ANTI-INFLAMMATORY COMPOUND, AND PREPARATION AND USE THEREOF

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to the field of pharmaceutical chemistry, and in particular to an anti-inflammatory compound, a preparation method, and use thereof in the treatment of inflammatory dermatological diseases, such aas atopic dermatitis and psoriasis.

2. Description of Related Art

[0002] Inflammation caused by human autoimmune conditions is a major factor causing many human diseases. People with degenerative diseases usually exhibit excessive levels of pro-inflammatory modulators in their blood. A class of such pro-inflammatory modulators are cytokines. Cytokines include pro-inflammatory cytokines (including IL-1, IL-1β, IL-2, IL-3, IL-6, IL-7, IL-9, IL-12, IL-17, IL-18, IL-23, TNF-α, LT, LIF, oncoproteins and IFN-); anti-inflammatory cytokines (IL-4, IL-10, IL-11, IL-13 and TGF-β); and chemokines (IL-8, Gro-a, MIP-1, MCP-1, ENA-78 and RANTES).

[0003] In many situations of inflammation, pro-inflammatory cytokines, especially TNF-α, IL-1β and IL-6, and anti-inflammatory cytokine IL-10, show important roles in the pathogenesis of various inflammation-related diseases and can thus be used as potential therapeutic agents. For example, elevated levels of pro-inflammatory cytokines (TNF-α, IFN, IL-1, IL-2, IL-6, and IL-12) and chemokines (IL-8, MCP-1, and RANTES) have been observed in inflammation-related diseases, such as eczema, psoriasis, enteritis, Graves' disease, and Hashimoto thyroiditis, with simultaneous increases in their soluble TNF receptors, IL-1 receptor antagonists, and anti-inflammatory cytokine IL-10. It has been confirmed that IL-10 inhibits the increase in production of pro-inflammatory cytokines in LPMC culture in vitro and in patients.

[0004] Phosphodiesterase (PDE) isozymes are involved in the regulation of signal transduction

rheumatic arthritis, psoriasis and irritant enteritis; and several drugs targeting IL-1 (Anakinra (Kineret)), IL-4 (dupilumab (Dupixent)), IL-6 (tocilizumab (Actemra), and siltuximab (Sylvant)), or IL-12/IL-23 (Ustekinumab (Stelara)) and Alefacept (Amevive) inhibiting T immune cells can be used for treating various immune diseases.

[0007] However, when these monoclonal antibody products are systemically administered, the immunity of patients is inhibited, resulting in infection or other systemic side effects. Therefore, these drugs are clinically approved for treating patients with moderate to severe inflammatory diseases. Most patients with psoriasis and eczema are mild to moderate, so these drugs cannot help them.

[0008] Crisaborole, a PDE4 inhibitor, has proved its efficacy and safety in the treatment of mild to moderate eczema in children and adults in Phase III clinical trials (research project Nos.: AD-301 and AD-302) of eczema (also known as allergic dermatitis, atopic dermatitis, or atopic dermatitis) (Paller AS et al., J Am Acad Dermatol. 2016; 75(3): 494-503). PDE4 is a key regulatory point for the production of inflammatory cytokines in eczema, which mainly acts by degrading cyclic adenosine monophosphate. In circulating inflammatory cells in patients with eczema, the PDE4 activity increases, and in-vitro tests show that when PDE4 in monocytes is inhibited, the release of cytokines that promote inflammatory response decreases.

[0009] Crisaborole has been proved to have good safety, but limited clinical effect, as indicated by a clinical effect on eczema that is only about 10% higher than that of the blank control. Also, a large proportion (about 50%) of patients cannot benefit from Crisaborole. Crisaborole has an insignificant clinical effect in the treatment of psoriasis due to the low activity (where the enzyme inhibition activity is about 100 nM, and the cell activity inhibiting cytokine release is about 500 nM) (not approved for treating psoriasis).

