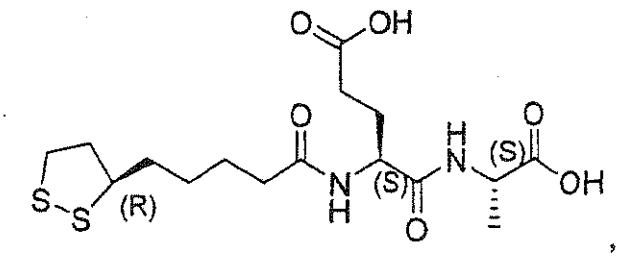
J., Myocardial reperfusion injury. *New England Journal of Medicine* 2007, 357:1121).

The prevalence of cardiovascular disease in the United States, and throughout the world, necessitates the development of therapies and therapeutic agents that can effectively prevent, reduce, or counteract ischemia and ischemia-reperfusion injury resulting from a heart attack or stroke. Current therapies for treating ischemia and ischemia-reperfusion injury caused by myocardial infarction, such as mechanical ischemic preconditioning, have proven to be clinically impractical, while other therapies, such as antagonists to block the influx of calcium and scavengers of reactive oxygen species, have yielded disappointing clinical outcomes (Otani, H., Ischemic preconditioning: From molecule mechanisms to therapeutic opportunities. *Antioxidants & Redox Signaling*, 2008, 10:207; Yellon, D. M., Hausenloy, D. J., Myocardial reperfusion injury. *New England Journal of Medicine* 2007, 357:1121).

Thus, there is a significant need for new and more effective therapies and therapeutic agents for the treatment of ischemia and ischemia-reperfusion injuries resulting from cardiovascular disease and other conditions.

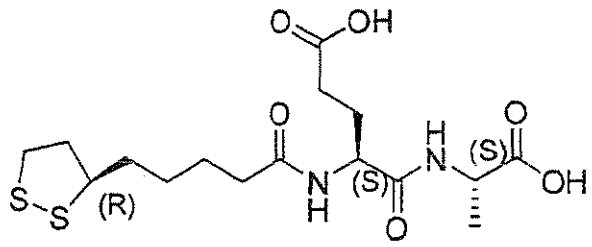
SUMMARY OF THE INVENTION

In a first aspect, the present invention refers to a composition comprising a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein the compound or pharmaceutically acceptable salt thereof is at least 90% enantiomerically pure.

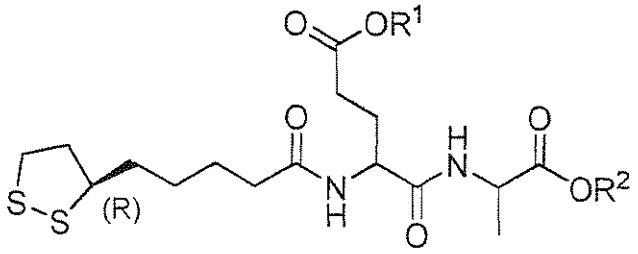
In a second aspect, the present invention refers to a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein the compound has a percent optical purity of at least 90% by weight relative to the other stereoisomers.

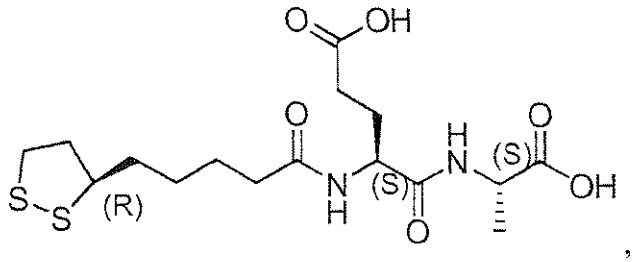
The invention described herein addresses a need for treating ischemia, ischemic injury and ischemia-reperfusion injury, including myocardial ischemia and ischemia-reperfusion injury, by activating kinases involved in cell signaling pathways that inhibit apoptosis and by scavenging reactive oxygen species. In particular, the present invention describes~~relates to~~ compositions comprising the disclosed compounds, or pharmaceutically acceptable salts thereof, and their effective use as activators of cytoprotective kinases.

