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

cascade in cells by regulating the cyclic nucleotide level. So far, a family of 11 PDE isozyme genes have been identified. The difference between these isozymes lies in their cell distribution and biochemical functions. High PDE4 activity was found in leukocytes of patients with atopic dermatitis, particularly children (Butle, JM, et al., J. Allergy Clin. Immunol.1983, 71: 490-497). PDE4 is a main isozyme in inflammatory cells, such as monocytes and monocyte-derived macrophages (Gantner et al., Br. J. Pharmacol.,1997, 121: 221-2317), eosinophils (Dent et al., J. Pharmacol. Exp. Ther., 1994, 271: 1167-1174) and B lymphocytes (Cooper et al., J. Invest. Dermatol., 2985, 84: 477-482). PDE4 inhibitors show a highly potent anti-inflammatory effect by increasing the intracellular cAMP level. By inhibiting cAMP degradation, the PDE4 inhibitors can regulate intracellular functions (e.g., reduce peroxide production) and gene transcription (e.g., inhibit the synthesis and/or release of inflammatory cytokines). Because PDE4 is also expressed in keratinocytes, these cells can be used as other possible pharmacological targets for controlling inflammatory skin diseases using PDE4 inhibitors.

[0005] PDE4 inhibitors are useful in diseases related to eosinophil activity, particularly inflammatory tracheal diseases, such as bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, eczema, allergic angiitis, inflammation and proliferative skin diseases, such as psoriasis or keratosis. These compounds can be administered possibly in the form of oral, transdermal, topical, inhalable and intranasal preparations.

[0006] In recent years, great changes have taken place in the treatment of inflammation-related diseases. Due to the more and more attention paid to the severity of these diseases and the insight into the important role of cytokines in their immune pathogenesis by the patients and physicians, many drugs targeting cytokines are available in the clinic and some are available in the market to treat these diseases related to the autoimmune system. Most of the efforts are focused on targeting TNF-α and IL-1. At present, many drugs are available on the market. For example, TNF-α inhibitors such as Etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira), certolizumab pegol (Cimzia) can be used for treating immune system-related diseases such as

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).

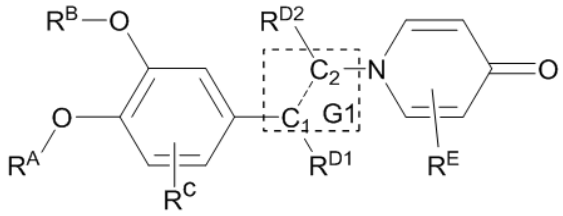
[0010] In view of this, it can be found that the existing drugs for eczema and psoriasis cannot meet the needs of patients, particularly the majority of mild-moderate patients, and more effective and safe topical drugs are still needed to be developed to treat most mild-moderate inflammatory

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:

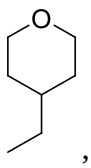
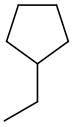


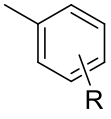
[0013] In the structural formula, R^A is hydrogen, alkyl, or aryl, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, aryl, or halogen,

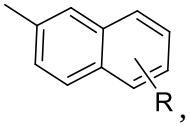
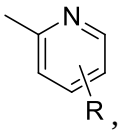
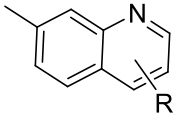
the alkyl is an alkyl group having 1 to 15 carbon atoms, generally a group having the general formula C_nH_{2n+1}-, and preferably a linear or branched alkyl group where n is not greater than 6;

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.

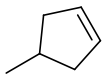
[0014] R^B is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, alkenyl, or alkynyl, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, or halogen, and one or more carbon atom(s) in the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

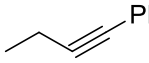
where the alkyl is as defined in the scenario of R^A;

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;

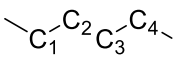
the heterocycloalkyl refers to an oxa/aza/thia three-membered, four-membered, five-membered, or six-membered ring;

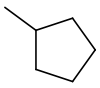
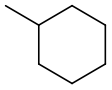
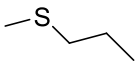
the alkenyl may be selected from linear or branched alkenyl with 2-10 carbon atoms, such as ethenyl (-=), 2-propenyl (-CH_2-=), 2-butenyl (-CH_2-=-CH_3), 3-butenyl (-CH_2-CH_2-=), cyclopentenyl (), and the like;

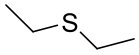
the alkynyl may be selected from linear or branched alkynyl with 2-10 carbon atoms, such as ethynyl (), 2-propynyl (), 

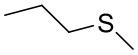
, and the like;

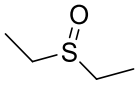
the "one or more hydrogen atom(s) attached to carbon in the groups is/are optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, or halogen" has the same meaning as in the scenario of R^A;

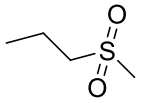
the "one or more carbon atom(s) in the groups is/are optionally substituted with sulfur, sulfoxide, sulfone, or sulfonyl refers to a situation in which one or more carbon atom(s) such as C_1 and C_2 on the structure 

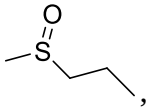
, , or  is/are replaced by S, (S=O), or (O=S=O), for example, 

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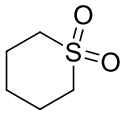
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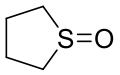
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the hydroxyl protecting group means that a protectant reacts with a hydroxyl group to converts the hydroxyl group into silicon ether, benzyl ether, methyl ether, allyl ether and other forms, so that it is not affected by oxidation, reduction and other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

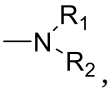
the alkoxy refers to the group -O-R, in which R is a branched or linear alkyl group with 1-20 carbon atoms;

[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;

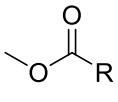
the amino refers to $-NH_2$;

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;

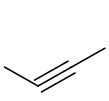
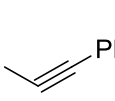
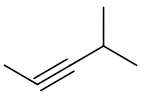
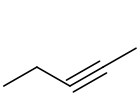
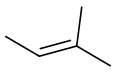
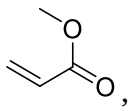
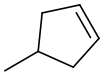
the alkenyl is as defined in the scenario of R^B;

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}.

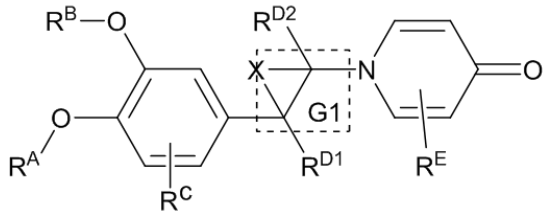
[0019] G1 is a single bond, a double bond or a ring comprising C_1 and C_2,

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;

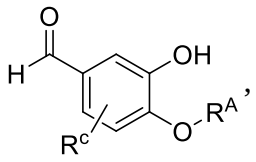
reacting the intermediate product B in the presence of trimethylsilyl cyanide to obtain an

intermediate product C;

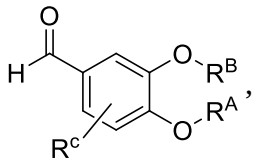
reducing the intermediate product C to obtain an intermediate product D having an amino group; and

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

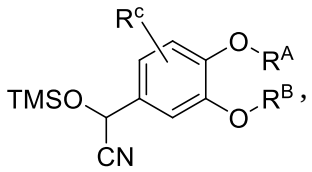
where the 3-hydroxybenzaldehyde derivative A is a compound having a structure shown below:



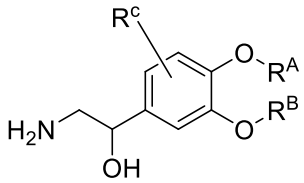
the intermediate product B is a compound having a structure shown below:



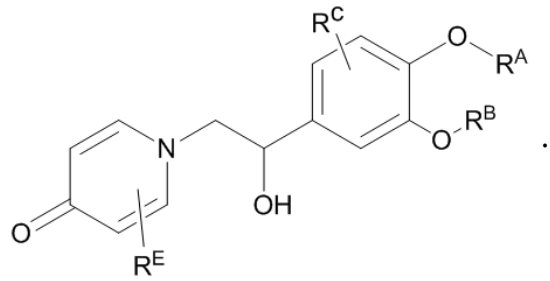
the intermediate product C is a compound having a structure shown below:



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

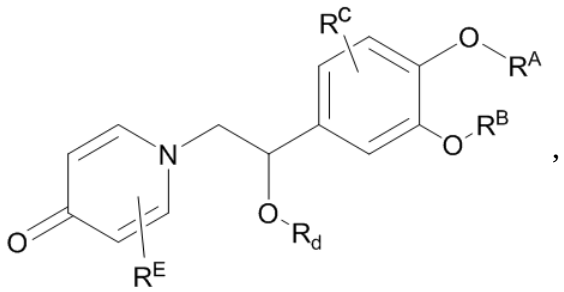


the type-A target product is a compound having a structure shown below:



[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,

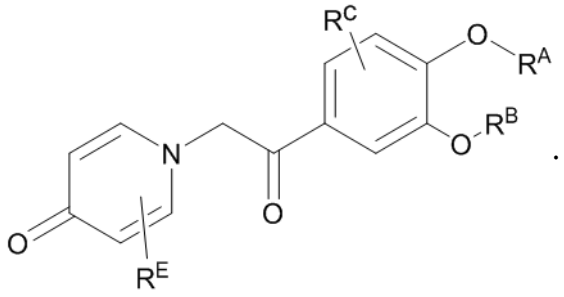
where the type-A-1 target product is a compound having a structure shown below:



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.

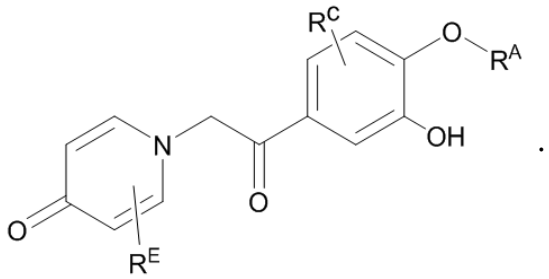
[0024] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises oxidizing the hydroxyl group on the middle bridge of the type-A target product to obtain a type-B target product,

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



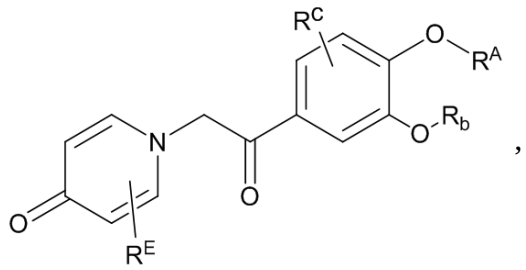
[0025] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises deprotecting the group R^B that is a hydroxyl protecting group on the type-B target product to obtain a type-B-1 target product,

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,

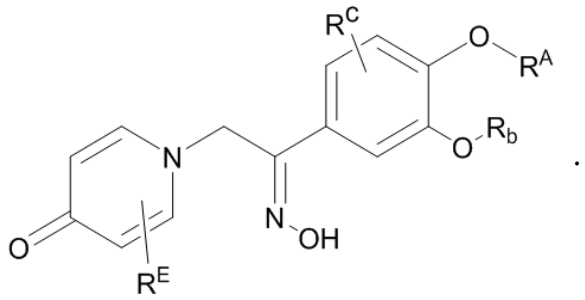
where the type-B-2 target product is a compound having a structure shown below:



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,

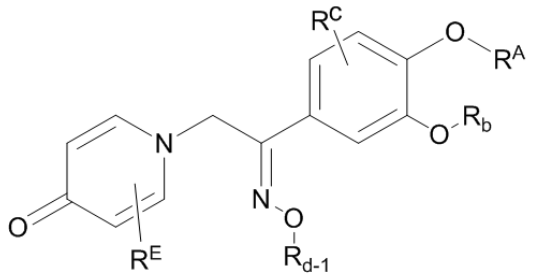
where the type-B-3 target product is a compound having a structure shown below:



[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:



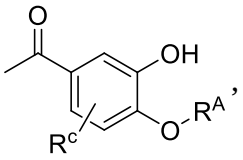
in which R_{d-1} is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the group is/are optionally substituted with alkyl, alkynyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

[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;

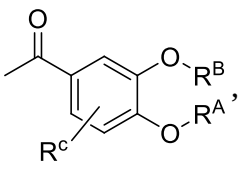
reacting the intermediate product II in the presence of a halogenating agent to obtain an intermediate product III; and

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

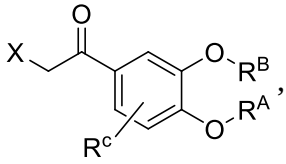
where the 3-hydroxyacetophenone derivative I is a compound having a structure shown below:



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



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

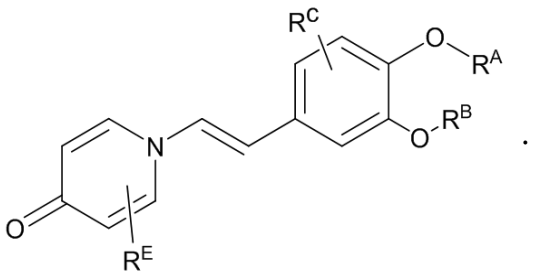

, in which X is halogen.

[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

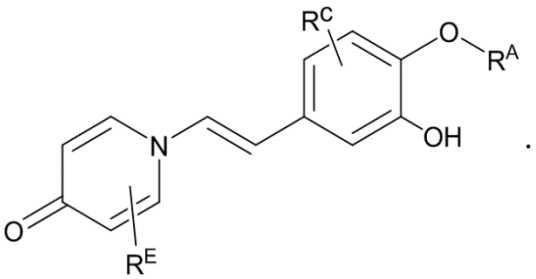
reducing and then eliminating the carbonyl group on the middle bridge of the type-B target product to obtain a type-C target product,

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


.

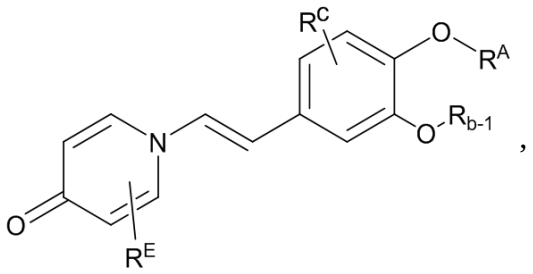
[0031] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reducing and then eliminating the carbonyl group on the middle bridge of the type-B-2 target product to obtain a type-C-1 target product,

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:



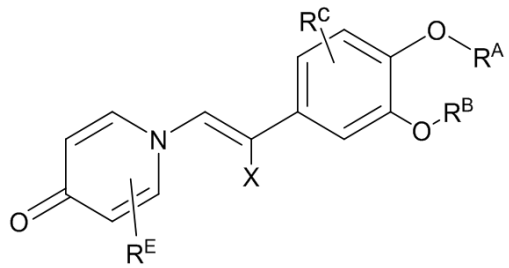
,

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

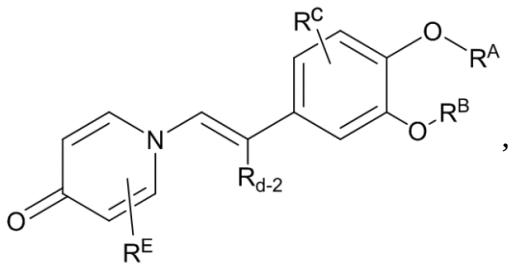
replacing the halogen in the intermediate product X1 to obtain a type-C-3 target product,

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.

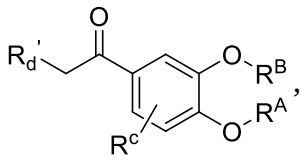
[0034] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises: reacting an acetophenone derivative 1 as a starting

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

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

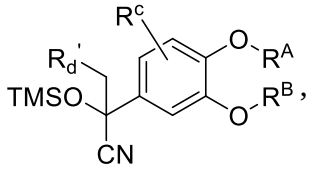
reacting the amino group in the intermediate product 3 with a six-membered oxygen-containing cyclic compound to obtain a type-A' target product,

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



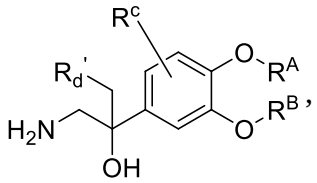
, in which R_d' is hydrogen, alkyl, aryl, alkynyl, or alkenyl, and in the above groups one or more hydrogen atom(s) attached to carbon in the group is/are substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl;

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



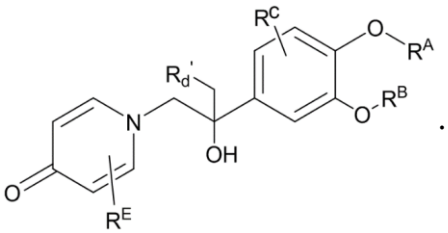
,

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:

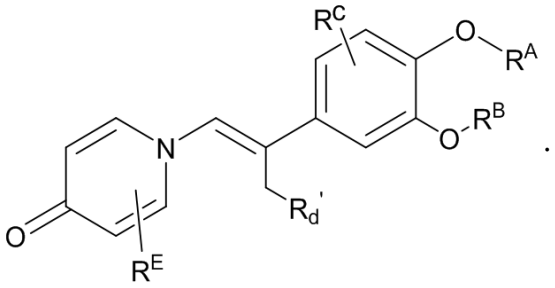


.

[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,

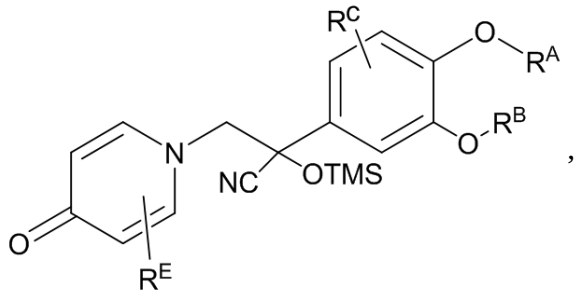
where the type-C' target product is a compound having a structure shown below:



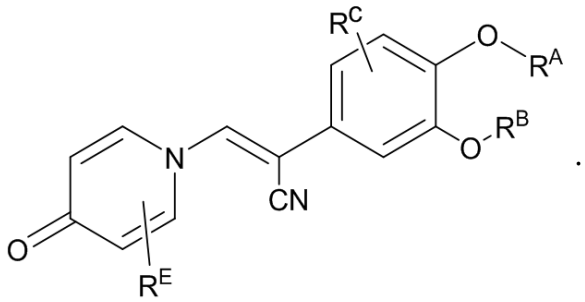
[0036] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises reacting the carbonyl group on the middle bridge of the type-B target product with trimethylsilyl cyanide to obtain an intermediate product Y1; and

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:



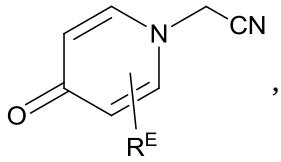
the type-C" target product is a compound having a structure shown below:



[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,

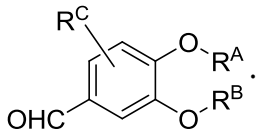
where the six-membered N-acetonitrile compound Z1 is a compound having a structure shown

below:



,

the benzaldehyde derivative Z2 is a compound having a structure shown below:



.

[0038] In addition, the present invention also provides a method for preparing the anti-inflammatory compound, which comprises: esterifying a cinnamic acid derivative 1 as a starting material, to obtain an intermediate product 2;

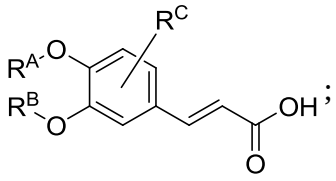
forming a ring from the double bond on the intermediate product 2 to obtain an intermediate product 3;

hydrolyzing the terminal ester group of the intermediate product 3 to give an intermediate product 4 having a carboxyl group;

aminating the terminal carboxyl group of the intermediate product 4 to obtain an intermediate product 5; and

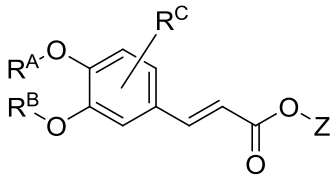
reacting the intermediate product 5 with a six-membered oxygen-containing cyclic compound to obtain a type-D target product,

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



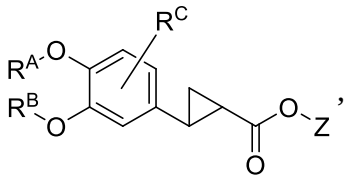
;

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

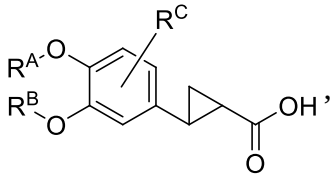


, in which Z is alkyl;

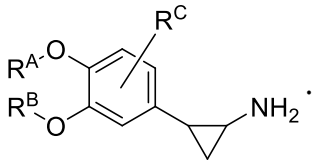
the intermediate product 3 is a compound having a structure shown below:



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.

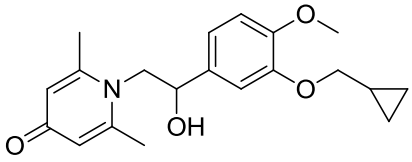
[0042] Function and effect:

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

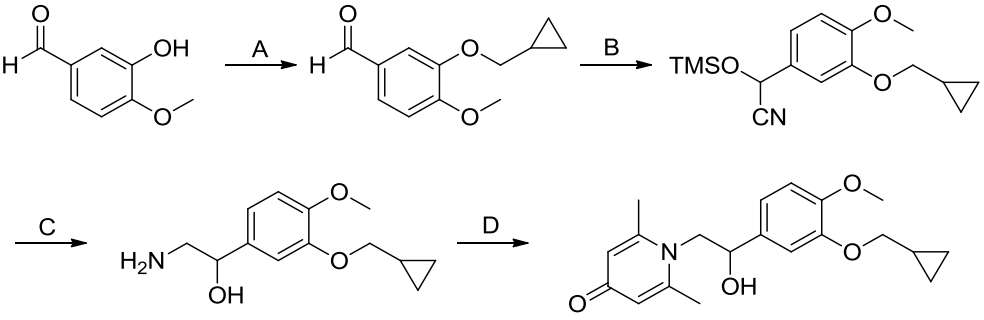
drug for treating eczema having good effects and no toxic side effects.

DESCRIPTION OF THE EMBODIMENTS

[0043] Example 1

[0044] 

[0045] The specific reaction scheme is as shown below:

[0046] 

[0047] Step A:

[0048] At room temperature, 3-hydroxy-4-methoxybenzaldehyde (3.04 g, 20 mmol) was dissolved in acetonitrile (80 mL), and then potassium carbonate (5.52 g, 40 mmol) and bromomethylcyclopropane (4.05 g, 30 mmol) were added in sequence, and heated to 80°C for 3 hours with stirring under nitrogen atmosphere. After the reaction was completed, a saturated aqueous sodium chloride solution (60 mL) was added, and extracted with dichloromethane (3 x 100 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain 3-cyclopropylmethoxy-4-methoxybenzaldehyde (3.50 g, 85%).

[0049] Step B:

[0050] 3-cyclopropylmethoxy-4-methoxybenzaldehyde (3.09 g, 15 mmol) was dissolved in dichloromethane (30 mL); and under nitrogen atmosphere, triethyl amine (4.16 mL, 30 mmol) and trimethylsilyl cyanide (3.75 g, 30 mmol) were added, and stirred for 6 hours at room temperature. The reaction solution was concentrated and rotary dried to obtain a crude product of 2-(3-

cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next reaction.

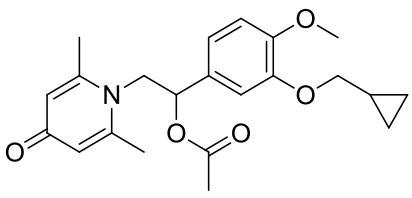
[0051] Step C:

[0052] 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile (4.57 g, 15 mmol) obtained in the above step was dissolved in anhydrous tetrahydrofuran (50 mL), and then lithium aluminum hydride (1.14 g, 30 mmol) was added portion-wise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, water (1.2 mL), an aqueous sodium hydroxide solution (1.2 mL, 15%), and water (3.6 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 2-amino-1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanol.

[0053] Step D:

[0054] 2-amino-1-(3-(cyclopropylmethoxy)-4-methoxyphenyl)ethanol obtained in the above step was dissolved in ethanol (20 mL), and then 2,6-dimethyl-4*H*-pyran-4-one (1 g, 10.41 mmol) and an aqueous sodium hydroxide solution (2 M, 20 mL) were added, and stirred overnight at 60°C. After the reaction was completed, the reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6, dimethylpyridin-4(1*H*)-one (2.01 g, yield 58%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 1.6 Hz, 2H), 6.90 (dd, J = 8.0, 1.6 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.05 (s, 2H), 5.03 (dd, J = 9.6, 3.2 Hz, 1H), 4.03 (dd, J = 15.2, 10.0 Hz, 1H), 3.93-3.84 (m, 6H), 2.47 (s, 6H), 1.39-1.26 (m, 1H), 0.69-0.64 (m, 2H), 0.40-0.36 (m, 2H); LC-MS: m/z 344.2 [M + H]$^+$.

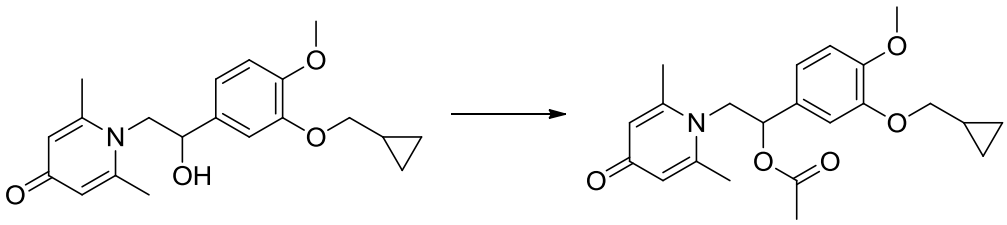
[0055] **Example 2**

[0056] 

[0057] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-

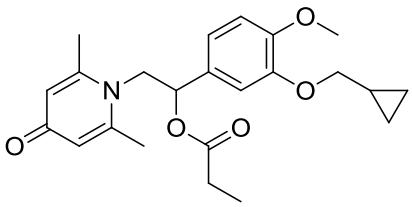
1(4*H*)-yl)ethyl) acetate

[0058] The specific reaction scheme is as shown below:

[0059] 

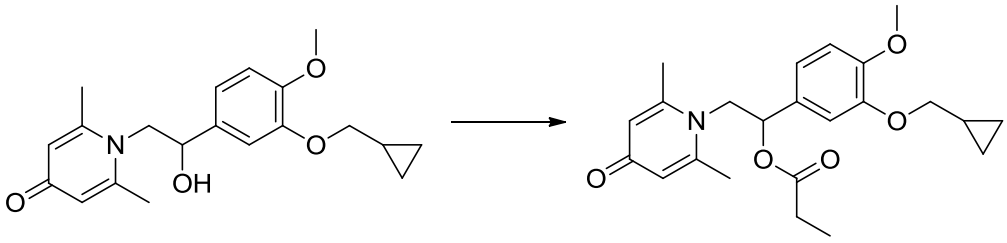
[0060] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then acetyl chloride (118 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) acetate (116 mg, yield 30%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.05-6.96 (m, 5H), 6.12-6.08 (m, 1H), 4.82-4.75 (m, 1H), 4.62-4.56 (m, 1H), 3.86-3.83 (m, 5H), 2.75 (s, 6H), 2.03 (s, 3H) 1.29-1.21 (m, 1H), 0.64-0.60 (m, 2H), 0.37-0.33 (m, 2H); LC-MS: m/z 386.2 $[M + H]^+$.

[0061] **Example 3**

[0062] 

[0063] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) propionate

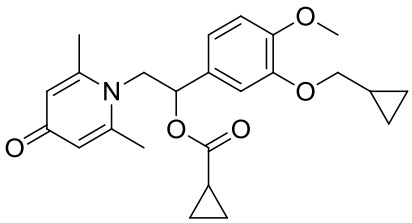
[0064] The specific reaction scheme is as shown below:

[0065] 

[0066] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-

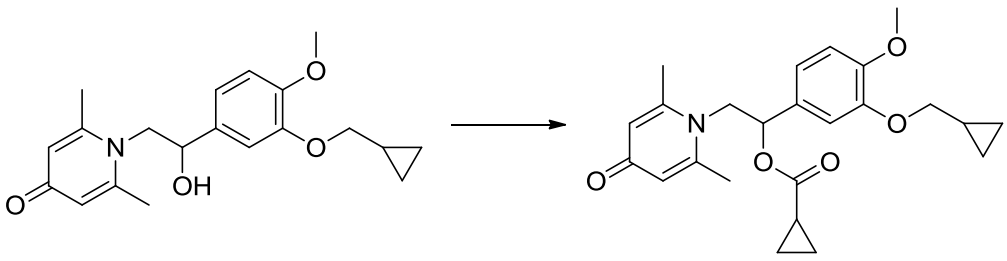
hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then propionyl chloride (139 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) propionate (140 mg, yield 35%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.05-6.97 (m, 5H), 6.15-6.12 (m, 1H), 4.82-4.76 (m, 1H), 4.64-4.59 (m, 1H), 3.86-3.83 (m, 5H), 2.77 (s, 6H), 2.38-2.29 (m, 2H), 1.29-1.24 (m, 1H), 1.05-1.01 (m, 3H), 0.64-0.60 (m, 2H), 0.36-0.33 (m, 2H); LC-MS: m/z 399.9 $[M + H]^+$.

[0067] Example 4

[0068] 

[0069] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) cyclopropylcarboxylate

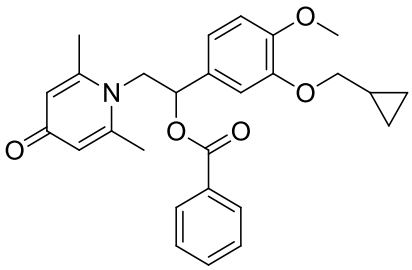
[0070] The specific reaction scheme is as shown below:

[0071] 

[0072] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then cyclopropanecarbonyl chloride (157 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl)

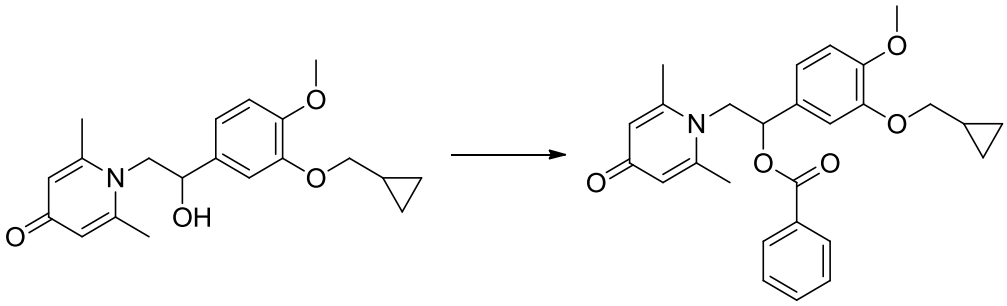
cyclopropylcarboxylate (103 mg, yield 25%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.04-7.01 (m, 2H), 6.95 (s, 1H), 6.35 (s, 2H), 6.11-6.06 (m, 1H), 4.56-4.50 (m, 1H), 4.37-4.32 (m, 1H), 3.89-3.81 (m, 5H), 2.53 (s, 6H), 0.92-0.81 (m, 6H), 0.66-0.62 (m, 2H), 0.39-0.36 (m, 2H); LC-MS: m/z 412.2 $[M + H]^+$.

[0073] Example 5

[0074] 

[0075] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) benzoate

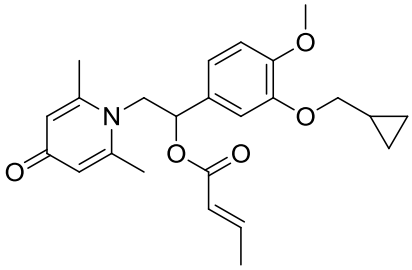
[0076] The specific reaction scheme is as shown below:

[0077] 

[0078] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then benzoyl chloride (211 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) benzoate (94 mg, yield 21%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 8.04-8.00 (m, 2H), 7.70-7.65 (m, 1H), 7.56-7.51 (m, 2H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.00 (s, 2H), 6.48-6.44 (m, 1H), 5.00-4.93 (m, 1H), 4.81-4.75 (m, 1H),

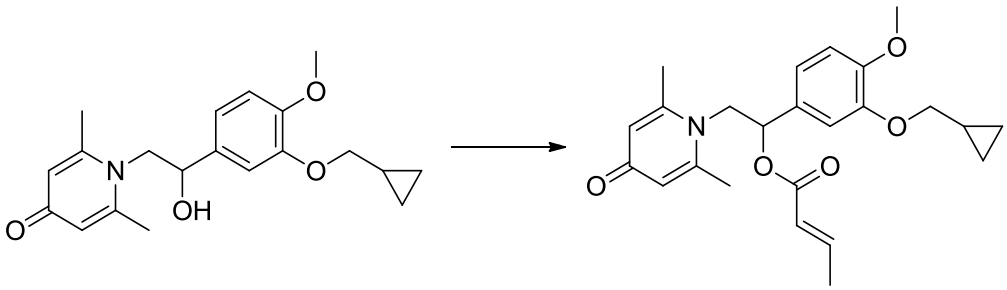
3.91-3.87 (m, 5H), 2.82 (s, 6H), 2.03 (s, 3H) 1.32-1.25 (m, 1H), 0.66-0.61 (m, 2H), 0.39-0.35 (m, 2H); LC-MS: m/z 448.2 $[M + H]^+$.

[0079] Example 6

[0080] 

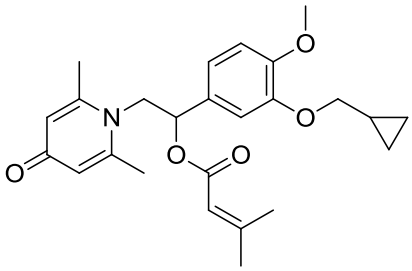
[0081] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) crotonate

[0082] The specific reaction scheme is as shown below:

[0083] 

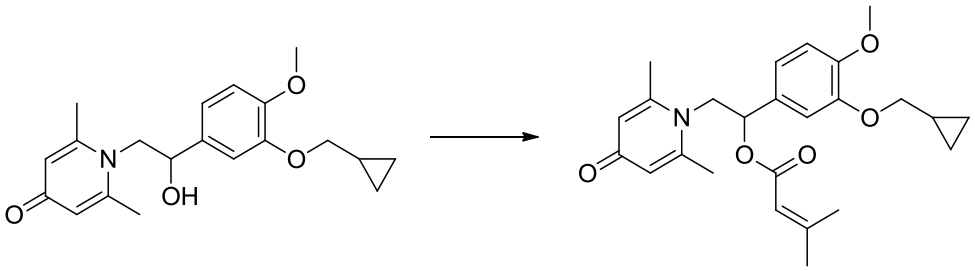
[0084] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then crotonyl chloride (157 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) crotonate (127 mg, yield 31%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 8.4 Hz, 1H), 6.82 (dd, J = 8.4, 2.0 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.33 (s, 2H), 5.98-5.89 (m, 1H), 5.86-5.76 (m, 1H), 4.37-4.28 (m, 1H), 4.13-4.04 (m, 1H), 3.88 (s, 3H), 3.84 (d, J = 6.8 Hz, 2H), 2.37 (s, 6H), 1.33-1.28 (m, 1H), 0.69-0.64 (m, 2H), 0.39-0.35 (m, 2H); LC-MS: m/z 412.2 $[M + H]^+$.

[0085] Example 7

[0086] 

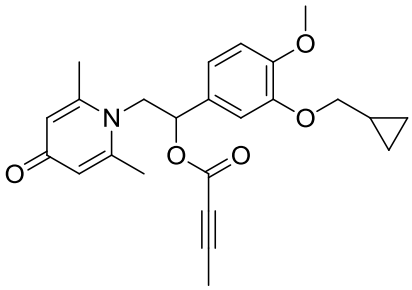
[0087] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) 3-methylcrotonate

[0088] The specific reaction scheme is as shown below:

[0089] 

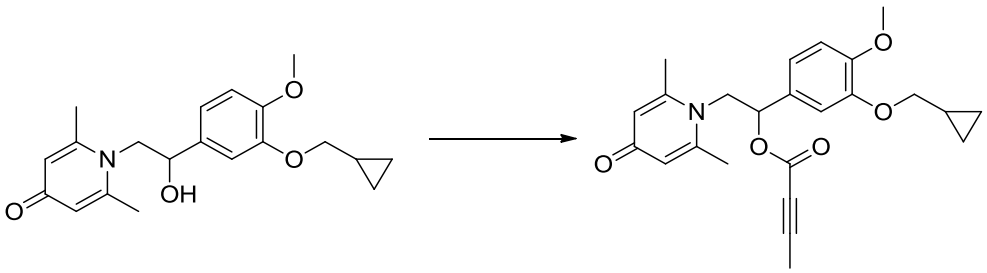
[0090] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (343 mg, 1.0 mmol) was dissolved in dichloromethane (8 mL), and then 3-methylcrotonyl chloride (178 mg, 1.5 mmol) and triethyl amine (202 mg, 2.0 mmol) were added in sequence, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl)3-methyl crotonate (137 mg, yield 32%, white solid). ^{1}H NMR (400 MHz, CDCl3) δ 6.87 (d, J = 8.4 Hz, 1H), 6.83 (dd, J = 8.4,2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.28 (s, 2H), 5.90 (dd, J = 9.2, 4.8 Hz, 1H), 4.91 (s, 1H), 4.30 (dd, J = 15.2, 9.2 Hz, 1H), 4.05 (dd, J = 15.2, 4.8 Hz, 1H), 3.88 (s, 3H), 3.83 (d, J = 7.2 Hz, 2H), 3.02 (s, 2H), 2.37 (s, 6H), 1.69 (s, 3H), 1.35-1.27 (m, 1H), 0.69-0.64 (m, 2H), 0.39-0.35 (m, 2H); LC-MS: m/z 426.2 $[M + H]^{+}$.