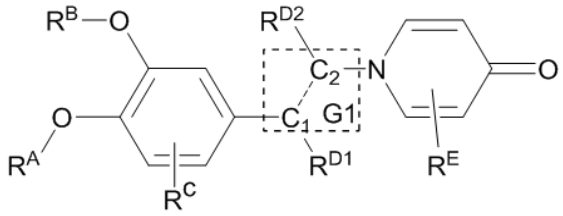
[0010] In view of this, it can be found that the existing drugs for eczema and psoriasis cannot meet the needs of patients, particularly the majority of mild-moderate patients, and more effective and safe topical drugs are still needed to be developed to treat most mild-moderate inflammatory

skin diseases (such as psoriasis, eczema, etc.).

SUMMARY OF THE INVENTION

[0011] The present invention provides a novel anti-inflammatory drug that has a potent inhibition effect on PDE4, an important target for autoimmune activation, and is easy to penetrate the skin, and readily degrade.

[0012] The present invention provides an anti-inflammatory compound, which is a compound having a structure shown below:

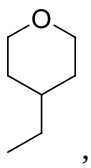
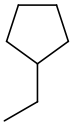


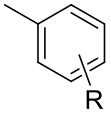
[0013] In the structural formula, R^A is hydrogen, alkyl, or aryl, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, aryl, or halogen,

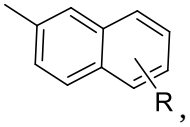
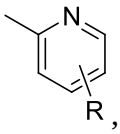
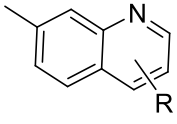
the alkyl is an alkyl group having 1 to 15 carbon atoms, generally a group having the general formula C_nH_{2n+1}-, and preferably a linear or branched alkyl group where n is not greater than 6;

the aryl group is selected from any aromatic groups consisting of pure carbocyclic or heterocyclic ring(s) with 5-24 carbon atoms, such as cyclopentadienyl, phenyl, naphthyl, quinolinyl, pyrrolyl, pyridinyl, furyl, and the like; and

the "one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl (which generally refers to an alkyl group with no more than 10 carbon atoms), cycloalkyl (three-, four-, five-, six-, or seven-membered), heterocycloalkyl (aza/thia/oxa-three/four/five/six/seven-membered), aryl (which generally refers to an aryl group having 5 to 20 carbon atoms), or halogen (fluoro, chloro, bromo, iodo)" means the forms of substitution of hydrogen on an alkyl group, for example, $-CH_2Cl$, $-CH_2CH_2Cl$, $-CH_2(Br)CH_3$, $-CH_2CH_2F$,

-CHF_2, -$CH(CH_3)CHF_2$, -$CH(Ph)CH_3$, , , , or -CH_2Ph,

or the forms of substitution of hydrogen on an aromatic group, for example, ,

, , , in which R is any one or several substituting alkyl groups (generally having no more than 6 carbon atoms), cycloalkyl groups (generally three-, four-, five-, or six-membered, which may be heterocycloalkyl), aryl groups (which generally refers to an aryl group having 5 to 20 carbon atoms, and may be heteroaryl), and halogen on the aromatic ring.

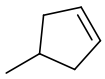
[0014] R^B is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, alkenyl, or alkynyl, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, or halogen, and one or more carbon atom(s) in the groups is/are optionally substituted with sulfur, sulfoxide, sulfone, or sulfonyl; or R^B is a hydroxyl protecting group,

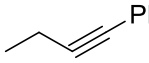
where the alkyl is as defined in the scenario of R^A;

the aryl is as defined in the scenario of R^A;

the cycloalkyl refers to a three-membered, four-membered, five-membered, or six-membered ring;

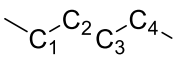
the heterocycloalkyl refers to an oxa/aza/thia three-membered, four-membered, five-membered, or six-membered ring;

