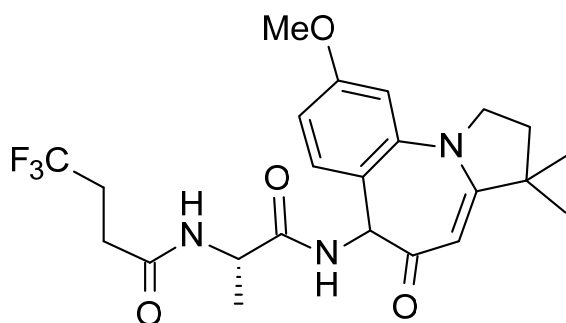


Atoh1 expression by inhibiting Notch pathway signaling. There is a further need to find compounds demonstrating desirable absorption, distribution, metabolism and excretion properties.

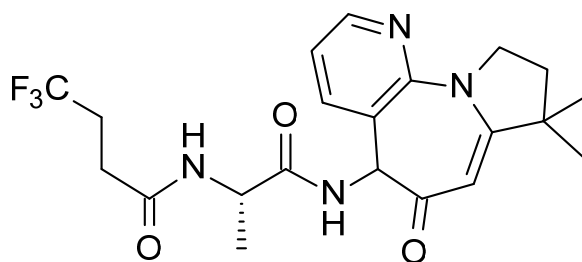
One aspect of the present disclosure is to provide a compound of the structure:



Compound 1

4,4,4-trifluoro-N-((2S)-1-((9-methoxy-3,3-dimethyl-5-oxo-2,3,5,6-tetrahydro-1H-benzo[f]pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxopropan-2-yl)butanamide, or a substantially diastereomerically pure isomer thereof, or a pharmaceutically acceptable salt of any of the above.

A further aspect of the present disclosure provides a compound of the structure:



Compound 2

N-((2S)-1-((8,8-dimethyl-6-oxo-6,8,9,10-tetrahydro-5H-pyrido[3,2-f]pyrrolo[1,2-a]azepin-5-yl)amino)-1-oxopropan-2-yl)-4,4,4-trifluorobutanamide, or a substantially

diastereomerically pure isomer thereof, or a pharmaceutically acceptable salt of any of the above.

Another aspect of the present disclosure provides a pharmaceutical composition comprising either Compound 1, or a substantially pure diastereomer thereof; or

5 Compound 2, or a substantially pure diastereomer thereof; or a pharmaceutically acceptable salt of any of the above, and a pharmaceutically acceptable carrier.

The present disclosure also provides a method of treating a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, 10 triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma, hepatocellular carcinoma, intrahepatic and extrahepatic 15 cholangiocarcinoma, and adenoid cystic carcinoma in a patient comprising administering to a patient in need thereof a therapeutically effective amount of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof.

20 The present disclosure further provides a method of treating lung cancer in a patient comprising administering to a patient in need thereof a therapeutically effective amount of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof.

25 The present disclosure also provides a method of treating sensorineural hearing loss caused by auditory hair cell loss in a patient in need thereof comprising administering a therapeutically effective amount of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, to said patient.

The present disclosure further provides a method of inducing auditory hair cell generation in a patient in need thereof, comprising administering a therapeutically effective amount of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a
5 pharmaceutically acceptable salt thereof, to said patient.

Another aspect of the present disclosure provides Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for use in therapy.

10 The present disclosure also provides Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia,
15 triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma, hepatocellular carcinoma, intrahepatic or extrahepatic cholangiocarcinoma, or
20 adenoid cystic carcinoma.

The present disclosure also further provides Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of lung cancer.

25 The present disclosure also provides Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof for use in the treatment of sensorineural hearing loss caused by auditory hair cell loss.

The present disclosure further provides Compound 1, a substantially pure
30 diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2,

a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for use in inducing auditory hair cell generation.

Another aspect of the present disclosure provides use of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma, hepatocellular carcinoma, intrahepatic or extrahepatic cholangiocarcinoma, or adenoid cystic carcinoma.

The present disclosure also provides a use of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of lung cancer.

Another aspect of the present disclosure provides use of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of sensorineural hearing loss caused by auditory hair cell loss.

A further aspect of the present disclosure provides use of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inducing auditory hair cell generation.

The present disclosure also provides a method of treating sensorineural hearing loss caused by auditory hair cell loss in a canine companion animal comprising administering a therapeutically effective amount of Compound 1, a substantially pure

diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, to said canine companion animal.

The present disclosure further provides a method of inducing auditory hair cell generation in a canine companion animal in need thereof, comprising administering a therapeutically effective amount of Compound 1, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, to said canine companion animal.

The phrase "Compound 1, a diastereomer thereof" means 4,4,4-trifluoro-N-((2S)-1-((9-methoxy-3,3-dimethyl-5-oxo-2,3,5,6-tetrahydro-1H-benzo[f]pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxopropan-2-yl)butanamide; or a diastereomer 4,4,4-trifluoro-N-((S)-1-(((S)-9-methoxy-3,3-dimethyl-5-oxo-2,3,5,6-tetrahydro-1H-benzo[f]pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxopropan-2-yl)butanamide or 4,4,4-trifluoro-N-((S)-1-(((R)-9-methoxy-3,3-dimethyl-5-oxo-2,3,5,6-tetrahydro-1H-benzo[f]pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxopropan-2-yl)butanamide. Similarly, the phrase "Compound 2, a diastereomer thereof" means N-((2S)-1-((8,8-dimethyl-6-oxo-6,8,9,10-tetrahydro-5H-pyrido[3,2-f]pyrrolo[1,2-a]azepin-5-yl)amino)-1-oxopropan-2-yl)-4,4,4-trifluorobutanamide; or a diastereomer N-((S)-1-(((S)-8,8-dimethyl-6-oxo-6,8,9,10-tetrahydro-5H-pyrido[3,2-f]pyrrolo[1,2-a]azepin-5-yl)amino)-1-oxopropan-2-yl)-4,4,4-trifluorobutanamide or N-((S)-1-(((R)-8,8-dimethyl-6-oxo-6,8,9,10-tetrahydro-5H-pyrido[3,2-f]pyrrolo[1,2-a]azepin-5-yl)amino)-1-oxopropan-2-yl)-4,4,4-trifluorobutanamide.

The term "patient" means mammal and "mammal" includes, but is not limited to, a human after the postnatal period. The postnatal period in a human is the period beginning immediately after childbirth and extending for 30 days.

"Therapeutically effective amount" or "effective amount" means the dosage of either Compound 1, a substantially pure diastereomer thereof, which is Isomer 1 or Isomer 2, or a pharmaceutically acceptable salt thereof, or Compound 2, a substantially pure diastereomer thereof, which is Isomer 1 or Isomer 2, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition containing any of the above, necessary to inhibit Notch signaling in a cancer patient, and either destroy the target

4. A compound of claim 1 or 2, or a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for use in therapy.

5. Use of a compound of claim 1 or 2, or a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, triple negative breast cancer, breast cancer, ovarian cancer, melanoma, lung cancer, non small cell lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, oral squamous cell carcinoma, skin cancer, medulloblastoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma, hepatocellular carcinoma, intrahepatic or extrahepatic cholangiocarcinoma, or adenoid cystic carcinoma.
6. The use of claim 5, for the manufacture of a medicament for the treatment of lung cancer.
7. Use of a compound of claim 1 or 2, or a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of sensorineural hearing loss caused by auditory hair cell loss.

8. Use of a compound of claim 1 or 2, or a substantially pure diastereomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inducing auditory hair cell generation.