CFTR potentiators and correctors and bifunctional (corrector/potentiator) compounds for treatment of Cystic Fibrosis

Tech ID: 20824 / UC Case 2008-050-0

FULL DESCRIPTION

UCSF investigators have isolated set of compounds to treat cystic fibrosis (CF). The compounds are anticipated to treat the underlying defects in patients with the delta F508 mutation of the CFTR gene, which is present in around 90% of the CF cases. Small molecule therapy directed toward correcting the deltaF508 defects in cellular processing and channel gating of CFTR is thought to hold considerable promise.

A panel of novel potentiators (which restore gating defects) and correctors (which restore protein folding and plasma membrane trafficking) are available for licensing. Several of the potentiators identified are very potent (some at submicromolar potency) in restoring the gating defect in both deltaF508 mutants and other CFTR gating mutants, including G551D. They have also identified several highly effective (micromolar potency) correctors of the deltaF508 mutant protein. When used in combination, these compounds may correct the defects caused by the deltaF508 mutation in the CFTR gene.

Additionally, the investigator is currently developing a bifunctional compound capable of both potentiation and corrector activity, with promising results. It is thought that both activities are required to fully address the protein folding/trafficking and gating defects present in this mutation, which is the most prevalent (90%US/66% world population). A single molecule that can address both defects in the deltaF508 mutation could provide a simplified approach that would be easier to study in clinical trials. The investigators believe the bifunctional compounds could be manufactured as either oral tablet or inhaled aerosol formulation.

PUBLICATIONS

- Yang et al. (2003) The Journal of Biological Chemistry. Nanomolar affinity small molecule correctors of defective deltaF508-CFTR chloride channel gating.
- Pedemonte et al. (2006) Molecular Pharmacology. Phenylglycine and Sulfonamide correctors of defective deltaF508 and G551D cystic fibrosis transmembrane conductance regulator chloride-channel gating.
- Pedemonte et al. (2005) Journal of Clinical Investigation. Small-molecule correctors of defective deltaF508-CFTR cellular processing identified by high-throughput screening.
- Suen et al. (2006) Bioorganic and Medicinal Chemistry Letters. Sulfamoyl-4-oxoquinoline-3-carbamides:Novel potentiators of defective deltaF508-CFTR chloride channel gating.

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INVENTORS

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OTHER INFORMATION

KEYWORDS

cystic fibrosis, folding, potentiators, correctors, CFTR

CATEGORIZED AS

- **Medical**
  - Disease: Respiratory and Pulmonary System
  - New Chemical Entities, Drug Leads

RELATED CASES

2008-050-0

▶ Yoo et al. (2008) Bioorganic and Medicinal Chemistry Letters. 4’-Methyl-4,5’-bithiazole-based correctors of deltaF508-CFTR cellular processing.

▶ Yu et al. (2008) Journal of Medicinal Chemistry. Potent s-cis-Locked Bithiazole correctors of deltaF508 CFTR cellular processing for cystic fibrosis therapy.

▶ Ye et al. Pyrazolylthiazole as DeltaF508-cystic fibrosis transmembrane conductance regulator correctors with improved hydrophilicity compared to bithiazoles. J Med Chem. 2010 May 13;53(9):3772-81.

RELATED MATERIALS

▶ 1. Yang et al. (2003) The Journal of Biological Chemistry. Nanomolar affinity small molecule correctors of defective deltaF508-CFTR chloride channel gating.

▶ 2. Pedemonte et al. (2006) Molecular Pharmacology. Phenylglycine and Sulfonamide correctors of defective deltaF508 and G551D cystic fibrosis transmembrane conductance regulator chloride-channel gating.

▶ 3. Pedemonte et al. (2005) Journal of Clinical Investigation. Small-molecule correctors of defective deltaF508-CFTR cellular processing identified by high-throughput screening.

▶ 4. Suen et al. (2006) Bioorganic and Medicinal Chemistry Letters. Sulfamoyl-4-oxoquinoline-3-carbamides:Novel potentiators of defective deltaF508-CFTR chloride channel gating.

▶ 5. Yoo et al. (2008) Bioorganic and Medicinal Chemistry Letters. 4’-Methyl-4,5’-bithiazole-based correctors of deltaF508-CFTR cellular processing.

▶ 6. Yu et al. (2008) Journal of Medicinal Chemistry. Potent s-cis-Locked Bithiazole correctors of deltaF508 CFTR cellular processing for cystic fibrosis therapy.

▶ 7. Ye et al. (2010) Pyrazolylthiazole as DeltaF508-cystic fibrosis transmembrane conductance regulator correctors with improved hydrophilicity compared to bithiazoles.

PATENT INFORMATION

UCSF has a large portfolio of both US and foreign patent applications covering the use of these compounds for treatment of CF.

Below are some selected patent application publications

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,389,736	03/05/2013	2008-050

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ SALT-SPARING UREA TRANSPORT INHIBITOR DIURETICS FOR TREATMENT OF CARDIOVASCULAR AND RENAL DISORDERS

▶ Potent TMEM16A Small Molecule Treatment for Inflammatory and Reactive Airway Diseases, Asthma, Hypertension, Pain and Cancer

▶ Novel Small Molecule Drug for the Treatment of Constipation and Oxalate Kidney Stones

▶ Small Molecule Pendrin Inhibitors for Treatment of Inflammatory Airway Diseases and Diuretic Resistance

▶ Immunotherapy for Treatment of Neuromyelitis Optica (NMO)

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