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(54) Title: WATER SOLUBLE PRODRUGS OF COX-2 INHIBITORS

(57) Abstract: Disclosed are water soluble compounds which are useful as prodrugs of COX-2 inhibitors, and pharmaceutical compositions comprising them.



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TITLE OF THE INVENTION

WATER SOLUBLE PRODRUGS OF COX-2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119 to U.S. provisional application serial no. 60/617,962, filed October 12, 2004.

FIELD OF THE INVENTION

The invention is directed to water soluble compounds which are useful as prodrugs of COX-2 inhibitors, and pharmaceutical compositions comprising the compounds of the invention. The invention is also directed to methods of treating patients for cyclooxygenase-mediated diseases, including stroke, by administering to the patient a compound or pharmaceutical composition of the invention.

BACKGROUND OF THE INVENTION

Cyclooxygenase (COX) is a prostaglandin G/H synthase. Non-steroidal, antiinflammatory drugs (NSAIDs) exert most of their antiinflammatory, analgesic and antipyretic activity through inhibition of prostaglandin G/H synthase.

COX has a constitutive form, COX-1, and an inducible form, COX-2. COX-1 is largely responsible for endogenous basal release of prostaglandins, and hence is important in their physiological functions, such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, COX-2 is mainly responsible for the pathological effects of prostaglandins, where rapid induction of the enzyme occurs in response to inflammatory agents, hormones, growth factors, and cytokines.

Thus, selective inhibitors of COX-2 have similar antiinflammatory, antipyretic and analgesic properties to conventional NSAIDs, but have a diminished ability to induce some of the mechanism-based side effects. In particular, selective COX-2 inhibitors have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Particular cyclooxygenase diseases or disorders for which COX-2 inhibitors may be useful include stroke. Stroke is a cerebrovascular event, which occurs when the normal bloodflow to the brain is disrupted, and the brain receives too much or too little blood. Stroke is one of the leading causes of death worldwide, and is also one of the most common causes of neurologic disability.

Ischemic stroke, which is the most common type of stroke, results from insufficient cerebral circulation of blood caused by obstruction of the inflow of arterial blood. Normally, adequate cerebral blood supply is ensured by a system of arteries within the brain. However, various disorders, including inflammation and atherosclerosis, can cause a thrombus, *i.e.*, a blood clot that forms in a blood vessel. The thrombus may interrupt arterial blood flow, causing brain ischemia and consequent neurologic symptoms. Ischemic stroke may also be caused by the lodging of an embolus (an air bubble)

from the heart in an intracranial vessel, causing decreased perfusion pressure or increased blood viscosity with inadequate cerebral blood flow. An embolus may be caused by various disorders, including atrial fibrillation and atherosclerosis.

A second type of stroke, hemorrhagic stroke, involves a hemorrhage or rupture of an artery leading to the brain. Hemorrhagic stroke results in bleeding into brain tissue, including the epidural, subdural, or subarachnoid space of the brain. A hemorrhagic stroke typically results from the rupture of an arteriosclerotic vessel that has been exposed to arterial hypertension or to thrombosis.

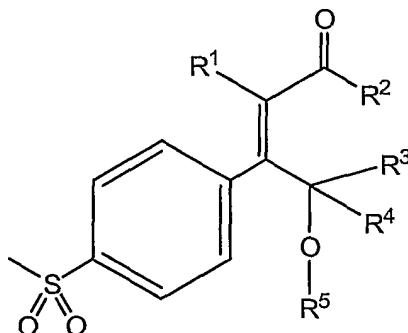
During acute ischemic stroke, *i.e.*, the period from the cerebrovascular event up to 24 hours after the event, the arterial occlusion results in an immediate infarcted core of brain tissue, where cerebral blood flow is significantly reduced, for example to less than 20% of the normal blood flow. The infarcted core suffers irreversible damage due to significant cell death. The length of time that ischemia persists, and the severity of the ischemia, contribute to the extent of injury. An area around the infarcted core, known as the ischemic penumbra, suffers a delayed and less severe infarct. For example, during acute stroke the penumbra may have a reduction in blood flow of from about 20-40%.

Potent and selective furan-2-one derivative COX-2 inhibitors, and prodrugs thereof, have been disclosed in U.S. Pat. Nos. 5,733,909, 5,849,943, 5,925,631, 6,020,343 and 6,057,319. Furan-2-one COX-2 inhibitors have demonstrated a reduction in infarct volume in the middle cerebral artery occlusion (MCAO) stroke model. For example, DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl-2(5*H*)-furanone), which is disclosed in U.S. Pat. No. 6,020,343, has been shown to be neuroprotective against hippocampal damage in gerbils subjected to a transient global ischemia event (Jalil, et al, *Brain Research*, 927, 2002, 212-215), and has also been shown to dose dependently reduce endotoxin-induced mortality in mice (Tunctan et al, *Pharmacological Res* 2003, 48, 37-48).

For the acute treatment of stroke, it is preferred that the selective COX-2 inhibitors be administered to the patient intravenously. However, the furan-2-one compounds disclosed in the above-referenced patents generally have very poor water solubility, and are thus unsuitable for intravenous formulation. A water soluble prodrug of furan-2-one COX-2 inhibitors would facilitate the preparation of intravenous formulations.

SUMMARY OF THE INVENTION

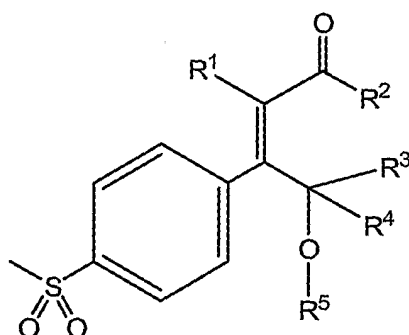
The invention is directed to water soluble compounds of formula (I)



wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined below, and pharmaceutical compositions comprising them. The invention is also directed to the use of the compounds of formula (I) as prodrugs of selective COX-2 inhibitors, in the treatment of stroke and other COX-2 mediated disorders and diseases.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to compounds of formula (I)



wherein:

R^1 is selected from the group consisting of

- (1) $-Q-R^a$,
- (2) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (3) $-C_{6-10}$ aryl, and
- (4) heteroaryl,

wherein said carbocyclic group, aryl and heteroaryl are unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) NO_2 ,
- (d) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) $-C_{1-6}$ alkoxy,
- (f) $-C(=O)-(O)-R^b$
- (g) $-C(=O)-NR^bR^{b'}$
- (h) $-O-C(=O)-R^b$
- (i) $-S-C_{1-6}$ alkyl,
- (j) $-S(O)_xR^b$,

- (k) $-S(O)_xNR^bR^{b'}$,
- (l) $-S(O)_xNR^bC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-NR^bR^{b'}$,
- (n) $-NR^b-C(=O)-R^{b'}$,
- (o) $-P(=O)R^bOH$,
- (p) $-P(=O)R^bNH_2$, and

Q is selected from the group consisting of

- (a) $-O-$,
- (b) $-S-$,
- (c) $-SO_2-$,
- (d) $-NR^b$,

R^a , R^b and $R^{b'}$ are independently selected from the group consisting of:

- (a) hydrogen,
- (b) $-C_{1-10}$ alkyl,
- (c) $-C_{2-10}$ alkenyl,
- (d) $-C_{2-10}$ alkynyl,
- (e) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (f) $-C_{6-10}$ aryl, and
- (g) heteroaryl,

wherein said carbocyclic group, alkyl, alkenyl, alkynyl, aryl and heteroaryl are unsubstituted or substituted with one or more

- (i) halogen,
- (ii) cyano,
- (iii) $-NO_2$,
- (iv) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (v) $-C_{1-6}$ alkoxy,
- (vi) $-C(=O)-(O)-R^c$
- (vii) $-C(=O)-NR^cR^{c'}$
- (viii) $-O-C(=O)-R^c$
- (ix) $-S-C_{1-6}$ alkyl,
- (x) $-S(O)_xR^c$,
- (xi) $-S(O)_xNR^cR^{c'}$,

- (xii) $-S(O)_xNR^cC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (xiii) $-NR^cR^{c'}$,
- (xiv) $-NR^c-C(=O)-R^{c'}$,
- (xv) $-P(=O)R^cOH$,
- (xvi) $-P(=O)R^cNH_2$,

and R^c and $R^{c'}$ are independently selected from the group consisting of

- (A) hydrogen,
- (B) $-C_{1-10}$ alkyl,
- (C) $-C_{2-10}$ alkenyl,
- (D) $-C_{2-10}$ alkynyl,
- (E) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (F) $-C_{0-10}$ alkyl- C_{6-10} aryl, and
- (G) heteroaryl;

R^2 is selected from the group consisting of

- (1) $-OR^d$,
- (2) $-NR^dR^{d'}$,
- (3) phosphate group $-P(O)OR^dR^{cd'}$,
- (4) an amino acid,
- (5) nicotinic acid,
- (6) a saccharide, and
- (7) choline,

and R^d and $R^{d'}$ are selected from the same group as R^c and $R^{c'}$;

R^3 and R^4 are independently selected from the group consisting of

- (1) hydrogen,
- (2) $-C_{1-10}$ alkyl,
- (3) $-C_{2-10}$ alkenyl,
- (4) $-C_{2-10}$ alkynyl,
- (5) $-C_{6-10}$ aryl, or
- (6) heteroaryl,

wherein said alkyl, alkenyl, alkynyl, aryl and heteroaryl are unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) NO₂,
- (d) C₁₋₆ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) -C₁₋₆ alkoxy,
- (f) -C(=O)-(O)-R^e
- (g) -C(=O)-NR^eR^{e'}
- (h) -O-C(=O)-R^e
- (i) -S-C₁₋₆ alkyl,
- (j) -S(O)_xR^e,
- (k) -S(O)_xNR^eR^{e'},
- (l) -S(O)_xNR^eC(=O)C₁₋₆ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) -N R^eR^{e'},
- (n) -NR^e-C(=O)-R^{e'},
- (o) -P(=O)R^eOH,
- (p) -P(=O)R^eNH₂,

or

R³ and R⁴ may be linked to form a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,

wherein said carbocyclic group is unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) -NO₂,
- (d) -C₁₋₆ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) -C₁₋₆ alkoxy,
- (f) -C(=O)-(O)-R^e
- (g) -C(=O)-NR^eR^{e'}
- (h) -O-C(=O)-R^e
- (i) -S-C₁₋₆ alkyl,
- (j) -S(O)_xR^e,

- (k) $-\text{S}(\text{O})_x\text{NR}^e\text{Re}'$,
- (l) $-\text{S}(\text{O})_x\text{NR}^e\text{C}(=\text{O})\text{C}_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-\text{NR}^e\text{Re}'$,
- (n) $-\text{NR}^e\text{-C}(=\text{O})\text{-Re}'$,
- (o) $-\text{P}(=\text{O})\text{ReOH}$,
- (p) $-\text{P}(=\text{O})\text{ReNH}_2$,

and Re and Re' are selected from the same group as R^c and $\text{R}^{c'}$;

R^5 is selected from the group consisting of

- (1) hydrogen,
- (2) $-\text{C}_{1-10}$ alkyl,
- (3) $-\text{C}_{2-10}$ alkenyl,
- (4) $-\text{C}_{2-10}$ alkynyl,
- (5) $-\text{C}_{0-10}$ alkyl- $\text{C}(=\text{O})\text{-R}^f$,
- (6) $-\text{C}_{2-10}$ alkenyl- $\text{C}(=\text{O})\text{-R}^f$,
- (7) $-\text{C}_{2-10}$ alkynyl- $\text{C}(=\text{O})\text{-R}^f$,
- (8) $-\text{C}_{0-10}$ alkyl- $\text{C}(=\text{O})\text{-NR}^f\text{R}^{f'}$,
- (9) $-\text{C}_{2-10}$ alkenyl- $\text{C}(=\text{O})\text{-NR}^f\text{R}^{f'}$,
- (10) $-\text{C}_{2-10}$ alkynyl- $\text{C}(=\text{O})\text{-NR}^f\text{R}^{f'}$,
- (11) phosphate group $-\text{P}(\text{O})\text{OR}^f\text{OR}^{f'}$,
- (12) an amino acid,
- (13) nicotinic acid,
- (14) a saccharide, and
- (15) choline;

wherein said alkyl, alkenyl and alkynyl, are substituted with one or more

unsubstituted or

- (a) halogen,
- (b) cyano,
- (c) $-\text{NO}_2$,
- (d) $-\text{C}_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) C_{1-6} alkoxy,
- (f) $-\text{C}(=\text{O})\text{-(O)-R}^f$
- (g) $-\text{C}(=\text{O})\text{-NR}^f\text{R}^{f'}$
- (h) $-\text{O-C}(=\text{O})\text{-R}^f$

- (i) $-S-C_{1-6}$ alkyl,
- (j) $-S(O)_xR^f$,
- (k) $-S(O)_xNR^fR^{f'}$,
- (l) $-S(O)_xNR^fC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-NR^fR^{f'}$,
- (n) $-NR^f-C(=O)-R^{f'}$,
- (o) $-P(=O)R^fOH$,
- (p) $-P(=O)R^fNH_2$, and

and R^f and $R^{f'}$ are selected from the same group as R^c and $R^{c'}$;

x is 1 or 2;

wherein at least one of R^2 and R^5 is a phosphate group, an amino acid, a nicotinic acid, a saccharide or choline;

and pharmaceutically acceptable salts thereof.

In one embodiment, R^1 is phenyl, which is unsubstituted or substituted with one or more halogen (preferably fluoro).

In one embodiment, R^2 is $-OR^c$. In another embodiment, R^2 is an amino acid, preferably an amino acid selected from the group consisting of serine, threonine and tyrosine. In another embodiment, R^2 is choline.

In preferred embodiments, R^2 or R^5 is selected from the group consisting of an amino acid, a saccharide and a choline. When R^5 is an amino acid, it is preferably an amino acid selected from the group consisting of glycine, alanine, arginine, asparagine, aspartic acid, glutamic acid, cystine, glutamine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine.

In one embodiment, R^c is selected from the group consisting of

- (1) hydrogen,
- (2) $-C_{1-10}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more
 - (a) $-NR^bR^{b'}$,
 - (b) $-C(=O)-OR^b$, and
 - (c) $-C(=O)-O(C_{1-6}$ alkyl)- $N(CH_3)_3$.

In certain embodiments, R^3 and R^4 are independently selected from the group consisting of

- (1) hydrogen, and
- (2) $-C_{1-6}$ alkyl. Preferably, R^3 and R^4 are each hydrogen.

In certain embodiments, the compounds of formula (I) are selected from the Examples 1-9 as described herein.

The compounds of Formula I are prodrugs of selective COX-2 inhibitors, and exert their action by conversion *in vivo* to these active and selective COX-2 inhibitors. The active compounds formed from the compounds of the present invention are described in U.S. Pat. Nos. 5,733,909, 5,849,943, 5,925,631, 6,020,343 and 6,057,319.

The compounds of the present invention have utility in treating, ameliorating or controlling stroke and the neurologic injuries caused by stroke.

As used herein, the term "stroke" refers to a clinical event involving impairment of cerebral circulation, resulting in neurologic injury. Typically, stroke is manifest by the abrupt onset of a focal neurologic deficit. Stroke results from a rupture or obstruction (as by a thrombus or embolus) of an artery of the brain.

Thus in further aspects, the invention encompasses pharmaceutical compositions for treating stroke as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above, and one or more ingredients such other COX-2 inhibitors, antioxidants, nitric oxide synthase inhibitors, rho kinase inhibitors, angiotension II type-1 receptor antagonists, glycogen synthase kinase 3 inhibitors, sodium or calcium channel blockers, p38 MAP kinase inhibitors, thromboxane AX-synthetase inhibitors, statins, beta andrenergic blockers, NMDA receptor antagonists (including NR2B antagonists), 5-HT_{1A} agonists, platelet fibrinogen receptor antagonists, DPIV inhibitors, PDEIV antagonists, PPAR inhibitors, AMPA receptor antagonists, neurokinin inhibitors, bradykinin inhibitors, thrombin inhibitors and vasodilators.

In addition to stroke, by virtue of its *in vivo* conversion to a compound with high inhibitory activity against COX-2 and a specificity for COX-2 over COX-1, the compounds of the invention are useful in treatment of cyclooxygenase mediated diseases or disorders, including for the relief of pain (including neuropathic pain), fibromyalgia, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, bumps, injuries, following surgical and dental procedures, and sepsis. In addition, the compounds of the invention may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compounds of Formula I may also be useful for the treatment of traumatic brain injury, spinal cord injury, memory impairment, dementia (including vascular dementia, pre-senile and senile dementia, and in particular, dementia associated with Alzheimer's Disease).

