

dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (prion protein processing defect), Fabry disease (lysosomal α -galactosidase A), Strausler-Scheinker syndrome, chronic obstructive pulmonary disease (COPD), dry eye disease, and Sjogren's Syndrome.

[0018] In addition to up-regulation of the activity of CFTR, anion secretion reduction by CFTR modulators may be beneficial for the treatment of secretory diarrheas, in which epithelial water transport is dramatically increased as a result of secretagogue activated chloride transport. The mechanism involves elevation of cAMP and stimulation of CFTR.

[0019] Regardless of the cause, excessive chloride transport is seen in all diarrheas, and results in dehydration, acidosis, impaired growth and death. Acute and chronic diarrheas remain a major medical problem worldwide, and are a significant factor in malnutrition, leading to death in children of less than five years old (5,000,000 deaths/year). Furthermore, in patients with chronic inflammatory bowel disease (IBD) and/or acquired immunodeficiency syndrome (AIDS), diarrhea is a dangerous condition

[0020] Accordingly, there is a need for novel compounds able to modulate CFTR. In particular, the present invention discloses compounds that may act as CFTR modulators for the treatment of cystic fibrosis. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for the treatment of cystic fibrosis by administering the compounds of the invention.

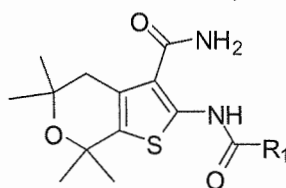
BRIEF DESCRIPTION OF THE FIGURES

Figure 1: shows the current increase measured in the TECC assay for comparative compound and a compound of the invention at various concentration of test compound (50, 100, and 200 nM)

SUMMARY OF THE INVENTION

[0021] The present ~~invention-disclosure~~ is based on the identification of novel compounds, and their ability to act as CFTR modulators and that they may be useful for the treatment of cystic fibrosis. The present ~~invention-disclosure~~ also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for the treatment of cystic fibrosis by administering compounds of the ~~invention~~present disclosure.

[0022] Accordingly, in a first aspect of the ~~invention~~present disclosure, ~~a compounds of the invention~~ are ~~is~~ provided having a Formula (I):



- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising one or more heteroatoms independently selected from N, O, and S, and
- -NHSO₂-C₁₋₄ alkyl;

each R⁴ is selected from

- halo,
- OH,
- C₃₋₇ monocyclic cycloalkyl,
- -CN, and
- C₁₋₄ alkoxy (optionally substituted with one or more independently selected R^{5c}),

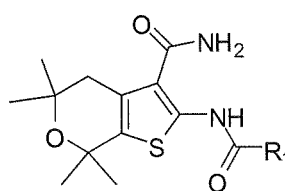
each R^{5a}, R^{5b}, and R^{5c} is independently selected from

- o halo,
- o OH,
- o -OP(=O)₂OH,
- o -CN,
- o -NR^{6a}R^{6b}, and
- o C₁₋₄ alkoxy; and

each R^{6a}, or R^{6b} is independently selected from H, and C₁₋₄ alkyl,

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof.

[0023] In another aspect embodiment of the invention present disclosure, compounds of the invention present disclosure are provided having a Formula (I):



I

wherein

R¹ is

- C₃₋₇ cycloalkyl optionally substituted with one or more independently selected R² groups,
- 4-7 membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from O, N, and S, substituted with one or more independently selected R² groups,
- C₆₋₁₀ mono or bicyclic aryl optionally substituted with one or more independently selected R³ groups,

- C₁₋₄ alkoxy; and

each R^{6a}, or R^{6b} is independently selected from H, and C₁₋₄ alkyl.

[0024] In a particular ~~aspect~~embodiment, the compounds of the ~~invention~~present disclosure are provided for use in the treatment of cystic fibrosis. In a particular ~~aspect~~embodiment, the compounds of the ~~invention~~present disclosure are provided for use in the treatment of cystic fibrosis caused by class I, II, III, IV, and/or VI mutations.

[0025] In an alternative embodiment, the compounds of the ~~invention~~present disclosure have a potentiator activity.

[0026] In another particular ~~aspect~~embodiment, the compounds of the ~~present disclosure~~invention exhibit low activity on CYP enzymes, which may result in low drug-drug interaction potential, and accordingly may be advantageous for patients under multiple therapies.

[0027] In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides pharmaceutical compositions comprising a compound as disclosed herein~~of the invention~~, and a pharmaceutical carrier, excipient or diluent. In an aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as disclosed herein. In a particular ~~aspect~~embodiment, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the ~~invention~~present disclosure. In a more particular ~~aspect~~embodiment, the further therapeutically active ingredient is an agent for the treatment of cystic fibrosis.

[0028] Moreover, the compounds of the ~~invention~~present disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0029] In a further ~~aspect~~embodiment of the ~~present disclosure~~invention, ~~this invention~~there is provideds a method of treating a mammal, in particular humans, with a condition selected from among those listed herein, and particularly cystic fibrosis, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the ~~present disclosure~~invention as described herein.

[0030] In another aspect, ~~The present invention~~disclosure also provides a compound or pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical compositions comprising a compound of the invention, and a suitable pharmaceutical carrier, excipient or diluent as disclosed herein for use in medicine. In a particular ~~aspect~~embodiment, the pharmaceutical composition is for use in the treatment of cystic fibrosis. In another aspect, there is provided the use of a compound or pharmaceutically acceptable salt thereof as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of cystic fibrosis.

[0031] In additional ~~aspects~~embodiments, ~~this invention~~there is provideds methods for synthesizing the compounds of the ~~present disclosure~~invention, with representative synthetic protocols and pathways disclosed later on herein.

[0032] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0033] It will be appreciated that compounds of the ~~present disclosure~~invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0034] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0035] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood

5,5,7,7-tetramethyl-2-[(3,3,3-trifluoro-2-hydroxy-propanoyl)amino]-4H-thieno[2,3-c]pyran-3-carboxamide,

6-Oxo-1,6-dihydro-pyridazine-3-carboxylic acid (3-carbamoyl-5,5,7,7-tetramethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-2-yl)-amide, and

2-(1,4-dioxane-2-carboxamido)-5,5,7,7-tetramethyl-5,7-dihydro-4H-thieno[2,3-c]pyran-3-carboxamide.

- 14) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of claims 1-13.
- 15) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-13, or a pharmaceutical composition according to claim 14, for use in medicine.
- 16) Use of a A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-13, or a pharmaceutical composition according to claim 14, ~~for use in the~~ manufacture of a medicament for the treatment of cystic fibrosis.