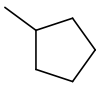
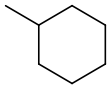
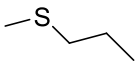
the alkenyl may be selected from linear or branched alkenyl with 2-10 carbon atoms, such as ethenyl (-=), 2-propenyl (-CH_2-=), 2-butenyl (-CH_2-=-CH_3), 3-butenyl (-CH_2-CH_2-=), cyclopentenyl (), and the like;

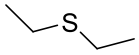
the alkynyl may be selected from linear or branched alkynyl with 2-10 carbon atoms, such as ethynyl (), 2-propynyl (), 

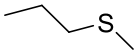
, and the like;

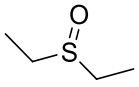
the "one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, or halogen" has the same meaning as in the scenario of R^A;

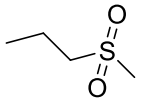
the "one or more carbon atom(s) in the groups is/are optionally substituted with sulfur, sulfoxide, sulfone, or sulfonyl refers to a situation in which one or more carbon atom(s) such as C_1 and C_2 on the structure 

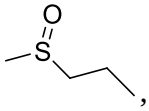
, , or  is/are replaced by S, (S=O), or (O=S=O), for example, 

, 

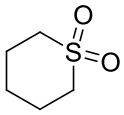
, 

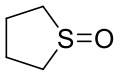
, 

, 

, 

, 

, 

, 

, 

, and 

; and

the hydroxyl protecting group means that a protectant reacts with a hydroxyl group to converts the hydroxyl group into silicon ether, benzyl ether, methyl ether, allyl ether and other forms, so that it is not affected by oxidation, reduction and other reactions.

[0015] R^C is hydrogen, alkyl, halogen, alkoxy, or cyano,

where the alkyl is selected from a linear or branched alkyl group with 1-20 carbon atoms; and

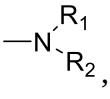
the alkoxy refers to the group -O-R, in which R is a branched or linear alkyl group with 1-20 carbon atoms;

[0016] R^{D1} is hydrogen, oxygen, nitrogen, hydroxy, cyano, amino, amido, alkyl, aryl, an ester group, carboxyl, alkynyl, or alkenyl, and in the above groups one or more hydrogen atom(s) attached to carbon/oxygen (that is, hydrogen in -OH)/nitrogen (that is, hydrogen in $-NH_2$, -NH(R), or =NH) in the groups is/are optionally substituted with alkyl, cycloalkyl, alkynyl, alkenyl, aryl, halogen, sulfonyl, a sulfoxide group, or an ether group, and one or more carbon

atom(s) in the groups is/are optionally substituted with sulfur, sulfoxide, sulfone, or sulfonyl,

where the alkyl is as defined in the scenario of R^A;

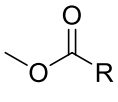
the amino refers to $-NH_2$;

the amido refers to a group denoted by , in which R_1 and R_2 may be any substituent, such as alkyl, aryl, and the like;

the aryl is as defined in the scenario of R^A;

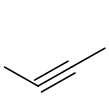
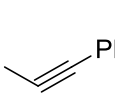
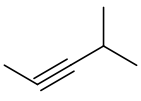
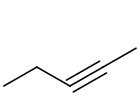
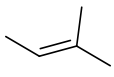
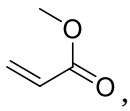
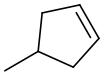
the alkenyl is as defined in the scenario of R^B;

the alkynyl is as defined in the scenario of R^B;

the ester group refers to a group denoted by , in which R is alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and the like,

where the alkyl is as defined in the scenario of R^B, and

the aryl is as defined in the scenario of R^B;

in the "one or more hydrogen atom(s) attached to carbon/oxygen/nitrogen in the groups is/are optionally substituted with alkyl, cycloalkyl, alkynyl, alkenyl, aryl, halogen, sulfonyl, a sulfoxide group, or an ether group", the alkyl, cycloalkyl, aryl, and halogen are as defined in the scenario of R^A; the alkynyl generally refers to an alkynyl substituent with no more than 20 carbon atoms, and may be , , , or ; the alkenyl generally refers to an alkenyl substituent with no more than 20 carbon atoms, and may be , , or ; and the ether group generally refers to an ether substituent with no more than 20 carbon atoms, and may be (-O-R); and

the "one or more carbon atom(s) in the groups is/are optionally substituted with sulfur, sulfoxide, sulfone, or sulfonyl" has the same meaning as in the scenario of R^B.