[0091] Example 8

[0092] 

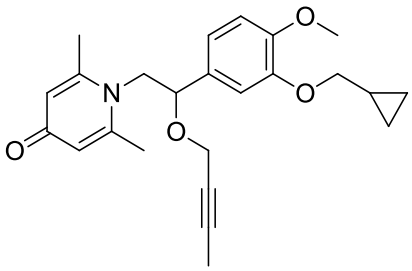
[0093] (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) but-2-ynoate

[0094] The specific reaction scheme is as shown below:

[0095] 

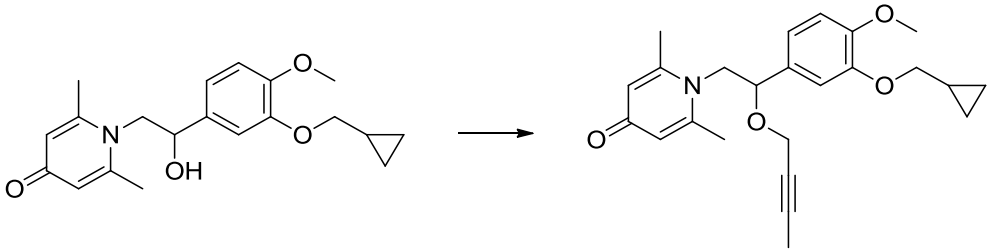
[0096] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (197 mg, 0.69 mmol) and 2-butynoic acid (72 mg, 0.86 mmol) were dissolved in dichloromethane (10 mL), and then 4-dimethylaminopyridine (105 mg, 0.86 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (165 mg, 0.86 mmol) were added in sequence, and stirred overnight at 30°C. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl)but-2-ynoate (37 mg, 9%, white solid). ^{1}H NMR (400 MHz, CDCl3) δ 6.88-6.82 (m, 2H), 6.77 (d, J = 1.6 Hz, 1H), 6.22 (s, 2H), 5.90 (dd, J = 8.4, 5.2 Hz, 1H), 4.31 (dd, J = 15.2, 8.4 Hz, 1H), 4.04 (dd, J = 15.2, 5.2 Hz, 1H), 3.88 (s, 3H), 3.84 (d, J = 7.2 Hz, 2H), 2.33 (s, 6H), 2.01 (s, 3H), 1.32-1.28 (m, 1H), 0.69-0.64 (m, 2H), 0.39-0.35 (m, 2H). LC-MS: m/z 410.4 $[M + H]^+$.

[0097] Example 9

[0098] 

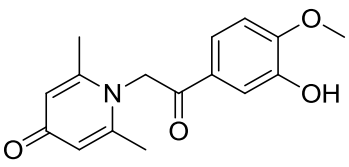
[0099] 1-(2-(but-2-yn-1-yloxy)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)ethyl)-2,26-dimethylpyridin-4-(1*H*)-one

[0100] The specific reaction scheme is as shown below:

[0101] 

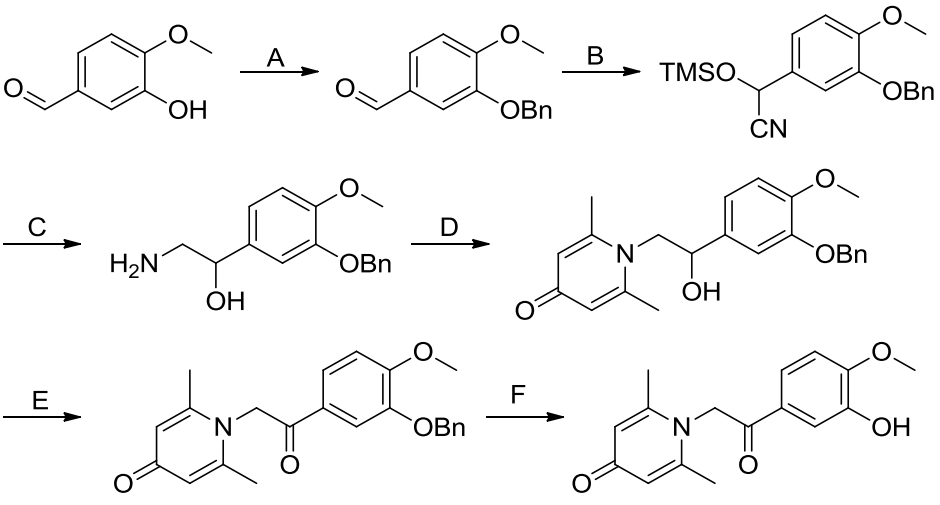
[0102] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then 1-bromo-2-butyne (40 mg, 0.30 mmol) and cesium carbonate (98 mg, 0.30 mmol) were added and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(but-2-yn-1-yloxy)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)ethyl)-2,26-dimethylpyridin-4-(1*H*)-one (19 mg, yield 32%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 7.6 Hz, 1H), 6.84-6.81 (m, 2H), 6.58 (s, 2H), 4.70-4.66 (m, 1H), 4.30-4.24 (m, 1H), 4.14-4.08 (m, 1H), 4.05-4.00 (m, 1H), 3.91-3.86 (m, 5H), 3.82-3.77 (m, 1H), 2.45 (s, 6H), 1.37-1.31 (m, 1H), 1.27 (s, 3H), 0.72-0.66 (m, 2H), 0.42-0.38 (m, 2H); LC-MS: m/z 396.1 $[M + H]^+$.

[0103] Example 10

[0104] 

[0105] 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0106] The specific reaction scheme is as shown below:

[0107] 

[0108] Step A:

[0109] At room temperature, 3-hydroxy-4-methoxybenzaldehyde (1.52 g, 10 mmol) was dissolved in acetonitrile (40 mL), and then potassium carbonate (2.76 g, 20 mmol) and benzyl bromide (2.56 g, 15 mmol) were added in sequence, and heated to 80°C for 3 hours with stirring under nitrogen atmosphere. After the reaction was completed, a saturated aqueous sodium chloride solution (30 mL) was added, and extracted with dichloromethane (3 x 50 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain 3-benzoxy-4-methoxybenzaldehyde (2.30 g, 95%, white solid).

[0110] Step B:

[0111] 3-benzoxy-4-methoxybenzaldehyde (2.30 g, 9.5 mmol) was dissolved in dichloromethane (30 mL), and then triethyl amine (1.92 g, 19 mmol) and trimethylsilyl cyanide (2.82 g, 28.5 mmol) were added in sequence in an ice bath and stirred for 16 hours under nitrogen atmosphere at room temperature. After the reaction was completed, direct rotary drying gave 2-(3-benzoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next

reaction.

[0112] Step C:

[0113] 2-(3-benzoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile obtained in the above step was dissolved in anhydrous tetrahydrofuran (40 mL), and lithium aluminum hydride (1.08 g, 28.5 mmol) was added portion-wise in an ice bath and stirred overnight at room temperature. After the reaction was completed, water (1.1 mL), an aqueous sodium hydroxide solution (1.1 mL, 15%), and water (3.3 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 2-amino-1-(3-benzoxy-4-methoxyphenyl)ethanol, which was directly used in the next reaction.

[0114] Step D:

[0115] 2-Amino-1-(3-benzoxy-4-methoxyphenyl)ethanol obtained in the above step was dissolved in ethanol (60 mL), and then 2,6-dimethyl-4*H*-pyran-4-one (1.24 g, 10 mmol), sodium hydroxide (800 mg, 20 mmol) and water (10 mL) were added in sequence, heated to 60°C, and stirred overnight under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-benzoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (1.62 g, 45%, white solid). LC-MS m/z 380.2 $[M + H]^+$.

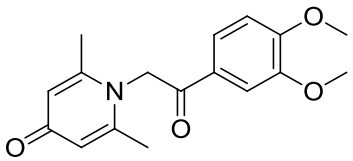
[0116] Step E:

[0117] 1-(2-(3-benzoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (1.62 g, 4.26 mmol) was dissolved in dichloromethane (30 mL), and then the Dess-Martin Periodinane (2.16 g, 5.11 mmol) was added and stirred at room temperature for 2 hours. The reaction solution was filtered, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain 1-(2-(3-benzoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (1.37 g, yield 85%, white solid). LC-MS m/z 378.2 $[M + H]^+$.

[0118] Step F:

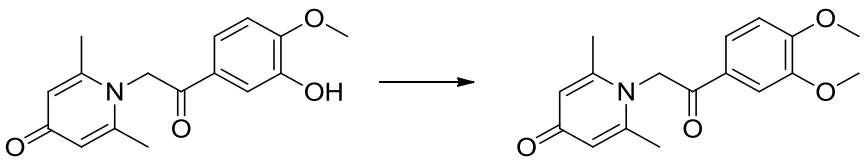
[0119] The compound 1-(2-(3-benzoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (1.37 g, 3.61 mmol) was dissolved in methanol (50 mL), then Pd/C (137 mg) and triethyl amine (1 mL) were added, and hydrogen was introduced. The system was stirred overnight at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (660 mg, yield 64%, gray solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.04 (s, 2H), 5.97 (s, 2H), 3.98 (s, 3H), 2.51 (s, 6H); LC-MS: m/z 288.2 $[M + H]^+$.

[0120] Example 11

[0121] 

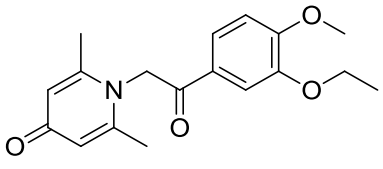
[0122] 1-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0123] The specific reaction scheme is as shown below:

[0124] 

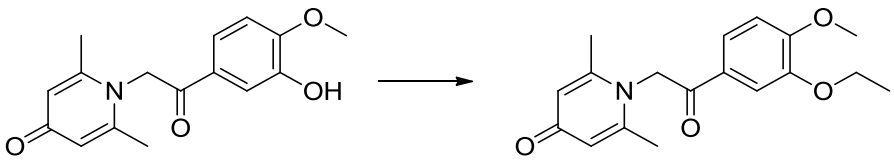
[0125] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (28 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then iodomethane (19 mg, 0.13 mmol) and potassium carbonate (21 mg, 0.15 mmol) were added and stirred for 1 hr at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, yield 30%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.05 (s, 2H), 6.02 (s, 2H), 4.07 (s, 3H), 3.96 (s, 3H), 2.52 (s, 6H); LC-MS: m/z 302.1 $[M + H]^+$.

[0126] Example 12

[0127] 

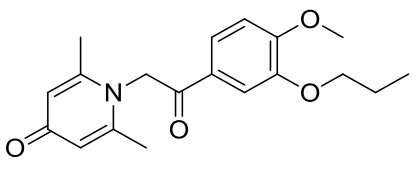
[0128] 1-(2-(3-ethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0129] The specific reaction scheme is as shown below:

[0130] 

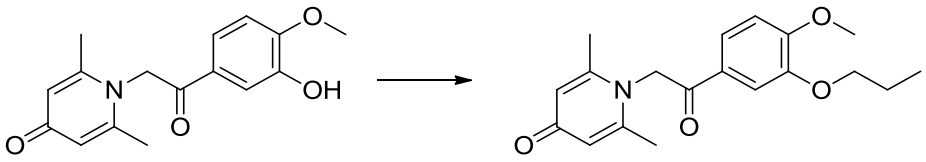
[0131] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (28 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then iodoethane (21 mg, 0.13 mmol) and potassium carbonate (21 mg, 0.15 mmol) were added and stirred for 1 hr at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-ethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (15 mg, yield 48%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.02 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.15 (s, 2H), 4.32 (q, J = 6.0 Hz, 2H), 3.92 (s, 3H), 2.62 (s, 6H), 1.51 (t, J = 6.0 Hz, 1H); LC-MS m/z 316.1 $[M + H]^+$.

[0132] Example 13

[0133] 

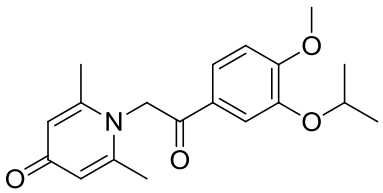
[0134] 1-(2-(3-propoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0135] The specific reaction scheme is as shown below:

[0136] 

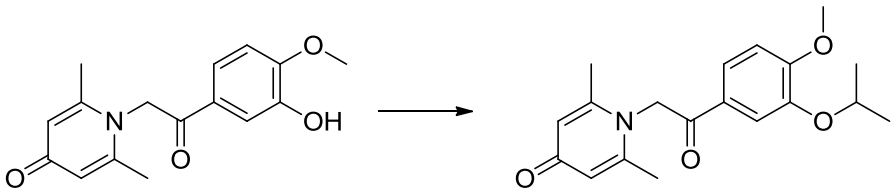
[0137] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, 0.07 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then bromopropane (10 mg, 0.08 mmol) and potassium carbonate (15 mg, 0.11 mmol) were added and stirred for 2 hours at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-propoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (8 mg, yield 34%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.4, 2.0 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.38 (s, 2H), 6.02 (s, 2H), 4.03 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 2.37 (s, 6H), 1.90-1.80 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H); LC-MS: m/z 330.2 $[M+H]^+$.

[0138] Example 14

[0139] 

[0140] 1-(2-(3-isopropoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

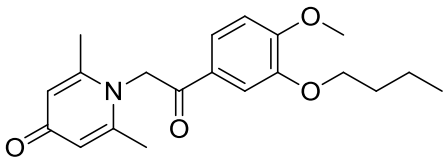
[0141] The specific reaction scheme is as shown below:

[0142] 

[0143] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (35 mg, 0.12 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then bromo-isopropane (17 mg, 0.14 mmol) and potassium carbonate (25 mg, 0.18 mmol) were added, and

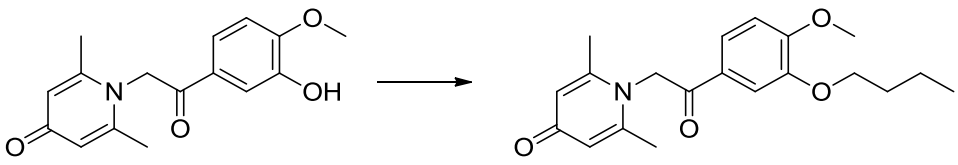
stirred for 2 hours at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-isopropoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, yield 63%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 8.4, 2.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 14.4 Hz, 1H), 6.60 (d, J = 14.4 Hz, 1H), 6.30 (s, 2H), 4.69-4.60 (m, 1H), 3.90 (s, 3H), 2.57 (s, 6H), 1.35 (d, J = 6.0 Hz, 6H); LC-MS: m/z 330.2 $[M+H]^+$.

[0144] Example 15

[0145] 

[0146] 1-(2-(3-n-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)- one

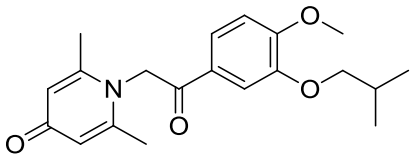
[0147] The specific reaction scheme is as shown below:

[0148] 

[0149] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then bromo-isopropane (95 mg, 0.7 mmol) and potassium carbonate (37 mg, 0.7mmol) were added, and stirred for 2 hours at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-n-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (26 mg, yield 42%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.05 (s, 2H), 6.02 (s, 2H), 4.07 (t, J = 6.4 Hz, 2H), 3.96 (s, 3H), 2.52 (s, 6H), 1.84-1.77 (m, 2H), 1.58-1.48 (m, 2H),

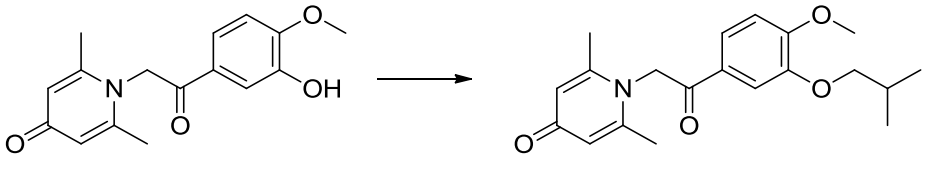
0.95 (t, *J* = 7.2 Hz, 3H); LC-MS: m/z 344.1 $[M + H]^+$.

[0150] Example 16

[0151] 

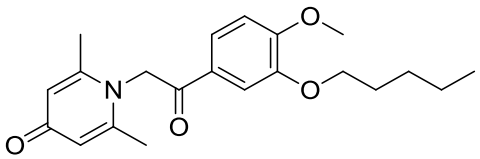
[0152] 1-(2-(3-iso-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0153] The specific reaction scheme is as shown below:

[0154] 

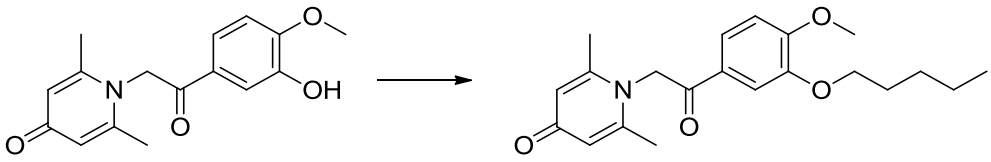
[0155] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then bromo-isobutane (27 mg, 0.2 mmol) and potassium carbonate (37 mg, 0.27 mmol) were added, and stirred for 2 hours at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-iso-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 40%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 14.4 Hz, 1H), 6.60 (d, *J* = 14.4 Hz, 1H), 6.30 (s, 2H), 3.92 (s, 3H), 3.81 (d, *J* = 6.8 Hz, 2H), 2.27 (s, 6H), 2.25-2.17 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 6H); LC-MS: m/z 344.1 $[M + H]^+$.

[0156] Example 17

[0157] 

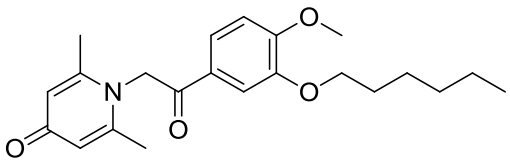
[0158] 1-(2-(3-n-pentyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0159] The specific reaction scheme is as shown below:

[0160] 

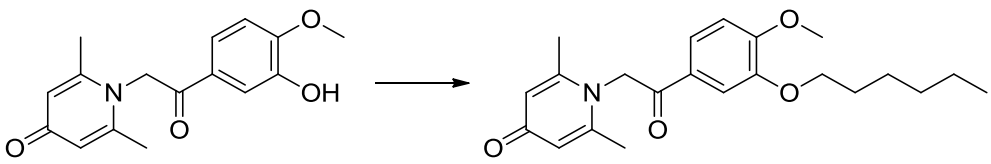
[0161] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 1-bromopentane (105 mg, 0.7 mmol) and potassium carbonate (97 mg, 0.7mmol) were added, and stirred for 5 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-n-pentyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 32%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.07 (s, 2H), 6.03 (s, 2H), 4.06 (t, J = 6.4 Hz, 2H), 3.96 (s, 3H), 2.53 (s, 6H), 1.86-1.79 (m, 2H), 1.52-1.36 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); LC-MS: m/z 358.1 $[M + H]^+$.

[0162] Example 18

[0163] 

[0164] 1-(2-(3-n-hexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

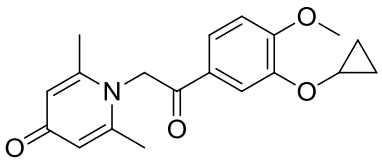
[0165] The specific reaction scheme is as shown below:

[0166] 

[0167] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 1-bromon-hexane (115 mg, 0.7 mmol) and potassium carbonate (97 mg, 0.7 mmol) were added and stirred for 5 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated

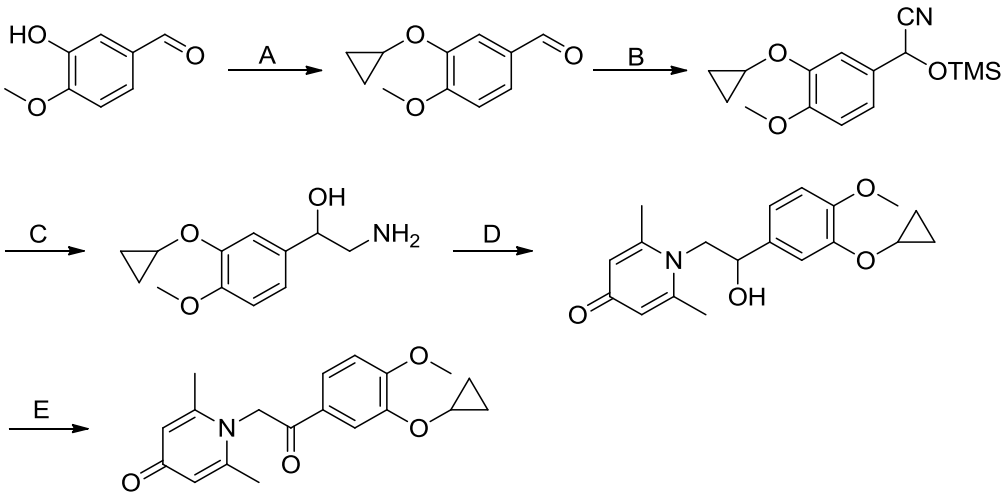
saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-n-hexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (43 mg, yield 66%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.08 (s, 2H), 6.04 (s, 2H), 4.07 (t, J = 6.4 Hz, 2H), 3.96 (s, 3H), 2.53 (s, 6H), 1.86-1.78 (m, 2H), 1.54-1.46 (m, 2H), 1.40-1.34 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); LC-MS: m/z 372.0 $[M + H]^+$.

[0168] Example 19

[0169] 

[0170] 1-(2-(3-cyclopropyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0171] The specific reaction scheme is as shown below:

[0172] 

[0173] Step A:

[0174] The compound 3-hydroxy-4-methoxybenzaldehyde (1 g, 6.6 mmol), bromo-cyclopropane (2.4 mg, 19.8 mmol), cesium carbonate (6.5 g, 19.8 mmol), and potassium iodide (168 mg,0.15 mmol) were dissolved in *N*, *N*-dimethylformamide (10 mL), stirred for 1 hr in a sealed tube at 180°Cunder nitrogen atmosphere, then heated to 220°C, and stirred for another 1 hr. After the reaction was completed, saturated saline (20 mL) was added, and extracted with

dichloromethane (3 x 20 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by column chromatography gave 3-cyclopropyloxy-4-methoxybenzaldehyde (170 mg, yield 13%, pale yellow oil). LC-MS: m/z 193.4 $[M + H]^+$.

[0175] Step B:

[0176] 3-cyclopropyloxy-4-methoxybenzaldehyde (170 mg, 0.88 mmol) was dissolved in dichloromethane (4 mL); and under nitrogen atmosphere, triethyl amine (356 mg, 3.52 mmol) and trimethylsilyl cyanide (349 mg, 3.52 mmol) were added, and stirred for 6 hours at room temperature. After the reaction was completed, the reaction solution was concentrated and rotary dried to obtain 2-(3-cyclopropyloxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next reaction.

[0177] Step C:

[0178] 2-(3-cyclopropyloxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile obtained in the above step was dissolved in anhydrous tetrahydrofuran (20 mL), and then lithium aluminum hydride (100 mg, 2.6 mmol) was added portion-wise in an ice bath and stirred overnight at room temperature. After the reaction was completed, water (0.1 mL), an aqueous sodium hydroxide solution (0.1 mL, 15%), and water (0.3 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, and filtered. The filtrate was rotary dried to obtain a crude product of 2-amino-1-(3-cyclopropyloxy-4-methoxyphenyl)ethanol (300 mg).

[0179] Step D:

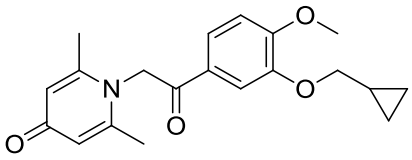
[0180] 2-Amino-1-(3-(cyclopropyloxy)-4-methoxyphenyl)ethanol obtained in the above step was dissolved in ethanol (5 mL), and then 2,6-dimethyl-4*H*-pyran-4-one (124 mg, 1 mmol) and aqueous sodium hydroxide solution (2 M, 2 mL) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropyloxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 34%, white solid). LC-MS: m/z 330.1 [M

+ H]$^+$.

[0181] Step E:

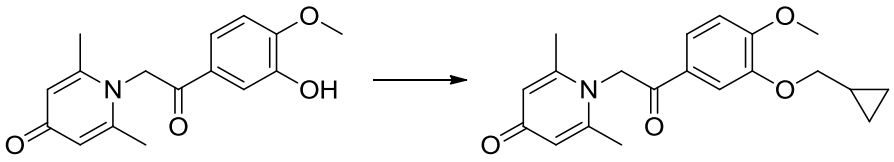
[0182] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, 0.1 mmol) was dissolved in dichloromethane (5 mL), and stirred for 2 hours at normal temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-cyclopropyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (15 mg, yield 45%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 6.44 (s, 2H), 5.75 (s, 2H), 4.02 (s, 3H), 2.32 (s, 6H), 2.23-2.19 (m, 1H), 0.94-0.90 (m, 4H); LC-MS: m/z 328.1 [M + H]$^+$.

[0183] **Example 20**

[0184] 

[0185] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxo)ethyl-2,6-dimethylpyridin-4(1*H*)-one

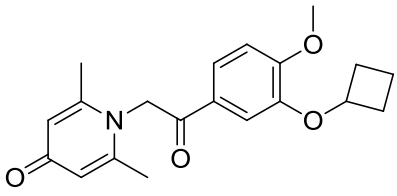
[0186] The specific reaction scheme is as shown below:

[0187] 

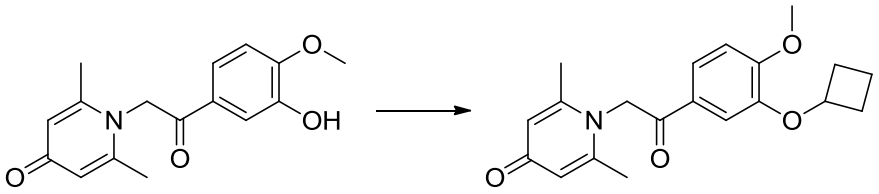
[0188] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromomethylcyclopropane (27 mg, 0.2 mmol) and potassium carbonate (37 mg, 0.27mmol) were added, and stirred for 2 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-

oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, yield 62%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (dd, J = 8.4, 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 5.99 (s, 2H), 5.62 (s, 2H), 3.90 (s, 3H), 3.53 (d, J = 6.8 Hz, 2H), 2.11 (s, 6H), 1.26-1.21 (m, 1H), 0.62-0.56 (m, 2H), 0.36-0.31 (m, 2H); LC-MS: m/z 342.1 $[M + H]^+$.

[0189] Example 21

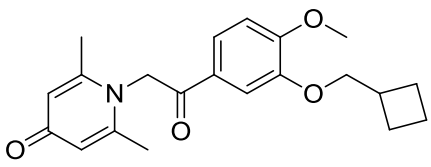
[0190] 

[0191] The specific reaction scheme is as shown below:

[0192] 

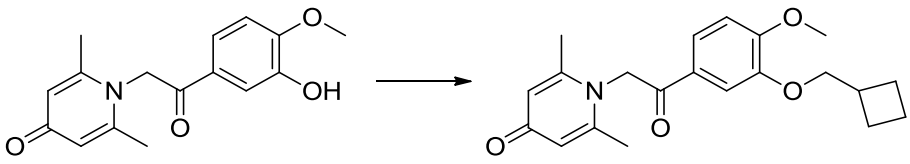
[0193] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then cyclobutyl bromide (69 mg, 0.51 mmol) and potassium carbonate (71 mg, 0.51 mmol) were added and stirred for 5 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-cyclobutyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (16 mg, yield 26%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.04 (s, 2H), 5.99 (s, 2H), 4.79-4.73 (m, 1H), 3.96 (s, 3H), 2.51 (s, 6H), 2.51-2.45 (m, 1H), 2.23-2.13 (m, 1H), 1.91-1.83 (m, 1H), 1.79-1.70 (m, 1H); LC-MS: m/z 342.1 $[M + H]^+$.

[0194] Example 22

[0195] 

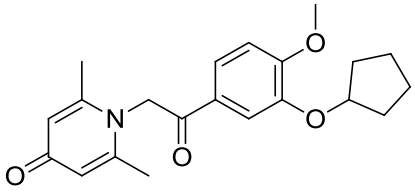
[0196] 1-(2-(3-cyclobutylmethoxy-4-methoxyphenyl)-2-oxo)ethyl-2,6-dimethylpyridin-4(1*H*)-one

[0197] The specific reaction scheme is as shown below:

[0198] 

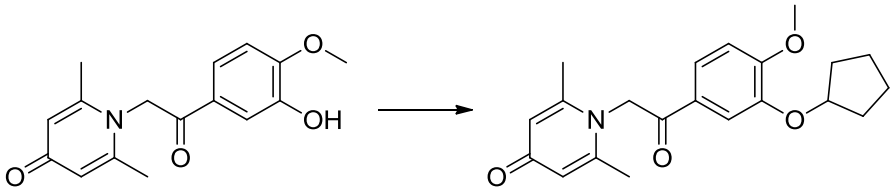
[0199] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromomethylcyclobutane (76 mg, 0.51 mmol) and potassium carbonate (71 mg, 0.51mmol) were added, and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-cyclobutylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (16 mg, yield 24%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.91 (s, 2H), 5.95 (s, 2H), 4.04 (d, J = 6.8 Hz, 2H), 3.95 (s, 3H), 2.84-2.78 (m, 1H), 2.47 (s, 6H), 2.20-2.10 (m, 2H), 2.02-1.86 (m, 4H); LC-MS: m/z 356.2 $[M + H]^+$.

[0200] Example 23

[0201] 

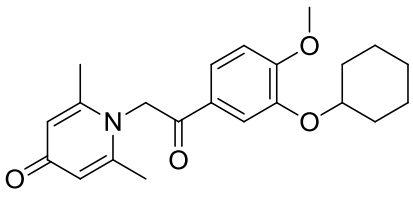
[0202] 1-(2-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0203] The specific reaction scheme is as shown below:

[0204] 

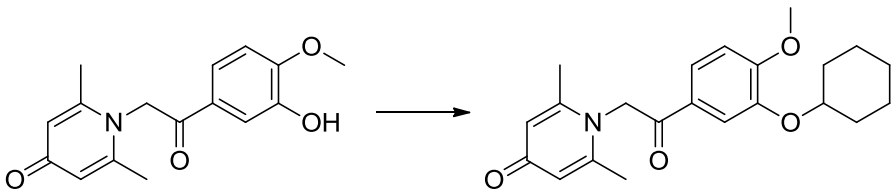
[0205] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromocyclopentane (76 mg, 0.51 mmol) and potassium carbonate (71 mg, 0.51mmol) were added, and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-cyclopentyl-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 33%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.39 (s, 2H), 5.71 (s, 2H), 4.95-4.91 (m, 1H), 3.96 (s, 3H), 2.31 (s, 6H), 2.01-1.80 (m, 6H), 1.71-1.61 (m, 2H); LC-MS m/z 356.2 $[M + H]^+$.

[0206] Example 24

[0207] 

[0208] 1-(2-(3-cyclohexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

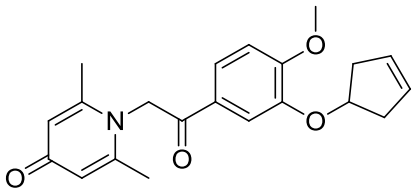
[0209] The specific reaction scheme is as shown below:

[0210] 

[0211] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromocycloohexane (83 mg, 0.51 mmol) and potassium carbonate (71 mg, 0.51mmol) were added,

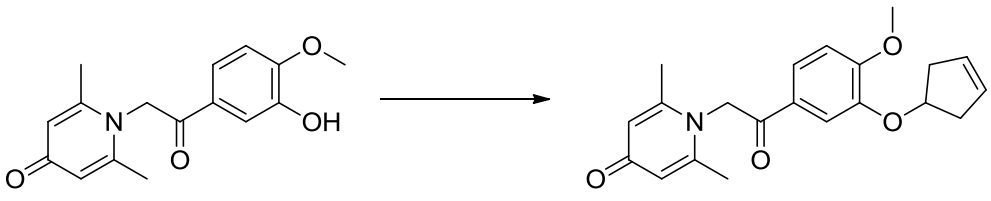
and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-cyclohexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (8 mg, yield 13%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.04 (s, 2H), 6.00 (s, 2H), 4.39-4.32 (m, 1H), 3.95 (s, 3H), 2.52 (s, 6H), 2.02-1.93 (m, 2H), 1.86-1.77 (m, 2H), 1.62-1.52 (m, 2H), 1.45-1.28 (m, 4H); LC-MS m/z 370.2 $[M + H]^+$.

[0212] Example 25

[0213] 

[0214] 1-(2-(3-(cyclopent-3-en-1-yloxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

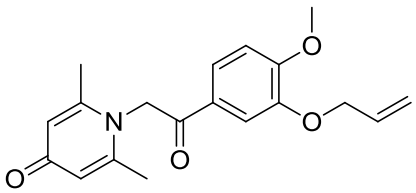
[0215] The specific reaction scheme is as shown below:

[0216] 

[0217] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, 0.11 mmol) was dissolved in acetonitrile (5 mL), and then cyclopent-3-en-1-yl methanesulfonate (68 mg, 0.42 mmol) and potassium carbonate (58 mg, 0.42 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-(cyclopent-3-en-1-yloxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (12 mg, yield 32%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.18 (s, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.04-5.91 (m, 2H), 5.77 (s, 2H), 5.17-5.11 (m, 1H), 3.96 (s, 3H),

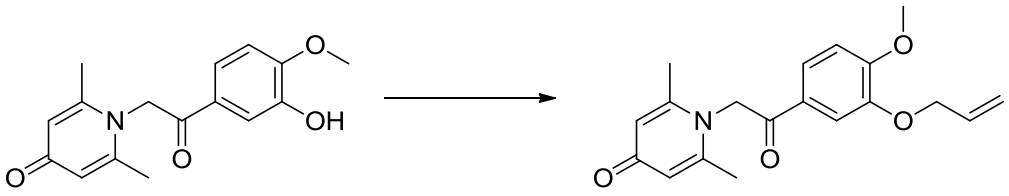
2.95-2.89 (m, 2H), 2.63-2.60 (m, 2H), 2.53 (s, 6H); LC-MS m/z 354.2 $[M + H]^+$.

[0218] Example 26

[0219] 

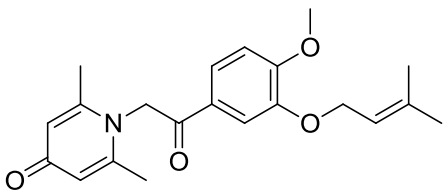
[0220] 1-(2-(3-allyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0221] The specific reaction scheme is as shown below:

[0222] 

[0223] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 3-bromopropene (26 mg, 0.21 mmol) and potassium carbonate (37 mg, 0.27 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-allyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 42%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.34 (s, 2H), 6.14-6.03(m, 1H), 5.68 (s, 2H), 5.43 (d, J = 17.2 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 4.64 (d, J = 4.8 Hz, 2H), 3.95 (s, 3H), 2.26 (s, 6H). LC-MS m/z 328.2 $[M + H]^+$.

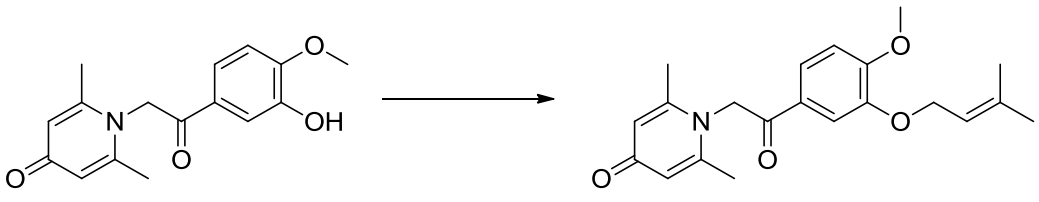
[0224] Example 27

[0225] 

[0226] 1-(2-(3-((3-methylbut-2-en-1-yl)oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-

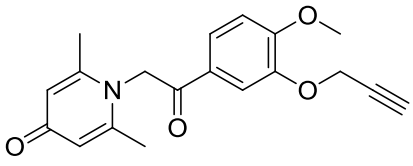
dimethylpyridin-4(1*H*)-one

[0227] The specific reaction scheme is as shown below:

[0228] 

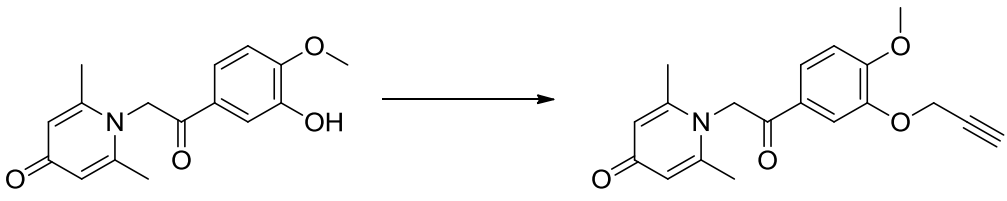
[0229] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 1-bromo-3-methyl-2-butene (31 mg, 0.21 mmol) and potassium carbonate (37 mg, 0.27 mmol) were added, and stirred for 1 hr 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-((3-methylbut-2-en-1-yl)oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 40%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.32 (s, 2H), 5.51 (d, J = 6.8 Hz, 1H), 5.32 (s, 2H), 4.65 (d, J = 6.8 Hz, 2H), 3.98 (s, 3H), 2.21 (s, 6H), 1.79 (s, 3H), 1.77(s, 3H); LC-MS m/z 356.2 $[M + H]^+$.

