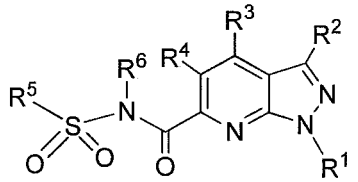
[0021] In one aspect thereis provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is G^{1A}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 haloalkyl and the C_1-C_6 alkyl are each optionally substituted with one G^{1A};

G^{1A}, at each occurrence, is independently phenyl, 5-6 membered monocyclic heteroaryl, 4-7 membered monocyclic heterocycle, 5-11 membered fused bicyclic heterocycle, or C_3-C_6 monocyclic cycloalkyl; wherein each G^{1A} is optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of R^{1a} and G^{1B};

G^{1B}, at each occurrence, is independently 4-7 membered monocyclic heterocycle which is optionally substituted with 1, 2, 3, or 4 independently selected R^{1b} groups;

R^2 is hydrogen, C_2-C_4 alkenyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-OR^{2xa}$, $-N(R^{2xa})(R^{2xb})$, or G^{2A};

R^{2xa}, at each occurrence, is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, or G^{2B};

R^{2xb} is hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

G^{2A} and G^{2B} are each independently a 4-7 membered monocyclic heterocycle or a C_3-C_6 monocyclic cycloalkyl; wherein G^{2A} and G^{2B} are each optionally substituted with 1, 2, or 3 independently selected R^{2a} groups;

R^3 is G^{3A}, $-G^{3B}$-L^1-G^{3C}, $-G^{3B}$-L^3-G^{3C}-G^{3E}, -(C_1-C_6 alkylenyl)-G^{3D}, $-OR^{3a}$, or $-N(R^{3a})(R^{3b})$;

R^{3a}, at each occurrence, is independently G^{3D}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 haloalkyl and the C_1-C_6 alkyl are each optionally substituted with one or two substituents independently selected from the group consisting of G^{3D}, $-OR^{3xa}$, and $-N(R^{3xb})_2$;

R^{3xa} and R^{3xb}, at each occurrence, are each independently hydrogen, C_1-C_6 haloalkyl, C_1-C_6 alkyl, or G^{3D};

R^{3b} is hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

$C(O)OR^m$, -(C_1-C_6 alkylenyl)-$C(O)N(R^m)_2$, -(C_1-C_6 alkylenyl)-$C(O)N(R^m)S(O)_2R^n$, -(C_1-C_6 alkylenyl)-$N(R^m)_2$, -(C_1-C_6 alkylenyl)-$N(R^m)C(O)R^n$, -(C_1-C_6 alkylenyl)-$N(R^m)S(O)_2R^n$, -(C_1-C_6 alkylenyl)-$N(R^m)C(O)O(R^n)$, -(C_1-C_6 alkylenyl)-$N(R^m)C(O)N(R^n)_2$, or -(C_1-C_6 alkylenyl)-$N(R^m)S(O)_2N(R^n)_2$;

R^m, at each occurrence, is independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

R^n, at each occurrence, is independently C_1-C_6 alkyl or C_1-C_6 haloalkyl;

R^6 is hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; or

R^5 and R^6 together form a C_1-C_6 alkylenyl or -$N(R^z)$-(C_1-C_6 alkylenyl)- wherein the $N(R^z)$ is attached to the $S(O)_2$ moiety of formula (I); and

R^z is hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0021a] In another aspect, there is provided benzyl 3-({3-cyclobutyl-4-[4-(methoxymethyl)piperidin-1-yl]-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carbonyl}sulfamoyl)pyrrolidine-1-carboxylate, or a pharmaceutically acceptable salt thereof.

[0021b] In another aspect, there is provided 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-{4-[2-(methoxymethyl)morpholin-4-yl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021c] In another aspect, there is provided 3-cyclobutyl-*N*-(morpholine-4-sulfonyl)-1-phenyl-4-{4-[(pyrrolidin-1-yl)methyl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021d] In another aspect, there is provided 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-(4-methoxy[1,4'-bipiperidin]-1'-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021e] In another aspect, there is provided 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-{4-[4-(propan-2-yl)piperazin-1-yl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021f] In another aspect, there is provided 3-cyclobutyl-N-(morpholine-4-sulfonyl)-4-[4-(morpholin-4-yl)piperidin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021g] In another aspect, there is provided 3-cyclobutyl-N-(methanesulfonyl)-4-[4-(methoxymethyl)piperidin-1-yl]-1-(2-methoxypyridin-4-yl)-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0021h] In another aspect, there is provided N-(2-acetamidoethanesulfonyl)-3-cyclobutyl-4-[4-(methoxymethyl)piperidin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

[0022] Another embodiment of the disclosure relates to pharmaceutical compositions comprising a compound of the dislosure, and a pharmaceutical carrier. In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier. Such compositions can be administered in accordance with a method of thedisclosure, typically as part of a therapeutic regimen for treatment or prevention of conditions and disorders related to Cystic Fibrosis Transmembrane Conductance Regulator activity. In a particular embodiment, the pharmaceutical compositions may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents. In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, one potentiator, and one or more additional correctors. In a more particular embodiment, the further therapeutically active ingredient is an agent for the treatment of cystic fibrosis.