[0017] C_1-R^{D1} bond is a single bond, or a double bond (e.g. C=O, C=N, and the like);

[0018] R^{D2} is hydrogen, cyano, alkyl, cycloalkyl, aryl, an ester group, or carboxyl, and in the above groups one or more hydrogen atom(s) attached to carbon/oxygen/nitrogen in the groups is/are optionally substituted with alkyl, cycloalkyl, alkynyl, alkenyl, aryl, halogen, sulfonyl, a sulfoxide group, or an ether group,

where the amino, amido, alkyl, cycloalkyl, aryl, ester group, "one or more hydrogen atom(s) attached to carbon/oxygen/nitrogen in the groups is/are optionally substituted with alkyl, cycloalkyl, alkynyl, alkenyl, aryl, halogen, sulfonyl, a sulfoxide group, or an ether group" have the same meaning as those in the scenario of R^{D1}.

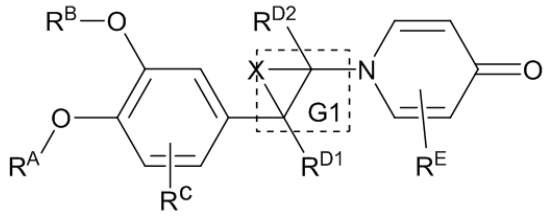
[0019] G1 is a single bond, a double bond or a ring comprising C_1 and C_2,

where the ring may be a ring-opening product of C_1 and C_2 double bonds, for example, cyclopropane, and propylene oxide; or a cyclization reaction product of a compound having a double bond or a triple bond such as cis-butadiene, cyclopentene and the like with C_1=C_2 double bond.

[0020] R^E is a group where one or more hydrogen atom(s) attached to carbon on the pyridinone ring of G1 is/are substituted with alkyl, aryl, cyano, or halogen,

where the alkyl, aryl and halogen are as defined in the scenario of R^A.

[0021] Further, the anti-inflammatory compound provided in the present invention is further characterized by G1 that is a three-membered ring, and having a specific structure shown below:



in which X is carbon, oxygen, nitrogen, or sulfur.

[0022] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises: using 3-hydroxybenzaldehyde derivative A as a starting material, and substituting the hydrogen in the hydroxyl group of the 3-hydroxybenzaldehyde derivative A with R^B to obtain an intermediate product B;

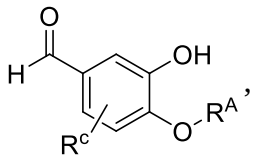
reacting the intermediate product B in the presence of trimethylsilyl cyanide to obtain an

intermediate product C;

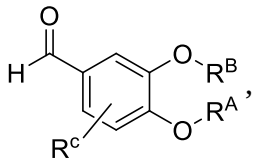
reducing the intermediate product C to obtain an intermediate product D having an amino group; and

reacting the amino group in the intermediate product D with a six-membered oxygen-containing cyclic compound to obtain a type-A target product,

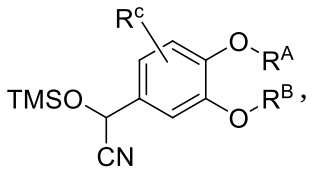
where the 3-hydroxybenzaldehyde derivative A is a compound having a structure shown below:



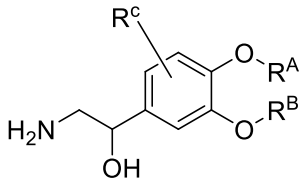
the intermediate product B is a compound having a structure shown below:



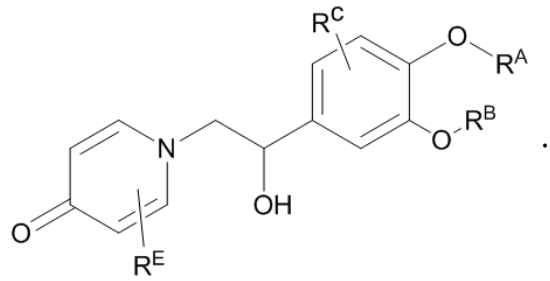
the intermediate product C is a compound having a structure shown below:



the intermediate product D is a compound having a structure shown below:

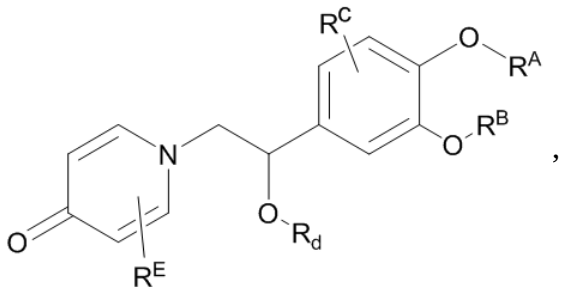


the type-A target product is a compound having a structure shown below:



[0023] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises subjecting the hydroxyl group on the middle bridge of the type-A target product to an addition/substitution reaction to obtain a type-A-1 target product,

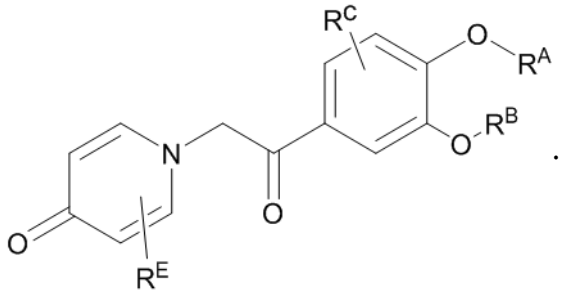
where the type-A-1 target product is a compound having a structure shown below:



in which R_d is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

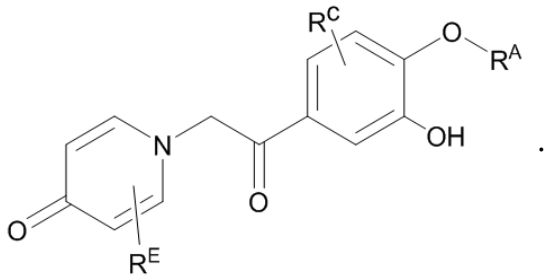
[0024] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises oxidizing the hydroxyl group on the middle bridge of the type-A target product to obtain a type-B target product,

where the type-B target product is a compound having a structure shown below:



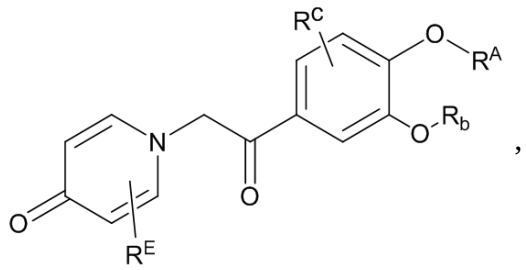
[0025] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises deprotecting the group R^B that is a hydroxyl protecting group on the type-B target product to obtain a type-B-1 target product,

where the type-B-1 target product is a compound having a structure shown below:



[0026] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises subjecting the hydroxyl group on the phenyl ring of the type B-1 target product to an addition/substitution reaction to obtain a type B-2 target product,

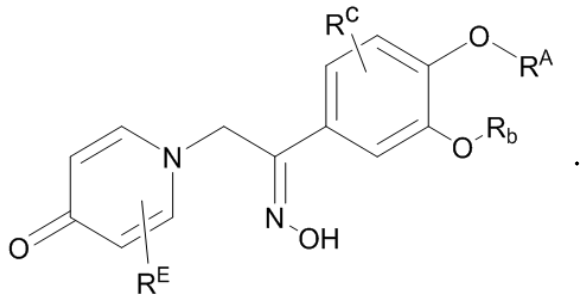
where the type-B-2 target product is a compound having a structure shown below:



in which R_d is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

[0027] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises oximating the carbonyl group on the middle bridge of the type-B target product to obtain a type B-3 target product,