[0230] **Example 28**

[0231] 

[0232] 1-(2-(3-propargyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin- 4(1*H*)-one

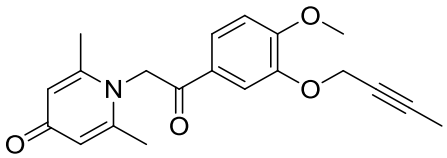
[0233] The specific reaction scheme is as shown below:

[0234] 

[0235] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-

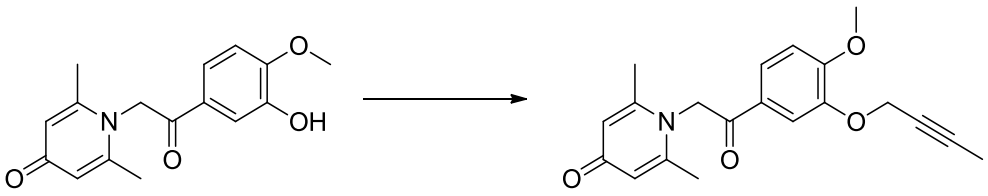
4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then propargyl bromide (25 mg, 0.21 mmol) and potassium carbonate (37 mg, 0.27 mmol) were added, and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-propargyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (21 mg, yield 35%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.03 (s, 2H), 5.78 (s, 2H), 4.85 (d, J = 2.4 Hz, 2H), 4.00 (s, 3H), 2.56 (t, J = 2.4 Hz, 3H), 2.46 (s, 6H); LC-MS: m/z 326.3 $[M + H]^+$.

[0236] Example 29

[0237] 

[0238] 1-(2-(3-(but-2-yn-1-yloxy)-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-4(1*H*)-one

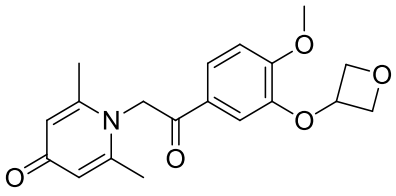
[0239] The specific reaction scheme is as shown below:

[0240] 

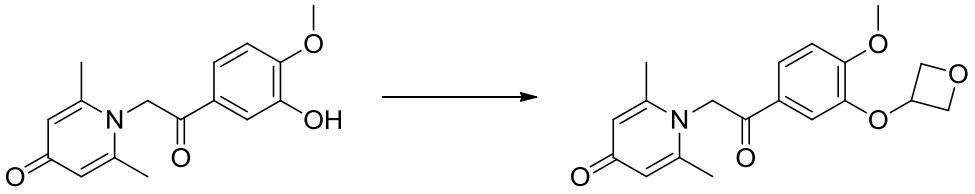
[0241] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 1-bromo-2-butyne (83 mg, 0.70 mmol) and potassium carbonate (97 mg, 0.70 mmol) were added, and stirred for 2 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-(but-2-yn-1-yloxy)-4-methoxyphenyl)-2-

oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (14 mg, yield 23%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (dd, J = 8.4, 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.09 (s, 2H), 6.03 (s, 2H), 4.78 (q, J = 2.4 Hz, 2H), 3.96 (s, 3H), 2.54 (s, 6H), 1.82 (t, J = 2.4 Hz, 3H); LC-MS: m/z 340.0 $[M + H]^+$.

[0242] Example 30

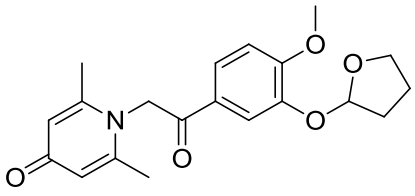
[0243] 

[0244] 1-(2-(3-(oxacyclobutan-3-yl-oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-4(1*H*)-one

[0245] 

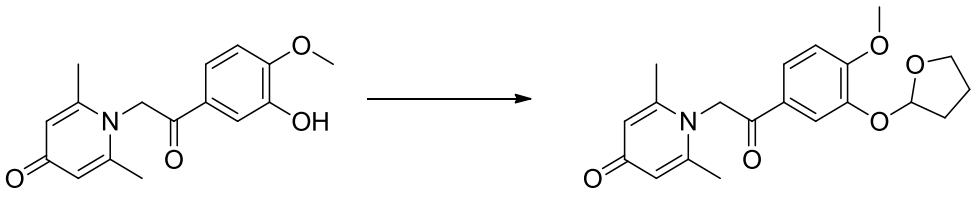
[0246] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (158 mg, 0.55 mmol), oxacyclobutan-3-ol (81.4 mg, 1.1 mmol) and triphenylphosphine (288 mg, 1.1 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL), the reaction solution was cooled in an ice bath, diisopropyl azodicarboxylate (222 mg, 1.1 mmol) was added dropwise over 5 min under nitrogen atmosphere, and then reacted for 24 hours at room temperature. After the reaction was completed, saturated saline (20 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-(oxacyclobutan-3-yl-oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (45 mg, yield 24%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (dd, J = 8.4, 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.13 (s, 2H), 6.06 (s, 2H), 5.38-5.32 (m, 1H), 5.06-5.02 (m, 2H), 4.78-4.75 (m, 2H), 4.00 (s, 3H), 2.56 (s, 6H); LC-MS: m/z 344.4 $[M + H]^+$.

[0247] Example 31

[0248] 

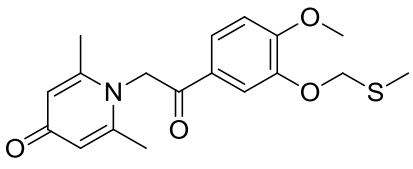
[0249] 1-(2-(3-(tetrahydrofuran-2-yl)oxy-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-4(1*H*)-one

[0250] The specific reaction scheme is as shown below:

[0251] 

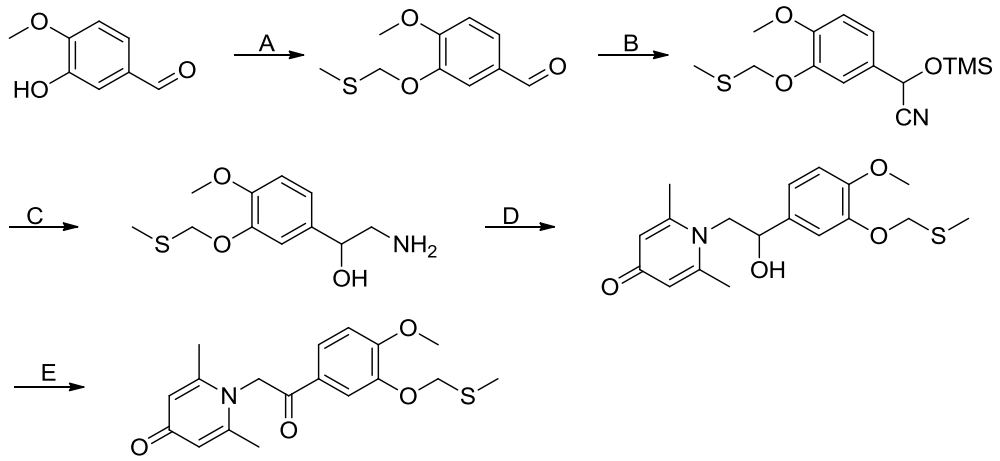
[0252] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in dichloromethane (5 mL), and then 2,3-dihydrofuran (68 mg, 0.42 mmol) and pyridinium toluene-4-sulphonate (4.6 mg, 0.018 mmol) were added, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-(tetrahydrofuran-2-yl)oxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (28 mg, yield 44%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (dd, J = 8.4, 2.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.40 (s, 2H), 5.87 (d, J = 4.4 Hz, 1H), 5.70 (s, 2H), 4.07-4.02 (m, 1H), 3.97-3.92 (m, 1H), 3.94 (s, 3H), 2.31-2.11 (m, 4H), 2.29 (s, 6H); LC-MS m/z 358.1 $[M + H]^+$.

[0253] Example 32

[0254] 

[0255] 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0256] The specific reaction scheme is as shown below:

[0257] 

[0258] Step A:

[0259] Under nitrogen atmosphere, 3-hydroxy-4-methoxybenzaldehyde (2 g, 13 mmol) was dissolved in *N*,*N*-dimethylformamide (20 mL), and then chloromethyl methyl sulfide (1.5 g, 15.6 mmol) and cesium carbonate (6 g, 19.5 mmol) were added and stirred overnight at room temperature under nitrogen atmosphere. After the reaction was completed, saturated saline (40 mL) was added, and extracted with dichloromethane (3 x 30 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by column chromatography gave 3-methylthiomethoxy-4-methoxybenzaldehyde (1.7 g, yield 61%, yellow oil). LC-MS: m/z 213.1 $[M + H]^+$.

[0260] Step B:

[0261] 3-methylthiomethoxy-4-methoxybenzaldehyde (1.7 g, 8 mmol) was dissolved in dichloromethane (20 mL); and under nitrogen atmosphere, triethyl amine (1.6 g, 16 mmol) and trimethylsilyl cyanide (1.6 g, 16 mmol) were added, and stirred for 6 hours at room temperature. The reaction solution was concentrated and rotary dried to obtain 2-(3-methylthiomethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next reaction.

[0262] Step C:

[0263] 2-(3-Methylthiomethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile obtained in the above step was dissolved in anhydrous tetrahydrofuran (50 mL), and then lithium aluminum hydride (608 mg, 16 mmol) was added portion-wise in an ice bath and stirred overnight at room

temperature. After the reaction was completed, water (0.6 mL), an aqueous sodium hydroxide solution (0.6 mL, 15%), and water (1.8 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, and filtered. The filtrate was rotary dried to obtain a crude product of 2-amino-1-(3-methylthiomethoxy-4-methoxyphenyl)ethanol.

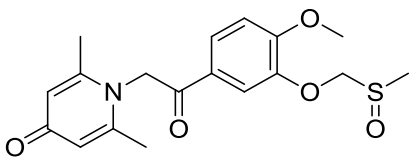
[0264] Step D:

[0265] 2-Amino-1-(3-(methylthiomethoxy)-4-methoxyphenyl)ethanol obtained in the above step was dissolved in ethanol (10 mL), and then 2,6-dimethyl-4-pyranone (1.24 g, 10 mmol) and an aqueous sodium hydroxide solution (2 M, 10 mL) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (1 g, 35%). LC-MS: m/z 350.1 $[M + H]^+$.

[0266] Step E:

[0267] 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.14 mmol) was dissolved in dimethylsulfoxide (5 mL), and then sulfur trioxide pyridine complex (111 mg, 0.7 mmol) in DMSO (2.5ml) was slowly added and stirred overnight at normal temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 51%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.28 (s, 2H), 5.31 (s, 2H), 5.23 (s, 2H), 3.93 (s, 3H), 3.68 (s, 3H), 2.12 (s, 6H); LC-MS: m/z 348.2 $[M + H]^+$.

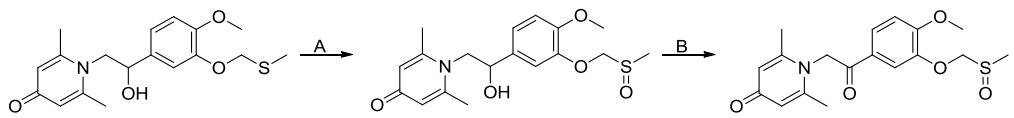
[0268] Example 33

[0269] 

[0270] 1-(2-(3-methylsulfoxidemethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-

4(1*H*)-one

[0271] The specific reaction scheme is as shown below:

[0272] 

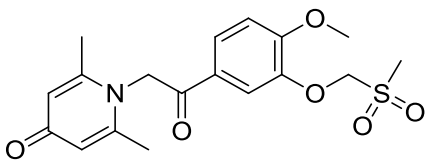
[0273] Step A:

[0274] 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 0.29 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (56 mg, 0.28 mmol) was added and stirred at room temperature for 2 hours. Then, a saturated aqueous sodium sulfite solution (5 mL) was added and stirred for 10 min. The reaction solution was extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by column chromatography gave 1-(2-(3-methylsulfoxidemethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (38 mg, yield 36%, white solid). LC-MS: m/z 366.2 $[M + H]^+$.

[0275] Step B:

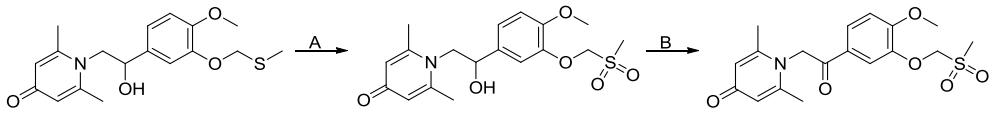
[0276] 1-(2-(3-methylsulfoxidemethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (38 mg, 0.1 mmol) was dissolved in dichloromethane (10 mL), and then the Dess-Martin Periodinane (85 mg, 0.2 mmol) was added and stirred at room temperature for 2 hours. The reaction solution was filtered, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-methylsulfoxidemethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, yield 37%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.26 (s, 2H), 5.25 (s, 2H), 5.23 (s, 2H), 3.93 (s, 3H), 3.68 (s, 3H), 2.12 (s, 6H); LC-MS: m/z 364.2 $[M + H]^+$.

[0277] Example 34

[0278] 

[0279] 1-(2-(3-methylsulfonemethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0280] The specific reaction scheme is as shown below:

[0281] 

[0282] Step A:

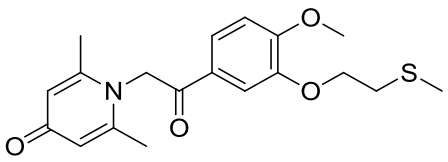
[0283] 1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 0.29 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (176 mg, 0.87 mmol) was added and stirred overnight at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added and stirred for 10 min. The reaction solution was extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by column chromatography gave 1-(2-(3-methylsulfonemethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, yield 55%, white solid). LC-MS: m/z 382.2 $[M + H]^+$.

[0284] Step B:

[0285] 1-(2-(3-methylsulfonemethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.13 mmol) was dissolved in dichloromethane (10 mL), and then the Dess-Martin Periodinane (110 mg, 0.26 mmol) was added and stirred at room temperature for 2 hours. The reaction solution was filtered, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-methylsulfoxidemethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 61%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.4, 2.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.26 (s, 2H), 5.35 (s,

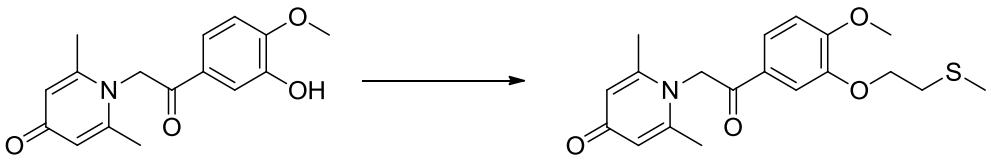
2H), 5.23 (s, 2H), 3.98 (s, 3H), 3.78 (s, 3H), 2.25 (s, 6H); LC-MS: m/z 380.1 $[M + H]^+$.

[0286] Example 35

[0287] 

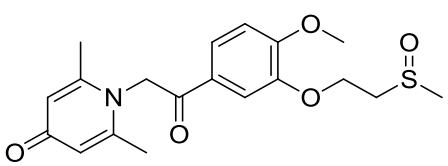
[0288] 1-(2-(3-methylthioethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0289] The specific reaction scheme is as shown below:

[0290] 

[0291] The compound 1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (287 mg, 1 mmol) was dissolved in *N*, *N*-dimethylformamide (5 mL), and then chloroethyl methyl sulfide (166 mg, 1.5 mmol) and potassium carbonate (276 mg, 2 mmol) were added and stirred for 2 hours at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave 1-(2-(3-methylthioethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one200 mg, yield 55%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.28 (s, 2H), 5.31 (s, 2H), 4.27 (t, J = 6.8 Hz, 2H), 3.98 (s, 3H), 2.95 (t, J = 6.8 Hz, 2H), 2.24 (s, 3H), 2.19 (s, 6H); LC-MS: m/z 362.2 $[M + H]^+$.

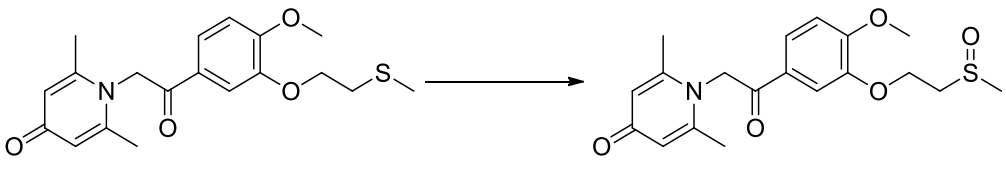
[0292] Example 36

[0293] 

[0294] 1-(2-(3-methylsulfoxideethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-

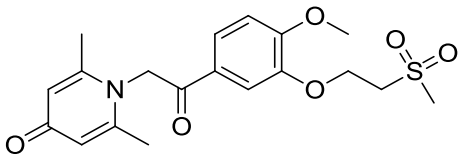
4(1*H*)-one

[0295] The specific reaction scheme is as shown below:

[0296] 

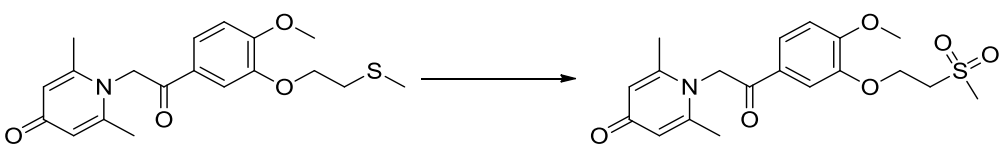
[0297] The compound 1-(2-(3-methylthioethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (28 mg, 0.14 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoxideethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 40%, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.4, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.26 (s, 2H), 5.32 (s, 2H), 4.57-4.54 (m, 2H), 3.97 (s, 3H), 3.35-3.31 (m, 1H), 3.15-3.09 (m, 1H), 2.75 (s, 3H), 2.18 (s, 6H); LC-MS: m/z 378.2 $[M + H]^+$.

[0298] **Example 37**

[0299] 

[0300] 1-(2-(3-methylsulfoneethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6- dimethylpyridin-4(1*H*)-one

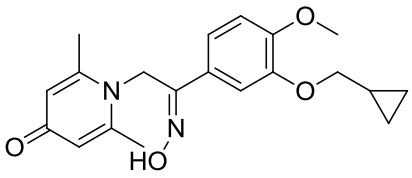
[0301] The specific reaction scheme is as shown below:

[0302] 

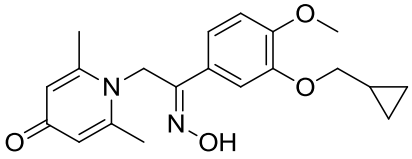
[0303] The compound 1-(2-(3-methylthioethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-

dimethylpyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (71 mg, 0.35 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoneethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 36%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.26 (s, 2H), 5.30 (s, 2H), 4.53 (t, J = 4.2 Hz, 2H), 3.95 (s, 3H), 3.51 (t, J = 4.2 Hz, 2H), 3.18 (s, 3H), 2.18 (s, 6H); LC-MS: m/z 394.2 $[M + H]^+$.

[0304] Example 38

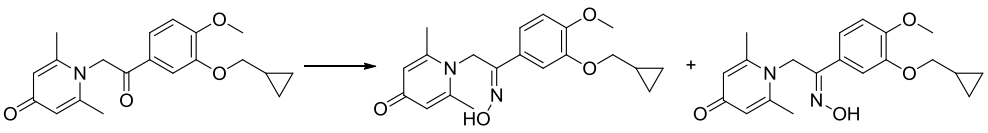
[0305] 

[0306] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0307] 

[0308] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0309] The specific reaction scheme is as shown below:

[0310] 

[0311] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (341 mg, 1 mmol) and hydroxylamine hydrochloride (139 mg, 2 mmol) were dissolved in pyridine (10 mL), and refluxed for 24 hours under nitrogen atmosphere. After

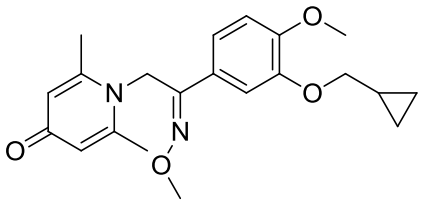
the reaction was completed, pyridine was rotary dried, and and the reaction solution was purified by reverse-phase HPLC to obtain (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (96 mg, yield 27%, white solid) and (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one(43 mg, yield 12%, white solid).

[0312] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.4, 2.0 Hz, 1H), 6.48 (s, 2H), 5.00 (s, 2H), 3.92 (s, 3H), 3.89 (d, J = 6.8 Hz, 2H), 2.41 (s, 6H), 1.42-1.32 (m, 1H), 0.68-0.62 (m, 2H), 0.40-0.35 (m, 2H); LC-MS: m/z 357.4 $[M + H]^+$.

[0313] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.4, 2.0 Hz, 1H), 6.49 (s, 2H), 5.00 (s, 2H), 3.92 (s, 3H), 3.89 (d, J = 6.8 Hz, 2H), 2.41 (s, 6H), 1.42-1.32 (m, 1H), 0.68-0.62 (m, 2H), 0.40-0.35 (m, 2H); LC-MS: m/z 357.4 $[M + H]^+$.

[0314] Example 39

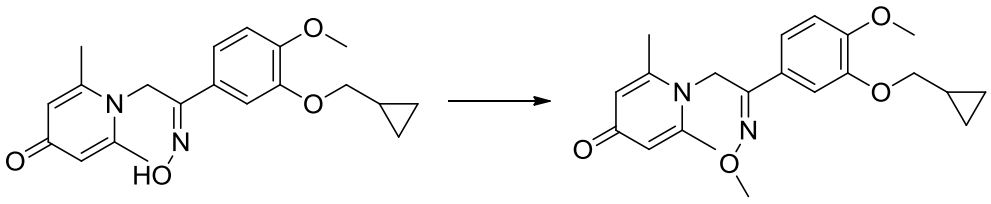
[0315]



[0316] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0317] The specific reaction scheme is as shown below:

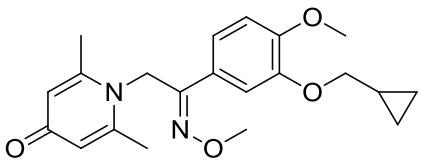
[0318]



[0319] The compound (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-

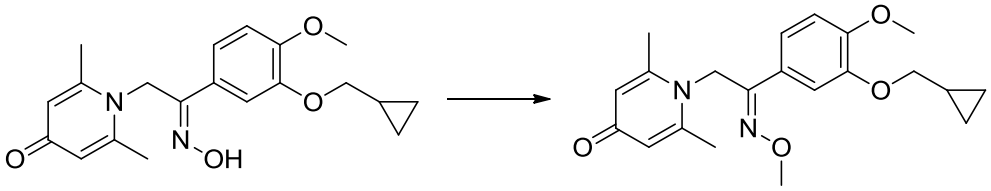
(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL), and then 60% sodium hydride (12 mg, 0.3 mmol) was added at 0°C, and stirred for half an hour. Then, iodomethane (28.4 mg, 0.2 mmol) was added, and stirred at room temperature for 4 hours. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 55%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.52 (s, 2H), 5.02 (s, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (d, *J* = 6.8 Hz, 2H), 2.45 (s, 6H), 1.32-1.23 (m, 1H), 0.70-0.65 (m, 2H), 0.50-0.38 (m, 2H); LC-MS: m/z 371.2 $[M + H]^+$.

[0320] Example 40

[0321] 

[0322] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxymethylimido) ethyl)-2,6-dimethylpyridin-4(1*H*)-one

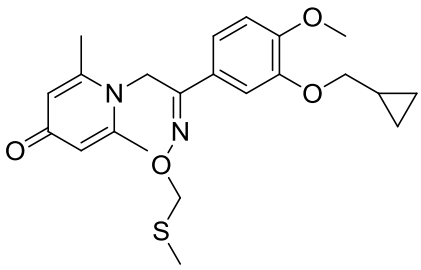
[0323] The specific reaction scheme is as shown below:

[0324] 

[0325] The compound (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL), and then 60% sodium hydride (12 mg, 0.3 mmol) was added at 0°C, and stirred for half an hour. Then, iodomethane (28.4 mg, 0.2 mmol) was added, and stirred at room temperature for 4 hours. After the reaction was completed, saturated saline (10 mL) was

added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (18 mg, yield 49%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.0 Hz, 1H), 6.46 (s, 2H), 5.00 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 2.49 (s, 6H), 1.42-1.32 (m, 1H), 0.68-0.62 (m, 2H), 0.40-0.35 (m, 2H); LC-MS: m/z 371.2 $[M + H]^+$.

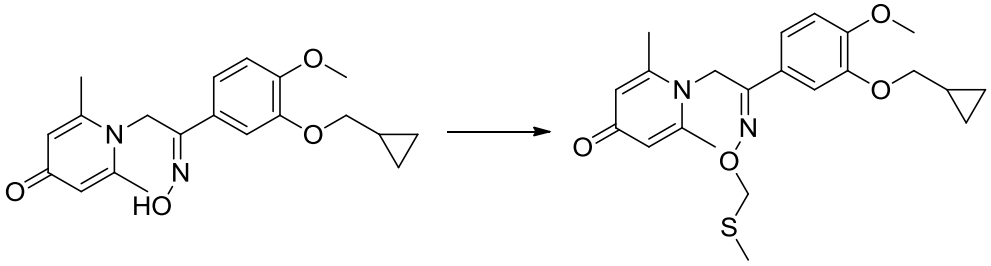
[0326] Example 41



[0327]

[0328] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0329] The specific reaction scheme is as shown below:

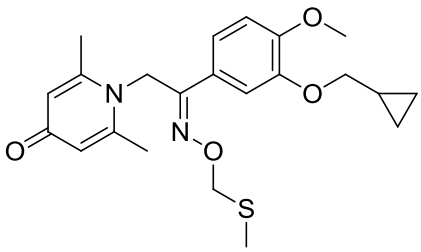


[0330]

[0331] The compound (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (300 mg, 0.84 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then cesium carbonate (548 mg, 1.68 mmol) and chloromethylmethyl sulfide (122 mg, 1.26 mmol) were added, and stirred overnight at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-

(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (200 mg, yield 57%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.96 (s, 2H), 6.35 (s, 2H), 5.18 (s, 2H), 3.91 (s, 2H), 3.85 (d, J = 6.8 Hz, 2H), 2.47 (s, 6H), 2.40 (s, 3H), 1.36-1.28 (m, 1H), 0.69-0.64 (m, 2H), 0.35-0.32 (m, 2H); LC-MS: m/z 417.1 $[M + H]^+$.

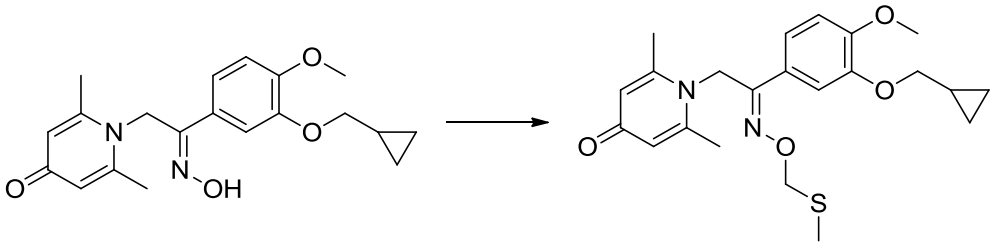
[0332] Example 42



[0333]

[0334] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0335] The specific reaction scheme is as shown below:

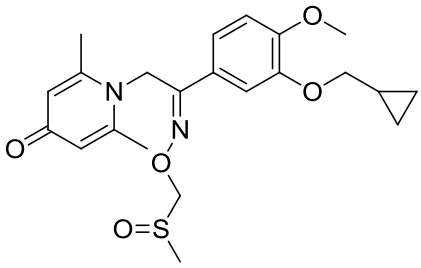


[0336]

[0337] The compound (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL), and then cesium carbonate (65 mg, 0.2 mmol) and chloromethylmethyl sulfide (15 mg, 0.15 mmol) were added. and stirred overnight at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 48%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.36

(d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 2H), 6.38 (s, 2H), 5.10 (s, 2H), 3.96 (s, 2H), 3.90 (d, *J* = 6.8 Hz, 2H), 2.47 (s, 6H), 2.40 (s, 3H), 1.36-1.28 (m, 1H), 0.69-0.64 (m, 2H), 0.35-0.32 (m, 2H); LC-MS: m/z 417.1 $[M + H]^+$.

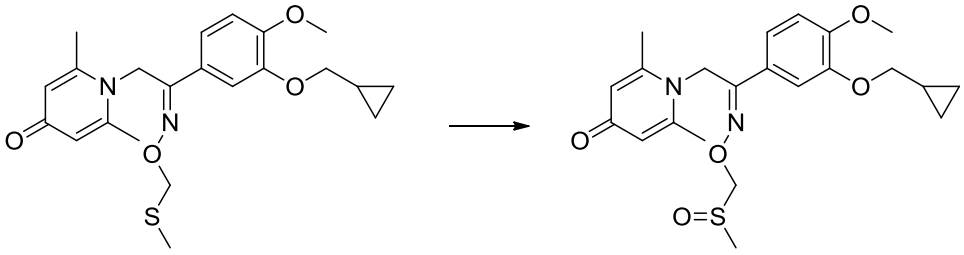
[0338] Example 43



[0339]

[0340] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfoxidemethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0341] The specific reaction scheme is as shown below:

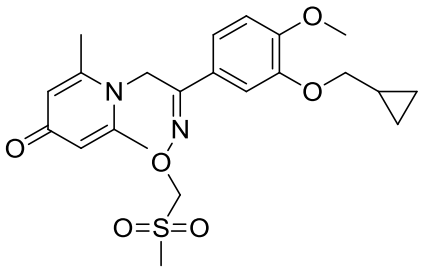


[0342]

[0343] The compound (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (42 mg, 0.1 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (18 mg, 0.09 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfoxidemethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 46%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, *J* = 8.4 Hz, 1H), 7.21 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.90 (s, 2H), 6.36 (s, 2H), 5.15 (s, 2H), 3.94 (s, 2H), 3.88 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 6H), 2.42 (s, 3H), 1.38-1.30 (m, 1H), 0.69-0.65 (m, 2H), 0.38-0.33 (m, 2H); LC-

MS: m/z 433.2 $[M + H]^+$.

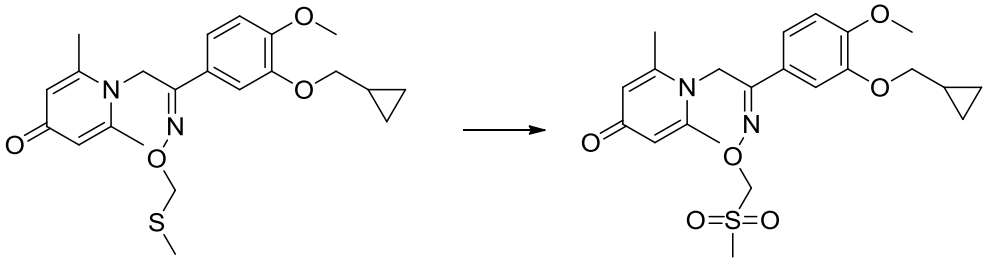
[0344] Example 44



[0345]

[0346] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfonemethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one

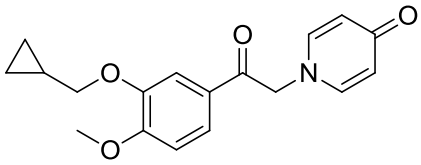
[0347] The specific reaction scheme is as shown below:



[0348]

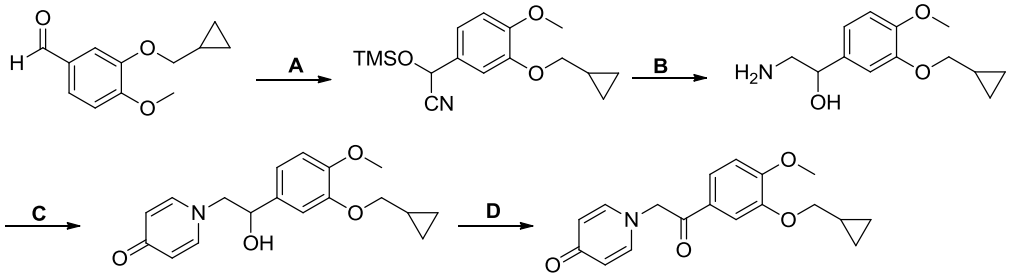
[0349] The compound (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (42 mg, 0.1 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (61 mg, 0.3 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfonemethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (26 mg, yield 58%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.96 (s, 2H), 6.35 (s, 2H), 5.18 (s, 2H), 3.91 (s, 2H), 3.85 (d, J = 6.8 Hz, 2H), 2.47 (s, 6H), 2.40 (s, 3H), 1.36-1.28 (m, 1H), 0.69-0.64 (m, 2H), 0.35-0.32 (m, 2H); LC-MS: m/z 449.2 $[M + H]^+$.

[0350] Example 45

[0351] 

[0352] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)pyridin-4(1*H*)-one

[0353] The specific reaction scheme is as shown below:

[0354] 

Step A:

[0355] 3-cyclopropylmethoxy-4-methoxybenzaldehyde (3.09 g, 15 mmol) was dissolved in dichloromethane (30 mL); and under nitrogen atmosphere, triethyl amine (4.16 mL, 30 mmol) and trimethylsilyl cyanide (3.75 g, 30 mmol) were added, and stirred for 6 hours at room temperature. The reaction solution was concentrated and rotary dried to obtain 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next reaction.

[0356] Step B:

[0357] The compound 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxyacetonitrile (4.57 g, 15 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL), and then lithium aluminum hydride (1.14 g, 30 mmol) was added portion-wise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, water (1.2 mL), an aqueous sodium hydroxide solution (1.2 mL, 15%), and water (3.6 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 2-amino-1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanol.

[0358] Step C:

[0359] The compound 2-amino-1-(3-(cyclopropylmethoxy)-4-methoxyphenyl)ethanol was dissolved in ethanol (20 mL), and then pyrone (1 g, 10.41 mmol) and aqueous sodium hydroxide

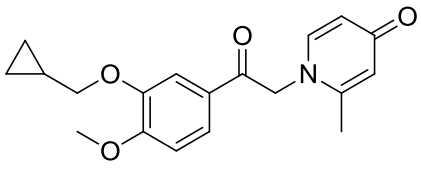
solution (2M, 20 mL) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (2 g, 63%). LC-MS: m/z 316.2 $[M + H]^+$.

[0360] Step D:

[0361] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (280 mg, 0.88 mmol) was dissolved in dichloromethane (10 mL); and under nitrogen atmosphere, Dess-Martin Periodinane (746 mg, 1.76 mmol) was added, and stirred for 3 hours at room temperature. After the reaction was completed, the reaction solution was concentrated, rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)pyridin-4(1*H*)-one (50 mg, yield 18%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 7.6 Hz, 2H), 7.68 (dd, J = 8.4, 1.2 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 7.6 Hz, 2H), 5.72 (s, 2H), 3.89 (s, 3H), 3.87 (d, J = 6.8 Hz, 2H), 1.26-1.21 (m, 1H), 0.62-0.56 (m, 2H), 0.36-0.31 (m, 2H); LC-MS: m/z 314.1 $[M + H]^+$.

[0362] **Example 46**

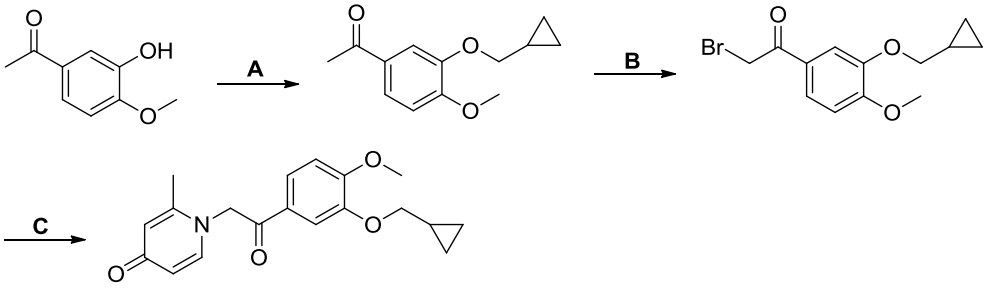
[0363]



[0364] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-methylpyridin-4(1*H*)-one

[0365] The specific reaction scheme is as shown below.

[0366]



[0367] Step A:

[0368] 3-hydroxy-4-methoxyacetophenone (1.66 g, 10 mmol) was dissolved in acetonitrile (30 mL); and under nitrogen atmosphere, potassium carbonate (2.76 g, 20 mmol) and bromomethylcyclopropane (2.0 g, 15mmol) were added, and stirred for 6 hours at 80°C. The reaction solution was filtered. The filtrate was concentrated, rotary dried, and purified by column chromatography to obtain 1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanone (2.1 g, yield 95%, white solid).

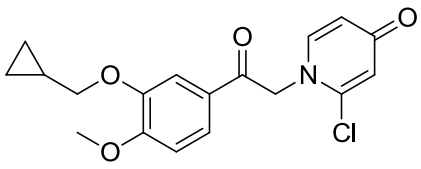
[0369] Step B:

[0370] The compound 1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanone (2.2 g, 10 mmol) was dissolved in methanol (30 mL), and then *N*-bromosuccinimide (2.14g, 12 mmol) and p-toluenesulfonic acid (1.7 g, 10 mmol) were added to the solution and reacted at 65°C for hours. After the reaction was completed, the reaction solution was concentrated, rotary dried, and purified by column chromatography to obtain 2-bromo-1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanone (800 mg, yield 27%, white solid).

[0371] Step C:

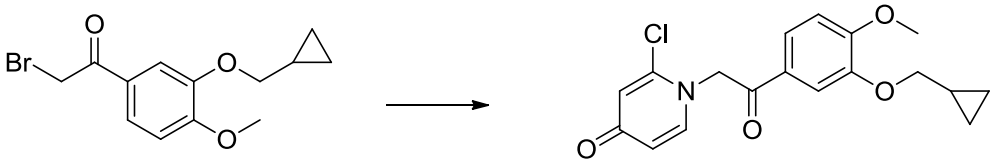
[0372] The compound 2-bromo-1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanone (185 mg, 1.5 mmol) and 4-methoxy-2methylpyridine (500 mg, 1.67 mmol) were dissolved in acetonitrile (10 mL), and stirred at 80°C for 48 hours. After the reaction was completed, the reaction solution was concentrated, rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-methylpyridin-4(1*H*)-one (300 mg, yield 61%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (dd, J = 8.4, 2.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 1.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.42-6.38 (m, 2H), 5.72 (s, 2H), 3.95 (s, 3H), 3.91 (d, J = 6.8 Hz, 2H), 2.24 (s, 3H), 1.34-1.24 (m, 1H), 0.66-0.60 (m, 2H), 0.39-0.34 (m, 2H); LC-MS: m/z 328.1 $[M + H]^+$.

