reticulum Ca^{2+} overload causes mitochondrial-dependent cell death in ventricular myocytes. *Circ Res* 2005, *97*:1009; Lopes-Neblina, F., Toledo, A.H., Toledu-Pereyra, L.H. Molecular biology of apoptosis in ischemia and reperfusion. *J Invest Surg* 2005, *18*:335). However, treatment of patients with acute myocardial infarction with antagonists that block the influx of calcium or with scavengers of the reactive oxygen species has yielded disappointing clinical outcomes (Yellon, D. M., Hausenloy, D. J., Myocardial reperfusion injury. *New England Journal of Medicine* 2007, *357*:1121).

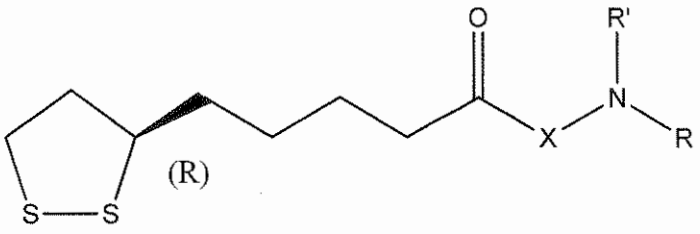
Another strategy for reducing ischemia-reperfusion injury is termed ischemic preconditioning. Short repeated bouts of ischemia followed by reperfusion will condition the myocardium to withstand a prolonged bout of ischemia (Otani, H., Ischemic preconditioning: From molecule mechanisms to therapeutic opportunities. *Antioxidants & Redox Signaling*, 2008, *10*:207). However, intentionally occluding a patient's coronary artery is associated with undue risks and is therefore undesirable.

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~~

The disclosure~~invention~~ described herein addresses a need for treating ischemia, ischemic injury and ischemia-reperfusion injury, including myocardial ischemia. In particular, the present invention relates to compositions comprising the disclosed compounds, or pharmaceutically acceptable salts or prodrugs thereof, and methods of using the disclosed compounds, or pharmaceutically acceptable salts or prodrugs thereof, to treat ischemia, ischemic injury, ischemia-reperfusion injury, and related conditions.

The compounds of the present disclosure~~invention~~ are represented by Structural Formula (I):

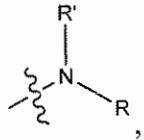


(I),

or a pharmaceutically acceptable salt or prodrug thereof, substantially separated from the (S)-lipoyl stereoisomer(s), or a pharmaceutically acceptable salt or prodrug thereof wherein:

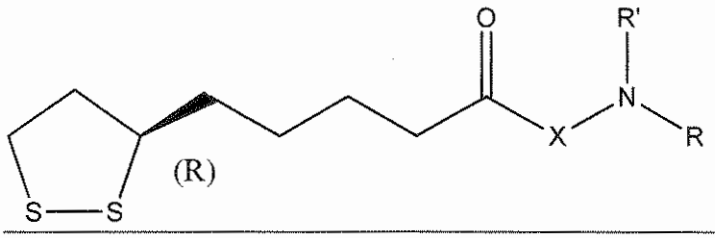
R is $(C_1\text{-}C_{18})$alkyl, $(C_6\text{-}C_{18})$aryl or $(C_6\text{-}C_{18})$aryl$(C_1\text{-}C_{18})$alkyl and is substituted with at least one acidic substituent selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH, wherein the aryl of the $(C_6\text{-}C_{18})$aryl or $(C_6\text{-}C_{18})$aryl$(C_1\text{-}C_{18})$alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, cyano, nitro, $(C_1\text{-}C_3)$alkoxy and thio(C_1C_3)alkyl;

R' is hydrogen or $(C_1\text{-}C_{18})$alkyl, wherein $(C_1\text{-}C_{18})$alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH; and

X is absent or is an amino acid, wherein the amino acid is oriented to form an amide linkage with 

, provided that the compound of Structural Formula (I) is not *N*-(R)-lipoyl-glutamylalanine, *N*-(R)-lipoyl-aminoethylphosphonic acid, or (R)-5-(5-(1,2-dithiolan-3-yl)pentanamido)-2-hydroxybenzoic acid.

