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# Design and synthesis of novel senkyunolide analogues as neuroprotective agents

Yuanying Fang [a,c], Rikang Wang [a,c], Qi Wang [a], Yongbing Sun [a], Saisai Xie [a], Zunhua Yang [b,*], Min Li [b], Yi Jin [a,*], Shilin Yang [a]

[a] National Engineering Research Center for Manufacturing Technology of TCM Solid Preparation, Jiangxi University of Traditional Chinese Medicine, Nanchang 330006, China
[b] College of Pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China

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ABSTRACT

A class of senkyunolide analogues bearing benzofuranone fragment were designed, synthesized and evaluated for their neuroprotective effect in models of oxygen glucose deprivation (OGD) and oxidative stress. All tested compounds showed neuroprotection profile based on the cell viability assay. In particular, derivatives **1f**–**1i** possessing furoxan-based nitric oxide releasing functionality exhibited significant biological activities in OGD models. More importantly, compound **1g** containing short linker with furoxan displayed the most potent neuroprotection at the concentration of 100 μM (cell survival up to 145.2%). Besides, **1g** also showed the middle level neuroprotective effect in model of oxidative stress.

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Cerebrovascular disorders constitute a serious public health problem worldwide, and among them, acute cerebral ischemia (ischemia stroke) represents one of the leading causes of death and neurological disability.[1] Although the pathological mechanism of acute cerebral ischemia is complex and not fully disclosed, significant progress has been made to describe the several pathological features that are in common with other neurodegenerative disorders.[2] Currently, there are two conventional treatment strategies for acute cerebral ischemia. One is using neuroprotective drug, which aims on blocking cascade of neuronal death to preserve and recover the neurological function in the ischemic regions. Another one is treatment of ischemia stroke by preventing or reducing vascular thrombosis, and dilating vessels that leads to supply oxygen and blood on the ischemic area.[3,4]

*Ligusticum chuanxiong Hort.* (Umbelliferae) is one of the most commonly used traditional Chinese medicinal herb for treating cardio-cerebrovascular diseases such as angina pectoris, coronary disease, ischemic encephalopathy and hyperviscosity syndrome.[5–9] Several abundant components were isolated from *Ligusticum chuanxiong Hort.* including various types of phthalide derivatives, such as ligustilide and senkyunolide (Fig. 1), which were reported to possess potent biological activities for treatment of ischemic diseases via improving cerebral blood flow, inhibiting thrombosis and preserving nerve cells function.[5,10,11] However, because of the instability and short half-life of those compounds, it's unpractical to develop them directly as clinical drugs. Butylphthalide (3-*n*-butylphthalide or NBP), a stable analogue of senkyunolide A, was approved in China for the treatment of cerebral ischemia in 2004.[4]

Nitric oxide (NO) has attracted a tremendous interest in a broad field of basic and applied research as one of the most significant physiological signalling molecule in the body.[12] NO could diffuse into vascular smooth muscle cells and react with the iron of soluble guanylate cyclase, leading to relaxation of the smooth muscle cells and dilation of blood vessels.[13] Therefore, a series of novel senkyunolide analogues containing benzofuranone framework and furoxan fragments as NO donors were designed and synthesized. Biological evaluation of these compounds was carried out including neuroprotective effect in oxygen glucose deprivation (OGD) model against acute cerebral ischemia and antioxidant activity in oxidative stress model. It was envisaged that these derivatives could cause significant pharmacological change.

Twelve final compounds (**1a**–**1l**) were designed in three various series. Compounds **1a**–**1e** are benzofuran-3-one derivatives with different methoxyl substitution in benzene ring and butylidene group or reduced butyl at 2-position. Compounds **1f**–**1i** are 5-hydroxyl benzofuran-3-one derivatives connected with furoxan moiety via ether linkages and succinate diester. Compounds **1j**–**1l** are benzofuran-2-one derivatives.

* Corresponding authors.
*E-mail addresses:* joshyyy@126.com (Z. Yang), yinghua616909@hotmail.com (Y. Jin).
[c] The authors contribute equally to this work.

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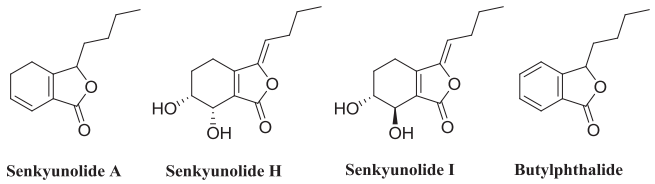
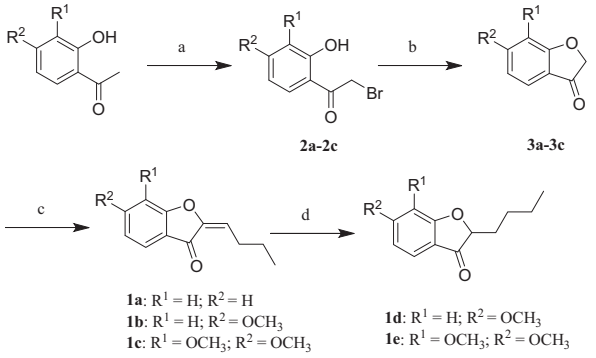