[0373] **Example 47**

[0374] 

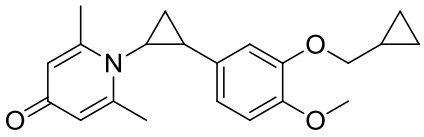
[0375] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-chloropyridin-4(1*H*)-one

[0376] The specific reaction scheme is as shown below:

[0377] 

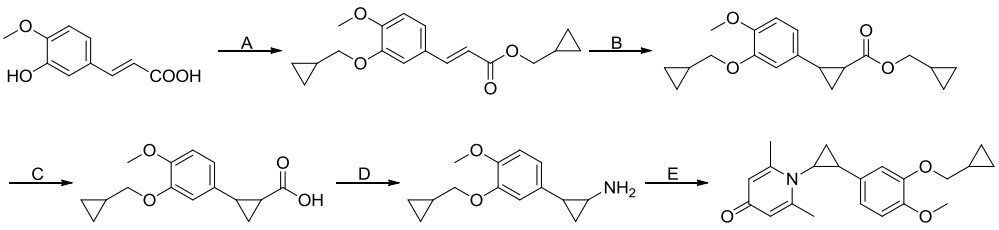
[0378] 2-bromo-1-(3-cyclopropylmethoxy-4-methoxyphenyl)ethanone (594 mg, 2 mmol) and 4-methoxy-2chloropyridine (288 mg, 2 mmol) were dissolved in acetonitrile (10 mL), and stirred at 80°C for 48 hours. After the reaction was completed, the reaction solution was concentrated, rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-chloropyridin-4(1*H*)-one (117 mg, yield 17%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.18 (dd, J = 8.0, 2.4 Hz, 1H), 5.77 (s, 2H), 3.89 (s, 3H), 3.87 (d, J = 6.8 Hz, 2H), 1.27-1.22 (m, 1H), 0.62-0.56 (m, 2H), 0.36-0.32 (m, 2H); LC-MS: m/z 348.0 $[M + H]^+$.

[0379] **Example 48**

[0380] 

[0381] 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropyl)-2,6-dimethylpyridin-4(1*H*)-one

[0382] The specific reaction scheme is as shown below:

[0383] 

[0384] Step A:

[0385] 3-hydroxy-4-methoxycinnamic acid (194 mg, 1 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromomethylcyclopropane (338 mg, 2.5 mmol) and potassium carbonate (414 mg, 3 mmol) were added. The reaction solution was stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain cyclopropylmethyl 3-cyclopropylmethoxy-4-methoxycinnamate (200 mg, yield 61%, yellow liquid). LC-MS: m/z 303.3 $[M + H]^+$.

[0386] Step B:

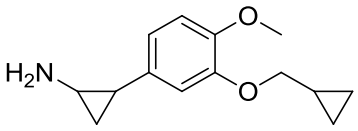
[0387] Under nitrogen atmosphere, dimethylsulfoxide (4 mL), 60% sodium hydride (28.8 mg, 0.36 mmol) and trimethylsulfoxonium iodide (160 mg, 0.36 mmol) were stirred for 20 min at room temperature. A solution (2 mL) of cyclopropylmethyl 3-cyclopropylmethyl-4-methoxycinnamate (200 mg, 0.66 mmol) in tetrahydrofuran was slowly added. After the dropwise addition, the reaction solution was stirred at room temperature for 1 hr, then heated to 50°C and continuously stirred for 1 hr. After the reaction was completed, the reaction solution was poured into iced water, and extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain cyclopropylmethyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylcarboxylate (80 mg, yield 56%, white solid). LC-MS: m/z 317.3 $[M + H]^+$.

[0388] Step C:

[0389] Cyclopropylmethyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylcarboxylate (80 mg, 0.25 mmol) was dissolved in methanol (2 mL),

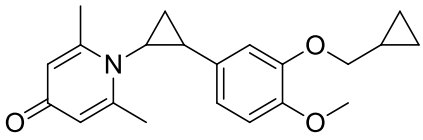
and then a sodium hydroxide solution (2N, 1 mL) was added, and stirred for 2 hr under reflux. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification gave 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylcarboxylic acid (50 mg, yield 76%, white solid).

[0390] Step D:

[0391] 

[0392] 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylcarboxylic acid (50 mg, 0.19 mmol) was dissolved in 1,4-dioxane (2 mL), and then triethyl amine (26 mg, 0.26 mmol) and diphenylphosphoryl azide(64 mg, 0.26 mmol) were added. This reaction solution was stirred for 16 hours at room temperature, then heated to 80°C and stirred for 1 hr. A mixture of 10% hydrochloric acid in 1,4-dioxane was added and continuously stirred at room temperature for 18 hours. After the reaction was completed, the reaction was quenched by adding a sodium hydroxide solution (1 mL, 3N), and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification gave 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylamine (12 mg, yield: 25%, yellow oil).

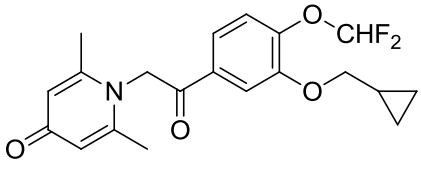
[0393] Step E

[0394] 

[0395] The compound 2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropylamine (60 mg, 0.24 mmol) was dissolved in ethanol (3 mL), and then 2.6-dimethyl-4*H*-pyran-4-one (45 mg, 0.36 mmol) and sodium hydroxide (20 mg, 0.48 mmol) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried, and purified to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropyl)-2,6-dimethylpyridin-

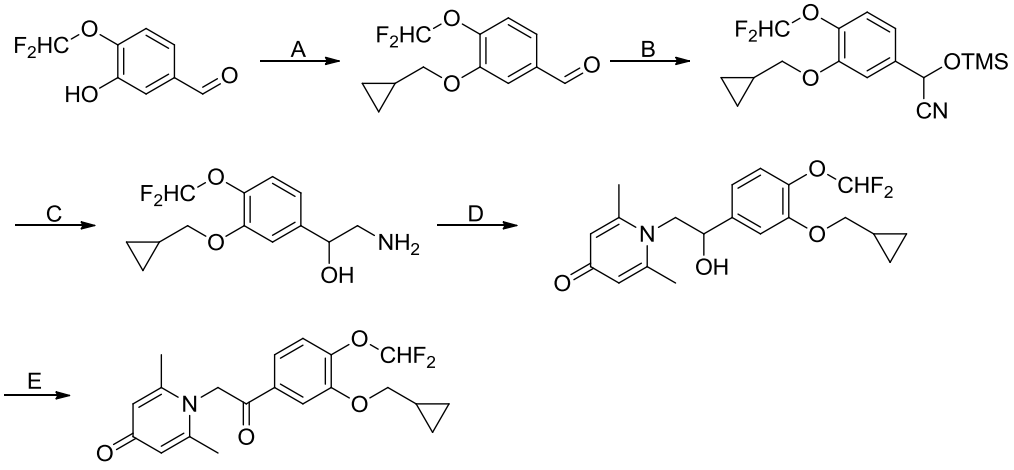
4(1*H*)-one (10 mg, yield 11%, yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (d, *J* = 8.8 Hz, 1H), 6.75-6.58 (m, 2H), 6.18 (s, 2H), 3.76 (d, *J* = 6.8 Hz, 2H), 3.73 (s, 3H), 2.40 (s, 6H), 1.63-1.54 (m, 2H), 1.29-1.12 (m, 2H), 0.54-0.48 (m, 2H), 0.26-0.22 (m, 2H); LC-MS: m/z 340.0 $[M + H]^+$.

[0396] Example 49

[0397] 

[0398] 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0399] The specific reaction scheme is as shown below:



[0400] Step A:

[0401] At room temperature, 3-hydroxy-4-difluoromethoxybenzaldehyde (1.88 g, 10.0 mmol) was dissolved in acetonitrile (10 mL), and then potassium carbonate (2.07 g, 15.0 mmol) and bromomethylcyclopropane (1.76 g, 13.0 mmol) were added in sequence, and heated to 80°C for 3 hours with stirring under nitrogen atmosphere. After the reaction was completed, saturated saline (30 mL) was added, and extracted with ethyl acetate (3 x 60 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by reverse-phase HPLC to obtain 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (2.20 g, 91%). LC-MS: m/z 243.2 $[M + H]^+$.

[0402] Step B:

[0403] The compound 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (2.20 g, 9.1 mmol) was dissolved in dichloromethane (30 mL), and then triethyl amine (1.84 g, 18.2 mmol) and trimethylsilyl cyanide (2.7 g, 27.3 mmol) were added in sequence in an ice bath and stirred for 16 hours under nitrogen atmosphere at room temperature. After the reaction was completed, the reaction solution was directly rotary dried to obtain the product 2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-trimethylsiloxyacetonitrile (3.1 g, 100%), which was directly used in the next reaction.

[0404] Step C:

[0405] The compound 2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-trimethylsiloxyacetonitrile (3.1 g, 9.1 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL), and then lithium aluminum hydride (1.04 g, 27.3 mmol) was added portion-wise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was diluted with anhydrous tetrahydrofuran (200 mL), and extracted with water (1 mL). An aqueous sodium hydroxide solution (3 mL, 1M) and then water (3 mL) were added, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 2-amino-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)ethanol (2.70 g, 100%). LC-MS: m/z 258.1 $[M-18+1]^+$.

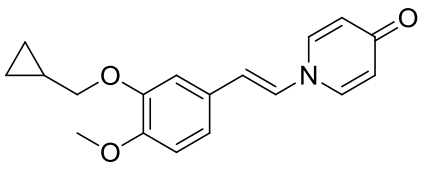
[0406] Step D:

[0407] The compound 2-amino-1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)ethanol (2.70 g, 9.1 mmol) was dissolved in ethanol (30 mL), and then 2,6-dimethyl-4*H*-pyran-4-one (1.86 g, 15.0 mmol), sodium hydroxide (0.60 g, 15.0 mmol) and water (10 mL) were added in sequence, heated to 60°C, and stirred for 16 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified to obtain 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.4 g, 69%). LC-MS: m/z 380.2 $[M + H]^+$.

[0408] Step E

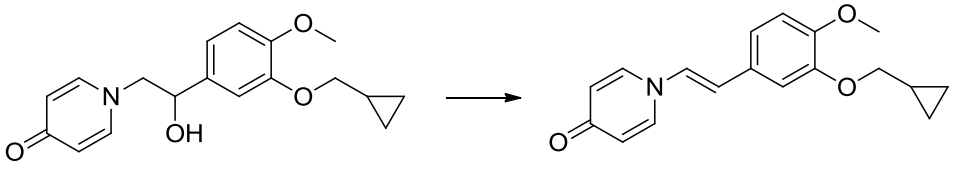
[0409] The compound 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.13 mmol) was dissolved in dichloromethane (10 mL), and then the Dess-Martin Periodinane (110 mg, 0.26 mmol) was added and stirred at room temperature for 2 hours. The reaction solution was filtered, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by reverse-phase HPLC to obtain 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one (35 mg, yield 72%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.79 (t, J_{H-F} = 74.4 Hz, 1H), 6.45 (s, 2H), 5.50 (s, 2H), 3.99 (d, J = 7.2 Hz, 2H), 2.26 (s, 6H) 1.37-1.28 (m, 1H), 0.72-0.66 (m, 2H), 0.43-0.37 (m, 2H); LC-MS: m/z 378.3 $[M + H]^+$.

[0410] **Example 50**

[0411] 

[0412] (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)pyridin-4(1*H*)-one

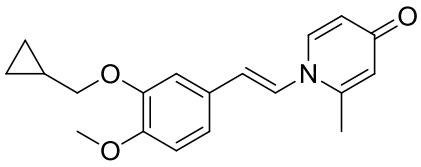
[0413] The specific reaction scheme is as shown below:

[0414] 

[0415] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)pyridin-4(1*H*)-one (270 mg, 0.86 mmol) and p-toluenesulfonic acid (443 mg, 2.58 mmol) were dissolved in toluene (5 mL), and stirred overnight under reflux. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)pyridin-4(1*H*)-one (50 mg, yield 20%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 14.4 Hz, 1H), 7.10 (s, 1H), 6.97-6.93 (m, 2H), 6.85 (d, J = 14.4 Hz, 1H), 6.21 (d, J = 7.6 Hz, 2H), 3.83 (d, J =

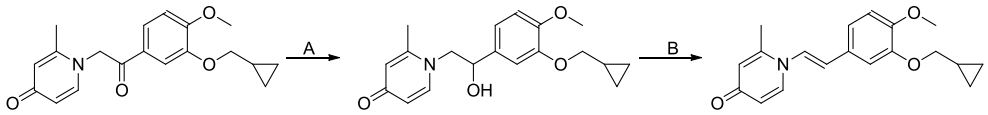
7.2 Hz, 2H), 3.77 (s, 3H), 1.26-1.21 (m, 1H), 0.62-0.56 (m, 2H), 0.36-0.31 (m, 2H); LC-MS: m/z 298.1 $[M + H]^+$.

[0416] Example 51

[0417] 

[0418] (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2-methylpyridin-4(1*H*)-one

[0419] The specific reaction scheme is as shown below:

[0420] 

[0421] Step A:

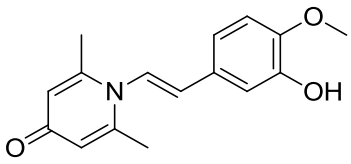
[0422] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-methylpyridin-4(1*H*)-one (654 mg, 2 mmol) was dissolved in methanol (10 mL), and then sodium borohydride (114 mg, 3 mmol) was added portion-wise and stirred at room temperature for 3 hours. After the reaction was completed, a saturated ammonium chloride solution (20 mL) was added, and the reaction solution was filtered, concentrated, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (620 mg, yield 95%, white solid). LC-MS: m/z 330.4 $[M + H]^+$

[0423] Step B:

[0424] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (620 mg, 1.88 mmol) and p-toluenesulfonic acid (970 mg, 5.64 mmol) were dissolved in toluene (15 mL), and stirred overnight under reflux. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2-methylpyridin-4(1*H*)-one (520 mg, yield 84%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 14.0 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.12 (dd, J = 8.4, 1.6 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H),

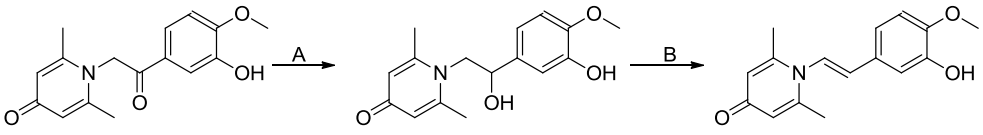
6.95 (d, *J* = 14.0 Hz, 1H), 6.66-6.62 (m, 2H), 3.86 (d, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 2.51(s, 3H), 1.28-1.22 (m, 1H), 0.62-0.57 (m, 2H), 0.36-0.31 (m, 2H); LC-MS: m/z 312.1 $[M + H]^+$.

[0425] Example 52

[0426] 

[0427] (*E*)-1-(3-hydroxy-4-methoxystyryl)-2-methylpyridin-4(1*H*)-one

[0428] The specific reaction scheme is as shown below:

[0429] 

[0430] Step A:

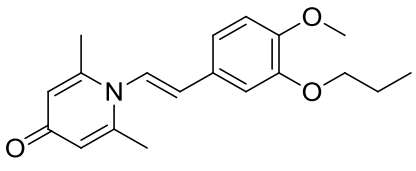
[0431] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-methylpyridin-4(1*H*)-one (5.74 g, 20 mmol) was dissolved in methanol (100 mL), and then sodium borohydride (1.14 g, 30 mmol) was added portion-wise and stirred at room temperature for 3 hours. After the reaction was completed, a saturated ammonium chloride solution (20 mL) was added, and the reaction solution was filtered, concentrated, and purified by column chromatography to obtain 1-(2-(3-hydroxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (5.09 g, yield 88%, colorless oil). LC-MS: m/z 290.4 $[M + H]^+$.

[0432] Step B:

[0433] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (5.09 g, 17.6 mmol) and p-toluenesulfonic acid (9.08 g, 52.8 mmol) were dissolved in toluene (100 mL), and stirred overnight under reflux. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2-methylpyridin-4(1*H*)-one (3.05 g, yield 64%, gray solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (s, 1H), 7.16 (s, 2H), 7.05 (d, *J* = 14.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 14.0 Hz, 1H), 3.92 (s, 2H),

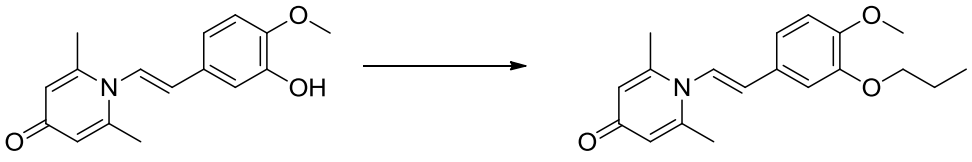
2.48(s, 6H); LC-MS: m/z 272.1 $[M + H]^+$.

[0434] Example 53

[0435] 

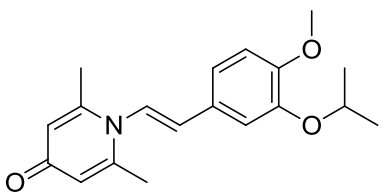
[0436] (*E*)-1-(3-propoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0437] The specific reaction scheme is as shown below:

[0438] 

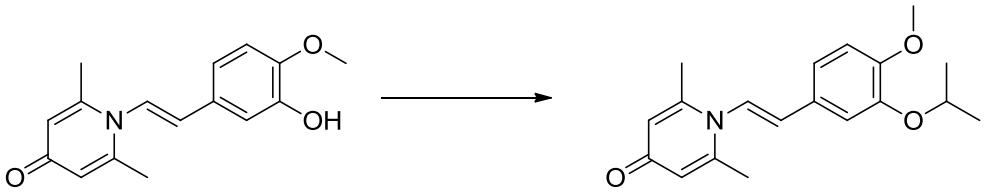
[0439] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromopropane (34.5 mg, 0.28 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 2 hours at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-propoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 44%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.22 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.4, 2.0 Hz, 1H), 7.09 (d, J = 14.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 14.2 Hz, 1H), 6.38 (s, 2H), 4.03 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 2.37 (s, 6H), 1.90-1.80 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H); LC-MS: m/z 314.2 $[M+H]^+$.

[0440] Example 54

[0441] 

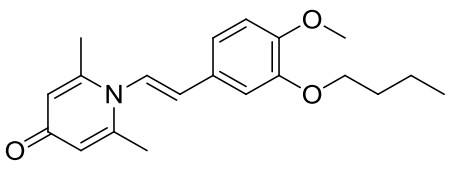
[0442] (*E*)-1-(3-isopropoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0443] The specific reaction scheme is as shown below:

[0444] 

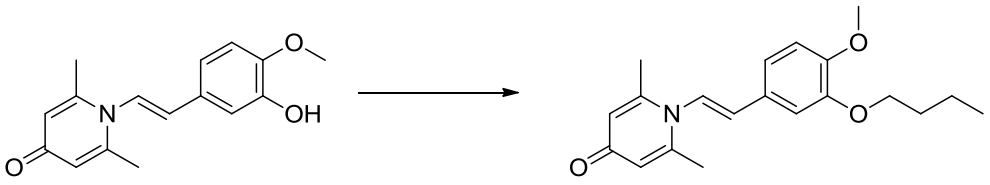
[0445] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromoisopropane (34.5 mg, 0.28 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 2 hours at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-isopropoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (8 mg, yield 14%, colorless oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.26 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 7.21 (d, J = 14.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.97 (s, 2H), 6.89 (d, J = 14.4 Hz, 1H), 4.69-4.60 (m, 1H), 3.90 (s, 3H), 2.57 (s, 6H), 1.35 (d, J = 6.0 Hz, 6H). LC-MS: m/z 314.2 $[M+H]^+$.

[0446] **Example 55**

[0447] 

[0448] (*E*)-1-((3-n-butoxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

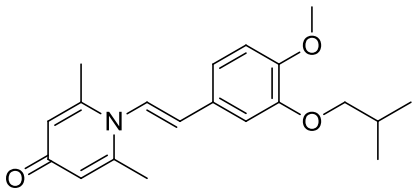
[0449] The specific reaction scheme is as shown below:

[0450] 

[0451] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then n-butyl bromide (38 mg, 0.28 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 2 hours at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and

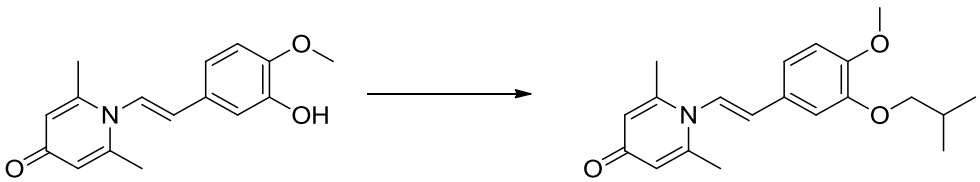
extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-n-butoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 34%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (s, 2H), 7.27 (d, J = 14.4 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 7.04-6.98 (m, 2H), 6.95 (d, J = 14.4 Hz, 1H), 4.34 (t, J = 6.4 Hz, 2H), 3.82 (s, 3H), 2.60 (s, 6H), 1.82-1.75 (m, 2H), 1.50-1.40 (m, 2H), 0.96 (t, J =7.2 Hz, 1H); LC-MS: m/z 328.2 [M + H]$^+$.

[0452] Example 56

[0453] 

[0454] (*E*)-1-(3-iso-butoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

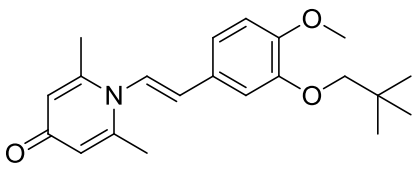
[0455] The specific reaction scheme is as shown below:

[0456] 

[0457] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL), and then bromoisobutane (38 mg, 0.28 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 2 hours at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-iso-butoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 42%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 8.4, 2.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 14.4 Hz, 1H), 6.60 (d, J = 14.4 Hz, 1H), 6.30 (s, 2H), 3.92 (s, 3H), 3.81 (d, J = 6.8 Hz, 2H), 2.27 (s, 6H), 2.24-2.17 (m, 1H), 1.08 (d, J = 6.8 Hz, 6H); LC-MS: m/z

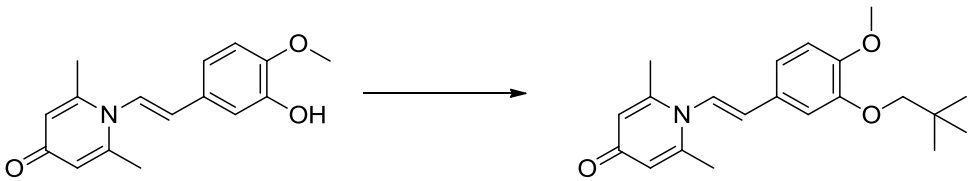
328.2 $[M+H]^+$.

[0458] Example 57

[0459] 

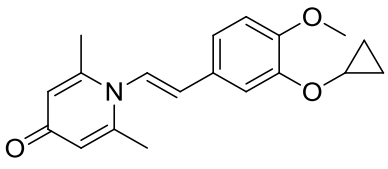
[0460] (*E*)-1-((3-neopentyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0461] The specific reaction scheme is as shown below:

[0462] 

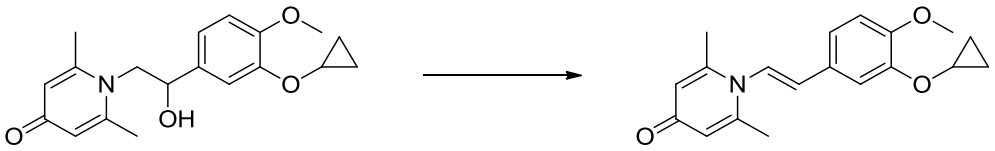
[0463] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1H)-one (200 mg, 0.74 mmol) was dissolved in *N*,*N* -dimethylformamide (5 mL), and then bromo-neopentane (224 mg, 1.48 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 24 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-neopentyloxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 8%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 7.05-7.00 (m, 2H), 6.97 (d, J = 14.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 14.4 Hz, 1H), 3.91 (s, 3H), 3.68 (s, 2H), 2.54 (s, 6H), 1.08 (s, 9H); LC-MS m/z 342.3 $[M + H]^+$.

[0464] Example 58

[0465] 

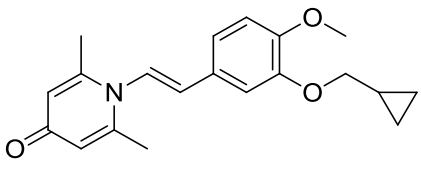
[0466] (*E*)-1-(3-cyclopropyloxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0467] The specific reaction scheme is as shown below:

[0468] 

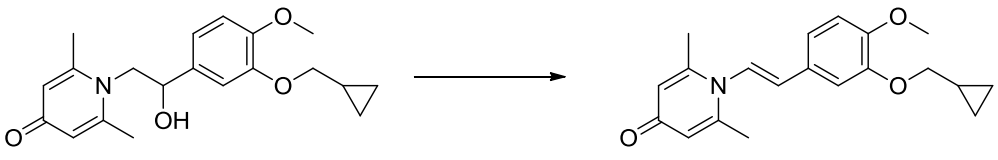
[0469] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 0.3 mmol) and p-toluenesulfonic acid (68.4 mg, 0.6 mmol) were dissolved in toluene (5 mL), and then *N*,*N*-dimethylformamide (1 mL) was added and stirred overnight under reflux. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropyloxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, yield 53%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 14.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 14.4 Hz, 1H), 6.32 (s, 2H), 4.02 (s, 3H), 2.32 (s, 6H), 2.23-2.19 (m, 1H), 0.94-0.90 (m, 4H); LC-MS m/z 312.3 $[M + H]^+$.

[0470] Example 59

[0471] 

[0472] (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

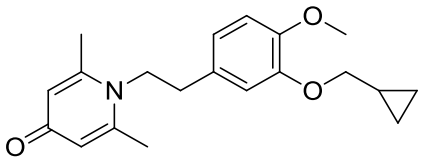
[0473] The specific reaction scheme is as shown below:

[0474] 

[0475] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (186 mg, 0.54 mmol) and p-toluenesulfonic acid (140 mg, 0.81 mmol) were dissolved in toluene (5 mL), and then *N*,*N*-dimethylformamide (1 mL) was added and stirred overnight under reflux. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one(80 mg, yield 45%, white solid). ^{1}H NMR (400

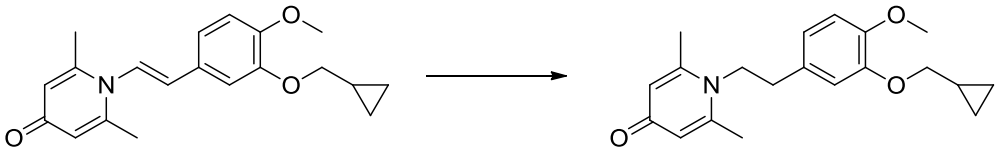
MHz, CD_3OD) δ 7.13 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 14.4 Hz, 1H), 7.11 (s, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 14.4 Hz, 1H), 6.41 (s, 2H), 3.89 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H), 2.36 (s, 6H), 1.33-1.24 (m, 1H), 0.65-0.60 (m, 2H), 0.38-0.34 (m, 2H); LC-MS: m/z 326.1 $[M + H]^+$.

[0476] Example 60

[0477] 

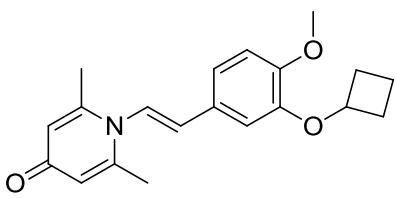
[0478] (*E*)-1-(3-cyclopropylmethoxy-4-methoxyphenethyl)-2,6-dimethylpyridin-4(1*H*)-one

[0479] The specific reaction scheme is as shown below:

[0480] 

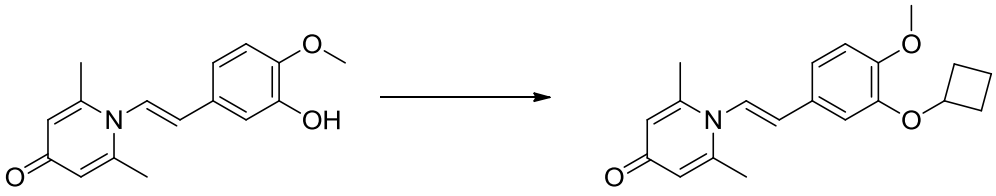
[0481] The compound (*E*)-1-(3-cyclopropyloxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, 0.03 mmol) was dissolved in ethanol (3 mL), and then Pd/C(50 mg) was added, and stirred for 2 hours under hydrogen atmosphere at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-cyclopropylmethoxy-4-methoxyphenethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.9 mg, yield 30%, colorless oil). ^1H NMR (400 MHz, CD_3OD) δ 7.13 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.11 (s, 2H), 6.99 (d, J = 8.4 Hz, 1H), 6.41 (s, 2H), 3.89 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H), 2.89-2.83 (m, 2H), 2.83-2.77 (m, 2H), 2.36 (s, 6H), 1.33-1.24 (m, 1H), 0.65-0.60 (m, 2H), 0.38-0.34 (m, 2H); LC-MS: m/z 328.1 $[M + H]^+$.

[0482] Example 61

[0483] 

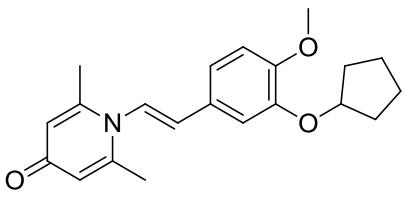
[0484] (*E*)-1-(3-cyclobutyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0485] The specific reaction scheme is as shown below:

[0486] 

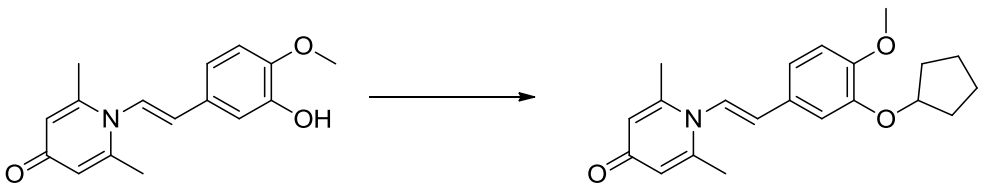
[0487] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 0.37 mmol) was dissolved in *N*,*N* -dimethylformamide (5 mL), and then bromocyclobutane (100 mg, 0.74 mmol) and cesium carbonate (241 mg, 0.74 mmol) were added, and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-cyclobutyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one(18 mg, yield 15%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.13 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05 (d, *J* = 14.4 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 14.4 Hz, 1H), 6.36 (s, 2H), 4.78-4.71 (m, 1H), 3.86 (s, 3H), 2.52-2.44 (m, 2H), 2.34 (s, 6H), 2.22-2.12 (m, 2H), 1.89-1.81 (m, 1H), 1.77-1.65 (m, 1H); LC-MS m/z 326.2 [M + H]$^+$.

[0488] **Example 62**

[0489] 

[0490] (*E*)-1-((3-cyclopentyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

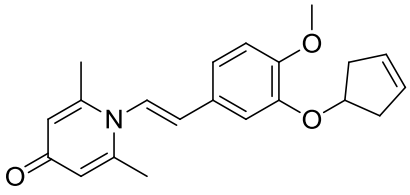
[0491] The specific reaction scheme is as shown below:

[0492] 

[0493] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

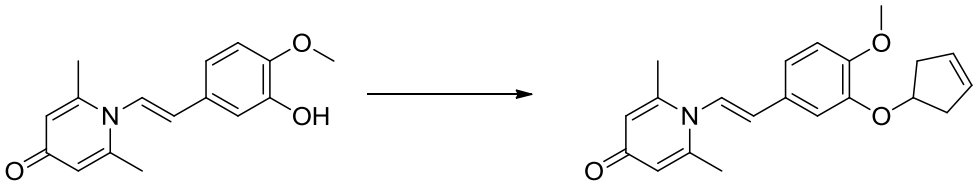
(100 mg, 0.37 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then bromocyclopentane (110 mg, 0.74 mmol) and cesium carbonate (241 mg, 0.74 mmol) were added, and stirred for 4 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-cyclopentyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one (25 mg, yield 20%, pale yellow solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.16 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 14.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 14.4 Hz, 1H), 6.36 (s, 2H), 3.35-3.83 (m, 1H), 3.86 (s, 3H), 2.52-2.44 (m, 2H), 2.35 (s, 6H), 1.93-1.79 (m, 6H), 1.69-1.58 (m, 2H); LC-MS m/z 340.2 $[M + H]^+$.

[0494] Example 63

[0495] 

[0496] (*E*)-1-(3-(cyclopent-3-en-1-yloxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

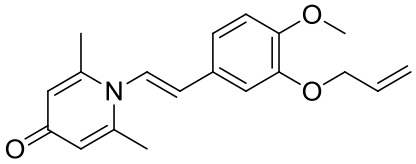
[0497] The specific reaction scheme is as shown below:

[0498] 

[0499] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (100 mg, 0.37 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then cyclopent-3-en-1-yl methanesulfonate (110 mg, 0.74 mmol) and cesium carbonate (241 mg, 0.74 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-(cyclopent-3-en-1-yloxy)-4-methoxystyryl)-

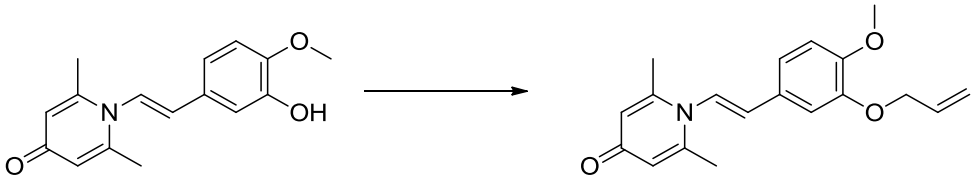
2,6-dimethylpyridin-4(1*H*)-one (22 mg, yield 15%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.02-6.99 (m, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 14.4 Hz, 1H), 5.77 (s, 2H), 5.12-5.05 (m, 1H), 3.90 (s, 3H), 2.89-2.82 (m, 2H), 2.69-2.63 (m, 2H), 2.58 (s, 6H); LC-MS m/z 338.1 $[M + H]^+$.

[0500] Example 64

[0501] 

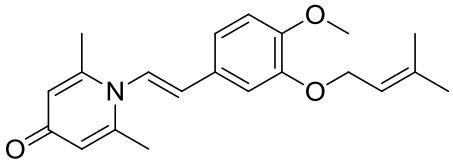
[0502] (*E*)-1-(3-allyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0503] The specific reaction scheme is as shown below:

[0504] 

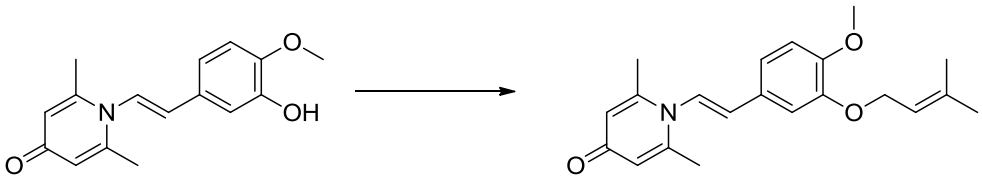
[0505] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 3-bromopropene (44 mg, 0.36 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 2 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-allyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one (12 mg, yield 20%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H), 7.09-6.92 (m, 4H), 6.73-6.69 (m, 1H), 6.16-6.05 (m, 1H), 5.45 (d, J = 17.2 Hz, 1H), 5.34 (d, J = 10.4 Hz, 1H), 4.67 (d, J = 4.0 Hz, 2H), 3.94 (s, 3H), 2.54 (s, 6H); LC-MS m/z 312.2 $[M + H]^+$.

[0506] Example 65

[0507] 

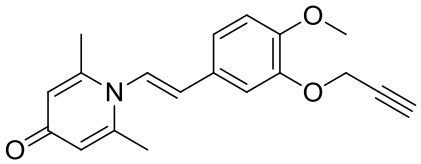
[0508] (*E*)-1-((3-(3-methylbut-2-en-1-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0509] The specific reaction scheme is as shown below:

[0510] 

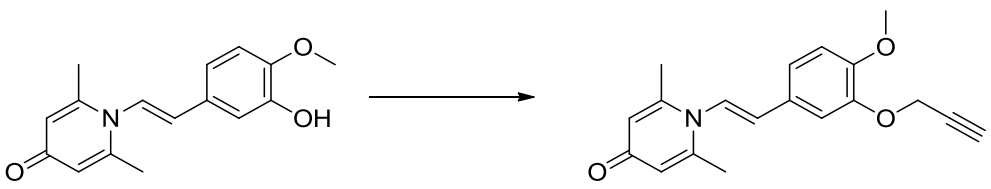
[0511] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then 1-bromo-3-methyl-2-butene (55 mg, 0.36 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 1 hr at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-((3-(3-methylbut-2-en-1-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (15 mg, yield 18%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 2H), 7.08-7.04 (m, 2H), 6.92-6.90 (m, 1H), 6.91 (d, J = 14.4 Hz, 1H), 6.69 (d, J = 14.4 Hz, 1H), 5.54 (t, J = 6.0 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 3.92 (s, 3H), 2.51 (s, 6H), 1.80 (s, 3H), 1.72 (s, 3H); LC-MS m/z 340.0 $[M + H]^+$.

