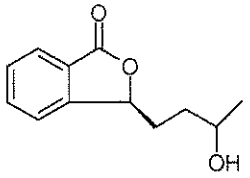
The purpose of the present ~~invention~~disclosure is to provide a derivative of 3-(3'-hydroxy)butylphthalide for ischemic stroke, and the preparation method and use thereof.

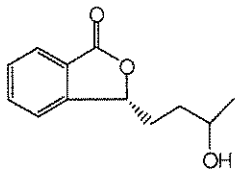
To achieve the purpose mentioned above, the present ~~invention~~disclosure employs the following technical solutions.

Preparing the compound of formula 1 as shown in the following figure,



formula I (S-configuration),

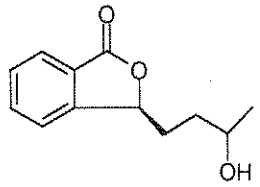
and preparing the compound in R-configuration as shown in the following figure,



R-configuration,

by asymmetric synthesis.

Thus, in one aspect, there is provided a compound for preventing and treating cerebral ischemic disease, the compound is as shown below:



I,

the chemical name is: (-)-(S)-3-(3'-hydroxy)-butylphthalide.

It is proved by animal tests that the compound in R-configuration does not have the effect of reducing the cerebral infarct volume of cerebral ischemia in rats, cannot improve the symptoms of cerebral ischemia, and does not have the effect of improving sleep, while the S-configuration has very good effects of improving the symptoms of cerebral ischemia, and can improve the sleeping state in animals.

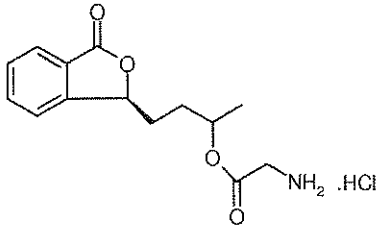
The compound of formula 1 is an oily substance insoluble in water. Therefore we allow it to form an ester with an acid, wherein the acid refers to a pharmaceutically acceptable inorganic or organic acid. The inorganic acid refers to nitric acid, sulfuric acid or phosphorus acid. The organic acid further contains one type of group, and at least one group selected from amino, hydroxy or carboxyl group in addition to acid radical. The salt from an ester is soluble in water and can be prepared into the dosage form of an injectable solution or lyophilized powder injection.

In another aspect, there is provided an ester obtained by reacting the compound as described herein with an acid, said acid selecting from a pharmaceutically acceptable inorganic acid or organic acid.

The organic acid can be amino acids, specifically refer to glycine, alanine, lysine, arginine, serine, phenylalanine, proline, tyrosine, aspartic acid, glutamic acid, histidine, lecine, methionine, threonine, pyroglutamic acid, tryptophan or valine.

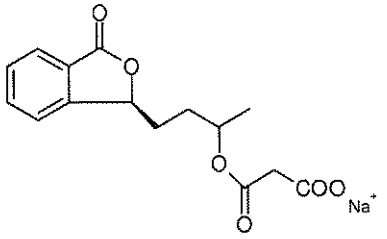
Wherein, an ester formed with glycine is preferred, which is as shown in the

An ester formed by the compound of formula I with glycine preferably forms a hydrochloride, which is as shown in the following figure:



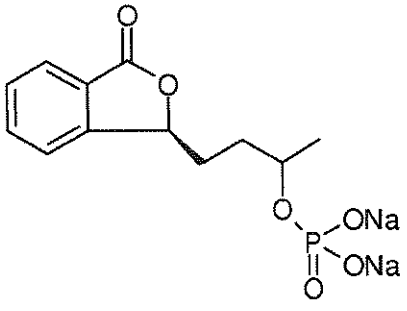
The present ~~invention~~disclosure further provides a salt of the dibasic acid esters of the compound of formula I, which refers to a salt formed with potassium, sodium, magnesium or organic amine. The organic amine radical can be tromethamine, diethanolamine, triethanolamine, glycine, lysine or arginine.

Wherein, the sodium salt is preferred, which is shown in the following figure:



In ordre to solve the problem of water-solubility, the ester formed by the compound of formula I with phosphoric acid can further form a salt with physiologically acceptable base, which refers to sodium salt, potassium salt, magnesium salt or organic amine salt. The organic amine includes lysine, glycine, arginine, tromethamine, diethanolamine or triethanolamine.

