15Lox1 Inhibitors For Stroke
Tech ID: 33579 / UC Case 2021-597-0

BACKGROUND

Stroke is a leading cause of mortality and disability worldwide and the economic costs of treatment and post-stroke care are substantial. Every year, more than 14 million people are affected by stroke, and over 6 million stroke patients die from this condition and associated complications.

2-(2,3,5-trisubstituted phenyl)oxazole compounds potently inhibit 12/15-LOX. Hence, the compounds of this disclosure are advantageously useful to treat or prevent various disorders where 12/15-LOX is implicated in the pathology of the disorder (e.g., stroke).

TECHNOLOGY DESCRIPTION

In collaboration with researchers at Partners Healthcare, UCSC Researchers helped develop compounds that inhibit 12/15 Lipoxygenase

\[
\begin{array}{c}
\text{R}^2 \quad \text{R}^1 \\
\text{X}^1 \quad \text{N} \\
\text{R}^4 \\
\text{R}^3
\end{array}
\]

X1 is selected from O and S;
R1, R2, and R3 are each independently selected from halo, CN, C1-3 alkyl, C1-3 haloalkyl, C1-3 alkoxy, and C1-3 haloalkoxy;
R4 is selected from H, C1-3 alkyl, and HO-C1-3 alkyne;
R5 is selected from C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C(O)ORa1, C(O)NRa12, P(=O)(ORa1)2, and C(O)Rb1;
wherein said C1-6 alkyl, C2-6 alkenyl and C2-6 alkynyl are each optionally substituted with a substituent selected from ORa1 and OP(=O)(ORa1)2;
each Ra1 is independently selected from H, C1-6 aryl, C6-10 ary1, C1-6 alkyl-C6-10 ary1, and C1-6 aryl-C1-6 alkyl, wherein said C1-6 alkyl, C6-10 ary1,
C1-6 alkyl-C6-10 ary1, and C6-10 alkyl-C1-6 ary1 are each optionally substituted with a substituent selected from amino, C1-6 alkylamino, (C1-6 haloalkyl)amino, di(C1-6 alkyl)amino, (C1-6 alkyl)(C1-6 haloalkyl)amino, (C ary1)amino, (C6-10 ary1)(C1-6 alkyl)amino, (5-6-membered heteroary1)amino, (5-6-membered heteroary1)(C1-6

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INVENTORS
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OTHER INFORMATION
KEYWORDS
12/15-LOX, Lipoxygenase,
Lipoxygenase inhibitors, Stroke,
Ischemia-Reperfusion Injury,
Subarachnoid hemorrhage, 12/15-Lipoxygenase

CATEGORIZED AS
- Medical
- Disease: Cardiovascular and Circulatory System
- Therapeutics

RELATED CASES
2021-597-0, 2020-252-0, 2016-385-0, 2021-934-0, 2022-800-0
alkyl)amino, C$_{6-10}$ aryl, 4-6 membered heterocycloalkyl, 5-6-membered heteroaryl, and OR$_{a2}$, wherein said C$_{6-10}$ aryl, 4-6 membered heterocycloalkyl, and 5-6-membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from amino, C$_{1-6}$ alkylamino, di(C$_{1-6}$ alkyl)amino, carboxy, and halo; each R$_{a2}$ is independently selected from H, C$_{1-3}$ alkyl, C$_{1-3}$ haloalkyl, C$_{1-3}$ alkoxy-C$_{1-3}$ alkyl, 4-7 membered heterocycloalkyl-C$_{1-3}$ alkyl, 5-6-membered heteroaryloxy-C$_{1-3}$ alkyl, C$_{6-10}$ aryl, and 5-6-membered heteroaryl, wherein said C$_{6-10}$ aryl and 5-6-membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C$_{1-3}$ alkoxy, C$_{1-3}$ haloalkoxy, C$_{1-3}$ alkyl, and C$_{1-3}$ haloalkyl; and R$_{b1}$ is C$_{1-6}$ alkyl, optionally substituted with a substituent selected from amino, C$_{1-6}$ alkylamino, di(C$_{1-6}$ alkyl)amino, and 4-7 membered heterocycloalkyl ring comprising at least one N atom.

In some embodiments, X$_1$ is O.

In some embodiments, X$_1$ is S.

Compounds demonstrated excellent solubility and specificity for 12/15 LOX, metabolic stability in human, mouse, and rat liver endosomes, and significant infarct size reduction in an MCAO ischemia/reperfusion injury mouse model as well as improved behavioral outcomes in a subarachnoid hemorrhage mouse model.

APPLICATIONS

Treatment of stroke, ischemia reperfusion injury, and subarachnoid hemorrhage.

ADVANTAGES

Improved solubility and specificity over other 12/15 LOX inhibitors.

Results demonstrated in animal studies.

INTELLECTUAL PROPERTY INFORMATION

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Additional Patents Pending

RELATED MATERIALS

- Contributions of 12/15-Lipoxygenase to Bleeding in the Brain Following Ischemic Stroke - 09/28/2019

RELATED TECHNOLOGIES

- ML351 As Treatment For Stroke And Ischemic Brain Injury
- Novel Human 12-Lipoxygenase (Lox) Inhibitors
- COMPOUNDS FOR MODULATING EPITHELIAL 15-(S)-LIP OXYGENASE-2 AND METHODS OF USE FOR SAME
- 15LOX1 Inhibitor Formulation Determination For IV Administration

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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- ML351 As Treatment For Stroke And Ischemic Brain Injury
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