[0512] **Example 66**

[0513] 

[0514] (*E*)-1-(3-(prop-2-yn-1-yloxy)-4-methoxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one

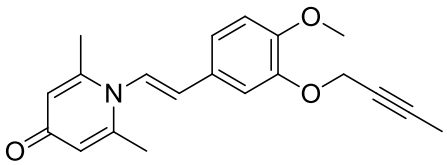
[0515] The specific reaction scheme is as shown below:

[0516] 

[0517] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50

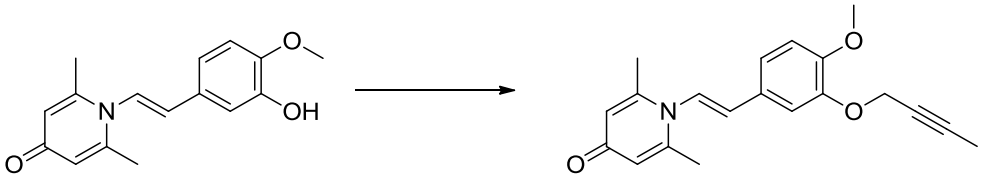
mg, 0.18 mmol) was dissolved in *N*,*N* -dimethylformamide (5 mL), and then 3-bromo-propyne (44 mg, 0.36 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 3 hours at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-(prop-2-yn-1-yloxy)-4-methoxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, yield 15%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.14 (m, 3H), 7.13 (s, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 14.4 Hz, 1H), 4.83 (s, 2H), 3.94 (s, 3H), 2.56 (s, 1H), 2.52 (s, 6H); LC-MS m/z 310.1 $[M + H]^+$.

[0518] Example 67

[0519] 

[0520] (*E*)-1-(3-(but-2-yn-1-yloxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

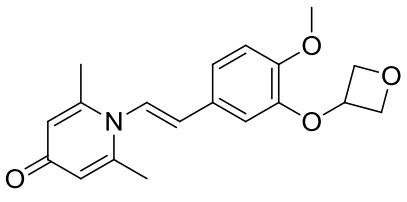
[0521] The specific reaction scheme is as shown below:

[0522] 

[0523] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.18 mmol) was dissolved in *N*,*N* -dimethylformamide (5 mL), and then 1-bromo-2-butyne (49 mg, 0.36 mmol) and cesium carbonate (117 mg, 0.36 mmol) were added, and stirred for 1 hr at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-(but-2-yn-1-yloxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (15 mg, yield 25%, yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.09 (s, 2H), 6.98 (d, J = 14.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 14.4 Hz, 1H),

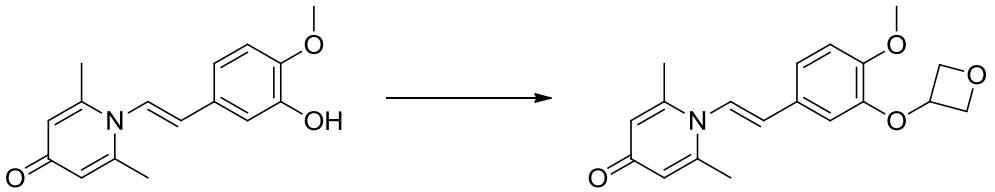
4.78 (s, 2H), 3.93 (s, 3H), 2.52 (s, 6H), 1.86 (s, 3H); LC-MS m/z 324.1 $[M + H]^+$.

[0524] Example 68

[0525] 

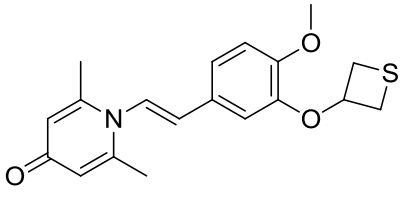
[0526] (*E*)-1-((3-(oxacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0527] The specific reaction scheme is as shown below:

[0528] 

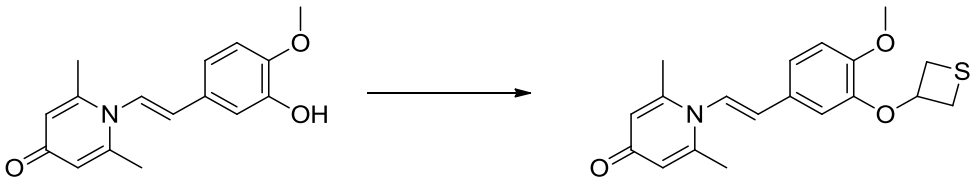
[0529] (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (150 mg, 0.55 mmol), oxacyclobutan-3-ol (81.4 mg, 1.1 mmol) and triphenylphosphine (288 mg, 1.1 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL), the reaction solution was cooled in an ice bath, diisopropyl azodicarboxylate(222 mg, 1.1 mmol) was added dropwise over 5 min under nitrogen atmosphere, and then reacted for 24 hours at room temperature. After the reaction was completed, saturated saline (20 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-((3-(oxacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (40 mg, yield 22%, white solid). ^{1}H NMR (400 MHz, CDCl3) δ 7.15 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 13.2 Hz, 1H), 6.70 (s, 1H), 6.69 (d, *J* = 13.2 Hz, 1H), 5.27 (m, 1H), 5.01 (m, 1H), 4.88 (m, 1H), 3.94 (s, 3H), 2.53 (s, 6H); LC-MS: m/z 328.2 $[M + H]^+$.

[0530] Example 69

[0531] 

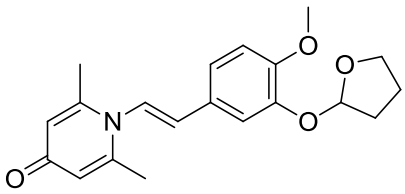
[0532] (*E*)-1-((3-(thiacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0533] The specific reaction scheme is as shown below:

[0534] 

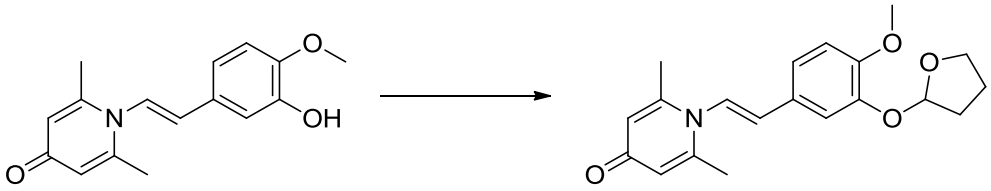
[0535] (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (150 mg, 0.55 mmol), thiacyclobutan-3-ol (99 mg, 1.1 mmol) and triphenylphosphine (288 mg, 1.1 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL), the reaction solution was cooled in an ice bath, diisopropyl azodicarboxylate(222 mg, 1.1 mmol) was added dropwise over 5 min under nitrogen atmosphere, and then reacted for 24 hours at room temperature. After the reaction was completed, saturated saline (20 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-((3-(thiacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 16%, pale yellow solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (s, 2H), 7.19 (d, J = 14.4 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 14.4 Hz, 1H), 5.77-5.69 (m, 1H), 3.90 (s, 3H), 3.65-3.61 (m, 2H), 3.57-3.53 (m, 2H), 2.66 (s, 6H); LC-MS: m/z 344.2 $[M + H]^+$.

[0536] **Example 70**

[0537] 

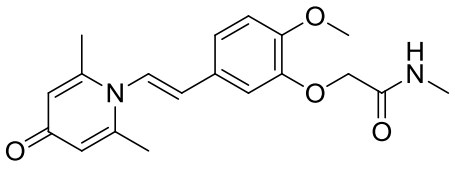
[0538] (*E*)-1-((3-(tetrahydrofuran-2-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0539] The specific reaction scheme is as shown below:

[0540] 

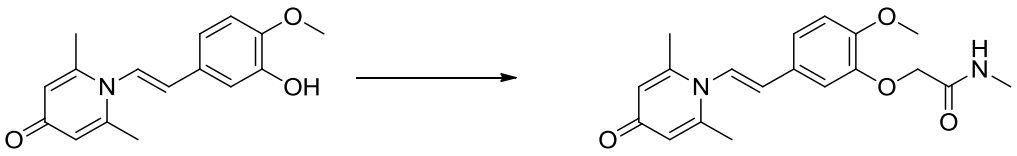
[0541] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1H)-one (50 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), and then 2,3-dihydrofuran (68 mg, 0.42 mmol) and pyridinium toluene-4-sulphonate (4.6 mg, 0.018 mmol) were added, and stirred for 3 hours at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-((3-(tetrahydrofuran-2-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (16 mg, yield 24%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 2.0 Hz, 1H), 7.26 (s, 2H), 7.09 (dd, J = 8.4, 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 14.4 Hz, 1H), 6.75 (d, J = 14.4 Hz, 1H), 5.82 (d, J = 4.4 Hz, 1H), 5.70 (s, 2H), 4.13-4.08 (m, 1H), 4.01-3.95 (m, 1H), 3.90 (s, 3H), 2.35 (s, 6H), 2.24 -2.14 (m, 2H), 2.02 -1.95 (m, 2H); LC-MS m/z 342.3 $[M + H]^+$.

[0542] **Example 71**

[0543] 

[0544] (*E*)-2-(5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethenyl)-2methoxyphenoxy)-*N*-methylacetamide

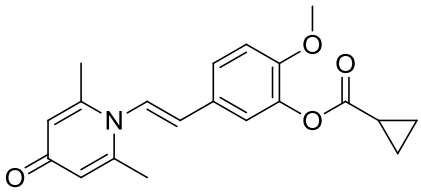
[0545] The specific reaction scheme is as shown below:

[0546] 

[0547] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (200 mg, 0.74 mmol) was dissolved in *N*,*N* -dimethylformamide (5 mL), and then 2-chloro-*N*-methylacetamide (119 mg, 1.11 mmol) and potassium carbonate (153 mg, 1.11 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-2-(5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-

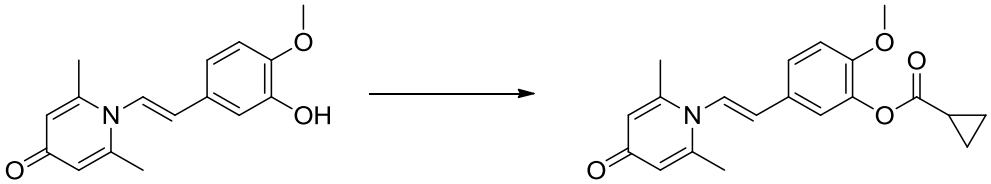
yl)ethenyl)-2methoxyphenoxy)-*N*-methylacetamide (100 mg, yield 40%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 14.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 14.2 Hz, 1H), 6.35 (s, 2H), 4.55 (s, 2H), 3.92 (s, 3H), 2.84 (s, 3H), 2.34 (s, 6H); LC-MS m/z 343.1 $[M + H]^+$.

[0548] Example 72

[0549] 

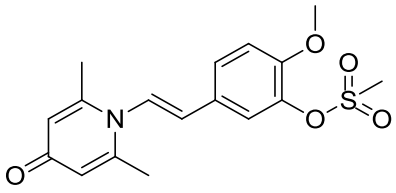
[0550] (*E*)-1-((3-cyclopropylformyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0551] The specific reaction scheme is as shown below:

[0552] 

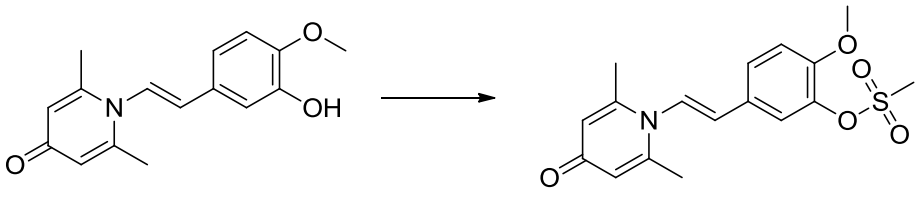
[0553] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.17 mmol) was dissolved in dichloromethane (5 mL), and then cyclopropanecarbonyl chloride (27 mg, 0.26 mmol) and potassium carbonate (36 mg, 0.26 mmol) were added and stirred for 2 hours at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-((3-cyclopropylformyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 35%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.11 (s, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 14.4 Hz, 1H), 6.72 (d, J = 14.4 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 6H), 1.96-1.89 (m, 1H), 1.25-1.21 (m, 2H), 1.12-1.06 (m, 2H); LC-MS: m/z 340.2 $[M+H]^+$.

[0554] Example 73

[0555] 

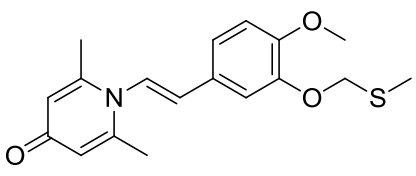
[0556] (*E*)-5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethenyl)-2-methoxyphenylmethyl sulfonate

[0557] The specific reaction scheme is as shown below:

[0558] 

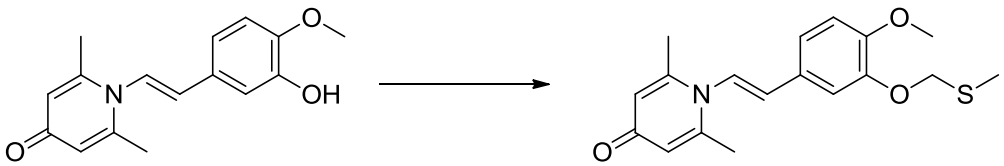
[0559] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (271 mg, 1.0 mmol) was dissolved in N, N-dimethylformamide (10 mL), and then triethyl amine (202 mg, 2.0mmol), and methylsulfonyl chloride (172 mg, 1.5 mmol) were added, and stirred overnight at room temperature. After the reaction was completed, saturated saline (20 mL) was added, and extracted with dichloromethane (3 x 20 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethenyl)-2-methoxyphenylmethyl sulfonate (130 mg, yield 40%, white solid). ^{1}H NMR (400 MHz, CD3OD) δ 7.61 (d, J = 2.4 Hz, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.28 (d, J = 14.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.05 (s, 2H), 6.96 (d, J = 14.4 Hz, 1H), 3.96 (s, 3H), 2.58 (s, 6H). LC-MS: m/z 350.1 $[M+H]^+$.

[0560] **Example 74**

[0561] 

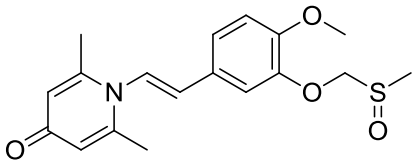
[0562] (*E*)-1-(3-methylthiomethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0563] The specific reaction scheme is as shown below:

[0564] 

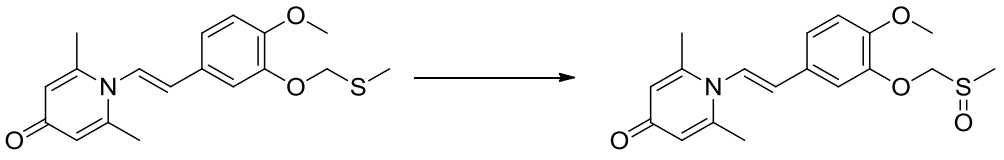
[0565] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (70 mg, 0.26 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then chloromethylmethyl sulfide(50 mg, 0.52 mmol) and cesium carbonate (170 mg, 0.52 mmol) were added, and stirred overnight at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylthiomethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one(50 mg, yield 58%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 2.0 Hz, 1H), 7.25(dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 14.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 14.4 Hz, 1H), 6.77 (s, 2H), 5.03 (s, 2H), 3.90 (s, 3H), 2.36 (s, 6H), 2.26 (s, 3H); LC-MS: m/z 332.5 $[M + H]^+$.

[0566] Example 75

[0567] 

[0568] (*E*)-1-(3-methylsulfoxidemethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

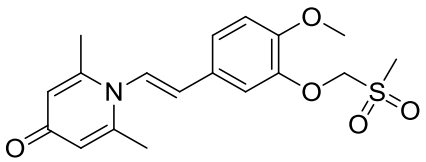
[0569] The specific reaction scheme is as shown below:

[0570] 

[0571] The compound (*E*)-1-(3-methylthiomethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (28 mg, 0.14 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and

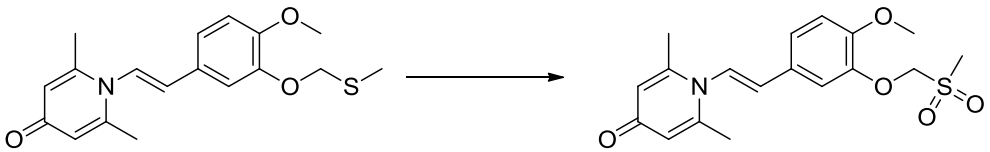
dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoxidemethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, yield 69%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.0 Hz, 1H), 7.28(dd, J = 8.4, 2.0 Hz, 1H), 7.09 (d, J = 14.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.03 (s, 2H), 6.68 (d, J = 14.4 Hz, 1H), 5.26 (d, J = 11.2 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 3.96 (s, 3H), 2.36 (s, 6H), 2.26 (s, 3H); LC-MS: m/z 348.2 $[M + H]^+$.

[0572] Example 76

[0573] 

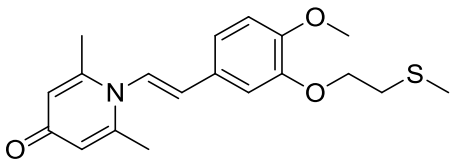
[0574] (*E*)-1-(3-methylsulfonemethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0575] The specific reaction scheme is as shown below:

[0576] 

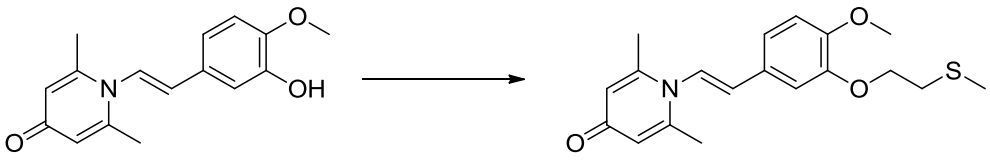
[0577] The compound (*E*)-1-(3-methylthiomethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, 0.09 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (54 mg, 0.27 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfonemethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (26 mg, yield 79%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 7.11 (d, J = 8.4, 1H), 7.10 (d, J = 14.0 Hz, 1H), 6.79 (d, J = 14.0 Hz, 1H), 6.37 (s, 2H), 5.20 (s, 2H), 3.93 (s, 3H), 3.11 (s, 3H), 2.35 (s, 6H); LC-MS m/z 364.1 $[M + H]^+$.

[0578] Example 77

[0579] 

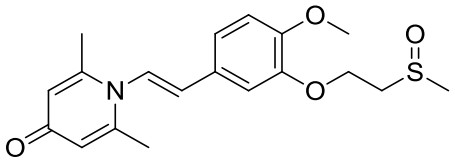
[0580] (*E*)-1-(3-methylthioethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0581] The specific reaction scheme is as shown below:

[0582] 

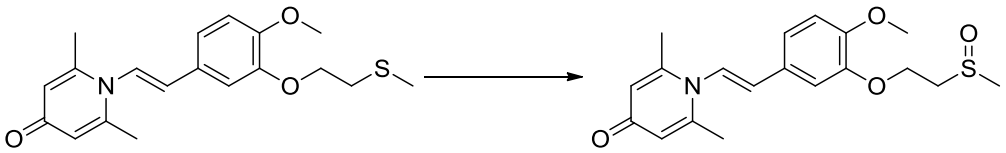
[0583] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (200 mg, 0.73 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then chloroethyl methyl sulfide (165 mg, 1.5 mmol) and cesium carbonate (489 mg, 1.5 mmol) were added, and stirred overnight at room temperature. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylthioethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (220 mg, yield 87%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 14.4 Hz, 1H), 6.59 (d, J = 14.4 Hz, 1H), 6.26 (s, 2H), 4.24 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H), 2.26 (s, 6H), 2.24 (s, 3H); LC-MS: m/z 346.5 $[M + H]^+$.

[0584] **Example 78**

[0585] 

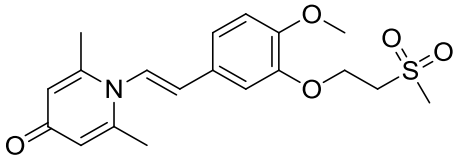
[0586] (*E*)-1-(3-methylsulfoxideethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0587] The specific reaction scheme is as shown below:

[0588] 

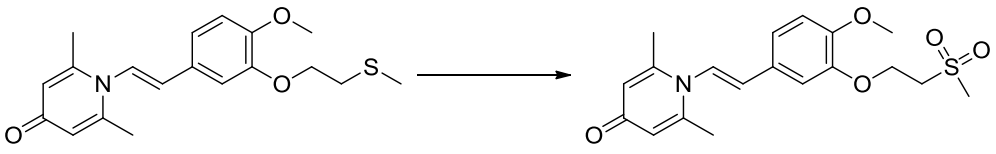
[0589] The compound (*E*)-1-(3-methylthioethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (28 mg, 0.14 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoxideethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 53%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 2.0 Hz, 1H), 6.99 (dd, J = 8.4, 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 14.4 Hz, 1H), 6.51 (d, J = 14.4 Hz, 1H), 6.17 (s, 2H), 4.50-4.41 (m, 2H), 3.83 (s, 3H), 3.27-3.20 (m, 1H), 3.07-3.01 (m, 1H), 2.68 (s, 3H), 2.17 (s, 6H); LC-MS: m/z 362.1 $[M + H]^+$.

[0590] Example 79

[0591] 

[0592] (*E*)-1-(3-methylsulfoneethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

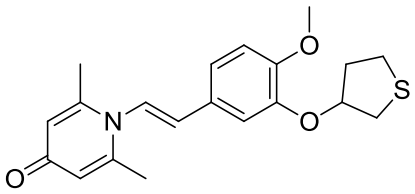
[0593] The specific reaction scheme is as shown below:

[0594] 

[0595] The compound (*E*)-1-(3-methylthioethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, 0.09 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (54 mg, 0.54 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10

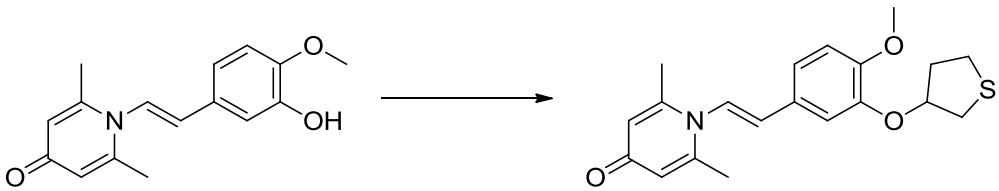
min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoneethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one(35 mg, yield 61%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 14.4 Hz, 1H), 6.58 (d, J = 14.4 Hz, 1H), 6.31 (s, 2H), 4.50 (t, J = 4.2 Hz, 2H), 3.89 (s, 3H), 3.50 (t, J = 4.2 Hz, 2H), 3.19 (s, 3H), 2.26 (s, 6H); LC-MS: m/z 378.1 $[M + H]^+$.

[0596] Example 80

[0597] 

[0598] (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

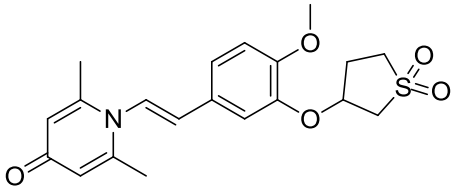
[0599] The specific reaction scheme is as shown below:

[0600] 

[0601] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (45 mg, 0.15 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then tetrahydrothiophen-3-yl methanesulfonate (53 mg, 0.29 mmol) and cesium carbonate (95 mg, 0.29 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (35 mg, yield 65%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H),

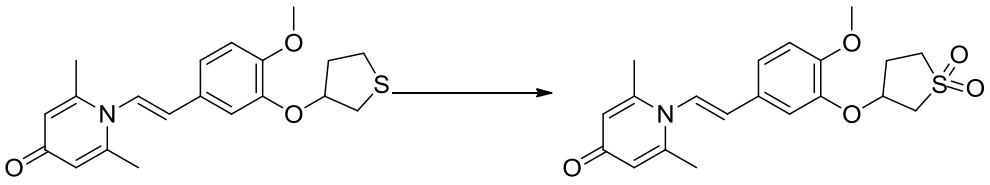
6.77 (d, *J* = 14.4 Hz, 1H), 6.58 (d, *J* = 14.4 Hz, 1H), 6.31 (s, 2H), 5.16-5.13 (m, 1H), 3.90 (s, 3H), 3.18-3.08 (m, 1H), 3.09 (d, *J* = 3.6 Hz, 2H), 2.98-2.93 (m, 1H), 2.49-2.42 (m, 1H), 2.27 (s, 6H), 2.08-1.99 (m, 1H); LC-MS: m/z 358.2 $[M + H]^+$.

[0602] Example 81

[0603] 

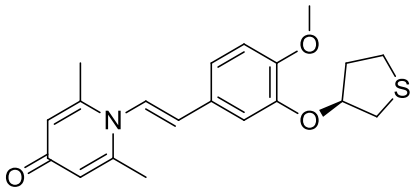
[0604] (*E*)-1-(3-((1,1, -dioxotetrahydrothiophen-3-yl)oxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0605] The specific reaction scheme is as shown below:

[0606] 

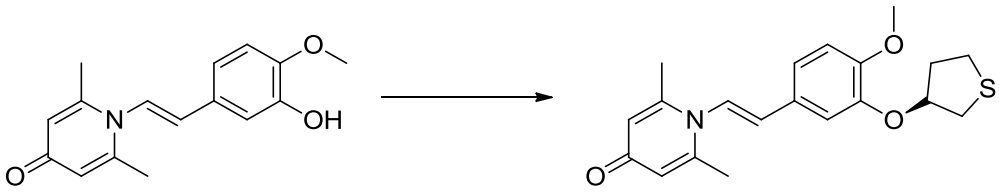
[0607] The compound (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (68 mg, 0.19 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (116 mg, 0.57 mmol) was added and stirred for 3 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-((1,1, -dioxotetrahydrothiophen-3-yl)oxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (62 mg, yield 86%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 14.4 Hz, 1H), 7.10 (s, 2H), 6.97 (d, *J* = 14.4 Hz, 1H), 5.34-5.27 (m, 1H), 3.91 (s, 3H), 3.52-3.44 (m, 1H), 3.41-3.32 (m, 2H), 3.23-3.17 (m, 1H), 2.70-2.61 (m, 1H), 2.58-2.47 (m, 1H), 2.54 (s, 6H); LC-MS: m/z 390.1 $[M + H]^+$.

[0608] Example 82

[0609] 

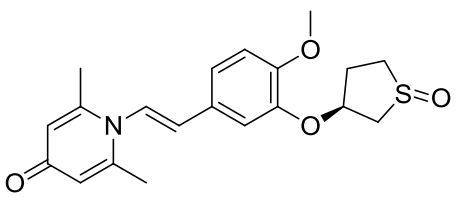
[0610] (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0611] The specific reaction scheme is as shown below:

[0612] 

[0613] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (45 mg, 0.15 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then (*R*)-tetrahydrothiophen-3-yl methanesulfonate (53 mg, 0.29 mmol) and cesium carbonate (95 mg, 0.29 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 56%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 14.4 Hz, 1H), 6.58 (d, J = 14.4 Hz, 1H), 6.31 (s, 2H), 5.16-5.13 (m, 1H), 3.90 (s, 3H), 3.18-3.08 (m, 1H), 3.09 (d, J = 3.6 Hz, 2H), 2.98-2.93 (m, 1H), 2.49-2.42 (m, 1H), 2.27 (s, 6H), 2.08-1.99 (m, 1H); LC-MS: m/z 358.1 $[M + H]^+$.

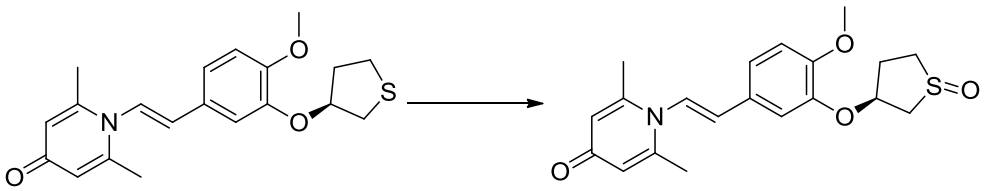
[0614] Example 83

[0615] 

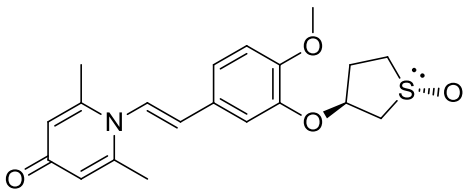
[0616] 1-((*E*)-4-methoxy-3-(((3*S*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-

dimethylpyridin-4(1*H*)-one

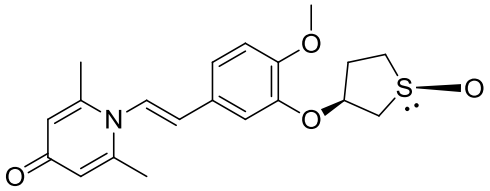
[0617] The specific reaction scheme is as shown below:

[0618] 

[0619] The compound (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (81 mg, 0.23 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (41 mg, 0.20 mmol) was added and stirred for 3 hours at 0°C. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave a diastereoisomer of 1-((*E*)-4-methoxy-3-(((3*S*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one show below:

[0620] 

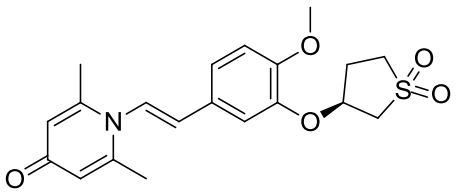
[0621] (25 mg, yield 29%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 7.12 (dd, J = 8.4, 1.6 Hz, 1H), 7.07 (d, J = 14.4 Hz, 1H), 7.01 (s, 2H), 6.94 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 14.4 Hz, 1H), 5.28-5.24 (m, 1H), 3.91 (s, 3H), 3.34-3.14 (m, 4H), 2.93-2.85 (m, 1H), 2.51 (s, 6H), 2.34-2.25 (m, 1H); LC-MS: m/z 374.1 $[M + H]^+$.

[0622] 

[0623] (20 mg, yield 23%, pale yellow oil)^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 7.07 (d, J = 14.4 Hz, 1H), 7.03 (s, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 14.4 Hz, 1H), 5.48-5.43 (m, 1H), 3.89 (s, 3H), 3.64 (d, J = 15.2 Hz, 1H), 3.21-3.07 (m, 3H), 2.83-

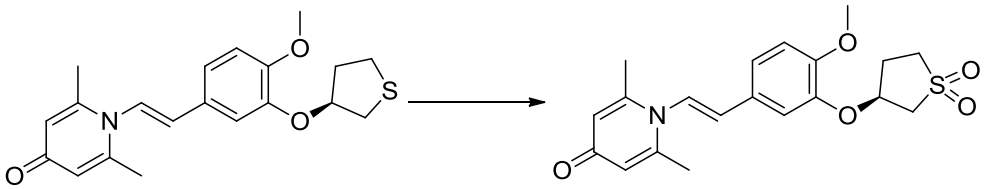
2.74 (m, 1H), 2.65-2.59 (m, 1H), 2.51 (s, 6H); LC-MS: m/z 374.1 $[M + H]^+$.

[0624] Example 84

[0625] 

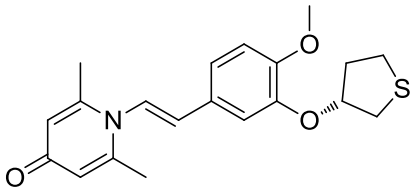
[0626] (S,*E*)-1-(3-((1,1-dioxotetrahydrothiophen-3-yl)oxy)-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0627] The specific reaction scheme is as shown below:

[0628] 

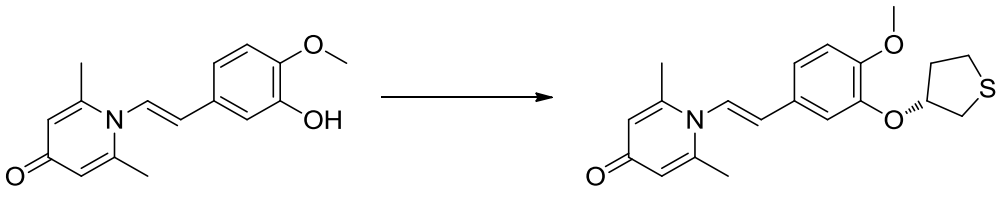
[0629] The compound (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (81 mg, 0.23 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (140 mg, 0.69 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-((1,1, -dioxotetrahydrothiophen-3-yl)oxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (58 mg, yield 66%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 14.4 Hz, 1H), 7.05 (s, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 14.4 Hz, 1H), 5.32-5.27 (m, 1H), 3.91 (s, 3H), 3.52-3.43 (m, 1H), 3.41-3.31 (m, 2H), 3.22-3.16 (m, 1H), 2.69-2.62 (m, 1H), 2.57-2.47 (m, 1H), 2.52 (s, 6H); LC-MS m/z 390.2 $[M + H]^+$.

[0630] Example 85

[0631] 

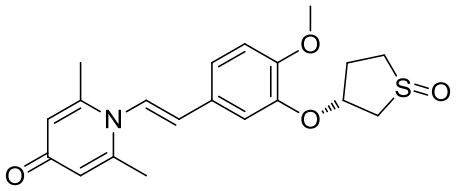
[0632] (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0633] The specific reaction scheme is as shown below:

[0634] 

[0635] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (45 mg, 0.15 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then (*S*)-tetrahydrothiophen-3-yl methanesulfonate (53 mg, 0.29 mmol) and cesium carbonate (95 mg, 0.29 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 56%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 14.4 Hz, 1H), 6.58 (d, J = 14.4 Hz, 1H), 6.31 (s, 2H), 5.16-5.13 (m, 1H), 3.90 (s, 3H), 3.18-3.08 (m, 1H), 3.09 (d, J = 3.6 Hz, 2H), 2.98-2.93 (m, 1H), 2.49-2.42 (m, 1H), 2.27 (s, 6H), 2.08-1.99 (m, 1H); LC-MS: m/z 358.1 $[M + H]^+$.

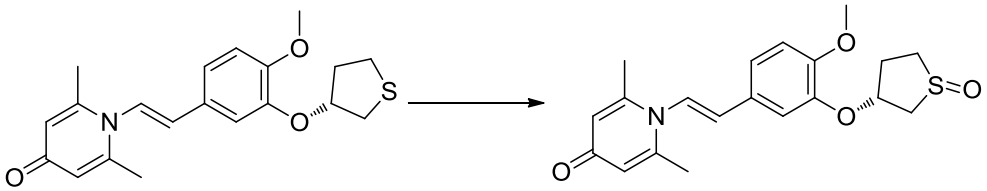
[0636] Example 86

[0637] 

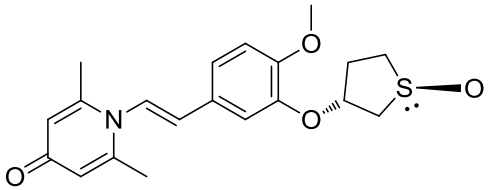
[0638] 1-((*E*)-4-methoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-

dimethylpyridin-4(1*H*)-one

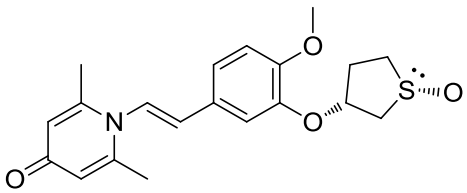
[0639] The specific reaction scheme is as shown below:

[0640] 

[0641] The compound (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (57 mg, 0.16 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (29 mg, 0.15 mmol) was added and stirred for 3 hours at 0°C. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave a diastereoisomer of 1-((*E*)-4-methoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one shown below:

[0642] 

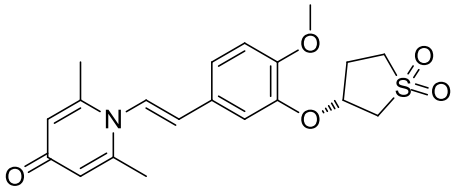
[0643] (15 mg, yield 25%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3OD) δ 7.26 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (d, J = 14.4 Hz, 1H), 6.99 (d, J = 7.6, 1H), 6.96 (s, 2H), 6.80 (d, J = 14.4, 1H), 5.18-5.13 (m, 1H), 3.80 (s, 3H), 3.36-3.25(m, 2H), 3.09-3.00 (m, 2H), 2.69-2.61 (m, 1H), 2.49 (s, 6H), 2.27-2.19(m, 1H); LC-MS: m/z 374.1 $[M + H]^+$.

[0644] 

[0645] (10 mg, yield 17%, pale yellow oil)^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.26 (d, J = 14.4 Hz, 1H), 7.10 (d, J = 7.6, 1H), 7.09 (s, 2H), 6.93 (d, J = 14.4, 1H), 5.52-5.49 (m, 1H), 3.89 (s, 3H), 3.76-3.71 (m, 1H), 3.30-3.22 (m, 2H),

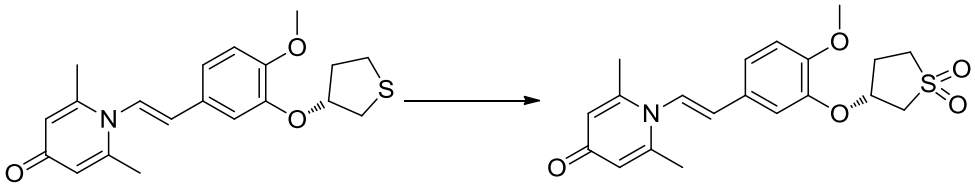
3.76-3.71 (m, 1H), 2.77-2.67 (m, 1H), 2.65-2.63 (m, 1H), 2.61 (s, 6H); LC-MS: m/z 374.1 [M + H]$^+$.

[0646] Example 87

[0647] 

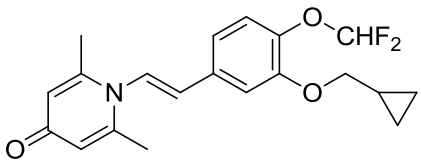
[0648] (R,*E*)-1-(3-((1,1-dioxotetrahydrothiophen-3-yl)oxy)-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0649] The specific reaction scheme is as shown below:

[0650] 

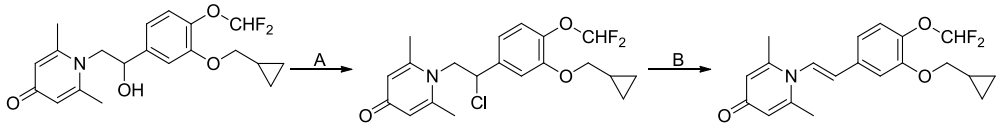
[0651] The compound (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, 0.08 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (49 mg, 0.24 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-((1,1, -dioxotetrahydrothiophen-3-yl)oxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (12 mg, yield 40%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (s, 1H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (d, J = 14.4 Hz, 1H), 7.10 (dd, J = 8.4, 2.0 Hz, 1H), 6.96 (s, 2H), 6.81 (d, J = 14.4, 1H), 5.20-5.16 (m, 1H), 3.80 (s, 3H), 3.38-3.28 (m, 2H), 3.25-3.24 (m, 1H), 3.13-3.07 (m, 1H), 2.49 (s, 6H), 2.47-2.34 (m, 2H); LC-MS: m/z 390.0 [M + H]$^+$.

