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15Lox1 Inhibitors For Stroke

Tech ID: 33579 / UC Case 2021-597-0

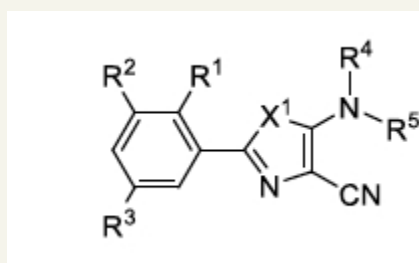
BACKGROUND

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



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 alkylene;

R₅ is selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C(O)OR_{a1}, C(O)N(R_{a1})₂, P(=O)(OR_{a1})₂, and C(O)R_{b1};

wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are each optionally substituted with a substituent selected from OR_{a1} and OP(=O)(OR_{a1})₂;

each R_{a1} is independently selected from H, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₆ alkyl-C₆₋₁₀ aryl, and C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆ alkyl, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl,

C₁₋₆ alkyl-C₆₋₁₀ aryl, and C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆ alkyl 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

aryl)amino, (C₆₋₁₀ aryl)(C₁₋₆ alkyl)amino, (5-6-membered heteroaryl)amino, (5-6-membered heteroaryl)(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, C₆₋₁₀ aryl, 4-6 membered heterocycloalkyl, 5-6-membered heteroaryl, and OR_{a2}, wherein said C₆₋₁₀ aryl, 4-6 membered heterocycloalkyl, and 5-6-membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, carboxy, and halo; each R_{a2} is independently selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy-C₁₋₃ alkyl, 4-7 membered heterocycloalkyl-C₁₋₃ alkyl, 5-6-membered heteroaryloxy-C₁₋₃ alkyl, C₆₋₁₀ aryl, and 5-6-membered heteroaryl, wherein said C₆₋₁₀ aryl and 5-6-membered heteroaryl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₁₋₃ alkyl, and C₁₋₃ haloalkyl; and R_{b1} is C₁₋₆ alkyl, optionally substituted with a substituent selected from amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, and 4-7 membered heterocycloalkyl ring comprising at least one N atom.

In some embodiments, X₁ is O.

In some embodiments, X₁ 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

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,287,279	05/14/2019	2016-385
United States Of America	Published Application	20240279190	08/22/2024	2020-252
European Patent Office	Published Application	4384161	06/19/2024	2021-597
European Patent Office	Published Application	3036226	06/29/2016	2016-385
Canada	Published Application	2015/027146 A1	02/26/2015	2016-385
Switzerland	Published Application			2016-385
Germany	Published Application			2016-385
France	Published Application			2016-385
United Kingdom	Published Application			2016-385
European Patent Office	Published Application			2020-252
Canada	Published Application			2021-597
China	Published Application			2021-597
Israel	Published Application			2021-597
India	Published Application			2021-597
Japan	Published Application			2021-597
Republic Of Korea (South Korea)	Published Application			2021-597
European Patent Office	Published Application			2021-934
Patent Cooperation Treaty	Published Application	WO 2024/019959	01/25/2024	2022-800
Patent Cooperation Treaty	Reference for National Filings	WO 2023/009347	02/02/2023	2021-934

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-\(S\)-LIPOXYGENASE-2 AND METHODS OF USE FOR SAME](#)
- ▶ [15LOX1 Inhibitor Formulation Determination For IV Administration](#)

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

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

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