

PI3K α INHIBITORS AND METHODS OF MAKING AND USING THE SAME**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/599,157, filed on November 15, 2023, the entirety of which is hereby incorporated by reference.

BACKGROUND

[0002] Phosphatidylinositol 3-kinases (PI3Ks) comprise a family of lipid kinases that catalyze the transfer of phosphate to the D-3' position of inositol lipids to produce phosphoinositol-3-phosphate (PIP), phosphoinositol-3,4-diphosphate (PIP₂) and phosphoinositol-3,4,5-triphosphate (PIP₃), which, in turn, act as second messengers in signaling cascades by docking proteins containing pleckstrin-homology, FYVE, Phox and other phospholipid-binding domains into a variety of signaling complexes often at the plasma membrane (Vanhaesebroeck et al., *Annu. Rev. Biochem.* 70:535 (2001); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615 (2001)). Of the two Class I PI3K sub-classes, Class 1A PI3Ks are heterodimers composed of a catalytic p110 subunit (alpha, beta, or delta isoforms) constitutively associated with a regulatory subunit that can be p85 alpha, p55 alpha, p50 alpha, p85 beta, or p55 gamma. The Class 1B sub-class has one family member, a heterodimer composed of a catalytic p110 gamma subunit associated with one of two regulatory subunits, p101 or p84 (Fruman et al., *Annu. Rev. Biochem.* 67:481 (1998); Suire et al., *Curr. Biol.* 15:566 (2005)). The modular domains of the p85/55/50 subunits include Src Homology (SH2) domains that bind phosphotyrosine residues in a specific sequence context on activated receptor and cytoplasmic tyrosine kinases, resulting in activation and localization of Class 1A PI3Ks. Class 1B PI3K is activated directly by G protein-coupled receptors that bind a diverse repertoire of peptide and non-peptide ligands (Stephens et al., *Cell* 89:105 (1997); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615-675 (2001)).

[0003] Consequently, the resultant phospholipid products of Class I PI3Ks link upstream receptors with downstream cellular activities including proliferation, survival, chemotaxis, cellular trafficking, motility, metabolism, inflammatory and allergic responses, transcription and translation (Cantley et al., *Cell* 64:281 (1991); Escobedo and Williams, *Nature* 335:85 (1988); Fantl et al., *Cell* 69:413 (1992)). In many cases, PIP₂ and PIP₃ recruit Akt, the product of the human homologue of the viral oncogene v-Akt, to the plasma membrane where it acts

as a nodal point for many intracellular signaling pathways important for growth and survival (Fantl et al., Cell 69:413-423 (1992); Bader et al., Nature Rev. Cancer 5:921 (2005); Vivanco and Sawyer, Nature Rev. Cancer 2:489 (2002)).

[0004] Aberrant regulation of PI3K, which often increases survival through Akt activation, is one of the most prevalent events in human cancer and has been shown to occur at multiple levels. The tumor suppressor gene PTEN, which dephosphorylates phosphoinositides at the 3' position of the inositol ring, and in so doing antagonizes PI3K activity, is functionally deleted in a variety of tumors. In other tumors, the genes for the p110 α isoform, PIK3CA, and for Akt are amplified, and increased protein expression of their gene products has been demonstrated in several human cancers. Furthermore, mutations and translocation of p85 α that serve to up-regulate the p85-p110 complex have been described in human cancers. Finally, somatic missense mutations in PIK3CA that activate downstream signaling pathways have been described at significant frequencies in a wide diversity of human cancers (Kang et al., Proc. Natl. Acad. Sci. USA 102:802 (2005); Samuels et al., Science 304:554 (2004); Samuels et al., Cancer Cell 7:561-573 (2005)). These observations show that deregulation of phosphoinositide-3 kinase, and the upstream and downstream components of this signaling pathway, is one of the most common deregulations associated with human cancers and proliferative diseases (Parsons et al., Nature 436:792 (2005); Hennessey et al., Nature Rev. Drug Disc. 4:988-1004 (2005)).

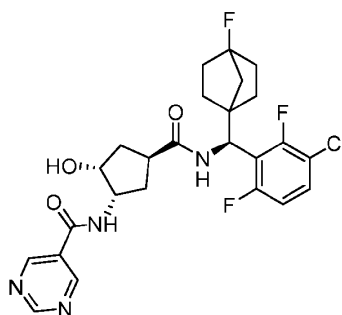
[0005] In view of the above, inhibitors of PI3K α would be of particular value in the treatment of proliferative disease and other disorders. While multiple inhibitors of PI3Ks have been developed (for example, taselisib, alpelisib, buparlisib and others), these molecules inhibit multiple Class 1A PI3K isoforms. Inhibitors that are active against multiple Class 1A PI3K isoforms are known as "pan-PI3K" inhibitors. A major hurdle for the clinical development of existing PI3K inhibitors has been the inability to achieve the required level of target inhibition in tumors while avoiding toxicity in cancer patients. Pan-PI3K inhibitors share certain target-related toxicities including diarrhea, rash, fatigue, and hyperglycemia. The toxicity of PI3K inhibitors is dependent on their isoform selectivity profile. Inhibition of PI3K α is associated with hyperglycemia and rash, whereas inhibition of PI3K δ or PI3K γ is associated with diarrhea, myelosuppression, and transaminitis (Hanker et al., Cancer Discovery (2019) PMID: 30837161).

[0006] Polymorphism is the ability of a substance to crystallize in more than one crystal lattice arrangement. Crystallization, or polymorphism, can influence many aspects of solid state properties of a drug substance. A crystalline form may differ considerably from an amorphous form, and different crystal forms of a substance may differ considerably from one another in many respects including solubility, dissolution rate and/or bioavailability. Generally, it is difficult to predict whether or not a given compound will form various crystalline solid state forms. It is even more difficult to predict the physical properties of these crystalline solid state forms. Further, it can be advantageous to have a crystalline form of a therapeutic agent for certain formulations, e.g., formulations suitable for subcutaneous use.

SUMMARY

[0007] This disclosure is generally directed to Compounds I and II, and solvates thereof, and solid forms thereof.

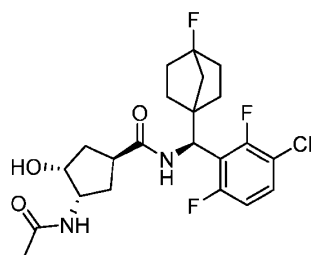
[0008] In some embodiments, the present disclosure provides a compound in solid form, wherein the compound is Compound I:



I,

or a solvate thereof.

[0009] In some embodiments, the present disclosure provides a compound in solid form, wherein the compound is Compound II:



II,

or a solvate thereof.

[0010] In another aspect, provided herein is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a solid form, as described herein, and a pharmaceutically acceptable excipient.

[0011] In another aspect, provided herein is a method of using a compound or a solvate thereof, or a solid form, or a pharmaceutical composition thereof, as described herein, for inhibiting PI3K α activity and for treating a disorder, disease, and/or condition as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 depicts an XRPD pattern of Compound I Form A.

[0013] FIG. 2 depicts an XRPD pattern of Compound I Form B.

[0014] FIG. 3 depicts an XRPD pattern of Compound I Form C.

[0015] FIG. 4 depicts an XRPD pattern of Compound II Form A.

[0016] FIG. 5 depicts an XRPD pattern of Compound II Form B.

[0017] FIG. 6 depicts a DSC and a TGA thermogram of Compound I Form A.

[0018] FIG. 7 depicts a DSC thermogram of Compound I Form B.

[0019] FIG. 8 depicts a DSC and a TGA thermogram of Compound I Form C.

[0020] FIG. 9 depicts a DSC and a TGA thermogram of Compound II Form A.

[0021] FIG. 10 depicts a DSC and a TGA thermogram of Compound II Form B.

DETAILED DESCRIPTION

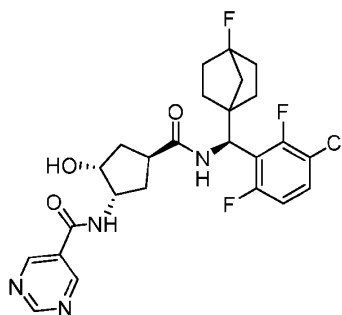
General Description of Certain Embodiments of the Disclosure

[0022] In some embodiments, Compounds I and II are PI3K α inhibitors and useful for treating disorders, diseases, and/or conditions, for example, the “PI3K α -mediated” disorders, diseases, and/or conditions as described herein. In some embodiments, this disclosure provides solid

forms of the compounds (e.g., as a freebase, or a salt, or a solvate) that imparts characteristics such as improved aqueous solubility, stability, and ease of formulation.

Solid Forms of Compound I

[0023] In some embodiments, provided herein is a compound in solid form, wherein the compound is Compound I:



I,

or a solvate thereof.

[0024] It is contemplated that Compound I (i.e., (N-((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)pyrimidine-5-carboxamide) can exist in a variety of physical forms. For example, Compound I can be in a solution, a suspension, or in a solid form. In certain embodiments, Compound I is in a solid form. When Compound I is in a solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0025] In some embodiments, Compound I is an amorphous solid. In some embodiments, the solid form of Compound I is crystalline. In some embodiments, the solid form of Compound I is a mixture of one or more crystalline forms. In some embodiments, the solid form of Compound I is a mixture of an amorphous solid and one or more crystalline forms.

[0026] In some embodiments, Compound I is an anhydrate. In some embodiments, Compound I is in a hydrate form. In some embodiments, Compound I is in a hemi-hydrate form.

[0027] In some embodiments, the present disclosure provides a form of Compound I substantially free of impurities. As used herein, the term “substantially free of impurities” means that the compound contains no significant amount of extraneous matter. Such extraneous

matter may include different forms of Compound I, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound I.

[0028] In some embodiments, a solid form of Compound I, or a solvate thereof, is present in an amount of at least about 95, 95.5, 96, 96.5, 97, 97.5, 98.0, 98.5, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 weight percent where the percentages are based on the total weight of the composition. In some embodiments, a solid form of Compound I, or a solvate thereof, contains no more than about 0.40, no more than about 0.35, no more than about 0.3, no more than about 0.25, no more than about 0.2, no more than about 0.15, no more than about 0.10, or no more than about 0.05 weight percent of any single impurity wherein the percentages are based on the total weight of the composition. In some embodiments, an impurity is selected from those as described in the Examples herein.

[0029] In some embodiments, a solid form of Compound I, or a solvate thereof, is present in an amount of at least about 95, 95.5, 96, 96.5, 97, 97.5, 98.0, 98.5, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 area percent by HPLC relative to the total area of the HPLC chromatogram. In some embodiments, a solid form of Compound I, or a solvate thereof, contains no more than about 0.4, no more than about 0.35, no more than about 0.3, no more than about 0.25, no more than about 0.2, no more than about 0.15, no more than about 0.10, or no more than about 0.05 area percent HPLC of any single impurity relative to the total area of the HPLC chromatogram. In some embodiments, an impurity is selected from those as described in the examples herein. In some embodiments, a HPLC method is selected from the HPLC methods as described in Examples herein.

[0030] The structure depicted for compound of Compound I is also meant to include all tautomeric forms. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

[0031] It has been found that Compound I can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein. In some embodiments, the crystalline form of Compound I is Form A, Form B, or Form C, as described herein.

[0032] In some embodiments, the crystalline form of Compound I is Form A. In some embodiments, Form A of Compound I has an X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 1.

[0033] In some embodiments, the crystalline form of Compound I is Form B. In some embodiments, Form B of Compound I has an X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 2.

[0034] In some embodiments, the crystalline form of Compound I is Form C. In some embodiments, Form C of Compound I has an X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 3.

Form A of Compound I

[0035] In some embodiments, the solid form of Compound I is Form A. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , and about 16.5 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , about 16.5 2θ , about 24.2 2θ , about 19.8 2θ , about 14.5 2θ , and about 18.2 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , about 16.5 2θ , about 24.2 2θ , about 19.8 2θ , about 14.5 2θ , and about 18.2 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , about 16.5 2θ , about 24.2 2θ , about 19.8 2θ , about 14.5 2θ , and about 18.2 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , about 16.5 2θ , about 24.2 2θ , about 19.8 2θ , about 14.5 2θ , and about 18.2 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2θ , each selected from the group consisting of about 17.4 2θ , about 13.3 2θ , about 16.5 2θ , about 24.2 2θ , about 19.8 2θ , about 14.5 2θ , and about 18.2 2θ . In some embodiments, Form A of Compound I may be characterized by a X-ray

powder diffraction pattern comprising characteristic peaks at about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .

[0036] In some embodiments, Form A of Compound I has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1. In some embodiments, Form A of Compound I may be characterized by a X-ray powder diffraction pattern with at least seven characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.1.

Table 1.1 Compound I, Form A XRPD peak listing (each peak is within ± 0.2 degrees 2 θ).

Degrees 2 θ	Relative Intensity [%]
3.9	13.7
7.8	25.8
8.7	10.9
9.3	8.4
10.8	11.3
12.1	18.6
13.3	78.6
14.1	6.1
14.5	34.4
15.7	9.4
16.5	50.7
17.4	100.0
17.8	16.0
18.2	30.1

18.7	10.7
19.4	27.2
19.8	35.0
20.6	26.9
21.3	16.7
21.7	10.5
22.1	13.4
22.8	15.5
23.5	14.4
24.2	36.0
24.9	14.6
25.1	15.3
25.4	16.1
26.6	16.9
27.3	12.3
27.7	20.5
28.9	9.2
30.9	10.2

[0037] As used herein, the term “about” in the context of peaks at degrees 2 θ means that a peak can be the given 2 θ value $\pm$ 0.2, or the given 2 θ value $\pm$ 0.1, or the given value. For example, a peak of “about 12.0 2 θ ” means a peak can be 11.8 2 θ , 11.9 2 θ , 12.0 2 θ , 12.1 2 θ , or 12.2 2 θ .

[0038] In some embodiments, Form A of Compound I has a thermogravimetric analysis (TGA) pattern substantially similar to that depicted in FIG. 6. In some embodiments, Form A of Compound I can be characterized by substantial similarity to two or more figures simultaneously (e.g., FIG. 1 and FIG. 6).

Form B of Compound I

[0039] In some embodiments, the solid form of Compound I is Form B. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , and about 17.5 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of about

18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ . In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern comprising characteristic peaks at about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ .

[0040] In some embodiments, Form B of Compound I has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2. In some embodiments, Form B of Compound I may be characterized by a X-ray powder diffraction pattern with at least seven characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.2.

Table 1.2 Compound I, Form B XRPD peak listing (each peak is within ± 0.2 degrees 2 θ).

Degrees 2 θ	Relative Intensity. [%]
4.9	7.6
5.7	34.6
7.5	2.4
9.5	6.5
9.8	10.8
10.5	10.6
10.7	22.0
11.4	48.0
11.7	7.2
11.9	4.5
12.4	2.1
13.1	4.1
13.3	12.3
13.6	24.4
13.9	11.7
14.8	4.1
15.2	4.2
15.5	12.6
15.8	15.7
16.9	14.4
17.3	22.6
17.5	37.1
17.8	18.4
18.5	100.0
19.1	12.8
19.4	15.8
20.0	19.5
20.6	16.5
21.0	11.2
21.2	15.1
21.7	7.3
22.0	8.9
22.3	12.2
22.6	8.8
22.8	11.4
23.6	9.1
24.1	6.7
24.6	12.3
25.1	6.6
25.7	4.6
26.4	5.2

27.4	5.6
28.1	3.5
28.8	3.0

[0041] In some embodiments, Form B of Compound I has a thermogravimetric analysis (TGA) pattern substantially similar to that depicted in FIG. 7. In some embodiments, Form B of Compound I can be characterized by substantial similarity to two or more figures simultaneously (e.g., FIG. 2 and FIG. 7).

Form C of Compound I

[0042] In some embodiments, the solid form of Compound I is Form C. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , and about 20.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2θ , each selected from the group consisting of about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern comprising characteristic peaks at about 19.3 2θ , about 19.9 2θ , about 20.0 2θ , about 10.1 2θ , about 19.6 2θ , about 15.2 2θ , and about 22.0 2θ . In some

embodiments, Form C of Compound I has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 3A.

[0043] In some embodiments, Form C of Compound I has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3. In some embodiments, Form C of Compound I may be characterized by a X-ray powder diffraction pattern with at least seven characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.3.

Table 1.3 Compound I, Form C XRPD peak listing (each peak is within ± 0.2 degrees 2θ).

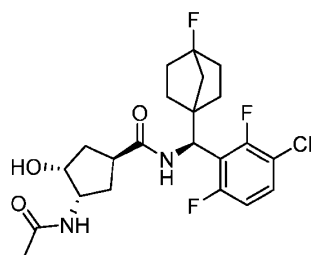
Degrees 2θ	Relative Intensity [%]
4.7	4.1
5.7	8.5
9.6	46.0
10.1	77.7
10.5	16.8
11.5	39.5
11.8	10.4
12.4	23.6
12.7	12.8
13.1	32.6
14.0	4.2
15.2	66.5
16.2	13.3
16.7	32.6

17.1	34.1
17.6	18.5
17.9	18.4
18.5	21.6
18.7	19.3
19.3	100.0
19.6	72.0
19.9	89.5
20.0	79.6
20.4	36.2
21.0	13.5
21.5	29.2
22.0	51.4
22.7	22.7
23.5	23.5
23.8	20.6
24.2	23.9
25.4	15.1
25.6	13.1
26.3	23.8
27.2	13.0
27.7	10.2
28.2	10.3
29.5	12.8
30.6	6.5

[0044] In some embodiments, Form C of Compound I has a thermogravimetric analysis (TGA) pattern substantially similar to that depicted in FIG. 8. In some embodiments, Form C of Compound I can be characterized by substantial similarity to two or more of these figures simultaneously (e.g., FIG. 3 and FIG. 8).

Solid Forms of Compound II

[0045] In some embodiments, provided herein is a compound in solid form, wherein the compound is Compound II:



II,

or a solvate thereof.

[0046] It is contemplated that Compound II (i.e., (1S,3S,4R)-3-acetamido-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide) can exist in a variety of physical forms. For example, Compound II can be in solution, suspension, or in solid form. In certain embodiments, Compound II is in solid form. When compound II is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0047] In some embodiments, Compound II is an amorphous solid. In some embodiments, the solid form of Compound II is crystalline. In some embodiments, the solid form of Compound II is a mixture of one or more crystalline forms. In some embodiments, the solid form of Compound II is a mixture of an amorphous solid and one or more crystalline forms.

[0048] In some embodiments, the solid form of Compound II is anhydrate. In some embodiments, the solid form of Compound II may be a hydrate. In some embodiments, the solid form of Compound II may be a hemi-hydrate.

[0049] In some embodiments, the present disclosure provides a solid form of Compound II substantially free of impurities. As used herein, the term “substantially free of impurities” means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include different forms of Compound II, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound II.

[0050] In some embodiments, a solid form of Compound II, or a solvate thereof, is present in an amount of at least about 95, 95.5, 96, 96.5, 97, 97.5, 98.0, 98.5, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 weight percent where the percentages are based on the total weight of the composition. In some embodiments, a solid form of Compound II, or a solvate thereof, contains no more than about 0.40, no more than about 0.35, no more than about 0.3, no more than about 0.25, no more than about 0.2, no more than about 0.15, no more than about 0.10, or

no more than about 0.05 weight percent of any single impurity wherein the percentages are based on the total weight of the composition. In some embodiments, an impurity is selected from those as described in the examples herein.

[0051] In some embodiments, a solid form of Compound II, or a solvate thereof, is present in an amount of at least about 95, 95.5, 96, 96.5, 97, 97.5, 98.0, 98.5, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 area percent by HPLC relative to the total area of the HPLC chromatogram. In some embodiments, a solid form of Compound II, or a solvate thereof, contains no more than about 0.4, no more than about 0.35, no more than about 0.3, no more than about 0.25, no more than about 0.2, no more than about 0.15, no more than about 0.10, or no more than about 0.05 area percent HPLC of any single impurity relative to the total area of the HPLC chromatogram. In some embodiments, an impurity is selected from those as described in the examples herein. In some embodiments, a HPLC method is selected from the HPLC methods as described in Examples herein.

[0052] The structure depicted for compound of Compound II is also meant to include all tautomeric forms. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

[0053] It has been found that compound II can exist in a variety of solid forms. Exemplary such forms include crystalline polymorphs such as those described herein. In some embodiments, the crystalline form of Compound II is Form A, or Form B, as described herein.

[0054] In some embodiments, the crystalline form of Compound II is Form A. In some embodiments, Form A of Compound II has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 4.

[0055] In some embodiments, the crystalline form of Compound II is Form B. In some embodiments, Form B of Compound II has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 5.

Form A of Compound II

[0056] In some embodiments, the solid form of Compound II is Form A. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about

15.7 2 θ , about 14.7 2 θ , and about 20.0 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ . In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern comprising characteristic peaks at about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .

[0057] In some embodiments, Form A of Compound II has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the

group consisting of the peaks listed in Table 1.4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.4. In some embodiments, Form A of Compound II may be characterized by a X-ray powder diffraction pattern with at least seven characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.4.

Table 1.4 Compound II, Form A XRPD peak listing (each peak is within ± 0.2 degrees 2 θ).