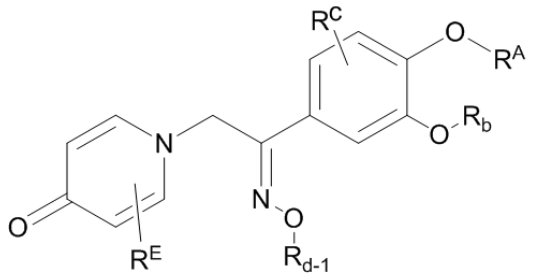
where the type-B-3 target product is a compound having a structure shown below:



[0028] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises subjecting the hydroxyl group on the oxime of the

type-B-3 target product to an addition/substitution reaction to obtain a type-B-4 target product,

where the type-B-4 target product is a compound having a structure shown below:



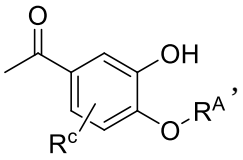
in which R_{d-1} is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the group is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

[0029] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises: using a 3-hydroxyacetophenone derivative I as a starting material, and substituting the hydrogen in the hydroxyl group of the 3-hydroxyacetophenone derivative I with R^B, to obtain an intermediate product II;

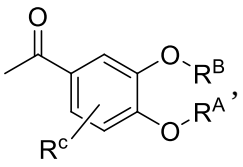
reacting the intermediate product II in the presence of a halogenating agent to obtain an intermediate product III; and

reacting the halogen in the intermediate product III with a six-membered oxygen-containing cyclic compound to obtain a type-B target product,

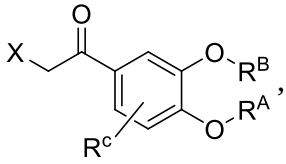
where the 3-hydroxyacetophenone derivative I is a compound having a structure shown below:



the intermediate product II is a compound having a structure shown below:



the intermediate product III is a compound having a structure shown below:

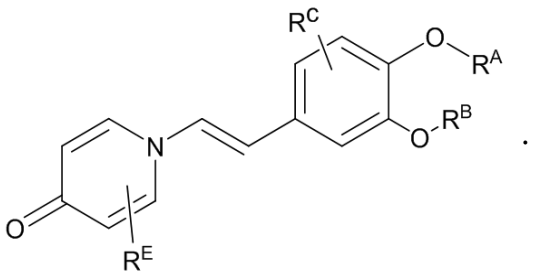

, in which X is halogen.

[0030] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises removing the hydroxyl group on the middle bridge of the type-A target product to obtain a type-C target product,

or

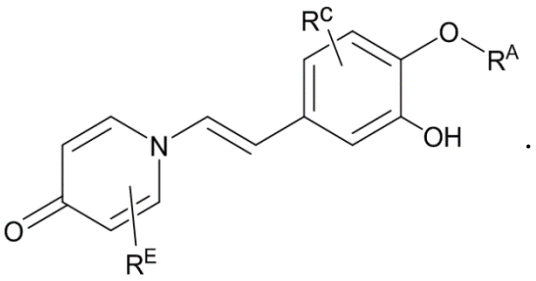
reducing and then eliminating the carbonyl group on the middle bridge of the type-B target product to obtain a type-C target product,

where the type-C target product is a compound having a structure shown below:


.

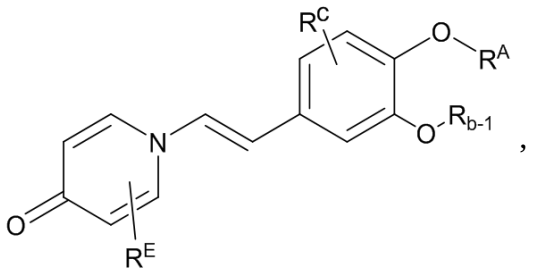
[0031] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reducing and then eliminating the carbonyl group on the middle bridge of the type-B-2 target product to obtain a type-C-1 target product,

where the type-C-1 target product is a compound having a structure shown below:


.