In one example~~embodiment~~, the disclosure~~invention~~ describes~~relates to~~ compositions comprising a substantially pure compound represented by Structural Formula I:



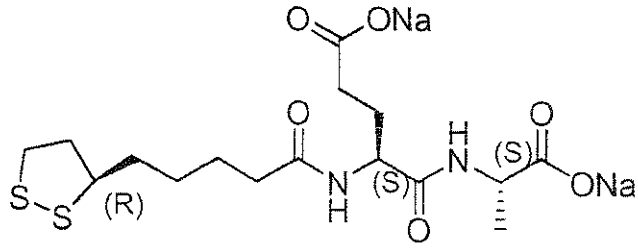
wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof.

In another example~~embodiment~~, the invention describes~~relates to~~ compositions comprising a substantially pure compound represented by Structural Formula II:

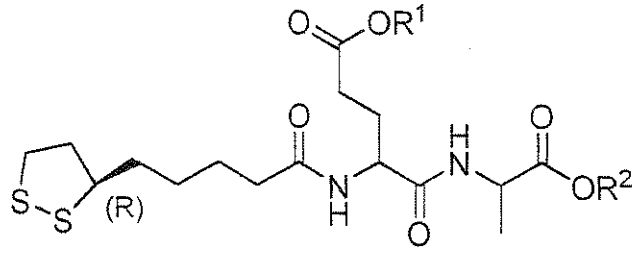


or a pharmaceutically acceptable salt thereof.

In a further example~~embodiment~~, the invention describes~~relates to~~ compositions comprising a substantially pure compound represented by Structural Formula III:

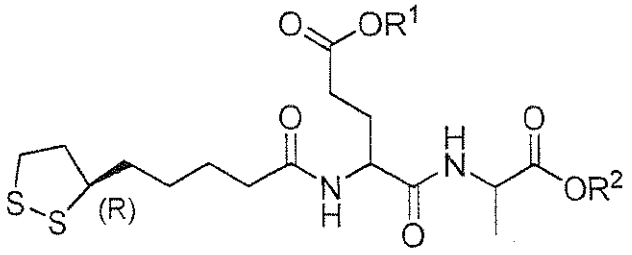


In another example~~embodiment~~, the invention describes~~relates to~~ a composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) a substantially pure compound represented by Structural Formula I:



wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof.

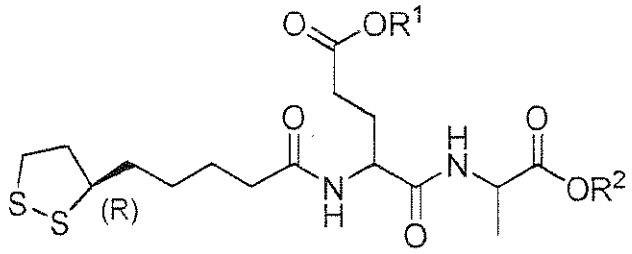
In an additional example~~embodiment~~, the invention describes~~relates to~~ a method of activating at least one cytoprotective kinase (*e.g.*, Akt kinase, IRK kinase, IGF1R kinase, Src kinase) in a cell, comprising contacting the cell with an effective amount of a compound represented by Structural Formula I:



,

wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof. In a particular example~~embodiment~~, the cytoprotective kinase is Akt kinase, or a kinase that functions in the same cell signaling pathway as Akt kinase (*e.g.*, IRK kinase).

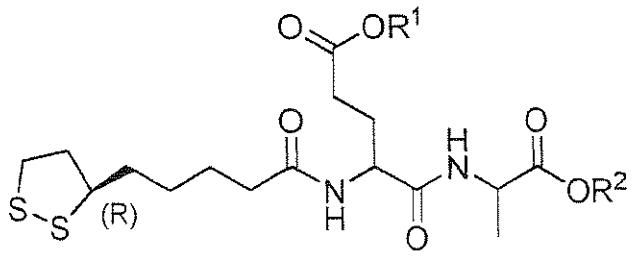
In another example~~embodiment~~, the invention describes~~relates to~~ a method of treating an ischemia or ischemia-reperfusion injury in a mammalian subject, comprising administering to the subject an effective amount of a compound represented by Structural Formula I:



,

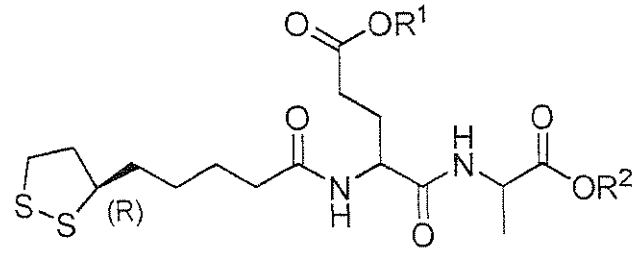
wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof. In a particular example~~embodiment~~, the ischemia or ischemia-reperfusion injury is a myocardial ischemia or ischemia-reperfusion injury.

In yet another example~~embodiment~~, the invention describes~~relates to~~ a method of inhibiting apoptosis in a subject, comprising administering to the subject an effective amount of a compound represented by Structural Formula I:



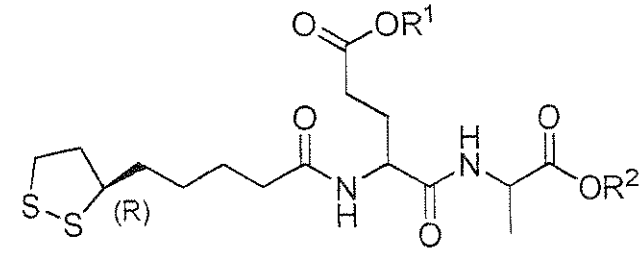
wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof.

In a further example~~embodiment~~, the invention describes~~relates to~~ a method of preventing cytosolic calcium overload in a subject, comprising administering to the subject an effective amount of a compound represented by Structural Formula I:



wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof.

In another example~~embodiment~~, the invention describes~~relates to~~ a method of increasing peroxyl radical absorbance in a subject (*e.g.*, a subject suffering from ischemia), comprising administering to the subject an effective amount of a compound represented by Structural Formula I:



wherein R^1 and R^2 are each independently H or a hydrolyzable group, or a pharmaceutically acceptable salt thereof.

In a third aspect, the present invention refers to a composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) a composition as defined above, or a compound as defined above, or a pharmaceutically acceptable salt thereof.

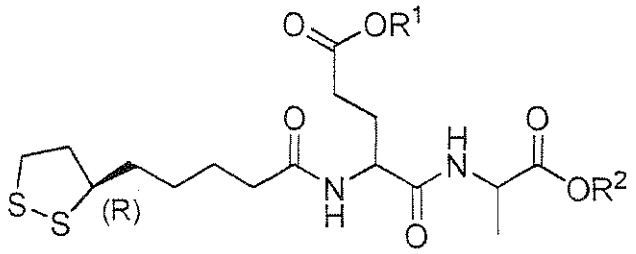
In a fourth aspect, the present invention refers to a composition as defined above, or a compound as defined above, for use in treating an ischemic injury or an ischemia reperfusion injury in a subject in need thereof.

In a fifth aspect, the present invention refers to a composition as defined above, or a compound as defined above, for use in treating an ischemic injury or an ischemia reperfusion injury in a subject in need thereof, the method comprising administering to the subject a single dose of the compound or a pharmaceutically acceptable salt.

In a sixth aspect, the present invention refers to a composition as defined above , or a compound as defined above, for use in a method for treating an ischemic injury or an ischemia-reperfusion injury consequent to a therapeutic intervention in a subject in need thereof, the method comprising administering to the subject at least two doses of the compound, or a pharmaceutically acceptable salt thereof, wherein a non-final dose of the compound and a final dose of the compound are administered to the subject prior to the therapeutic intervention, and wherein: (a) the final dose is administered to the subject at a time point within about two half-lives of the compound prior to the therapeutic intervention; and (b) the non-final dose is administered to the subject at a time point that is at least about four half-lives of the compound prior to administration of the final dose.

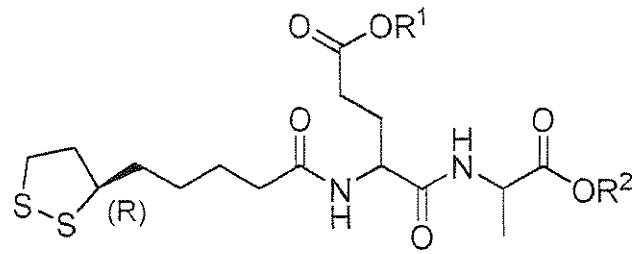
In another example~~mbodiment~~, the invention describes~~provides for~~ a method of treating ischemia, an ischemic injury or an ischemia-reperfusion injury in a mammalian subject comprising a multi-dose administration of the compounds described herein.