Degrees 2 θ	Relative Intensity [%]
5.2	10.9
8.8	6.2
10.0	10.7
10.5	7.4
12.6	8.9
13.3	23.1
13.7	3.4
14.1	3.9
14.7	76.0
15.7	100.0
16.1	15.8
16.5	25.6
17.1	6.8
17.5	23.1
18.1	16.6
18.4	19.2
18.7	12.2
19.4	4.9
20.0	73.5
21.0	61.1
22.3	21.4
23.2	31.0
23.8	15.4
24.2	22.2
26.7	13.4
27.3	18.7
28.2	5.6
29.5	9.4
30.3	11.1

[0058] In some embodiments, Form A of Compound II has a thermogravimetric analysis (TGA) pattern substantially similar to that depicted in FIG. 9. In some embodiments, Form A

of Compound II can be characterized by substantial similarity to two or more figures simultaneously (e.g., FIG. 4 and FIG. 9).

Form B of Compound II

[0059] In some embodiments, the solid form of Compound II is Form B. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , and about 16.9 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least three characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2θ , each selected from the group consisting of about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ . In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern comprising characteristic peaks at about 23.6 2θ , about 10.9 2θ , about 16.9 2θ , about 15.1 2θ , about 26.1 2θ , about 12.9 2θ , and about 19.4 2θ .

[0060] In some embodiments, Form B of Compound II has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least two characteristic peaks, in degrees 2θ , each selected from the group consisting of the peaks listed in Table 1.5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder

diffraction pattern with at least three characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least four characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least five characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least six characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.5. In some embodiments, Form B of Compound II may be characterized by a X-ray powder diffraction pattern with at least seven characteristic peaks, in degrees 2 θ , each selected from the group consisting of the peaks listed in Table 1.5.

Table 1.5 Compound II, Form B XRPD peak listing (each peak is within ± 0.2 degrees 2 θ).

Degrees 2 θ	Relative Intensity [%]
6.7	3.7
10.1	21.7
10.3	13.4
10.9	94.8
11.5	34.6
11.7	21.9
12.9	66.7
13.2	5.3
13.8	2.3
15.1	79.6
16.1	15.9
16.9	83.3
17.8	18.4
18.4	42.2
19.0	48.0
19.4	54.2
20.0	10.0
20.2	23.7
20.6	26.3
21.1	12.8
22.0	12.0
22.5	45.0
23.1	6.3
23.6	100.0

24.0	12.1
25.1	6.7
25.6	7.1
26.1	69.2
26.3	34.8
26.8	7.4
27.1	8.2
27.6	13.7
28.3	14.4
29.9	4.9
30.5	15.9
31.3	11.1

[0061] In some embodiments, Form B of Compound II has a thermogravimetric analysis (TGA) pattern substantially similar to that depicted in FIG. 10. In some embodiments, Form B of Compound II can be characterized by substantial similarity to two or more figures simultaneously (e.g., FIG. 5 and FIG. 10).

Compositions

[0062] Another aspect of the disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, topical, buccal, ocular, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral, subcutaneous or intravenous administration.

[0063] Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compound of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is

included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[0064] In some embodiments, pharmaceutically acceptable compositions can contain a disclosed compound and/or a pharmaceutically acceptable salt thereof at a concentration ranging from about 0.01 to about 2.0 wt%, such as 0.01 to about 1 wt% or about 0.05 to about 0.5 wt%. The composition can be formulated as a solution, suspension, ointment, or a capsule, and the like. The pharmaceutical composition can be prepared as an aqueous solution and can contain additional components, such as preservatives, buffers, tonicity agents, antioxidants, stabilizers, viscosity-modifying ingredients and the like.

[0065] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0066] Pharmaceutically acceptable carriers are well-known to those skilled in the art, and include, e.g., adjuvants, diluents, excipients, fillers, lubricants and vehicles. In some embodiments, the carrier is a diluent, adjuvant, excipient, or vehicle. In some embodiments, the carrier is a diluent, adjuvant, or excipient. In some embodiments, the carrier is a diluent or adjuvant. In some embodiments, the carrier is an excipient. Often, the pharmaceutically acceptable carrier is chemically inert toward the active compounds and is non-toxic under the conditions of use. Examples of pharmaceutically acceptable carriers may include, e.g., water or saline solution, polymers such as polyethylene glycol, carbohydrates and derivatives thereof, oils, fatty acids, or alcohols. Non-limiting examples of oils as pharmaceutical carriers include oils of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical carriers may also be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. Other examples of suitable pharmaceutical carriers are described in e.g., Remington's: The Science and Practice

of Pharmacy, 22nd Ed. (Allen, Loyd V., Jr. ed., Pharmaceutical Press (2012)); Modern Pharmaceutics, 5th Ed. (Alexander T. Florence, Juergen Siepmann, CRC Press (2009)); Handbook of Pharmaceutical Excipients, 7th Ed. (Rowe, Raymond C.; Sheskey, Paul J.; Cook, Walter G.; Fenton, Marian E. eds., Pharmaceutical Press (2012)) (each of which hereby incorporated by reference in its entirety).

[0067] In some embodiments, the compounds of the disclosure are formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration *in vivo*. According to another aspect, the present disclosure provides a pharmaceutical composition comprising a disclosed compound in admixture with a pharmaceutically acceptable diluent and/or carrier. The pharmaceutically-acceptable carrier is “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. The pharmaceutically-acceptable carriers employed herein may be selected from various organic or inorganic materials that are used as materials for pharmaceutical formulations and which are incorporated as analgesic agents, buffers, binders, disintegrants, diluents, emulsifiers, excipients, extenders, glidants, solubilizers, stabilizers, suspending agents, tonicity agents, vehicles and viscosity-increasing agents. Pharmaceutical additives, such as antioxidants, aromatics, colorants, flavor-improving agents, preservatives, and sweeteners, may also be added. Examples of acceptable pharmaceutical carriers include carboxymethyl cellulose, crystalline cellulose, glycerin, gum arabic, lactose, magnesium stearate, methyl cellulose, powders, saline, sodium alginate, sucrose, starch, talc and water, among others. In some embodiments, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0068] Surfactants such as, *e.g.*, detergents, are also suitable for use in the formulations. Specific examples of surfactants include polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and of vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol or polyoxyethylenated esters of sorbitan; lecithin or sodium carboxymethylcellulose; or acrylic derivatives, such as methacrylates and others, anionic surfactants, such as alkaline stearates, in particular sodium, potassium or ammonium stearate; calcium stearate or triethanolamine stearate; alkyl sulfates, in particular sodium lauryl sulfate and sodium cetyl sulfate; sodium dodecylbenzenesulphonate or sodium dioctyl

sulphosuccinate; or fatty acids, in particular those derived from coconut oil, cationic surfactants, such as water-soluble quaternary ammonium salts of formula $N^+R'R''R'''Y^-$, in which the R radicals are identical or different optionally hydroxylated hydrocarbon radicals and Y^- is an anion of a strong acid, such as halide, sulfate and sulfonate anions; cetyltrimethylammonium bromide is one of the cationic surfactants which can be used, amine salts of formula $N^+R'R''$, in which the R radicals are identical or different optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is one of the cationic surfactants which can be used, non-ionic surfactants, such as optionally polyoxyethylenated esters of sorbitan, in particular Polysorbate 80, or polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids or copolymers of ethylene oxide and of propylene oxide, amphoteric surfactants, such as substituted lauryl compounds of betaine.

[0069] When administered to a subject, the disclosed compound and pharmaceutically acceptable carriers can be sterile. Suitable pharmaceutical carriers may also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, polyethylene glycol 300, water, ethanol, polysorbate 20, and the like. The present compositions, if desired, may also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0070] The pharmaceutical formulations of the present disclosure are prepared by methods well-known in the pharmaceutical arts. Optionally, one or more accessory ingredients (*e.g.*, buffers, flavoring agents, surface active agents, and the like) also are added. The choice of carrier is determined by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

[0071] Additionally, the compounds and/or compositions of the present disclosure are administered to a human or animal subject by known procedures including oral administration, sublingual or buccal administration. In some embodiments, the compound and/or composition is administered orally.

[0072] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following:

(1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0073] For oral administration, a formulation of the compounds of the disclosure may be presented in dosage forms such as capsules, tablets, powders, granules, or as a suspension or solution. Capsule formulations may be gelatin, soft-gel or solid. Tablets and capsule formulations may further contain one or more adjuvants, binders, diluents, disintegrants, excipients, fillers, or lubricants, each of which are known in the art. Examples of such include carbohydrates such as lactose or sucrose, dibasic calcium phosphate anhydrous, corn starch, mannitol, xylitol, cellulose or derivatives thereof, microcrystalline cellulose, gelatin, stearates, silicon dioxide, talc, sodium starch glycolate, acacia, flavoring agents, preservatives, buffering agents, disintegrants, and colorants. Orally administered compositions may contain one or more optional agents such as, *e.g.*, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preservative agents, to provide a pharmaceutically palatable preparation.

[0074] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or

prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[0075] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[0076] Suspensions, in addition to the subject composition, may contain suspending agents, such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0077] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[0078] Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0079] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0080] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as

chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0081] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronic, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0082] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0083] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. For example, crystalline forms provided herein may be milled to obtain a particular particle size, and in at least some embodiments, such crystalline forms may remain substantially stable upon milling.

[0084] For example, provided herein is a composition suitable for subcutaneous administration, comprising a suspension of the disclosed crystalline form. Subcutaneous

administration can be advantageous over intravenous administration, which typically requires a doctor visit, and can be more painful and invasive. A typical dose of the crystalline compound, when administered to a patient, may be about 1 mg to about 8 mg of compound. In an embodiment, disclosed herein is a pharmaceutically acceptable composition formed from a disclosed crystalline form, e.g. by mixing a crystalline form with an excipient and/or a solvent.

[0085] In an embodiment, provided herein is a composition comprising a disclosed crystalline form suitable for subcutaneous administration at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.001 mg/kg to about 4 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, from about 1 mg/kg to about 25 mg/kg, of subject body weight, administered daily, one or more times a day, every other day, every third or fourth day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, or ten administrations). In certain embodiments, administration may occur once, twice, or thrice weekly.

[0086] Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result, for example a weight loss target, is achieved. A treatment regimen can include a corrective phase, during which dose sufficient to provide reduction of weight is administered, and can be followed by a maintenance phase, during which a e.g., lower dose sufficient to weight gain is administered. A suitable maintenance dose is likely to be found in the lower parts of the dose ranges provided herein, but corrective and maintenance doses can readily be established for individual subjects by those of skill in the art without undue experimentation, based on the disclosure herein. Maintenance doses can be employed to maintain body weight in subjects whose body weight has been previously controlled by other means, including diet and exercise, bariatric procedures such as bypass or banding surgeries, or treatments employing other pharmacological agents.

[0087] In certain embodiments, provided herein is a pharmaceutical composition comprising a crystalline form of Compound I, or II, or a solvate thereof, as described herein. In certain embodiments, provided herein is a pharmaceutical composition comprising a crystalline form

of Compound I, including, for example, Form A, Form B, or Form C, or a solvate thereof, as described herein. In certain embodiments, provided herein is a pharmaceutical composition comprising a crystalline form of Compound II, including, for example, Form A or Form B, or a solvate thereof, as described herein. In certain embodiments, a pharmaceutical composition provided herein comprises one or more pharmaceutically acceptable excipient, as described herein.

Kits

[0088] In one embodiment, a kit for treating or mitigating a contemplated disease of disorder is provided. For example, a disclosed kit comprises a disclosed crystalline compound, e.g., a crystalline form of a Compound I, disposed in a first container. In some embodiments, a kit may further include a pharmaceutically acceptable excipient, disposed in a second container. Such contemplated kits may include written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the crystalline form. For example, the written instructions may describe preparing a pharmaceutically acceptable form for patient administration by mixing an excipient and a crystalline compound disclosed herein. Disclosed kits may further comprise written instructions describing how to administer the resulting composition to the patient.

Processes

[0089] In some embodiments, a process for preparing a disclosed, crystalline form of a Compound I is contemplated herein, comprising: (a) preparing a solution of a Compound I; (b) adjusting the temperature so that solid crystalline form of a Compound I precipitates out of the solution; and (c) isolating the solid crystalline form. In some embodiments, a solution of a compound of Formula (I) comprises a solvent selected from Water, Methanol, Ethanol, Acetone, Methyl ethyl ketone, Ethyl acetate, Isopropyl acetate, Acetonitrile, t-Butyl methyl ether, Dichloromethane, Tetrahydrofuran, 1,4-Dioxane, Benzyl alcohol, 2-MeTHF, IPAc, and MtBE. In some embodiments, a solution of a Compound I comprises a solvent selected from those as described in the examples herein.

[0090] In some embodiments, a process for preparing a disclosed, crystalline form of a Compound I is contemplated herein, comprising: (a) preparing a solution of a Compound I in a solvent; (b) adjusting the temperature; (c) adding heptane to the solution; and (d) isolating the solid crystalline form. In some embodiments, a solution of a Compound I comprises a solvent selected from Water, Methanol, Ethanol, Acetone, Methyl ethyl ketone, Ethyl acetate,

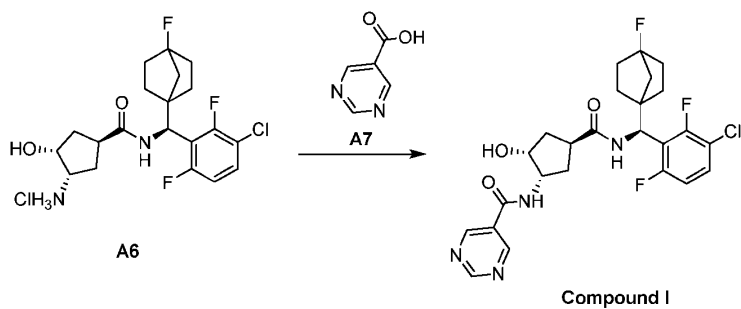
Isopropyl acetate, Acetonitrile, t-Butyl methyl ether, Dichloromethane, Tetrahydrofuran, 1,4-Dioxane, Benzyl alcohol, 2-MeTHF, IPAc, and MtBE. In some embodiments, a solution of Compound I comprises a solvent selected from those as described in the examples herein.

[0091] In some embodiments, a process for preparing a disclosed, crystalline form of Compound II is contemplated herein, comprising: (a) preparing a solution of Compound II; (b) adjusting the temperature so that solid crystalline form of a compound of Compound II precipitates out of the solution; and (c) isolating the solid crystalline form. In some embodiments, a solution of a Compound II comprises a solvent selected from Water, Methanol, Ethanol, Acetone, Methyl ethyl ketone, Ethyl acetate, Isopropyl acetate, Acetonitrile, t-Butyl methyl ether, Dichloromethane, Tetrahydrofuran, 1,4-Dioxane, Benzyl alcohol, 2-MeTHF, IPAc, and MtBE. In some embodiments, a solution of Compound II comprises a solvent selected from those as described in the examples herein.

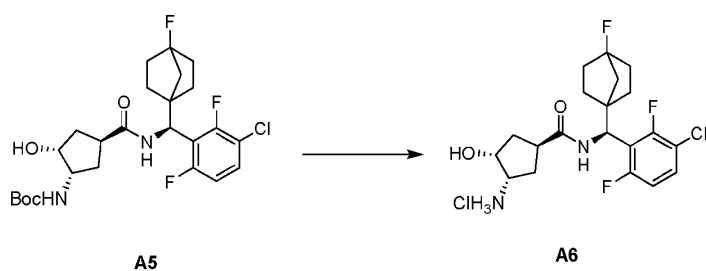
[0092] In some embodiments, a process for preparing a disclosed, crystalline form of a Compound II is contemplated herein, comprising: (a) preparing a solution of a Compound II in a solvent; (b) adjusting the temperature; (c) adding heptane to the solution; and (d) isolating the solid crystalline form. In some embodiments, a solution of a Compound II comprises a solvent selected from Water, Methanol, Ethanol, Acetone, Methyl ethyl ketone, Ethyl acetate, Isopropyl acetate, Acetonitrile, t-Butyl methyl ether, Dichloromethane, Tetrahydrofuran, 1,4-Dioxane, Benzyl alcohol, 2-MeTHF, IPAc, and MtBE. In some embodiments, a solution of Compound II comprises a solvent selected from those as described in the examples herein.

[0093] In some embodiments, the step of adjusting the temperature comprises heating the solution. In some embodiments, heating the solution comprises heating the solution to about 50 °C. In some embodiments, adjusting the temperature comprises cooling the solution. In some embodiments, cooling the solution comprises cooling the solution to about 0 °C, about 5 °C, or about 25 °C.

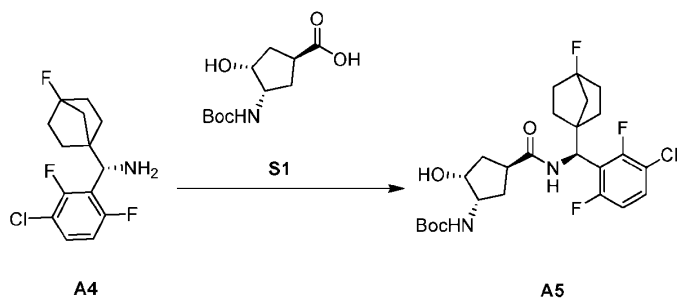
[0094] In other embodiments, a disclosed process further comprises a step of coupling Compound A6 and Compound A7, thereby forming Compound I:



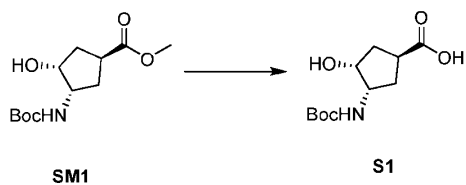
[0095] In other embodiments, a disclosed process further comprises a step converting Compound A5 to Compound A6:



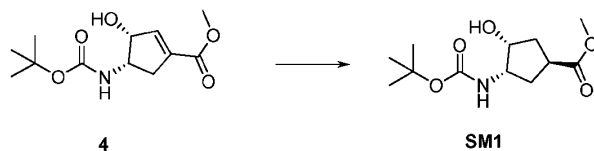
[0096] In other embodiments, a disclosed process further comprises a step of coupling compound A4 with compound S1, thereby forming Compound A5:



[0097] In other embodiments, a disclosed process further comprises a step of converting Compound SM1 to Compound S1:

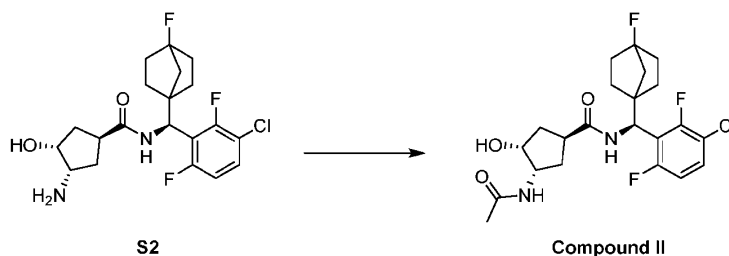


[0098] In other embodiments, a disclosed process further comprises a step of converting Compound 4 to Compound SM1:



In some embodiments, the step of converting Compound 4 to Compound SM1 further comprises the step of adding an enzyme catalyst.

[0099] In other embodiments, a disclosed process further comprises the step of converting Compound S2 to Compound II:



Methods

[0100] Compounds and compositions described herein are generally useful for the inhibition of a kinase or a mutant thereof. In some embodiments, the kinase inhibited by the compounds and compositions described herein is a phosphatidylinositol 3-kinase (PI3K). In some embodiments, the kinase inhibited by the compounds and compositions described herein is one or more of a PI3K α , PI3K δ , and PI3K γ . In some embodiments, the kinase inhibited by the compounds and compositions described herein is a PI3K α . In some embodiments, the kinase inhibited by the compounds and compositions described herein is a PI3K α containing at least one of the following mutations: E542X, E545X, Q546X, H1047X, and G1049X, wherein X is any amino acid besides its wildtype. In some embodiments, the kinase inhibited by the compounds and compositions described herein is a PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the kinase inhibited by the compounds and compositions described herein is a PI3K α containing at least one of the following mutations: E542K, E545K, and H1047R.

[0101] Compounds or compositions of the disclosure can be useful in applications that benefit from inhibition of PI3K enzymes. For example, PI3K inhibitors of the present disclosure are useful for the treatment of cellular proliferative diseases generally. Compounds or compositions of the disclosure can be useful in applications that benefit from inhibition of PI3K α enzymes. For example, PI3K α inhibitors of the present disclosure are useful for the treatment of cellular proliferative diseases generally.

[0102] Aberrant regulation of PI3K, which often increases survival through Akt activation, is one of the most prevalent events in human cancer and has been shown to occur at multiple levels. The tumor suppressor gene PTEN, which dephosphorylates phosphoinositides at the 3' position of the inositol ring, and in so doing antagonizes PI3K activity, is functionally deleted in a variety of tumors. In other tumors, the genes for the p110 α isoform, PIK3CA, and for Akt are amplified, and increased protein expression of their gene products has been demonstrated in several human cancers. Furthermore, mutations and translocation of p85 α that serve to up-regulate the p85-p110 complex have been described in human cancers. Finally, somatic missense mutations in PIK3CA that activate downstream signaling pathways have been described at significant frequencies in a wide diversity of human cancers (Kang et al., Proc. Natl. Acad. Sci. USA 102:802 (2005); Samuels et al., Science 304:554 (2004); Samuels et al., Cancer Cell 7:561-573 (2005)). These observations show that deregulation of phosphoinositide-3 kinase, and the upstream and downstream components of this signaling pathway, is one of the most common deregulations associated with human cancers and proliferative diseases (Parsons et al., Nature 436:792 (2005); Hennessey et al., Nature Rev. Drug Disc. 4:988-1004 (2005)).