[0652] Example 88

[0653] 

[0654] (*E*)-1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0655] The specific reaction scheme is as shown below:

[0656] 

[0657] Step A:

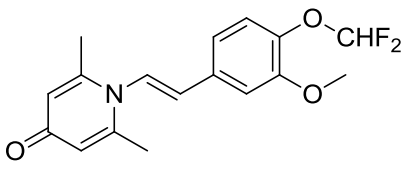
[0658] The compound 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (80 mg, 0.21 mmol) was dissolved in trichloromethane (10 mL), and heated to 80°C. Then thionyl chloride (0.5 mL) was added and stirred at 80°C for 15 min. After the reaction was completed, the reaction solution was directly rotary dried to obtain a crude product of 1-(2-chloro-2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (85 mg, 100%). LC-MS: m/z 398.2 $[M + H]^+$.

[0659] Step B:

[0660] The compound 1-(2-chloro-2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)ethyl)-2,6-dimethylpyridin-4(1*H*)-one (85 mg, 0.21 mmol) was dissolved in ethanol (10 mL), and then sodium hydroxide (64 mg, 1.60 mmol) and water (2 mL) were added in sequence, heated to 100°C, and stirred for 16 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified to obtain (*E*)-1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, 26%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 14.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.4, 2.0 Hz, 1H), 7.12 (t, $J_{H\text{-}F}$ = 74.4 Hz, 1H), 6.91 (d, J = 14.4 Hz, 1H), 6.49 (s, 2H), 3.95 (d, J = 7.2 Hz, 2H), 2.34 (s, 6H), 1.31-1.21 (m, 1H), 0.62-0.57 (m, 2H), 0.37-0.33 (m,

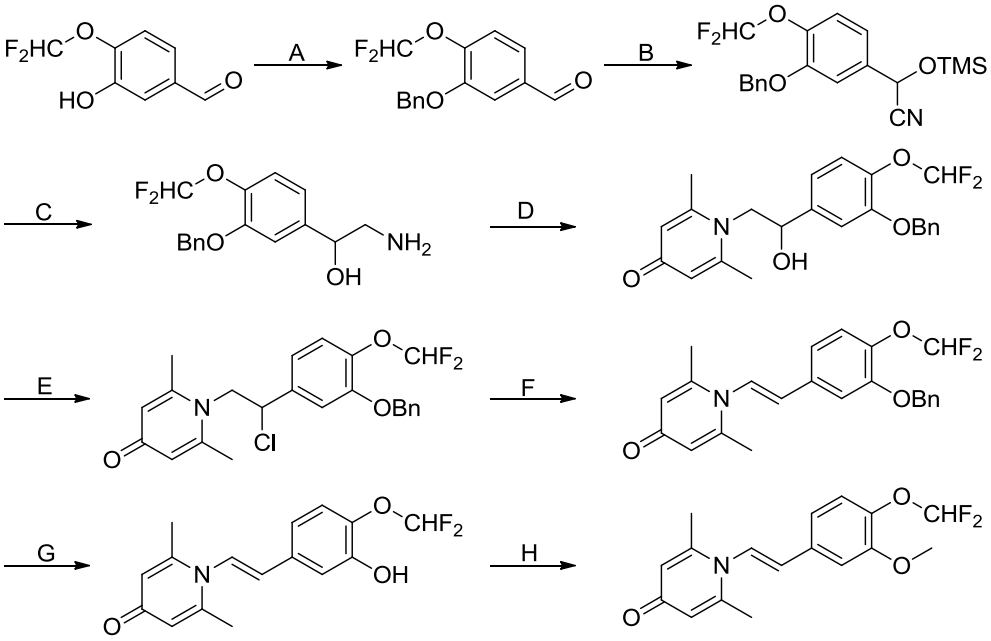
2H); LC-MS: m/z 362.2 $[M + H]^+$.

[0661] Example 89

[0662] 

[0663] (*E*)-1-(3-methoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0664] The specific reaction scheme is as shown below:

[0665] 

[0666] Step A:

[0667] At room temperature, 3-hydroxy-4-difluoromethoxybenzaldehyde (2.36 g, 12.5 mmol) was dissolved in acetonitrile (40 mL), and then potassium carbonate (3.46 g, 25.1 mmol) and benzyl bromide (2.79 g, 16.3 mmol) were added in sequence, and heated to 80°C for 3 hours with stirring under nitrogen atmosphere. After the reaction was completed, a saturated aqueous sodium chloride solution (30 mL) was added, and extracted with dichloromethane (3 x 120 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified by column chromatography to obtain 3-benzoxy-4-difluoromethoxybenzaldehyde (3.30 g, 95%).

[0668] Step B:

[0669] 3-benzoxy-4-difluoromethoxybenzaldehyde (3.30 g, 11.9 mmol) was dissolved in dichloromethane (30 mL), and then triethyl amine (2.40 g, 23.7 mmol) and trimethylsilyl cyanide (3.53 g, 35.6 mmol) were added in sequence in an ice bath and stirred for 16 hours under nitrogen atmosphere at room temperature. After the reaction was completed, the reaction solution was directly rotary dried to obtain 2-(3-benzoxy-4-difluoromethoxyphenyl)-2-trimethylsiloxyacetonitrile, which was directly used in the next reaction.

[0670] Step C:

[0671] The compound 2-(3-benzoxy-4-difluoromethoxyphenyl)-2-trimethylsiloxyacetonitrile (4.47 g, 11.9 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL), and then lithium aluminum hydride (1.35 g, 35.6 mmol) was added portion-wise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, the reaction was diluted with anhydrous tetrahydrofuran (200 mL), and then water (1.35 mL), an aqueous sodium hydroxide solution (1.35 mL, 15%), and water (4.05 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 2-amino-1-(3-benzoxy-4-difluoromethoxyphenyl)ethanol, which was directly used in the next reaction.

[0672] Step D:

[0673] The compound 2-amino-1-(3-benzoxy-4-difluoromethoxyphenyl)ethanol (3.67 g, 11.9 mmol) was dissolved in ethanol (60 mL), and then 2,6-dimethyl-4H-pyran-4-one (2.19 g, 17.7 mmol), sodium hydroxide (708 mg, 17.7 mmol) and water (10 mL) were added in sequence, heated to 60°C, and stirred for 16 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-benzoxy-4-difluoromethoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.3 g, 47%). LC-MS m/z 416.2 $[M + H]^+$.

[0674] Step E:

[0675] The compound 1-(2-(3-benzoxy-4-difluoromethoxyphenyl)-2-hydroxyethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.3 g, 5.3 mmol) was dissolved in trichloromethane (80 mL), and

then heated to 90°C. Thionyl chloride (3 mL) was added and stirred at 90°C for 15 min. After the reaction was completed, the reaction solution was directly rotary dried to obtain a crude product of 1-(2-(3-benzoxy-4-difluoromethoxyphenyl)-2-chloroethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.15 g, 93%). LC-MS m/z 434.2 $[M + H]^+$.

[0676] Step F:

[0677] The compound 1-(2-(3-benzoxy-4-difluoromethoxyphenyl)-2-chloroethyl)-2,6-dimethylpyridin-4(1*H*)-one (2.15 g, 5.0 mmol) was dissolved in ethanol (40 mL), and then sodium hydroxide (1.2 g, 30 mmol) and water (15 mL) were added in sequence, heated to 90°C, and stirred for 16 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified to obtain (*E*)-1-(3-benzoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one(1.5 g, 75%). LC-MS: m/z 398.2 $[M + H]^+$.

[0678] Step G:

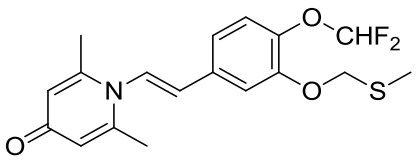
[0679] The compound (*E*)-1-(3-benzoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (400 mg, 1.0 mmol) was dissolved in anhydrous dichloromethane (100 mL), and titanium tetrachloride (1 M, 2 mL, 2.0 mmol) was slowly added dropwise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, the reaction solution was rotary dried, and purified to obtain (*E*)-1-(3-hydroxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 16%). LC-MS: m/z 308.2 $[M + H]^+$.

[0680] Step H:

[0681] The compound (*E*)-1-(3-hydroxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.16 mmol) was dissolved in acetonitrile (5 mL), and then iodomethane (30 mg, 0.21 mmol) and potassium carbonate (90 mg, 0.65 mmol) were added, and stirred for 2 hours at 80°C under nitrogen atmosphere. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-methoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one (38 mg, yield 71%, white solid). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 1H), 7.08-7.05 (m, 2H), 6.96 (d, J = 14.0 Hz, 1H),

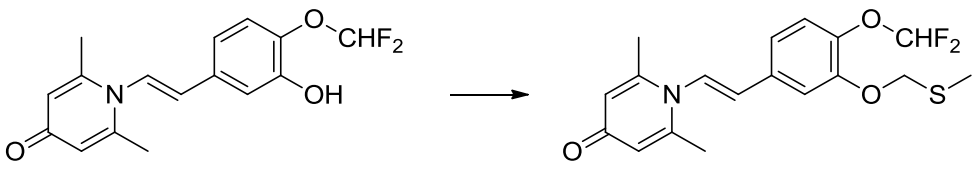
6.69 (d, J = 14.0 Hz, 1H), 6.59 (t, $J_{H\text{-}F}$ = 74.8 Hz, 1H), 6.41 (s, 2H), 3.95 (s, 3H), 2.31 (s, 6H); LC-MS: m/z 322.2 $[M + H]^+$.

[0682] Example 90

[0683] 

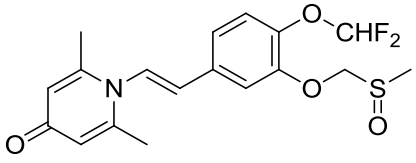
[0684] (*E*)-1-(3-methylthiomethoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0685] The specific reaction scheme is as shown below:

[0686] 

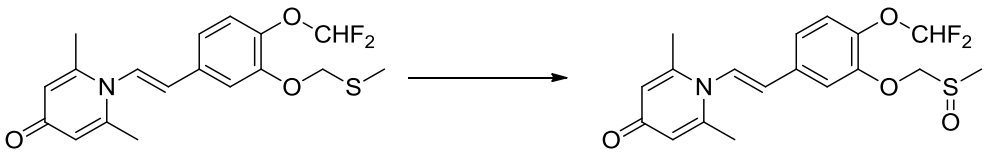
[0687] The compound (*E*)-1-(3-hydroxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one (35 mg, 0.11 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then chloromethylmethyl sulfide (22 mg, 0.23 mmol) and cesium carbonate (150 mg, 0.46 mmol) were added, and stirred for 1 hr at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylthiomethoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one(30 mg, yield 71%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.22 (m, 2H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 14.4 Hz, 1H), 6.77 (s, 2H), 6.76 (d, J = 14.4 Hz, 1H), 6.59 (t, $J_{H\text{-}F}$ = 74.0 Hz, 1H), 5.29 (s, 2H), 2.41 (s, 6H), 2.29 (s, 3H); LC-MS: m/z 368.4 $[M + H]^+$.

[0688] Example 91

[0689] 

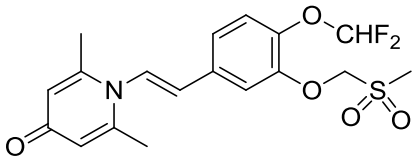
[0690] (*E*)-1-(3-methylsulfoxidemethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0691] The specific reaction scheme is as shown below:

[0692] 

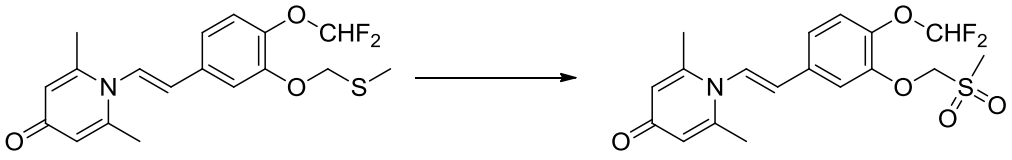
[0693] The compound (*E*)-1-(3-methylthiomethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (78 mg, 0.21 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (39 mg, 0.19 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoxidemethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (64 mg, yield 78%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.27 (d, J = 14.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.03 (s, 2H), 6.80 (d, J = 14.8 Hz, 1H), 6.64 (t, $J_{H\text{-}F}$ = 73.6 Hz, 1H), 5.26 (d, J = 11.2 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 2.77 (s, 3H), 2.52 (s, 6H); LC-MS: m/z 384.0 $[M + H]^+$.

[0694] **Example 92**

[0695] 

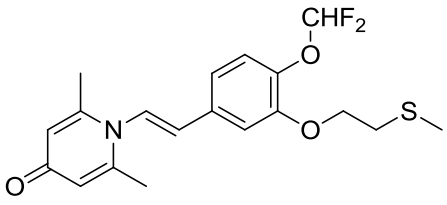
[0696] (*E*)-1-(3-methylsulfonemethoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0697] The specific reaction scheme is as shown below:

[0698] 

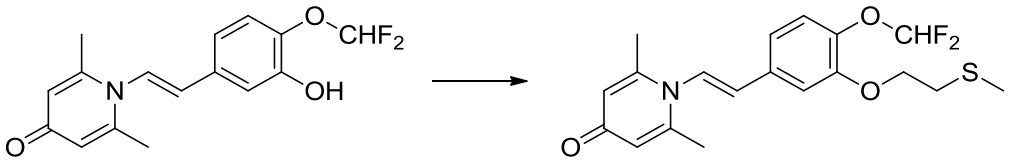
[0699] The compound (*E*)-1-(3-methylthiomethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (78 mg, 0.21 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (128 mg, 0.63 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfonemethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one(35 mg, yield 41%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.4, 2.0 Hz, 1H), 7.26 (d, J = 14.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.97 (s, 2H), 6.91 (d, J = 14.4 Hz, 1H), 6.79 (t, J_{H-F} = 73.6 Hz, 1H), 5.23 (s, 2H), 3.01 (s, 3H), 2.49 (s, 6H); LC-MS: m/z 399.9 $[M + H]^+$.

[0700] Example 93

[0701] 

[0702] (*E*)-1-(3-methylthioethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

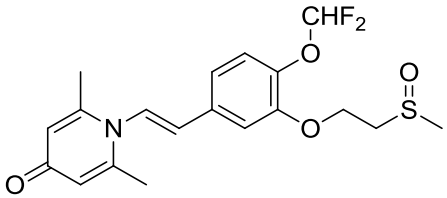
[0703] The specific reaction scheme is as shown below:

[0704] 

[0705] At room temperature, (*E*)-1-(4-(difluoromethoxy)-3-hydroxystyryl)-2,6-dimethylpyridin-4(1H)- one (50 mg, 0.16 mmol) was dissolved in N,N -dimethylformamide (2 mL), and then potassium carbonate (34 mg, 0.24 mmol) and chloroethyl methyl sulfide (36 mg, 0.33 mmol) were added in sequence, and heated to 80°C for 16 hours with stirring under nitrogen atmosphere. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(3-methylthioethoxy-4-difluoromethoxystyryl)-

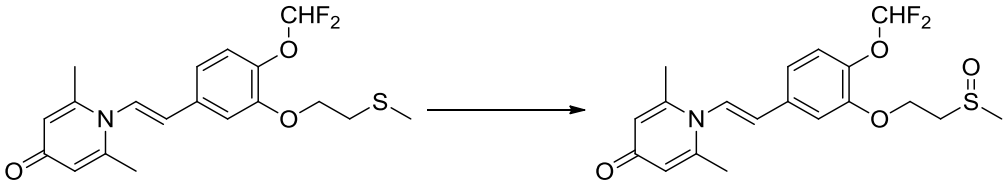
2,6-dimethylpyridin-4(1*H*)-one (8 mg, 14%). ^{1}H NMR (400 MHz, CDCl3) δ 7.18 (d, J = 8.4 Hz, 1H), 7.06-6.99 (m, 2H), 6.84 (d, *J* = 14.0 Hz, 1H), 6.59 (t, *J* = 14.0 Hz, 1H), 6.58 (d, J_{H-F} = 75.2 Hz, 1H), 6.19 (s, 2H), 4.20 (t, J = 6.4 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 2.19 (s, 6H), 2.16 (s, 3H); LC-MS: m/z 382.2 $[M + H]^+$.

[0706] Example 94

[0707] 

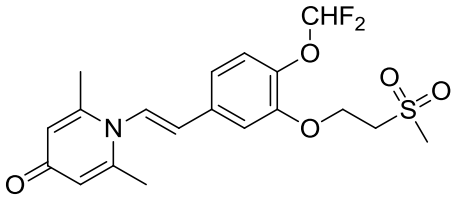
[0708] (*E*)-1-(3-methylsulfoxideethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0709] The specific reaction scheme is as shown below:

[0710] 

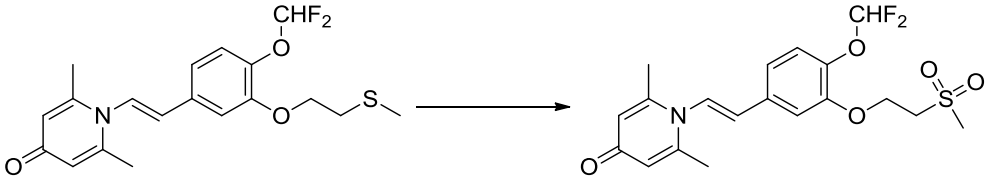
[0711] The compound (*E*)-1-(3-methylthioethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (55 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (27 mg, 0.13 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoxideethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (16 mg, yield 28%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.26 (d, *J* = 14.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 2H), 6.79 (d, *J* = 14.4 Hz, 1H), 6.58 (t, J_{H-F} = 74.0 Hz, 1H), 4.60 (t, *J* = 8.8 Hz, 1H), 3.33-3.26 (m, 1H), 3.16-3.10 (m, 1H), 2.75 (s, 3H), 2.51 (s, 6H); LC-MS: m/z 398.0 $[M + H]^+$.

[0712] Example 95

[0713] 

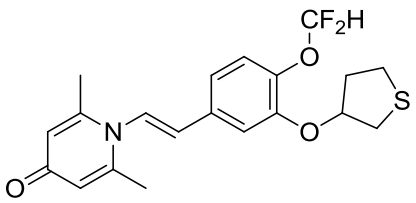
[0714] (*E*)-1-(3-methylsulfoneethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0715] The specific reaction scheme is as shown below:

[0716] 

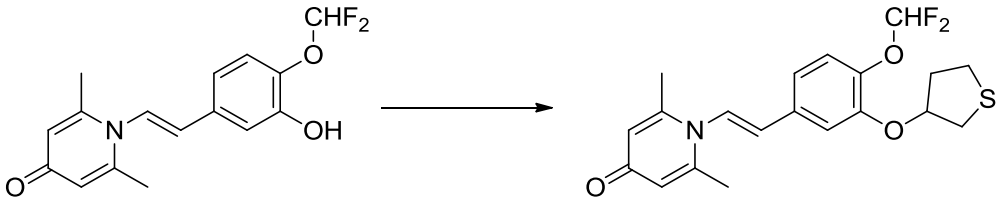
[0717] The compound (*E*)-1-(3-methylthioethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (55 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL), and then m-chloroperoxybenzoic acid (85 mg, 0.42 mmol) was added and stirred for 2 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-methylsulfoneethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (33 mg, yield 75%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.36 (d, J = 14.4 Hz, 1H), 7.30-7.25 (m, 2H), 7.04 (s, 2H), 7.00 (d, J = 14.4 Hz, 1H), 6.58 (t, J_{H-F} = 74.4 Hz, 1H), 4.55 (t, J = 5.2 Hz, 1H), 3.66 (t, J = 5.2 Hz, 1H), 3.15 (s, 3H), 2.59 (s, 6H); LC-MS: m/z 414.0 $[M + H]^+$.

[0718] **Example 96**

[0719] 

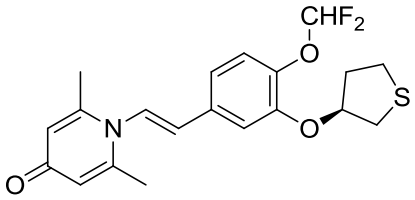
[0720] (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one

[0721] The specific reaction scheme is as shown below:

[0722] 

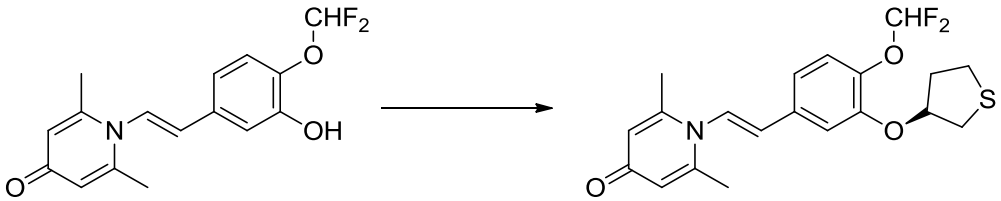
[0723] The compound (*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (42 mg, 0.14 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then tetrahydrothiophen-3-yl methanesulfonate (53 mg, 0.29 mmol) and cesium carbonate (95 mg, 0.29 mmol) were added, and stirred for 1 hr at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 54%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 14.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 14.4 Hz, 1H), 6.79 (t, J_{H-F} = 75.0 Hz, 1H), 6.65 (s, 2H), 5.36-5.32 (m, 1H), 3.16 (dd, J = 12.0, 4.4 Hz, 1H), 3.11-3.02 (m, 2H), 2.99-2.94 (m, 1H), 2.49-2.41 (m, 1H), 2.45 (s, 6H), 2.10-2.01 (m, 1H); LC-MS: m/z 394.2 $[M + H]^+$.

[0724] **Example 97**

[0725] 

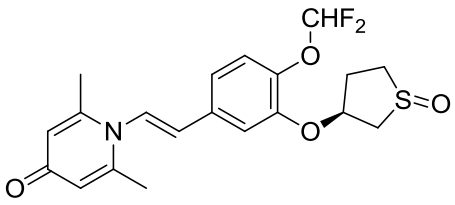
[0726] (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0727] The specific reaction scheme is as shown below:

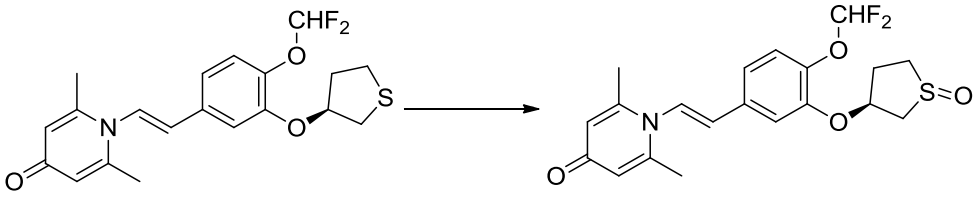
[0728] 

[0729] The compound (*E*)-1-(3-hydroxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (50 mg, 0.15 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then (*R*)-tetrahydrothiophen-3-yl methanesulfonate (53 mg, 0.29 mmol) and cesium carbonate (95 mg, 0.29 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (10 mg, yield 17%, pale yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 8.4, 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 14.4 Hz, 1H), 6.77 (d, J = 14.4 Hz, 1H), 6.64 (d, J = 14.4 Hz, 1H), 6.61 (t, $J_{H\text{-}F}$ = 74.8 Hz, 1H), 6.29 (s, 2H), 5.21-5.16 (m, 1H), 3.16-3.09 (m, 3H), 3.03-2.97 (m, 1H), 2.52-2.47 (m, 1H), 2.26 (s, 6H), 2.11-2.02 (m, 1H); LC-MS: m/z 394.2 $[M + H]^+$.

[0730] Example 98

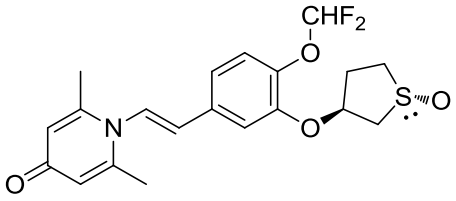
[0731] 

[0732] The specific reaction scheme is as shown below:

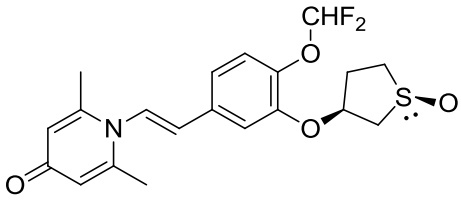
[0733] 

[0734] The compound (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (103 mg, 0.26 mmol) was dissolved in dichloromethane (5 mL), and

then 85% m-chloroperoxybenzoic acid (48 mg, 0.24 mmol) was added and stirred for 2 hours at 0°C. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave a diastereoisomer of 1-((*E*)-4-difluoromethoxy-3-(((3*S*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one shown below:

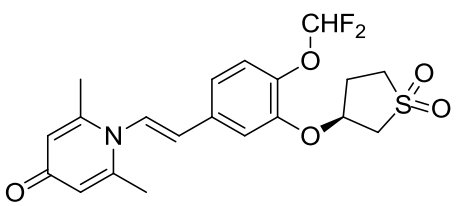
[0735] 

[0736] (42 mg, yield 39%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37 (d, J = 14.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.94 (s, 2H), 6.81 (d, J = 14.4 Hz, 1H), 6.80 (t, J_{H-F} = 72.4 Hz, 1H), 5.46-5.38 (m, 1H), 3.46-3.38 (m, 1H), 3.33-3.17 (m, 3H), 2.94-2.85 (m, 1H), 2.54 (s, 6H), 2.41-2.32 (m, 1H); LC-MS: m/z 410.1 $[M + H]^+$.

[0737] 

[0738] (30 mg, yield 28%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.30 (d, J = 14.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.4, 1.2 Hz, 1H), 6.95 (s, 2H), 6.82 (d, J = 14.4 Hz, 1H), 6.48 (t, J_{H-F} = 73.6 Hz, 1H), 5.58-5.53 (m, 1H), 3.60 (d, J = 15.2 Hz, 1H), 3.17 (dd, J = 15.2, 4.8 Hz, 1H), 3.11-3.07 (m, 2H), 2.90-2.80 (m, 1H), 2.65-2.61 (m, 1H), 2.51 (s, 6H); LC-MS: m/z 410.1 $[M + H]^+$.

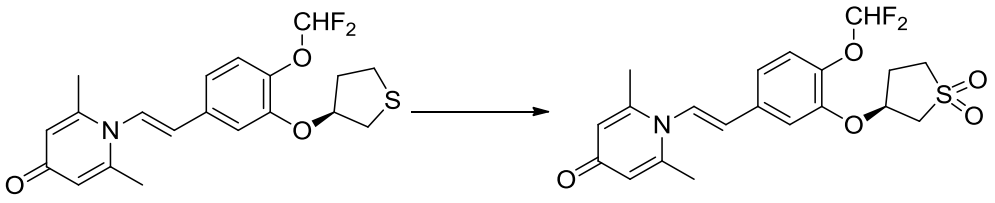
[0739] Example 99

[0740] 

[0741] (S,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-

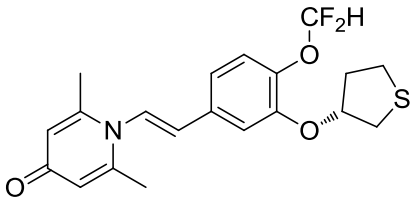
dimethylpyridin-4(1*H*)-one

[0742] The specific reaction scheme is as shown below:

[0743] 

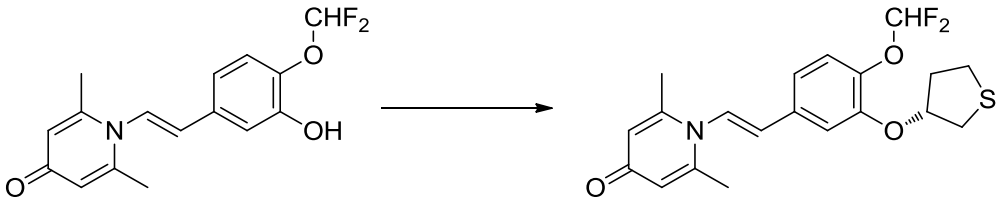
[0744] The compound (*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one (55 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (85 mg, 0.42 mmol) was added and stirred for 3 hours at room temperature. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (S,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (52 mg, yield 86%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.36 (d, J = 14.0, Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.96 (s, 2H), 6.81 (d, J = 14.0 Hz, 1H), 6.60 (t, $J_{H\text{-}F}$ = 73.6 Hz, 1H), 5.45-5.40 (m, 1H), 3.50-3.35 (m, 3H), 3.27-2.21(m, 1H), 2.70-2.58 (m, 2H), 2.53 (s, 6H); LC-MS m/z 426.0 $[M + H]^+$.

[0745] **Example 100**

[0746] 

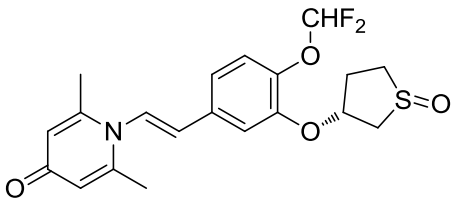
[0747] (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0748] The specific reaction scheme is as shown below:

[0749] 

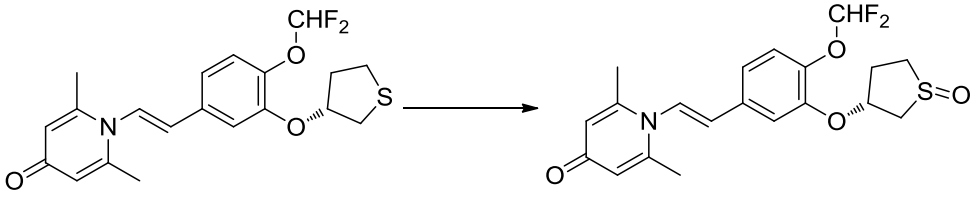
[0750] The compound (*E*)-1-(3-hydroxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (200 mg, 0.58 mmol) was dissolved in N,N-dimethylformamide (10 mL), and then (*S*)-tetrahydrothiophen-3-yl methanesulfonate (212 mg, 1.16 mmol) and cesium carbonate (758 mg, 2.3 mmol) were added, and stirred overnight at 80°C under nitrogen atmosphere. After the reaction was completed, saturated saline (20 mL) was added, and extracted with dichloromethane (3 x 20 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (30 mg, yield 13%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.4 2.0 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 14.4 Hz, 1H), 6.65 (d, *J* = 14 Hz, 1H), 6.60 (m, *J* = 14.4 Hz, 1H), 6.63 (t, *J* = 74.8 Hz, 1H), 6.31 (s, 2H), 5.21-5.16 (m, 1H), 3.16-3.09 (m, 3H), 3.03-2.97 (m, 1H), 2.52-2.47 (m, 1H), 2.26 (s, 6H), 2.11-2.02 (m, 1H); LC-MS m/z 394.0 $[M + H]^+$.

[0751] Example 101

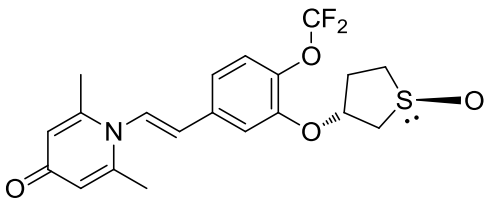
[0752] 

[0753] 1-((*E*)-4-difluoromethoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one

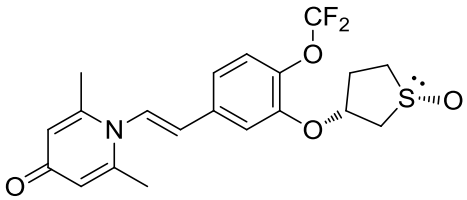
[0754] The specific reaction scheme is as shown below:

[0755] 

[0756] The compound (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (55 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (26 mg, 0.13 mmol) was added and stirred for 3 hours at 0°C. Then, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave a diastereoisomer of 1-((*E*)-4-difluoromethoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one shown below:

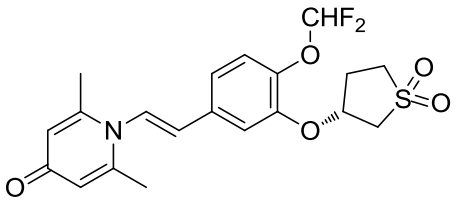
[0757] 

[0758] (20 mg, yield 35%, pale yellow oil). ^{1}H NMR (400 MHz, CD_3Cl) δ 7.50 (s, 1H), 7.20 (d, J = 12.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.95 (s, 2H), 6.82 (s, 1H), 6.80 (m, J = 76.4 Hz, 1H), 5.43 (m, 1H), 3.44-3.38 (m, 2H), 3.29-3.16 (m, 2H), 2.92-2.89 (m, 1H), 2.54 (s, 6H), 2.41-2.33 (m, 1H); LC-MS: m/z 410.0 $[M + H]^+$.

[0759] 

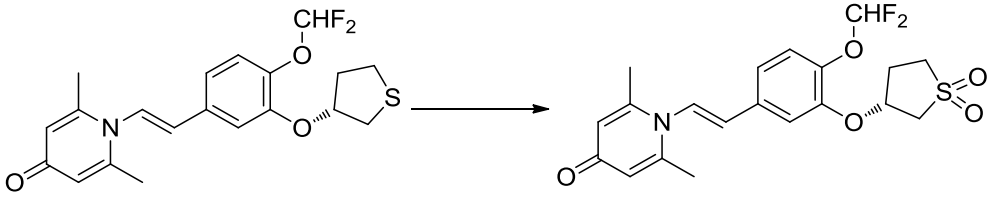
[0760] (10 mg, yield 17%, pale yellow oil)^{1}H NMR (400 MHz, CD_3Cl) δ 7.34 (s, 1H), 7.30 (d, J = 14.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.94 (s, 2H), 6.82 (d, J = 14.4 Hz, 1H), 6.48 (t, J = 73.6 Hz, 1H), 5.55 (m, 1H), 3.59 (d, J = 14.8 Hz, 1H), 3.19-3.14 (m, 1H), 3.11-3.08 (m, 2H), 2.90-2.81 (m, 1H), 2.64-2.61 (m, 1H), 2.54 (s, 6H); LC-MS: m/z 410.0 $[M + H]^+$.

[0761] Example 102

[0762] 

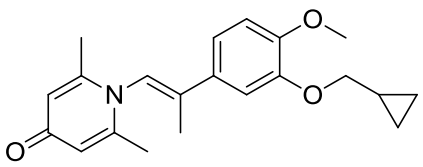
[0763] (*R*,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one

[0764] The specific reaction scheme is as shown below:

[0765] 

[0766] The compound (*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (40 mg, 0.1 mmol) was dissolved in dichloromethane (5 mL), and then 85% m-chloroperoxybenzoic acid (61 mg, 0.3 mmol) was added and stirred for 2 hours at room temperature. After the reaction was completed, a saturated aqueous sodium sulfite solution (10 mL) was added, stirred for 10 min, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*R*,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one (33 mg, yield 75%, white solid). ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, J = 1.6 Hz, 1H), 7.38 (dd, J = 8.4, 2.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.06 (s, 2H), 7.01 (d, J = 14.4 Hz, 1H), 6.87 (t, J = 75.2 Hz, 1H), 5.43-5.39 (m, 1H), 3.56-8.51 (m, 1H), 3.44-3.36 (m, 2H), 3.31-3.25 (m, 1H), 2.66-2.62 (m, 2H), 2.61 (s, 6H); LC-MS: m/z 426.0 $[M + H]^+$.

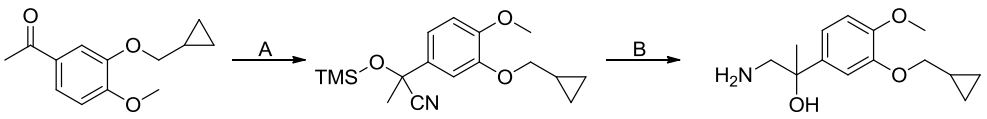
[0767] **Example 103**

[0768] 

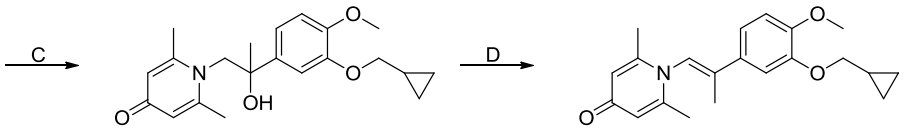
[0769] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-methylethenyl)-2,6-

dimethylpyridin-4(1*H*)-one

[0770] The specific reaction scheme is as shown below:



[0771]



[0772] Step A:

[0773] 3-Cyclopropylmethoxy-4-methoxyphenylacetophenone (220 mg, 1.0 mmol) was dissolved in acetonitrile (2 mL); and under nitrogen atmosphere, cesium fluoride (76 mg, 0.50 mmol) was added, trimethylsilyl cyanide (149 mg, 1.50 mmol) was slowly added dropwise at 0°C, and stirred for 5 hours. The reaction solution was filtered, and rotary dried to obtain a crude product of 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxy-propionitrile. LC-MS: m/z 320.2 $[M + H]^+$.

[0774] Step B:

[0775] The compound 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-trimethylsiloxy-propionitrile (319 mg, 1.0 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL); and under nitrogen atmosphere, lithium aluminum hydride (96 mg, 2.0 mmol) was slowly added dropwise at 0°C, and the solution was stirred at room temperature for 1 hr. After the reaction was completed, sodium sulfate decahydrate was added to quench the reaction. Then, the reaction solution was filtered, and the filtrate was rotary dried to obtain a crude product of 1-amino-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-2-propanol. LC-MS: m/z 252.2 $[M + H]^+$.