In a particular example~~embodiment~~, the invention describes~~relates to~~ a method for treating an ischemic injury or an ischemia-reperfusion injury in a subject in need thereof, comprising administering to the subject at least two doses of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group and the compound, or pharmaceutically acceptable salt thereof, is at least 90% enantiomerically pure. The method comprises administering a non-final dose of the compound or pharmaceutically acceptable salt thereof and a final dose of the compound or pharmaceutically acceptable salt thereof to the subject. As described herein, the final dose is administered immediately prior to the injury, and the non-final dose and the final dose are administered at a dosage interval that potentiates the efficacy of the compound for treating the injury relative to a single-dose administration of the compound.

In yet another example~~embodiment~~, the invention describes~~provides~~ a method for treating an ischemic injury or an ischemia-reperfusion injury in a subject in need thereof, comprising administering to the subject at least two doses of a compound represented by the following structural formula:

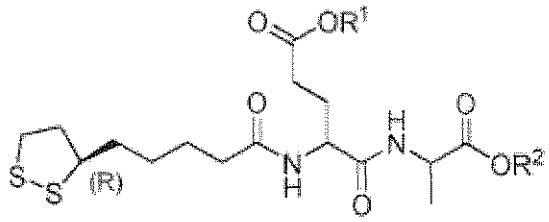


or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group and the compound, or pharmaceutically acceptable salt thereof, is at least 90% enantiomerically pure. The

CLAIMS

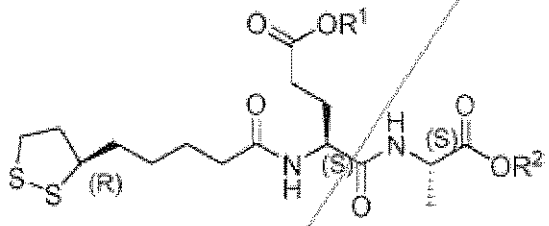
What is claimed is:

1. A composition comprising a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group, and wherein the compound or pharmaceutically acceptable salt thereof is at least 90% enantiomerically pure.

2. The composition of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group.

3. The composition of Claim 1, wherein the hydrolyzable group is selected from the group consisting of $(C_1\text{-}C_{10})$alkyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_1\text{-}C_{10})$alkoxy$(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_{10})$alkoxy$(C_1\text{-}C_{10})$alkoxy$(C_1\text{-}C_{10})$alkyl, aryl and aryl$(C_1\text{-}C_{10})$alkyl, wherein each is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, nitro, cyano, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, amino, $(C_1\text{-}C_6)$alkylamino,

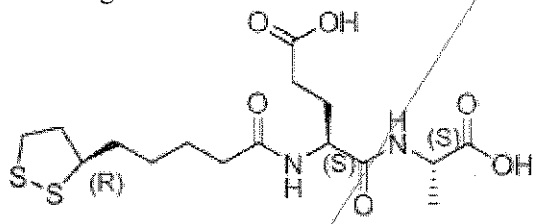
di(C_1-C_6)alkylamino, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, morpholino, phenyl, and benzyl.

4. The composition of Claim 2, wherein the hydrolyzable group is selected from the group consisting of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, allyl, ethoxymethyl, methoxyethyl, methoxyethoxymethyl, methoxyethoxyethyl, benzyl, pentafluorophenyl, 2-N-(morpholino)ethyl, dimethylaminoethyl and para-methoxybenzyl.

5. The composition of Claim 1, wherein the pharmaceutically acceptable salt comprises a monovalent cation or a divalent cation.

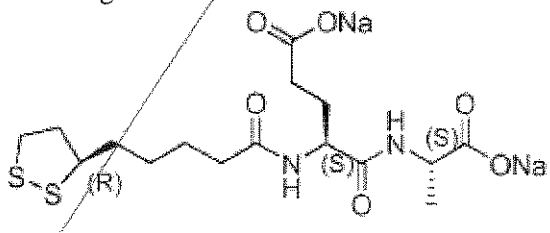
6. The composition of Claim 5, wherein the monovalent cation is a monovalent metal cation and the divalent cation is a divalent metal cation.