Treatment of Disorders

[0103] Provided compounds are inhibitors of PI3K α and are therefore useful for treating one or more disorders associated with activity of PI3K α or mutants thereof. Thus, in certain embodiments, the present disclosure provides a method of treating a PI3K α -mediated disorder in a subject, comprising administering a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition of either of the foregoing, to a subject in need thereof. In certain embodiments, the present disclosure provides a method of treating a PI3K α -mediated disorder in a subject comprising administering a therapeutically effective amount of a compound of the

present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the subject has a mutant PI3K α . In some embodiments, the subject has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the subject has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S.

[0104] As used herein, the term “PI3K α -mediated” disorders, diseases, and/or conditions means any disease or other deleterious condition in which PI3K α or a mutant thereof is known to play a role. Accordingly, another embodiment of the present disclosure relates to treating or lessening the severity of one or more diseases in which PI3K α , or a mutant thereof, is known to play a role. Such PI3K α -mediated disorders include, but are not limited to, cellular proliferative disorders (e.g. cancer). In some embodiments, the PI3K α -mediated disorder is a disorder mediated by a mutant PI3K α . In some embodiments, the PI3K α -mediated disorder is a disorder mediated by a PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the subject has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the subject has PI3K α containing at least one of the mutations in Table A:

[0105] Table A.

M1*	R4L	G8D	E9_M16del
M1I	R4P	G8R	E9_P17>A
M1L	R4Q	G8S	E9_P17del
M1R	R4_P17del	G8V	E9_P18>CPT
M1T	R4_P18del	G8_P17del	E9_P18>GCPT
M1V	P5T	G8_P18del	E9_P18del
P2H	P5_R19del	G8_R19del	E9_R19>G
P2L	S6L	E9*	E9_R19del
P2S	S6_I13del	E9A	E9fs*6
P3A	S7*	E9G	L10P
P3L	S7L	E9K	L10Q
P3S	S7_P18del	E9Q	L10R
P3T	S7_R19del	E9_I20>V	L10V
R4*	S7fs*3	E9_L15>G	L10_L15>R
R4G	G8C	E9_M16>V	L10_L15del

L10_L21del
L10_M16del
L10_P17>T
L10_P17del
L10_P18>Q
L10_P18del
W11*
W11C
W11G
W11L
W11R
W11S
W11_H14del
W11_L15del
W11_L21del
W11_M16del
W11_P17>S
W11_P18>S
W11_P18>CG
W11_P18del
W11_R19del
W11_V22del
W11del
G12C
G12D
G12S
G12V
G12_L21del
G12_P17>A
G12_P18>I
I13F
I13M
I13N
I13V
I13_P18del
I13del
H14D
H14N
H14Y
H14_I20del
H14_L21del
L15S

L15V
L15W
M16I
M16K
M16L
M16R
M16T
M16V
P17A
P17L
P17R
P17S
P18L
P18Q
P18S
P18T
P18fs*4
R19*
R19I
R19K
I20M
I20T
I20fs*3
L21I
L21R
L21V
V22G
V22I
V22L
E23K
E23Q
C24F
C24Y
L25*
L25F
L25S
P27S
G29K
G29R
M30I
M30V
M30fs*9

I31M
I31V
V32A
V32L
V32M
T33A
T33I
T33S
E35*
E35K
E35Q
C36*
L37F
L37I
R38C
R38G
R38H
R38L
R38S
R38_I43>L
E39*
E39A
E39D
E39K
E39Q
A40V
T41I
L42*
L42F
I43L
I43M
T44F
T44I
I45L
I45T
I45V
K46M
H47L
H47Q
H47Y
E48*
E48K

E48Q
E48V
F50L
F50fs*22
K51R
E52*
E52K
E52Q
A53S
A53V
A53fs*19
R54I
R54K
K55I
K55Q
Y56*
Y56H
P57H
P57L
P57S
L58F
L58R
L58V
L58fs*13
L58fs*14
H59L
H59N
H59R
H59Y
Q60*
Q60E
Q60L
Q60P
L61F
L61I
L61R
L62F
L62I
L62del
Q63*
Q63E
Q63H

Q63L
Q63fs*9
D64G
D64H
D64N
D64V
D64Y
D64_S72>VL
E65*
E65A
E65G
E65K
E65V
S66C
S66F
S66Y
S67A
S67C
S67F
S67Y
S67del
Y68C
Y68H
I69F
I69L
I69N
I69S
I69V
F70V
V71G
V71I
V71L
S72G
S72R
S72T
S72fs*27
V73A
V73I
T74A
T74I
T74S
Q75*

Q75E
Q75H
Q75L
Q75P
E76Q
E76del
A77G
A77P
E78*
E78G
E78K
E78Q
E78_R79insVSK NTYLSKCYS
R79M
R79W
R79_E80>K
E80K
E80_E81>KK
E81*
E81A
E81D
E81G
E81K
E81Q
E81V
E81_F82>V
E81del
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F82L
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F83I
F83K
F83L
F83S
F83V
F83Y
F83del
F83fs*17
D84H
D84N
D84Y

D84fs*1
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E85Q
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R87G
R87I
R87S
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R88L
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R88Q
L89F
L89H
C90F
C90G
C90S
C90W
C90Y
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L92F
L92I
R93G
R93L
R93L
R93P
R93Q
R93W
L94F
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F95S
F95fs*2
Q96*
Q96E
Q96H
Q96K
Q96R
Q96fs*4
P97F

P97H
P97L
P97S
F98C
F98L
F98V
L99*
L99F
L99V
L99fs*1
K100*
K100N
K100del
V101A
V101I
V101L
V101del
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I102M
I102T
I102V
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I102_P104>K
I102_P104>T
I102_P104del
I102_V105del
I102del
I102fs*6
E103*
E103D
E103G
E103K
E103Q
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E103_V105>A

E103_V105>D
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P104A
P104K
P104L
P104Q
P104R
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P104_G106>S
P104_G106del
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E110_K111>M
E110_K111>V
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E110_N114>D
E110_R115>G
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F119L
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E127D
E127K
E127Q
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D129N
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N145S
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E172G
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S173C
S173Y
S174L
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E176Q
L177*
L177F
P178S
K179N
K179Q
H180N
H180P
H180R

I181V
Y182F
Y182H
N183H
N183T
K184E
K184N
K184Q
K184R
K184T
L185*
L185F
L185S
D186A
D186E
D186G
D186N
D186Y
K187E
K187Q
K187R
G188R
Q189*
Q189fs*14
I190L
I190V
V192L
V192M
V193L
I194M
W195*
W195C
W195R
V196L
I197M
I197T
I197V
V198D
V198F
V198I
S199F
S199P

S199Y
P200A
P200L
P200R
P200S
N201D
N201S
N202D
N202fs*9
D203G
D203H
D203N
D203Y
K204T
Q205*
Q205H
Q205K
Q205P
Q205R
K206E
Y207S
T208A
L209V
K210R
I211M
I211V
N212S
H213P
H213Y
D214E
D214G
D214Y
D214_C215>ER
C215S
C215T
C215Y
V216A
V216I
V216L
P217L
P217R
P217S

E218D
E218K
E218Q
E218fs*4
Q219H
Q219K
V220L
I221N
I221V
E223D
E223G
E223K
E223Q
A224G
A224S
A224T
A224V
I225M
I225S
I225T
I225V
R226G
R226S
R226T
K227*
K228N
T229A
T229P
T229S
T229fs*9
T229fs*11
R230*
R230G
R230L
R230Q
R230fs*7
S231R
M232I
M232L
M232V
L233F
L233S

L233V
L234fs*8
S235C
S235F
S235P
S235T
S236C
S236F
S236T
S236Y
E237K
E237Q
Q238K
Q238L
L239I
L239Q
L239R
L239V
K240N
K240Q
K240T
V243D
V243G
V243I
V243L
V243fs*15
E245K
Y246C
Q247*
Q247H
Q247L
Q247R
G248C
G248V
K249*
K249N
K249T
Y250C
Y250F
Y250H
Y250N
I251N

K253I
K253N
K253T
V254G
V254L
V254M
V254_C255>LW
C255F
C255Y
C255fs*3
G256*
G256A
G256E
G256R
G256V
C257R
D258E
D258G
D258H
D258N
E259Q
Y260C
Y260H
F261L
F261V
F261Y
E263*
E263D
E263K
E263Q
E263fs*5
K264Q
K264T
K264fs*4
Y265*
Y265C
P266H
P266L
P266R
P266S
L267M
L267P

L267V
S268N
S268T
Q269*
Q269H
Q269L
Q269R
Q269fs*4
Y270F
Y270N
K271N
K271R
Y272C
Y272F
Y272H
I273L
I273M
I273T
R274G
R274I
R274K
R274T
S275C
S275I
S275N
C276*
C276F
C276G
I277L
I277T
I277V
I277fs*7
M278I
M278K
M278L
M278T
M278fs*23
L279F
L279H
L279I
L279R
L279V

G280A
G280E
G280K
G280R
G280V
G280W
R281M
R281S
R281fs*5
M282I
P283L
P283S
N284H
N284K
N284S
N284Y
L285F
L285M
M286I
L287F
M288I
M288T
A289T
A289V
K290N
E291*
E291K
E291Q
S292C
S292I
S292N
S292R
L293F
Y294*
Y294H
Y294fs*25
S295A
S295C
S295F
S295Y
Q296*
Q296E

Q296K
Q296R
L297P
L297R
P298A
P298Q
P298R
P298S
M299I
M299L
M299T
D300A
D300E
D300H
D300N
C301*
C301F
C301G
C301S
C301W
C301Y
F302C
F302Y
T303A
T303K
T303R
M304I
M304L
M304T
M304V
P305S
P305_N319>H
S306A
S306C
S306F
S306P
S306Y
S306fs*13
Y307F
Y307H
S308A
S308C

S308F
S308Y
R309G
R309_R310>S
R310C
R310H
R310L
I311F
I311N
S312C
S312F
S312fs*18
T313I
T313K
T315I
P316L
P316Q
P316S
P316T
Y317C
Y317F
Y317H
M318I
M318T
M318V
M318fs*15
N319S
N319T
G320*
G320A
G320E
G320R
G320V
E321A
E321K
E321Q
E321V
S323A
S323C
S323F
S323P
S323Y

T324I
K325E
K325Q
K325R
K325_I330del
K325fs*6
S326A
S326C
S326F
S326P
S326Y
L327F
L327H
L327I
L327fs*4
W328*
W328C
W328L
W328R
W328S
V329F
V329G
V329I
I330L
I330V
N331H
S332I
S332T
A333S
A333T
A333V
L334F
R335I
R335K
R335S
R335T
R335_I336ins18
R335fs*2
R335fs*17
R335fs*33
I336M
I336fs*8

K337Q
K337T
I338F
I338N
I338S
I338T
I338fs*7
L339F
L339I
L339R
L339V
C340F
C340R
C340_A341insV
KILC
A341S
A341V
A341_T342insIKI
LCA
A341_T342insLR
IKILCA
A341_T342insYK
ILCA
T342A
T342I
T342S
T342_N345>H
T342_Y343ins37
T342_Y343insRI
KILCAT
Y343C
Y343F
Y343I
Y343L
Y343S
Y343_N345del
Y343_V344>L
Y343_V344insA
TY
Y343_V344insER
IKILCATY
Y343_V344insLC
ATY
V344A

V344E
V344F
V344G
V344L
V344M
V344R
V344_N345>RFS
AFWLRSS
V344_N345insK
V344_N345insM
V344_N345insV
V344_N345insIL
CATYV
V344_N345insK
V
V344_N345insKI
LCATYV
V344_N345insT
TYV
V344_N345insT
YV
V344_N347del
N345D
N345H
N345I
N345K
N345S
N345T
N345Y
N345_I348>K
N345_I348del
N345_K353del
N345_V346>K
N345_V346>KL
N345_V346>KA
TYVNV
N345_V346insA
TYVN
V346A
V346E
V346G
V346L
V346L
V346Q

V346_N347>RTY
VNVN
V346_N347insK
V346_N347insV
V346_N347insE
KIKKKKKK
V346_N347insK
NV
V346_N347insM
NV
V346_N347insV
NV
V346>GK
N347D
N347I
N347K
N347T
N347Y
N347_I348insR
N347_I348insVN
I348M
I348S
I348V
I348_R349insLN
I
R349*
R349Q
R349_D350insIR
R349_D350insV
R
D350G
D350H
D350K
D350N
D350Y
D350_I351insKK
ILCATYVNVNIRD
D350_I351insRI
KILCATYVNVNIRD
D
D350del
I351F
I351S
I351_D352>E

I351_D352>KYL
Q
I351_D352insGI
KILCATYVNVNIRD
DI
I351_D352insVN
VNIRDI
D352H
D352N
D352Y
D352>RDIN
K353M
K353N
K353_I354insVV
NVNIRDIDK
I354D
I354F
I354L
I354N
I354S
I354T
I354V
Y355C
Y355_V356insY
V356A
V356F
V356I
V356L
R357*
R357G
R357L
R357Q
R357fs*10
T358A
T358K
T358S
T358_G359insA
G359A
G359C
G359R
G359V
I360F
I360T

I360V
Y361C
Y361F
Y361H
Y361_H362insQI
YVRTGIY
H362N
H362R
H362Y
G363A
G363E
G363V
G363_G364insY
VRTGIYHG
G363>YHR
G364E
G364K
G364R
G364_E365insV
RTGIYHGG
E365D
E365K
E365Q
E365V
P366F
P366H
P366L
P366R
P366S
P366T
P366fs*5
C368Y
D369G
D369N
D369Y
N370D
N370K
N370S
N372S
T373I
T373P
T373S
Q374*

Q374E
Q374H
R375G
R375I
R375K
R375S
V376I
P377L
P377S
C378F
C378L
C378R
C378W
C378Y
S379C
S379F
N380K
N380Y
P381A
P381S
R382K
R382W
R382fs*6
W383*
W383C
W383L
E385K
W386R
L387Q
L387V
N388D
N388I
N388T
Y389C
Y389F
Y389S
D390A
D390H
D390N
D390Y
I391V
I391fs*36

Y392*
Y392H
P394S
P394_D395ins23
D395H
D395N
D395V
D395Y
L396F
L396I
L396P
L396V
P397A
P397R
P397S
P397T
R398C
R398H
R398L
A399D
A399G
A399S
A399T
A399V
R401*
R401L
R401Q
R401S
L402V
C403R
L404F
L404I
L404V
S405F
S405T
S405Y
I406F
I406M
I406V
C407F
C407R

C407W
C407Y
C407fs*21
S408C
S408P
V409F
V409I
K410_G411insG
RKGAKYFRR
K
K410fs*6
G411D
G411R
G411S
G411V
R412*
R412L
R412Q
K413N
K413_G414insR
K
G414A
G414D
G414R
G414S
G414V
G414fs*13
A415D
K416E
K416I
E417D
E417G
E417K
E417Q
E417V
E418*
E418A
E418K
E418Q
E418_C420>D
E418_P421>A
H419L
H419P

H419Q
H419R
H419Y
H419_C420>R
H419_C420del
H419_L422>T
H419_L422>LM
H419_L422>PW
H419_L422del
H419_L422del
H419_P421>L
H419_P421>P
H419_P421>Q
H419_P421>R
H419_P421>T
H419_P421del
H419fs*11
C420R
C420S
C420Y
C420_P421del
C420_L422>W
C420_A423>W
C420_A423>Y
C420_A423del
C420_I427>WH
GNV
P421A
P421L
P421R
P421S
P421T
P421_A423>H
P421_A423>H
P421_A423del
P421_L422del
P421>RR
L422E
L422F
L422S
L422W
L422_A423>F

A423E
A423S
A423T
A423V
W424*
W424C
W424G
W424L
W424R
W424_G425insF
W424_I427del
G425E
G425R
G425V
N426D
N426S
N426fs*6
I427K
I427M
I427T
I427V
N428K
N428S
N428Y
L429F
L429V
L429fs*2
F430C
F430L
Y432F
Y432H
Y432fs*5
T433A
T433R
T433_D434>NT D
T433_D434insTL VSGKMALNLWP VPHGLE
D434E
D434H
D434fs*2
T435I

T435N
T435S
L436P
L436V
L436fs*1
L436fs*32
V437E
V437G
V437I
S438A
S438C
S438fs*30
G439A
G439E
G439K
G439R
G439fs*5
K440E
K440N
K440fs*45
M441I
M441V
E441fs*3
M441fs*3
M441fs*28
A442T
A442V
L443F
N444H
N444K
N444_G451>K
N444_L455>H
L445F
L445I
L445_W446insL
W446*
W446S
W446_D454del
W446_E453del
W446_G451del
W446_G460>C
W446_H450>R

W446_H450del
W446_I459del
W446_L456del
W446_P447ins W
W446_P458del
W446_V461del
P447A
P447L
P447S
P447_L452del
P447_L455del
P447_V448ins24
P447_V448insLF DYTDTLVSGKMA LNLWP
V448A
V448E
V448G
V448L
V448_D454del
V448_E453>K
V448_E453>P
V448_E453>YK
V448_E453del
V448_G451del
V448_L452del
V448_L455del
V448_P449insS GKMALNLWPV
V448_P449insV SGKMALNLWPV
V448fs*14
P449A
P449H
P449L
P449R
P449S
P449T
P449_D454>R
P449_D454del
P449_E453>Q
P449_E453del

P449_H450insL VSGKMALNLWP VP
P449_H450insP VP
P449_H450insP VP
P449_I459del
P449_L452del
P449_L455del
P449_L456del
P449_P458del
H450D
H450N
H450Q
H450R
H450Y
H450_D454del
H450_E453del
H450_G451>PR G
H450_G460>R
H450_I459>L
H450_I459del
H450_L452del
H450_L455>P
H450_L455>Q
H450_L455>KM
H450_L455del
H450_L455del
H450_L455del
H450_L456>P
H450_L456del
H450_N457del
H450_P458>LIH
H450_P458del
H450_V461>GS
G451A
G451E
G451K
G451R
G451V
G451_D454>RR

G451_D454del
G451_E453del
G451_G460del
G451_I459>A
G451_I459>V
G451_L452>KKK KK
G451_L452insF GKMALNLWPVP HG
G451_L455>A
G451_L455>V
G451_L455>GT M
G451_L455del
G451_L456>K
G451_L456>V
G451_N457del
G451_P458>V
G451_P458del
L452S
L452_E453del
L452_E453ins21
L452_E453insA GKMALNLWPVP HGL
L452_E453insVS GKMALNLWPVP HGL
L452_G460>F
L452_G460del
L452_I459>FRRF
L452_I459>PLW ARL
L452_I459del
L452_I459del
L452_L455>W
L452_N457>T
L452_N457>Y
L452_P458>F
L452_T462>QKT
L452_V461>F
E453*
E453A

E453D
E453G
E453K
E453Q
E453V
E453_D454>KN
E453_D454del
E453_D454insG KMALNLWPVP GLE
E453_D454insV SGKMALNLWPV PHGLE
E453_D454insV VSGKMALNLWP VPHGLE
E453_G460>C
E453_G460del
E453_G463del
E453_I459>G
E453_I459>V
E453_I459del
E453_L455>G
E453_L455>V
E453_L455del
E453_L455del
E453_L456>M
E453_L456>V
E453_L456del
E453_P458del
E453_T462del
E453_T462del
E453>GLK
E453del
D454E
D454G
D454H
D454K
D454N
D454Y
D454_I459del
D454_K468del
D454_L455>V

D454_L455del
D454_N467>VS
D454_P458>Y
D454del
L455F
L455_G460>C
L455_G460del
L455_I459>C
L455_I459>C
L455_I459>F
L455_I459del
L455_L456>FM
L455_L456insPG KMALNLWPVP GLEDL
L455_N467>SD
L455_N467del
L455_P458del
L455_T462del
L455_V461>F
L456M
L456P
L456R
L456V
L456_I459del
L456_N457insKK KKKKREDLL
N457D
N457K
N457S
N457_G460>S
N457_G463>R
N457_I459>K
N457_I459>K
N457_P458>TR
N457_T462del
N457_V461del
P458A
P458L
P458R
P458S
P458_G463>R

P458_I459insM NLWPVPHGLEDL LNP
P458_K468del
P458_V461>L
I459M
I459N
I459S
I459T
I459V
I459_T462del
G460A
G460C
G460D
G460R
G460V
V461A
V461_N465del
T462I
T462_N465del
T462_S464del
T462fs*12
G463*
G463A
G463E
G463R
G463V
G463_K468del
S464*
S464L
N465I
N465K
N465S
N465T
N465Y
N465_P466ins2 7
P466L
P466Q
P466S
P466_N467insKL LNPIGVTGSNP
N467H

N467K
N467T
K468*
K468R
K468T
K468_E469ins31
K468_E469ins35
K468_E469insVE RLLNPIGVTGSNP NK
K468_E469insVL LNPIGVTGSNPN K
E469*
E469A
E469D
E469G
E469K
E469V
E469_T470>D
E469>DK
T470I
T470N
T470P
T470S
T470fs*4
P471A
P471I
P471L
P471Q
P471S
P471T
P471>QTL
C472S
C472W
C472>FF
L473I
L473V
L473_E474insL
L473_E474insAC L
L473_L475>FGV WSLEL

E474A
E474K
E474Q
E474V
L475*
L475F
E476G
E476K
E476Q
E476_F477insLE
D478A
D478E
D478G
D478H
D478N
D478Y
W479C
W479S
F480L
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S481N
S481R
S481T
S482C
S482N
V483A
V483L
V483M
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V484I
V484L
K485E
K485R
K485T
F486L
F486Y
P487L
P487Q
P487R
P487S
D488G
D488H

D488N
D488_S490del
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M489V
S490P
V491G
V491L
V491M
I492F
I492M
I492T
E493K
E493Q
E494*
E494D
E494K
E494Q
E494V
H495L
H495N
H495Q
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A496S
A496T
A496V
N497S
W498*
W498C
W498L
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W498S
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S499Y
V500L
V500fs*9
S501F
S501T
S501Y
R502*
R502G
R502Q
E503G

