

HETEROARYL SUBSTITUTED PYRIDINES AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/345,315, filed June 3, 2016, which is incorporated herein by its entirety for all purposes.

[0001a] The inventions claimed herein were made by or on behalf of AbbVie S.à.r.l., Luxembourg (LU) and Galapagos NV, Mechelen (BE), who are parties to a joint research agreement that was in effect on or before the date the claimed invention was made. The claimed invention was made as the result of activities undertaken within the scope of the joint research agreement.

BACKGROUND OF THE INVENTION

Technical Field

[0002] The invention relates to substituted pyridine compounds that are modulators of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein, useful in treating diseases and conditions mediated and modulated by CFTR. The invention also relates to compositions containing compounds of the invention, processes for their preparation, and methods of treatment using them.

Description of Related Technology

[0003] ABC transporters are a family of homologous membrane transporter proteins regulating the transport of a wide variety of pharmacological agents (for example drugs, xenobiotics, anions, etc.) that bind and use cellular adenosine triphosphate (ATP) for their specific activities. Some of these transporters were found to defend malignant cancer cells against chemotherapeutic agents, acting as multidrug resistance proteins (like the MDR1-P glycoprotein, or the multidrug resistance protein, MRP 1). So far, 48 ABC transporters, grouped into 7 families based on their sequence identity and function, have been identified.

[0004] ABC transporters provide protection against harmful environmental compounds by regulating a variety of important physiological roles within the body, and therefore represent important potential drug targets for the treatment of diseases associated with transporter defects, outwards cell drug transport, and other diseases in which modulation of ABC transporter activity may be beneficial.

[0005] The cAMP/ATP-mediated anion channel, CFTR, is one member of the ABC transporter family commonly associated with diseases, which is expressed in a variety of cell types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. The activity of CFTR in epithelial cells is essential for the maintenance of electrolyte transport throughout the body,

disease (APP and presenilins), Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluyasian, 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 Sjögren's syndrome.

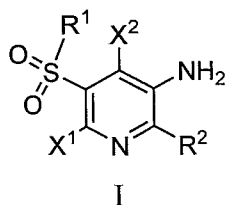
[0018] In addition to up-regulation of the activity of CFTR, anion secretion reduction by CFTR modulators may be beneficial for the treatment of secretory diarrheas, in which epithelial water transport is dramatically increased as a result of secretagogue activated chloride transport. The mechanism involves 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 preparation of these compounds, pharmaceutical compositions comprising these compounds and methods for the treatment of cystic fibrosis by administering the compounds of the invention.

SUMMARY

[0021] In one aspect, there is provided a compound of Formula I, or pharmaceutically acceptable salts thereof,



wherein

H;

C₁₋₄ alkyl; and

C₃₋₇ cycloalkyl; and

each R¹⁰ is independently selected from the group consisting of

C₁₋₆ alkyl; and

phenyl; wherein phenyl is optionally substituted with one or more independently selected R^A groups;

each R¹¹ is independently selected from the group consisting of

4-6 membered monocyclic heterocycle comprising 1 or 2 heteroatoms independently selected from the group consisting of O, S, and N; wherein the monocyclic heterocycle is optionally substituted with one or more independently selected R^A groups;

5-6 membered monocyclic heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from the group consisting of O, S, and N; wherein the monocyclic heteroaryl is optionally substituted with one or more independently selected R^A groups;

C₃₋₇ cycloalkyl; wherein the C₃₋₇ cycloalkyl is optionally substituted with one or more independently selected R^A groups; and

phenyl; wherein phenyl is optionally substituted with one or more independently selected R^A groups; and

each R^A is independently selected from the group consisting of

-CN,

halo;

C₁₋₄ alkyl optionally substituted with one or more independently selected halo; and

C₁₋₄ alkoxy optionally substituted with one or more independently selected halo.

[0022] Another embodiment of the disclosure relates to pharmaceutical compositions comprising a compound of the disclosure, and a pharmaceutical carrier. In one aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound 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 the disclosure, 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 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. In another aspect, there is provided a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and one or more correctors. In another aspect, there is provided a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.

[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. In another aspect, there is provided use of a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof. In another aspect, there is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one or more correctors. In another aspect, there is provided use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one or more additional therapeutic agents.

[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.

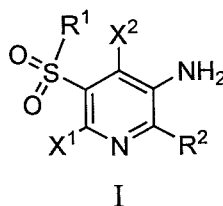
[0026] In a particular embodiment, the compounds of the disclosure are provided for use in the treatment of cystic fibrosis. In a particular embodiment, the compounds of the disclosure are provided for use in the treatment of cystic fibrosis caused by class I, II, III, IV, V, and/or VI mutations.

[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 disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition 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 disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in the treatment of cystic fibrosis. In another aspect, there is provided (5-{3-amino-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol, a pharmaceutically acceptable salt thereof.

[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,



wherein X^1 , X^2 , R^1 , and R^2 are defined above in the Summary 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 included.

[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

(5-{3-amino-5-[4-(trifluoromethyl)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-thiadiazol-2-yl)methanol;

(5-{3-amino-6-bromo-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol;

(5-{3-amino-6-chloro-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol;

(5-{3-amino-5-[2-(propan-2-yl)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol;

(5-{3-amino-4-bromo-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol; and

2-(5-{3-amino-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,2,4-oxadiazol-3-yl)ethan-1-ol.

14. 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.

15. A compound of claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14, for use in medicine.

16. A compound of claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14, for use in the treatment of cystic fibrosis.

17. Use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof.

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

19. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one or more correctors.
20. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.
21. The pharmaceutical composition of claim 20 wherein the additional therapeutic agents are selected from the group consisting of CFTR modulators and CFTR amplifiers.
22. The pharmaceutical composition of claim 20 wherein the additional therapeutic agents are CFTR modulators.
23. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cystic fibrosis in a subject in need thereof, wherein the medicament is to be administered with one or more additional therapeutic agents.
24. The use of claim 23 wherein the additional therapeutic agents are selected from the group consisting of CFTR modulators and CFTR amplifiers.
25. The use of claim 23 wherein the additional therapeutic agents are CFTR modulators.
26. The use of claim 23, wherein the additional therapeutic agents are CFTR correctors.
27. The use of claim 23, wherein the compound of claim 1, or a pharmaceutically acceptable salt thereof, is to be administered with one CFTR corrector.
28. The use of claim 23, wherein the compound of claim 1, or a pharmaceutically acceptable salt thereof, is to be administered with two CFTR correctors.
29. (5-{3-amino-5-[4-(trifluoromethoxy)benzene-1-sulfonyl]pyridin-2-yl}-1,3,4-oxadiazol-2-yl)methanol, a pharmaceutically acceptable salt thereof.