The ester formed by the compound of formula I with phosphoric acid preferably forms a disodium salt, which has the following structural formula:



The present ~~invention~~disclosure further provides a pharmaceutical composition for treating ischemic stroke, characterized in that the composition comprises a therapeutic effective

amount of the compound of general formula (1) or a salt thereof and a pharmaceutical acceptable carrier. The pharmaceutical composition can be an oral formulation or an injectable formulation.

In yet another aspect, there is provided use of the compound as described herein the manufacture of a medicament for treating cerebral ischemic diseases.

In yet another aspect, there is provided use of the compound as described herein in the manufacture of a medicament for improving sleep.

In yet another aspect, there is provided use of the compound as described herein the manufacture of a medicament for treating cerebral ischemic diseases and improving sleep.

In yet another aspect, there is provided use of the compound as described herein the manufacture of a medicament for treating ischemic diseases and improving sleep.

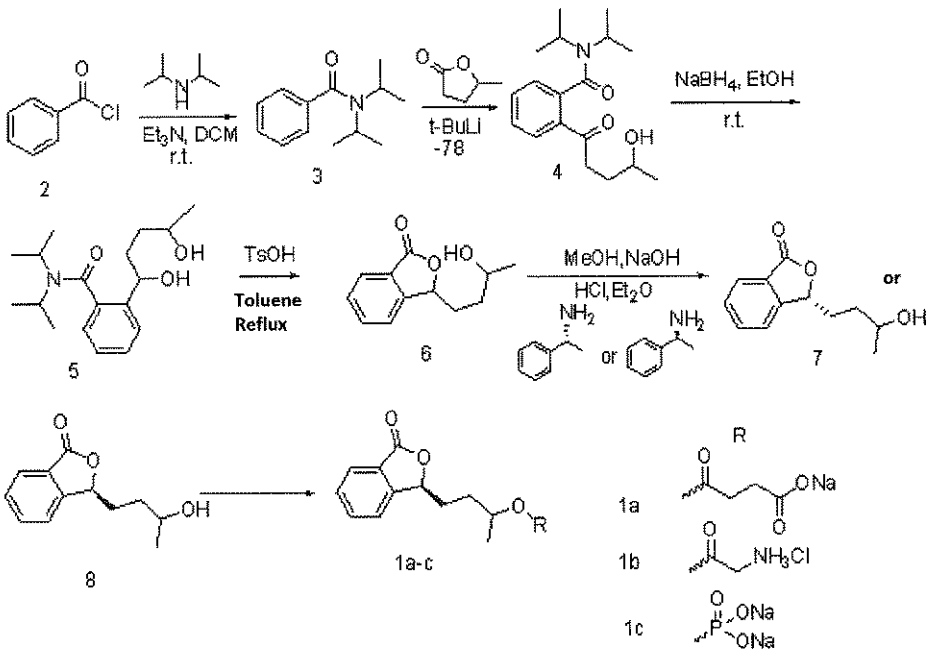
In yet another aspect, there is provided a pharmaceutical composition, comprising an effective amount of compound as described herein a pharmaceutically acceptable carrier.

Experiments for muscular and vascular irritations indicate that, it is administered by injection after the ester formed by the compound of formula I with an acid further forming a salt. No muscular and vascular irritations are observed, so that it can be used as injectable formulation.

DETAILED EMBODIMENTS

Example 1: Preparation of various compounds:

The compounds herein have very strong continuity. Therefore, in order to describe the preparation method of various compounds in a detailed, accurate and convenient way, the method is illustrated by way of one example. In the following synthetic route, each compound is indicated by a serial number. For a more concise illustration, in the preparation method below, the compounds are replaced by the serial numbers.



When the R in the above scheme is different groups, different compounds 1a, 1b and 1c are obtained.

(1). Synthesis of Coupound 3:

Diisopropylamine (1.3 mol) was placed into a 2000 mL round bottom flask, and 1000 mL anhydrous dichloromethane was added. After dissolving, triethylamine (2.0 mol) was added, and Compound 2 (1.0 mol) was added dropwise in an ice bath. After completing the dropwise addition, the reaction mixture was warmed to room temperature,