The compounds of formula (I) will also prove useful as an alternative to conventional NSAID'S, particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anaemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H2 antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

As used herein, the term "ischemic stroke" refers to stroke characterized by localized tissue anemia due to obstruction of the inflow of arterial blood. Ischemic stroke is usually caused by atherothrombosis or embolism of a major cerebral artery, but may also be caused by coagulation disorders or nonatheromatous vascular disease.

The subject or patient to whom the compounds of the present invention is administered is generally a human being, male or female, in whom treatment of stroke is desired, but may also encompass other mammals, such as dogs, cats, mice, rats, cattle, horses, sheep, rabbits, monkeys, chimpanzees or other apes or primates, for which treatment of stroke is desired.

As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting stroke or the symptoms of stroke in an animal that is experiencing or displaying the pathology or symptomatology of stroke (*i.e.*, arresting further development of the pathology and/or symptomatology, such as by enhancing plasticity of the stroke patient), or (2) ameliorating stroke or the symptoms of stroke in an animal that is experiencing or displaying the pathology or symptomatology of stroke (*i.e.*, reversing the pathology and/or symptomatology). The term "controlling" includes preventing, treating, eradicating, ameliorating or otherwise reducing the severity of stroke, or reducing the risk of stroke.

In preferred embodiments, the invention is directed to compounds useful for the treatment of stroke. One class of patients to which a compound of the invention may be administered is a patient at risk for stroke. As used herein, the term "patient at risk for stroke" means an individual who

has had a previous stroke, or has a risk factor for stroke. Known risk factors for stroke include atherosclerosis, arterial hypertension, lipohyalinosis, hyperlipidemia, hypercholesterolemia, atrial fibrillation, smoking, inflammatory markers (including C-reactive protein), infection, homocysteine, sleep-disordered breathing, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), migraine headaches, sickle-cell anemia, antiphospholipid antibody syndrome, arterial dissection, cocaine abuse and obesity.

Efforts at "controlling" stroke (including preventing stroke) can be divided into the primary prevention of stroke (treatment of patients who have not had any prior transient ischemic attacks of strokes, and have no neurological symptoms) and secondary prevention of stroke (treatment of patients who have had a prior transient ischemic attack or stroke). Primary prevention of stroke includes non-pharmacologic interventions, such as smoking cessation, healthy eating patterns, increased physical activity and weight management. Primary prevention also includes certain pharmacologic interventions, such as blood pressure control, treatment of atrial fibrillation, and management of diabetes, if appropriate. As part of the primary prevention of stroke, patients at high risk of coronary heart disease are often treated with aspirin. As part of primary prevention, patients having high amounts of low density lipoprotein (LDL) are often subject to blood lipid management, to reduce LDL levels to acceptable levels, *e.g.* below 160mg/dl.

The secondary prevention of stroke often involves the same pharmacologic and non-pharmacologic interventions used for primary prevention, including blood pressure control, treatment of atrial fibrillation, management of diabetes, treatment with aspirin, and blood lipid management. Additional common secondary prevention interventions include the use of antiplatelet agents (such as clopidogrel), anticoagulants (such as warfarin), and anti-hypertension agents (such as beta adrenergic antagonists).

A second class of patients to which a compound of the invention may be administered are acute stroke patients, *i.e.*, patients who have suffered ischemic stroke within the last 7 days. One preferred class of acute stroke patients are those who have suffered stroke within the last 3 days. A more preferred class of acute stroke patients are those who have suffered stroke within the last 48 hours, even more preferably within the last 24 hours. As common in the art of treating stroke, patients may be classified according to the period of time when stroke occurred. So, for example, one class of acute stroke patients are those who have suffered stroke within the last 18 hours. Another class of acute stroke patients are those who have suffered stroke within the last 12 hours. Another class of acute stroke patients are those who have suffered stroke within the last 8 hours. Another class of acute stroke patients are those who have suffered stroke within the last 6 hours. Another class of acute stroke patients are those who have suffered stroke within the last 4 hours. Another class of acute stroke patients are those who have suffered stroke within the last 3 hours.

Treatment of acute stroke, *i.e.* treatment during the cerebral event causing stroke and the 7 days thereafter, involve treatment with thrombolytics such as recombinant tissue plasminogen activator

(rtPA). However, rtPA has only been approved for treatment of acute stroke for use within the first three hours after stroke. Another potential agent for treatment of acute stroke is the neuroprotectant edaravone, which has been approved in Japan.

During acute ischemic stroke, the arterial occlusion caused by the thrombus or embolus results in an immediate infarcted core of brain tissue, where cerebral blood flow is significantly reduced, for example to less than 20% of the normal blood flow. The infarcted core suffers irreversible damage due to significant cell death. The length of time that ischemia persists, and the severity of the ischemia, contribute to the extent of the infarct. An area around the infarcted core, known as the ischemic penumbra, suffers a delayed and less severe infarct. For example, during acute stroke the penumbra may have a reduction in blood flow of from about 20-40%.

Patients who have suffered stroke more than 24 hours previously often develop cerebral edema which typically occurs at from one to five days after stroke. As used herein, the term "cerebral edema" refers to fluid collecting in brain tissue due to cellular swelling and the breakdown of the blood-brain barrier. Post-stroke cerebral edema may also involve the exuding of cerebrospinal fluid from ependymal lining, or the creation of an osmotic environment due to blood clots or tissue injury. The osmotic environment allows the movement of water into interstitial spaces. Post-stroke cerebral edema is often responsible for a worsening in the stroke patient's clinical status.

A third class of patients to which a compound of the present invention may be administered are patients who have suffered stroke more than 7 days previously, who are typically in need of restorative treatment (including enhancing plasticity).

The invention is also directed to a method for the manufacture of a medicament or a composition for treating stroke or other COX-2 mediated diseases, comprising combining a compound of the present invention of formula (I) with a pharmaceutical carrier or diluent.

As used herein, the term "alkyl," by itself or as part of another substituent, means a saturated straight or branched chain hydrocarbon radical having the number of carbon atoms designated (e.g., C₁₋₁₀ alkyl means an alkyl group having from one to ten carbon atoms). Preferred alkyl groups for use in the invention are C₁₋₆ alkyl groups, having from one to six carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like.

As used herein, the term "alkoxy," by itself or as part of another substituent, means the group -O- alkyl, wherein alkyl is defined above, having the number of carbon atoms designated (e.g., C₁₋₁₀ alkoxy means an alkoxy group having from one to ten carbon atoms). Preferred alkoxy groups for use in the invention are C₁₋₆ alkoxy groups, having from one to six carbon atoms. Exemplary preferred alkoxy groups include methoxy, ethoxy, propoxy, butoxy, sec-butoxy and pentoxy. Especially preferred alkoxy groups are C₁₋₃ alkoxy.

As used herein, the term "alkenyl," by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical having a single carbon-carbon double bond and the number of carbon atoms designated (e.g., C₂₋₁₀ alkenyl means an alkenyl group having from two to ten

carbon atoms). Preferred alkenyl groups for use in the invention are C₂₋₆ alkenyl groups, having from two to six carbon atoms. Exemplary alkenyl groups include ethenyl and propenyl.

As used herein, the term "alkynyl," by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical having a single carbon-carbon triple bond and the number of carbon atoms designated (*e.g.*, C₂₋₁₀ alkynyl means an alkynyl group having from two to ten carbon atoms). Preferred alkynyl groups for use in the invention are C₂₋₆ alkynyl groups, having from two to six carbon atoms. Exemplary alkynyl groups include ethynyl and propynyl.

As used herein, the term "cycloalkyl," by itself or as part of another substituent, means a saturated cyclic hydrocarbon radical having the number of carbon atoms designated (*e.g.*, C₃₋₁₂ cycloalkyl means a cycloalkyl group having from three to twelve carbon atoms). The term cycloalkyl as used herein includes mono-, bi- and tricyclic saturated carbocycles, as well as bridged and fused ring carbocycles, such as spiro fused ring systems.

Preferred cycloalkyl groups for use in the invention are monocyclic C₃₋₈ cycloalkyl groups, having from three to eight carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Exemplary bridged cycloalkyl groups include adamantyl and norbornyl. Exemplary fused cycloalkyl groups include decahydronaphthalene.

As used herein, the term "carbocyclic," by itself or as part of another substituent, means a cycloalkyl group as defined above, or a non-aromatic heterocyclic group. A non-aromatic heterocyclic group, by itself or as part of another substituent, means a cycloalkyl group as defined above in which one or more of the ring carbon atoms is replaced with a heteroatom (such as N, S or O). Suitable non-aromatic heterocyclic groups for use in the invention include piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrazolidinyl and imidazolindinyl.

When a non-aromatic heterocyclic group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heterocyclic group, or to a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a non-aromatic heterocyclic group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heterocyclic group, or on a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits attachment. Preferably, the attachment is at a ring carbon atom.

As used herein, the term "aryl," by itself or as part of another substituent, means an aromatic or cyclic radical having the number of carbon atoms designated (*e.g.*, C₆₋₁₀ aryl means an aryl group having from six to ten carbons atoms). The term "aryl" includes multiple ring systems as well as single ring systems. Preferred aryl groups for use in the invention include phenyl and naphthyl.

The term "halo" or "halogen" includes fluoro, chloro, bromo and iodo.

As used herein, the term "heteroaryl," by itself or as part of another substituent, means an aromatic cyclic group having at least one ring heteroatom (O, N or S). The term "heteroaryl" includes multiple ring systems as well as single ring systems. Exemplary heteroaryl groups for use in the

invention include furyl, pyranyl, benzofuranyl, isobenzofuranyl, chromenyl, thienyl, benzothiophenyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, benzimidazolyl, quinolyl, tetrazolyl and isoquinolyl.

When a heteroaryl group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heteroaryl group, or to a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a heteroaryl group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heteroaryl group, or on a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits attachment. Preferably, the attachment is at a ring carbon atom.

As used herein, the term "endogenous chemical entity" or "endogenous chemical moiety" refers to a chemical moiety or group which is commonly found in the mammalian body, preferably in the human body. Exemplary endogenous chemical entities for use in the invention include saccharides, nicotinic acid, amino acids and choline. In a preferred embodiment, one or both of R² and R⁵ is a water soluble endogenous chemical entity. The presence of the endogenous moiety is believed to facilitate recognition by endogenous enzymatic processes *in vivo*, so as to facilitate generation of the parent pharmaceutically active COX-2 inhibiting compound. Further, release of an endogenous chemical entity (as opposed to a xenobiotic entity) should reduce the risk of adverse side effects.

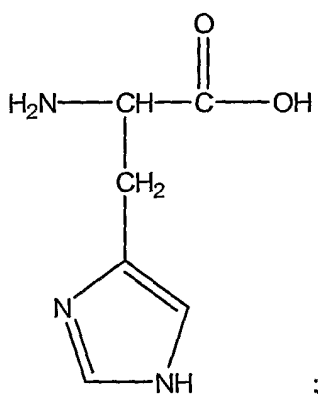
The term "saccharides" as used herein refers to monosaccharides, such as glucose and dextrose; disaccharides, such as maltose, sucrose and lactose, which are formed from two linked saccharide molecules; oligosaccharides, which contain from 10-12 linked saccharide molecules; and polysaccharides, such as cellulose, starch and glycogen, which may contain thousands of linked saccharide molecules.

As used herein, the term "monosaccharide" refer to a sugar molecule having the molecular formula C_nH_{2n}O_n or C_nH_{2n-2}O_{n-1}. Suitable monosaccharide groups for use in the invention are trioses, having three carbon atoms, such as glyceraldehyde and dihydroxyacetone; tetroses, having four carbon atoms, such as erythrose, threose and erythrulose; pentoses, having five carbon atoms, such as ribose, arabinose, xylose, lyxose, ribulose and xylulose; and hexoses, such as allose, altrose, glucose, mannose, gulose, idose, galactose, talose, psicose, fructose, sorbose and tagatose. Preferred saccharide groups for use in the invention are in the dextrorotatory or "D" configuration. Thus, preferred saccharides for use in the invention include D- glyceraldehydes, D-dihydroxyacetone, D-erythrose, D-threose, D-erythrulose, D-ribose, D-arabinose, D-xylose, D-lyxose, D-ribulose, D-xylulose, D-allose, D-altrose, D-glucose (which is also known as dextrose), D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-psicose, D-fructose (which is also known as levulose), D-sorbose and D-tagatose.

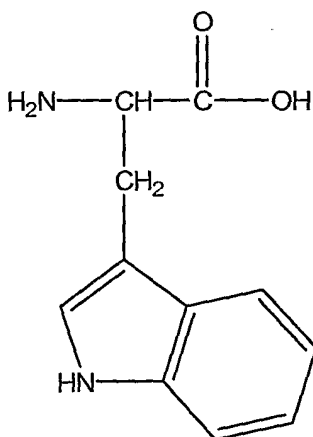
The hexose saccharides for use in the invention may be in open-chain form or may be present in cyclic form, as a pyranose. Similarly, the pentose saccharides for use in the invention may be in open-chain form or may be present in cyclic form, as a furanose.

As used herein, the term "amino acid" refers to any of the naturally occurring amino acids which serve as the units of peptides and proteins. Suitable amino acids include monoaminomonocarboxylic acid amino acids, of general structure $\text{NH}_2\text{-R-COOH}$, such as glycine ($\text{NH}_2\text{-COOH}$), alanine ($\text{NH}_2\text{CH}(\text{CH}_3)\text{-COOH}$), valine ($\text{NH}_2\text{CH-COOHCH}(\text{CH}_3)_2$), leucine ($\text{NH}_2\text{CH-COOHCH}_2\text{-CH}(\text{CH}_3)_2$), isovaline ($\text{NH}_2\text{C}(\text{CH}_3)\text{-COOHCH}(\text{CH}_3)_2$), phenylalanine ($\text{NH}_2\text{CH-COOHCH}_2\text{Ph}$), tyrosine ($\text{NH}_2\text{CH-COOHCH}_2\text{PhOH}$), serine ($\text{NH}_2\text{CH-COOHCH}_2\text{OH}$), cysteine ($\text{NH}_2\text{CH-COOHCH}_2\text{SH}$), methionine ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_2\text{S}(\text{CH}_3)$), isoleucine ($\text{NH}_2\text{CH-COOHCH}(\text{CH}_3)\text{-Et}$), and threonine ($\text{NH}_2\text{CH-COOHCHOH}(\text{CH}_3)$).

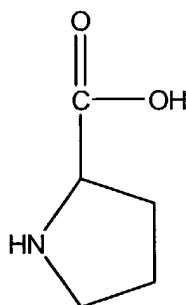
Other suitable amino acids include monoaminodicarboxylic acids, such as aspartic acid ($\text{NH}_2\text{CH-COOH}(\text{CH}_2\text{COOH})$) and glutamic acid ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_2\text{-COOH}$), diaminomonomocarboxylic acids, of general formula $(\text{NH}_2)_2\text{-R-COOH}$, such as arginine ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_3\text{-NH-CN}(\text{NH}_2)$), lysine ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_4\text{-NH}_2$), ornithine ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_3\text{-NH}_2$), asparagine ($\text{NH}_2\text{CH-COOHCH}_2\text{-CONH}_2$), citrulline ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_3\text{-NH-CONH}_2$), glutamine ($\text{NH}_2\text{CH-COOH}(\text{CH}_2)_2\text{-CONH}_2$), and heterocyclic amino acids, such as histidine:



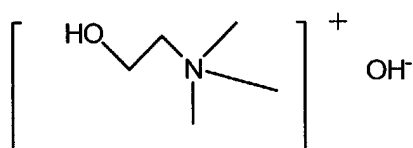
tryptophan:



and proline:

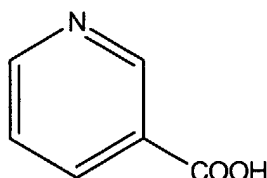


As used herein, the term “choline” refers to a naturally occurring quaternary ammonium base compound of structure:



Choline is derived from the phospholipid lecithin, which is a glyceride containing two fatty acid ester groups, such as stearic acid and oleic acid, and a phosphocholine group. Upon saponification, the phosphocholine yields inorganic phosphate and choline.

As used herein, the term “nicotinic acid” refers to the group 3-pyridinecarboxylic acid, of structure below:



Some of the compounds of the instant invention have at least one asymmetric center. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of these compounds.

Compounds described herein may contain one or more double bonds, and may thus give rise to *cis/trans* isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount.

The terms "effective amount" or "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers to the treatment of stroke, particularly in a patient who demonstrates symptoms of stroke.