[0776] Step C:

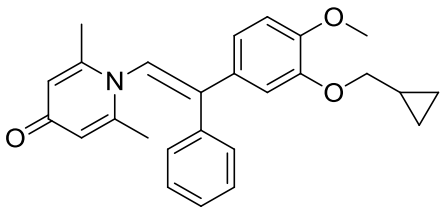
[0777] The compound 1-amino-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-2-propanol (251 mg, 1.0 mmol) was dissolved in ethanol (3 mL), and then 2.6-dimethyl-4H-pyran-4-one (186 mg, 1.5 mmol) and sodium hydroxide (80 mg, 2.0 mmol) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried,

and purified to obtain 1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-2-hydroxypropyl)-2,6-dimethylpyridin-4(1*H*)-one (40 mg, yield 11%). LC-MS: m/z 358.0 $[M + H]^+$.

[0778] Step D:

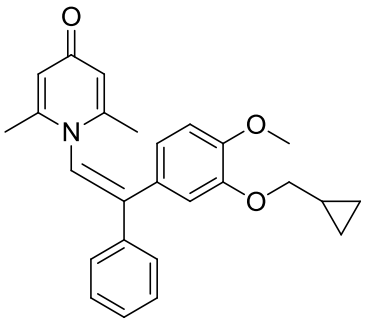
[0779] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxypropyl)-2,6-dimethylpyridin-4(1*H*)-one (36 mg, 0.1 mmol) was dissolved in toluene (3 mL), and then p-toluenesulfonic acid (29 mg, 0.15 mmol) was added and stirred overnight at 110°C. The reaction was complete as indicated by TLC. The reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-methylethenyl)-2,6-dimethylpyridin-4(1*H*)-one (27 mg, yield 80%, white solid). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.05-7.03 (m, 1H), 6.92-6.90 (m, 2H), 6.68(s, 2H), 6.10 (s, 1H), 3.92 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.52 (s, 6H), 1.12-1.06 (m, 1H), 0.72-0.68 (m, 2H), 0.40-0.36 (m, 2H); LC-MS: m/z 340.2 $[M + H]^+$.

[0780] **Example 104**



[0781]

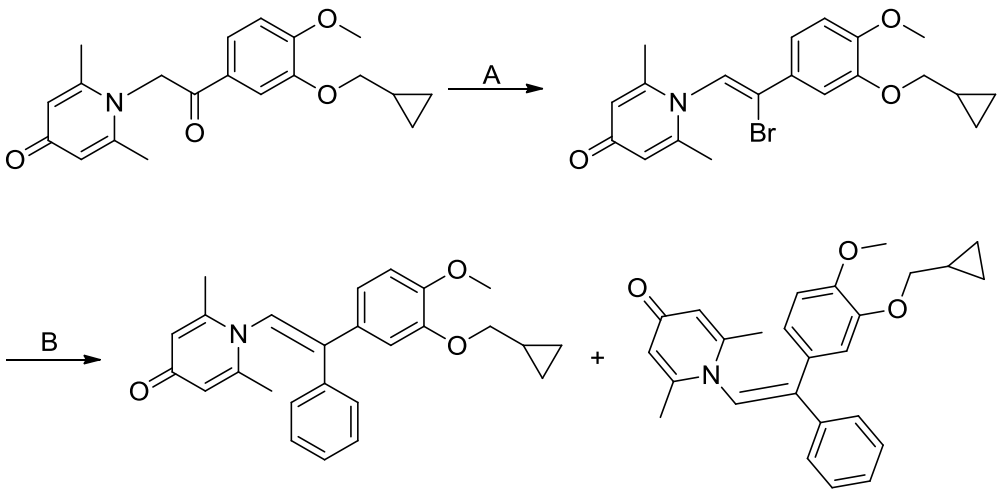
[0782] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one



[0783]

[0784] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one

[0785]



[0786] Step A:

[0787] Trisphenyl phosphite (1.49 g, 4.80 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL), and then triethyl amine (0.53 mg, 5.20 mmol) and the compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)pyridin-2,6-dimethyl-4(1*H*)-one (1.36 mg, 4.00 mmol) was slowly added to the reaction solution at -60°C and stirred for 15 min. Then, bromine (0.77 mg, 4.80 mmol) was slowly added to the reaction solution. After the reaction was completed, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-bromoethenyl)-2,6-dimethylpyridin-4(1*H*)-one (708 mg, yield 44%). LC-MS: m/z 403.9 $[M + H]^+$.

[0788] Step B:

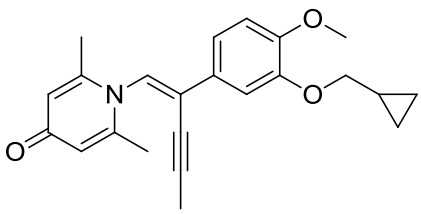
[0789] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-bromoethenyl)-2,6-dimethylpyridin-4(1*H*)-one (200 mg, 0.50 mmol) was dissolved in tetrahydrofuran (2 mL) and water (1 mL). Under nitrogen atmosphere, palladium acetate (5.5 mg, 5 mol%), sodium carbonate (5 mg, 0.50 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) were added to the reaction solution, and stirred at 80°C for 1 hr. After the reaction was completed, a saturated ammonium chloride solution (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. The reaction solution was filtered, rotary dried, and purified by reverse-phase HPLC to obtain (*E*)-1-(2-(3-

cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one (69 mg, yield 34%, white solid) and (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one (30.4 mg, yield 15%, white solid).

[0790] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one: ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.35 (s, 1H), 8.06-8.04 (m, 2H), 7.68-7.66 (m, 3H), 7.26-7.20 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.33 (m, 1H), 3.85 (d, *J* = 6.8Hz, 2H), 3.81 (s, 3H), 2.83 (s, 6H), 0.89-0.82 (m, 1H), 0.62-0.58 (m, 2H), 0.34-0.30 (m, 2H); LC-MS: m/z 401.9 $[M + H]^+$.

[0791] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.39 (s, 1H), 8.12-8.08 (m, 2H), 7.65-7.62 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.10-7.00 (m, 2H), 6.13 (m, 1H), 3.86(d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.83 (s, 6H), 0.89-0.82 (m, 1H), 0.62-0.58 (m, 2H), 0.34-0.30 (m, 2H); LC-MS: m/z 401.9 $[M + H]^+$.

[0792] Example 105

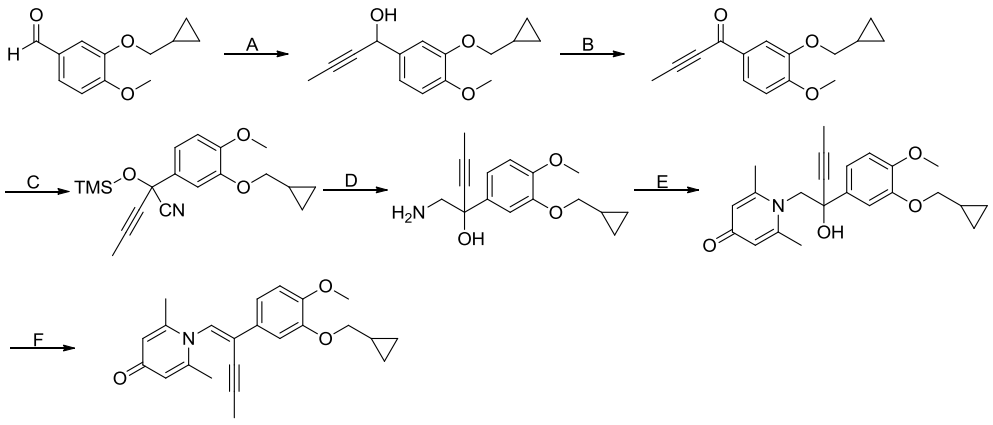


[0793]

[0794] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one

[0795] The specific reaction scheme is as shown below:

[0796]



[0797] Step A:

[0798] 3-(cyclopropylmethoxy)-4-methoxybenzaldehyde (1.03 g, 5 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL); and under nitrogen atmosphere, 1-ethynylmagnesium bromide (0.5 M, 12 mL, 6 mmol) was added dropwise at 0°C, warmed to room temperature, and stirred for 3 hours at room temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution, and extracted with dichloromethane (3 x 30 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-alkynyl-1-butanol (1.50 g). LC-MS: m/z 228.9 $[M - 17]^+$.

[0799] Step B:

[0800] The compound 1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-alkynyl-1-butanol (1.50 g, 5 mmol) was dissolved in dichloromethane (20 mL); and Dess-Martin Periodinane (3.18g, 7.5 mmol) and solid sodium bicarbonate (6.30 g, 75 mmol) were added at 35°C, and stirred for 1 hr. After the reaction was completed, a saturated sodium bicarbonate solution was added, and extracted with dichloromethane (3 x 30 mL). The organic phases were combined, and dried over anhydrous sodium sulfate, filtered, rotary dried, and purified to obtain a crude product of 1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-alkynyl-1-butanol, which was directly used in the next reaction. LC-MS: m/z 249.9 $[M + H]^+$.

[0801] Step C:

[0802] The compound 1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-alkynyl-1-butanone (336 mg, 1.5 mmol) was dissolved in acetonitrile (5 mL); and under nitrogen atmosphere, cesium fluoride (114 mg, 0.75 mmol) was added, trimethylsilyl cyanide (225 mg, 2.25 mmol) was slowly added dropwise at 0°C, and stirred for 1.5 hours. After the reaction was completed, the reaction solution was filtered, and rotary dried to obtain a crude product of 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(trimethylsiloxy)pent-3-ynyl nitrile. LC-MS: m/z 344.2 $[M + H]^+$.

[0803] Step D:

[0804] The compound 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(trimethylsiloxy)-3-alkynylpentyl nitrile (413 mg, 1.5 mmol) was dissolved in anhydrous tetrahydrofuran (4 mL); and under nitrogen atmosphere, lithium aluminum hydride (114 mg, 3.0 mmol) was slowly added dropwise at 0°C, and the solution was stirred at room temperature for 1 hr. After the reaction was completed, sodium sulfate decahydrate was added to quench the reaction. The reaction solution was filtered, and the filtrate was rotary dried to obtain a crude product of 1-amino-2-(3-cyclopropylmethoxy)4-methoxyphenyl)-3-alkynyl-2-pentanol. LC-MS: m/z 276.2 $[M + H]^+$.

[0805] Step E:

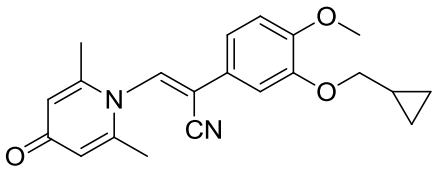
[0806] The compound 1-amino-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-3-alkynyl-2-pentanol (413 mg, 1.5 mmol) was dissolved in ethanol (5 mL), and then 2.6-dimethylpyran-4-one (279 mg, 2.25 mmol) and sodium hydroxide (120 mg, 3.0 mmol) were added, and stirred overnight at 60°C. The reaction was complete as indicated by LCMS. The reaction solution was rotary dried, and purified to obtain 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxypent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, yield 3%). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.12-7.07 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 6.10 (s, 1H), 4.22-4.12 (m, 2H), 3.88 (s, 3H), 3.83 (d, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.20 (s, 3H), 1.88 (s, 3H), 1.34-1.28 (m, 1H), 0.67-0.62 (m, 2H), 0.39-0.35 (m, 2H); LC-MS: m/z 381.9 $[M + H]^+$.

[0807] Step F:

[0808] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxypent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (20 mg, 0.05 mmol) was dissolved in toluene (3 mL), and then p-toluenesulfonic acid (15 mg, 0.08 mmol) was added and stirred overnight at 60°C. The reaction was complete as indicated by TLC. The reaction solution was rotary dried, and purified to obtain (*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (18 mg, yield 90%, white solid). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.16 (*J* = 8.4 Hz, 1H), 6.92-6.90 (m, 2H), 6.31 (s, 2H), 3.92-3.90 (m, 5H), 2.25 (s, 6H), 1.98 (s, 3H), 1.40-1.31 (m, 1H), 0.70-0.65 (m, 2H), 0.41-0.37 (m, 2H). LC-MS: m/z 363.9 [M +

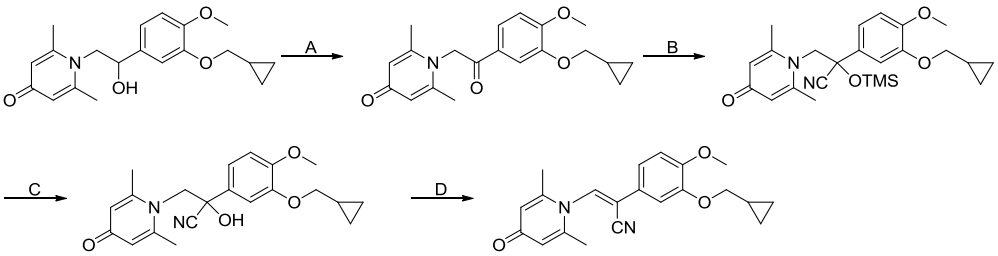
H]$^+$.

[0809] Example 106

[0810] 

[0811] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyanoethenyl)-2,6-dimethylpyridin-4(1*H*)-one

[0812] The specific reaction scheme is as shown below:

[0813] 

Step A:

[0814] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2, 6-dimethylpyridin-4(1*H*)-one (2.50 g, 7.3 mmol) was dissolved in dichloromethane (50 mL); and Dess-Martin Periodinane (4.80 g, 11.0 mmol) and sodium bicarbonate (9.00 g, 110 mmol) were slowly added at 35°C, and stirred for 1 hr. After the reaction was completed, a saturated sodium bicarbonate solution (50 mL) was added, and extracted with dichloroethane (3 x 30 mL). The organic phases were combined and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification gave 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2, 6-dimethylpyridin-4(1*H*)-one (1.98 g, yield 80%, white solid). LC-MS: m/z 342.4 [M + H]$^+$.

[0815] Step B:

[0816] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2, 6-dimethylpyridin-4(1*H*)-one (500 mg, 1.5 mmol) was dissolved in acetonitrile (25 mL); and under nitrogen atmosphere, triethyl amine (456 mg, 4.5 mmol) was added, trimethylsilyl cyanide (600 mg, 6.0 mmol) was slowly added dropwise at 0°C, and stirred for 4 hours. The reaction solution was rotary dried to obtain a crude product of 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-

cyano-2-(trimethylsilyloxy)ethyl)-2, 6-dimethylpyridin-4(1*H*)-one. LC-MS: m/z 441.4 $[M + H]^+$.

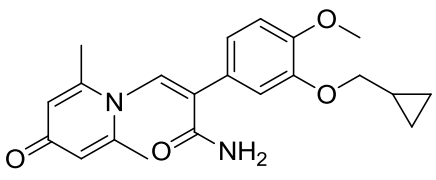
[0817] Step C:

[0818] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyano-2-(trimethylsilyloxy)ethyl)-2, 6-dimethylpyridin-4(1*H*)-one (660 mg, 1.5 mmol) was dissolved in acetonitrile (25 mL), and aqueous hydrochloric acid (3M, 1.5 mL) was added and stirred at 80°C for 0.5 hours. The reaction was complete as indicated by TLC. The reaction solution was rotary dried to obtain a crude product of 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyano-2-hydroxyethyl)-2, 6-dimethylpyridin-4(1*H*)-one. LC-MS: m/z 369.4 $[M + H]^+$.

[0819] Step D:

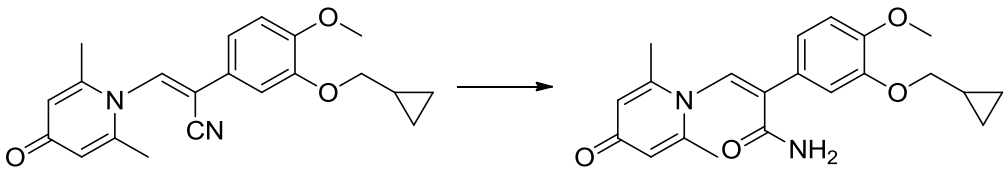
[0820] The compound 1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyano-2-hydroxyethyl)-2, 6-dimethylpyridin-4(1*H*)-one (552 mg, 1.5 mmol) was dissolved in chloroform (25 mL), and then thionyl chloride (1.0 mL) was added and stirred for 0.5 hours at 80°C. The reaction was complete as indicated by TLC. The reaction solution was rotary dried, and purified to obtain (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyanoethenyl)-2,6-dimethylpyridin-4(1*H*)-one (283 mg, 54%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.14 (d, *J* =1.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.36 (s, 2H), 3.95-3.92 (m, 5H), 2.30(s, 6H), 1.38-1.30 (m, 1H), 0.71-0.67 (m, 2H), 0.42-0.38 (m, 2H). LC-MS: m/z 351.4 $[M + H]^+$.

[0821] **Example 107**

[0822] 

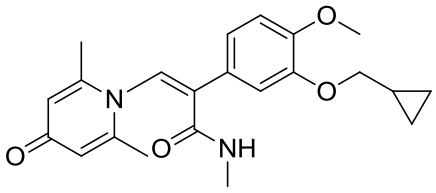
[0823] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide

[0824] The specific reaction scheme is as shown below:

[0825] 

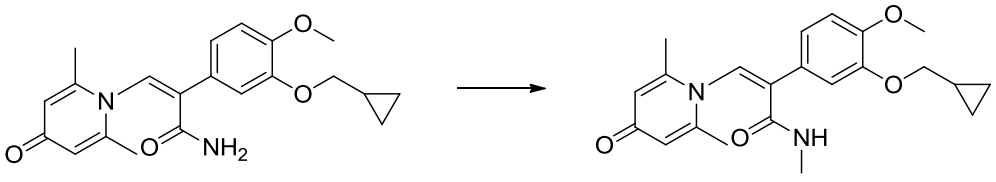
[0826] (*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyanoethenyl)-2,6-dimethylpyridin-4(1*H*)-one (500 mg, 1.4 mmol) was dissolved in acetonitrile (10 mL), and then potassium hydroxide (10 wt%, 10 mL) was added at room temperature and stirred at 80°C for 2 hours. The reaction was complete as indicated by TLC. The reaction solution was directly rotary dried, and purified by column chromatography to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide (140 mg, 27%, white solid). ^{1}H NMR(400 MHz, DMSO-d_6) δ 7.73 (s, 1H), 7.56 (s, 1H), 7.13 (s, 1H), 7.04 (s, 2H), 6.99 (s, 1H), 5.96 (s, 2H), 3.85 (d, J = 7.2 Hz, 2H), 3.80 (s, 3H), 2.27 (m, 6H), 0.87-0.84 (m, 1H), 0.61-0.56 (m, 2H), 0.35-0.31 (m, 2H); LC-MS: m/z 369.1 $[M + H]^+$.

[0827] **Example 108**

[0828] 

[0829] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*-methylacrylamide

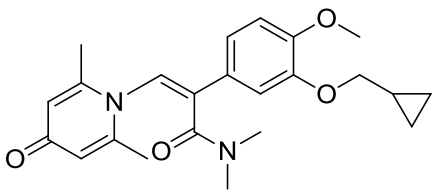
[0830] The specific reaction scheme is as shown below:

[0831] 

[0832] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide (30 mg, 0.08 mmol) was dissolved in *N*, *N*-dimethylformamide (0.5 mL), and then 60% sodium hydride (16 mg, 0.4 mmol) was added, and stirred at 70°C for 0.5 hours. Iodomethane (12 mg, 0.08 mmol) was added to the reaction solution,

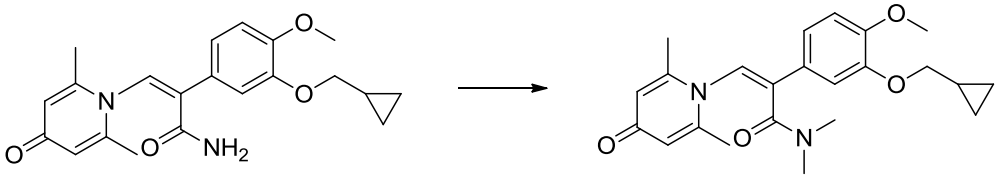
and stirred at 70°C for another 1 hr. The reaction solution was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried, and purified by column chromatography to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2, 6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*-methylacrylamide (5 mg, 17%, white solid). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.04-7.02 (m, 1H), 6.93-6.91 (m, 2H), 6.63(s, 1H), 6.28 (s, 2H), 6.02 (s, 1H), 3.92 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 2.81 (t, J = 4.8 Hz, 3H), 2.34 (s, 6H), 0.97-0.83 (m, 1H), 0.76-0.62 (m, 2H), 0.40-0.36 (m, 2H); LC-MS: m/z 383.1 $[M + H]^+$.

[0833] Example 109

[0834] 

[0835] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-dimethylacrylamide

[0836] The specific reaction scheme is as shown below:

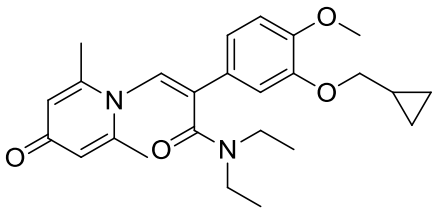
[0837] 

[0838] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide (30 mg,0.08 mmol) was dissolved in N, N-dimethylformamide (0.5 mL), and then 60% sodium hydride (16 mg,0.4 mmol) was added, and stirred at 70°C for 0.5 hours. Iodomethane (24 mg, 0.16 mmol) was added to the reaction solution, and stirred at 70°C for another 1 hr. The reaction was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried and purified by column chromatography to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-dimethylacrylamide (10 mg, 50%, white solid). ^{1}H NMR(400MHz,$CDCl_3$) δ 6.70-6.97 (m, 1H), 6.93-6.91 (m, 2H), 6.70(s, 1H), 6.27 (s, 2H), 3.92 (s,

3H), 3.88 (d, *J* = 6.8 Hz, 2H), 2.92 (s, 3H), 2.78 (s, 3H), 2.37 (s, 6H), 1.37-1.29 (m, 1H), 0.69-0.65 (m, 2H), 0.40-0.36 (m, 2H). LC-MS: m/z 397.1 $[M + H]^+$.

[0839] Example 110

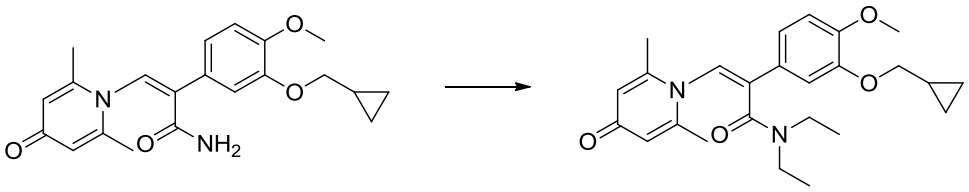
[0840]



[0841] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-diethylacrylamide

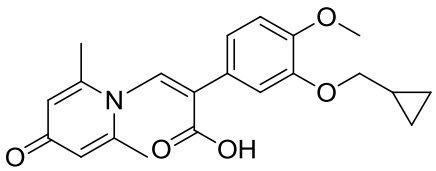
[0842] The specific reaction scheme is as shown below:

[0843]



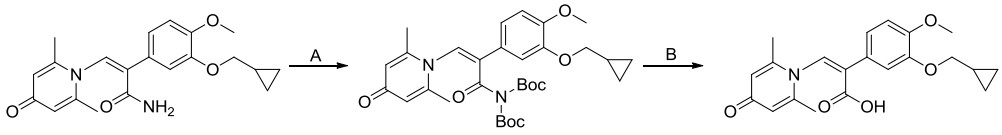
[0844] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide (20 mg, 0.06 mmol) was dissolved in N, N-dimethylformamide (0.5 mL), and then 60% sodium hydride (12 mg, 0.3 mmol) was added, and stirred at 70°C for 0.5 hours. Iodoethane (19 mg, 0.12mmol) was added to the reaction solution, and stirred at 70°C for another 1 hr. The reaction was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried and purified by column chromatography to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-diethylacrylamide (6 mg, 30%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-7.01 (m, 1H), 6.95-6.91 (m, 2H), 6.72(s, 1H), 6.41 (s, 2H), 3.92 (s, 3H), 3.88 (d, *J* = 7.2 Hz, 2H), 3.34-3.31 (m, 2H), 3.18 (q, *J* = 6.8 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.90-0.82 (m, 1H), 0.81 (t, *J* = 7.2 Hz, 3H), 0.69-0.65 (m, 2H), 0.40-0.36 (m, 2H); LC-MS: m/z 425.1 $[M + H]^+$.

[0845] Example 111

[0846] 

[0847] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylic acid

[0848] The specific reaction scheme is as shown below:

[0849] 

[0850] Step A:

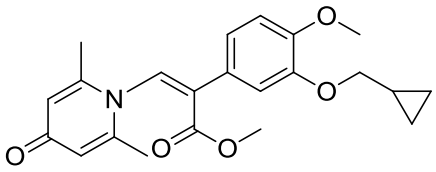
[0851] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-diethylacrylamide (60.0 mg, 0.16 mmol) was dissolved in N,N-dimethylformamide (5 mL). 4-dimethylaminopyridine (4.0 mg, 0.03 mmol) and triethyl amine (36 mg, 0.36 mmol) were added at 35°C, and then di-tert butyl dicarbonate (71 mg, 0.33 mmol) was slowly added to the reaction solution and stirred for 2 hours. After the reaction was completed, the reaction solution was rotary dried to obtain a crude product of (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-di-tert butyloxycarbonylacrylamide. LC-MS: m/z 569.2 $[M + H]^+$.

[0852] Step B:

[0853] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-di-tert butyloxycarbonylacrylamide (90 mg, 0.16 mmol) was dissolved in methanol (2 mL), and a sodium hydroxide solution (2N, 1 mL) was added to the reaction solution at 35°C and stirred for 2 hours. After the reaction was completed, water (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylic acid (23.1mg, yield 39%, white solid). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.18-7.16 (d, J = 8.0 Hz, 1H),

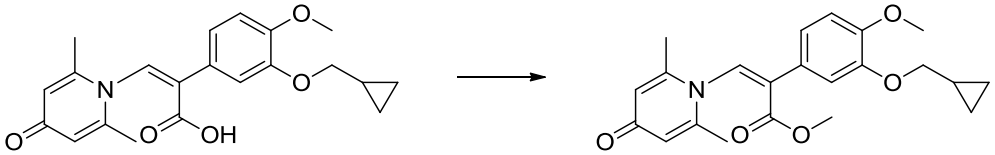
7.11(s, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.82 (s, 1H), 3.92 (s, 3H), 3.90(d, *J* = 6.4 Hz, 2H), 2.6 (s, 6H), 1.33-1.27 (m, 1H), 0.68-0.63 (m, 2H), 0.41-0.35 (m, 2H). LC-MS: m/z 370.1 $[M + H]^+$.

[0854] Example 112

[0855] 

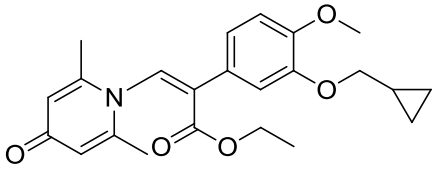
[0856] (*Z*)-methyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate

[0857] The specific reaction scheme is as shown below:

[0858] 

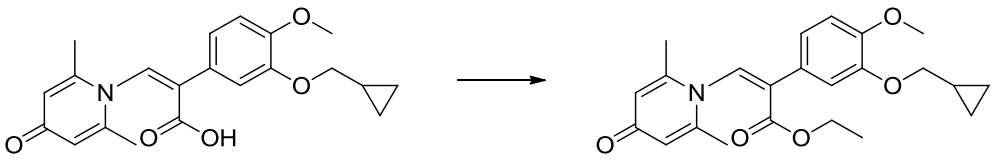
[0859] The compound (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylic acid (10 mg, 0.03 mmol) was dissolved in dichloromethane (0.5 mL), and one drop of N,N-dimethylformamide was added to the reaction solution. Oxalyl chloride (8 mg, 0.03 mmol) was slowly added to the reaction solution, and stirred for 1 hr. Then, methanol (0.5 mL) was added to the reaction solution. After the reaction was completed, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried and purified by column chromatography to obtain (*Z*)-methyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate (3 mg, yield 26%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H),7.95 (s, 2H), 7.15 (s, 1H), 7.09(d, *J* = 8.4Hz, 1H), 6.94(d, *J* = 8.4Hz, 1H), 3.94-3.93 (m, 5H), 3.70 (s, 3H), 2.83 (s, 6H), 1.70-1.59 (m, 1H), 0.68-0.63 (m, 2H), 0.40-0.39(m, 2H); LC-MS: m/z 384.3 $[M + H]^+$.

[0860] Example 113

[0861] 

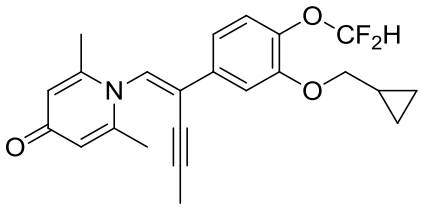
[0862] (*Z*)-ethyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate

[0863] The specific reaction scheme is as shown below:

[0864] 

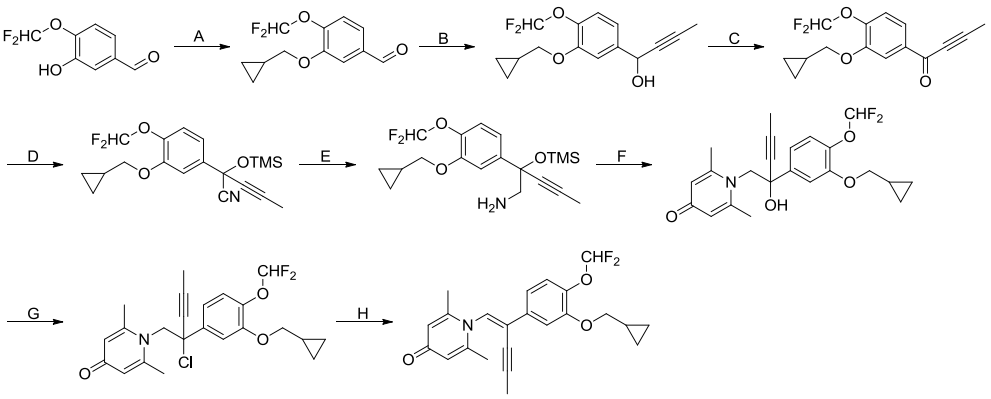
[0865] (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylic acid (10 mg, 0.03 mmol) was dissolved in dichloromethane (0.5 mL), and one drop of *N*,*N*-dimethylformamide was added to the reaction solution. Oxalyl chloride (8 mg, 0.03 mmol) was slowly added to the reaction solution, and stirred for 1 hr. Then, ethanol (0.5 mL) was added to the reaction solution. After the reaction was completed, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the reaction solution was directly rotary dried and purified by column chromatography to obtain (*Z*)-ethyl 2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate (4 mg, yield 34%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.65 (s, 2H), 7.28 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.92(d, J = 8.4 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.00(d, J = 6.8 Hz, 2H), 3.92(m, 3H), 2.92 (s, 6H), 1.45-1.32 (m, 1H), 1.15(t, J = 14.4 Hz, 3H), 0.67-0.63 (m, 2H), 0.44-0.40 (m, 2H); LC-MS: m/z 398.3 $[M + H]^+$.

[0866] **Example 114**

[0867] 

[0868] (*Z*)-1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one

[0869] The specific reaction scheme is as shown below:

[0870] 

[0871] Step A:

[0872] At room temperature, 4-(difluoromethoxy)-3-hydroxybenzaldehyde (0.964 g, 5.13 mmol) was dissolved in acetonitrile (10 mL), and then potassium carbonate (1.06 g, 7.69 mmol) and bromomethylcyclopropane (0.9 g, 6.67 mmol) were added in sequence, and heated to 80°C for 3 hours with stirring under nitrogen atmosphere. After the reaction was completed, water (30 mL) was added, and extracted with dichloromethane (3 x 30 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified to obtain 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (1.16 g, yield 93%). LC-MS: m/z 343.2 [M + H]$^+$.

[0873] Step B:

[0874] The compound 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (1.16 g, 4.79 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL), and then prop-1-yn-1-ylmagnesium bromide (0.5 N, 19.2 mL, 9.6 mmol) was slowly added in an ice bath, and stirred for 16 hours at room temperature under nitrogen atmosphere. After the reaction was completed, the reaction solution was quenched with water (30 mL), and extracted with ethyl acetate (3 x 60 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, rotary dried, and purified to obtain 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)but-2-yn-1-ol (1.01 g, 74%).

[0875] Step C:

[0876] The compound 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)but-2-yn-1-ol (1.01

g, 3.58 mmol) was dissolved in dichloromethane (50 mL), and then Dess-Martin periodinane (3.04 g, 7.16 mmol) were added and stirred overnight at room temperature. After the reaction was completed, the reaction solution was filtered, rotary dried, and purified to obtain 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)but-2-yn-1-one (0.96 g, yield 96%).

[0877] Step D:

[0878] The compound 1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)but-2-yn-1-one (0.96 g, 3.43 mmol) was dissolved in dichloromethane (10 mL), and then triethyl amine (0.693 g, 6.86 mmol) and trimethylsilyl cyanide (1.02 g, 10.29 mmol) were added in sequence in an ice bath and stirred for 16 hours under nitrogen atmosphere at room temperature. After the reaction was completed, the reaction solution was directly rotary dried to obtain a crude product of 2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(trimethylsiloxy)pent-3-ynyl nitrile, which was directly used in the next reaction.

[0879] Step E:

[0880] The compound 2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(trimethylsiloxy)pent-3-ynyl nitrile (1.30 g, 3.43 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL); and then lithium aluminum hydride (0.391 g, 10.29 mmol) was added portion-wise in an ice bath, and stirred overnight at room temperature. After the reaction was completed, water (0.4 mL), a 15% aqueous sodium hydroxide solution (0.4 mL), and water (1.2 mL) were added in sequence, stirred for half an hour, dried over anhydrous sodium sulfate, filtered, and rotary dried to obtain a crude product of 1-amino-2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)pent-3-yn-2-ol, which was directly used in the next reaction.

[0881] Step F:

[0882] The compound 1-amino-2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)pent-3-yn-2-ol (1.07 g, 3.43 mmol) was dissolved in ethanol (40 mL), and then 2,6-dimethyl-4*H*-pyran-4-one (0.553 g, 4.46 mmol), sodium hydroxide (206 mg, 5.15 mmol) and water (6 mL) were added in sequence, heated to 60°C, and stirred for 72 hours under nitrogen atmosphere. After the reaction

was completed, the reaction solution was rotary dried, and purified by column chromatography to obtain 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-hydroxypent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (120 mg, yield 8%). LC-MS: m/z 418.2 $[M + H]^+$.

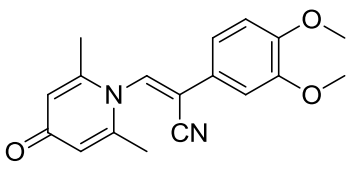
[0883] Step G:

[0884] The compound 1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-hydroxypent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (120 mg, 0.29 mmol) was dissolved in trichloromethane (10 mL), and heated to 90°C. Then thionyl chloride (0.5 mL) was added and stirred at 90°C for 15 min. After the reaction was completed, the reaction solution was directly rotary dried to obtain a crude product of 1-(2-chloro-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)pent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one. LC-MS: m/z 436.2 $[M + H]^+$.

[0885] Step H:

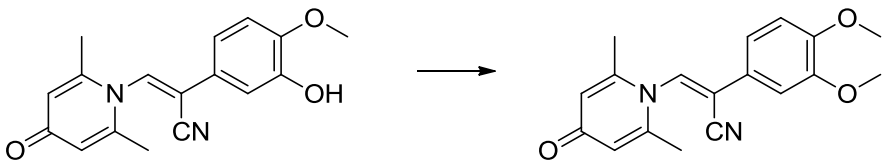
[0886] The compound 1-(2-chloro-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)pent-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (125 mg, 0.29 mmol) was dissolved in ethanol (10 mL), and then sodium hydroxide (72 mg, 1.8 mmol) and water (2 mL) were added in sequence, heated to 90°C, and stirred for 16 hours under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified by reverse-phase HPLC to obtain the product (*Z*)-1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one (2.3 mg, yield 2%, white solid). ^{1}H NMR (400 MHz, CDCl3) δ 7.38-7.28 (m, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.01 (s, 2H), 6.69 (t, J = 75.2 Hz, 1H), 3.97 (d, J = 6.4 Hz, 2H), 2.48 (s, 6H), 1.95 (s, 3H), 1.35-1.25 (m, 1H), 0.70-0.65 (m, 2H), 0.42-0.36 (m, 2H); LC-MS: m/z 400.1 $[M + H]^+$.

[0887] Example 115

[0888] 

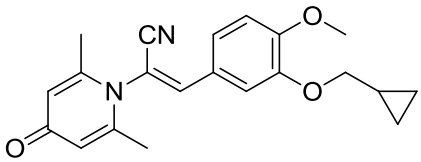
[0889] (*Z*)-2-(3,4-dimethoxyphenyl)-3-(2,6dimethyl-4-carbonylpyridine)-1(4*H*)-yl)acrylonitrile

[0890] The specific reaction scheme is as shown below:

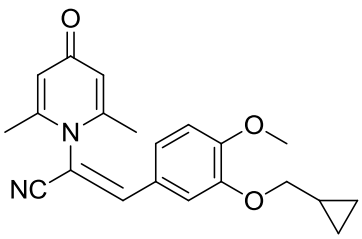
[0891] 

[0892] The compound (*Z*)-3-(2,6dimethyl-4-carbonylpyridine)-1(4*H*)-yl)-2-(3-hydroxy4-methoxyphenyl)acrylonitrile (100 mg, 0.34 mmol) was dissolved in acetonitrile (10 mL), and then iodomethane (96 mg, 0.68 mmol) and potassium carbonate (187 mg, 1.35 mmol) were added and stirred for 5 hours at 85°C under nitrogen atmosphere. After the reaction was completed, the reaction solution was filtered, and the filtrate was rotary dried, and purified by reverse-phase HPLC to obtain (*Z*)-2-(3,4-dimethoxyphenyl)-3-(2,6dimethyl-4-carbonylpyridine)-1(4*H*)-yl)acrylonitrile (21 mg, yield 33%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.29 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 2.37 (s, 6H); LC-MS m/z 311.2 $[M + H]^+$.

