Novel Human 12-Lipoxygenase (Lox) Inhibitors

Tech ID: 33578 / UC Case 2020-252-0

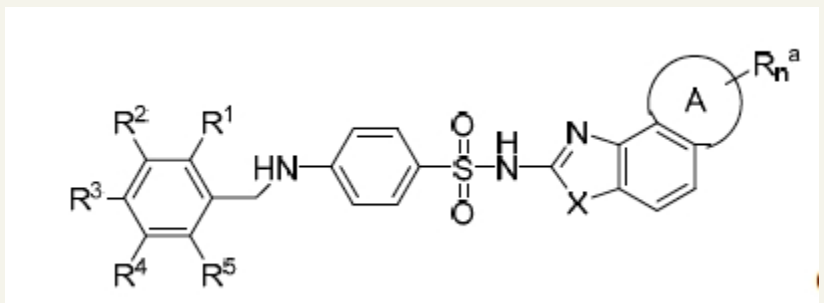
BACKGROUND

Human Platelet-type 12-(S)-lipoxygenase (12-LOX) is a non-heme iron-containing oxygenase that catalyzes the regio- and stereo-specific addition of molecular oxygen to polyunsaturated fatty acids (PUFA). 12-LOX belongs to a family of enzymes that also include 5- LOX and 15-LOX, which oxygenate arachidonic acid (AA) at their corresponding carbon positions. The hydroperoxyeicosatetraenoic acid (HPETE) product is subsequently reduced by cellular peroxidases to form the hydroxyeicosatetraenoic acid (HETE), which in the case of 12- LOX is 12-(S)-HETE.

Although 12-LOX expression is predominantly restricted to platelets (~14,000 molecules per platelet), it is also expressed in some hematopoietic and solid tumors. To date, 12-LOX is the only LOX isoform identified to be present in platelets, and its activity is part of a number of platelet functions, including granule secretion, platelet aggregation, and normal adhesion through specific agonist-mediated pathways, such as collagen and the thrombin receptor, PAR4. Normal platelet activation plays a central role in the regulation of hemostasis, but uncontrolled activation can lead to pathologic thrombotic events, such as ischemic coronary heart disease.

TECHNOLOGY DESCRIPTION

Compounds of the structure are as provided below:



where R1, R2, R3, R4 and R5 are each independently selected from hydrogen, hydroxy, alkoxy, amine, cyano, thiol, halogen, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl,cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl; X is S or O; the A ring is a substituted or unsubstituted 5 to 12 membered ring; n is an integer from 0 to 12; and each R_a is independently selected from hydrogen, hydroxy, alkoxy, amine, cyano, thiol, halogen, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and substituted heteroarylalkyl, or a salt, solvate or hydrate thereof.