7. The composition of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

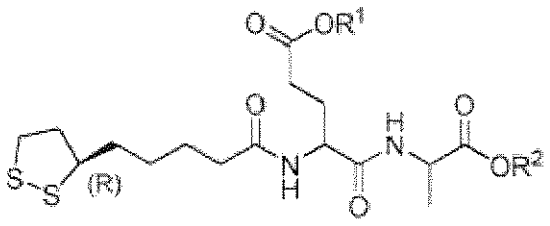
8. The composition of Claim 1, wherein the compound is represented by the following structural formula:



9. A composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

10. A composition of any one of Claims 1-9 for use in treating an ischemic injury or an ischemia-reperfusion injury in a subject in need thereof.

11. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group and the compound, or pharmaceutically acceptable salt thereof, is at least 90% enantiomerically pure, for use in treating an ischemic injury or an ischemia-reperfusion injury in a subject in need thereof, wherein said compound is to be administered in at least two doses, comprising

a non-final dose of the compound, or a pharmaceutically acceptable salt thereof, and a final dose of the compound, or a pharmaceutically acceptable salt thereof, prior to the injury, and wherein:

(a) the final dose is to be administered immediately prior to the injury; and

(b) the non-final dose and the final dose are to be administered at a dosage interval that potentiates the efficacy of the compound for treating the injury relative to a single-dose administration of the compound.

12. The compound of Claim 11, wherein the dosage interval between the non-final dose and the final dose is at least about 4 hours.

13. The compound of Claim 12, wherein the dosage interval between the non-final dose and the final dose is at least about 6 hours.

14. The compound of Claim 13, wherein the dosage interval between the non-final dose and the final dose is at least about 8 hours.

15. The compound of any one of Claims 11-14, wherein the final dose is to be administered to the subject at a time point in the range of about 0 minutes to about 90 minutes prior to the injury.

16. The compound of Claim 15, wherein the final dose is to be administered to the subject at least about 30 minutes prior to the injury.

17. The compound of Claim 16, wherein the final dose is to be administered to the subject at least about 60 minutes prior to the injury.

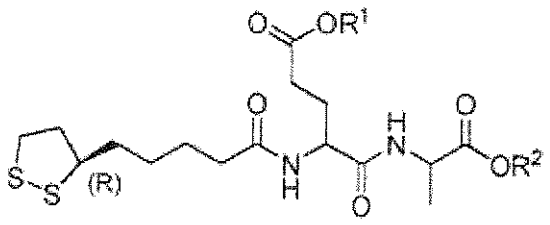
18. The compound of any one of Claims 11-17, wherein the compound, or pharmaceutically acceptable salt thereof, has a concentration that is less than 10% of its C_{max} in a blood sample obtained from the subject after administration of the non-final dose and immediately prior to administration of the final dose.

19. The compound of any one of Claims 11-18, wherein the non-final dose is to be administered to the subject at a time point within about 48 hours prior to the injury.

20. The compound of any one of Claims 11-19, wherein one or more additional doses of the compound is to be administered to the subject prior to administration of the non-final dose.

21. The compound of Claim 20, wherein three doses of the compound are to be administered to the subject prior to the injury.

22. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 in the compound are each independently H or a hydrolyzable group and the compound, or pharmaceutically acceptable salt thereof, is at least 90% enantiomerically pure, for use in treating an ischemic injury or an ischemia-reperfusion injury in a subject in need thereof, wherein said compound is to be administered in at least two doses, comprising

a non- final dose of the compound, or a pharmaceutically acceptable salt thereof, and a final dose of the compound, or a pharmaceutically acceptable salt thereof, prior to the injury, and wherein:

(a) the final dose is to be administered to the subject at a time point within about two half- lives of the compound prior to the injury; and

(b) the non- final dose is to be administered to the subject at a time point that is at least about four half- lives of the compound prior to administration of the final dose.

23. The compound of Claim 22, wherein the final dose is to be administered to the subject at a time point in the range of about 0.25 half- lives to about 2 half- lives of the compound prior to the injury.

24. The compound of Claim 23, wherein the final dose is to be administered to the subject about one half-life of the compound prior to the injury.

25. The compound of any one of Claims 22-24, wherein the compound, or pharmaceutically acceptable salt thereof, has a concentration that is less than 10% of its C_{max} in a blood sample obtained from the subject after administration of the non-final dose and immediately prior to administration of the final dose.

26. The compound of any one of Claims 22-25, wherein one or more additional doses of the compound is to be administered to the subject prior to the non-final dose.