E503K
E503Q
E503del
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G505E
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F506L
F506V
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S507I
S507R
S507T
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Y508H
Y508N
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H510Y
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G512*
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G512E
G512R
G512V
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L513V
L513fs*5
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S514R
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R516I
R516K
R516T
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L517P
L517R
L517V

A518G
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R519T
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D520H
D520N
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N521K
N521S
E522*
E522K
E522Q
L523F
L523V
L523fs*1
R524K
R524M
R524S
R524fs*36
E525*
E525A
E525G
E525K
E525fs*35
N526S
N526fs*34
D527E
D527G
D527H
D527N
K528E
E529K
E529Q
Q530*
Q530H
Q530K
Q530R
L531R
A533T

I534N
I534V
S535C
S535F
S535Y
T536A
T536K
T536S
R537*
R537L
R537Q
D538A
D538E
D538G
D538H
D538N
D538Y
D538_S541>A
D538del
P539A
P539H
P539L
P539R
P539S
P539T
P539del
L540F
L540H
L540I
L540P
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L540V
S541A
S541C
S541F
S541L
S541P
S541T
S541_E542insAl
STRDRLS
S541fs*1
E542A

E542D
E542G
E542I
E542K
E542L
E542Q
E542R
E542V
I543V
I543_E545del
T544N
T544S
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E545D
E545G
E545K
E545L
E545N
E545P
E545Q
E545R
E545S
E545T
E545V
E545W
E545_Q546>DK
E545_Q546>DL
Q546E
Q546H
Q546K
Q546L
Q546P
Q546R
E547*
E547D
E547G
E547K
E547Q
K548N
K548Q
K548R
D549G

D549H
D549N
D549Y
D549fs*21
F550C
F550L
F550V
L551I
L551P
L551V
L551fs*8
L551fs*9
W552*
W552C
W552G
W552R
S553C
S553G
S553N
S553R
S553T
H554D
H554Q
H554R
H554Y
R555G
R555K
R555T
H556D
Y557C
Y557S
C558F
C558S
V559I
V559L
T560I
T560P
T560S
I561M
I561V
P562L
P562S

E563D
E563K
I564S
P566L
P566S
K567Q
L569I
L570M
L570P
S571C
V572A
V572I
V572fs*9
K573R
W574L
N575I
N575K
S576F
S576T
S576Y
R577G
R577I
R577K
R577S
R577T
D578E
D578H
D578N
D578V
D578Y
E579*
E579D
E579K
E579Q
V580A
V580E
V580L
A581T
A581V
Q582*
Q582L
Q582R

M583I
Y584H
C585F
C585G
L586F
L586M
V587I
V587fs*10
K588N
K588fs*8
D589E
D589H
D589Y
W590*
P591T
P592A
P592L
P592S
P592T
P592fs*32
I593M
I593N
I593V
P595L
P595T
E596K
E596Q
E596V
E596fs*28
Q597H
Q597K
Q597R
Q597_A598>HT
A598D
A598T
M599L
M599_E600>IK
E600*
E600A
E600K
L602M
L602R

L602_D603insT
D603N
D603Y
C604R
C604Y
N605H
N605K
N605S
N605Y
P607A
P607L
D608Y
P609G
P609H
P609L
P609S
M610I
M610L
M610T
V611I
R612*
R612G
R612L
R612P
R612Q
R612fs*1
G613D
G613V
A615V
V616A
V616L
R617Q
R617W
C618R
C618W
L619S
L619V
K621*
K621I
K621N
K621Q
Y622*

L623F
L623I
L623V
T624I
T624P
T624S
D625F
D625H
D625V
D625Y
D626E
D626G
D626N
D626Y
K627N
K627Q
K627R
L628I
L628P
L628R
L628V
S629C
S629F
S629P
S629Y
Q630*
Q630E
Q630H
Q630P
Q630R
Y631C
L632*
L632F
I633L
Q634*
Q634E
Q634H
V636A
V636L
V636R
Q637*
Q637K

Q637L
V638A
V638I
K640Q
K640R
Y641*
E642K
E642Q
Q643H
Q643L
Q643R
Y644*
Y644C
L645F
D646E
D646H
N647K
N647S
N647T
L648F
L648V
L649F
V650A
R651K
R651S
L653*
L653fs*2
L653fs*8
L654V
K655N
K656N
K656T
A657P
A657S
A657V
L658F
T659A
T659N
T659S
N660D
N660S
Q661E

Q661K
Q661fs*11
R662K
R662M
R662S
I663S
I663del
G664E
G664W
H665fs*7
F666C
F666L
F667L
W669*
W669C
W669G
W669R
W669fs*6
H670N
H670Q
H670R
L671F
L671I
L671V
L671fs*1
K672I
K672N
S673C
S673F
S673T
E674A
E674D
E674G
E674K
E674Q
E674V
M675I
M675T
M675V
H676R
H676Y
H676fs*24

N677H
N677K
N677S
K678*
K678E
K678T
T679R
V680A
V680D
V680I
V680fs*19
S681C
S681I
S681N
S681R
S681T
Q682*
Q682H
Q682R
R683K
R683M
R683S
R683T
F684Y
G685S
G685V
L687F
L687I
L688M
E689K
E689Q
S690F
S690Y
Y691C
C692*
C692R
R693C
R693G
R693H
R693L
R693P
R693S

A694T
A694V
G696R
G696W
M697fs*3
Y698*
Y698C
Y698H
L699F
L699V
H701Q
L702V
R704S
R704T
R704W
Q705H
Q705L
V706F
V706I
E707*
E707D
E707K
E707Q
A708T
M709I
M709V
E710K
K711E
K711N
K711Q
K711R
K711T
L712F
L712H
L712I
L712V
N714D
N714H
N714I
N714K
N714Y
L715V

T716A	D725del	Q738fs*2	P754A
T716I	E726*	M739I	P754S
T716N	E726A	R741*	P754T
T716S	E726D	R741Q	P754del
D717E	E726G	P742A	L755I
D717H	E726K	P742R	L755Q
D717N	E726Q	P742S	L755V
D717V	E726V	P742T	L755_N756>P
D717_D725del	T727A	D743E	N756K
I718L	T727K	D743G	N756S
I718V	T727R	D743H	N756Y
I718_L719del	T727S	D743N	P757L
L719F	T727del	D743V	P757S
L719I	Q728K	F744I	P757fs*5
L719R	Q728R	F744L	A758S
L719V	K729N	F744V	A758T
K720E	V730A	M745I	A758V
K720I	V730I	M745L	H759D
Q721E	V730L	M745T	H759N
Q721H	Q731E	D746A	H759Q
Q721K	Q731H	D746G	H759Y
Q721P	Q731K	D746H	Q760*
E722D	Q731R	D746N	Q760E
E722K	M732I	D746V	Q760L
E722Q	K733N	D746Y	Q760R
E722del	K733T	L748V	L761R
K723N	F734I	L748fs*5	G762E
K723R	F734L	Q749*	G762R
K723T	F734V	Q749H	N763T
K724T	L735I	Q749K	L764F
K724del	L735S	G750A	L764I
D725A	L735V	G750C	L764P
D725E	V736A	G750D	L764V
D725G	V736F	G750E	R765G
D725H	V736I	G750S	R765S
D725V	V736L	F751S	L766P
D725Y	E737*	F751V	L766fs*10
D725_E726del	E737D	L752R	E767G
D725_K729del	E737K	L752V	E767K
D725_Q728>L	E737Q	S753F	E767Q
D725_Q728del	Q738E	S753T	E768*
D725_T727del	Q738R	S753Y	E768D

E768K
E768Q
C769W
R770*
R770L
R770Q
I771L
I771N
I771S
I771T
M772I
M772V
S773F
S773P
S774C
S774F
A775V
K776R
R777K
R777S
R777fs*5
R777fs*22
P778S
L779V
W780S
L781F
L781S
L781W
N782D
W783*
W783S
E784D
N785I
N785S
P786A
P786Q
P786S
P786T
D787G
D787V
I788F
I788V

I788del
M789I
M789S
M789T
M789V
S790*
S790A
S790P
E791*
E791D
E791Q
L792*
L792F
L793V
L793fs*5
Q795*
Q795E
Q795H
Q795R
N796H
N796I
E798D
E798K
E798Q
I799L
I799M
I799V
I800F
I800M
F801L
F801N
F801V
N803H
N803Y
G804R
D805G
D805N
D805Y
D806G
D806Y
L807S
L807V

R808L
R808W
Q809*
Q809H
Q809K
D810H
D810Y
M811I
T813A
L814V
Q815*
Q815R
I816N
I816S
I816T
I816V
I817F
I817V
I817_I819del
I817fs*14
R818C
R818G
R818H
R818L
I819N
I819V
M820I
M820L
E821G
E821K
N822D
N822I
I823F
I823M
I823T
I823V
W824*
W824F
W824G
Q825*
Q827E
Q827K

G828D
L829F
L829I
L829P
D830G
D830N
D830V
L831F
L831I
L831V
R832*
R832L
R832Q
M833I
M833V
M833fs*1
L834S
L834V
P835A
P835L
P835T
Y836C
G837C
G837D
G837N
G837S
G837fs*30
C838F
C838Y
L839V
S840*
S840L
S840fs*27
I841V
I841fs*3
G842C
G842S
D843G
D843N
C844F
C844R
C844S

C844Y
V845L
V845W
V845_G846insC V
V845fs*4
G846*
L847F
L847H
L847R
L847V
I848L
I848M
I848T
E849*
E849D
E849K
E849Q
V850A
V850G
V850M
V851E
R852*
R852G
R852Q
N853K
N853S
S854A
S854C
S854F
S854P
H855L
H855R
H855S
H855T
H855Y
T856S
I857L
I857V
I860M
I860V
Q861*

Q861E
Q861H
Q861K
C862W
K863I
G864S
G865D
G865S
L866F
L866V
L866W
K867I
K867N
K867R
G868A
G868C
G868S
A869T
A869V
Q871L
F872L
F872V
N873D
N873H
N873K
N873S
S874N
H875N
H875R
H875Y
T876A
T876I
T876K
L877I
L877V
H878Y
Q879*
Q879H
Q879K
Q879L
Q879R
L881I

L881V
K882T
D883E
D883G
D883H
D883N
D883V
D883Y
K884*
K884N
N885S
K886E
K886N
K886R
G887A
G887E
G887R
E888D
E888G
E888K
E888Q
I889L
I889M
I889T
Y890C
Y890N
A892V
A893S
A893T
A893V
A893fs*3
I894L
I894V
D895E
D895H
D895N
D895Y
L896M
L896P
F897L
F897fs*18
T898I

T898P
T898fs*19
R899C
R899G
R899H
C901F
C901S
C901W
C901fs*19
A902P
A902T
A902V
G903*
G903A
G903E
Y904*
C905S
V906I
V906L
A907V
T908fs*15
F909C
F909L
I910L
I910V
L911F
L911M
L911fs*9
G912R
G914E
G914R
D915N
R916C
R916H
S919G
S919T
N920S
I921N
I921V
I921del
M922I
V923L

V923M
K924R
D925E
D926N
G927R
G927V
Q928R
L929F
L929M
F930S
H931N
H931Y
I932L
D933N
F934C
F934fs*23
H936R
F937fs*1
L938M
L938fs*19
D939G
D939N
H940R
H940Y
K941N
K941R
K942M
K942N
K943N
K944I
K944R
K944del
F945C
F945I
F945L
F945fs*4
F945fs*12
G946C
G946D
G946V
Y947*
Y947F

R949*
R949Q
E950*
E950D
E950Q
R951C
R951H
R951L
V952A
V952L
F954Y
F954fs*7
F954fs*11
V955F
L956F
T957I
T957P
Q958*
Q958H
Q958K
Q958L
Q958R
D959Y
F960L
L961F
I962M
I962T
V963M
I964N
I964fs*2
I964fs*22
S965N
S965T
K966I
K966R
G967A
G967E
G967R
A968S
A968T
A968V
Q969*

Q969H
Q969K
Q969R
E970*
E970A
E970G
E970K
E970Q
C971G
T972R
K973N
T974K
T974R
T974fs*3
R975K
R975T
E976*
E976D
E976G
E976K
E976Q
F977C
F977L
E978D
E978K
E978Q
R979M
R979S
F980V
Q981*
Q981E
Q981H
Q981K
Q981L
Q981R
E982D
E982K
E982Q
M983I
M983L
C984R
C984S

Y985C
Y985D
Y985H
Y985N
Y985S
K986fs*5
A987T
A987V
Y988H
Y988N
Y988S
L989Q
L989R
L989V
A990G
A990_I991>V*
I991V
I991fs*26
R992*
R992Q
A995V
N996I
N996K
L997F
L997H
L997I
L997V
F998L
F998fs*14
I999M
I999R
I999V
N1000H
N1000K
N1000S
L1001F
L1001I
L1001V
L1001fs*4
L1001fs*17
F1002C
F1002I

F1002L
F1002V
S1003K
S1003L
S1003fs*15
M1004I
M1004L
M1004R
M1004V
M1004del
M1005I
M1005V
L1006F
L1006H
L1006R
G1007C
G1007D
G1007R
S1008C
G1009A
G1009E
G1009R
M1010I
M1010I
M1010V
P1011A
P1011L
P1011S
E1012D
E1012Q
Q1014K
Q1014R
S1015C
S1015F
S1015Y
F1016I
F1016L
F1016S
F1016V
F1016Y
D1017G
D1017H

D1017V
D1017Y
D1018N
I1019M
I1019S
I1019T
A1020K
A1020S
A1020T
A1020V
Y1021C
Y1021F
Y1021H
Y1021N
Y1021S
I1022M
I1022T
I1022_R1023ins FLYVCTIAYI
R1023*
R1023L
R1023P
R1023Q
K1024N
K1024T
T1025A
T1025I
T1025N
T1025S
L1026P
A1027T
A1027V
L1028F
L1028I
L1028S
L1028V
D1029E
D1029G
D1029H
D1029N
D1029Y
K1030*

K1030E
K1030R
T1031A
T1031N
T1031P
E1032*
E1032A
E1032D
E1032K
Q1033E
Q1033K
Q1033P
Q1033R
E1034G
E1034K
E1034Q
A1035T
A1035V
L1036F
L1036K
L1036S
E1037D
E1037K
E1037Q
Y1038C
Y1038F
Y1038H
Y1038N
Y1038S
F1039I
F1039S
M1040I
M1040K
M1040L
K1041*
Q1042R
Q1042fs*25
1043_1044MN> IY
M1043I
M1043L
M1043T

M1043V
M1043_N1044> IK
M1043_N1044> IR
N1044D
N1044H
N1044I
N1044K
N1044R
N1044S
N1044T
N1044Y
D1045A
D1045G
D1045H
D1045N
D1045V
D1045Y
A1046T
H1047A
H1047D
H1047I
H1047L
H1047N
H1047Q
H1047R
H1047Y
H1047_H1048> RR
H1048L
H1048N
H1048R
G1049A
G1049C
G1049D
G1049R
G1049S
G1049W
G1050A
G1050D
G1050S
W1051C

W1051L	H1065fs*?
W1051fs*16	H1065fs*4
T1052A	H1065fs*5
T1052I	H1065fs*8
T1052K	H1065fs*8
T1052R	H1065fs*1+
T1053fs*15	H1065fs*15
K1054T	H1065fs*6+
K1054_M1055> NGLDLPHN*TAC IEM	A1066_*1069>? A1066_L1067ins CV
M1055I	A1066fs*2+
M1055L	A1066fs*4
M1055V	A1066fs*5
D1056H	A1066fs*5+
D1056N	A1066fs*8
W1057*	A1066I
W1057C	A1066L
I1058F	A1066L
I1058L	L1067F
I1058M	L1067V
H1060L	L1067W
T1061I	L1067_*1069>F
T1061K	KLKKN*
I1062L	L1067fs*4
I1062V	L1067fs*5
K1063*	L1067fs*6
Q1064H	L1067fs*7
Q1064_H1065in sQWTTKMDWIF HTIKQ	L1067fs*7
Q1064fs*6	L1067fs*11+
Q1064fs*7	L1067fs*20
Q1064fs*9	L1067fs*5+
Q1064fs*24	N1068K
Q1064fs*5+	N1068fs*1
H1065L	N1068fs*3
H1065Q	N1068fs*4
H1065R	N1068fs*5
H1065Y	N1068fs*5
H1065_*1069>?	N1068fs*7
H1065_A1066>L KLK	N1068fs*1+
	N1068fs*10
	N1068fs*11
	N1068fs*21

[0106] In some embodiments, the present disclosure provides a method for treating a cellular proliferative disease, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition of either of the foregoing. In some embodiments, the present disclosure provides a method for treating a cellular proliferative disease, said method comprising administering to a patient in need thereof, a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable composition thereof.

[0107] In some embodiments, the method of treatment comprises the steps of: i) identifying a subject in need of such treatment; (ii) providing a disclosed compound, or a pharmaceutically acceptable salt thereof; and (iii) administering said provided compound in a therapeutically effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment. In some embodiments, the subject has a mutant PI3K α . In some embodiments, the subject has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the subject has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S.

[0108] In some embodiments, the method of treatment comprises the steps of: i) identifying a subject in need of such treatment; (ii) providing a composition comprising a disclosed compound, or a pharmaceutically acceptable salt thereof; and (iii) administering said composition in a therapeutically effective amount to treat, suppress and/or prevent the disease state or condition in a subject in need of such treatment. In some embodiments, the subject has a mutant PI3K α . In some embodiments, the subject has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the subject has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S.

[0109] Another aspect of the disclosure provides a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of either of the foregoing, for use in the treatment of a disorder described herein. Another aspect of the disclosure provides the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of either of the foregoing, for the treatment of a disorder described herein. Similarly, the disclosure provides

the use of a compound according to the definitions herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disorder described herein.

Cellular Proliferative Diseases

[0110] In some embodiments, the disorder is a cellular proliferative disease. In some embodiments, the cellular proliferative disease is cancer. In some embodiments, the cancer is a tumor. In some embodiments, the cancer is a solid tumor. In some embodiments, the cellular proliferative disease is a tumor and/or cancerous cell growth. In some embodiments, the cellular proliferative disease is a tumor. In some embodiments, the cellular proliferative disease is a solid tumor. In some embodiments, the cellular proliferative disease is a cancerous cell growth.

[0111] In some embodiments, the solid tumor has PI3K α containing at least one of the following mutations: E542X, E545X, Q546X, H1047X, and G1049X, wherein X is any amino acid besides its wildtype. In some embodiments, the solid tumor has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the solid tumor has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K.

[0112] In some embodiments, the cancer is selected from sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal; colon; rectum; carcinoma; colon carcinoma; adenoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); multiple myeloma; esophagus; a leukemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphoma; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; neck; head; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom macroglobulinemia.

[0113] In some embodiments, the cancer is selected from lung; bronchus; prostate; breast (including sporadic breast cancers and Cowden disease); pancreas; gastrointestinal; colon;

rectum; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; endometrial; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); esophagus; a leukemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; neck; and head. In some embodiments, the cancer is selected from sarcoma; carcinoma; colon carcinoma; adenoma; colorectal adenoma; glioma; glioblastoma; melanoma; multiple myeloma; a carcinoma of the brain; non-Hodgkin lymphoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphoma; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom macroglobulinemia.

[0114] In some embodiments, the cancer is selected from lung; bronchus; prostate; breast (including sporadic breast cancers and Cowden disease); pancreas; gastrointestinal; colon; rectum; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; endometrial; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary (including clear cell ovarian cancer); esophagus; brain; oral cavity and pharynx; larynx; small intestine; neck; and head. In some embodiments, the cancer is a leukemia. In some embodiments, the cancer is acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; or myeloid leukemia.

[0115] In some embodiments, the cancer is breast cancer (including sporadic breast cancers and Cowden disease). In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is ER+/HER2- breast cancer. In some embodiments, the cancer is ER+/HER2- breast cancer, and the subject is intolerant to, or ineligible for, treatment with alpelisib. In some embodiments, the cancer is sporadic breast cancer. In some embodiments, the cancer is Cowden disease.

[0116] In some embodiments, the cancer is ovarian cancer. In some embodiments, the ovarian cancer is clear cell ovarian cancer.

[0117] In some embodiments, the cancer is squamous cell carcinoma. In some embodiments, the cancer is squamous cell carcinoma of the head and neck.

[0118] In some embodiments, the cancer is cervical cancer.

[0119] In some embodiments, the cellular proliferative disease has mutant PI3K α . In some embodiments, the cancer has mutant PI3K α . In some embodiments, the breast cancer has

mutant PI3K α . In some embodiments, the ovarian cancer has mutant PI3K α . In some embodiments, the clear cell ovarian cancer has mutant PI3K α .

[0120] In some embodiments, the cellular proliferative disease has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the cellular proliferative disease has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the cancer has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the cancer has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the breast cancer has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the breast cancer has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the ovarian cancer has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the ovarian cancer has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S. In some embodiments, the clear cell ovarian cancer has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the clear cell ovarian cancer has PI3K α containing at least one of the following mutations: E542K, E542Q, E545A, E545G, E545K, E545Q, Q546E, Q546K, Q546L, Q546P, Q546R, H1047R, H1047L, H1047Y, G1049R, and G1049S.

[0121] In some embodiments, the cancer is adenoma; carcinoma; sarcoma; glioma; glioblastoma; melanoma; multiple myeloma; or lymphoma. In some embodiments, the cancer is a colorectal adenoma or avillous colon adenoma. In some embodiments, the cancer is colon carcinoma; a carcinoma of the brain; a mammary carcinoma; basal cell carcinoma; or a squamous cell carcinoma. In some embodiments, the cancer is a neoplasia or a neoplasia of epithelial character. In some embodiments, the cancer is non-Hodgkin lymphoma. In some embodiments, the cancer is actinic keratosis; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; or Waldenstrom macroglobulinemia.

