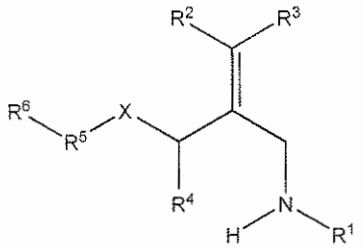
Summary

[0025] The present ~~invention~~ disclosure provides substituted haloallylamine compounds that inhibit SSAO/VAP-1. Surprisingly, modification of 2-substituted-3-haloallylamine structures described previously has led to the development of novel compounds that are potent inhibitors of the human SSAO/VAP-1 enzyme and which have much improved pharmacological and safety properties. These compounds are very potent on SSAO/VAP-1 and were surprisingly found to be very weak inhibitors of other family members, such as monoamine oxidase A, monoamine oxidase B, diamine oxidase, lysyl oxidase, and lysyl-like amine oxidases LOX1-4.

[0026] In a ~~A~~ first aspect, ~~of the invention~~ there is provide~~s~~d ~~for~~ a compound of f~~F~~ormula I:



Formula I

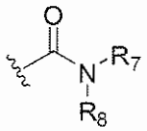
or a stereoisomer, pharmaceutically acceptable salt, polymorphic form, solvate or prodrug thereof; wherein:

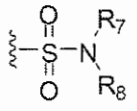
R^1 and R^4 are independently hydrogen or optionally substituted C_{1-6}alkyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen, chlorine and fluorine; provided, however, that R^2 and R^3 are not hydrogen at the same time;

R^5 is an optionally substituted arylene group;

R^6 is selected from





R^7 and R^8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-6}alkyl and optionally substituted C_{3-7}cycloalkyl; and

X is CH_2, oxygen, sulfur or SO_2.

[0027] In a~~A~~ second aspect, there is ~~of the invention~~ provided~~s for~~ a pharmaceutical composition comprising a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

[0027a] In a third aspect, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, or a composition as disclosed herein, for use in inhibiting the amine oxidase activity of SSAO/VAP-1 in a subject in need thereof, wherein said compound or composition is to be administered to said subject in an effective amount to effect a positive therapeutic response.

[0028] In one embodiment, there is ~~A third aspect of the invention~~ provided~~s for~~ a method of inhibiting the amine oxidase activity of SSAO/VAP-1 in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, or a composition as disclosed herein.

[0028a] In a fourth aspect, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, or a composition as disclosed herein, for use in the treatment of a disease associated with or modulated by SSAO/VAP-1 protein, wherein said compound or composition is to be administered to a subject in need thereof in a therapeutically effective amount.

[0029] In one~~A fourth~~ embodiment~~aspect of the invention~~, there is provided~~s for~~ a method of treating a disease associated with or modulated by SSAO/VAP-1 protein, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, or a composition as disclosed herein ~~according to the second aspect of the invention~~.

[0030] In one ~~A fifth~~ embodiment~~aspect of the invention~~, there is provided~~s for~~ a method of treating a disease associated with or modulated by SSAO/VAP-1, said method comprising administering to

a subject in need thereof a therapeutically effective amount of a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, or a composition as disclosed herein ~~according to the second aspect of the invention~~.

[0031a] In a fifth aspect, there is provided use of a compound as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a disease associated with or modulated by SSAO/VAP-1 protein.

[0031] In one ~~A sixth~~ embodiment ~~aspect of the invention~~, there is provided ~~s for~~ use of a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a disease associated with or modulated by SSAO/VAP-1 protein.

[0032] In one ~~A seventh embodiment aspect of the invention~~, there is provided ~~s for~~ a compound as disclosed herein ~~according to the first aspect of the invention~~, or a pharmaceutically acceptable salt or solvate thereof, for use in treating a disease associated with or modulated by SSAO/VAP-1 protein.

[0033] In another embodimentaspect, the present disclosureinvention describes the synthesis and use of compounds which inhibit the amine oxidase activity of SSAO/VAP-1, and describes the use of such inhibitors to treat patients suffering inflammatory diseases.

[0034] The compounds of the present disclosureinvention are useful for the treatment of the symptoms of inflammation and/or fibrosis in human subjects as well as in pets and livestock. Human inflammatory diseases contemplated for treatment herein include arthritis, Crohn's disease, irritable bowel disease, psoriasis, eosinophilic asthma, severe asthma, virally exacerbated asthma, chronic pulmonary obstructive disease, cystic fibrosis, bronchiectasis, atherosclerosis, inflammation due to diabetes, inflammatory cell-mediated tissue destruction following stroke, and the like. Human fibrotic diseases and disorders contemplated for treatment herein include idiopathic pulmonary fibrosis or other interstitial lung diseases, liver fibrosis, kidney fibrosis, fibrosis of other organs and tissues, radiation induced fibrosis, and the like.

[0035] The compounds of the present disclosureinvention are also useful for the treatment of bacteria-induced lung inflammation associated with cystic fibrosis. Treatment can be both prophylactic and therapeutic. Furthermore, the compounds of the present disclosure-invention are useful for the treatment of other bacteria-induced lung diseases such as sepsis, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), transfusion induced lung injury (TRALI), and the like.

[0036] The compounds of the present disclosureinvention are also useful for the treatment of ocular diseases, such as uveitis and macular degeneration.

[0037] The compounds of the present disclosureinvention are also useful as an adjunct therapy to treat cancer. In combination with standard and novel chemotherapeutic agents, the compounds of the present disclosureinvention can lead to better control of the cancer, and to help reduce metastatic secondary cancers.

