a hexane side chain at C-3 position to generate selenium-containing NBP analogue **26** in 2015 [96]. **26** demonstrated robust inhibitory activity against platelet aggregation, with an inhibition rate approximately double that of NBP (8.4%) at 0.1 mmol·L^{-1} concentration. Moreover, its hydroxyl radical scavenging efficacy (IC_{50} 2.18 mmol·L^{-1}) was significantly superior to NBP (IC_{50} 14.44 mmol·L^{-1}) and comparable to edaravone (IC_{50} 2.12 mmol·L^{-1}), indicating its potential for further investigation.

Angelicae Sinensis Radix, commonly known as Danggui, has been employed extensively for treating cardiovascular and cerebrovascular disorders [97]. *Z*-Ligustilide (**27**, LIG), a primary lipophilic component of Danggui, has demonstrated significant prevention of transient ischemic brain injury (Fig. 7). Research indicates that the inhibition of mitochondrial-related caspase-3 apoptotic pathway and inducible nitric oxide synthase (iNOS)-related pathway by **27** contributes to its neuroprotective effect [98]. To further evaluate the protective effect of **27** on focal cerebral ischemia, Peng et al. assessed its effects in a permanent MCAO model in rats [99]. The findings revealed that oral administration of **27** at doses of 20 and 80 mg·kg^{-1} reduced cerebral infarct volume by 48.29% and 84.87%, and alleviated brain edema by 43.4% and 83.4%, respectively. Additionally, **27** significantly improved behavioral deficits in the treated animals. As a natural product structurally similar to NBP, **27** may hold substantial therapeutic and research implications for IS. However, its precise mechanisms and safety require further validation.

In 2022, Wu et al. investigated the neuroprotective effects and specific mechanisms of the novel phthalide neuroprotectant CD21 (**28**) in acute IS (Fig. 7) [100]. The research demonstrated that **28** exhibited enhanced neuroprotective efficacy at doses of 6.89 and 13.79 mg·kg^{-1} compared to equimolar doses of NBP (5 and 10 mg·kg^{-1}) in tMCAO rats. The compound dose-dependently inhibited platelet aggregation induced by ADP, as well as platelet-rich thrombus formation mediated by ferric chloride, arteriovenous shunt and COL-epinephrine combination. Furthermore, administration of **28** resulted in decreased expression of peptidylarginine deiminase 4 (PDA4) and components of neutrophil extracellular traps (NET). Pretreatment with an inhibitor of AMPK significantly reversed this inhibitory effect. These findings suggest that **28** may modulate the platelet-NET-thrombin axis through AMPK activation and provide partial protection against ischemic brain injury.

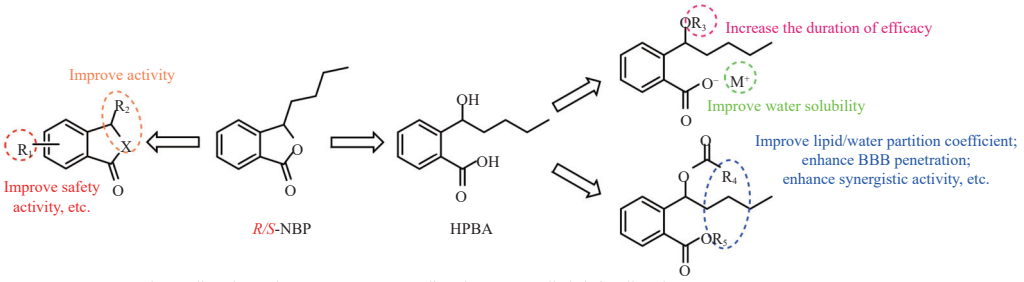
In 2023, Yang et al. addressed the low stability of phthalide derivatives by substituting the phthalide ring with 6-hydroxybenzofuran-3(2*H*)-one to design the NBP analogue **29** (Fig. 7) [101]. In the OGD model, **29** exhibited superior neuroprotective effects compared to the positive controls, edaravone and NBP. In the oxidative damage model of PC12 cells, **29** demonstrated moderate antioxidant effects at relatively low doses. Compound **29** significantly reduced the infarct area in the rat MCAO model, and following administration (40 μmol·L^{-1}) for 14 times, the infarct volume decreased to 15.7%. Moreover, **29** effectively reduced the expression of ionised calcium-binding adaptor molecule 1 (Iba-1) and glial fibrillary acidic protein (GFAP) in inflammatory cells while increasing nerve growth factor (NGF) expression, demonstrating pronounced anti-inflammatory effects. These comprehensive results indicate that compound **29** may provide substantial therapeutic benefits for IS.