27. The compound of any one of Claims 11-26, wherein one or more additional doses of the compound is to be administered to the subject after the injury.

28. The compound of any one of Claims 11-27, wherein each dose is equivalent.

29. The compound any one of Claims 11-28, wherein the compound is to be administered intravenously and each dose has a concentration ranging from about 0.5 mg/kg to about 5.0 mg/kg.

30. The compound of any one of Claims 11-29, wherein the ischemic injury is a myocardial ischemic injury.

31. The compound of any one of Claims 11-30, wherein the ischemic injury is consequent to an ischemia selected from the group consisting of a cardiovascular ischemia, a cerebrovascular ischemia, a renal ischemia, a hepatic ischemia, a ischemia-reperfusion cardiomyopathy, a cutaneous ischemia, a bowel ischemia, an intestinal ischemia, a gastric ischemia, a pulmonary ischemia, a pancreatic ischemia, a skeletal muscle ischemia, an abdominal muscle ischemia, a limb ischemia, an ischemia-reperfusion colitis, a mesenteric ischemia and a silent ischemia.

32. The compound of any one of Claims 11-29, wherein the ischemia-reperfusion injury is a myocardial ischemia-reperfusion injury.

33. The compound of Claim 32, wherein the myocardial ischemia-reperfusion injury is consequent to a myocardial infarction.

34. The compound of Claim 33, wherein the myocardial infarction is an acute myocardial infarction.

35. The compound of any one of Claims 11-29, wherein the ischemia-reperfusion injury is a cerebral ischemia-reperfusion injury.

36. The compound of Claim 35, wherein the cerebral ischemia-reperfusion injury is consequent to a stroke.

37. The compound of any one of Claims 11-29, wherein the ischemia-reperfusion injury is selected from the group consisting of a cerebrovascular ischemia-reperfusion injury, a renal ischemia-reperfusion injury, a hepatic ischemia-reperfusion injury, an ischemia-reperfusion cardiomyopathy, a cutaneous ischemia-reperfusion injury, a bowel ischemia-reperfusion injury, an intestinal ischemia-reperfusion injury, a gastric ischemia-reperfusion injury, a pulmonary ischemia-reperfusion injury, a pancreatic ischemia-reperfusion injury, a skeletal muscle ischemia-reperfusion injury, an abdominal muscle ischemia-reperfusion injury, a limb ischemia-reperfusion injury, ischemia- reperfusion colitis, a mesenteric ischemia-reperfusion injury and a silent ischemia-reperfusion injury.

38. The compound of any one of Claims 11-37, wherein the injury includes perioperative cardiac damage.

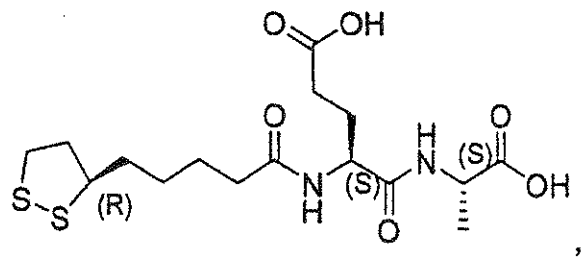
39. The compound of any one of Claims 11-38, wherein the injury is consequent to a therapeutic intervention.

40. The compound of Claim 39, wherein the therapeutic intervention is selected from the group consisting of a coronary artery bypass graft surgery, a coronary angioplasty surgery, a transplant surgery and a cardiopulmonary bypass surgery.

41. The compound of any one of Claims 11-40, wherein the subject is a human.

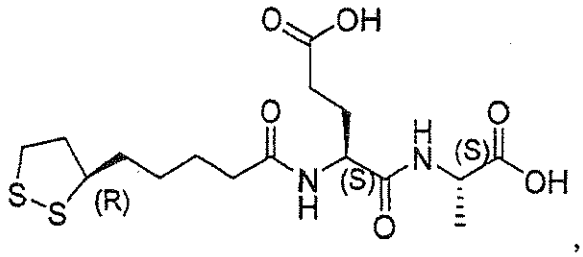
Claims

1. A composition comprising a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein the compound or pharmaceutically acceptable salt thereof is at least 90% enantiomerically pure.