[0038] Since SSAO/VAP-1 small molecule inhibitors actively attenuate neutrophil levels in the lipopolysaccharide (LPS) mouse model of lung neutrophilia, such molecules have the potential to treat steroid resistant asthma in human subjects. Accordingly, in accordance with one embodimentaspect of the present disclosureinvention, there are provided methods for treating patients with an inhibitor of SSAO/VAP-1 either as a prophylactic or therapeutic agent to reduce neutrophil levels and treat the symptoms of severe asthma.

[0039] In accordance with another embodimentaspect of the present disclosureinvention, there are provided methods for treating patients with an inhibitor of SSAO/VAP-1 either as a prophylactic agent or as a therapeutic agent to treat on-going disease.

[0040] In accordance with still another embodimentaspect of the present disclosureinvention, there are provided methods for the use of an SSAO/VAP-1 inhibitor to modulate the concentration of neutrophils in the airways and to treat the underlying cause of inflammation in patients suffering from inflammation of the airways.

[0041] In accordance with yet another embodimentaspect of the present disclosureinvention, there are provided methods for treating patients suffering from liver fibrosis with an SSAO/VAP-1 inhibitor.

[0042] In accordance with a further embodimentaspect of the present disclosureinvention, there are provided methods for treating patients suffering from ocular disease with an SSAO/VAP-1 inhibitor to treat symptoms of the disease.

[0043] Since SSAO/VAP-1 is expressed in various cancer types, in accordance with yet another embodimentaspect of the present disclosureinvention, there is contemplated the use of SSAO/VAP-1 inhibitors as adjunctive therapy to treat patients suffering from cancers which express SSAO/VAP-1.

[0044] In one embodiment of the methods and uses of the present disclosureinvention the disease is inflammation. In another embodiment the inflammation is associated with liver disease. In a further embodiment the inflammation is associated with respiratory disease. In a still further embodiment the inflammation is associated with cystic fibrosis. In another embodiment the inflammation is associated with asthma or chronic obstructive pulmonary disease. In a further embodiment the inflammation is associated with ocular disease.

[0045] In one embodiment of the methods and uses of the present disclosureinvention the disease is a diabetes-induced disease selected from the group consisting of diabetic nephropathy, glomerulosclerosis, diabetic retinopathy, non-alcoholic fatty liver disease and choroidal neovascularisation.

[0046] In another embodiment of the methods and uses of the present disclosure~~invention~~ the disease is a neuroinflammatory disease. In a further embodiment of the methods and uses of the present disclosure~~invention~~ the disease is selected from the group consisting of liver fibrosis, liver cirrhosis, kidney fibrosis, idiopathic pulmonary fibrosis and radiation-induced fibrosis. In a still further embodiment of the methods and uses of the present disclosure~~invention~~ the disease is cancer.

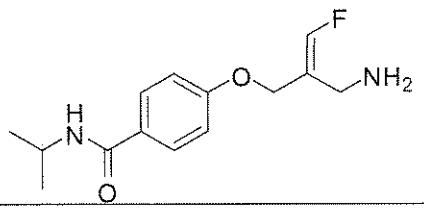
Definitions

[0047] The following are some definitions that may be helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention to those terms alone, but are put forth for a better understanding of the following description.

[0048] Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

[0049] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers, but not the exclusion of any other step or element or integer or group of elements or integers. Thus, in the context of this specification, the term "comprising" means "including principally, but not necessarily solely".

[0050] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

39		*(E)*-4-(2-(Aminomethyl)-3-fluoroallyloxy)-*N*-isopropylbenzamide;

or a pharmaceutically acceptable salt or solvate thereof.

6. A compound of Claim 1 wherein said compound is selected from the group consisting of:

(*Z*)-4-(2-(Aminomethyl)-3-fluoroallyloxy)benzene-sulfonamide, and

(*E*)-4-(2-(Aminomethyl)-3-fluoroallyloxy)-*N*-*tert*-butylbenzamide,

or a pharmaceutically acceptable salt or solvate thereof.

7. A composition comprising a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, carrier or diluent.

8. A ~~method of~~ compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to claim 7, for use in inhibiting the amine oxidase activity of SSAO/VAP-1 in a subject in need thereof, wherein said ~~method~~ compound or composition is to be administered~~comprising administering~~ to said subject in an effective amount ~~of a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to Claim 7~~ to effect a positive therapeutic response.

9. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to claim 7, for use in the treatment of ~~method of treating~~ a disease associated with or modulated by SSAO/VAP-1 protein, wherein said compound or composition is to be administered ~~method comprising administering~~ to a subject in need thereof in a therapeutically effective amount ~~of a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to Claim 7~~.

10. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 9 wherein the disease is inflammation.

11. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 10 wherein said inflammation is associated with liver disease.

12. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 10 wherein said inflammation is associated with respiratory disease.

13. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 12 wherein said inflammation is associated with cystic fibrosis.

14. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 12 wherein said inflammation is associated with asthma or chronic obstructive pulmonary disease.

15. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 10 wherein said inflammation is associated with ocular disease.

16. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 9 wherein the disease is a diabetes-induced disease selected from the group consisting of diabetic nephropathy, glomerulosclerosis, diabetic retinopathy, non-alcoholic fatty liver disease and choroidal neovascularisation.

17. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 9 wherein the disease is a neuroinflammatory disease.

18. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 9 wherein the disease is selected from the group consisting of liver fibrosis, liver cirrhosis, kidney fibrosis, idiopathic pulmonary fibrosis and radiation-induced fibrosis.

19. The compound or pharmaceutically acceptable salt or solvate thereof, or composition ~~method~~ of Claim 9 wherein the disease is cancer.

20. Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a disease associated with or modulated by SSAO/VAP-1 protein.