4. Discussion

NBP demonstrates significant potential in treating cerebral ischemia due to its multi-target properties and diverse biological activities. However, its overall therapeutic efficacy remains limited, and its extremely poor water solubility somewhat restricts its clinical application. To address these limitations, researchers have actively pursued structural modification and transformation, resulting in the development of promising NBP derivatives as racemates or pure enantiomers. Structural derivatization has primarily focused on three aspects: improving water solubility for convenient injection administration, optimizing the lipid-water partition coefficient to enhance BBB penetration, and introducing active fragments or gas donors to amplify activity through synergistic effects. Understanding the complex relationship between NBP derivative structures and their anticerebral ischemic activity is crucial for developing more potent novel NBP derivatives (Fig. 8).

Table S2 comprehensively summarizes the reported properties of selected NBP derivatives, including their aqueous solubility, *in vitro* antiplatelet aggregation activity, *in vivo* anticerebral infarction efficacy, and LD_{50} values. Notably, the *S*-enantiomer of NBP demonstrates superior biological activities compared to the racemate and *R*-enantiomer. This pattern extends to compounds **1**, **14**, and **18**, where compound **1** represents a major metabolite of NBP, while both **14** and **18** metabolically convert to NBP within the body. Given their metabolic relationship, these compounds predictably follow the same enantiomeric activity order as NBP itself.

Within the cyclic structure of NBP, the C-6 position of the benzene ring functions as the primary site for modification. Scientists have synthesized various NBP derivatives by incorporating structural units including fluorine, bromine, NO donors, ALA (a natural antioxidant), isopentenylphenol, 1,3,4-oxadia zole, and sulfoxide. These modifications aim to enhance NBP's anticerebral ischemia activity. Notably, compound **8** demonstrates exception-



R_1: H, F, Br, OH, methoxy, alkenyl, NO donor, ALA, 1, 3, 4-oxadia zole, etc. R_2: alkyl chain, alkenyl, etc.
X: O, S, Se, NH, etc. R_3: H, Acetyl, etc.
M: Na, K, L-Arg, etc.
R_4: CH, *N*, *N*-dimethylethylamine, dimethylamine, NO donor, HS donor, polar group, etc.
R_5: *N*, *N*-dimethylethanamine, isosorbide, edaravone, TMP, FA, NO donor, HS donor, active fragment, etc.

Fig. 8 Structure-activity relationships of NBP derivatives.

al performance, showing potent inhibition of platelet aggregation *in vitro*, with an IC_{50} value below 30 μmol·L^{-1}, representing approximately 30-fold greater activity than NBP. Additionally, this compound exhibits significant improvements in *in vivo* activity, PK properties, and BBB penetration compared to NBP, primarily due to the 1,3,4-oxadia zole and sulfoxide moieties. This achievement highlights the potential of incorporating active pharmacophores into core bioactive natural products as a drug development approach. Furthermore, compounds **3** and **4** exhibited notably higher LD_{50} values in mouse studies, indicating that halogen atom introduction may enhance NBP's safety profile.

