COMPOUNDS FOR MODULATING EPITHELIAL 15-(S)-LIPOXYGENASE-2 AND METHODS OF USE FOR SAME

Tech ID: 33373 / UC Case 2021-934-0

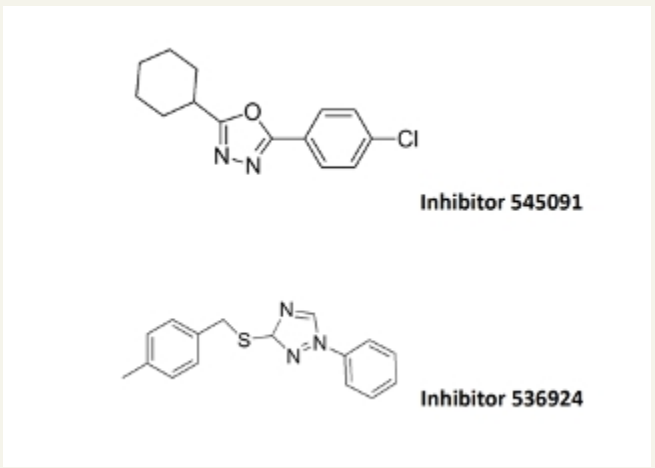
BACKGROUND

Lipoxygenases (LOX) are enzymes that catalyze the peroxidation of certain fatty acids. The cell membrane is mostly made of lipids (which include fatty acids), and peroxidation can cause damage to the cell membrane. The human genome contains six functional LOX genes that encode for six LOX enzyme variants, or isozymes. The role that each LOX isozyme plays in health and disease varies greatly, spanning issues such as asthma, diabetes, and stroke. LOX enzymes are extremely difficult to target due to high hydrophobicity. Potential leads are often ineffective because they are either not readily soluble or not selective for a particular LOX enzyme.

Studies have implicated human epithelial 15-lipoxygenase-2 (h15-LOX-2, ALOX15B) in various diseases. h15-LOX-2 is highly expressed in atherosclerotic plaques and is linked to the progression of macrophages to foam cells, which are present in atherosclerotic plaques. h15-LOX-2 mRNA levels are also highly elevated in human macrophages isolated from carotid atherosclerotic lesions in symptomatic patients. Children with cystic fibrosis had reduced levels of h15-LOX-2, which affects the lipoxin A_4 to leukotriene B_4 ratio. Furthermore, the interactions of h15-LOX-2 and PEBP1 changes the substrate specificity of h15-LOX-2 from free polyunsaturated fatty acids (PUFA) to PUFA-phosphatidylethanolamines (PE), leading to the generation of hydroperoxyeicosatetraenoic acid (HpETE) esterified into PE (HpETE-PE). Accumulation of these hydroperoxyl membrane phospholipids has been shown to cause ferroptotic cell death, which implicates h15-LOX-2 in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases.

TECHNOLOGY DESCRIPTION

Researchers at UC Santa Cruz, in collaboration with a researcher at UC San Francisco, have discovered compounds that inhibit h15-LOX-2. These compounds can modulate ferroptosis and generation of HpETEs, and can modulate eicosanoid mediator biosynthesis from leukotrienes (LTs) to pro-resolving mediator class of lipoxins (LXs). The inhibitors are potent and selective against h15-LOX-2, and underlines the importance of further investigating h15-LOX-2 as a therapeutic target for drug discovery.



APPLICATIONS

- drug discovery

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OTHER INFORMATION

KEYWORDS

lipoxygenase, LOX, 15-LOX, ALOX15B, human epithelial 15-lipoxygenase, cardiovascular disease, neurodegenerative disease, cystic fibrosis

CATEGORIZED AS

- **Materials & Chemicals**
  - Chemicals
- **Medical**
  - Disease: Autoimmune and Inflammation
  - Disease: Cardiovascular and Circulatory System
  - Disease: Central Nervous System
  - Disease: Respiratory and Pulmonary System
  - New Chemical Entities, Drug Leads
  - Screening
  - Therapeutics
- **Research Tools**
  - Other
  - Screening Assays

RELATED CASES

2021-934-0

- cardiovascular disease
- neurodegenerative disease
- cystic fibrosis

ADVANTAGES

- potent and selective against h15-LOX-2

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
European Patent Office	Published Application	4377297	06/05/2024	2021-934

Additional Patent Pending

RELATED MATERIALS

- Kinetic and Structural Investigations of Novel Inhibitors of Human Epithelial 15-Lipoxygenase-2 - 08/05/2021

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ML351 As Treatment For Stroke And Ischemic Brain Injury
- 15LOX1 Inhibitor Formulation Determination For IV Administration
- 15Lox1 Inhibitors For Stroke
- Novel Human 12-Lipoxygenase (Lox) Inhibitors

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