[0032] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises subjecting the hydroxyl group on the phenyl ring of the type C-1 target product to an addition/substitution reaction to obtain a type C-2 target product,

where the type-C-2 target product is a compound having a structure shown below:



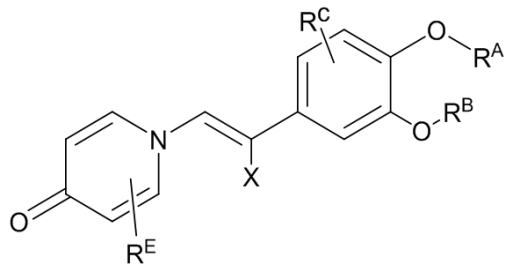
,

in which R_{b-1} is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

[0033] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reacting the carbonyl group on the middle bridge of the type-B target product with a halogenating reagent to obtain an intermediate product X1; and

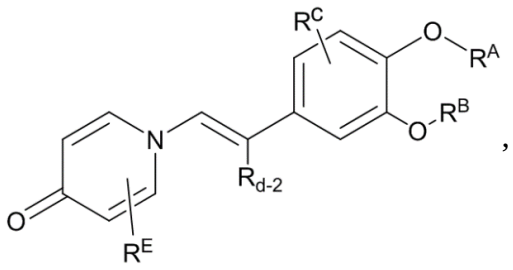
replacing the halogen in the intermediate product X1 to obtain a type-C-3 target product,

where the intermediate product X1 is a compound having a structure shown below:



, in which X is halogen; and

where the type-C-3 target product is a compound having a structure shown below:



,

in which R_{d-2} is aryl, alkyl, cycloalkyl, an ether group, or an ester group where one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

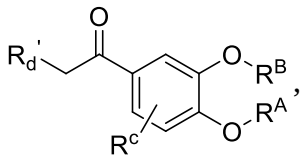
[0034] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises: reacting an acetophenone derivative 1 as a starting

material with trimethylsilyl cyanide, to obtain an intermediate product 2;

reducing the intermediate product 2 to obtain an intermediate product 3; and

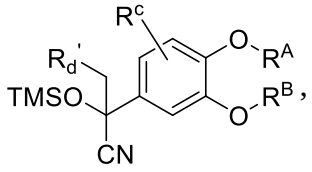
reacting the amino group in the intermediate product 3 with a six-membered oxygen-containing cyclic compound to obtain a type-A' target product,

where the acetophenone derivative 1 is a compound having a structure shown below:



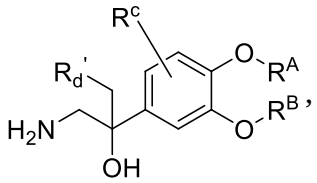
, in which R_d' is hydrogen, alkyl, aryl, alkynyl, or alkenyl, and in the above groups one or more hydrogen atom(s) attached to carbon in the group is/are substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl;

the intermediate product 2 is a compound having a structure shown below:



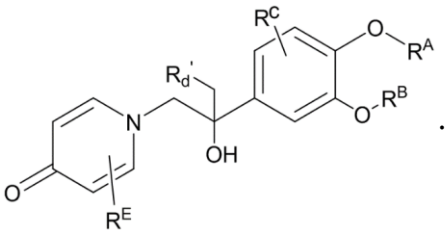
,

the intermediate product 3 is a compound having a structure shown below:



,

the type-A' target product is a compound having a structure shown below:

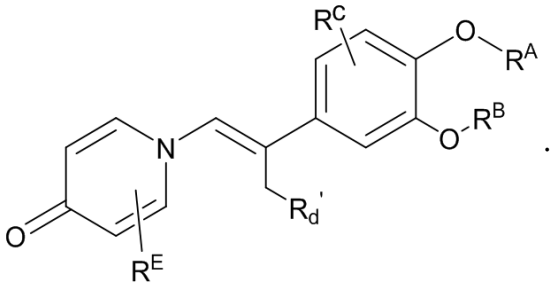


.