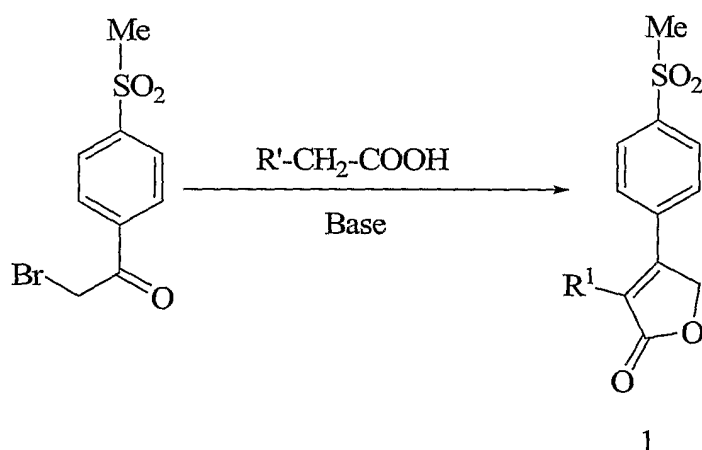
As used herein, the term "prodrug" refers to a molecule that is inert, *i.e.* not pharmacologically active, but that has pharmacological activity upon activation by a biological system. For example, a prodrug is a compound which is inert when in a tablet, capsule or other pharmaceutical composition, but is modified and becomes pharmacologically active *in vivo*, upon ingestion by a mammal. Thus, compounds of formula (I), which are modified *in vivo* to release compounds which are pharmacologically active in the treatment of stroke, are prodrugs.

Methods of Synthesis

The compounds of the invention are derived from a class of potent and selective furan-2-one derivative COX-2 inhibitors, and prodrugs thereof, which have been disclosed in U.S. Pat. Nos. 5,733,909, 5,849,943, 5,925,631, 6,020,343 and 6,057,319 (all of which are hereby incorporated by reference). In order to form the compounds of the invention, the aforementioned furan-2-one derivatives are structurally modified at the R² and/or R⁵ groups, to improve water solubility and improve blood brain barrier penetration.

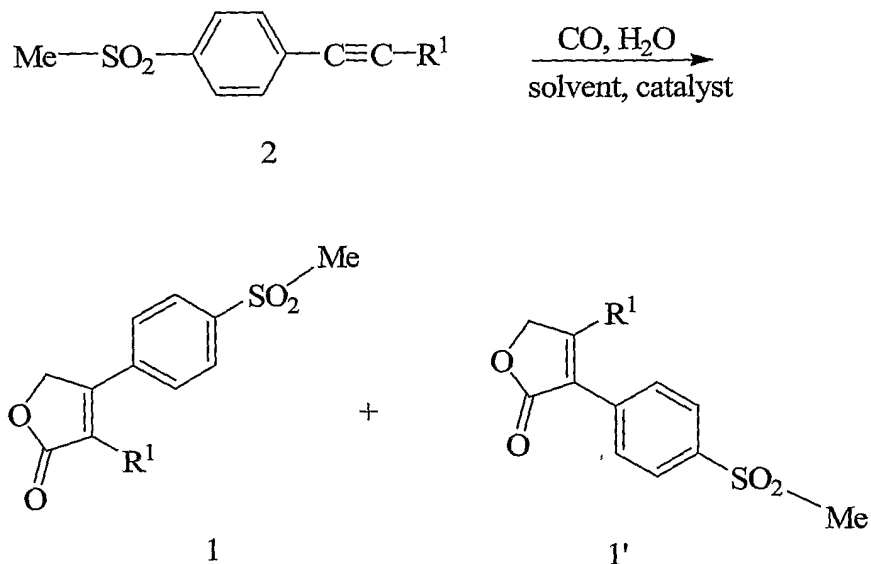
The compounds of the present invention can be prepared according to the following methods:

Method A



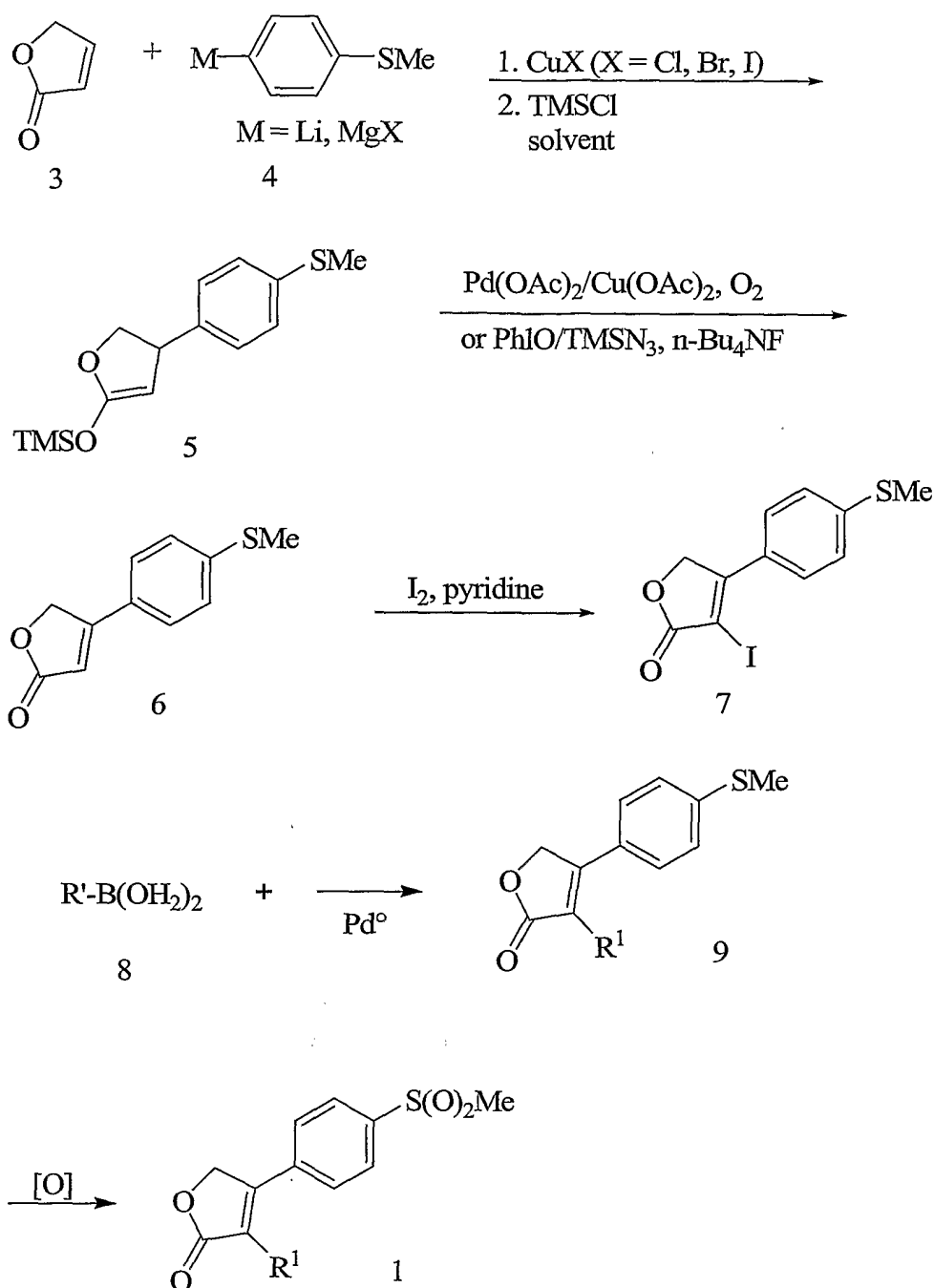
According to Method A, as shown above, an appropriately substituted aryl bromomethyl ketone is reacted with an appropriately substituted aryl acetic acid in a solvent such as acetonitrile in the presence of a base such as triethylamine, and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the lactone 1.

Method B



According to Method B, as shown above, a mixture of **1** and its isomer **1'** may be obtained by reacting an acetylene **2** with carbon monoxide and water in the presence of a suitable catalyst. The isomers are separable by standard procedures in the art such as chromatography or crystallization. Examples of useful catalysts and conditions are PdCl_2 in aqueous HCl and EtOH , heated at $50^\circ\text{-}150^\circ\text{C}$ and 50-150 atmospheres of pressure, or $\text{Rh}(\text{CO})_{12}$ (or $\text{Rh}_6(\text{CO})_{16}$) in aqueous THF (or acetone, acetonitrile, benzene, toluene, EtOH , MeOH) containing a trialkylamine, at $50^\circ\text{-}150^\circ\text{C}$ and 20-300 atmospheres pressure. See Takahashi et al., *Organometallics* 1991, 10, 2493-2498; and Tsuji et al., *J. Am. Chem. Soc.* 1966, 88, 1289-1292.

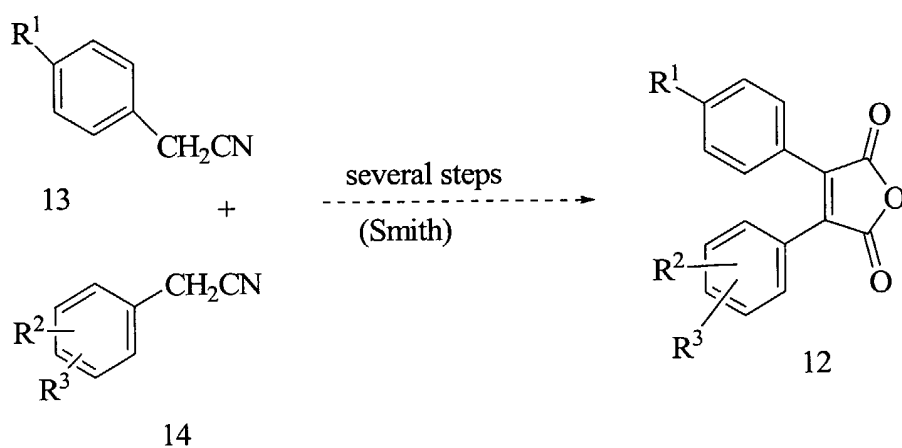
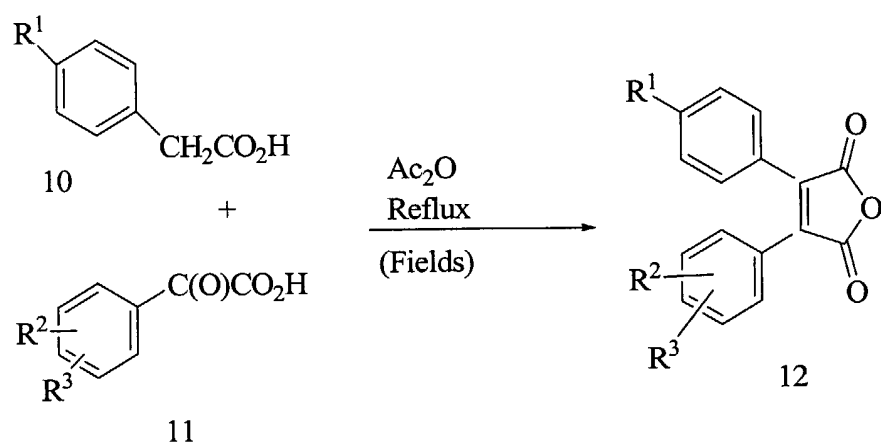
Method C

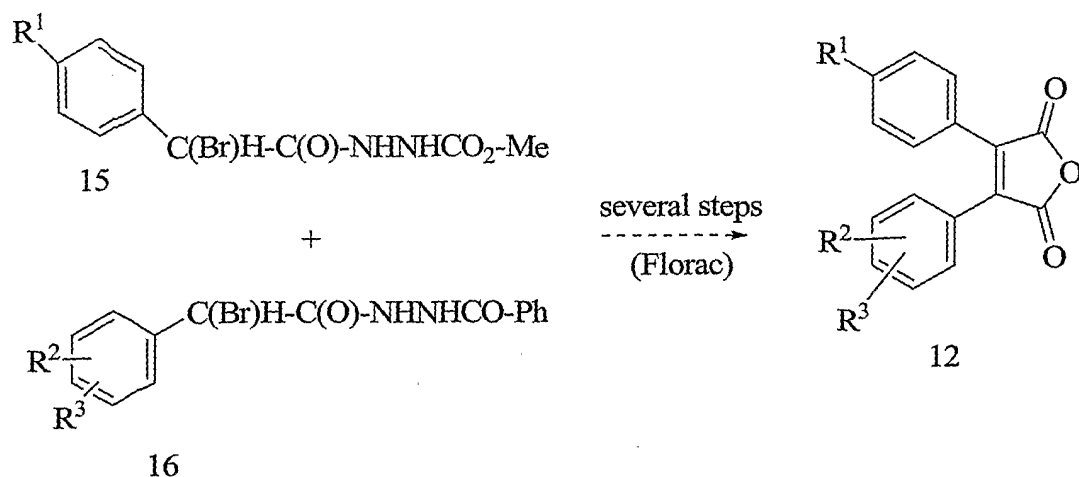


In another method of synthesis, depicted in Method C above, 1, 4-addition to **3** of 4-methylthiophenyl organometallic reagents **4** in the presence of copper salts and the trapping of the resultant enolate with trialkyl silyl chloride such as TMSCl or TIPSCl provide the ketene acetal **5**. The ketene acetal **5** can then be oxidized to the substituted butenolide **6** by the method of Ito using catalytic amounts of $\text{Pd}_2(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2$ and O_2 in MeOH or by the method of Magnus using PhIO/TMSN_3 and Bu_4NF . Introduction of the iodine can be accomplished by treating **6** with I_2 in the presence of pyridine to afford **7**. Palladium catalyzed Suzuki or Stille coupling of **7** with the appropriate aryl partner

such as the boronic acid **8** provides the butenolide **9**. The sulfide can be oxidized to a sulfone by various oxidizing agents such as peracetic acid, MMPP or H_2O_2 to give the desired compound **1**. See Y. Ito et al *J. Am. Chem. Soc.* 1979, 101, 494, footnote 2, and P. Magnus et al., *Tet. Lett.* 1992, 2933.