In NBP ring-opening derivatives, hydroxyl and carboxyl groups serve as primary sites for structural modifications. The carboxyl group forms salts with metal ions, substantially improving water solubility and enabling injection administration while optimizing PK properties. Additionally, carboxyl and hydroxyl groups undergo esterification to introduce various functional fragments, including amine groups (e.g., *N*,*N*-dimethylethylamine, dimethylamine), active molecules (such as isosorbide, edaravone, TMP, FA), and gas donors. FA functions as a linker connecting NBP with gas donors. Compound **14** demonstrates superior activity among ring-opening derivatives, with platelet aggregation inhibition *in vitro* exceeding 8 times that of *S*-NBP, primarily due to enhanced BBB penetration facilitated by piperazine and synergistic effects from *in vivo* conversion to *S*-NBP and isosorbide. Gas donor-type NBP derivatives (compounds **18**–**23**) consistently show superior bioactivity, with IC_{50} values for *in vitro* platelet aggregation inhibition below 20 μmol·L^{-1}, highlighting NO and H_2S therapeutic potential in IS management. This mechanism suggests promising research directions, though comprehensive studies regarding *in vivo* activity and biological safety of these gas donor derivatives remain limited.

NBP analogue development primarily involves atomic substitution and side chain introduction. The oxygen atom in the NBP lactone ring can be substituted with sulfur or selenium atoms, while alkyl or alkoxy chains typically serve as side chain substituents. Compounds **25**, **26**, and NBP share structural similarities, with sulfur-containing compound **25** showing optimal activity, followed by selenium-containing compound **26**. These results indicate that sulfur and selenium atom introduction can enhance activity. Compounds **25**, **27**, and **28** demonstrate improved *in vitro* and *in vivo* activity compared to NBP. Notably, the *R*-enantiomer of **25** exhibits higher activity than its racemate and *S*-enantiomer, likely due to sulfur substitution. However, NBP analogs' effectiveness appears modest compared to other derivatives, possibly due to limited modification strategies. Future analog design should incorporate diverse active fragments to leverage synergistic effects and enhance biological activity.

Compounds **2**, **10**, **11**, and **12** have progressed to clinical trials. These compounds share a common feature in their salt forms, which significantly enhance water solubility, facilitating intravenous administration. Except for compound **2**, the remaining compounds are ring-opening derivatives functioning as NBP prodrugs, releasing NBP through enzymatic hydrolysis *in vivo*. This prodrug strategy extends NBP's action duration and potentially improves biological safety. These findings provide valuable guidance for developing more effective and safer NBP derivatives.

5. Summary and outlook

IS initiates various pathophysiological cascades, including energy metabolism disruption, oxidative stress, inflammatory responses, and apoptosis, leading to neural cell damage and neurological dysfunction. While current interventional approaches like thrombolysis and mechanical thrombectomy are available, these methods may potentially aggravate neural cell injury and induce IRI. Dl-NBP, approved by the NMPA in 2002 as a neuroprotective agent for acute IS treatment, demonstrates multiple therapeutic mechanisms including antithrombosis, oxidative stress reduction, inflammatory response suppression, mitochondrial function protection, and apoptosis inhibition, showing considerable promise in initial IS applications.

Despite its potential, NBP monotherapy demonstrates moderate efficacy, mild hepatotoxicity, and limited water solubility. To address these limitations, extensive structural modifications have been undertaken. Through various approaches including substituent introduction, ring-opening derivation, esterification, and atom substitution, numerous derivatives and analogues have been developed, yielding improvements in efficacy, safety, and water solubility. The incorporation of halogen atoms appears to enhance safety profiles, while salt formation significantly improves water solubility, enabling injectable administration. The addition of amine groups enhances BBB penetration, thereby improving bioavailability and safety. Integration of active fragments into NBP's core structure creates synergistic effects that amplify its activity. Furthermore, gas-donor NBP derivatives demonstrate superior efficacy, suggesting potential for future therapeutic advancement.

Future research directions for NBP and its derivatives remain extensive. Current literature lacks comprehensive reports on detailed mechanisms of action and molecular pathways, representing a critical area requiring thorough investigation. Additionally, efforts to improve NBP's water solubility must maintain adequate BBB permeability, which remains essential for cerebral ischemia treatment. Moreover, optimization of dosage regimens, innovation of administration methods, and combination of therapy approaches constitute key research priorities.

In conclusion, NBP and its derivatives demonstrate significant potential in cerebral ischemia treatment, though additional research remains necessary to fully realize their therapeutic potential and provide enhanced treatment options for cerebral ischemia patients.

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Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

The authors declare no competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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