[0893] **Example 116**

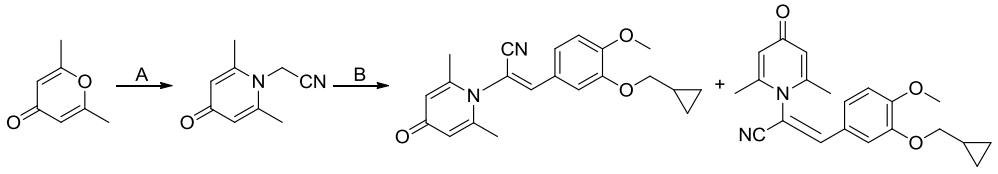
[0894] 

[0895] (*E*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile

[0896] 

[0897] (*Z*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile

[0898] The specific reaction scheme is as shown below:

[0899] 

[0900] Step A

[0901] 2,6-dimethyl-4*H*-pyran-4-one (620 mg, 5 mmol) and aminoacetonitrile hydrochloride (463 mg, 6 mmol) were dissolved in pyridine (10 mL), and stirred for 46 hours at 80°C under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried, and purified by column chromatography to obtain 2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acetonitrile (583 mg, yield 72%, white solid). LC-MS: m/z 163.1 $[M + H]^+$.

[0902] Step B

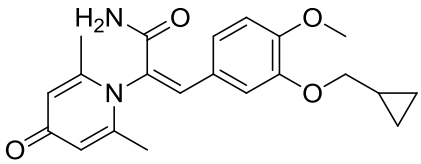
[0903] 2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acetonitrile (162 mg, 1 mmol) and 3-cyclopropylmethoxy-4-methoxybenzaldehyde (206 mg, 1mmol) were dissolved in pyridine (10 mL), and stirred overnight at 100°C under nitrogen atmosphere. After the reaction was completed, the reaction solution was rotary dried to remove pyridine, and purified by reverse-phase HPLC to obtain (*E*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile (126 mg, yield 36%, white solid) and (*Z*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile (20 mg, yield 6%, white solid).

[0904] (*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.0 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 6.38 (s, 2H), 3.92 (s, 3H), 3.88 (d, J = 6.8 Hz, 2H), 2.22 (s, 6H), 1.26-1.17 (m, 1H), 0.65-0.58 (m, 2H), 0.32-0.26 (m, 2H); LC-MS: m/z 351.2 $[M + H]^+$.

[0905] (*Z*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 1H), 7.23 (d, J = 8.4 Hz, 1H),

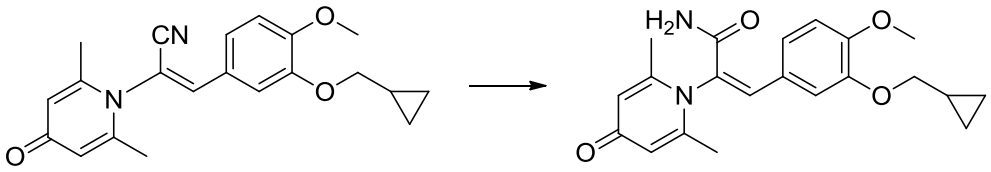
6.97 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 6.09 (s, 2H), 3.80 (s, 3H), 3.53 (d, *J* = 6.8 Hz, 2H), 3.34 (s, 6H), 2.02 (s, 6H), 1.16-1.11 (m, 1H), 0.56-0.52 (m, 2H), 0.27-0.23 (m, 2H); LC-MS: m/z 351.2 $[M + H]^+$.

[0906] Example 117

[0907] 

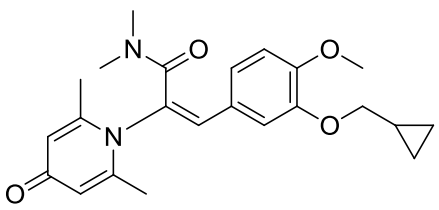
[0908] (*E*)-3-(3-propylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylamide

[0909] The specific reaction scheme is as shown below:

[0910] 

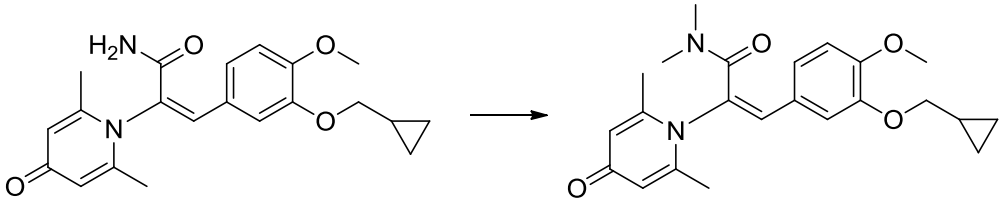
[0911] (*E*)-3-(3-cyclopropylmethoxy-4methoxyphenyl)-2(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile (350 mg, 1 mmol) was dissolved in acetonitrile (10 mL), and then potassium hydroxide (10 wt%, 10 mL) was added at room temperature and stirred at 80°C for 2 hours. After the reaction was completed, the reaction solution was directly rotary dried, and purified by reverse-phase HPLC to obtain (*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide (247 mg, 67%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 6.14 (s, 2H), 3.80 (s, 3H), 3.51 (d, *J* = 6.8 Hz, 2H), 1.94 (s, 6H), 1.16-1.07 (m, 1H), 0.56-0.51 (m, 2H), 0.27-0.24 (m, 2H); LC-MS: m/z 369.4 $[M + H]^+$.

[0912] Example 118

[0913] 

[0914] (*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridine)-1(4*H*)-yl)-*N*, *N*-dimethylacrylamide

[0915] The specific reaction scheme is as shown below:

[0916] 

[0917] The compound (*E*)-3-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridine)-1(4*H*)acrylamide (37 mg, 0.1 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL), and then 60% sodium hydride (24 mg, 0.6 mmol) was added at 0°C, and stirred for half an hour. Then, iodomethane (43 mg, 0.3 mmol) was added, and stirred at room temperature for 4 hours. After the reaction was completed, saturated saline (10 mL) was added, and extracted with dichloromethane (3 x 10 mL). The organic phases were combined, and dried over anhydrous sodium sulfate. Filtration, rotary drying, and purification by reverse-phase HPLC gave (*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridine)-1(4*H*)-yl)-*N*, *N*-dimethylacrylamide (22 mg, yield 55%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.4, 1.6 Hz, 1H), 6.49 (d, J = 1.6 Hz, 1H), 6.09 (s, 2H), 3.80 (s, 3H), 3.53 (d, J = 6.8 Hz, 2H), 3.34 (s, 6H), 2.02 (s, 6H), 1.16-1.11 (m, 1H), 0.56-0.52 (m, 2H), 0.27-0.23 (m, 2H); LC-MS: m/z 397.2 $[M + H]^+$.

[0918] Example 119

[0919] Determination of the inhibition of the compounds on PDE4B1 activity by using cAMP HTRF® assay

[0920] The inhibitory effect of the compounds on human PDE4B1 enzyme activity was determined by quantifying the 5'-adenosine monophosphate (5'-AMP) formed from 3',5'-cyclic adenosine monophosphate (cAMP).

[0921] The test compound or water (control) and human recombinant PDE4B1 enzyme (4.8 U) were mixed in a buffer solution (pH 7.4) consisting of 1x Hanks' balanced salt solution (HBSS),

5 mM HEPES, 3 mM MgCl2, and 0.1% BSA and incubated for 10 min. A cAMP enzyme substrate (final concentration 40 nM) was added, and the mixture was incubated at room temperature for 60 min. Then a fluorescent acceptor (Dye2 labeled with cAMP), a fluorescent donor (anti-cAMP antibody labeled with europium cryptate) and a non-specific phosphodiesterase inhibitor IBMX (3-isobutyl-1-methyl xanthine; final concentration 1 mM) were added. After 60 min, the fluorescence transfer related to the amount of remaining cAMP was measured on a microplate reader (Rubystar, BMG) at λex = 337 nm, λem = 620 nm and λem = 665 nm. The enzyme activity is calculated from the ratio of the signals measured at 665 nm and 620 nm. The results are expressed as percent inhibition of the enzyme activity of the control (without PDE4 inhibitor). The enzyme was omitted for measurement of the basic control. The IC50 value (IC50 = the concentration that caused the half-maximum inhibition of the specific activity of the control) is derived from dose-response measurements with eight different concentrations (n=2; repeated 2 times)

[0922] The experimental results obtained are listed in Table 1.

Example	IC_{50} (nM)		Example	IC_{50} (nM)		Example	IC_{50} (nM)
1	760		42	8.2		83-2	106
2	125		43	4.9		84	230
3	39		44	30		85	3.8
4	36		45	170		86-1	310
5	5		46	25		86-2	81
6	19		47	7.1		87	78
7	5.7		48	420		88	2.8
8	23		49	2.9		89	6.9
9	25		50	180		90	3.8
10	3300		51	57		91	75

11	44		52	N.A.		92	94
12	N.A.		53	15		93	12.9
13	4.9		54	26		94	137
14	21		55	54		95	260
15	33		56	16		96	2.4
16	10.3		57	100		97	3.7
17	16		58	5.5		98-1	97
18	4.5		59	5.1		98-2	12.5
19	4.6		60	1200		99	59
20	13		61	6.2		100	1.5
21	4.6		62	10.2		101-1	99
22	20		63	11.1		101-2	26
23	5		64	43		102	50
24	23		65	520		103	14
25	11.5		66	270		104-1	1700
26	39		67	170		104-2	8400
27	65		68	27		105	3
28	92		69	5200		106	2.7
29	93		70	8.1		107	450
30	116		71	1420		108	760
31	26		72	3900		109	180
32	13.9		73	2000		110	460
33	830		74	38		111	6600
34	420		75	290		112	138
35	32		76	105		113	170

36	1250		77	26.4		114	1.6
37	510		78	36		115	9.9
38-1	1090		79	160		116-1	460
38-2	71		80	7		116-2	35
39	1070		81	1.15		117	3600
40	6.8		82	7.5		118	320
41	1.22		83-1	550			

[0923] Example 120

[0924] Inhibition of the compounds on proinflammatory cytokine release by peripheral blood mononuclear cells (PBMCs)

[0925] The effect of the compounds on the release characteristics of TNFa cytokines in frozen human peripheral blood mononuclear cells (PBMCs) was determined.

[0926] Fresh human PBMCs were isolated, and suspended in a fresh medium. The PBMC medium (CM) is RPMI1640 containing 10% FBS, 1% PBS, and 2 mM L-glutamine. The cells were plated at a density of 2*10^5 cells/well (100ul). The test compound was dissolved in DMSO to form a 10 mM sample (DMS0, 100%). The compound was diluted with PBMC medium to the required concentrations. The sample (50 uL) was incubated for 1 hr with cells at 37°C, 5% CO2, after which the inducer (LPS, 1ug/mL) was added. The inducer+vehicle (LPS+0.05%DMS0) was used as a control in this experiment. The vehicle without inducer was used as a negative control. Crisaborole was used as a positive control. After 24 hours of incubation, the supernatant was extracted and stored at -80°C. The supernatant was thawed and the TNFα level in the supernatant was measured by Luminex4-plex assay.

[0927] Result:

[0928] Using this experimental method, it is determined that the EC50 of Example 77 is = 11 nM, the EC50 of Example 80 is <5 nM; and the EC50 of Example 88 is <5 nM.

[0929] Example 121

[0930] Test of Inhibition on allergic dermatitis on mouse ear induced by topically administered phorbol ester

[0931] The test compounds are used to treat various skin diseases such as itching, redness, dryness, crusting, desquamation, inflammation and discomfort.

[0932] The test compound was topically applied to the right ear of the test animal 30 minutes before and 15 minutes after the administration of (12-)phorbol myristate (-13-) acetate (PMA). The dosing volume was 20 ul/ear for a solvent vehicle or 20 mg/ear for a cream.

[0933] Male CD-1 mice weighing 24±2g were used. All animals were maintained in an environment at a controlled temperature (22°C-23°C) and humidity (70%-80%), with a 12-h-light and 12-h-dark photoperiod. The animals were raised in the animal room for at least 1 week before they are used for experimental test. The mice were allowed to access food and drinking water freely. Generally, all aspects of this work were carried out in accordance with the guidelines of Care and Use of Laboratory Animals (National Academy Press, Washington, D.C., 1996), including animal breeding, experimentation, and handling.

[0934] Each group had 5 mice. PMA (4 pg in 20 uL acetone) was applied topically to the front and back surfaces of the right ear of each animal. The vehicle (ethanol: acetone/1:1, 20 μL/ear) or test compound (specified dose in 20 uL of 1:1 acetone: ethanol, for each ear) was applied 30 minutes before and 15 minutes after PMA administration, and crisaborole was administered as a positive control. Then, 6 hours after PMA administration, ear swelling was measured as an indicator of inflammation using a staining micrometer. The percentage of inhibition is calculated according to the following formula: ([IC-IT]/IC)X100%, where IC and IT means the increase in ear thickness (mm) of mice in the control and treatment groups, respectively. 30% or more inhibition is considered to have significant anti-inflammatory activity.

[0935] Example 123

[0936] Formulation of topical preparations.

[0937] Compounds of the present invention, such as compound 88, can be administered as a gel, lotion, ointment and solution, and the route of administration includes, but is not limited to, topical administration, instillation, aerosol, transdermal patch, via insertion, or oral administration.

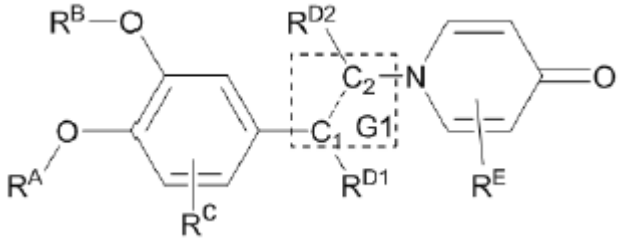
[0938] The following is a preparation method of 1% ointment preparation (weight percentage):

[0939] 1% compound, 15% PEG400, 0.02% butylated hydroxytoluene, 2% span 80, 10% white wax, and 71.98% white petrolatum were mechanically stirred until an ointment was formed.

CLAIMS

WHAT IS CLAIMED IS:

1. An anti-inflammatory compound, which is a compound having a structure shown below:



wherein 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 substituted with alkyl, cycloalkyl, aryl, or halogen;

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 substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, or halogen, and one or more carbon atom(s) in the groups is/are substituted with sulfur, sulfoxide, sulfone, or sulfonyl; or R^B is a hydroxyl protecting group;

R^C is hydrogen, alkyl, halogen, alkoxy, or cyano;

R^{D1} is hydrogen, oxygen, nitrogen, hydroxy, cyano, amino, amido, alkyl, aryl, an ester group, carboxyl, alkenyl, or alkynyl, and in the above groups one or more hydrogen atom(s) attached to carbon/oxygen/nitrogen in the groups is/are 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 substituted with sulfur, sulfoxide, sulfone, or sulfonyl;

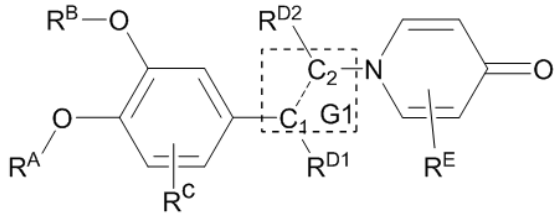
C_1-R^{D1} bond is a single bond or a double bond;

R^{D2} is hydrogen, cyano, alkyl, cycloalkyl, aryl, an ester group, or carboxyl, and in the 163above groups one or more hydrogen atom(s) attached to carbon/oxygen/nitrogen in the group is/are substituted with alkyl, cycloalkyl, alkynyl, alkenyl, aryl, halogen, sulfonyl, a sulfoxide group, or an ether group;

G1 is a single bond, a double bond or a ring, that comprises C_I and C_2; and

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

2. The anti-inflammatory compound according to claim 1, wherein the compound has a structure shown below:



wherein R^A is hydrogen, alkyl comprising from 1 to 6 carbon atoms, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with alkyl comprising from 1 to 6 carbon atoms, cycloalkyl which is three-membered, four-membered, five-membered or six-membered cycle, or halogen;

R^B is hydrogen, alkyl comprising from 1 to 6 carbon atoms, cycloalkyl which is a three-membered, four-membered, five-membered or six-membered cycle, heterocycloalkyl which is an oxa/thia three-membered, four-membered, five-membered or six-membered cycle, alkenyl comprising from 2 to 4 carbon atoms, or alkynyl comprising from 2 to 4 carbon atoms, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with alkyl comprising from 1 to 6 carbon atoms, cycloalkyl which is a three-

membered, four-membered, five-membered or six-membered cycle, or halogen, and one or more carbon atom(s) in the groups is/are substituted with a sulfur atom, sulfoxide, sulfone, or sulfonyl;

R^C is hydrogen;

R^{D1} is hydrogen, oxygen, nitrogen, hydroxy, cyano, alkyl comprising from 1 to 6 carbon atoms, phenyl, an ester group, carboxyl, or alkynyl comprising from 2 to 4 carbon atoms, and in the above groups one or more hydrogen atom(s) attached to carbon/oxygen in the groups is/are substituted with alkyl comprising 1 to 6 carbon atoms, cycloalkyl which is a three-membered, a four-membered, five-membered or six-membered ring, alkynyl comprising from 2 to 4 carbon atoms, alkenyl comprising from 2 to 4 carbon atoms, or phenyl, and one or more carbon atom(s) in the groups is/are substituted with a sulfur atom;

C_1-R^{D1} bond is a single bond or a double bond;

R^{D2} is hydrogen or cyano;

G1 is a single bond, a double bond or cyclopropane comprising C_1 and C_2; and

R^E is a group where one or more hydrogen atom(s) attached to carbon on the pyridinone ring is/are substituted with alkyl comprising from 1 to 6 carbon atoms or halogen.

3. The anti-inflammatory compound according to claim 1, wherein

wherein R^A is alkyl comprising from 1 to 6 carbon atoms, and in the above group one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with halogen;

R^B is alkyl comprising from 1 to 6 carbon atoms or heterocycloalkyl which is an oxo/thia three-membered, four-membered, five-membered or six-membered cycle, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with cycloalkyl which is a three-membered, four-membered, five-membered or six-membered

cycle;

R^{D1} is hydrogen;

R^{D2} is hydrogen;

G1 is a double bond comprising C_1 and C_2; and

R^E is a group where one or more hydrogen atom(s) attached to carbon on the pyridinone ring is/are substituted with alkyl comprising from 1 to 6 carbon atoms.

4. The anti-inflammatory compound according to claim 3, wherein

wherein R^A is alkyl comprising from 1 to 6 carbon atoms, and in the above group one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with halogen;

R^B is heterocycloalkyl which is a thia five-membered cycle;

R^{D1} is hydrogen;

R^{D2} is hydrogen;

G1 is a double bond comprising C_1 and C_2; and

R^E is a group where one or more hydrogen atom(s) attached to carbon on the pyridinone ring is/are substituted with alkyl comprising from 1 to 6 carbon atoms.

5. The anti-inflammatory compound according to claim 3, wherein

wherein R^A is alkyl comprising from 1 to 6 carbon atoms, and in the above group one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with halogen;

R^B is alkyl comprising from 1 to 6 carbon atoms, and in the above group one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with cycloalkyl which is a three-membered, four-membered, five-membered or six-membered cycle;

R^{D1} is hydrogen;

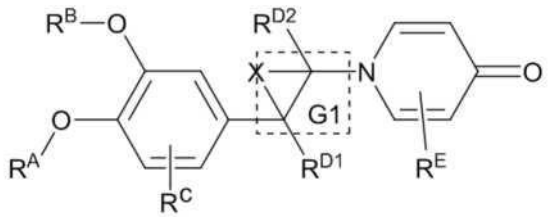
R^{D2} is hydrogen;

G1 is a double bond comprising C_1 and C_2; and

R^E is a group where one or more hydrogen atom(s) attached to carbon on the pyridinone ring is/are substituted with alkyl comprising from 1 to 6 carbon atoms.

6. The anti-inflammatory compound according to claim 1, wherein

G1 is a three-membered ring having a specific structure shown below:



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

7. A method for preparing the anti-inflammatory compound according to claim 1, comprising:

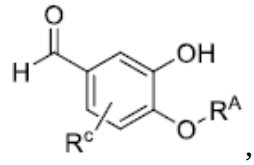
using a 3-hydroxybenzaldehyde derivative A as a starting material, and substituting the hydrogen in the hydroxyl group of the 3-hydroxybenzaldehyde derivative A with R^B to obtain an intermediate product B;

reacting the intermediate product B with trimethylsilyl cyanide to obtain an intermediate product C;

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

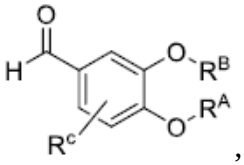
reacting the amino group in the intermediate product D with a six-membered oxygen-containing cyclic compound to obtain a type-A target product,

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



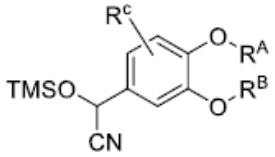
,

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



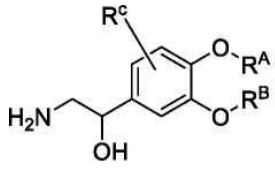
,

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



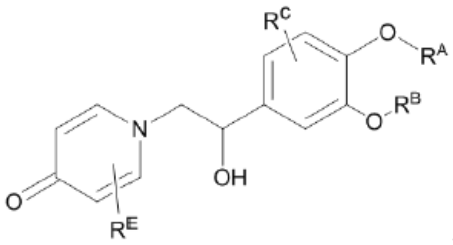
,

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



, and

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



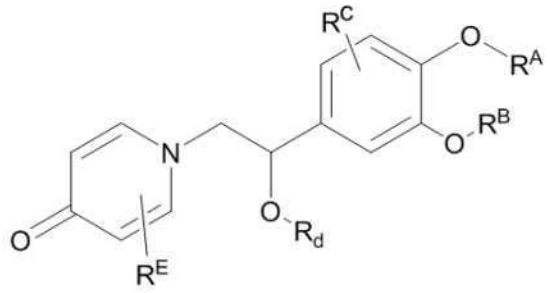
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8. A method for preparing the anti-inflammatory compound according to claim 1,

comprising:

subjecting the hydroxyl group on the middle bridge of the type-A target product according to claim 7 to an addition/substitution reaction to obtain a type-A-1 target product,

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

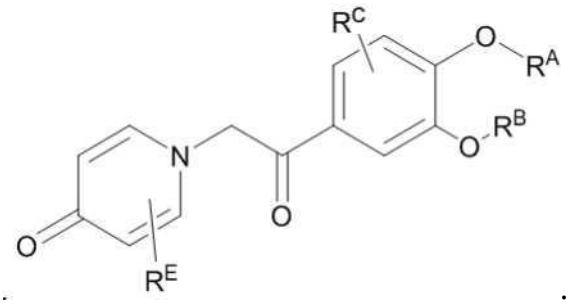


in which Rd is alkyl, cycloalkyl, or an ester group, and in the above groups one or more hydrogen atom(s) attached to carbon in the groups is/are substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

9. A method for preparing the anti-inflammatory compound according to claim 1, comprising:

oxidizing the hydroxyl group on the middle bridge of the type-A target product according to claim 7 to obtain a type-B target product,

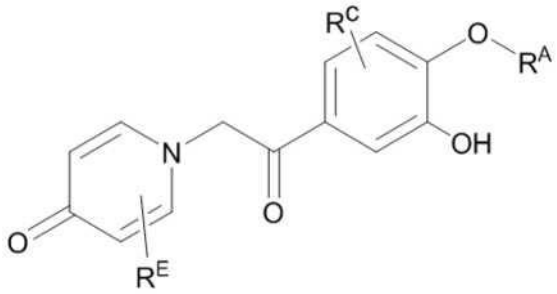
wherein the type-B target product is a compound having a structure shown below:



10. The method for preparing the anti-inflammatory compound according to claim 9, comprising:

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,

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

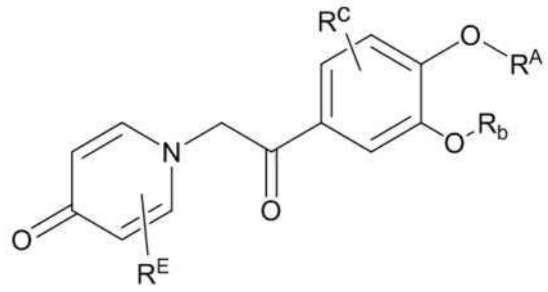


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11. A method for preparing the anti-inflammatory compound according to claim 1, comprising:

subjecting the hydroxyl group on the benzene ring of the type-B-1 target product according to claim 6 to an addition/ substitution reaction to obtain a type-B-2 target product,

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



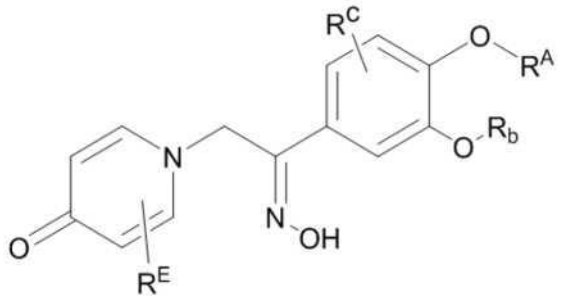
,

in which R_b 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 substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

12. A method for preparing an anti-inflammatory compound according to claim 1, comprising:

oximating the carbonyl group on the middle bridge of the type-B target product according to claim 9 to obtain a type-B-3 target product,

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

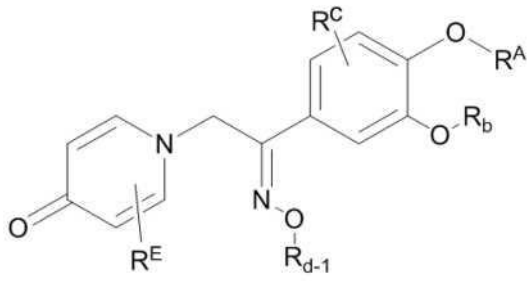


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13. A method for preparing an anti-inflammatory compound according to claim 1, comprising:

subjecting the hydroxyl group on the oxime of the type-B-3 target product according to claim 12 to an addition/ substituti on reaction to obtain a type-B-4 target product,

wherein 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 groups is/are substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

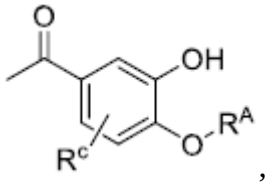
14. The method for preparing the anti-inflammatory compound according to claim 9, comprising:

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 RB 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

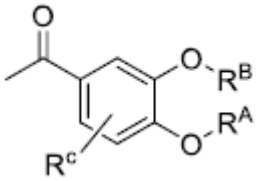
reacting the halogen of the intermediate product III with a six-membered oxygen-containing cyclic compound to obtain the type-B target product,

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



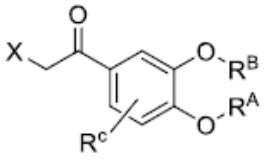
,

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



, and

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



, in which X is halogen.

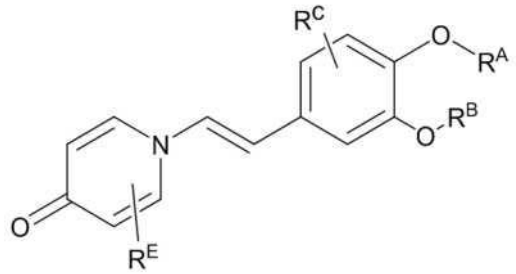
15. A method for preparing the anti-inflammatory compound according to claim 1, comprising: removing the hydroxyl group on the middle bridge of the type-A target product according to claim 7 to obtain a type-C target product,

or

reducing and then eliminating the carbonyl group on the middle bridge of the

type-B target product according to claim 9 to obtain a type-C target product,

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

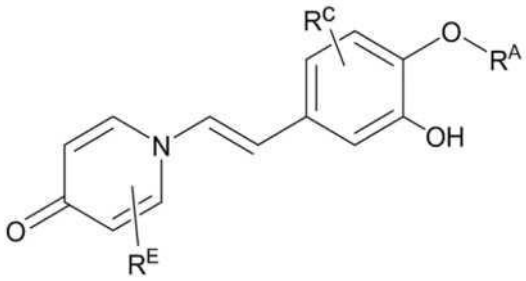


.

16. A method for preparing the anti-inflammatory compound according to claim 1, comprising:

reducing and then eliminating the carbonyl group on the middle bridge of the type-B-2 target product according to claim 11 to obtain a type-C-1 target product,

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

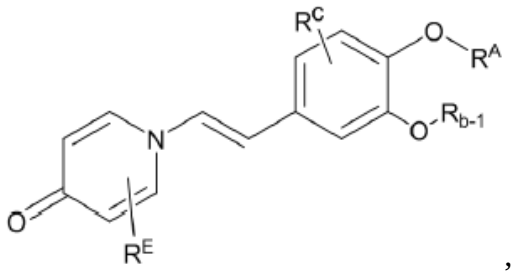


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17. A method for preparing the anti-inflammatory compound according to claim 1, comprising:

subjecting the hydroxyl group on the phenyl ring of the type-C-1 target product according to claim 16 to an addition/ substitution reaction to obtain a type-C-2 target product,

wherein 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 substituted with alkyl, alkynyl, alkenyl, cycloalkyl, aryl, halogen, hydroxy, thio, cyano, or thioalkyl.

18. A method for preparing an anti-inflammatory compound according to claim 1, comprising:

using a cinnamic acid derivative 1 as a starting material, and esterifying the cinnamic acid derivative 1 to obtain an intermediate product 2;

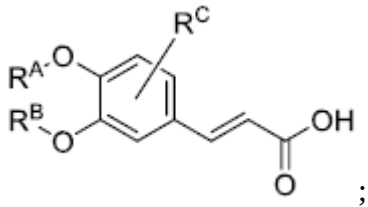
forming a ring from the double bond on the intermediate product 2 to obtain an intermediate product 3;

hydrolyzing the terminal ester group on the intermediate product 3 to give an intermediate product 4 having a carboxyl group;

aminating the terminal carboxyl group of the intermediate product 4 to obtain an intermediate product 5; and

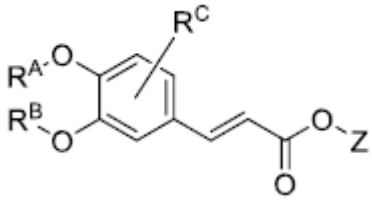
reacting the intermediate product 5 with a six-membered oxygen-containing cyclic compound to obtain a type-D target product,

wherein the cinnamic acid derivative 1 is a compound having a structure shown below:



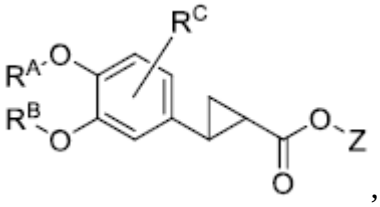
;

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



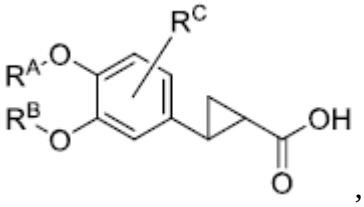
, in which Z is alkyl;

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



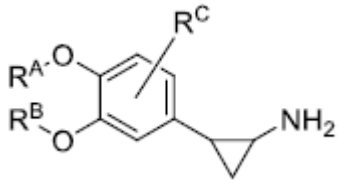
,

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



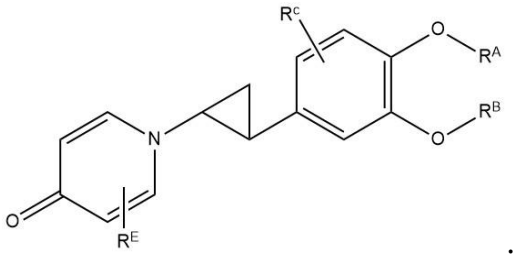
,

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



, and

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



19. The compound according to claim 1, wherein the compound is selected from the group consisting of:

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-hydroxyethyl)-2,6, dimethylpyridin-4(1H)-one;

(1-(3-cyclopropylmethoxy-4methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4H)-yl)ethyl) acetate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) propionate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) cyclopropylcarboxylate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) benzoate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) crotonate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) 3-methylcrotonate;

(1-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethyl) but-2-ynoate;

1-(2-(but-2-yn-1-yloxy)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)ethyl)-2,6-dimethylpyridin-4-(1*H*)-one;

1-(2-(3-hydroxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-ethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-propoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-isopropoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-n-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)- one;

1-(2-(3-iso-butoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-n-pentyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-n-hexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclopropyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxo)ethyl-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclobutyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclobutylmethoxy-4-methoxyphenyl)-2-oxo)ethyl-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclohexyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-(cyclopent-3-en-1-yloxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-allyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-((3-methylbut-2-en-1-yl)oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-propargyloxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-(but-2-yn-1-yloxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-(oxacyclobutan-3-yl-oxy)-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-(tetrahydrofuran-2-yl)oxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylthiomethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylsulfinylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylsulfonylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-

dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylthioethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylsulfinylethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-methylsulfonylethoxy-4-methoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(hydroxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methoxylimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylthiomethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfinylmethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(methylsulfonylmethoxyimido)ethyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)pyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-methylpyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-oxoethyl)-2-chloropyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclopropyl)-2,6-dimethylpyridin-4(1*H*)-one;

1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-oxoethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)pyridin-4(1*H*)-one;

(*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2-methylpyridin-4(1*H*)-one;

(*E*)-1-(3-hydroxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-propoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-isopropoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-n-butoxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-iso-butoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-neopentyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-cyclopropyloxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-cyclopropylmethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-cyclopropylmethoxy-4-methoxyphenethyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-cyclobutyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-cyclopentyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-(cyclopent-3-en-1-yloxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-allyloxy-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(3-methylbut-2-en-1-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-(prop-2-yn-1-yloxy)-4-methoxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-(but-2-yn-1-yloxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(oxacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(thiacyclobutan-3-yl-oxy)-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(tetrahydrofuran-2-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-2-(5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethenyl)-2-methoxyphenoxy)-*N*-methylacetamide;

(*E*)-1-((3-cyclopropylformyloxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-5-(2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)ethenyl)-2-methoxyphenylmethyl sulfonate;

(*E*)-1-(3-methylthiomethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfinylmethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfonylmethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylthioethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfinylethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfonylethoxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-methoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-((1,1,-dioxotetrahydrothiophen-3-yl)oxy)-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

1-((*E*)-4-methoxy-3-(((3*S*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(S,*E*)-1-(3-((1,1-dioxotetrahydrothiophen-3-yl)oxy)-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-methoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

1-((*E*)-4-methoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(R,*E*)-1-(3-((1,1-dioxotetrahydrothiophen-3-yl)oxy)-4-methoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)styryl)-2,6-dimethylpyridin-

4(1*H*)-one;

(*E*)-1-(3-methoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylthiomethoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfinylmethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfonylmethoxy-4-difluoromethoxy-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

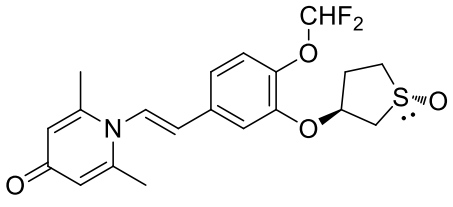
(*E*)-1-(3-methylthioethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(3-methylsulfinylethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

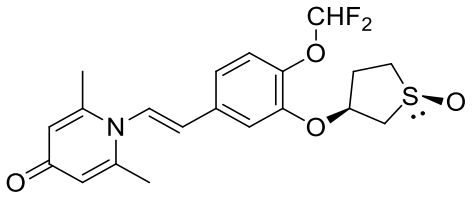
(*E*)-1-(3-methylsulfonylethoxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-((3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxy)-styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*S*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;



;



;

(S,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*R*,*E*)-1-(3-(tetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

1-((*E*)-4-difluoromethoxy-3-(((3*R*)-1-oxotetrahydrothiophen-3-yl)oxy)styryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*R*,*E*)-1-(3-(1,1-dioxotetrahydrothiophen-3-yl)oxy-4-difluoromethoxystyryl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-methylethenyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-phenylethenyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one;

(*E*)-1-(2-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-cyanoethenyl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylamide;

(*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-

carbonylpyridin-1(4*H*)-yl)-*N*-methylacrylamide;

(*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-dimethylacrylamide;

(*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-*N*,*N*-diethylacrylamide;

(*Z*)-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylic acid;

(*Z*)-methyl-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate;

(*Z*)-ethyl-2-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)-acrylate;

(*Z*)-1-(2-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)pent-1-en-3-yn-1-yl)-2,6-dimethylpyridin-4(1*H*)-one;

(*Z*)-2-(3,4-dimethoxyphenyl)-3-(2,6-dimethyl-4-carbonylpyridine)-1(4*H*)-yl)acrylonitrile;

(*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylonitrile;

(*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridin-1(4*H*)-yl)acrylamide; and

(*E*)-3-(3-cyclopropylmethoxy-4-methoxyphenyl)-2-(2,6-dimethyl-4-carbonylpyridine)-1(4*H*)-yl)-*N*,*N*-dimethylacrylamide.

20. Use of the anti-inflammatory compound according to claim 1 in the manufacture of a PDE4 inhibitor.

21. Use of the anti-inflammatory compound according to claim 1 in the manufacture of a medicament for treatment of inflammatory skin diseases.

22. A drug for treating the inflammatory skin diseases, comprising

0.01-10% of the anti -inflammatory compound according to claim 1; and

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

wherein 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.