Method D



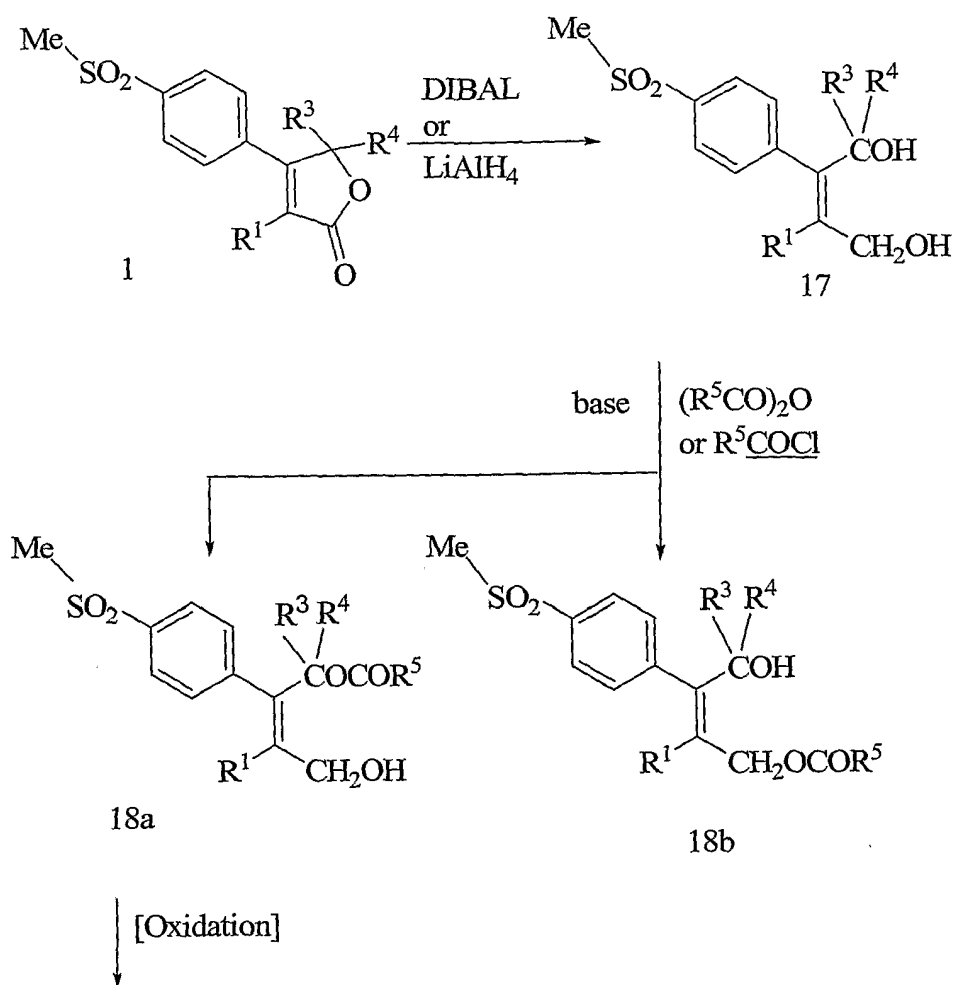


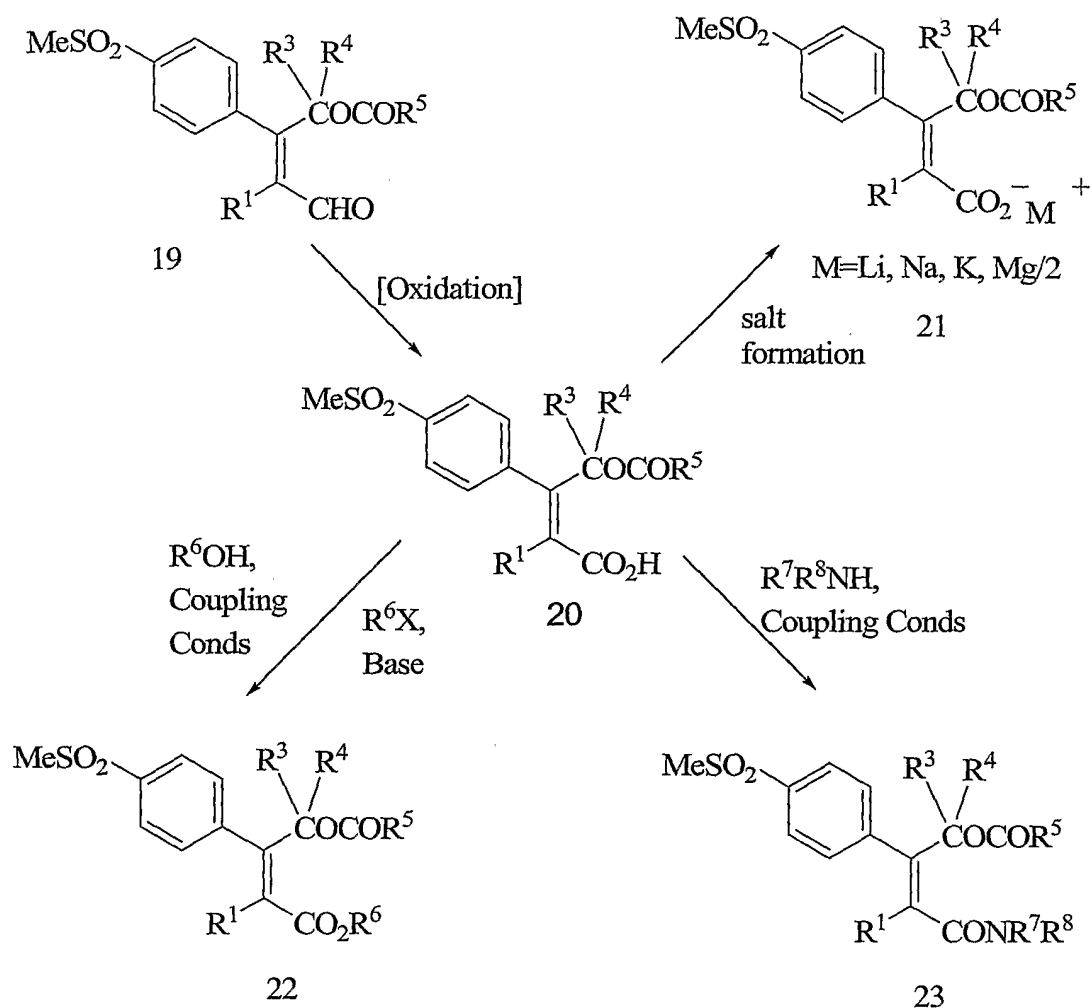
Method D describes methods of synthesis wherein a diaryl furanone is prepared. For example, the 2,3-diphenyl maleic anhydride **12** can be prepared by the method of Fields (*J. Org. Chem.*, 55:5165-70 (1990); U.S. Pat. No. 4,596,867), in which a phenylacetic acid **10** is made to react with an α -oxophenylacetic acid **11** (preferably as its potassium salt) in refluxing acetic anhydride.

A multi-step sequence to **12** from phenylacetonitriles such as **13** and **14** is described by Smith, et. al., *J. Org. Chem.*, 55:3351-62 (1990).

Florac et al, in *Tetrahedron*, 46:445-52 (1990) describe another synthesis of **12** in several steps from α -bromo phenylaceto hydrazides **15** and **16**.

Method E

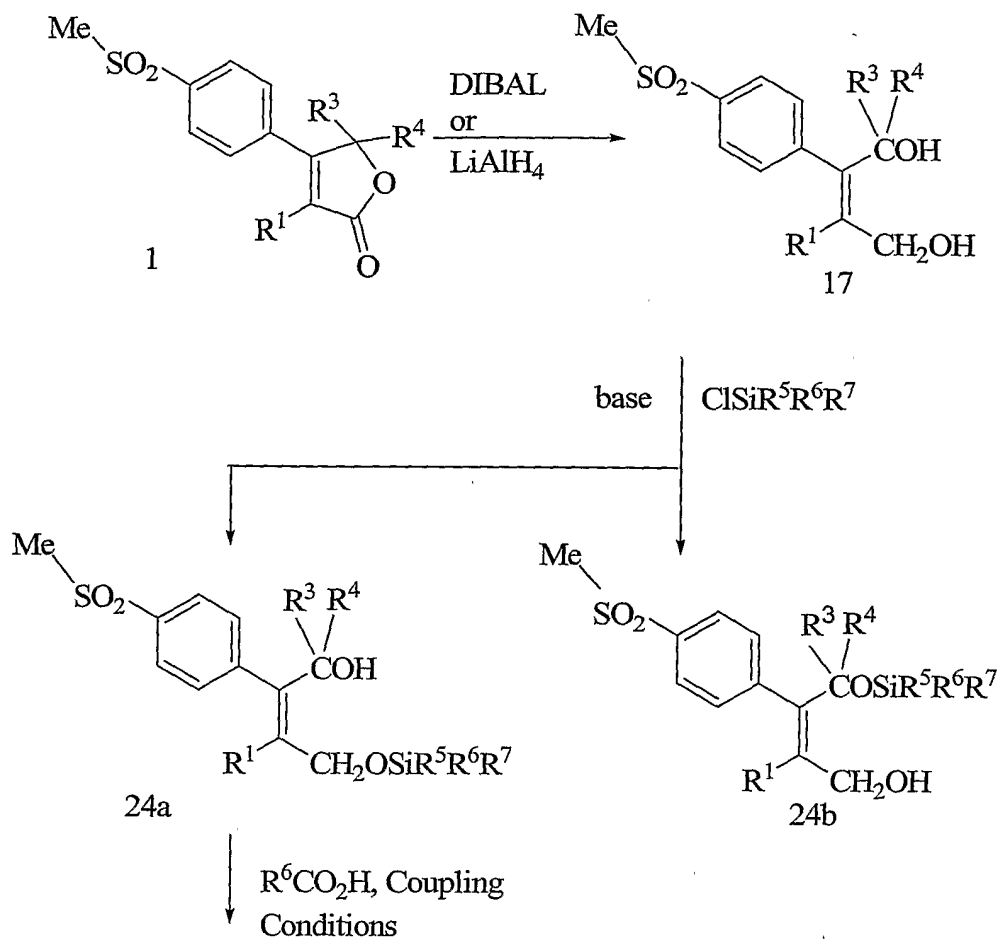


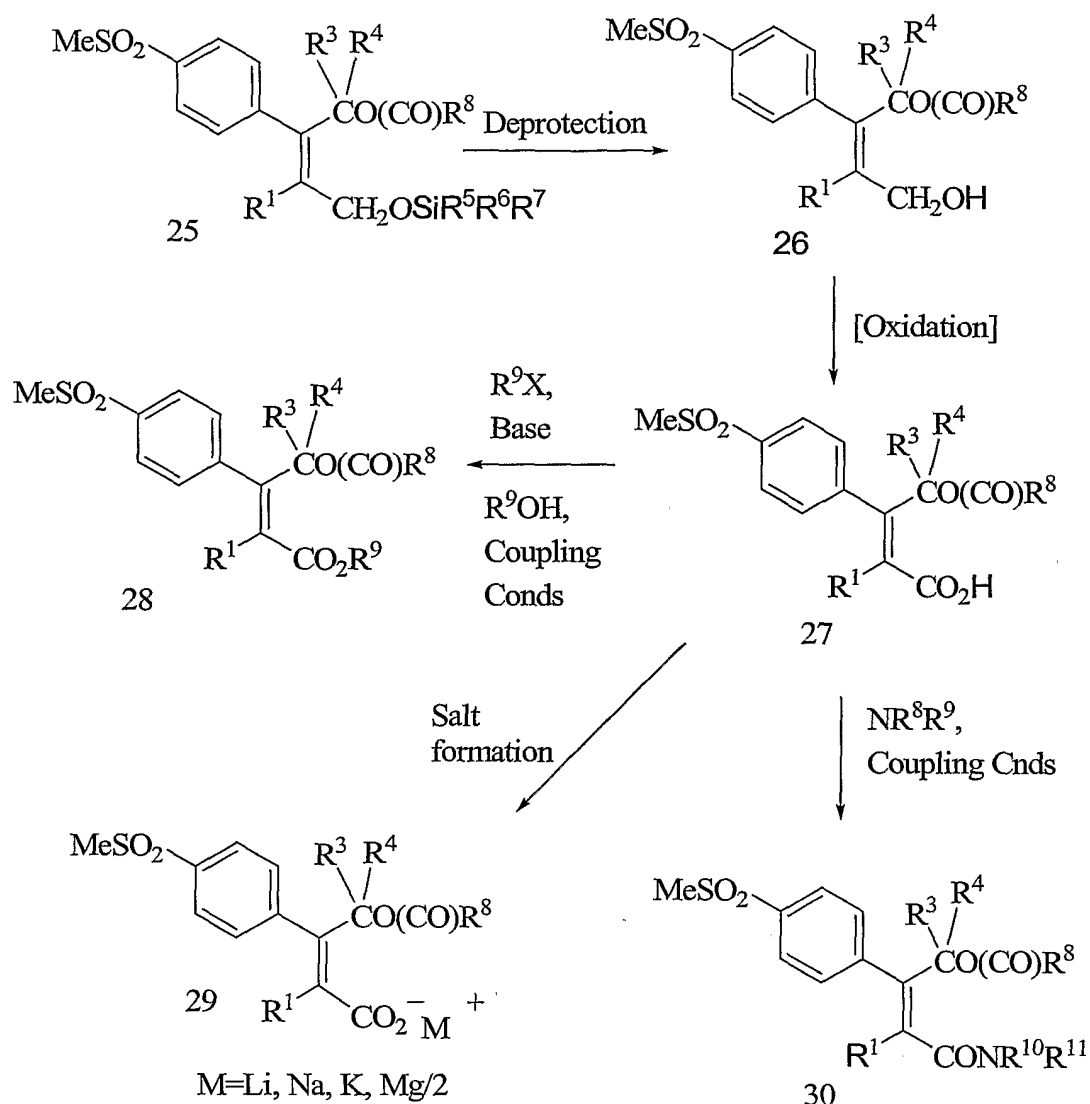


As depicted above in Method E, a lactone **1** may be reduced to the corresponding diol **17** by a suitable reducing agent such as diisobutyl aluminum hydride or lithium aluminum hydride in an appropriate solvent such as toluene, hexane, tetrahydrofuran or ether. The diol **17** is acylated with an anhydride or an acid chloride in the presence of a base such as pyridine, triethylamine or aqueous sodium hydroxide, resulting in the formation of desired isomer **18a** and undesired isomer **18b**. Isomers **18a** and **18b** may be separated by chromatography or crystallization. Compound **18a** may be oxidized to the aldehyde **19** by a reagent such as manganese dioxide or Dess-Martin periodinane. Aldehyde **19** can then be oxidized to acid **20** with Cr⁶⁺ reagents, NaClO₂ or other suitable oxidants. Base treatment of **20** generates the salt **21**. Esters **22** (having a choline or phosphate water soluble group) can be prepared by reacting **20** with an halogenated choline (R⁶ is choline or a phosphate group) in the presence of a base or by reacting with an alcohol under suitable coupling conditions such as triphenylphosphine / diisopropylazodicarboxylate or HATU / NMM. Amides **23** (having an amino acid or saccharide water soluble group) can be prepared by reacting **20** with an amine (wherein one or both of R⁷ and R⁸ is an amino acid or saccharide) in the presence suitable of coupling conditions such as HATU / NMM. The

methyl ester of **20** is conveniently prepared on a small scale by the reaction of **20** with diazomethane in ether.

Method F

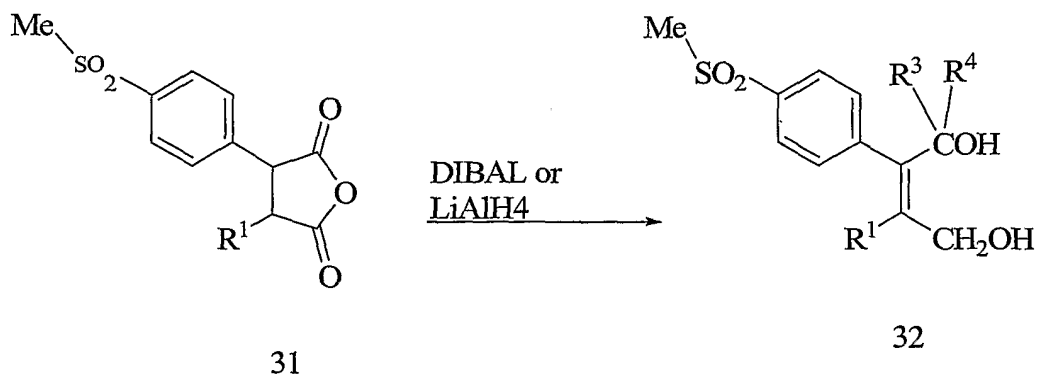




As depicted above in Method F, a lactone 1 may be reduced to the corresponding diol 17 by a suitable reducing agent such as diisobutyl aluminum hydride or lithium aluminum hydride in an appropriate solvent such as toluene, hexane, tetrahydrofuran or ether. The diol 17 is silylated with a silylchloride in the presence of base resulting in the formation of desired isomer 24a and undesired isomer 24b. Isomers 24a and 24b may be separated by chromatography or crystallization. Alcohol 24a may then be coupled with a carboxylic acid R^8CO_2H , wherein R^8 is an amino acid, nicotinic acid, or other desirable carboxylic acid, under suitable coupling conditions such as HATU / NMM or prior formation of an acid chloride to give ester 25. Subsequent deprotection of the silyl ether using fluoride gives the free alcohol 26 which may be oxidized to acid 27 with Cr^{6+} reagents, Dess Martin Peridininane / $NaClO_2$ or other suitable oxidants. Esters 28 can be prepared by reacting 27 with an alkylhalide (R^9X) or an alcohol containing amino acid (R^9OH), such as serine, threonine or tyrosine) in the presence of a

base or by reacting with an alcohol under suitable coupling conditions such as triphenylphosphine / diisopropylazodicarboxylate or HATU / NMM. Reaction with R^9OH will form an ester **28** containing an amino acid water soluble group. Alternatively salt **29** may be prepared by reacting acid **27** with a suitable base. Amides **30** can be prepared by reacting **27** with an amine in the presence of suitable coupling conditions such as HATU / NMM.

Method G



An alternative method of obtaining diol **32** is illustrated in Method G above where a diphenyl maleic anhydride **31** can be reduced to the diol **32** with suitable hydride reducing agents; such as diisobutyl aluminum hydride or lithium aluminum hydride. Solvents such as toluene, tetrahydrofuran or ether, or a mixture thereof, are suitable for the reduction.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N' -dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N -ethyl-morpholine, N -ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric,

pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, trifluoroacetic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, trifluoroacetic and tartaric acids.

The compounds of the invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of formula (I), is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds represented by Formula (I), or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents,

coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations

may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can also be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms "effective amount" or "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers to the treatment of the mentioned conditions, particularly in a patient who demonstrates symptoms of the disease or disorder.

The invention is also directed to a therapeutically effective intravenous formulation of the compounds of the invention, which is solution stable and isotonic with human blood. The intravenous formulation preferably can be packaged in plastic or glass, and meets government and compendial (USP in the US) particulate standards, and can be used as effective therapy to treat stroke.

The intravenous formulation may contain a buffer which can maintain the pH of the intravenous formulation within a desirable range. The buffering agent also preferably acts as a complexing agent to maintain metal ions in solution which are leached out of the glass container. Both of these effects, maintaining the lower pH and complexing metal ions, prevents metal ions from precipitating and can maintain the intravenous formulation in an acceptable particulate profile for storage and subsequent use.

Pharmaceutical intravenous formulations of the invention will generally include a therapeutically effective amount of a compound of the invention to treat stroke, in addition to one or more pharmaceutically acceptable excipients. The compositions are advantageously prepared together with liquid inert carriers, such as water. Suitable liquid excipients/carriers are Water for Injection (US Pharmacopeia) and saline solution. The solution should be pyrogen-free, and also should be absent of particulate matter. Limits for the amount of particulate matter (*i.e.*, extraneous, mobile undissolved substances, other than gas bubbles) which may be found in IV fluids are defined in the US Pharmacopeia.

Other suitable excipients and other additives include solvents such as ethanol, glycerol, propylene glycol, and mixtures thereof; stabilizers such as EDTA (ethylene diamine tetraacetic acid), citric acid, and mixtures thereof; antimicrobial preservatives, such as benzyl alcohol, methyl paraben, propyl paraben, and mixtures thereof; buffering agents, such as citric acid/sodium citrate, potassium hydrogen tartrate, sodium hydrogen tartrate, acetic acid/sodium acetate, maleic acid/sodium maleate, sodium hydrogen phthalate, phosphoric acid/potassium dihydrogen phosphate, phosphoric acid/disodium hydrogen phosphate, and mixtures thereof; tonicity modifiers, such as sodium chloride, mannitol, dextrose, and mixtures thereof; fluid and nutrient replenishers such as synthetic amino acids, dextrose, sodium chloride, sodium lactate, Ringer's solution, and other electrolyte solutions.

The buffer system is generally a mixture of a weak acid and a soluble salt thereof, e.g., sodium citrate/citric acid; or the monocation or dication salt of a dibasic acid, e.g., potassium hydrogen tartrate; sodium hydrogen tartrate, phosphoric acid/potassium dihydrogen phosphate, and phosphoric acid/disodium hydrogen phosphate. The amount of buffer system used is dependent on the desired pH and the amount of the compound of the invention. The choice of appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

The following abbreviations are used throughout the text:

Me = methyl

MeOH = methanol

Et = ethyl

EtOAc = Ethyl Acetate

Bu = butyl

t-Bu = tert butyl

tBuOH = tert butyl alcohol

DCM = dichloromethane

HATU = O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

PBS = Phosphate buffer system

NMM = N-Methylmorpholine

DMF = dimethylformamide

TFA = Trifluoroacetic Acid

BOC = t-butyl carbamate

DMR = Dess-Martin Reagent

MeCN = Acetonitrile

THF = Tetrahydrofuran

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DIBAL-H = Diisobutylaluminum hydride

DMAP = 4,4'-dimethoxytrityl chloride 4-dimethylamino pyridine

TMS = trimethylsilyl

TMSCl = trimethylsilyl chloride

TIPSCl = triisopropylsilyl chloride

TBDMS = tert butyl dimethyl silyl

MMPP = magnesium monoperoxyphthalate

HPLC = High Pressure Liquid Chromatography

TLC = Thin Layer Chromatography

MS = Mass Spectrometry

aq = aqueous

rt = room temperature

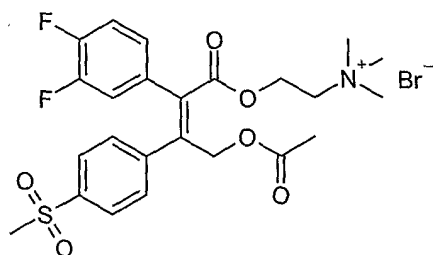
h = hour

min = minutes

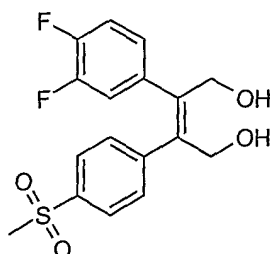
M = molar

EXAMPLE 1

2-((2Z)-4-(acetoxy)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl}oxy)-N,N,N-trimethylethanaminium bromide



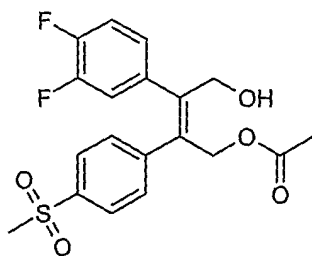
Intermediate 1: (2Z)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-ene-1,4-diol



To a solution of 3-(3,4-difluorophenyl)-4-[4-(methylsulfonyl)phenyl]furan-2(5H)-one, as described in U.S. Pat. No. 5,849,943, at col. 31-32 (15.0 g, 43.8 mmol) in CH₂Cl₂ (500 mL) at -78 °C was added DIBAL-H (20 wt% in CH₂Cl₂, 86 mL, 103.2 mmol) dropwise and the reaction was warmed to rt over 4 h.

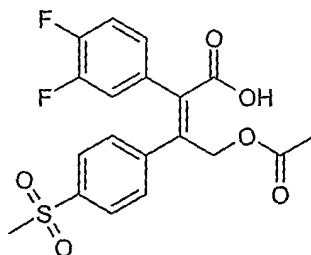
After disappearance of starting material as judged by TLC, the reaction was cooled to 0 °C and quenched with aqueous NaOH (1.0N). Saturated aqueous sodium potassium tartrate was added, and the aqueous layer was extracted five times with CH₂Cl₂. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **1** as a colorless oil; ¹H-NMR (500 MHz, CDCl₃) δ 7.74 (d, 2H), 7.26 (d, 2H), 6.96-6.87 (m, 2H), 6.74-6.72 (m, 1H), 4.60 (d, 4H), 3.01 (s, 3H), 2.77 (t, 1H), 2.69 (t, 1H).

Intermediate 2: (2Z)-3-(3,4-difluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl acetate



To a solution of **1** (13.1 g, 37.0 mmol), triethylamine (10.3 mL, 74.9 mmol), and DMAP (0.45 g, 3.7 mmol) in CH₂Cl₂ (250 mL) at 0 °C was added acetyl chloride (2.65 mL, 37.3 mmol) dropwise. After stirring for 30 min, the reaction was washed with aqueous HCl (1.0N) and the organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography (40-70% EtOAc/toluene) to give 3.1 g (21%) of **2** as a colorless oil. The regioisomeric monoacetate was obtained, and the diacetate was isolated; ¹H-NMR (500 MHz, CDCl₃) δ 7.75 (d, 2H), 7.21 (d, 2H), 6.96-6.88 (m, 2H), 6.77-6.74 (m, 1H), 5.15 (s, 2H), 4.60 (d, 2H), 3.01 (s, 3H), 2.83 (t, 1H), 1.99 (s, 3H).

Intermediate 3: (2Z)-4-(acetoxy)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid



To a solution of **2** (2.0 g, 5.0 mmol) in CH₂Cl₂ (100 mL) was added Dess-Martin periodinane (2.67 g, 6.3 mmol). After stirring for 1 h at rt, water (2 mL) was added and the mixture was stirred for 30 min. The suspension was filtered over a small pad of silica gel, eluting with EtOAc, and the filtrate was concentrated to give the crude aldehyde, which was used directly in the next step.

The aldehyde was dissolved in THF/tBuOH (1/1, 100 mL) and 2-methyl-2-butene (2.0M, 20 mL, 40 mmol) was added. Next, a solution of NaClO₂ (2.4 g, 26.5 mmol) and NaH₂PO₄ (4.4 g, 36.7 mmol) in

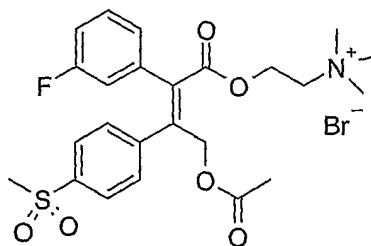
H₂O (20 mL) was added. After stirring for 1 h, the reaction was partitioned between EtOAc and H₂O and the aqueous layer was extracted three times with EtOAc. The combined organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (10-75% EtOAc/hexanes) to give **3** as a thick oil; ¹H-NMR (500 MHz, CDCl₃) δ 7.79 (d, 2H), 7.28 (d, 2H), 6.97-6.92 (m, 2H), 6.78-6.75 (m, 1H), 5.26 (s, 2H), 3.03 (s, 3H), 1.93 (s, 3H).

2-({(2Z)-4-(acetoxy)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl}oxy)-N,N,N-trimethylethanaminium bromide

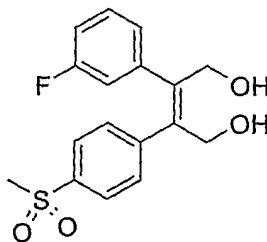
To a mixture of **3** (0.20 g, 0.49 mmol) and K₂CO₃ (0.14 g, 1.01 mmol) in DMF (5 mL) was added (2-bromoethyl)trimethylammonium bromide (0.30 g, 1.21 mmol). After stirring for 72 h at rt, the DMF solution was pipetted from the K₂CO₃ solid and concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (30-80% MeCN/H₂O) to give 50 mg (21%) of the desired product as an off-white residue. The product was dissolved in minimal H₂O and freeze-dried overnight to give the product (Example 1) as a white solid; ¹H-NMR (500 MHz, MeOD) δ 7.81 (d, 2H), 7.37 (d, 2H), 7.11-7.06 (m, 2H), 6.89-6.87 (m, 1H), 5.41 (s, 2H), 4.68 (br s, 2H), 3.72 (br s, 2H), 3.03 (s, 12H), 1.86 (s, 3H); MS (ESI) 498.12 (M+H).

EXAMPLE 2

2-({(2Z)-4-(acetoxy)-2-(3-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl}oxy)-N,N,N-trimethylethanaminium bromide

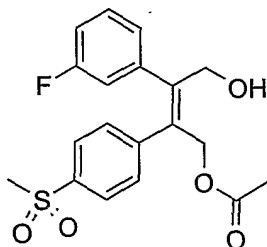


Intermediate 4: (2Z)-2-(3-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-ene-1,4-diol



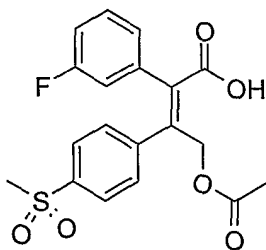
To a solution of 3-(3-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]furan-2(5*H*)-one, as described in U.S. Pat. No. 5,849,943, at col. 35 (25.0 g, 75.2 mmol) in THF (250 mL) at -78 °C was added DIBAL-H (1.0M in CH₂Cl₂, 165 mL, 165 mmol) over 30 min. The cooling bath was removed and the reaction was stirred overnight. An additional portion of DIBAL-H (30 mL, 30 mmol) was added to the reaction was stirred for 3 h. The reaction was then cooled to 0 °C and EtOAc (50 mL) was added. After stirring for 1 h at rt, the solution was recooled to 0 °C and a freshly saturated Na₂SO₄ solution was added. The mixture was vigorously stirred for 30 min, then filtered through Celite, eluting with EtOAc. The filtrate was concentrated and the crude product purified by silica gel chromatography to give **4** as a white foam; ¹H-NMR (500 MHz, CDCl₃) δ 7.69 (d, 2H), 7.26 (d, 2H), 7.09-7.11 (m, 1H), 6.75-6.83 (m, 3H), 4.58-4.61 (m, 4H), 3.06 (br s, 1H), 2.99 (s, 3H), 2.91 (br s, 1H).

Intermediate 5: (2*Z*)-3-(3-fluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl acetate



To a solution of **4** (15.2 g, 45.2 mmol), triethylamine (13 mL, 93.3 mmol), and DMAP (0.75 g) in CH₂Cl₂ (635 mL) at 0 °C was added a solution of acetyl chloride (3.3 mL, 46.5 mmol) in CH₂Cl₂ (15 mL) over 30 min. At this point, analysis of the reaction by thin-layer chromatography indicated the presence of the four expected compounds (diol, bis-acetate and two mono-acetates). The reaction was washed with a 10% aqueous HCl solution and the organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography to give **5** as a white solid; ¹H-NMR (500 MHz, CDCl₃) δ 7.73 (d, 2H), 7.22 (d, 2H), 7.08-7.10 (m, 1H), 6.80-6.83 (m, 3H), 5.17 (s, 2H), 4.63 (d, 2H), 2.99 (s, 3H), 2.67 (t, 1H), 2.00 (s, 3H).

Intermediate 6: (2*Z*)-4-(acetoxymethyl)-2-(3-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid



To a solution of **5** (9.0 g, 23.8 mmol) in CH_2Cl_2 (75 mL) was added Dess-Martin periodinane (11.3 g, 26.7 mmol). After stirring for 30 min at rt, water (15 mL) was added and the solution was stirred for 15 min. The reaction was filtered through a pad of silica gel, eluting with EtOAc, and the filtrate was concentrated to provide the crude aldehyde, which was used directly in the next step.

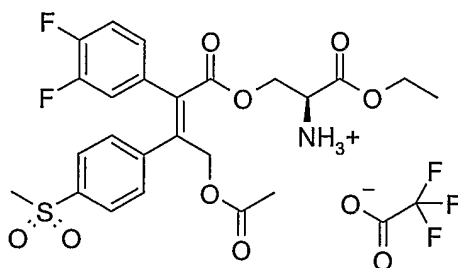
The aldehyde was dissolved in THF/tBuOH (1/1, 150 mL) and 2-methyl-2-butene (2.0M, 63 mL, 126 mmol) was added. Next, a solution of sodium chlorite (11.0 g, 122 mmol) and sodium dihydrogen phosphate (20.0 g, 145 mmol) dissolved in water (88 mL) was added. After stirring for 30 min at rt, the reaction was diluted with EtOAc (150 mL) and washed with a saturated NH_4Cl solution. The organic layer was dried over MgSO_4 , filtered, and concentrated to give a crude semi-solid that was purified by silica gel chromatography (0%-25% MeOH/ CH_2Cl_2) to give **6** as a white solid; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.77 (d, 2H), 7.29 (d, 2H), 7.11-7.13 (m, 1H), 6.81-6.88 (m, 3H), 5.28 (s, 2H), 3.00 (s, 3H), 1.94 (s, 3H); MS (ESI) 392.9 (M+H).

2-((2*Z*)-4-(acetoxo)-2-(3-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl}oxy)-*N,N,N*-trimethylethanaminium bromide

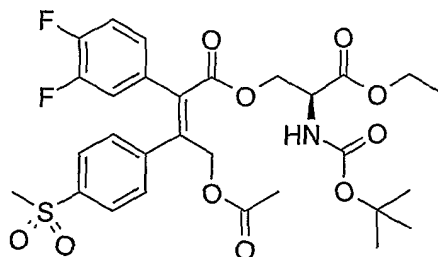
To a mixture of **6** (8.8 g, 22.4 mmol) and K_2CO_3 (7.8 g, 56.5 mmol) in DMF (120 mL) was added (2-bromoethyl)trimethylammonium bromide (11.3 g, 45.7 mmol). After stirring for 60 h at rt, the reaction was filtered and concentrated. The crude product was purified by silica gel chromatography (5%-20% MeOH/ CH_2Cl_2) to give a pale yellow solid that was further purified by trituration in $\text{Et}_2\text{O}/\text{MeOH}$ (10/1) to give the product (Example 2) as a white solid; $^1\text{H-NMR}$ (500 MHz, MeOD) δ 7.79 (d, 2H), 7.38 (d, 2H), 7.17-7.20 (m, 1H), 6.88-6.93 (m, 3H), 5.42 (s, 2H), 4.67-4.69 (m, 2H), 3.73-3.75 (m, 2H), 3.05 (s, 12H), 1.87 (s, 3H); MS (ESI) 478.0 (M+).