[0023] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0024] Yet another embodiment of the disclosure relates to a method for treating, or preventing conditions and disorders related to Cystic Fibrosis Transmembrane Conductance Regulator activity in mammals. More particularly, the method is useful for treating or preventing conditions and disorders related to cystic fibrosis, Sjögren's syndrome, pancreatic insufficiency, chronic obstructive lung disease, or chronic obstructive airway disease. Accordingly, the compounds and compositions of the disclosure are useful as a medicament for treating or preventing Cystic Fibrosis Transmembrane Conductance Regulator modulated disease.

[0025] The compounds, compositions comprising the compounds, methods for making the compounds, and methods for treating or preventing conditions and disorders by administering the compounds are further described herein.

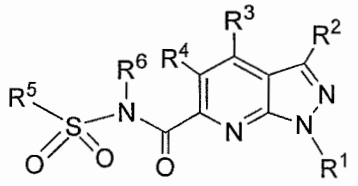
[0026] In a particular embodiment, the compounds of the disclosure are provided for use in the treatment of cystic fibrosis. In a particular embodiment, the compounds of the disclosure are provided for use in the treatment of cystic fibrosis caused by class I, II, III, IV, V, and/or VI mutations. In another aspect, there is provided use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof. In another aspect, there is provided use of a compound as described herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one potentiator, and one or more additional correctors. In another aspect, there is provided use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof, wherein the medicament is to be admininstered with one or more additional therapeutic agents.

[0027] The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier for use in medicine. In another aspect, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in medicine. In a particular embodiment, the pharmaceutical composition is for use in the treatment of cystic fibrosis. In another aspect, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in the treatment of cystic fibrosis.

[0028] These and other objects of the disclosure are described in the following paragraphs. These objects should not be deemed to narrow the scope of the disclosure.

DETAILED DESCRIPTION OF THE INVENTION

[0029] Described herein are compounds of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5, and R^6, are defined above in the Summary of the Invention and below in the Detailed Description. Further, compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also described.

[0030] Compounds included herein may contain one or more variable(s) that occur more than one time in any substituent or in the formulae herein. Definition of a variable on each occurrence is independent of its definition at another occurrence. Further, combinations of substituents are permissible only if such combinations result in stable compounds. Stable compounds are compounds, which can be isolated from a reaction mixture.

Definitions

[0031] It is noted that, as used in this specification and the intended claims, the singular form "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a single compound as well as one or more of the same or different compounds; reference to "a pharmaceutically acceptable carrier" means a single pharmaceutically acceptable carrier as well as one or more pharmaceutically acceptable carriers, and the like.

2-methylpropyl 4-{3-cyclobutyl-1-(4-fluorophenyl)-6-[(morpholine-4-sulfonyl)carbamoyl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl}piperazine-1-carboxylate;

2-methylpropyl 4-{3-cyclobutyl-1-(4-fluorophenyl)-6-[(2-methoxyethanesulfonyl)carbamoyl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl}piperazine-1-carboxylate;

2-methylpropyl 4-{3-cyclobutyl-1-(4-fluorophenyl)-6-[(methylsulfamoyl)carbamoyl]-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl}piperazine-1-carboxylate;

3-cyclobutyl-1-(4-fluorophenyl)-4-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)-*N*-(morpholine-4-sulfonyl)-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide; and

N-(2-aminopyridine-3-sulfonyl)-3-cyclobutyl-1-(4-fluorophenyl)-4-[4-(methoxymethyl)piperidin-1-yl]-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide.

33. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

34. A compound of claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33, for use in medicine.

35. A compound of claim 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 33, for use in the treatment of cystic fibrosis.

36. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof.

37. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, one potentiator, and one or more additional correctors.

38. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one potentiator, and one or more additional correctors.

39. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.

40. The pharmaceutical composition of claim 39 wherein the additional therapeutic agents are selected from the group consisting of CFTR modulators and CFTR amplifiers.

41. The pharmaceutical composition of claim 39 wherein the additional therapeutic agents are CFTR modulators.

42. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cystic fibrosis in a subject in need thereof, wherein the medicament is to be admininstered with one or more additional therapeutic agents.

43. The use of claim 42 wherein the additional therapeutic agents are selected from the group consisting of CFTR modulators, corrected CFTR stabilizers and CFTR amplifiers.

44. The use of claim 42 wherein the additional therapeutic agents are CFTR modulators.

45. Benzyl 3-({3-cyclobutyl-4-[4-(methoxymethyl)piperidin-1-yl]-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carbonyl}sulfamoyl)pyrrolidine-1-carboxylate, or a pharmaceutically acceptable salt thereof.

46. 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-{4-[2-(methoxymethyl)morpholin-4-yl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

47. 3-cyclobutyl-*N*-(morpholine-4-sulfonyl)-1-phenyl-4-{4-[(pyrrolidin-1-yl)methyl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

48. 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-(4-methoxy[1,4'-bipiperidin]-1'-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

49. 3-cyclobutyl-*N*-(dimethylsulfamoyl)-1-(4-fluorophenyl)-4-{4-[4-(propan-2-yl)piperazin-1-yl]piperidin-1-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

50. 3-cyclobutyl-N-(morpholine-4-sulfonyl)-4-[4-(morpholin-4-yl)piperidin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

51. 3-cyclobutyl-N-(methanesulfonyl)-4-[4-(methoxymethyl)piperidin-1-yl]-1-(2-methoxypyridin-4-yl)-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

52. N-(2-acetamidoethanesulfonyl)-3-cyclobutyl-4-[4-(methoxymethyl)piperidin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxamide, or a pharmaceutically acceptable salt thereof.