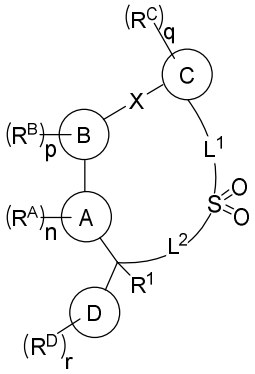
resulting in chronic infection and inflammation. In the lung, the loss of CFTR-function leads to numerous physiological effects downstream of altered anion conductance that result in the dysfunction of additional organs such as the pancreas, intestine and gall bladder.

[005] By studying the mechanistic aspects of CFTR misfolding and corrections, small molecules have been identified as CF modulators, that can act as stabilizers.

[006] Despite the identification of compounds that modulate CFTR, there is no cure for this fatal disease and identification of new compounds and new methods of therapy are needed as well as new methods for treating or lessening the severity of cystic fibrosis and other CFTR mediated conditions and diseases in a patient.

Summary

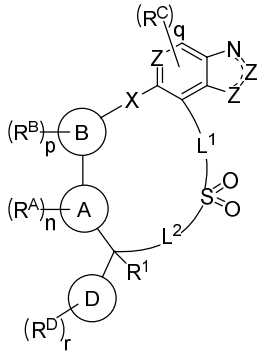
[007] The present disclosure includes a compound of formula A:



A

or a pharmaceutically acceptable salt thereof. Additionally, the present disclosure includes, among other things, pharmaceutical compositions, methods of using and methods of making a compound of formula A.

[007a] In one aspect, the present disclosure refers to a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein

L^1 is an optionally substituted C_{1-6} alkylene chain wherein 1-3 of the methylene units is optionally and independently replaced by -O-, -N(R^2), -C(O)-, -S-, -S(O)-, -S(O)$_2$-, an optionally substituted 3-6 membered carbocyclyl, , optionally substituted C_2 alkenylene, or optionally substituted 5-6-membered heteroaryl;

L^2 is an optionally substituted C_{1-6} alkylene chain wherein 1-3 of the methylene units is optionally and independently replaced by -C(CD_3)$_2$-, -O-, -N(R^2)-, -C(O)-, -S-, -S(O)-, an optionally substituted 3-6 membered carbocyclyl, -S(O)$_2$-, optionally substituted C_2 alkenylene, or optionally substituted 5-6-membered heteroaryl;

Ring A is an optionally substituted 5-membered heteroaryl comprising 1-4 heteroatoms selected from the group consisting of N, O or S;
Ring B is optionally substituted phenyl or optionally substituted 6-membered heteroaryl;
Ring D is optionally substituted phenyl or optionally substituted 5-6-membered heteroaryl;
X is selected from the group consisting of -O-, -S-, $-CH_2-$, -C(OH)H-, $-CHCH_3$, -SO-, -CO-, $-SO_2-$, -CFH-, $-CF_2-$, and $-N(R^2)-$;
each R^A is independently selected from the group consisting of halogen, cyano, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 alkoxy, and $-CD_3$;
each R^B is independently selected from the group consisting of halogen, cyano, $-C(O)N(R^2)_2$, $C(O)OR^2$, $-OR^2$, $-N(R^2)_2$, optionally substituted C_1-C_6 aliphatic and optionally substituted C_1-C_6 alkoxy;
each R^C is independently selected from the group consisting of hydrogen, halogen, cyano, $-(CH_2)_{0-3}C(O)OH$, optionally substituted C_1-C_6 aliphatic or optionally substituted C_1-C_6 alkoxy;
each R^D is independently selected from the group consisting of halogen, cyano, $-C(O)N(R^2)_2$, $-C(O)OR^2$, $-OR^2$, $-N(R^2)_2$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_3 alkoxy, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S, wherein each R^D is optionally substituted with 1-6 instances of R^d;
wherein two instances of R^D may be taken together to form an optionally substituted 5-7 membered carbocyclic ring, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S;
each R^d is independently selected from the group consisting of hydrogen, -OH, $-CD_3$, $-C(O)N(R^2)_2$, $C(O)OR^2$, $-OR^2$, $-N(R^2)_2$, $-S(O)_2R^2$ optionally substituted C_1-C_6 aliphatic, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S;
R^1 is selected from the group consisting of hydrogen, cyano, $-OR^2$, $-(CH_2)_{0-3}N(R^2)_2$, optionally substituted C_1-C_3 aliphatic, 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S, and $-CD_3$;
each R^2 is independently selected from hydrogen, optionally substituted C_1-C_6 aliphatic, -OH, C_1-C_6 alkoxy, $-S(O)_2$(optionally substituted C_1-C_6 aliphatic);
each Z independently is -CH=, -N= or -NH-;
n is 0, 1, 2 or 3;
p is 0, 1, 2, 3 or 4;
q is 0, 1 2, or 3; and
r is 0, 1, 2, 3, 4 or 5.

[007b] In one aspect, the present disclosure refers to a compound selected from a compound of Table 1 or a pharmaceutically acceptable salt thereof.

[007c] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[007d] In one aspect, the present disclosure refers to use of a compound disclosed herein or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a CFTR-mediated disease or disorder.

[007e] In one aspect, the present disclosure refers to use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cystic fibrosis in a subject.

Detailed Description

[008] In some embodiments, the present disclosure includes a compound of Formula A: