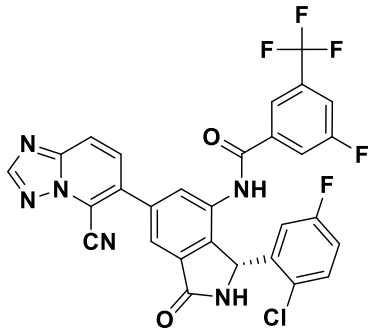
enabling sufficient target inhibition in the tumor while avoiding dose-limiting toxicity in cancer patients.

SUMMARY

[0006] This disclosure is generally directed to the compounds of formulae I-III and solvates thereof, and crystalline forms thereof.

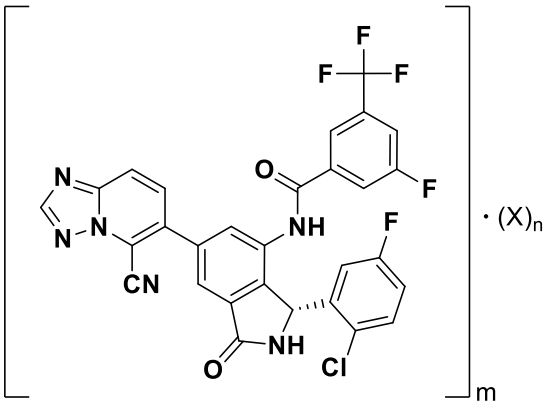
[0006a] In an aspect of the present disclosure, there is provided a compound in solid form, wherein the compound is compound I-1:



I-1,

or a solvate thereof.

[0006b] In another aspect of the present disclosure, there is provided a compound in solid form, wherein the compound is a compound of Formula (I):



(I),

or a solvate thereof;

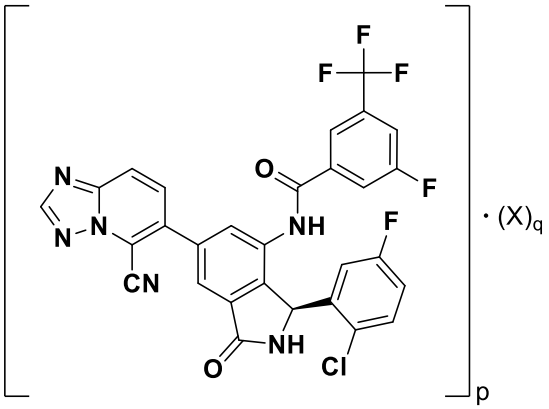
wherein:

m is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

n is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid.

[0006c] In a further aspect of the present disclosure, there is provided a compound in solid form, wherein the compound is of Formula (II)



(II),

or a solvate thereof,

wherein:

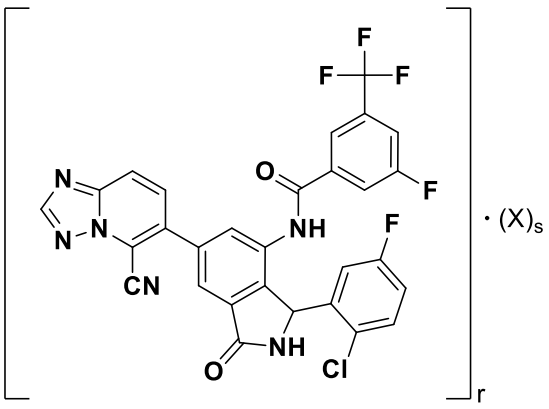
p is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

q is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid; optionally,

wherein the compound is amorphous or crystalline.

[0006d] In another aspect of the present disclosure, there is provided a compound in solid form, wherein the compound is of Formula III:



III,

or a solvate thereof,

wherein:

r is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

s is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid; optionally,

wherein the compound is amorphous or crystalline.

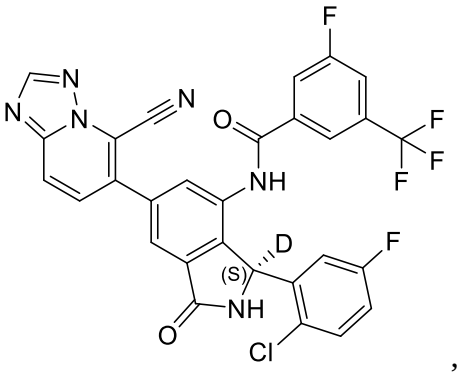
[0006e] In a further aspect of the present disclosure, there is provided a process for preparing:

(a) a crystalline form of a compound of Formula (I), comprising: a) preparing a solution of a compound of Formula (I); b) adjusting the temperature so that solid crystalline form of a compound of Formula (I) precipitates out of the solution; and c) isolating the solid crystalline form; or

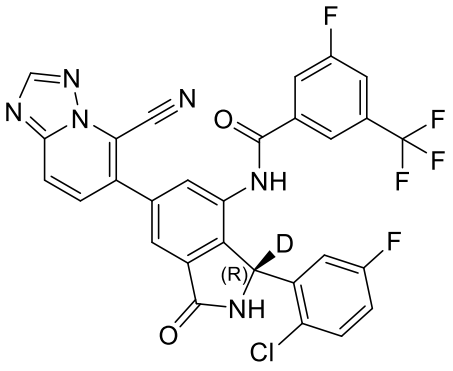
(b) a crystalline form of a compound of Formula (II), comprising: a) preparing a solution of a compound of Formula (II); b) adjusting the temperature so that solid crystalline form of a compound of Formula (II) precipitates out of the solution; and c) isolating the solid crystalline form; or

(c) a crystalline form of a compound of Formula (III), comprising: a) preparing a solution of a compound of Formula (III); b) adjusting the temperature so that solid crystalline form of a compound of Formula (III) precipitates out of the solution; and c) isolating the solid crystalline form.

[0006f] In another aspect of the present disclosure, there is provided a compound of Formula (IV-1) or Formula (IV-2):



,



(IV-1), (IV-2),

or a pharmaceutically acceptable salt thereof.

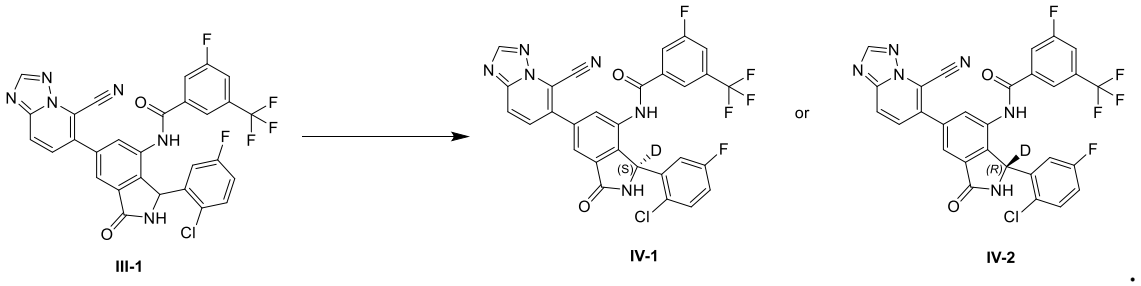
[0006g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier.

[0006h] In another aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical

composition disclosed herein, in the manufacture of a medicament for inhibiting PI3Kα activity or for treating a cancer in a subject in need thereof, optionally wherein: the compound or pharmaceutical composition is to be administered with a therapeutically effective amount of an antibody, an antibody-drug conjugate, a kinase inhibitor, an immunomodulator, or a histone deacetylase inhibitor.