[0122] In some embodiments, the cellular proliferative disease displays overexpression or amplification of PI3K α , somatic mutation of PIK3CA, germline mutations or somatic mutation of PTEN, or mutations and translocation of p85 α that serve to up-regulate the p85-p110 complex. In some embodiments, the cellular proliferative disease displays overexpression or amplification of PI3K α . In some embodiments, the cellular proliferative disease displays somatic mutation of PIK3CA. In some embodiments, the cellular proliferative disease displays germline mutations or somatic mutation of PTEN. In some embodiments, the cellular proliferative disease displays mutations and translocation of p85 α that serve to up-regulate the p85-p110 complex.

Additional Disorders

[0123] In some embodiments, the PI3K α -mediated disorder is selected from the group consisting of: polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, asthma, COPD, ARDS, PROS (PI3K-related overgrowth syndrome), venous malformation, Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves' disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

[0124] In some embodiments, the PI3K α -mediated disorder is polycythemia vera, essential thrombocythemia, or myelofibrosis with myeloid metaplasia. In some embodiments, the PI3K α -mediated disorder is asthma, COPD, ARDS, PROS (PI3K-related overgrowth syndrome), venous malformation, Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), or bronchopulmonary aspergillosis. In some embodiments, the PI3K α -mediated disorder is polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, or scleroderma. In some embodiments, the PI3K α -mediated disorder is vitiligo, hypersensitivity angitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, or autoimmune haematological disorders (e.g., haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia). In some embodiments, the PI3K α -mediated disorder is systemic lupus erythematosus, polyarthritides, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, or autoimmune inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease).

[0125] In some embodiments, the PI3K α -mediated disorder is endocrine ophthalmopathy, Graves' disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, or psoriatic arthritis. In some embodiments, the PI3K α -mediated disorder is glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, or reperfusion injuries. In some embodiments, the PI3K α -mediated disorder is retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

Routes of Administration and Dosage Forms

[0126] The compounds and compositions, according to the methods of the present disclosure, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder (e.g., a proliferative disorder). The exact amount required will vary from subject to subject, depending on the species, age, and general condition

of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the disclosure are preferably formulated in unit dosage form for ease of administration and uniformity of dosage. The expression “unit dosage form” as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0127] Pharmaceutically acceptable compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like. In certain embodiments, the compounds of the disclosure may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0128] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0129] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable

solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0130] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0131] In order to prolong the effect of a compound of the present disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0132] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0133] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating

agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0134] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0135] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0136] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically

acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Dosage Amounts and Regimens

[0137] In accordance with the methods of the present disclosure, the compounds of the disclosure are administered to the subject in a therapeutically effective amount, *e.g.*, to reduce or ameliorate symptoms of the disorder in the subject. This amount is readily determined by the skilled artisan, based upon known procedures, including analysis of titration curves established *in vivo* and methods and assays disclosed herein.

[0138] In some embodiments, the methods comprise administration of a therapeutically effective dosage of the compounds of the disclosure. In some embodiments, the therapeutically effective dosage is at least about 0.0001 mg/kg body weight, at least about 0.001 mg/kg body weight, at least about 0.01 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.1 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.3 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1 mg/kg body weight, at least about 2 mg/kg body weight, at least about 3 mg/kg body weight, at least about 4 mg/kg body weight, at least about 5 mg/kg body weight, at least about 6 mg/kg body weight, at least about 7 mg/kg body weight, at least about 8 mg/kg body weight, at least about 9 mg/kg body weight, at least about 10 mg/kg body weight, at least about 15 mg/kg body weight, at least about 20 mg/kg body weight, at least about 25 mg/kg body weight, at least about 30 mg/kg body weight, at least about 40 mg/kg body weight, at least about 50 mg/kg body weight, at least about 75 mg/kg body weight, at least about 100 mg/kg body weight, at least about 200 mg/kg body weight, at least about 250 mg/kg body weight, at least about 300 mg/kg body weight, at least about 350 mg/kg body weight, at least about 400 mg/kg body weight, at least about 450 mg/kg body weight, at least about 500 mg/kg body weight, at least about 550 mg/kg body weight, at least about 600 mg/kg body weight, at least about 650 mg/kg body weight, at least about 700 mg/kg body weight, at least about 750 mg/kg body weight, at least about 800 mg/kg body weight, at least about 900 mg/kg body weight, or at least about 1000 mg/kg body weight. It will be recognized that any of the dosages listed

herein may constitute an upper or lower dosage range, and may be combined with any other dosage to constitute a dosage range comprising an upper and lower limit.

[0139] In some embodiments, the therapeutically effective dosage is in the range of about 0.1 mg to about 10 mg/kg body weight, about 0.1 mg to about 6 mg/kg body weight, about 0.1 mg to about 4 mg/kg body weight, or about 0.1 mg to about 2 mg/kg body weight.

[0140] In some embodiments the therapeutically effective dosage is in the range of about 1 to 500 mg, about 2 to 150 mg, about 2 to 120 mg, about 2 to 80 mg, about 2 to 40 mg, about 5 to 150 mg, about 5 to 120 mg, about 5 to 80 mg, about 10 to 150 mg, about 10 to 120 mg, about 10 to 80 mg, about 10 to 40 mg, about 20 to 150 mg, about 20 to 120 mg, about 20 to 80 mg, about 20 to 40 mg, about 40 to 150 mg, about 40 to 120 mg or about 40 to 80 mg.

[0141] In some embodiments, the methods comprise a single dosage or administration (*e.g.*, as a single injection or deposition). Alternatively, in some embodiments, the methods comprise administration once daily, twice daily, three times daily or four times daily to a subject in need thereof for a period of from about 2 to about 28 days, or from about 7 to about 10 days, or from about 7 to about 15 days, or longer. In some embodiments, the methods comprise chronic administration. In yet other embodiments, the methods comprise administration over the course of several weeks, months, years or decades. In still other embodiments, the methods comprise administration over the course of several weeks. In still other embodiments, the methods comprise administration over the course of several months. In still other embodiments, the methods comprise administration over the course of several years. In still other embodiments, the methods comprise administration over the course of several decades.

[0142] The dosage administered can vary depending upon known factors such as the pharmacodynamic characteristics of the active ingredient and its mode and route of administration; time of administration of active ingredient; age, sex, health and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment and the effect desired; and rate of excretion. These are all readily determined and may be used by the skilled artisan to adjust or titrate dosages and/or dosing regimens.

Inhibition of Protein Kinases

[0143] According to one embodiment, the disclosure relates to a method of inhibiting protein kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. According to another embodiment, the disclosure relates to a method of inhibiting activity of a PI3K, or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. According

to another embodiment, the disclosure relates to a method of inhibiting activity of PI3K α , or a mutant thereof, in a biological sample comprising the step of contacting said biological sample with a compound of this disclosure, or a composition comprising said compound. In some embodiments, the PI3K α is a mutant PI3K α . In some embodiments, the PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K.

[0144] In another embodiment, the disclosure provides a method of selectively inhibiting PI3K α over one or both of PI3K δ and PI3K γ . In some embodiments, a compound of the present disclosure is more than 5-fold selective over PI3K δ and PI3K γ . In some embodiments, a compound of the present disclosure is more than 10-fold selective over PI3K δ and PI3K γ . In some embodiments, a compound of the present disclosure is more than 50-fold selective over PI3K δ and PI3K γ . In some embodiments, a compound of the present disclosure is more than 100-fold selective over PI3K δ and PI3K γ . In some embodiments, a compound of the present disclosure is more than 200-fold selective over PI3K δ and PI3K γ . In some embodiments, the PI3K α is a mutant PI3K α . In some embodiments, the PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K.

[0145] In another embodiment, the disclosure provides a method of selectively inhibiting a mutant PI3K α over a wild-type PI3K α . In some embodiments, a compound of the present disclosure is more than 5-fold selective for mutant PI3K α over wild-type PI3K α . In some embodiments, a compound of the present disclosure is more than 10-fold selective for mutant PI3K α over wild-type PI3K α . In some embodiments, a compound of the present disclosure is more than 50-fold selective for mutant PI3K α over wild-type PI3K α . In some embodiments, a compound of the present disclosure is more than 100-fold selective for mutant PI3K α over wild-type PI3K α . In some embodiments, a compound of the present disclosure is more than 200-fold selective for mutant PI3K α over wild-type PI3K α . In some embodiments, the mutant PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K.

[0146] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0147] Inhibition of activity of a PI3K (for example, PI3K α , or a mutant thereof) in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0148] Another embodiment of the present disclosure relates to a method of inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound.

[0149] According to another embodiment, the disclosure relates to a method of inhibiting activity of a PI3K, or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound. In some embodiments, the disclosure relates to a method of inhibiting activity of PI3K α , or a mutant thereof, in a patient comprising the step of administering to said patient a compound of the present disclosure, or a composition comprising said compound. In some embodiments, the PI3K α is a mutant PI3K α . In some embodiments, the PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K.

[0150] According to another embodiment, the present disclosure provides a method for treating a disorder mediated by a PI3K, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present disclosure or pharmaceutically acceptable composition thereof. In some embodiments, the present disclosure provides a method for treating a disorder mediated by PI3K α , or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present disclosure or pharmaceutically acceptable composition thereof. In some embodiments, the PI3K α is a mutant PI3K α . In some embodiments, the PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K.

[0151] According to another embodiment, the present disclosure provides a method of inhibiting signaling activity of PI3K α , or a mutant thereof, in a subject, comprising administering a therapeutically effective amount of a compound according to the present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the present disclosure provides a method of inhibiting PI3K α signaling activity in a subject, comprising administering a therapeutically effective amount of a compound according to the present disclosure, or a pharmaceutically acceptable composition thereof, to a subject in need thereof. In some embodiments, the PI3K α is a mutant PI3K α . In some embodiments, the PI3K α contains at least one of the following mutations: H1047R, E542K, and E545K. In some embodiments, the subject has a mutant PI3K α . In some embodiments, the subject has PI3K α containing at least one of the following mutations: H1047R, E542K, and E545K.

[0152] The compounds described herein can also inhibit PI3K α function through incorporation into agents that catalyze the destruction of PI3K α . For example, the compounds can be incorporated into proteolysis targeting chimeras (PROTACs). A PROTAC is a bifunctional molecule, with one portion capable of engaging an E3 ubiquitin ligase, and the other portion having the ability to bind to a target protein meant for degradation by the cellular protein quality control machinery. Recruitment of the target protein to the specific E3 ligase results in its tagging for destruction (i.e., ubiquitination) and subsequent degradation by the proteasome. Any E3 ligase can be used. The portion of the PROTAC that engages the E3 ligase is connected to the portion of the PROTAC that engages the target protein via a linker which consists of a variable chain of atoms. Recruitment of PI3K α to the E3 ligase will thus result in the destruction of the PI3K α protein. The variable chain of atoms can include, for example, rings, heteroatoms, and/or repeating polymeric units. It can be rigid or flexible. It can be attached to the two portions described above using standard techniques in the art of organic synthesis.

Combination Therapies

[0153] Depending upon the particular disorder, condition, or disease, to be treated, additional therapeutic agents, that are normally administered to treat that condition, may be administered in combination with compounds and compositions of this disclosure. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[0154] Additionally, PI3K serves as a second messenger node that integrates parallel signaling pathways, and evidence is emerging that the combination of a PI3K inhibitor with inhibitors of other pathways will be useful in treating cancer and cellular proliferative diseases.

[0155] Accordingly, in certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with one or more additional therapeutic agents. In certain other embodiments, the methods of treatment comprise administering the compound or composition of the disclosure as the only therapeutic agent.

[0156] Approximately 20-30% of human breast cancers overexpress Her-2/neu-ErbB2, the target for the drug trastuzumab. Although trastuzumab has demonstrated durable responses in some patients expressing Her2/neu-ErbB2, only a subset of these patients respond. Recent work has indicated that this limited response rate can be substantially improved by the combination of trastuzumab with inhibitors of PI3K or the PI3K/AKT pathway (Chan et al., Breast Can. Res. Treat. 91:187 (2005), Woods Ignatoski et al., Brit. J. Cancer 82:666 (2000), Nagata et al., Cancer Cell 6:117 (2004)). Accordingly, in certain embodiments, the method of

treatment comprises administering the compound or composition of the disclosure in combination with trastuzumab. In certain embodiments, the cancer is a human breast cancer that overexpresses Her-2/neu-ErbB2.

[0157] A variety of human malignancies express activating mutations or increased levels of Her1/EGFR and a number of antibody and small molecule inhibitors have been developed against this receptor tyrosine kinase including tarceva, gefitinib and erbitux. However, while EGFR inhibitors demonstrate anti-tumor activity in certain human tumors (e.g., NSCLC), they fail to increase overall patient survival in all patients with EGFR-expressing tumors. This may be rationalized by the fact that many downstream targets of Her1/EGFR are mutated or deregulated at high frequencies in a variety of malignancies, including the PI3K/Akt pathway.

[0158] For example, gefitinib inhibits the growth of an adenocarcinoma cell line in in vitro assays. Nonetheless, sub-clones of these cell lines can be selected that are resistant to gefitinib that demonstrate increased activation of the PI3/Akt pathway. Down-regulation or inhibition of this pathway renders the resistant sub-clones sensitive to gefitinib (Kokubo et al., Brit. J. Cancer 92:1711 (2005)). Furthermore, in an in vitro model of breast cancer with a cell line that harbors a PTEN mutation and over-expresses EGFR inhibition of both the PI3K/Akt pathway and EGFR produced a synergistic effect (She et al., Cancer Cell 8:287-297 (2005)). These results indicate that the combination of gefitinib and PI3K/Akt pathway inhibitors would be an attractive therapeutic strategy in cancer.

[0159] Accordingly, in certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with an inhibitor of Her1/EGFR. In certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with one or more of tarceva, gefitinib, and erbitux. In certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with gefitinib. In certain embodiments, the cancer expresses activating mutations or increased levels of Her1/EGFR.

[0160] The combination of AEE778 (an inhibitor of Her-2/neu/ErbB2, VEGFR and EGFR) and RAD001 (an inhibitor of mTOR, a downstream target of Akt) produced greater combined efficacy than either agent alone in a glioblastoma xenograft model (Goudar et al., Mol. Cancer. Ther. 4:101-112 (2005)).

[0161] Anti-estrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status

of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to anti-estrogen resistance (Donovan, et al, J. Biol. Chem. 276:40888, (2001)). As reported by Donovan et al., inhibition of MAPK signaling through treatment with MEK inhibitor reversed the aberrant phosphorylation status of p27 in hormone refractory breast cancer cell lines and in so doing restored hormone sensitivity. Similarly, phosphorylation of p27Kip by Aid also abrogates its role to arrest the cell cycle (Viglietto et al., Nat. Med. 8:1145 (2002)).

[0162] Accordingly, in certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with a treatment for a hormone-dependent cancer. In certain embodiments, the method of treatment comprises administering the compound or composition of the disclosure in combination with tamoxifen. In certain embodiments, the cancer is a hormone dependent cancer, such as breast and prostate cancers. By this use, it is aimed to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

[0163] In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-Abl tyrosine kinase. The afflicted patients are responsive to imatinib, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Abl kinase activity. However, many patients with advanced stage disease respond to imatinib initially, but then relapse later due to resistance-conferring mutations in the Abl kinase domain. In vitro studies have demonstrated that BCR-Abl employs the Ras-Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional protection against resistance-conferring mutations.

[0164] Accordingly, in another aspect, the compounds and compositions of the disclosure are used in combination with at least one additional agent selected from the group of kinase inhibitors, such as imatinib, in the treatment of hematological cancers, such as chronic myelogenous leukemia (CML). By this use, it is aimed to reverse or prevent resistance to said at least one additional agent.

[0165] Because activation of the PI3K/Akt pathway drives cell survival, inhibition of the pathway in combination with therapies that drive apoptosis in cancer cells, including radiotherapy and chemotherapy, will result in improved responses (Ghobrial et al., CA Cancer J. Clin 55:178-194 (2005)). As an example, combination of PI3 kinase inhibitor with carboplatin demonstrated synergistic effects in both in vitro proliferation and apoptosis assays as well as in in vivo tumor efficacy in a xenograft model of ovarian cancer (Westfall and Skinner, Mol. Cancer Ther. 4:1764-1771 (2005)).

[0166] In some embodiments, the one or more additional therapeutic agents is selected from antibodies, antibody-drug conjugates, kinase inhibitors, immunomodulators, and histone deacetylase inhibitors. Synergistic combinations with PIK3CA inhibitors and other therapeutic agents are described in, for example, Castel et al., *Mol. Cell Oncol.* (2014)1(3) e963447.

[0167] In some embodiments, the one or more additional therapeutic agent is selected from the following agents, or a pharmaceutically acceptable salt thereof: BCR-ABL inhibitors (see e.g. Ultimo et al. *Oncotarget* (2017) 8 (14) 23213-23227); e.g. imatinib, inilotinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, danusertib, saracatinib, PF03814735; ALK inhibitors (see e.g. Yang et al. *Tumour Biol.* (2014) 35 (10) 9759-67); e.g. crizotinib, NVP-TAE684, ceritinib, alectinib, brigatinib, entrectinib, lorlatinib; BRAF inhibitors (see e.g. Silva et al. *Mol. Cancer Res.* (2014) 12, 447-463); e.g. vemurafenib, dabrafenib; FGFR inhibitors (see e.g. Packer et al. *Mol. Cancer Ther.* (2017) 16(4) 637-648); e.g. infigratinib, dovitinib, erdafitinib, TAS-120, pemigatinib, BLU-554, AZD4547; FLT3 inhibitors: e.g. sunitinib, midostaurin, tanutinib, sorafenib, lestaurtinib, quizartinib, and crenolanib; MEK Inhibitors (see e.g. Jokinen et al. *Ther. Adv. Med. Oncol.* (2015) 7(3) 170-180); e.g. trametinib, cobimetinib, binimetinib, selumetinib; ERK inhibitors: e.g. ulixertinib, MK 8353, LY 3214996; KRAS inhibitors: e.g. AMG-510, MRTX849, ARS-3248; Tyrosine kinase inhibitors (see e.g. Makhov et al. *Mol. Cancer. Ther.* (2012) 11(7) 1510-1517); e.g. erlotinib, linifanib, sunitinib, pazopanib; Epidermal growth factor receptor (EGFR) inhibitors (see e.g. She et al. *BMC Cancer* (2016) 16, 587); gefitinib, osimertinib, cetuximab, panitumumab; HER2 receptor inhibitors (see e.g. Lopez et al. *Mol. Cancer Ther.* (2015) 14(11) 2519-2526); e.g. trastuzumab, pertuzumab, neratinib, lapatinib, lapatinib; MET inhibitors (see e.g. Hervieu et al. *Front. Mol. Biosci.* (2018) 5, 86); e.g. crizotinib, cabozantinib; CD20 antibodies: e.g. rituximab, tositumomab, ofatumumab; DNA Synthesis inhibitors: e.g. capecitabine, gemcitabine, nelarabine, hydroxycarbamide; Antineoplastic agents (see e.g. Wang et al. *Cell Death & Disease* (2018) 9, 739); e.g. oxaliplatin, carboplatin, cisplatin;; Immunomodulators: e.g. afutuzumab, lenalidomide, thalidomide, pomalidomide; CD40 inhibitors: e.g. dacetuzumab; Pro-apoptotic receptor agonists (PARAs): e.g. dulanermin; Heat Shock Protein (HSP) inhibitors (see e.g. Chen et al. *Oncotarget* (2014) 5 (9). 2372-2389); e.g. tanespimycin; Hedgehog antagonists (see e.g. Chaturvedi et al. *Oncotarget* (2018) 9 (24), 16619-16633); e.g. vismodegib; Proteasome inhibitors (see e.g. Lin et al. *Int. J. Oncol.* (2014) 44 (2), 557-562); e.g. bortezomib; PI3K inhibitors: e.g. pictilisib, dactolisib, alpelisib, buparlisib, taselisib, idelalisib, duvelisib, umbralisib; SHP2 inhibitors (see e.g. Sun et al. *Am. J. Cancer Res.* (2019) 9 (1), 149-159; e.g. SHP099, RMC-4550, RMC-4630); BCL-2 inhibitors (see e.g. Bojarczuk

et al. *Blood* (2018) 133 (1), 70-80); e.g. venetoclax; Aromatase inhibitors (see e.g. Mayer et al. *Clin. Cancer Res.* (2019) 25 (10), 2975-2987); exemestane, letrozole, anastrozole, fulvestrant, tamoxifen; mTOR inhibitors (see e.g. Woo et al. *Oncogenesis* (2017) 6, e385); e.g. temsirolimus, ridaforolimus, everolimus, sirolimus; CTLA-4 inhibitors (see e.g. O'Donnell et al. (2018) 48, 91-103); e.g. tremelimumab, ipilimumab; PD1 inhibitors (see O'Donnell, supra); e.g. nivolumab, pembrolizumab; an immunoadhesin; Other immune checkpoint inhibitors (see e.g. Zappasodi et al. *Cancer Cell* (2018) 33, 581-598, where the term "immune checkpoint" refers to a group of molecules on the cell surface of CD4 and CD8 T cells. Immune checkpoint molecules include, but are not limited to, Programmed Death 1 (PD-1), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), B7H1, B7H4, OX-40, CD 137, CD40, and LAG3. Immunotherapeutic agents which can act as immune checkpoint inhibitors useful in the methods of the present disclosure, include, but are not limited to, inhibitors of PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD 160, 2B4 and/or TGFR beta); e.g. pidilizumab, AMP-224; PDL1 inhibitors (see e.g. O'Donnell supra); e.g. MSB0010718C; YW243.55.S70, MPDL3280A; MEDI-4736, MSB-0010718C, or MDX-1105;; Histone deacetylase inhibitors (HDI, see e.g. Rahmani et al. *Clin. Cancer Res.* (2014) 20(18), 4849-4860); e.g. vorinostat;; Androgen Receptor inhibitors (see e.g. Thomas et al. *Mol. Cancer Ther.* (2013) 12(11), 2342-2355); e.g. enzalutamide, abiraterone acetate, orteronel, galeterone, seviteronel, bicalutamide, flutamide; Androgens: e.g. fluoxymesterone; CDK4/6 inhibitors (see e.g. Gul et al. *Am. J. Cancer Res.* (2018) 8(12), 2359-2376); e.g. alvocidib, palbociclib, ribociclib, trilaciclib, abemaciclib.

[0168] In some embodiments, the one or more additional therapeutic agent is selected from the following agents: anti-FGFR antibodies; FGFR inhibitors, cytotoxic agents; Estrogen Receptor-targeted or other endocrine therapies, immune-checkpoint inhibitors, CDK inhibitors, Receptor Tyrosine Kinase inhibitors, BRAF inhibitors, MEK inhibitors, other PI3K inhibitors, SHP2 inhibitors, and SRC inhibitors. (See Katoh, *Nat. Rev. Clin. Oncol.* (2019), 16:105-122; Chae, et al. *Oncotarget* (2017), 8:16052-16074; Formisano et al., *Nat. Comm.* (2019), 10:1373-1386; and references cited therein.).

[0169] In some embodiments, the estrogen receptor targeted therapy is a selective estrogen receptor degrader (SERD, e.g. fulvestrant, elacestrant, giredestrant). In some embodiments, the estrogen receptor targeted therapy is an estrogen receptor degrading PROTAC (e.g. ARV-471). In some embodiments, the endocrine therapy is an aromatase inhibitor (e.g. anastrozole, letrozole, exemestane).

[0170] In some embodiments, the one or more additional therapeutic agents are inhibitors of one or more of CDK2, CDK4, and CDK6 enzymes. In some embodiments, the CDK inhibitor is a CDK2 inhibitor (e.g. PF-07104091). In some embodiments, the CDK inhibitor is a CDK4 inhibitor (e.g. PF-07220060, AU2-94). In some embodiments, the CDK inhibitor is a dual CDK4/6 inhibitor (e.g. palbociclib, abemaciclib, ribociclib, trilaciclib). In some embodiment,s the CDK inhibitor is an inhibitor of CDK2/4/6.

[0171] In some embodiments, more than one CDK inhibitor is administered together with compound of the disclosure. In some embodiments, the additional therapeutic agents comprise one or more CDK inhibitors and an estrogen receptor targeted therapy. In some embodiments, the additional therapeutic agent comprises a selective estrogen receptor degrader and one or more CDK inhibitors.

[0172] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[0173] A compound of the current disclosure may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0174] A compound of the current disclosure can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the disclosure and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current disclosure can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[0175] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this disclosure in a single composition. If administered as part of a multiple dosage regime, the two active agents may

be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0176] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this disclosure. For example, a compound of the present disclosure may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present disclosure provides a single unit dosage form comprising a compound of the current disclosure, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0177] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this disclosure should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[0178] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this disclosure may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 µg/kg body weight/day of the additional therapeutic agent can be administered.

[0179] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0180] The compounds of this disclosure, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a

pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this disclosure are another embodiment of the present disclosure.

[0181] Any of the compounds and/or compositions of the disclosure may be provided in a kit comprising the compounds and/or compositions. Thus, in some embodiments, the compound and/or composition of the disclosure is provided in a kit.

[0182] The disclosure is further described by the following non-limiting Examples.

EXAMPLES

[0183] Examples are provided herein to facilitate a more complete understanding of the disclosure. The following examples serve to illustrate the exemplary modes of making and practicing the subject matter of the disclosure. However, the scope of the disclosure is not to be construed as limited to specific embodiments disclosed in these examples, which are illustrative only.

[0184] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to other classes and subclasses and species of each of these compounds, as described herein. Additional compounds of the disclosure were prepared by methods substantially similar to those described herein in the Examples and methods known to one skilled in the art.

[0185] In the description of the synthetic methods described below, unless otherwise stated, it is to be understood that all reaction conditions (for example, reaction solvent, atmosphere, temperature, duration, and workup procedures) are selected from the standard conditions for that reaction, unless otherwise indicated. The starting materials for the Examples are either commercially available or are readily prepared by standard methods from known materials.

[0186] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. The following non-limiting examples illustrate the disclosures herein.

Instruments and Methodology

X-ray Powder Diffraction (XRPD)

[0187] Method. Instrument: PANalytical Empyrean. XRPD diffractograms were collected on a PANalytical Empyrean diffractometer using Cu K α radiation (45 kV, 40 mA) in transmission geometry. A 0.5° slit, 4 mm mask and 0.04 rad Soller slits with a focusing mirror were used on the incident beam. A PIXcel^{3D} detector, placed on the diffracted beam, was fitted with a

receiving slit and 0.04 rad Soller slits. The software used for data collection was X'Pert Data Collector using X'Pert Operator Interface. The data were analyzed and presented using HighScore Plus. Samples were prepared and analyzed in either a metal or Millipore 96 well-plate in transmission mode. X-ray transparent film was used between the metal sheets on the metal well-plate and powders (approximately 1 – 2 mg) were used as received. The Millipore plate was used to isolate and analyze solids from suspensions by adding a small amount of suspension directly to the plate before filtration under a light vacuum. The scan mode for the metal plate used the gonio scan axis, whereas a 2θ scan was utilized for the Millipore plate. The parameters of the standard screening data collection method are:

Angular range: 2.5 to 32.0° 2θ

Step size: 0.0130° 2θ

Collection time: 12.75 s/step (total collection time of 2.07 min)

Differential Scanning Calorimetric (DSC)

[0188] Method 1. Instrument: TA Instruments Discovery DSC. DSC data were collected on a TA Instruments Discovery DSC equipped with a 50 position auto-sampler. Typically, 0.5 - 3 mg of each sample, in a pin-holed aluminum pan, was heated at 10 °C/min from 25 °C to 300 °C. A purge of dry nitrogen at 50 ml/min was maintained over the sample. The instrument control software was TRIOS and the data were analyzed using TRIOS or Universal Analysis.

[0189] Method 2. Instrument: TA Instruments DSC2500. DSC data were collected on a TA Instruments DSC2500 equipped with a 54 position auto-sampler. Typically, 0.5 - 3 mg of each sample, in a pin-holed aluminum pan, was heated at 10 °C/min from 25 °C to 300 °C. A purge of dry nitrogen at 50 ml/min was maintained over the sample. Modulated temperature DSC (MDSC) was carried out using an underlying heating rate of 2 °C/min and temperature modulation parameters of ± 0.64 °C (amplitude) every 60 seconds (period). The instrument control software was TRIOS and the data were analyzed using TRIOS or Universal Analysis.

Thermal Gravimetric Analysis (TGA)

Instrument Discovery 5500 or Q5000

Sample pan Aluminum, open

Start temperature Ambient condition (below 35°C)

Final temperature 300°C or abort next segment if weight < 80% (w/w)

(The weight loss of the compound is no more than 20% (w/w))

Heating rate 10°C/min

Nitrogen flow Balance 10mL/min; sample chamber 25mL/min

Sample mass About 2-10mg

Dynamic Vapor Sorption (DVS)

Method 1

Instrument Intrinsic, Advantage or Adventure

Total gas flow 200 sccm

Oven temperature 25°C

Solvent Water

Method Cycle: 40-0-95-0-40%RH

Stage Step: 10%

Equilibrium: 0.002 dm/dt (%/min)

Minimum dm/dt stability duration: 60min

Maximum dm/dt stage time: 360min

Method 2

Instrument Intrinsic, Advantage or Adventure

Total gas flow 200 sccm

Oven temperature 25°C

Solvent Water

Method Cycle: 40-95-0-95-40%RH

Stage Step: 10%

Equilibrium: 0.002 dm/dt (%/min)

Minimum dm/dt stability duration: 60min

Maximum dm/dt stage time: 360min

[0190] Nuclear Magnetic Resonance (NMR)

Instrument Bruker Avance-AV 400M (for ¹H-NMR, ¹⁹F-NMR and ³¹P-NMR)

Bruker Avance-III 400M (for ¹³C-NMR)

Frequency 400MHz

Probe 5 mm PABBO BB/19F-1H/D Z-GRD Z108618/0406 (for ¹H-NMR, ¹⁹F-NMR and ³¹P-NMR)

5 mm PABBO BB-1H/D Z-GRD Z108618/0229 (for ¹³C NMR)

Number of scan 8

Temperature 297.6K

Relaxation delay 1 second

[0191] High Performance Liquid Chromatograph (HPLC)

Instrument Agilent 1260, SHIMADZU CBM-40,

Chiral purity Wave length: 220nm
 Column: Daicel OD-RH (4.6×150 mm×5 μm)
 Detector: DAD, PDA
 Column temperature: 40°C
 Flow rate: 1mL/min
 Mobile phase A: 10mM NH₄OAc in water
 Mobile phase B: ACN
 Diluent: ACN
 Injection volume: 5μL
 Sample Preparation: 2mg/mL
 Needle Wash Solvent: ACN:H₂O=90:10(v/v)
 Gradient: Isocratic elution

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	55	45
30	55	45

FeSSIF (fed state simulated intestinal fluid)

[0192] *Acetate Base Buffer (FeSSIF), pH 5.0:* Sodium hydroxide (4.061 g), acetic acid (8.25 ml) and sodium chloride (11.88 g) were dissolved in *Ca.* 800 ml of deionized water in a 1000 ml volumetric flask. This solution was mixed thoroughly and then the pH adjusted to 5.0 ± 0.05 with 1M hydrochloric acid/sodium hydroxide. The solution was then made to volume with deionized water and the pH recorded (pH 5.00).

[0193] *FeSSIF Media:* Phares SIF (simulated intestinal fluid) powder (0.56 g) was dissolved in *Ca.* 40ml of base buffer in a 50 ml volumetric flask. This solution was mixed thoroughly and then made to volume with the same base buffer. The final pH was recorded (pH 4.93).

FaSSIF (fasted state simulated intestinal fluid)

[0194] *Phosphate Base Buffer (FaSSIF), pH 6.5:* Sodium hydroxide (0.403 g), sodium phosphate monobasic (3.95 g) and sodium chloride (6.50 g) were dissolved in *Ca.* 800 ml of deionized water in a 1000 ml volumetric flask. This solution was mixed thoroughly and then the pH adjusted to 6.5 ± 0.05 with 1M hydrochloric acid/sodium hydroxide. The solution was then made to volume with deionized water and the pH recorded (pH 6.47).

[0195] *FaSSIF Media:* Phares SIF (simulated intestinal fluid) powder (0.112 g) was dissolved in *Ca.* 40ml of base buffer in a 50 ml volumetric flask. This solution was mixed thoroughly and then made to volume with the same base buffer. The final pH was recorded (pH 6.46).

FaSSGF (fasted state simulated gastric fluid)

[0196] *Base Buffer (FaSSGF), pH 1.6*: Sodium chloride (1.99 g) was dissolved in *Ca.* 800 ml of deionized water in a 1000 ml volumetric flask. This solution was mixed thoroughly and then the pH adjusted to 1.6 ± 0.05 with concentrated hydrochloric acid. The solution was then made to volume with deionized water and the pH recorded (pH 1.60).

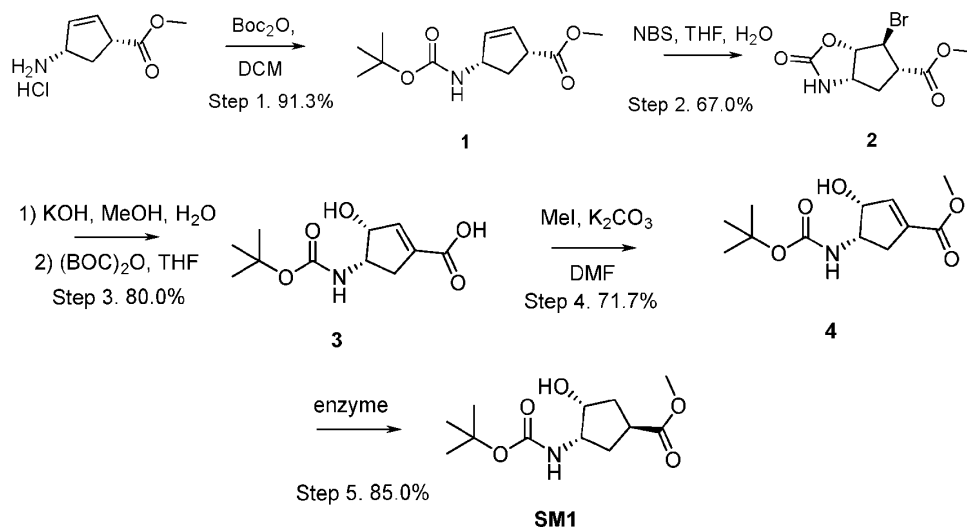
[0197] *FaSSGF Media*: Phares SIF (simulated intestinal fluid) powder (0.03 g) was dissolved in *Ca.* 40 ml of base buffer in a 50 ml volumetric flask. This solution was mixed thoroughly and then made to volume with the same base buffer. The final pH was recorded (pH 1.63).

Abbreviations	Full name
MeOH	Methanol
EtOH	Ethanol
ACN	Acetonitrile
TFA	Trifluoroacetic acid
DMSO	Dimethyl sulfoxide
IPAc	Isopropyl acetate
DCM	Dichloromethane
EA	Ethyl acetate
THF	Tetrahydrofuran
MTBE	Methyl tert-butyl ether
DMF	Dimethylformamide
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uranium
HOBt	Hydroxybenzotriazole
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
NBS	N-bromosuccinimide
DIEA (or DIPEA)	Diisopropylethylamine

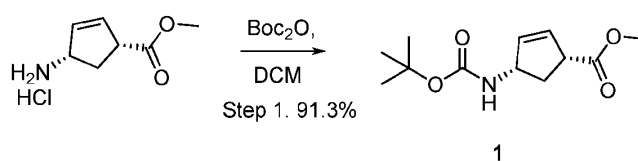
Example 1

Preparation of Synthetic Intermediates

1.1. Preparation of Intermediate SM1



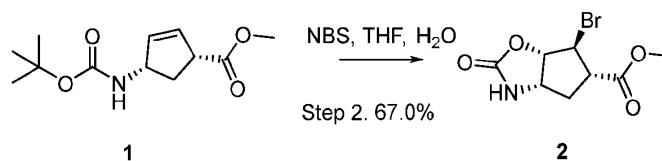
Step 1. Preparation of Methyl (1R,4S)-4-((tert-butoxycarbonyl)amino)cyclopent-2-ene-1-carboxylate (1)



[0198] A solution of methyl (1R,4S)-4-aminocyclopent-2-ene-1-carboxylate hydrochloride (5000.00 g, 28.149 mol, 1 eq) in DCM (30 L) at 0 °C was treated with triethylamine (2.848 kg, 28.149 mol, 1.0 eq). The temperature was controlled to 0-5 °C. Di-tert-butyl dicarbonate (6.143 kg, 28.149 mol, 1.0 eq) was added dropwise to the resulting mixture at 0-5 °C, and the internal temperature of the mixture was maintained below 10 °C. The mixture was allowed to warm to 22 °C and was stirred for 16 hrs.

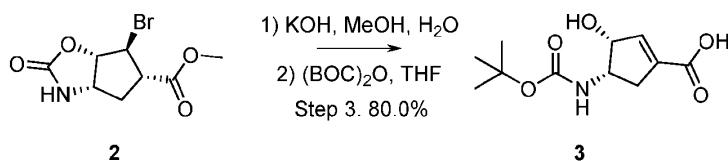
[0199] The reaction was diluted with water (8000 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (5000.0mL), and the DCM layer was washed with brine (5.0 L), dried over anhydrous MgSO₄, filtered and concentrated. Methyl (1R,4S)-4-((tert-butoxycarbonyl)amino) cyclopent -2-ene-1-carboxylate was obtained as a white solid (6.20 kg, 91.3% yield).

Step 2. Preparation of Methyl (3aR,5R,6R,6aR)-6-bromo-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxylate (2)



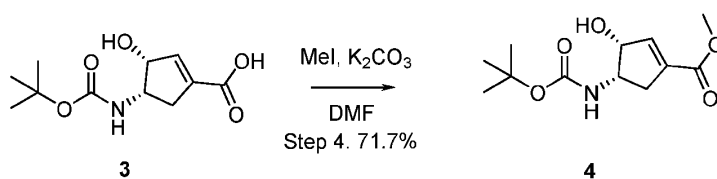
[0200] A solution of methyl (1R,4S)-4-((tert-butoxycarbonyl)amino)cyclopent-2-ene-1-carboxylate (5500.00 g, 22.795 mol, 1 eq) in THF (22 L) and H₂O (2.2 L) was cooled to 0 °C. Then N-bromosuccinimide (4.463 kg, 25.074 mol, 1.1 eq) was added in batches. The mixture was allowed to warm to room temperature and stirred for 16 hrs. The solution was concentrated to dryness. The residue was slurried in DCM (15 L) and washed with 1M HCl (5 L), saturated Na₂SO₃ (6 L), brine (6.0L), dried over anhydrous MgSO₄, filtered and concentrated. The residue was slurried in n-heptane (4 L) for 30 min, filtered, and dried to obtain methyl (3aR,5R,6R,6aR)-6-bromo-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxylate as a white solid (4.033kg, 67.0%).

Step 3. Preparation of (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylic acid (3)



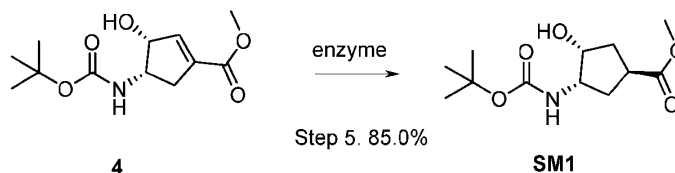
[0201] A solution of methyl (3aR,5R,6R,6aR)-6-bromo-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxylate (2000.00 g, 7.574 mol, 1 eq) in MeOH (10 L) and H₂O (10 L) was cooled to 0 °C. Then KOH (1.700 kg, 30.295 mol, 4.0 eq) was added in batches. The mixture was heated at 80 °C for 16 hrs. The mixture was cooled to 20 °C and concentrated under vacuum. Di-tert-butyl dicarbonate (1.653 kg, 7.574 mol, 1 eq) in THF (4.0 L) was added dropwise to the residue. The mixture was allowed to warm to room temperature and stirred for 16 hrs. The mixture was redissolved in EA (3 L) and H₂O (3 L), 1M HCl was added dropwise into the mixture to adjust pH=3~4 and extracted with EA (5 L x 3). The organic layer was separated, washed with brine (5 L), dried over anhydrous MgSO₄, filtered and concentrated to dryness. (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylic acid (1.48 kg, 80.0% yield) was obtained as a white solid.

Step 4. Preparation of Methyl (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylate (4)



[0202] A solution of (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylic acid (3, 2900.00 g, 11.922 mol, 1 eq) in DMF (14.5 L) was cooled to 0 °C, then K₂CO₃ (2.471 kg, 17.882 mol, 1.5 eq) was added in batches. The mixture was allowed to warm to room temperature and stirred for 1 hrs. Methyl iodide (3.384 kg, 23.843 mol, 2.0 eq) was added dropwise to the resulting mixture at 0-5 °C. The mixture was allowed to warm to room temperature and was stirred for 16 hrs. The mixture was quenched with H₂O (40.0 L) and then extracted with EA (10 L x 2). The organic layer was separated, washed with brine (5L), dried over anhydrous MgSO₄, filtered, and concentrated to dryness. The residue was slurried in (PE:EA=3:1 (2 L)) for 30 min, filtered, and dried to obtain methyl (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylate (2.200 kg, 71.7% yield) as a white solid.

Step 5. Preparation of Methyl (1S,3S,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylate (SM1)

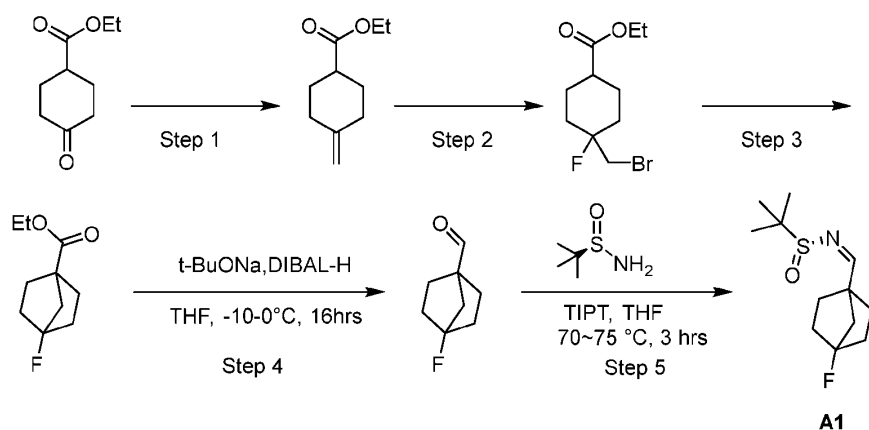


[0203] Glucose (1800.00g) was dissolved in 14.4 L of 100 mM potassium phosphate buffer at pH=7. Then, 800.00g wet whole cells of *E. coli* BL21(DE3) overexpressing the enzyme, Ene Reductase 10 (PE10), was added to the potassium phosphate buffer and fully suspended to obtain a uniform suspension. Then, 8.00 g of glucose dehydrogenase powder and nicotinamide adenine dinucleotide phosphate were added to the potassium phosphate buffer. To this was added 800.00g of the substrate (methyl (3R,4S)-4-((tert-butoxycarbonyl)amino)-3-hydroxycyclopent-1-ene-1-carboxylate) in DMSO as a cosolvent. The mixture was stirred at 37 °C. Due to the production of gluconic acid during the reaction process, 3M K₂CO₃ is used to adjust the pH and control it at 7.0. The mixture was stirred for 16 hrs.