EXAMPLE 3

***O*-[(2*Z*)-4 acetyloxy-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-oxo-2-butenyl]-L-serine ethyl ester mono(trifluoroacetate)**



Intermediate 7: *O*-[(2*Z*)-4 acetyloxy-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-oxo-2-butenyl]-*N*-[(1,1-dimethyloxy)carbonyl] L-serine ethyl ester



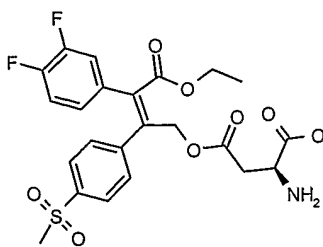
A mixture containing (2*Z*)-4-(acetoxo)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid (Intermediate 3) (132 mg, 0.32 mmol), Boc-Serine Ethyl Ester (75 mg, 0.32 mmol), and triphenylphosphine (93 mg, 0.36 mmol) in THF (100 μ L) was sonicated for 15 min until the solution was homogeneous. Diisopropylazodicarboxylate (70 μ L, 0.36 mmol) was added in four portions over a two minute period and the solution was sonicated for an additional 30 min. After stirring overnight at room temperature, the reaction was concentrated and the residue was purified by silica gel chromatography to give 7 as an oil; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.79 (d, 2H), 7.28 (d, 2H), 6.85-6.96 (m, 2H), 6.69-6.72 (m, 1H), 5.33 (br s, 1H), 5.21 (d, 1H), 5.12 (d, 1H), 4.56-4.58 (m, 3H), 4.12-4.21 (m, 2H), 3.02 (s, 3H), 1.95 (s, 3H), 1.45 (s, 9H), 1.24 (t, 3H); MS (ESI) 526.6 (M-Boc).

O-[(2*Z*)-4 acetyloxy-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-oxo-2-butenyl]-L-serine ethyl ester mono(trifluoroacetate)

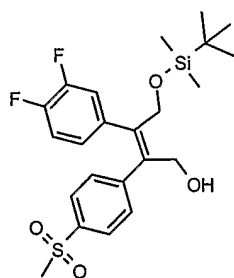
To a solution containing 7 (35 mg, 0.056 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.2 mL). After stirring for 1 h at rt, the solution was concentrated and the crude product was purified by silica gel chromatography (5% MeOH/ CH_2Cl_2) to provide the product (Example 3); $^1\text{H-NMR}$ (500 MHz, MeOD) δ 7.82 (d, 2H), 7.37 (d, 2H), 7.04-7.07 (m, 2H), 6.77-6.81 (m, 1H), 5.35 (d, 1H), 5.24 (d, 1H), 4.71 (d, 2H), 4.51 (t, 1H), 4.16-4.26 (m, 2H), 3.07 (s, 3H), 1.88 (s, 3H), 1.22 (t, 3H); MS (ESI) 526.0 (M+H).

EXAMPLE 4

L-aspartic acid 4-[(2*Z*)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxo-2-butenyl] ester

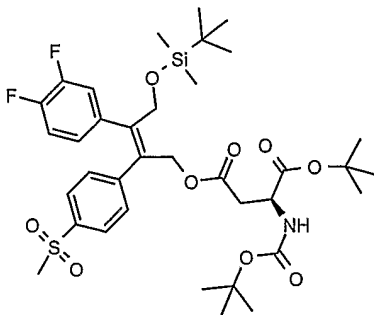


Intermediate 8: (2Z)-4-{{tert-butyl(dimethyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-ol



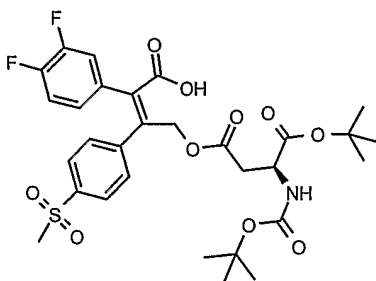
To 11g (1 eq) of **1** in 200mL of 4:1 THF:EtOAc was added 4.6g (2.2eq) of imidazole (2.2eq). The reaction was cooled in an ice bath. Then 5.6g (1.2 eq) of TBDMS chloride as a 10 mL solution in THF. The reaction mixture was allowed to warm to rt. After 30 min, the reaction mixture was quenched with pH7 1M PBS. The organic layer was isolated and concentrated. The crude material was partitioned between DCM and water. The organic layer was isolated and concentrated. Silica gel chromatography (gradient 40% to 60% EtOAc:Hexanes) gave **8** as a white solid. LC-MS calculated for $C_{23}H_{30}F_2O_4SSi$ 468, observed m/e 469.4 ($M+H$)⁺. ¹H-NMR (500MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.2 (m, 2H), 6.6-6.9 (m, 3H), 4.5 (s, 2H), 3.0 (s, 2H), 1.0 (s, 9H), 0.0 (s, 6H).

Intermediate 9: 1-tert-butyl 4-{{(2Z)-4-{{tert-butyl(dimethyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl} N-(tert-butoxycarbonyl)aspartate



To 330 mg (1eq) of Boc-Asp-OtBu in 1 mL DMF was added 160 μ L (1.2eq) NMM and 480 mg (1.1eq) HATU. After 5 min, this HATU-activated acid solution was added to a 1 mL DMF solution containing 500 mg (1.07mmol) of **8**. After 16h, 0.30mL of DBU was added to push the reaction to completion. After 1h, the reaction mixture was quenched with pH7 1M PBS, extracted with DCM three times, and the organics concentrated to residue. Silica gel chromatography (gradient 20% to 60% EtOAc:Hexanes) gave **9**. LC-MS calculated for $C_{36}H_{51}F_2NO_9SSi$ 739, observed m/e 640.8 ($M+H-BOC$)⁺. ¹H-NMR (500MHz, $CDCl_3$) δ 7.8 (m, 2H), 7.2 (m, 2H), 6.7-6.9 (m, 3H), 5.1 (m, 2H), 4.6 (m, 2H), 4.4 (m, 1H), 3.0 (s, 3H), 2.8 (m, 2H), 1.4 (d, 9H), 0.9 (s, 9H), 0.0 (s, 6H).

Intermediate 10: *N*-[(1,1-dimethyloxy)carbonyl] L-aspartic acid 4-[(2*Z*)-3-carboxy-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenyl] 1-(1,10-dimethylethyl) ester



To 640 mg (1eq) of **9** in 20 mL MeCN was added 2 mL tBuOH and 0.12 mL of 35% w/w fluorosilicic acid (aq). After 2h, the reaction mixture was quenched with 20 mL of pH7 1M PBS and 20 mL water, extracted with DCM two times, and the organics concentrated to residue. Co-evaporation with DCM gave the alcohol intermediate as a white foam. To this, was added 10 mL DCM and 438 mg (1.2eq) of fresh DMR. After 30 min, 4 mL water was added. The reaction mixture was vigorously stirred for 5 min. The organic layer was isolated, flushed through silica gel with 100% EtOAc, and concentrated to residue. To this residue was added 12 mL THF, 12 mL tBuOH and 6 mL 2-methyl-2-butene followed by a 12 mL water solution containing 400 mg $NaClO_2$ and 72 mg NaH_2PO_4 . After 10 min, the reaction mixture was diluted with EtOAc, washed with saturated ammonium chloride, dried ($MgSO_4$), and concentrated. Silica gel chromatography (gradient 1% to 6% MeOH:DCM) gave **10**. LC-MS calculated for $C_{30}H_{35}F_2NO_{10}S$ 639, observed m/e 640.8 ($M+H$)⁺.

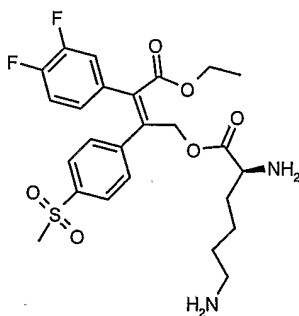
L-aspartic acid 4-[(2*Z*)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxo-2-butenyl] ester

To 235mg (1eq) of **10** in 2 mL DMF was added 153 mg (1.1eq) HATU and 48 μ L (1.2eq) NMM. After 30min, 1mL of ethanol was added. After 3 days, the reaction mixture was purified without workup. Reverse phase preparative HPLC (gradient 25% to 100% MeCN:water) gave protected intermediate. To this was added 50% TFA/DCM. After 1h the reaction mixture was concentrated. Reverse phase preparative HPLC (gradient 25% to 100% MeCN:H₂O) gave the product (Example 4) as the TFA salt.

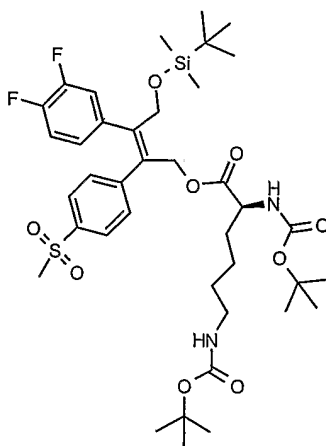
LC-MS calculated for $C_{23}H_{23}F_2NO_8S$ 511, observed m/e 512.4 $(M+H)^+$. ^1H -NMR (500MHz, d-acetone) δ 7.9 (m, 2H), 7.7 (m, 2H), 6.8-7.2 (m, 3H), 5.4 (m, 2H), 4.4 (m, 1H), 4.2 (m, 2H), 4.1 (m, 2H), 3.1 (s, 3H), 1.3 (m, 3H).

EXAMPLE 5

(2Z)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxobut-2-en-1-yl lysinate



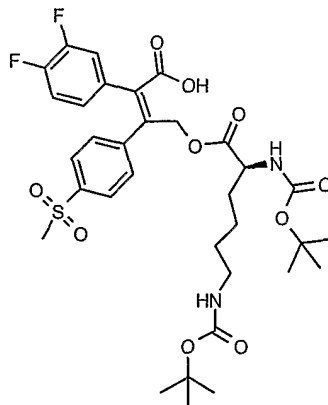
Intermediate 11: (2Z)-4-[[tert-butyl(dimethyl)silyl]oxy]-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl *N*-2,2,6,6-tetramethylpiperidine-1-carboxylate



To 607 mg (1eq) of Bis-Boc-Lys in 1mL DMF, was added 160 μ L (1.2 eq) NMM and 480 mg (1.1eq) HATU. After 5 min, this HATU-activated acid solution was added to a 1mL DMF solution containing 500mg (1.07mmol) of (2Z)-4-[[tert-butyl(dimethyl)silyl]oxy]-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-ol (Intermediate 8). After 16h the reaction mixture was quenched with pH7 1M PBS, extracted with DCM three times, and the organics concentrated to residue. Silica gel chromatography (gradient 20% to 60% EtOAc:Hexanes) gave 11. LC-MS calculated for $C_{39}H_{58}F_2N_2O_9SSi$ 796, observed m/e 597.8 $(M+H-2BOC)^+$. ^1H -NMR (500MHz, $CDCl_3$) δ 7.8 (m, 2H),

7.2 (m, 2H), 6.7-6.9 (m, 3H), 5.2 (m, 2H), 4.6 (m, 2H), 4.2 (m, 1H), 3.0 (m, 5H), 2.0-1.0 (m, 24H), 0.9 (s, 9H), 0.0 (s, 6H).

Intermediate 12: (2Z)-4-{[N-2~,N-6~-bis(tert-butoxycarbonyl)lysyl]oxy}-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid



To 610 mg (1eq) of 11 in 20 mL MeCN and 2 mL t-BuOH was added 110 μ L of 35% w/w fluorosilicic acid (aq). After 2h, an additional 50 μ L of 35% w/w fluorosilicic acid was added. After 1h, the reaction was quenched with 20 mL pH7 1M PBS and 20 mL water. Two extractions with DCM, concentration of the organics, followed by co-evaporation with DCM gave the crude alcohol intermediate as a white foam. To this, was added 10 mL DCM and 438 mg (1.2eq) of fresh DMR. After 30min, the reaction mixture was quenched with 4 mL water. After 5 min of vigorous stirring, the organic layer was isolated, flushed through silica gel with 100% EtOAc, and concentrated to residue. To this residue was added 12mL THF, 12mL tBuOH, 6mL 2-methyl-2-butene and a 12 mL water solution containing 400mg NaClO₂ and 72mg NaH₂PO₄. After 10 min, the reaction was diluted with EtOAc, washed with saturated ammonium chloride, dried (MgSO₄), filtered and concentrated. Silica gel chromatography (gradient 1% to 6% MeOH:DCM) gave 12. LC-MS calculated for C₃₃H₄₂F₂N₂O₁₀S 696, observed m/e 597.7 (M+H-BOC)⁺.

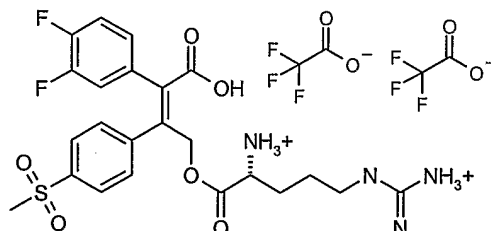
(2Z)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxobut-2-en-1-yl lysinate

To 180mg (1eq) of 12 in 3 mL DMF was added 110 mg (1.1eq) HATU and 35 μ L (1.2eq) NMM. After 30min, 1mL of ethanol was added. After 3 days, the reaction mixture was purified without workup. Reverse phase preparative HPLC (gradient 25% to 100% MeCN:water) gave pure protected intermediate. This intermediate was dissolved into 50% DCM/TFA and after 1h the reaction was concentrated. Reverse phase preparative HPLC (gradient 25% to 100% MeCN:water) gave the product (Example 5) as the bis-TFA salt. LC-MS calculated for C₂₅H₃₀F₂N₂O₆S 524, observed m/e 525.6 (M+H)⁺. ¹H-NMR

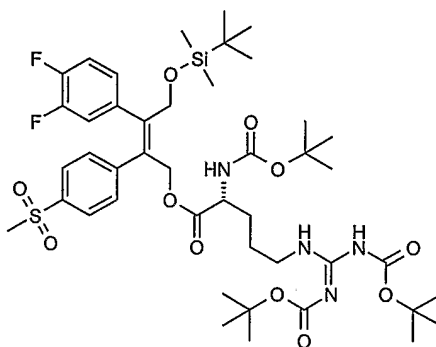
(500MHz, d-acetone) δ 7.7 (m, 2H), 7.4 (m, 2H), 6.7-7.1 (m, 3H), 5.3-5.4 (m, 2H), 4.7 (m, 1H), 4.2 (m, 2H), 3.6 (m, 2H), 3.0 (s, 3H), 1.4-1.9 (m, 6H), 1.1 (m, 3H).

EXAMPLE 6

(2Z)-4-{{N-5~(diaminomethyl)ornithyl}oxy}-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid

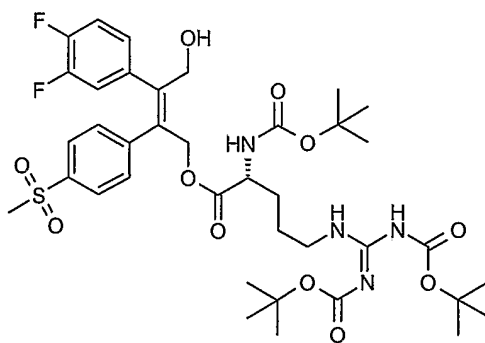


Intermediate 13: (2Z)-4-{{tert-butyl(dimethyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl *N*-2~(tert-butoxycarbonyl)-*N*-5~{(E)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}ornithinate



To 540 mg (1eq) of Tris-Boc-Arg in 1mL DMF was added 155 μ L (1.2eq) NMM and 480 mg (1.1eq) HATU. After 5 min, this HATU-activated acid solution was added to a 1mL DMF solution containing 500 mg (1.07mmol) of (2Z)-4-{{tert-butyl(dimethyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-ol (Intermediate 8). After 1h, 300 μ L of DBU was added to push the reaction to completion. After 2h, the reaction mixture was quenched with pH7 1M PBS, extracted with DCM three times. The organics were concentrated. Silica gel chromatography (gradient 10% to 60% EtOAc:Hexanes) gave **13**. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ 7.8 (m, 2H), 7.2 (m, 2H), 6.6-6.9 (m, 3H), 5.1-5.4 (m, 3H), 4.6 (m, 2H), 3.8 (m, 2H), 3.0 (s, 3H), 1.4 (m, 27H), 0.8 (s, 9H), 0.0 (s, 6H).

Intermediate 14: (2Z)-3-(3,4-difluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl *N*-2~(tert-butoxycarbonyl)-*N*-5~{(E)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl}ornithinate



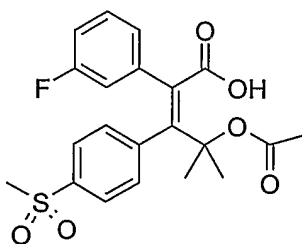
To 550 mg (1eq) of **13** was added 15 mL of 9:1 MeCN:tBuOH and 300 μ L of 35% w/w fluorosilicic acid (aq). After 2h, the reaction mixture was quenched with water. The organics were combined from two DCM extractions and concentrated. Silica gel chromatography (gradient 20% to 70% EtOAc:Hexanes) gave **14**. $^1\text{H-NMR}$ (500MHz, CDCl_3) δ 7.6 (m, 2H), 7.1 (m, 2H), 6.5-6.9 (m, 3H), 4.9-5.1 (m, 2H), 4.4 (m, 2H), 3.9-4.0 (m, 3H), 2.8 (s, 3H), 1.1-1.9 (m, 31H).

