15Lox1 Inhibitors For Stroke

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

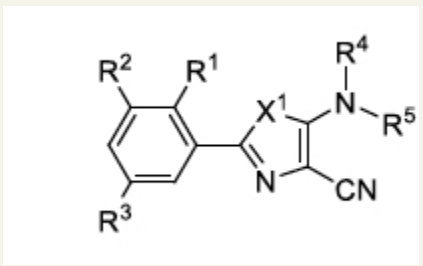
BACKGROUND

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 that 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;

R_1, R_2, and R_3 are each independently selected from halo, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy;

R_4 is selected from H, C_{1-3} alkyl, and HO-C_{1-3} alkylene;

R_5 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)OR_{a1}$,$C(O)N(R_{a1})_2$, $P(=O)(OR_{a1})_2$, and $C(O)R_{b1}$;

wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} 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, C_{1-6} alkyl, C_{6-10} aryl, C_{1-6} alkyl-C_{6-10} aryl, and C_{1-6} alkyl-C_{6-10} aryl-C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{6-10} aryl,

C_{1-6} alkyl-C_{6-10} aryl, and C_{1-6} alkyl-C_{6-10} aryl-C_{1-6} alkyl are each optionally substituted with a substituent selected from amino, C_{1-6} alkylamino, (C_{1-6} haloalkyl)amino, di(C_{1-6} alkyl)amino, (C_{1-6} alkyl)(C_{1-6} haloalkyl)amino, (C aryl)amino, (C_{6-10} aryl)(C_{1-6} alkyl)amino, (5-6-membered heteroaryl)amino, (5-6-membered heteroaryl)(C_{1-6}

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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, X1 is S.

Compounds demonstrated excellent solubility and specificity for 12/15 LOX, metabolic stabilty 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 solubilty 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
European Patent Office	Published Application	4558508	05/28/2025	2022-800
United States Of America	Published Application	2024-033664	10/10/2024	2021-597
Japan	Published Application	2024-531142	08/29/2024	2021-597
European Patent Office	Published Application	4384161	06/19/2024	2021-597
European Patent Office	Published Application	4377297	06/05/2024	2021-934
India	Published Application	202417016587A	03/15/2024	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
Republic Of Korea (South Korea)	Published Application			2021-597
Patent Cooperation Treaty	Reference for National Filings	WO 2022/236086	11/10/2022	2020-252

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

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ML351 As Treatment For Stroke And Ischemic Brain Injury

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