[0204] The reaction mixture was filtered over diatomaceous earth. The filtrate was extracted with EA (3L x 3), and the filter cake was slurried with 8L EA. The combined organic layers

were washed with brine (5L), dried over anhydrous MgSO_4 , filtered, and concentrated to dryness. The residue was slurried in n-heptane (1 L) for 30 min, filtered, and dried to obtain methyl (1S,3S,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylate (0.685 kg, 85.0% yield) as a white solid. ^1H NMR (400MHz, CDCl_3) δ 4.81 (s, 1H), 4.28 (s, 1H), 3.67 (s, 3H), 3.08 - 3.15 (m, 1H), 2.07 - 2.27 (m, 1H), 2.02 - 2.05 (m, 2H), 1.84 - 1.86 (m, 2H), 1.44 (s, 9H). HPLC purity=98.80%. e.e%=100%.

1.2. Preparation of Intermediate A1



Step 1. Preparation of ethyl 4-methylenecyclohexane-1-carboxylate

[0205] A reaction vessel was charged with Ph_3MeBr (28.35 kg, 1.5 eq) in THF (72.0 L, 8.0 V) under N_2 . To the vessel was added $t\text{-BuOK}$ (8.91 kg, 1.5 eq) at $\sim 0^\circ\text{C}$. To the mixture was added ethyl 4-oxocyclohexane-1-carboxylate (9.00 kg, 1.00 eq) in THF (18.0 L, 2.0V) dropwise, and the resulting mixture was stirred at $\sim 0^\circ\text{C}$ for 10 min. Then, 30% aq. citric acid (1V) was added to the reaction vessel to adjust the pH to ~ 4.5 . The mixture was stirred at $20\text{--}25^\circ\text{C}$ for 30 min. The aqueous phase was extracted with heptane (2 x 4V) and the organic phases were combined, concentrated to $\sim 1\text{V}$, charged with heptane (2V) in a vessel, which was stirred for 30 min. The mixture was filtered, dried over MgSO_4 , and concentrated to afford ethyl 4-methylenecyclohexane-1-carboxylate as a light yellow liquid (6.93 kg, 78% yield).

Step 2. Preparation of ethyl 4-(bromomethyl)-4-fluorocyclohexane-1-carboxylate

[0206] A reaction vessel was charged with DCM (93.3 L, 10 V) and ethyl 4-methylenecyclohexane-1-carboxylate (9.33 kg, 1.0 eq). To this was added triethylamine trihydrofluoride (22.39 kg, 2.5 eq) at $\sim 0^\circ\text{C}$ for 10 min. The mixture was then charged with N-bromosuccinimide (14.74 kg, 1.5 eq) and stirred at $20\text{--}25^\circ\text{C}$ for 10 min. Then, distilled water (140.0 kg, 15.0 V) was added, and the mixture was stirred for 30 min. The mixture was washed

with additional distilled water (93.0 kg, 10.0 V) and the organic layers were combined, dried over MgSO_4 , filtered and concentrated to afford crude ethyl 4-(bromomethyl)-4-fluorocyclohexane-1-carboxylate as a brown liquid (10.81 kg crude).

Step 3. Preparation of ethyl 4-fluorobicyclo[2.2.1]heptane-1-carboxylate

[0207] A reaction vessel was charged with THF (20L, 10V), MTBE (6.0L, 3V), and crude ethyl 4-(bromomethyl)-4-fluorocyclohexane-1-carboxylate (2.0 kg, 1.0 eq). To the solution potassium bis(trimethylsilyl)amide (13.1 L, 1.75 eq) was added at 30-40 °C for 60 min. Then, 10% aq. Ammonium chloride (5V) was added dropwise to the mixture, which was stirred at ~0 °C for 30 min. The aqueous phase was extracted with MTBE (4V) twice, and the combined organic layer was concentrated to a crude light yellow liquid. To a separate vessel was added N-(2-hydroxyethyl)-2-pyrrolidone (5.0V), activated carbon (10%), and the crude light yellow concentrate under N_2 . The mixture was stirred, filtered, and concentrated to afford ethyl 4-fluorobicyclo[2.2.1]heptane-1-carboxylate as a brown liquid (2.51 kg, 58.7% yield).

Step 4. Preparation of 4-fluoronorbornane-1-carbaldehyde

[0208] Preparation of SDBBA reductant: To a solution of *t*-BuONa (1.500 kg, 15.608 mol, 1.938 eq) in THF (20.0 L), was added DIBAL-H (2.115 kg, 14.98 mol, 9.99 L, 1.860 eq) dropwise at -10~0 °C. The reaction mixture was stirred at 25 °C for 2 hrs to give the reductant SDBBA.

[0209] To a solution of ethyl 4-fluorobicyclo[2.2.1]heptane-1-carboxylate (1500.0 g, 8.055 mol, 1.0 eq) in THF (20.0 L) was added the fresh made SDBBA at -10~0 °C and the mixture was stirred at -10~0 °C for 16 hrs. The reaction was afterwards quenched with addition of 1N HCl (30.0 L) dropwise and stirred for 2 hrs. The mixture was extracted with MTBE (10.0 L x 3), the combined organic layers were dried over MgSO_4 , filtered and concentrated at 10~20 °C to give a residue. The residue was redissolved in MTBE (1.0 L), sat. solution of NaHSO_3 (6 L) was added and stirred at 25 °C for 16 hrs. The mixture was extracted with MTBE (5.0 L x 4) and water layer was collected. pH of the water layer was adjusted by addition of sat. Na_2CO_3 (10 L) to pH = 9~10 and stirred at 25 °C for further 16 hrs. The resulting mixture was extracted with MTBE (5.0 L x 5), the organic phases were combined and dried over MgSO_4 , filtered and concentrated at 15~20 °C to give 4-fluorobicyclo[2.2.1]heptane-1-carbaldehyde (640.6 g, 74.488% yield) as colorless oil.

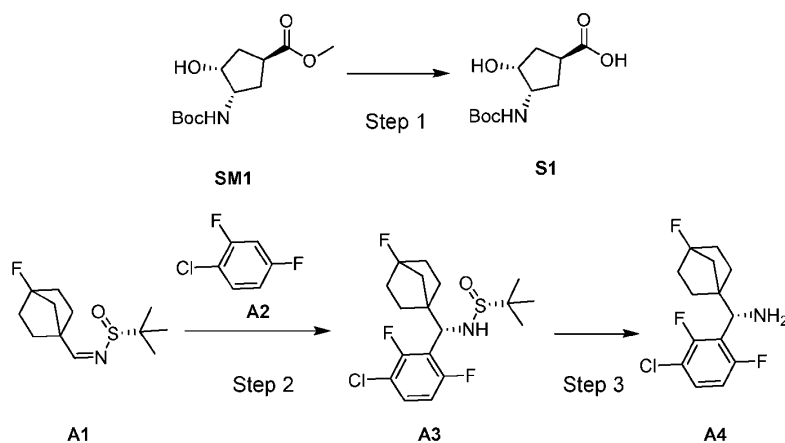
Step 5. Preparation of (R,Z)-N-[(4-fluoronorbornan-1-yl)methylene]-2-methyl-propane-2-sulfinamide (A1)

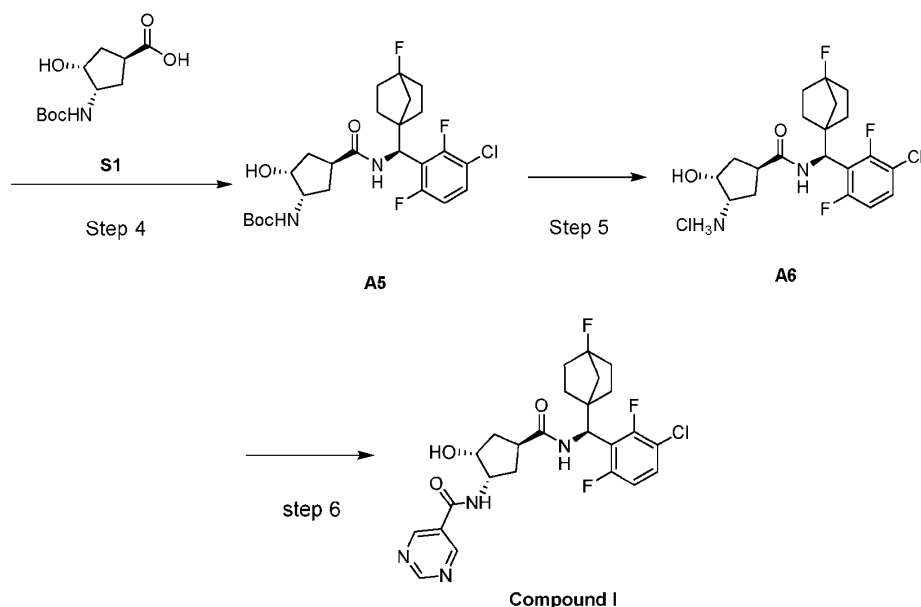
[0210] To a solution of 4-fluorobicyclo[2.2.1]heptane-1-carbaldehyde (640.0 g, 4.502 mol, 1.0 eq) in THF (15.0 L) was added (R)-2-methylpropane-2-sulfinamide (545.60g, 4.502 mol, 1.0

eq), and tetra isopropyl titanate (TIPT, 2.561kg, 9.003 mol, 2.0 eq) at 25 °C. The reaction mixture was stirred at 70~75 °C for 3 hrs. The reaction mixture was cooled to 25 °C naturally and diluted with EA (10.0 L), then poured into water (10.0 L) at 10~20 °C. The mixture was extracted with EA (10.0 L x 3), the combined organic layers were washed with sat. NaCl solution (4.5 L), dried over MgSO₄, filtered, and concentrated at 35~45 °C to give a residue. The residue was triturated with (*n*-heptane:EA = 10:1) (1.5 L) at 0-10 °C for 2 hrs then filtered to give (R,Z)-N-[(4-fluoronorbornan-1-yl)methylene]-2-methyl-propane-2-sulfinamide (521.02 g, 47.172%) as white solid.

Example 2

Synthesis of Compound I





Step 1. Preparation of (1S,3S,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylic acid (S1)

[0211] To a solution of methyl (1R,3R,4S)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylate (700 g, 1.00 eq) in THF (1.4 L, 2V) and MeOH (1.4 L, 2V) was added 1M aq. LiOH solution (3.5 L, 5V) at 0-5 °C, the mixture was stirred at 0-5 °C for 1 hr. The reaction was monitored by HPLC and LCMS. The reaction mixture was neutralized with 1N HCl to pH 6-7 at 0-5 °C. The reaction mixture was concentrated below 40 °C to remove organic solvent. The solution was acidified with 1N HCl to pH 2-3 at 20-25 °C and extracted with 2-MeTHF (10V x 3). The combined organic layer was washed with brine (10V) and dried over sodium sulfate. After filtration and concentration at 40 °C, the product was dried under vacuum at 50 °C to give (1S,3S,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylic acid (S1) as a white solid (191 g, 92.9% yield).

Step 2. Preparation of (R)-N-((S)-((3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-2-methylpropane-2-sulfonamide

[0212] To a solution of 1-chloro-2,4-difluorobenzene (590.5 g, 1.30 eq) in THF (5.25 L, 7 V) was added n-BuLi (2.50 M, 1585 mL, 1.30 eq) at -65 °C under a N₂ atmosphere. The mixture was stirred at -65 °C for 0.5 hr, then a solution of (R,Z)-N-((4-fluorobicyclo[2.2.1]heptan-1-yl)methylene)-2-methylpropane-2-sulfonamide (750 g, 1.0 eq) in THF (3.75 L, 5V) was added dropwise at -65 °C. The mixture was stirred at -65 °C for 2 hrs. The reaction was monitored by HPLC and LCMS. The reaction mixture was added into saturated NH₄Cl solution (11.25 L,

15V) at -10-0 °C. The aqueous phase was extracted with ethyl acetate (10 V x 2). The combined organic phase was washed with saturated brine (15 V x 2), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give a crude product. The crude product was dissolved in ethanol (750 mL, 1V). Water(3.75, 5V) was added, and the mixture was stirred for 2h. The resulting solid was filtered. The solid was slurried with Heptane/EA (10:1, 5V) for 5h, filtered, and the solid was dried in the air at 50°C to give pure (R)-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-2-methylpropane-2-sulfinamide as a white solid (995 g, 79% yield).

Step 3. Preparation of (S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methanamine

[0213] To a solution of (R)-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-2-methylpropane-2-sulfinamide (995 g, 1.00 eq) in MeOH (2985 mL, 3V) was added HCl/MeOH (3980 mL, 4V) at 25 °C, the mixture was stirred at 25 °C for 1 hr. The reaction was monitored by HPLC and LCMS. The reaction mixture was concentrated in vacuum to give a crude product. The residue was triturated with Ethyl acetate/n-heptane (1:10, 5 V) at 25 °C for 2h, filtered, and the filter cake was dried in vacuum at 50 °C. Compound (S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methanamine was obtained as a white solid (738 g, 90.5% yield).

Step 4. Preparation of tert-butyl ((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)carbamate

[0214] To a solution of (1S,3S,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclopentane-1-carboxylic acid (490 g, 1.0eq) in DCM (7V) was added DIEA (4.0eq) and HOBt (1.3eq) at 0-5 °C, followed by the addition of (S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methanamine (619 g, 0.95eq) under N₂ atmosphere. To the mixture was added EDCI (497.8 g, 1.3eq). The resulting reaction mixture was stirred at 0-5 °C under N₂ for 24h and monitored by HPLC and LCMS. The reaction mixture was washed with half sat. K₂CO₃ (15V x 2), 1N HCl (15V x 2), and then brine (15V). The organic phase was separated and concentrated under reduced pressure at 40 °C. The crude product was crystallized with EtOAc/n-heptane (1.5V:6V). Solids were filtered and the filter cake was dried in vacuum at 50 °C to give tert-butyl ((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)carbamate as a white solid (852 g, 83% yield).

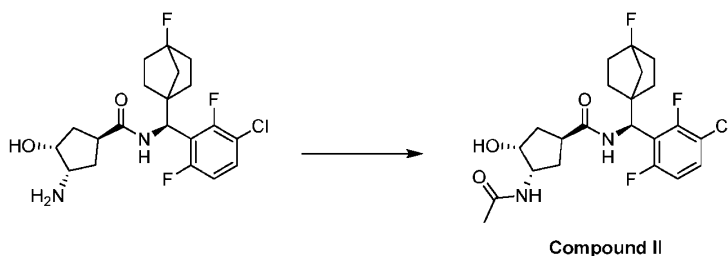
Step 5. Preparation of (1S,3S,4R)-3-amino-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide HCl

[0215] To a solution of tert-butyl ((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)carbamate (880 g, 1.00 eq) in DCM (2640 mL, 3V) was added con. HCl (425.5 mL, 3 eq) at 25 °C, and the mixture was stirred at 25 °C for 3 hr. The reaction was monitored by HPLC and LCMS. The reaction mixture was concentrated in vacuum to give a crude product as a semi oil used in the next step without further purification (770 g crude net weight).

Step 6. Preparation of N-((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)pyrimidine-5-carboxamide (Compound I)

[0216] To a solution of pyrimidine-5-carboxylic acid (232.8 g, 1.05eq) in DCM (5670 mL, 7V) was added N-methylmorpholine (542 g, 3.0eq) at 0-5 °C under N₂ atmosphere, followed by the addition of (1S,3S,4R)-3-amino-N-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide HCl (810 g net weight, 1.0eq) in DCM (2430 mL, 3V) at 0-5 °C. Then to the mixture was finally added HATU (747.4 g, 1.1eq) at 0-5 °C under N₂. The resulting reaction mixture was stirred at 0-5 °C under N₂ for 2h and monitored by HPLC and LCMS. To the reaction mixture was added N-methylmorpholine (361 g, 2.0eq) at 0-5 °C and then washed with sat. Na₂CO₃ (12.15 L, 15V). The organic phase was concentrated under reduced pressure at 40 °C and dissolved with EA (1.0 L, 10V). The resulting solution was washed with 0.5N HCl (15V x 3) and then with brine (15V). The organic phase was separated and concentrated under reduced pressure at 40 °C to give the crude product. It was purified by silica gel column chromatography eluting with 0~10% MeOH in DCM and dried under vacuum at 40 °C to give N-((1S,2R,4S)-4-(((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)carbamoyl)-2-hydroxycyclopentyl)pyrimidine-5-carboxamide (Compound I) as an off-white solid (733 g, 82% yield).

Example 3
Synthesis of Compound II



Step 1. Synthesis of (1S,3S,4R)-3-acetamido-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide

[0217] A round bottomed flask was charged with (1S,3S,4R)-3-amino-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide (1.45 g, 3.48 mmol), acetic acid (209 mg, 3.48 mmol), NaHCO₃ (1.46 g, 17.4 mmol), HATU (2.64 g, 6.96 mmol) and a stir bar. DMF (15 mL) was added, and the solution was stirred for 1 hour at room temperature. The resulting crude material was purified by preparative HPLC (column: LuxCellulose-34.6*100 mm, 3 µm; mobile phase A: water, mobile phase B: MeOH (0.5% 2M NH₃ in MeOH); flow rate: 4 mL/min; gradient: 20% B isocratic) to give (1S,3S,4R)-3-acetamido-N-((S)-(3-chloro-2,6-difluorophenyl)(4-fluorobicyclo[2.2.1]heptan-1-yl)methyl)-4-hydroxycyclopentane-1-carboxamide (1.34 g, 2.93 mmol) as an off-white amorphous solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.61-7.48 (m, 2H), 7.19-7.09 (m, 1H), 5.26 (d, *J* = 8.1 Hz, 1H), 4.78 (d, *J* = 3.3 Hz, 1H), 3.96-3.85 (m, 2H), 3.15-3.03 (m, 1H), 1.82 (d, *J* = 5.0 Hz, 2H), 1.81 (s, 3H), 1.75 (ddd, *J* = 21.1, 11.5, 8.1 Hz, 8H), 1.59 (d, *J* = 8.8 Hz, 2H), 1.45 (d, *J* = 9.6 Hz, 2H). [M+H]⁺ 459.05.

Example 4

Preparation and Characterization of Crystal Forms

Compound I, Form A

[0218] A sample of Compound I (30 mg) was weighed into HPLC vials and 5 volumes of ethyl acetate was added. The sample was matured for 24 hours cycling between RT and 50 °C in a maturation chamber (~4 hours for each increase of 1 °C). Then, 500 µl of heptane was added to the sample vial, which was allowed to mature for a further 24 hours. The suspension was filtered through a XRPD Millipore plate under vacuum for 10 minutes to give a crystalline solid. The observed pattern by XRPD analysis was assigned as crystalline Form A of Compound I (see FIG. 1).

[0219] Form A appeared to be an essentially anhydrous form as only trace amounts of ethyl acetate (0.09 eq) was detected in the NMR spectra and the total weight loss observed from TGA analysis would also add up to 0.09 eq of ethyl acetate. A broad endotherm was observed at the beginning of the thermal trace (loss of solvent) then the melt endotherm at 174 °C. After storage at 40 °C 75 % RH the sample had remained Form A as monitored by X-ray powder diffraction.

Table 2. Characterization of Compound I, Form A

Method	Maturation in ethyl acetate after addition of heptane
XRPD	Form A
NMR	Shows Compound I and 0.09 eq of ethyl acetate and trace heptane
TGA	Weight loss of 0.56 % w/w between RT and 95 °C (0.16 eq water or 0.03 eq ethyl acetate). Weight loss of 1.06 % w/w between 95 and 183 °C (0.06 eq ethyl acetate or 0.31 eq water) (see FIG. 6)
DSC	Broad endotherm at onset 25.5 °C (10 J/g). Endotherm at onset 173.9 °C (54 J/g). (see FIG. 6)
Static Storage 1-week (40 °C 75 % RH)	Form A

Compound I, Form B

[0220] A sample of Compound I (30 mg) was weighed into HPLC vials and 10 volumes of isopropyl acetate was added. The sample was matured for 24 hours cycling between RT and 50 °C in a maturation chamber (~4 hours for each increase of 1 °C). The sample was allowed to mature for a further 24 hours. The suspension was filtered through a XRPD Millipore plate under vacuum for 10 minutes to give a crystalline solid. The observed pattern by XRPD analysis was assigned as crystalline Form B of Compound I (see FIG. 2).

[0221] The characterization of Form B suggests that this may also be an anhydrous form based on the small amount of isopropyl acetate (0.26 eq) contained in the sample. The DSC trace of Form B showed a broad endotherm at the beginning of the trace (likely solvent loss) followed by another endotherm at 141 °C then finally the melt endotherm at 172 °C. Form B was also observed to have converted to Form A post accelerated storage conditions at 40 °C 75 % RH.