[0035] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises removing the hydroxyl group on the middle bridge of

the type-A' target product to obtain a type-C' target product,

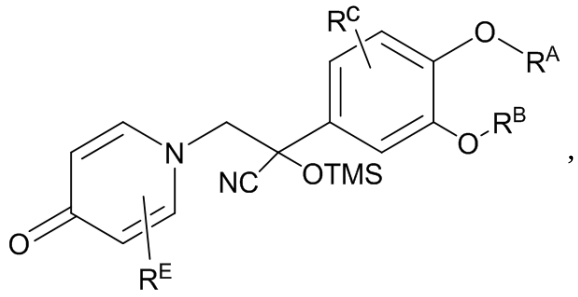
where the type-C' target product is a compound having a structure shown below:



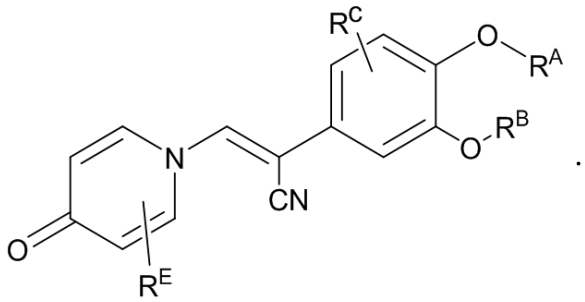
[0036] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reacting the carbonyl group on the middle bridge of the type-B target product with trimethylsilyl cyanide to obtain an intermediate product Y1; and

subjecting the intermediate product Y1 to reduction and elimination to obtain a type-C" target product,

where the intermediate product Y1 is a compound having a structure shown below:



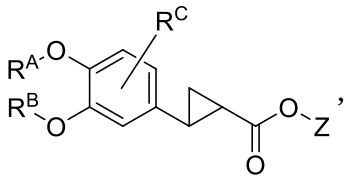
the type-C" target product is a compound having a structure shown below:



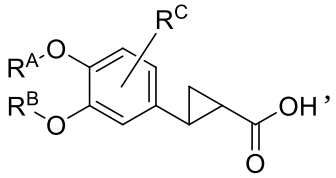
[0037] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reacting a six-membered N-acetonitrile compound Z1 with a benzaldehyde derivative Z2 to obtain a type-C" target product,

where the six-membered N-acetonitrile compound Z1 is a compound having a structure shown

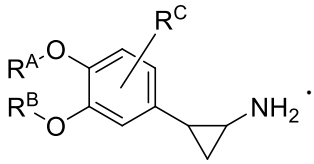
the intermediate product 3 is a compound having a structure shown below:



the intermediate product 4 is a compound having a structure shown below:



the intermediate product 5 is a compound having a structure shown below:



[0039] In addition, the present invention also provides use of the anti-inflammatory compound as a PDE4 inhibitor.

[0040] In addition, the present invention also provides use of the anti-inflammatory compound in the treatment of inflammatory skin diseases.

[0041] In addition, the present invention also provides a drug comprising 0.01-10% of the anti-inflammatory compound mentioned above; and

other components selected from a surfactant, a lipid compound, and an auxiliary agent;

where the amount of the surfactant accounts for 10-30% of the total weight of the drug;

the amount of the lipid compound accounts for 50-85% of the total weight of the drug; and

the amount of the auxiliary agent accounts for 10-30% of the total weight of the drug.

[0042] Function and effect:

The present invention provides a novel anti-inflammatory compound that has a potent inhibition effect on PDE4, an important target for autoimmune activation, and is easy to penetrate the skin, and readily degradable. It is more effective than existing drugs (such as Eucrisa) or has fewer side effects than existing drugs (such as hormones, and tacrolimus), thus being a topical