In a first aspect, there is provided a compound represented by Structural Formula (I):



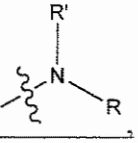
(I),

or a pharmaceutically acceptable salt thereof, wherein:

the enantiomeric excess or diastereomeric excess of the compound or pharmaceutically acceptable salt thereof is at least 90%;

R is (C_1-C_{18})alkyl, (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl and is substituted with at least one acidic substituent selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH, wherein the aryl of the (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, cyano, nitro, (C_1-C_3)alkoxy and thio(C_1-C_3)alkyl;

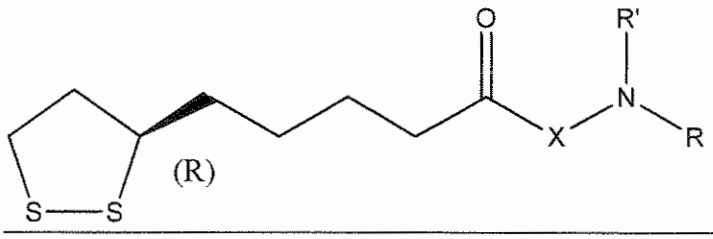
R' is hydrogen or (C_1-C_{18})alkyl, wherein (C_1-C_{18})alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH; and

X is absent or is an amino acid, wherein the amino acid is aspartic acid, tyrosine, glutamic acid or alanine and is oriented to form an amide linkage with 

,

provided that the compound of Structural Formula (I) is not *N*-(R)-lipoyl-glutamylalanine, *N*-(R)-lipoyl-aminoethylphosphonic acid, or (R)-5-(5-(1,2-dithiolan-3-yl)pentanamido)-2-hydroxybenzoic acid.

In a second aspect, there is provided a compound represented by Structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

the enantiomeric excess or diastereomeric excess of the compound or pharmaceutically acceptable salt thereof is at least 90%;

R is (C_1-C_{18})alkyl, (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl and is substituted with at least one acidic substituent selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH, wherein the aryl of the (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, cyano, nitro, (C_1-C_3)alkoxy and thio(C_1-C_3)alkyl;

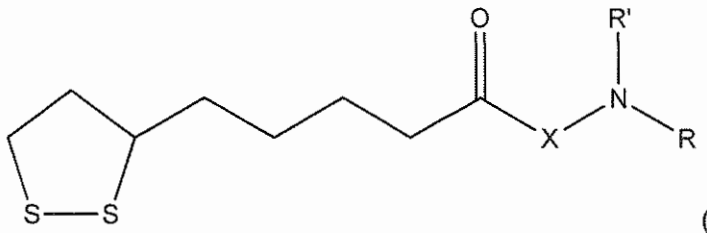
R' is hydrogen or (C_1-C_{18})alkyl, wherein (C_1-C_{18})alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH; and

X is absent,

provided that the compound of Structural Formula (I) is not *N*-(R)-lipoyl-aminoethylphosphonic acid, or (R)-5-(5-(1,2-dithiolan-3-yl)pentanamido)-2-hydroxybenzoic acid.

In a third aspect, there is provided a composition, comprising a pharmaceutically acceptable carrier or diluent and one or more compounds as defined herein, or a pharmaceutically acceptable salt thereof.

The present disclosure~~invention~~ also provides a method of treating ischemic injury or ischemia-reperfusion injury in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by Structural Formula (Ia):

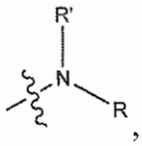


(Ia),

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R is (C_1-C_{18})alkyl, (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl and is substituted with at least one acidic substituent selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH, wherein the aryl of the (C_6-C_{18})aryl or (C_6-C_{18})aryl(C_1-C_{18})alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, (C_1-C_3)alkyl, halo(C_1-C_3)alkyl, cyano, nitro, (C_1-C_3)alkoxy and thio(C_1-C_3)alkyl;

R' is hydrogen or (C_1-C_{18})alkyl, wherein (C_1-C_{18})alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of -CO_2H, -SO_3H, -PO_3H_2, -OSO_3H, -OPO_3H_2, -$B(OH)_2$ and -NHOH; and

X is absent or is an amino acid, wherein the amino acid is oriented to form an amide linkage with , provided that the compound of Structural Formula (Ia) is not *N*-lipoyl-glutamylalanine, *N*-lipoyl-aspartylglycine, *N*-lipoyl-glutamylglycine or 5-(5-(1,2-dithiolan-3-yl)pentanamido)-2-hydroxybenzoic acid.

In another embodiment, the disclosure~~invention~~ relates to a method of inhibiting cell death in a subject, comprising administering to the subject an effective amount of a compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof.

In yet another embodiment, the disclosure~~invention~~ relates to a method of inhibiting cell death in a cell, tissue or organ, wherein the cell, tissue or organ has experienced an ischemia or other condition or disorder that results in excessive or unwanted cell death, comprising administering to the cell, tissue or organ an effective amount of a

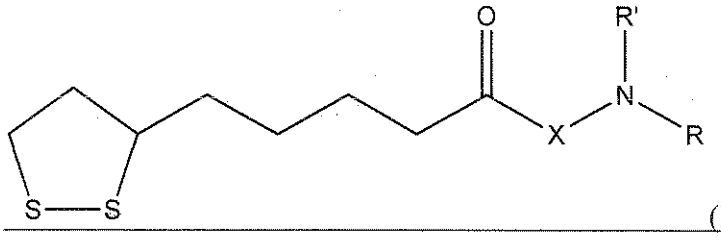
compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof.