**Fig. 1.** The structures of senkyunolide and butylphthalide.



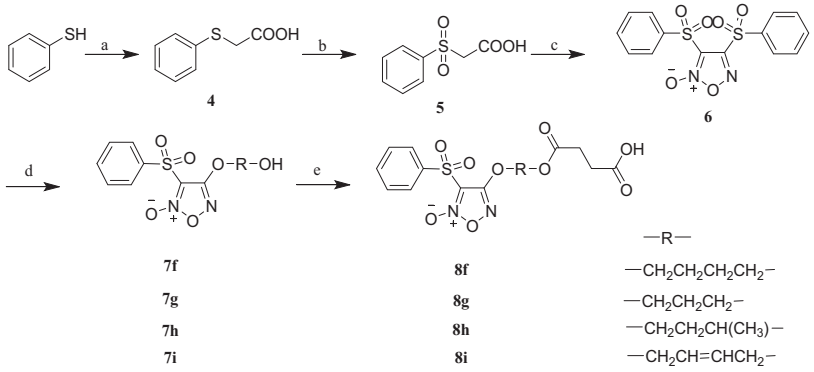

**Scheme 1.** Reagents and conditions: (a) $CuBr_2$, EtOAc, $CHCl_3$, 65 °C, overnight; (b) KF, DMF, R.T., overnight; (c) butyraldehyde, $Al_2O_3$, $CH_2Cl_2$, R.T., 0.5 h; (d) Pd/C, $H_2$, MeOH, R.T., 2 h.

Compounds **1a**–**1e** were generated from substituted acetophenones following the procedures and conditions as shown in Scheme 1. The starting acetophenones were reacted with copper (II) bromide to afford bromides **2a**–**2c**, which were treated with KF to give benzofuranones **3a**–**3c**.[14,15] Condensation of intermediates **3a**–**3c** with butyraldehyde gave target compounds **1a**–**1c** with *E*-isomer as the major product (85%–95%) according to the chemical shifts of olefinic proton in $^1$H NMR spectra and reported data.[16] Catalytic hydrogenation of **1b** and **1c** using Pd/C in $H_2$ afforded butyl compounds **1d** and **1e**.

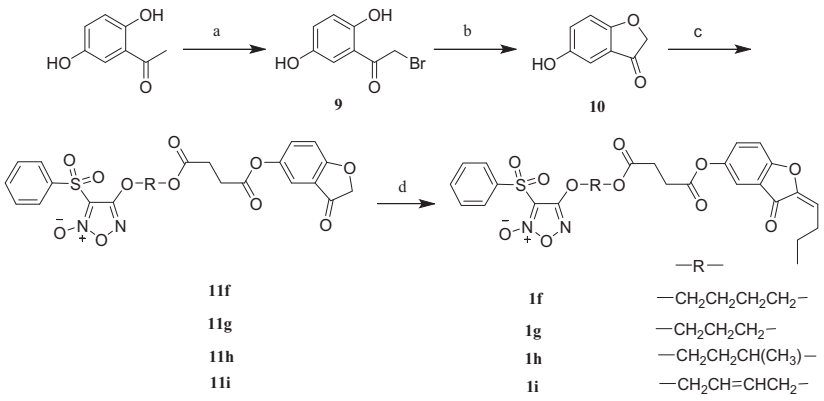
As shown in Scheme 2, the synthetic precursor **6** of furoxan moiety was prepared from thiophenol according to the precedent literatures.[17–19] The diphenylsulfonylfuroxan **6** was treated with kinds of diols and 25% NaOH aqueous solution at room temperature yielded the monoalchohols **7f**–**7i** with linker of different length, which were reacted with succinic anhydride in DMF to give the NO-donor fragments **8f**–**8i**. Compound **7i** was a mixture including *E* and *Z* form due to 2-butene-1,4-diol containing *cis*- and *trans*-isomers.

5-Hydroxyl benzofuran-3-one **10** was obtained using the similar procedure with compounds **1a**. Esterification between **10** and NO-donors **8f**–**8i** with EDCI and HOBt furnished the key intermediates **11f**–**11i**, which was coupled with butyraldehyde to afford final compounds **1f**–**1i** (Scheme 3).

The substituted acetophenones were explored to generated compounds **1j**–**1l**, which were shown in Scheme 4.[20–23] Willgerodt-Kindler reaction of the starting **12j**–**12l** with morpholine and sulphur formed thio-morpholide adduct following by hydrolysis to afford acid **13j**–**13l**. Cyclization of **13j**–**13l** in the presence of phosphorus oxychloride gave lactone **14j**–**14l**. Reaction of **14j**–**14l** and butyraldehyde with KOH yielded target compounds **1j**–**1l** with *E*-isomer as the major product based on $^1$H NMR spectra.




**Scheme 2.** Reagents and conditions: (a) $ClCH_2COOH$, NaOH, reflux, 2 h; (b) 30% $H_2O_2$, $CH_3COOH$, R.T., 2.5 h; (c) fuming $HNO_3$, 90 °C, 1.5 h; (d) Diol, 25% NaOH aq., THF, R.T., 3 h; (e) succinic anhydride, DMAP, DMF, 85 °C, 6 h.




**Scheme 3.** Reagents and conditions: (a) $CuBr_2$, EtOAc, $CHCl_3$, 65 °C, overnight; (b) KF, DMF, R.T., overnight; (c) **8f**–**8i**, EDCI, HOBt, DIPEA, $CH_2Cl_2$, R.T., overnight; (d) butyraldehyde, $Al_2O_3$, $CH_2Cl_2$, R.T., 0.5 h.

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