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- Nadler, Jerry

OTHER INFORMATION

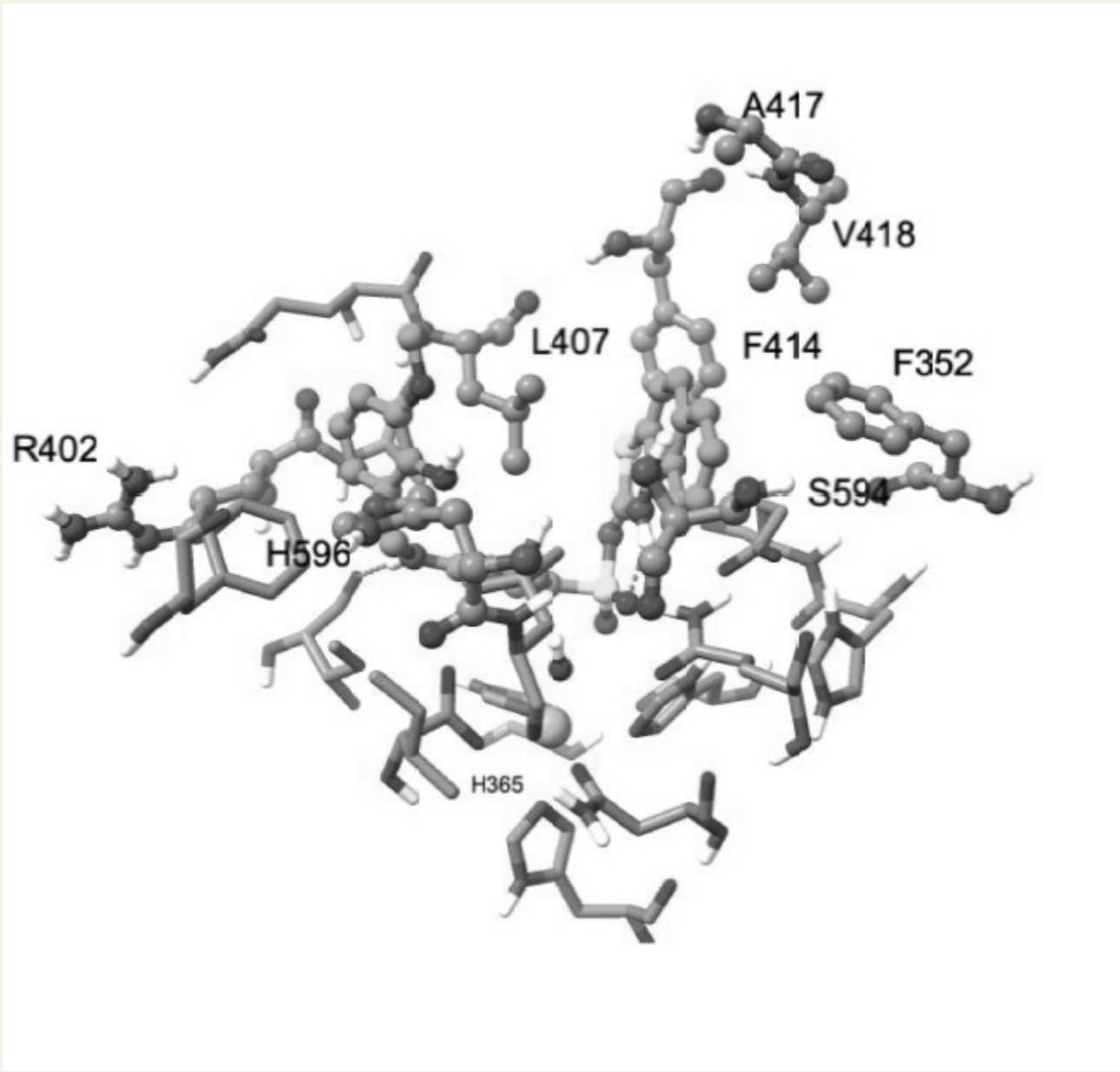
CATEGORIZED AS

- **Medical**
  - Disease: Cardiovascular and Circulatory System
  - Therapeutics

RELATED CASES

2020-252-0, 2021-597-0, 2021-934-0, 2022-800-0

The predicted binding mode of Compound LOX-12-001 with wt12-LOX is shown below. Residues that interact with the inhibitor are shown. Residues that mutated in the present study are shown in ball-and-stick representation and they are labelled.



APPLICATIONS

- Treating or preventing an immune-mediated thrombocytopenia or thrombosis disorder.
- Treating diabetes, type II diabetes, diabetic kidney disease, diabetic nerve disease, cardiovascular disease, non-alcoholic steatohepatitis, platelet hemostasis, heparin-induced thrombocytopenia, thrombosis, Alzheimer's disease and cancer.

ADVANTAGES

Greater specificity and better solubility than other 12-LOX inhbitors.

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
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
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	4377297	06/05/2024	2021-934
India	Published Application	202417016587A	03/15/2024	2021-597
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

Additional Patents Pending

RELATED MATERIALS

- Docking and mutagenesis studies lead to improved inhibitor development of ML355 for human platelet 12-lipoxygenase - 09/15/2021

RELATED TECHNOLOGIES

- ML351 As Treatment For Stroke And Ischemic Brain Injury
- 15LOX1 Inhibitor Formulation Determination For IV Administration
- COMPOUNDS FOR MODULATING EPITHELIAL 15-(S)-LIPOXYGENASE-2 AND METHODS OF USE FOR SAME

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
- 15Lox1 Inhibitors For Stroke

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