Also included in the present disclosure~~invention~~ is the use of a compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof, for treating ischemic injury or ischemia-reperfusion injury in a subject.

In another embodiment, the disclosure~~invention~~ relates to the use of a compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof, for inhibiting cell death in a subject.

The present disclosure~~invention~~ also includes the use of a compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for treating ischemic injury or ischemia-reperfusion injury in a subject.

In a fourth aspect, there is provided the use of an effective amount of a compound represented by Structural Formula (Ia):

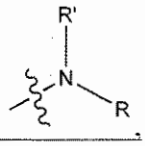


(Ia),

or a pharmaceutically acceptable salt thereof, wherein:

R is $(C_1$-$C_{18})$alkyl, $(C_6$-$C_{18})$aryl or $(C_6$-$C_{18})$aryl$(C_1$-$C_{18})$alkyl and is substituted with at least one acidic substituent selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH, wherein the aryl of the $(C_6$-$C_{18})$aryl or $(C_6$-$C_{18})$aryl$(C_1$-$C_{18})$alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, $(C_1$-$C_3)$alkyl, halo$(C_1$-$C_3)$alkyl, cyano, nitro, $(C_1$-$C_3)$alkoxy and thio$(C_1$-$C_3)$alkyl;

R' is hydrogen or $(C_1$-$C_{18})$alkyl, wherein $(C_1$-$C_{18})$alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH; and

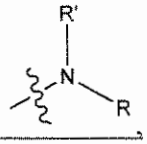
X is an amino acid, wherein the amino acid is oriented to form an amide linkage with ,

provided that the compound of Structural Formula (Ia) is not *N*-lipoyl-glutamylalanine, *N*-lipoyl-aspartylglycine, or *N*-lipoyl-glutamylglycine; or

the compound is an (R)-lipoyl stereoisomer of a compound represented by Structural Formula (Ia), or a pharmaceutically acceptable salt thereof and the enantiomeric excess or diastereomeric excess of the compound or pharmaceutically acceptable salt thereof is at least 90%; and

R is $(C_1\text{-}C_{18})$alkyl, $(C_6\text{-}C_{18})$aryl or $(C_6\text{-}C_{18})$aryl$(C_1\text{-}C_{18})$alkyl and is substituted with at least one acidic substituent selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH, wherein the aryl of the $(C_6\text{-}C_{18})$aryl or $(C_6\text{-}C_{18})$aryl$(C_1\text{-}C_{18})$alkyl is optionally further substituted with one or more substituents selected from the group consisting of hydroxy, halo, $(C_1\text{-}C_3)$alkyl, halo$(C_1\text{-}C_3)$alkyl, cyano, nitro, $(C_1\text{-}C_3)$alkoxy and thio$(C_1\text{-}C_3)$alkyl;

R' is hydrogen or $(C_1\text{-}C_{18})$alkyl, wherein $(C_1\text{-}C_{18})$alkyl is optionally substituted with one or more acidic substituents selected from the group consisting of $-CO_2H$, $-SO_3H$, $-PO_3H_2$, $-OSO_3H$, $-OPO_3H_2$, $-B(OH)_2$ and -NHOH; and

X is absent or is an amino acid, wherein the amino acid is oriented to form an amide linkage with ,

provided that the compound of Structural Formula (Ia) is not *N*-lipoyl-glutamylalanine, *N*-lipoyl-aspartylglycine, *N*-lipoyl-glutamylglycine or 5-(5-(1,2-dithiolan-3-yl)pentanamido)-2-hydroxybenzoic acid in the manufacture of a medicament for treating ischemic injury or ischemia reperfusion injury in a subject in need thereof.

The disclosure~~invention~~ also includes the use of a compound represented by Structural Formula (I) and/or (Ia), or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for inhibiting cell death in a subject.

The compounds (also referred to herein as "the disclosed compounds"), compositions and methods of the present disclosure~~invention~~ are efficacious for

treating tissue damage resulting from ischemia and ischemic injuries, including ischemia-reperfusion injuries.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The disclosed compounds may exist in various stereoisomeric forms unless otherwise specified. "Stereoisomers" are compounds that differ only in their spatial arrangement. "Enantiomers" are pairs of stereoisomers that are non-superimposable mirror images of one another, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center.

"Diastereomers" are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted