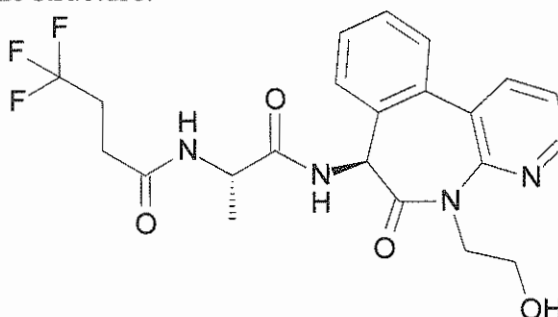


Figure 1 is a representative X-ray powder diffraction pattern for the compound of Example 2.

One aspect of the ~~invention~~present disclosure is to provide a Notch signaling inhibitor compound of the structure:



Compound 1

or a pharmaceutically acceptable salt or hydrate thereof.

A second aspect of the ~~present invention~~present disclosure provides a pharmaceutical composition comprising 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier. In a particular embodiment, the pharmaceutical composition comprises 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzoazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

~~A third aspect of the present invention~~A third aspect of the present disclosure also provides a method of inhibiting Notch signaling in a cancer patient in need thereof, comprising administering a therapeutically effective amount of, 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, to said patient.

~~A fourth aspect of the present invention~~A fourth aspect of the present disclosure also provides a method of treating a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer,

ovarian cancer, melanoma, lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, squamous cell carcinoma (oral), skin cancer or medulloblastoma in a patient comprising administering to a patient in need thereof a therapeutically effective amount of 4,4,4-trifluoro-N-[(1S)-2-
5 [[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof.

~~A fifth aspect of the present invention~~disclosure further provides a method of treating a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer,
10 melanoma, pancreatic cancer, glioblastoma or colorectal cancer in a patient comprising administering to a patient in need thereof a therapeutically effective amount of 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof.

~~A sixth aspect of the present invention~~disclosure also provides a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-
15 d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in therapy.

~~A thirdseventh aspect of the present invention~~disclosure provides a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-
20 d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer,
25 melanoma, lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, squamous cell carcinoma (oral), skin cancer or medulloblastoma.

~~An eighth aspect of the present invention~~disclosure further provides a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-
30 d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer, melanoma, pancreatic cancer, glioblastoma or colorectal cancer.

A fourth aspect of the present disclosure provides a compound as defined above, or a pharmaceutically acceptable salt or hydrate thereof, for use in the treatment of a cancer which is T-cell acute lymphoblastic leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer, melanoma, pancreatic cancer, glioblastoma or colorectal cancer.

A ~~fifth~~^{ninth} aspect of the present invention~~disclosure~~ provides use of a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for the treatment of a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer, melanoma, lung cancer, pancreatic cancer, glioblastoma, colorectal cancer, head and neck cancer, cervical cancer, prostate cancer, liver cancer, squamous cell carcinoma (oral), skin cancer or medulloblastoma.

A ~~sixth~~^{tenth} aspect of the present invention~~disclosure~~ provides use of a compound 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for the treatment of a cancer which is T-cell acute lymphoblastic leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, erythroleukemia, breast cancer, ovarian cancer, melanoma, pancreatic cancer, glioblastoma or colorectal cancer.

The term "patient" means mammal and "mammal" includes, but is not limited to, a human.

"Therapeutically effective amount" or "effective amount" means the dosage of the compound, or pharmaceutically acceptable salt or hydrate thereof, or pharmaceutical composition containing the compound, or pharmaceutically acceptable salt or hydrate thereof, necessary to inhibit Notch signaling in a cancer patient, and either destroy the target cancer cells or slow or arrest the progression of the cancer in a patient. Anticipated dosages of Compound 1 or a pharmaceutically acceptable salt or hydrate thereof are in the range of 0.1 to 200 mg/patient/day. Preferred dosages are anticipated to be in the range of 1 to 175 mg/patient/day. Most preferred dosages are anticipated to be in the range of 5 to 150 mg/patient/day. The exact dosage required to treat a patient and the length of treatment time will be determined by a physician in view of the stage and severity of the disease as well as the specific needs and response of the individual patient. Although expressed as dosage on a per day basis, the dosing regimen may be adjusted to provide a more optimal therapeutic benefit to a patient and to manage and ameliorate mucoid

enteropathy (hypersecretion and accumulation of mucus in the gastrointestinal tract). In addition to daily dosing, dosing every other day (Q2D); every other day over a five day period followed by two days without dosing (T.I.W.); or every third day (Q3D) may be appropriate. A dosing regimen of every other day, T.I.W., or every third day is preferred
5 along with administration (pre-, concomitant, or post-administration of Compound 1 of dexamethasone to manage or ameliorate mucoid enteropathy.

The terms "treatment," "treat," and "treating," are meant to include the full spectrum of intervention for the cancer from which the patient is suffering, such as administration of the active compound to alleviate to slow or reverse one or more of the
10 symptoms and to delay progression of the cancer even if the cancer is not actually eliminated. The patient to be treated is a mammal, in particular a human being.