(2Z)-4-([N-5-~-(diaminomethyl)ornithyl]oxy)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid

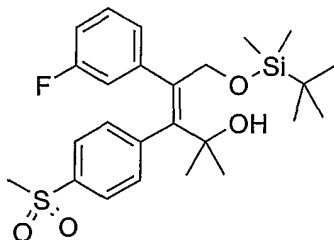
To 220 mg (1eq) of **14** in 3 mL DCM, was added 700 μ L (1.2eq) of 15% DMR (in DCM). After 1h, an equal volume of water was added and after vigorous stirring for 5 min, the organic layer was isolated, flushed through silica gel with 50% EtOAc:Hexanes, and concentrated to residue. To the residue was added 6 mL THF, 6 mL tBuOH, and 3 mL 2-methyl-2-butene, followed by a 6 mL water solution containing 360 mg NaH_2PO_4 and 200 mg NaClO_2 . After 5 min, the reaction mixture was diluted with EtOAc and washed with ammonium chloride. The organic layer was isolated and concentrated. A 50% TFA/DCM solution was then added and, after 1h, the reaction mixture was concentrated. Reverse phase preparative HPLC (gradient 20% to 50% MeCN:water) gave the product (Example 6) as the bis TFA salt. LC-MS calculated for $\text{C}_{23}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_6\text{S}$ 524, observed m/e 524.8 ($\text{M}+\text{H}$) $^+$. $^1\text{H-NMR}$ (500MHz, MeOD) δ 7.9 (m, 2H), 7.5 (m, 2H), 6.9-7.2 (m, 3H), 5.2-5.4 (m, 2H), 4.0 (m, 1H), 3.1 (s, 3H), 3.0 (m, 2H), 1.6-1.9 (m, 4H).

EXAMPLE 7

(2Z)-4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-pent-2-enoic acid

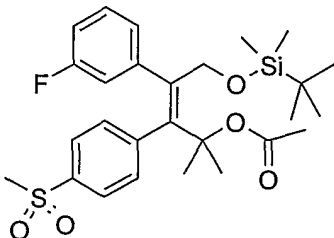


Intermediate 15: 1-(t-Butyldimethylsilyl)-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-penten-4-ol



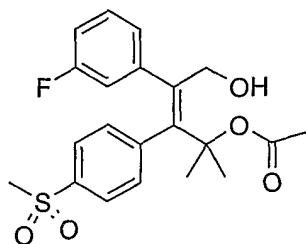
To a solution of 2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-penten-1,4-diol, as described in U.S. Pat. No. 5,925,631, at col. 38-39 (1.4 g, 3.8 mmol) and imidazole (0.63 g, 9.3 mmol) in CH_2Cl_2 (12 mL) was added t-butyldimethylsilyl chloride (0.63 g, 4.2 mmol). After stirring for 16 h at rt, the reaction was quenched by the addition of MeOH (1 mL). The solution was washed with brine and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was dried over MgSO_4 , filtered, and concentrated. The crude product was purified by silica gel chromatography to give **15** as a white solid; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.66 (d, 2H), 7.14 (d, 2H), 6.97-6.99 (m, 1H), 6.65-6.67 (m, 1H), 6.56-6.62 (m, 2H), 4.70 (s, 2H), 4.52 (s, 1H), 2.94 (s, 3H), 1.38 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H).

Intermediate 16: 4-acetoxy-1-(t-Butyldimethylsilyl)-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-pentene



To a solution of **15** (225 mg, 0.47 mmol) and DMAP (57 mg, 0.47 mmol) in CCl_4 (8 mL) was added acetic anhydride (1 mL). After stirring at reflux for 2 h, the solution was washed with water and extracted with CH_2Cl_2 . The combined organic layer was dried over MgSO_4 , filtered, and concentrated to give **16** as a solid that was used without further purification; $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.65 (d, 2H), 7.34 (d, 2H), 6.92-6.94 (m, 1H), 6.61-6.64 (m, 3H), 4.64 (s, 2H), 2.92 (s, 3H), 2.12 (s, 3H), 1.46 (s, 6H), 0.78 (s, 9H), -0.22 (s, 6H).

Intermediate 17: 4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2-(Z)-penten-1-ol



To a solution of **16** (605 mg, 1.16 mmol) in THF (10 mL) cooled to 0 °C was added HF-pyridine (1 mL) over 10 min. After 30 min, additional HF-pyridine (0.4 mL) was added and the solution was warmed to rt over 2h. The solution was diluted with ether (25 mL) and quenched with NaHCO₃ until the aqueous layer was neutral or slightly basic. The aqueous layer was extracted with ether and the combined organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography to give **17**; ¹H-NMR (500 MHz, CDCl₃) δ 7.67 (d, 2H), 7.35 (d, 2H), 7.01-7.04 (m, 1H), 6.65-6.71 (m, 3H), 4.69 (s, 2H), 2.94 (s, 3H), 2.15 (s, 3H), 1.70 (s, 1H), 1.49 (s, 6H).

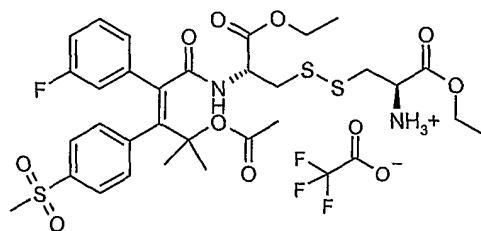
(2Z)-4-(acetoxymethyl)-2-(3-fluorophenyl)-4-methyl-3-[4-(methylsulfonyl)phenyl]pent-2-enoic acid

To a solution of **17** (248 mg, 0.61 mmol) in CH₂Cl₂ (10 mL) was added Dess-Martin periodinane (324 mg, 0.76 mmol). After stirring for 1h at rt, water (1 mL) was added and the mixture was stirred for 30 min. The suspension was filtered over a small pad of silica gel, eluting with EtOAc, and the filtrate was concentrated to give the crude aldehyde, which was used directly in the next step.

The aldehyde was dissolved in THF:*t*BuOH (1/1, 8 mL) and 2-methyl-2-butene (2.0M, 2.5 mL, 5 mmol) was added. Next, a solution of NaClO₂ (290 mg, 3.2 mmol) and NaH₂PO₄ (530 mg, 4.4 mmol) in H₂O (4 mL) was added. After stirring for 1 h, the reaction was partitioned between EtOAc and H₂O and the aqueous layer was extracted three times with EtOAc. The combined organic layer was dried over MgSO₄, filtered, and concentrated. The crude residue was triturated in hexanes/CH₂Cl₂, filtered and dried to give the product (Example 7) as a white solid; ¹H-NMR (DMSO-*d*₆, 500 MHz) δ 7.76 (d, 2H), 7.42 (d, 2H), 7.15-7.17 (m, 1H), 6.79-6.92 (m, 3H), 2.99 (s, 3H), 2.01 (s, 3H), 1.51 (s, 6H).

EXAMPLE 8

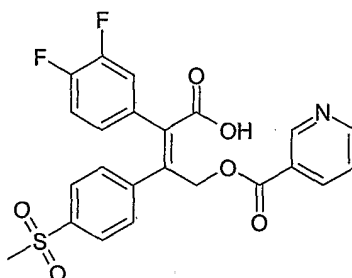
Diethyl *N*-{(2Z)-4-(acetyloxy)-2-(3-fluorophenyl)-4-methyl-3-[4-(methylsulfonyl)phenyl]pent-2-enoyl}cystinate



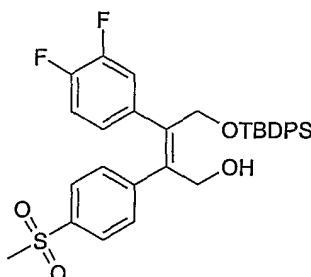
To 85mg (1eq) of (2Z)-4-(acetoxymethyl)-2-(3-fluorophenyl)-4-methyl-3-[4-(methylsulfonyl)phenyl]pent-2-enoic acid (Example 7) in 1 mL DMF was added 95 mg (1.1eq) HATU and 30 μ L (1.2eq) NMM. After 5 min, this HATU-activated acid solution was added to a 1 mL DMF solution containing 22mg of Cystine diethylester dihydrochloride and 1.2mmol (6eq) DBU. After 2h and without workup, the reaction mixture was purified. Reverse phase preparative HPLC (gradient 5% to 100% MeCN:water) gave the product (Example 8) as the TFA salt. LC-MS calculated for $C_{31}H_{39}FN_2O_9S_3$ 698, observed m/e 639.5 $(M+H-AcO)^+$. ^1H -NMR (500MHz, D_2O) δ 7.7 (m, 2H), 7.4 (m, 2H), 6.8-7.1 (m, 4H), 4.8 (m, 1H), 4.4 (m, 1H), 4.2 (m, 2H), 4. (m, 2H), 3.2 (m, 2H), 3.0 (s, 3H), 2.9 (m, 2H), 2.0 (s, 3H), 1.6 (s, 3H), 1.5 (s, 3H), 1.2 (t, 3H), 1.1 (t, 3H).

EXAMPLE 9

(2Z)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-4-[(pyridin-3-ylcarbonyl)oxy]but-2-enoic acid



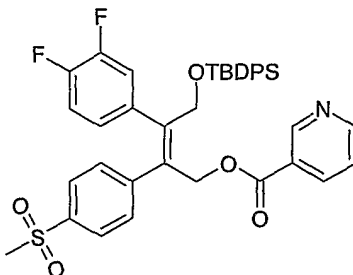
Intermediate 18: (2*Z*)-4-{{*tert*-butyl(diphenyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-ol



To a solution of **1** (7.20 g, 20.3 mmol) in THF (200 mL) was added TBDPS-Cl and Et₃N (6.22 mL) dropwise. After stirring at rt for 12 hr, the solution was concentrated and purified on silica gel to separate the isomers and afford **18** as the more polar isolated compound; ¹H-NMR (benzene-d₆, 500 MHz) δ 7.75

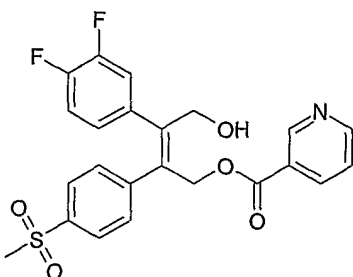
(d, 4H), 7.68 (d, 4H), 7.32 (m, 6H), 7.01 (d, 2H), 6.72 (dd, 1H), 6.50 (dd, 1H), 6.47 (m, 1H), 4.60 (s, 2H), 4.29 (d, 2H), 2.25 (s, 3H), 1.17 (s, 9H).

Intermediate 19: (2Z)-4-{{*tert*-butyl(diphenyl)silyl}oxy}-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl nicotinate



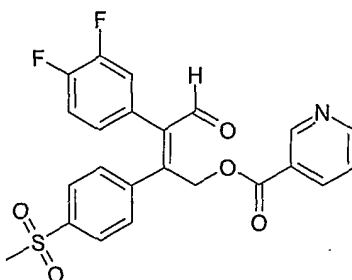
To a solution of **18** (300 mg, 0.51 mmol) in pyridine (2 mL) was added nicotinyl chloride hydrochloride (200 mg, 1.10 mmol) and stirred at rt for 12 hrs. The solution was diluted with EtOAc, washed with sat'd aq. sodium bicarbonate solution, the organic phase separated and dried (MgSO₄). After filtering and evaporation under reduced pressure the residue was purified by column chromatography eluting with a gradient of EtOAc in CH₂Cl₂ (0 to 50%) to afford **19**. ¹H-NMR (benzene-d₆, 500 MHz) δ 9.23 (s, 1H), 8.37 (s, 1H), 7.82 (d, 1H), 7.46 (m, 4H), 7.54 (d, 2H), 7.20 (m, 6H), 6.82 (d, 2H), 6.62 (m, 1H), 6.51 (m, 1H), 6.39 (m, 1H), 6.28 (m, 1H), 5.04 (s, 2H), 4.62 (s, 2H), 2.14 (s, 3H), 1.16 (s, 9H).

Intermediate 20: (2Z)-3-(3,4-difluorophenyl)-4-hydroxy-2-[4-(methylsulfonyl)phenyl]but-2-en-1-yl nicotinate



To a solution of **19** (959 mg, 1.67 mmol) in THF (10 mL) was added HF.pyridine (0.6 mL) and stirred at rt for 2 hrs. The reaction mixture was then diluted with EtOAc, washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was then purified on silica gel (EtOAc) to afford **20**. ¹H-NMR (CDCl₃, 500 MHz) δ 9.02 (s, 1H), 8.75 (s, 1H), 8.13 (d, 1H), 7.74 (d, 2H), 7.39 (m, 1H), 7.25 (d, 2H), 7.05 (m, 1H), 6.92 (m, 1H), 6.78 (m, 1H), 5.45 (s, 2H), 4.70 (s, 2H), 2.99 (s, 3H).

Intermediate 21: (2Z)-3-(3,4-difluorophenyl)-2-[4-(methylsulfonyl)phenyl]-4-oxobut-2-en-1-yl nicotinate



To a solution of **20** (698 mg, 1.52 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (660 mg, 1.56 mmol) and stirred at rt. After 10 minutes, TLC indicated complete reaction and the suspension was diluted with CH_2Cl_2 , washed with sat'd. aq. sodium bicarbonate solution, the organic phase separated, dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified on silica gel using a gradient elution of EtOAc in hexanes (0 to 80%) to yield **21**. $^1\text{H-NMR}$ (benzene- d_6 , 500 MHz) δ 9.94 (s, 1H), 9.07 (s, 1H), 8.33 (d, 1H), 7.73 (m, 1H), 7.48 (d, 2H), 6.70 (d, 2H), 6.45 (m, 1H), 6.35 (dd, 1H), 6.10 (d, 1H), 5.21 (s, 2H), 2.11 (s, 3H).

(2Z)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-4-[(pyridin-3-ylcarbonyl)oxy]but-2-enoic acid

To a suspension of aldehyde **21** (470 mg, 1.02 mmol) in *t*-BuOH (8.7 mL) and THF (8.7 mL) was added 2-methyl-2-butene (2M soln in THF; 4.7 mL, 9.4 mmol) and sodium dihydrogen phosphate (1.0g). The solution was then cooled to 0°C and a 2 mL of a solution of sodium chlorite (530 mg in 8.7 mL H_2O) was added. After 10 minutes a further 1 mL of the oxidizing solution was added and the reaction mixture was allowed to attain rt. After TLC analysis indicated complete reaction the solution was diluted with EtOAc, washed with water and the aqueous layer extracted with EtOAc. The combined organic phases were dried (MgSO_4), filtered, evaporated under reduced pressure and the residue triturated with ether to afford the title compound as a colorless solid. LC-MS calculated for $\text{C}_{23}\text{H}_{17}\text{F}_2\text{NO}_6\text{S}$ 473.5, observed m/e 473.9 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}$ (Acetone- d_6 , 500 MHz) δ 8.89 (s, 1H), 8.77 (d, 1H), 8.12 (d, 1H), 7.85 (2H, d), 7.61 (d, 2H), 7.50 (m, 1H), 7.25 (m, 1H), 7.17 (dd, 1H), 6.99 (m, 1H), 3.05 (s, 3H).

Assays for Determining Biological Activity

The compounds of Formula I can be tested using the following assays to determine their biological activity.

Inhibition of Cyclooxygenase Activity

Compounds are tested as inhibitors of cyclooxygenase activity in whole cell and microsomal cyclooxygenase assays. Both of these assays measure prostaglandin E2 (PGE_2) synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for whole cell assays, and from which microsomes are prepared for microsomal assays, are human osteosarcoma 143 cells (which specifically express cyclooxygenase-2) and human U-937 cells (which specifically express

cyclooxygenase-1). In these assays, 100% activity is defined as the difference between prostaglandin E2 synthesis in the absence and presence of arachidonate addition. IC₅₀ values represent the concentration of putative inhibitor required to return PGE₂ synthesis to 50% of that obtained as compared to the uninhibited control.

Representative Rat Paw Edema Assay

Protocol: Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given p.o., either vehicle (1% methocell) or a test compound in the morning. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_{0h}) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarily with 50 μ l of a 1% carrageenan solution in saline (Sigma Chem) into the paw using an insulin syringe with a 25-gauge needle (i.e., 500 μ g carrageenan per paw). Three hr later, the paw volume (V_{3h}) is measured and the increases in paw volume ($V_{3h} - V_{0h}$) are calculated. Paw edema data are compared with the vehicle-control group and percent inhibition calculated taking the values in the control group as 100%. All treatment groups are coded to eliminate observer bias.

NSAID-Induced Gastropathy In Rats

Rationale: The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. Rats are sensitive to the actions of NSAIDs and have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring urinary ⁵¹Cr excretion after oral dosing of ⁵¹Cr-EDTA. Urinary ⁵¹Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods: Male Sprague-Dawley rats (150-200 g) are administered orally a test compound either once (acute dosing) or in multiple doses for a few days (chronic dosing). Immediately after the administration of the last dose, the rats are given an oral dose of ⁵¹Cr-EDTA (10 μ Ci/rat). The animals are placed individually in metabolism cages with food and water *ad lib*. Urine is collected for a 24 hr period and ⁵¹Cr urinary excretion is calculated as a percent of total ingested dose.

Protein-Losing Gastrophathy in Squirrel Monkeys

Rationale: Protein-losing gastrophathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to NSAIDs. This can be quantitatively assessed by intravenous administration or ⁵¹CrC13 solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 hr after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastrophathy.

Rationale: Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with 1% methocel or a test compounds at multiple doses for a few days. Intravenous ^{51}Cr (5 $\mu\text{Ci/kg}$ in 1 ml/kg PBS) is administered 1 hr after the last drug/vehicle dose, and feces collected for 24 hr in a metabolism cage and assessed for excreted ^{51}Cr by gamma-counting. ^{51}Cr fecal excretion is calculated as a percent of total injected dose.

Rat Aortic Smooth Muscle flings in Male Sprague-Dawley Rats

Preparation of rat aortic smooth muscle rings Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) are euthanized by intraperiton injection of a high dose 5 of sodium pentobarbitone (80-100 mg/kg). The thoracic aorta is rapidly excised and immediately placed in a Petri dish containing warm (37°C) oxygenated (95% O_2 and 5% CO_2), Krebs's buffer (composition per millimolar: NaCl (119); KCl (4.69); $\text{CaCl}_2 \cdot \text{H}_2\text{O}$ (2.52); $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (0.57); NaHCO_3 (25); $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (1.01) and glucose (11.1)). Under a stereoscopic dissecting microscope, the aorta is cleaned, freed from adhering fat and connective tissues. The tissue is cut into ring segments, each approximately 2-3 mm in length.

For experiments to measure relaxation of the tissue under various conditions, a stainless steel tissue holder and an U-shaped stainless steel wire are inserted into the lumen of the aortic ring. The tissue holder anchors the ring at the bottom of the organ bath whereas the end of the U-shaped steel wire is tied with fine silk thread so that it connects to the FT-202 transducer. The tissue holder and the steel wire along with the aortic ring are then suspended in a 5-ml doublejacketed temperature-controlled glass organ bath (Radnoti Glass Technology, Inc., Monrovia, CA) filled with fresh Krebs's buffer. A mixture of 95% O_2 and 5% CO_2 is bubbled through a porous sintered disc at the bottom of the bath. The rings are given an initial resting tension of 1.5 g and the preparation is allowed to equilibrate at the initial tension for about 90 minutes. During this equilibration period, the bath fluid is changed every 15 min and replaced with fresh pre-warmed (37°C) Krebs's buffer. The isometric tension of the aortic muscle at rest and its response to different stimuli are recorded on a Power Macintosh 6100 computer via a MacLab 8/S computer interface (CB Sciences, Inc. Milford, MA) after an initial amplification through a low- noise ETH-400 bioamplifier (CB Sciences, Inc. Milford, MA). Contractile responsiveness of the tissue strips is established with 10 μM phenylephrine, and the strips are incubated with the drug for 20 min to establish a steady level of contraction. To test the relaxation effects, test compounds are added to the phenylephrine precontracted strips in the tissue bath at cumulative concentrations of 0.1 μM to 0.1 mM. Concentration of test compounds is increased only after relaxation at the previous concentration reaches a 30 plateau level.

Rodent Stroke Assay

Blood flow into the middle cerebral artery (MCA) of male Sprague-Dawley rats was occluded by threading a small filament into the common carotid artery and advancing the tip to the

anterior carotid artery effectively occluding the origin of the MCA. After a 90-min occlusion period the filament was gently withdrawn to allow blood to reperfuse into the MCA. After a 70.5 hr reperfusion period, brains were removed and infarct volumes were assessed by 2,3,5-triphenyltetrazolium chloride (TTC) staining.

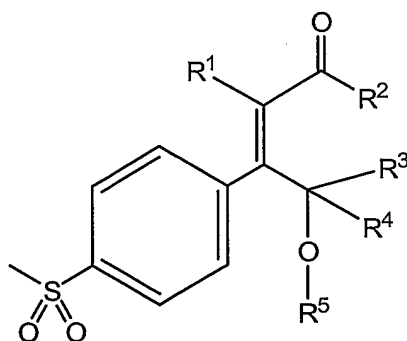
A compound of the invention was delivered as a 10mg/kg i.v. bolus followed by a 5mg/kg/hr constant i.v. infusion starting at the time of reperfusion. This dose was chosen to achieve steady-state parent compound concentrations in the brain corresponding to 10 X the parent compound's IC50 value in the human COX-2 whole blood assay. Vehicle controls were treated accordingly and a positive control was dosed i.p. 3mg/kg, 15 minutes prior to occlusion. Body temperature and limb flexion, which correlates well with infarct volume, were also recorded. All animals were evaluated on days 1, 2 and 3.

Results – Treatment with a compound of the invention produced a greater than 50% reduction in infarct volumes compared to vehicle controls. Limb flexion was also significantly improved by treatment with the compound of the invention in this tMCAO model.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

What is claimed is:

1. A compound of formula (I)



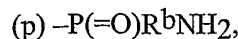
wherein:

R¹ is selected from the group consisting of

- (1) -Q-R^a,
- (2) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (3) -C₆₋₁₀ aryl, and
- (4) heteroaryl,

wherein said carbocyclic group, aryl and heteroaryl are unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) -NO₂,
- (d) -C₁₋₆ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) -C₁₋₆ alkoxy,
- (f) -C(=O)-(O)-R^b
- (g) -C(=O)-NR^bR^{b'}
- (h) -O-C(=O)-R^b
- (i) -S-C₁₋₆ alkyl,
- (j) -S(O)_xR^b,
- (k) -S(O)_xNR^bR^{b'},
- (l) -S(O)_xNR^bC(=O)C₁₋₆ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) -NR^bR^{b'},
- (n) -NR^b-C(=O)-R^{b'},
- (o) -P(=O)R^bOH, and



Q is selected from the group consisting of

- (a) $-O-$,
- (b) $-S-$,
- (c) $-SO_2-$,
- (d) $-NR^b$,

R^a , R^b and $R^{b'}$ are independently selected from the group consisting of:

- (a) hydrogen,
- (b) $-C_{1-10}$ alkyl,
- (c) $-C_{2-10}$ alkenyl,
- (d) $-C_{2-10}$ alkynyl,
- (e) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (f) $-C_{6-10}$ aryl, and
- (g) heteroaryl,

wherein said carbocyclic group, alkyl, alkenyl, alkynyl, aryl and heteroaryl are unsubstituted or substituted with one or more

- (i) halogen,
- (ii) cyano,
- (iii) $-NO_2$,
- (iv) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (v) $-C_{1-6}$ alkoxy,
- (vi) $-C(=O)-(O)-R^c$
- (vii) $-C(=O)-NR^cR^{c'}$
- (viii) $-O-C(=O)-R^c$
- (ix) $-S-C_{1-6}$ alkyl,
- (x) $-S(O)_xR^c$,
- (xi) $-S(O)_xNR^cR^{c'}$,
- (xii) $-S(O)_xNR^cC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (xiii) $-N R^cR^{c'}$,
- (xiv) $-NR^c-C(=O)-R^{c'}$,
- (xv) $-P(=O)R^cOH$,
- (xvi) $-P(=O)R^cNH_2$,

and R^c and $R^{c'}$ are independently selected from the group consisting of

- (A) hydrogen,
- (B) $-C_{1-10}$ alkyl,
- (C) $-C_{2-10}$ alkenyl,
- (D) $-C_{2-10}$ alkynyl,
- (E) a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,
- (F) $-C_{0-10}$ alkyl- C_{6-10} aryl, and
- (G) heteroaryl,

R^2 is selected from the group consisting of

- (1) $-OR^d$,
- (2) $-NR^dR^{d'}$,
- (3) phosphate group $-P(O)OR^dR^{cd'}$,
- (4) an amino acid,
- (5) nicotinic acid,
- (6) a saccharide, and
- (7) choline;

and R^d and $R^{d'}$ are selected from the same group as R^c and $R^{c'}$,

R^3 and R^4 are independently selected from the group consisting of

- (1) hydrogen,
- (2) $-C_{1-10}$ alkyl,
- (3) $-C_{2-10}$ alkenyl,
- (4) $-C_{2-10}$ alkynyl,
- (5) $-C_{6-10}$ aryl, or
- (6) heteroaryl,

wherein said alkyl, alkenyl, alkynyl, aryl and heteroaryl are unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) $-NO_2$,
- (d) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) $-C_{1-6}$ alkoxy,

- (f) $-C(=O)-(O)-R^e$
- (g) $-C(=O)-NR^eR^{e'}$
- (h) $-O-C(=O)-R^e$
- (i) $-S-C_{1-6}$ alkyl,
- (j) $-S(O)_xR^e$,
- (k) $-S(O)_xNR^eR^{e'}$,
- (l) $-S(O)_xNR^eC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-NR^eR^{e'}$,
- (n) $-NR^e-C(=O)-R^{e'}$,
- (o) $-P(=O)R^eOH$,
- (p) $-P(=O)R^eNH_2$,

or

R^3 and R^4 may be linked to form a carbocyclic group having from 3 to 8 ring atoms, optionally having from one to three ring heteroatoms selected from the group consisting of S, N and O,

wherein said carbocyclic group is unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) $-NO_2$,
- (d) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) $-C_{1-6}$ alkoxy,
- (f) $-C(=O)-(O)-R^e$
- (g) $-C(=O)-NR^eR^{e'}$
- (h) $-O-C(=O)-R^e$
- (i) $-S-C_{1-6}$ alkyl,
- (j) $-S(O)_xR^e$,
- (k) $-S(O)_xNR^eR^{e'}$,
- (l) $-S(O)_xNR^eC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-NR^eR^{e'}$,
- (n) $-NR^e-C(=O)-R^{e'}$,
- (o) $-P(=O)R^eOH$,
- (p) $-P(=O)R^eNH_2$,

and R^e and $R^{e'}$ are selected from the same group as R^c and $R^{c'}$,

R^5 is selected from the group consisting of

- (1) hydrogen,
- (2) $-C_{1-10}$ alkyl,
- (3) $-C_{2-10}$ alkenyl,
- (4) $-C_{2-10}$ alkynyl,
- (5) $-C_{0-10}$ alkyl- $C(=O)-R^f$,
- (6) $-C_{2-10}$ alkenyl- $C(=O)-R^f$,
- (7) $-C_{2-10}$ alkynyl- $C(=O)-R^f$,
- (8) $-C_{0-10}$ alkyl- $C(=O)-NR^fR^{f'}$,
- (9) $-C_{2-10}$ alkenyl- $C(=O)-NR^fR^{f'}$,
- (10) $-C_{2-10}$ alkynyl- $C(=O)-NR^fR^{f'}$,
- (11) a phosphate group $-P(O)OR^fOR^{f'}$,
- (12) an amino acid,
- (13) nicotinic acid,
- (14) a saccharide, and
- (15) choline;

wherein said alkyl, alkenyl and alkynyl, are unsubstituted or substituted with one or more

- (a) halogen,
- (b) cyano,
- (c) $-NO_2$,
- (d) $-C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (e) $-C_{1-6}$ alkoxy,
- (f) $-C(=O)-(O)-R^f$
- (g) $-C(=O)-NR^fR^{f'}$
- (h) $-O-C(=O)-R^f$
- (i) $-S-C_{1-6}$ alkyl,
- (j) $-S(O)_xR^f$,
- (k) $-S(O)_xNR^fR^{f'}$,
- (l) $-S(O)_xNR^fC(=O)C_{1-6}$ alkyl, wherein said alkyl is unsubstituted or substituted with one or more halogen,
- (m) $-NR^fR^{f'}$,
- (n) $-NR^f-C(=O)-R^{f'}$,
- (o) $-P(=O)R^fOH$,
- (p) $-P(=O)R^fNH_2$, and

and R^f and $R^{f'}$ are selected from the same group as R^c and $R^{c'}$,

x is 1 or 2;

wherein at least one of R^2 and R^5 is a phosphate group, an amino acid, nicotinic acid, a saccharide, or choline;

and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein R^1 is phenyl, which is unsubstituted or substituted with one or more halogen.

3. The compound of Claim 2 wherein R^1 is phenyl which is substituted with one or more halogen.

4. The compound of Claim 3 wherein R^1 is phenyl which is substituted with one or more fluoro.

5. The compound of Claim 1 wherein R^2 is $-OR^c$.

6. The compound of Claim 1 wherein R^2 is an amino acid.

7. The compound of Claim 6 wherein R^2 is selected from the group consisting of serine, threonine and tyrosine.

8. The compound of Claim 1 wherein either R^2 is or R^5 is selected from the group consisting of an amino acid, a saccharide and a choline.

9. The compound of Claim 1 wherein R^5 is an amino acid selected from the group consisting of glycine, alanine, arginine, asparagine, aspartic acid, glutamic acid, cystine, glutamine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine.

10. The compound of Claim 1 wherein R^2 is choline.

11. The compound of Claim 5 wherein R^c is selected from the group consisting of (1) hydrogen,

(2) -C₁₋₁₀ alkyl, wherein said alkyl is unsubstituted or substituted with one or more

- (a) -NR^bR^{b'},
- (b) -C(=O)-OR^b, and
- (c) -C(=O)-O(C₁₋₆ alkyl)-N(CH₃)₃.

12. The compound of Claim 1 wherein R³ and R⁴ are independently selected from the group consisting of

- (1) hydrogen, and
- (2) C₁₋₆ alkyl.

13. The compound of Claim 1 wherein R³ and R⁴ are each hydrogen.

14. The compound of Claim 1 which is selected from the group consisting of
 2-({(2Z)-4-(acetoxy)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl} oxy)-N,N,N-trimethylethanaminium;
 2-({(2Z)-4-(acetoxy)-2-(3-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoyl} oxy)-N,N,N-trimethylethanaminium;
 O-[(2Z)-4 acetyloxy-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-oxo-2-butenyl]-L-serine ethyl ester mono(trifluoroacetate);
 L-aspartic acid 4-[(2Z)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxo-2-butenyl] ester;
 (2Z)-3-(3,4-difluorophenyl)-4-ethoxy-2-[4-(methylsulfonyl)phenyl]-4-oxobut-2-en-1-yl lysinate;
 (2Z)-4-{[N~5~-(diaminomethyl)ornithyl]oxy}-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]but-2-enoic acid;
 (2Z)-4-acetoxy-2-(3-fluorophenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-pent-2-enoic acid;
 Diethyl N-[(2Z)-4-(acetyloxy)-2-(3-fluorophenyl)-4-methyl-3-[4-(methylsulfonyl)phenyl]pent-2-enoyl]cystinate; and
 (2Z)-2-(3,4-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-4-[(pyridin-3-ylcarbonyl)oxy]but-2-enoic acid..

15. A method of treating stroke, comprising administering a compound of Claim 1 to a patient in need thereof.

16. The method of Claim 16, wherein the patient is an acute stroke patient.

17. A pharmaceutical composition suitable for intravenous administration, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

18. A method of treating stroke, comprising administering a composition of Claim 18 to a patient in need thereof.

19. The method of Claim 18, wherein the patient is an acute stroke patient.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/36031

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) : C07D 211/32, 69/76, 69/773; A61K 31/4406; 31/24; 31/235

US CL : 514/356, 532, 533; 546/322; 560/8, 17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/356, 532, 533; 546/322; 560/8, 17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN International, HCAPLUS Database; EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	SMITH et al Water soluble prodrug of a COX-2 selective inhibitor suitable for intravenous administration in models of cerebral ischemia Bioorganic & Medicinal Chemistry Letters (2005) Vol. 15 Issue 13 pages 3197-3200, especially page 3198.	1-19
A	US 5,849,943 A (ATKINSON et al) 15 Dec 1998 (15.12.1998), col. 25, lines 1-60.	1-19
A	US 5,733,909 A (BLACK et al) 31 March 1998 (31.03.1998), col. 27, lines 45-67 and col. 28, lines 1-60.	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 January 2006 (28.01.2006)

Date of mailing of the international search report

22 MAR 2006

Name and mailing address of the ISA/US

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