Table 3. Characterization of Compound I, Form B

Method	Maturation in isopropyl acetate
XRPD	Form B

NMR	Shows Compound I and 0.26 eq of isopropyl acetate
DSC	Broad endotherm at onset 28.4 °C (14 J/g). Endotherm at onset 141.2 °C (36 J/g). Endotherm at onset 172.4 °C (10 J/g). (see FIG. 7)
Static Storage 1-week (40 °C 75 % RH)	Converted to Form A

Compound I, Form C

[0222] A sample of Compound I (30 mg) was weighed into HPLC vials and 5 volumes of ethanol was added. The sample was matured for 24 hours cycling between RT and 50 °C in a maturation chamber (~4 hours for each increase of 1 °C). Then, 500 µl of heptane was added to the sample, which was allowed to mature for a further 24 hours. The suspension was filtered through a XRPD Millipore plate under vacuum for 10 minutes to give a crystalline solid. The observed pattern by XRPD analysis was assigned as crystalline Form C of Compound I (see FIG. 3).

[0223] Analysis of Form C suggests that it was an ethanol solvate. NMR analysis showed about 0.82 eq of ethanol was contained in the sample and the weight loss from TGA analysis also showed approximately 0.9 eq of ethanol. The sample converted to amorphous material after storage at accelerated storage conditions.

Table 4. Characterization of Compound I, Form C

Method	Maturation in ethanol after addition of heptane
XRPD	Form C
NMR	Shows Compound I and 0.82 eq of ethanol
TGA	Weight loss of 7.36 % w/w between 50 and 150 °C (0.9 eq ethanol) (see FIG. 8)
DSC	Broad endotherm at onset 29.1 °C (7 J/g). Split endotherm at onset 104.8 °C, peak temperatures at 121.1 and 143.8 °C (split into 95 and 4 J/g). (see FIG. 8)

Static Storage 1-week (40 °C 75 % RH)	Amorphous
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Compound II, Form A

[0224] A sample of Compound II (30 mg) was weighed into HPLC vials and 20 volumes of water was added. The sample was matured for 24 hours cycling between RT and 50 °C in a maturation chamber (~4 hours for each increase of 1 °C). The sample was allowed to mature for a further 24 hours. The suspension was filtered through a XRPD Millipore plate under vacuum for 10 minutes to give a crystalline solid. The observed pattern by XRPD analysis was assigned as crystalline Form A of Compound II (see FIG. 4).

[0225] Form A TGA analysis showed a weight loss of water (1.79 eq water) similar to that seen in the KF (1.31 eq). The difference in the quantity of water seen by TGA and KF is likely surface bound water that had evaporated before KF analysis. The DSC showed a broad endotherm at 46.8 °C onset, which is likely the loss of water from the sample, followed by several endothermic events and an exotherm at 129.6 °C with the melt likely at 225.1 °C.

[0226] The GVS analysis showed a reversible weight loss of 1.8 % w/w between 20 and 90 % RH, then w (0.47 eq water) then significant loss/ absorption of 4.46 % w/w (1.19 eq water) between 20 and 0 % RH which suggests this is a monohydrated form. The sample remained Form A post GVS and static storage conditions, with little change in the purity of the samples as measured by XRPD. On heating to 160 °C at 10 °C/ min and cooling to RT, the sample had converted to Form B.

Table 5. Characterization of Compound II, Form A

Method	Maturation in water
XRPD	Form A
NMR	Shows Compound II and trace amount of water
DSC	Broad three split endotherms initially with onset at 46.8 °C (121 J/g), then onset 76.5 °C (68 J/g), then peak 109 °C (6 J/g). Exotherm at onset 129.6 °C (71 J/g). Endotherm at onset 225.1 °C (90 J/g). (see FIG. 9)

TGA	Weight loss of 6.55 % w/w between 40 and 130 °C (1.79 eq water) (see FIG. 9)
GVS	Gradual absorption and desorption of water between 20 and 90 % RH of 1.8 % w/w (0.47 eq water) then significant loss of 4.46 % w/w (1.19 eq water) between 10 and 0 % RH on desorption cycle and between 0 and 20 % RH for the absorption cycle. XRPD: Form A
Static storage (1-week)	40 °C 75 % RH: Form A (HPLC: 98.5 %) 25 °C 97 % RH: Form A (HPLC: 98.4 %)
Heating to 160 °C, then analyzed by XRPD	On heating to 160 °C at 10 °C/ min and cooling to RT, the sample had converted to Form B

Compound II, Form B

[0227] A sample of Compound II (30 mg) was weighed into HPLC vials and 20 volumes of ethyl acetate was added. The sample was matured for 24 hours cycling between RT and 50 °C in a maturation chamber (~4 hours for each increase of 1 °C). The sample was allowed to mature for a further 24 hours. The suspension was filtered through a XRPD Millipore plate under vacuum for 10 minutes to give a crystalline solid. The observed pattern by XRPD analysis was assigned as crystalline Form B of Compound II (see FIG. 5).

[0228] Form B appeared to be anhydrous based on the small amount of residual organic solvent (ethyl acetate, 0.02 eq) observed in the NMR trace, and the lack of weight loss that was seen in the TGA thermal trace. The only endotherm that was observed for Form B was the melt endotherm at onset 229 °C. The sample then began to degrade above 250 °C. The sample remained Form B post static storage conditions at 40 °C 75 % RH.

Table 6. Characterization of Compound II, Form B

Method	Maturation in ethyl acetate
XRPD	Form B
NMR	Matches reference. 0.02 eq ethyl acetate

TGA	No weight loss observed in sample until degradation temperature (above 250 °C) (see FIG. 10)
DSC	Sharp endotherm at onset 228.9 °C (96 J/g) (see FIG. 10)
Static Storage	Form B

Example 5

Solubility Assessment of Crystal Forms in Media

Compound I, Form A

[0229] The solubility of Form A remained high, especially in FeSSIF media at 2.3 mg/ ml. Solubility in FaSSIF was 0.51 mg/ ml (slightly less than amorphous) and 0.34 mg/ ml in FaSSGF and 0.45 mg/ ml in deionized water. XRPD analysis of the residues has shown that the samples have remained Form A.

Form	Media	Appearance	Final pH	Solubility (mg/ml)	Average Solubility (mg/ml)	XRPD
Compound I, Form A	FeSSIF	Fine colorless suspension with colorless granules	4.9	2.2	2.3	Form A
			4.9	2.3		
	FaSSIF		6.4	0.51	0.51	Form A
			6.5	0.50		
	FaSSGF		1.6	0.34	0.34	Form A
			1.6	0.33		
	Deionized water		8.6	0.44	0.45	Form A
			8.5	0.45		

Compound I, Form B

[0230] The solubility assessment for Form B showed very high solubility in the selected media. XRPD analysis of the residues post solubility analysis however, confirmed that the crystal structure of Form B collapsed leaving mostly amorphous material. This shows that the high

solubility of the sample is due to the sample converting to amorphous material and not related to the actual solubility of Form B.

Form	Media	Appearance	Final pH	Solubility (mg/ml)	Average Solubility (mg/ml)	XRPD
Compound I, Form B	FeSSIF	Fine colorless suspension with colorless granules	5.1	4.7	5.7	Mostly Amorphous
			5.0	6.6		
	FaSSIF		5.0	0.78	0.78	Mostly Amorphous
			5.1	0.77		
	FaSSGF	5.0	0.47	0.47	Mostly Amorphous	
		5.1	0.46			
	Deionized water	5.0	0.51	0.49	Mostly Amorphous	

Compound II, Form A

[0231] The solubility assessment of Form A showed the highest solubility was in FeSSIF at 0.3 mg/ ml, with solubility in the three other media all around 0.1 mg/ ml. XRPD analysis of the residues post the solubility assessment have shown that the samples have remained Form A.

Form	Media	Appearance	Final pH	Solubility (mg/ml)	Average Solubility (mg/ml)	XRPD
Compound II, Form A	FeSSIF	Fine colorless suspension	4.9	0.30	0.30	Form A
			4.9	0.30		
	FaSSIF		6.5	0.10	0.10	Form A
			6.5	0.10		
	FaSSGF		1.6	0.08	0.08	Form A
			1.6	0.08		

	Deionized water		9.0	0.09	0.09	Form A
			9.0	0.09		

Compound II, Form B

[0232] The solubility of Form B was slightly less than Form A (but mostly comparable) and residues collected post solubility analysis showed the solid had remained Form B.

Form	Media	Appearance	Final pH	Solubility (mg/ml)	Average Solubility (mg/ml)	XRPD
Compound II, Form B	FeSSIF	Fine colorless suspension	5.0	0.20	0.20	Form B
			4.9	0.19		
	FaSSIF		6.4	0.10	0.09	Form B
			6.5	0.07		
	FaSSGF		1.6	0.08	0.08	Form B
			1.6	0.07		
	Deionized water		9.0	0.09	0.08	Form B
			9.0	0.06		

Example 6**Competitive Slurry Experiments****Compound I (Form A and Form B)**

[0233] Compound I, Form A (100 mg) and Compound I, Form B (100 mg) were each weighed into a 4 ml vial and mixed for 2 hours. The sample was recovered and analyzed by XRPD for use as a reference. Saturated solutions were prepared at the same time by pipetting 500 µl of selected solvent systems into a HPLC vial and stirring at 5, 25 and 50 °C (see Table below). To each of the sample vials, Compound I was added until a suspension formed. After 1 hour, all samples were observed to have remained suspensions, and were left to stir for a further 24 hours.

[0234] All samples were found to have remained suspensions. Each suspension was pipetted into a syringe and filtered through a nylon filter cartridge where the solutions were collected

into fresh vials. To each of the solutions, 15 mg of the reference (1:1 Form A/Form B) was added, and the sample vials were stirred at their respective temperatures for 24 hours. Observations of sample vials were recorded, and a first aliquot was pipetted into a metal XRPD plate and analyzed by XRPD. Samples were stirred for a further 5 days before a second aliquot was taken and XRPD analysis was performed.

[0235] The competitive slurries for Compound I after 24 hours has shown that all of samples had remained suspensions after slurrying at 50 and 5 °C. XRPD analysis of these samples has shown that several samples fully converted to Form A, although several are still mixtures of Form A and B.

[0236] After a further 5 days (6 days total) all of the samples had remained suspensions and XRPD analysis of these samples showed that more samples had fully converted to purely Form A. Samples that were still mixtures were notably in heptane, although all two of the three samples had mostly formed Form A with some small peaks related to Form B, and this is possibly due to lower solubility in heptane slowing the conversions to Form A. This suggests that given enough time, full conversion to Form A would likely occur.

Solvent	Temp. (deg °C)	Observations 1st Aliquot	XRPD	Observations 2nd Aliquot	XRPD
Heptane	5	Suspension	Form A and B mix	Suspension	Mostly Form A, two small peaks related to Form B present
Heptane: isopropyl acetate (1:1)	5	Suspension	Form A and B mix	Suspension	Form A
Heptane: THF(1:1)	5	Light suspension	Insufficient material	suspension	Insufficient material
Water	5	Suspension	Form A	Suspension	Form A
Heptane	25	Suspension	Form A and B mix	Suspension	Mostly Form A, two small peaks related to Form B present

Heptane: isopropyl acetate (1:1)	25	Suspension	Form A	Suspension	Form A
Heptane: THF(1:1)	25	Light suspension	Insufficient material	suspension	Form A
Water	25	Suspension	Form A	Suspension	Form A
Heptane	50	Suspension	Form A and B mix	Suspension	Form A and B mix
Heptane: isopropyl acetate (1:1)	50	Suspension	Form A	Suspension	Form A
Heptane: THF(1:1)	50	Suspension	Form A	Suspension	Form A
Water	50	Suspension	Form A	Suspension	Form A

Compound II (Form A and Form B)

[0237] Compound II, Form A (100 mg) and Compound II, Form B (100 mg) were each weighed into a 4 ml vial and mixed for 2 hours. The sample was recovered and analyzed by XRPD for use as a reference. Saturated solutions were prepared at the same time by pipetting 500 µl of selected solvent systems into a HPLC vial and stirring at 5, 25 and 50 °C (see Table below). To each of the sample vials, Compound II was added until a suspension formed. After 1 hour, all samples were observed to have remained suspensions, and were left to stir for a further 24 hours.

[0238] All samples were found to have remained suspensions. Each suspension was pipetted into a syringe and filtered through a nylon filter cartridge where the solutions were collected into fresh vials. To each of the solutions, 15 mg of the reference (1:1 Form A/Form B) was added, and the sample vials were stirred at their respective temperatures for 24 hours. Observations of sample vials were recorded, and a first aliquot was pipetted into a metal XRPD plate and analyzed by XRPD. Samples were stirred for a further 5 days before a second aliquot was taken and XRPD analysis was performed.

[0239] All of the samples had remained suspensions and XRPD analysis of these samples showed full conversion to Form B after 24 hours. The samples had remained suspensions after

a further 5 days, all of which had remained Form B. This suggests that Form B may be a more thermodynamically stable form when compared to Form A.

Solvent	Temp (deg °C)	Observations 1st Aliquot	XRPD	Observations 2nd Aliquot	XRPD
IPA	5	Suspension	Form B	Suspension	Form B
ACN:water (9:1)	5	Suspension	Form B	Suspension	Form B
MEK	5	Suspension	Form B	Suspension	Form B
THF	25	Suspension	Form B	Suspension	Form B
IPA	25	Suspension	Form B	Suspension	Form B
ACN:water (9:1)	25	Suspension	Form B	Suspension	Form B
MEK	25	Suspension	Form B	Suspension	Form B
THF	50	Suspension	Form B	Suspension	Form B
IPA	50	Suspension	Form B	Suspension	Form B
ACN:water (9:1)	50	Suspension	Form B	Suspension	Form B
MEK	50	Suspension	Form B	Suspension	Form B

INCORPORATION BY REFERENCE

[0240] All publications and patents mentioned herein are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

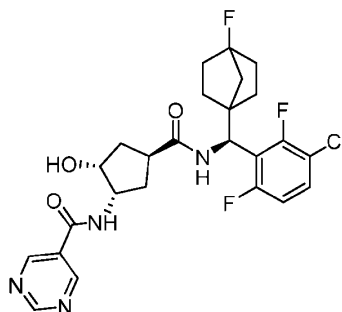
[0241] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the present disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of

the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0242] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

CLAIMS

1. A compound in solid form, wherein the compound is Compound I:



I,

or a solvate thereof.

2. The compound of claim 1, wherein the compound is amorphous.
3. The compound of claim 1, wherein the compound is crystalline.
4. The compound of claim 1 or 3, wherein the solid form is crystalline Form A, Form B, or Form C.
5. The compound of any one of claims 1, 3, and 4, wherein the solid form is Form A.
6. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , and about 16.5 2 θ .
7. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .
8. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .

9. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .
10. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .
11. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, each selected from the group consisting of about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .
12. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising peaks at about 17.4 2 θ , about 13.3 2 θ , about 16.5 2 θ , about 24.2 2 θ , about 19.8 2 θ , about 14.5 2 θ , and about 18.2 2 θ .
13. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.1.
14. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.1.
15. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.1.
16. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.1.

17. The compound of claim 5, wherein the solid form has a X-ray powder diffraction pattern comprising at least seven peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.1.

18. The compound of claim 5, wherein the solid form has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 1.

19. The compound of any one of claims 1, 3, and 4, wherein the solid form is Form B.

20. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about $18.5\ 2\theta$, about $11.4\ 2\theta$, and about $17.5\ 2\theta$.

21. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about $18.5\ 2\theta$, about $11.4\ 2\theta$, about $17.5\ 2\theta$, about $5.7\ 2\theta$, about $13.6\ 2\theta$, about $17.3\ 2\theta$, and about $10.7\ 2\theta$.

22. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, each selected from the group consisting of about $18.5\ 2\theta$, about $11.4\ 2\theta$, about $17.5\ 2\theta$, about $5.7\ 2\theta$, about $13.6\ 2\theta$, about $17.3\ 2\theta$, and about $10.7\ 2\theta$.

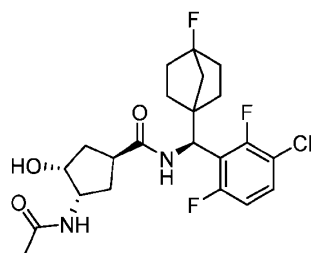
23. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, each selected from the group consisting of about $18.5\ 2\theta$, about $11.4\ 2\theta$, about $17.5\ 2\theta$, about $5.7\ 2\theta$, about $13.6\ 2\theta$, about $17.3\ 2\theta$, and about $10.7\ 2\theta$.

24. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, each selected from the group consisting of about $18.5\ 2\theta$, about $11.4\ 2\theta$, about $17.5\ 2\theta$, about $5.7\ 2\theta$, about $13.6\ 2\theta$, about $17.3\ 2\theta$, and about $10.7\ 2\theta$.

25. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, each selected from the group consisting of about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ .
26. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising peaks at about 18.5 2 θ , about 11.4 2 θ , about 17.5 2 θ , about 5.7 2 θ , about 13.6 2 θ , about 17.3 2 θ , and about 10.7 2 θ .
27. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.2.
28. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.2.
29. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.2.
30. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.2.
31. The compound of claim 19, wherein the solid form has a X-ray powder diffraction pattern comprising at least seven peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.2.
32. The compound of claim 19, wherein the solid form has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 2.
33. The compound of any one of claims 1, 3, and 4, wherein the solid form is Form C.

34. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , and about 20.0 2 θ .
35. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .
36. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .
37. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .
38. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .
39. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, each selected from the group consisting of about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .
40. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising peaks at about 19.3 2 θ , about 19.9 2 θ , about 20.0 2 θ , about 10.1 2 θ , about 19.6 2 θ , about 15.2 2 θ , and about 22.0 2 θ .

41. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.3.
42. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.3.
43. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.3.
44. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.3.
45. The compound of claim 33, wherein the solid form has a X-ray powder diffraction pattern comprising at least seven peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.3.
46. The compound of claim 33, wherein the solid form has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 3.
47. A compound in solid form, wherein the compound is Compound II:



II,

or a solvate thereof.

48. The compound of claim 47, wherein the compound is amorphous.
49. The compound of claim 47, wherein the compound is crystalline.
50. The compound of claim 47 or claim 49, wherein the solid form is Form A or Form B.
51. The compound of any one of claims 47, 49, and 50, wherein the solid form is Form A.
52. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , and about 20.0 2 θ .
53. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .
54. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .
55. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .
56. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, each selected from the group consisting of about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .
57. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, each selected from the group consisting of about 15.7

2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .

58. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising peaks at about 15.7 2 θ , about 14.7 2 θ , about 20.0 2 θ , about 21.0 2 θ , about 23.2 2 θ , about 16.5 2 θ , about 17.5 2 θ , and about 13.3 2 θ .

59. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.4.

60. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.4.

61. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.4.

62. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.4.

63. The compound of claim 51, wherein the solid form has a X-ray powder diffraction pattern comprising at least seven peaks, in degrees 2 θ , selected from the group consisting of the peaks listed in Table 1.4.

64. The compound of claim 51, wherein the solid form has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 4.

65. The compound of any one of claims 47, 49, and 50, wherein the solid form is Form B.

66. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , and about 16.9 2 θ .
67. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least two peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .
68. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .
69. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .
70. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .
71. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, each selected from the group consisting of about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .
72. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising peaks at about 23.6 2 θ , about 10.9 2 θ , about 16.9 2 θ , about 15.1 2 θ , about 26.1 2 θ , about 12.9 2 θ , and about 19.4 2 θ .

73. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least three peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.5.
74. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least four peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.5.
75. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least five peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.5.
76. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least six peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.5.
77. The compound of claim 65, wherein the solid form has a X-ray powder diffraction pattern comprising at least seven peaks, in degrees 2θ , selected from the group consisting of the peaks listed in Table 1.5.
78. The compound of claim 65, wherein the solid form has a X-Ray powder diffraction pattern substantially similar to that depicted in FIG. 5.
79. A pharmaceutical composition comprising a compound of any one of claims 1-78, and a pharmaceutically acceptable carrier.
80. A method of inhibiting PI3K α activity in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of any of claims 1-78, or a pharmaceutical composition of claim 79, to the subject.
81. A method of treating a cancer in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of any one of claims 1-78, or a pharmaceutical composition of claim 79, to the subject.

82. The method of claim 80 or 81, further comprising administering a therapeutically effective amount of an antibody, an antibody-drug conjugate, a kinase inhibitor, an immunomodulator, or a histone deacetylase inhibitor.

83. A kit comprising a compound of any of claims 1-78.

84. The kit of claim 83, further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the solid form or compound.

85. The kit of claim 83 or 84, further comprising written instructions describing how to administer the resulting composition to the patient.

86. The kit of any one of claims 83-85, further comprising a pharmaceutically acceptable excipient.

87. A process for preparing a crystalline form of Compound I, comprising: (a) preparing a solution of Compound I; (b) adjusting the temperature so that solid crystalline form of Compound I precipitates out of the solution; and (c) isolating the solid crystalline form.

88. A process for preparing a crystalline form of a Compound I, comprising: (a) preparing a solution of a Compound I in a solvent; (b) adjusting the temperature; (c) adding heptane to the solution; and (d) isolating the solid crystalline form.

89. A process for preparing a crystalline form of Compound II, comprising: (a) preparing a solution of a Compound II; (b) adjusting the temperature so that solid crystalline form of Compound II precipitates out of the solution; and (c) isolating the solid crystalline form.

90. A process for preparing a crystalline form of a Compound II, comprising: (a) preparing a solution of a Compound II in a solvent; (b) adjusting the temperature; (c) adding heptane to the solution; and (d) isolating the solid crystalline form.