The compound of the present ~~invention~~disclosure is preferably formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and administered by a variety of routes. Preferably, such compositions are for oral administration. Such
15 pharmaceutical compositions and processes for preparing them are well known in the art. *See, e.g.*, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, *et al.*, eds., 19th ed., Mack Publishing Co., 1995). In a particular embodiment, the pharmaceutical composition comprises 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzoazepin-7-yl]amino]-1-methyl-2-oxo-
20 ethyl]butanamide, or a pharmaceutically acceptable salt or hydrate thereof, together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients particularly for treatment of cancer generally or a specific cancer type.

The compound of the present ~~invention~~disclosure is capable of reaction with a number of inorganic and organic acids to form pharmaceutically acceptable acid addition
25 salts. Such pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. *See, e.g.*, P. Stahl, *et al.*, HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

30 Compound 1, or a pharmaceutically acceptable salt or hydrate thereof, may be prepared by a variety of procedures known in the art, as well as those described below.

The specific synthetic steps may be combined in different ways to prepare Compound 1, or a pharmaceutically acceptable salt or hydrate thereof.

Compound 1 is named: 4,4,4-trifluoro-N-[(1S)-2-[[[(7S)-5-(2-hydroxyethyl)-6-oxo-7H-pyrido[2,3-d][3]benzazepin-7-yl]amino]-1-methyl-2-oxo-ethyl]butanamide; and
5 may also be named: N-[(1S)-2-[[[(7S)-6,7-dihydro-5-(2-hydroxyethyl)-6-oxo-5H-pyrido[3,2-a][3]benzazepin-7-yl]amino]-1-methyl-2-oxoethyl]-4,4,4-trifluorobutanamide; and other names may be used to unambiguously identify Compound 1.

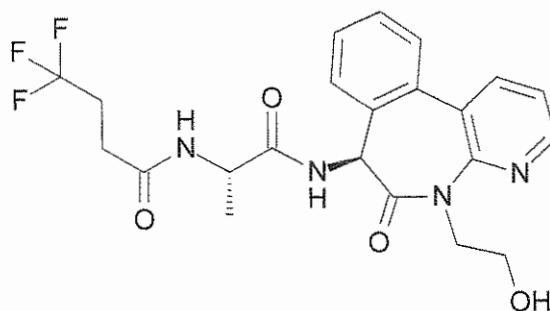
It will be understood Compound 1 is depicted as a single stereoisomer. There are two chiral centers giving rise to four stereoisomers. As used herein, references to
10 Compound 1 are meant to also include racemic mixtures including Compound 1. Herein, the Cahn-Ingold-Prelog designations of (R)- and (S)- are used to refer to specific isomers. Specific stereoisomers can be prepared by stereospecific synthesis using enantiomerically pure or enriched starting materials. The specific stereoisomers of either starting materials, intermediates, or racemic mixtures including Compound 1 can be resolved by
15 techniques well known in the art, such as those found in Stereochemistry of Organic Compounds, E. I. Eliel and S. H. Wilen (Wiley 1994) and Enantiomers, Racemates, and Resolutions, J., Jacques, A. Collet, and S. H. Wilen (Wiley 1991), including chromatography on chiral stationary phases, enzymatic resolutions, or fractional crystallization or chromatography of diastereomers formed for that purpose, such as
20 diastereomeric salts. While all mixtures containing the compound of the present ~~invention~~disclosure are contemplated within the present ~~invention~~disclosure, the preferred embodiment is Compound 1.

It has also been found that Compound 1 exists as atropisomers, or specific conformers. In aqueous solutions, 8-9% of atropisomer 2 (minor atropisomer) is detected
25 by ¹H NMR and LC-MS in equilibrium with atropisomer 1 (major atropisomer) at ambient temperature after 24 hours. In organic solvents, at ambient temperature after 24 hours, approximately 1-2% of atropisomer 2 is detected by ¹H NMR and LC-MS in equilibrium with atropisomer 1. Although detectable by ¹H NMR and LC-MS analysis, atropisomer 2 is not isolable.

30 The compounds employed as initial starting materials in the synthesis of the compound of the present ~~invention~~disclosure are well known and, to the extent not commercially

We claim:

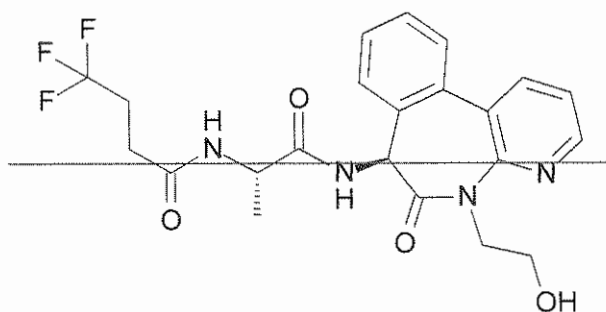
1. A compound of the structure:



Compound 1

or a pharmaceutically acceptable salt or hydrate thereof.

2. A compound of claim 1 which is ~~the~~ structure:



Compound 1

or a pharmaceutically acceptable salt thereof.