2. A compound represented by the following structural formula:

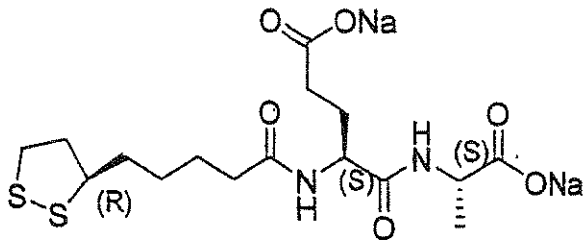


or a pharmaceutically acceptable salt thereof, wherein the compound has a percent optical purity of at least 90% by weight relative to the other stereoisomers.

3. The composition of Claim 1, or the compound of Claim 2, wherein the pharmaceutically acceptable salt comprises a monovalent cation or a divalent cation.

4. The composition or compound of Claim 3, wherein the monovalent cation is a monovalent metal cation and the divalent cation is a divalent metal cation.

5. The composition of Claim 1, or the compound of Claim 2, wherein the compound is represented by the following structural formula:



6. The compound of Claim 2, wherein the compound has a percent optical purity by weight of at least 99%.

7. A composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) a composition according to any one of Claims 1 and 3 to 5, or a compound of Claims 2 to 6, or a pharmaceutically acceptable salt thereof.

8. A composition as defined in any one of Claims 1 and 3 to 5, or a compound as defined in any one of Claims 2 to 6, for use in treating an ischemic injury or an ischemia reperfusion injury in a subject in need thereof.

9. A composition as defined in any one of Claims 1 and 3 to 5, or a compound as defined in any one of Claims 2 to 6, for use in treating an ischemic injury or an ischemia reperfusion injury in a subject in need thereof, the method comprising administering to the subject a single dose of the compound or a pharmaceutically acceptable salt.

10. A composition as defined in any one of Claims 1 and 3 to 5, or a compound as defined in any one of Claims 2 to 6, for use in a method for treating an ischemic injury or an ischemia-reperfusion injury consequent to a therapeutic intervention in a subject in need thereof, the method comprising administering to the subject at least two doses of the compound, or a pharmaceutically acceptable salt thereof, wherein a non-final dose of the compound and a final dose of the compound are administered to the subject prior to the therapeutic intervention, and wherein:

    (a) the final dose is administered to the subject at a time point within about two half-lives of the compound prior to the therapeutic intervention; and
    (b) the non-final dose is administered to the subject at a time point that is at least about four half-lives of the compound prior to administration of the final dose.

11. The composition or compound for use according to Claim 10, wherein the final dose is administered to the subject at a time point in the range of about 0.25 half-lives to about 2 half-lives of the compound prior to the therapeutic intervention,
optionally wherein the final dose is administered to the subject about one half-life of the compound prior to the therapeutic intervention.

12. The composition or compound for use according to Claim 10 or Claim 11, wherein:

    the method further comprises administering one or more additional doses of the compound to the subject prior to the non-fmal dose;
    the method further comprises administering one or more additional doses of the compound to the subject after the therapeutic intervention;
    each dose is equivalent; and/or
    the compound is administered intravenously and each dose has a concentration ranging from about 0.5 mg/kg to about 5.0 mg/kg.

13. The composition or compound for use according to any one of Claims 8 to 12, wherein the ischemic injury is a myocardial ischemic injury.

14. The composition or compound for use according to any one of Claims 8 to 13, wherein the ischemic injury is consequent to an ischemia selected from the group consisting of a cardiovascular ischemia, a cerebrovascular ischemia, a renal ischemia, a hepatic ischemia, a ischemia-reperfusion cardiomyopathy, a cutaneous ischemia, a bowel ischemia, an intestinal ischemia, a gastric ischemia, a pulmonary ischemia, a pancreatic ischemia, a skeletal muscle ischemia, an abdominal muscle ischemia, a limb ischemia, an ischemia-reperfusion colitis, a mesenteric ischemia and a silent ischemia.

15. The composition or compound for use according to Claim 14, wherein the ischemic injury is consequent to a renal ischemia.

16. The composition or compound for use according to any one of Claims 10-12, wherein the therapeutic intervention is selected from the group consisting of a coronary artery bypass graft surgery, a coronary angioplasty surgery, a transplant surgery and a cardiopulmonary bypass surgery.

17. The composition or compound for use according to any one of Claims 10-12, wherein the therapeutic intervention is a kidney transplant.