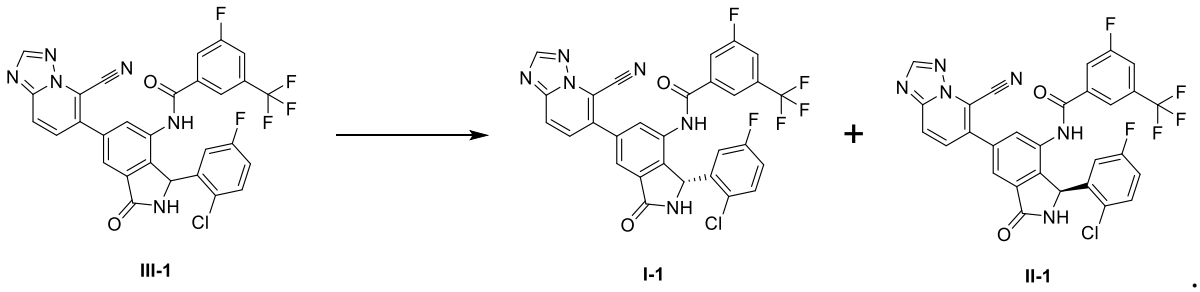
[0006i] In a further aspect of the present disclosure, there is provided a kit comprising a compound disclosed herein, optionally further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the solid form or compound, and/or written instructions describing how to administer the resulting composition to the patient, further optionally comprising a pharmaceutically acceptable excipient.

[0006j] In another aspect of the present disclosure, there is provided a process for preparing a compound of Formula IV-1 and a compound of Formula IV-2, comprising deuteration of compound III-1 followed by a purification step to separate the enantiomers, thereby forming compounds IV-1 and IV-2:



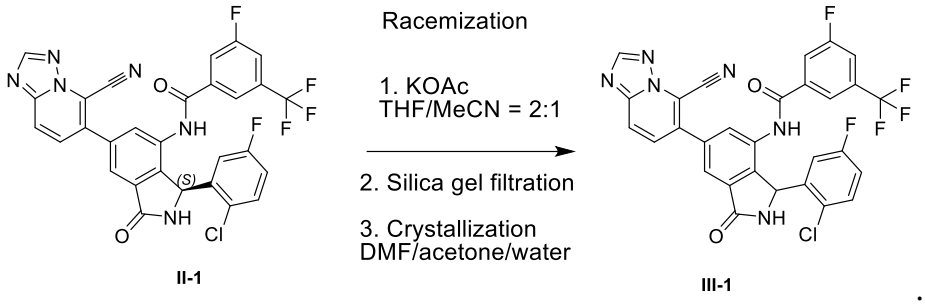
.

[0006k] In a further aspect of the present disclosure, there isp provided a process for preparing a compound of Formula I-1 and a compound of Formula II-1, comprising subjecting compound III-1 to a SMB separation, for example, as described in Example 1-A, thereby forming compounds I-1 and II-1:



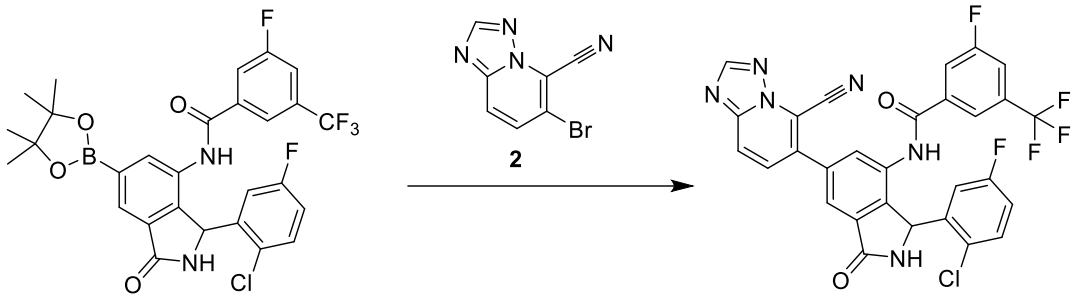
.

[0006l] In another aspect of the present disclosure, there is provided a process for preparing a compound of Formula III-1, comprising a racemization of compound II-1:



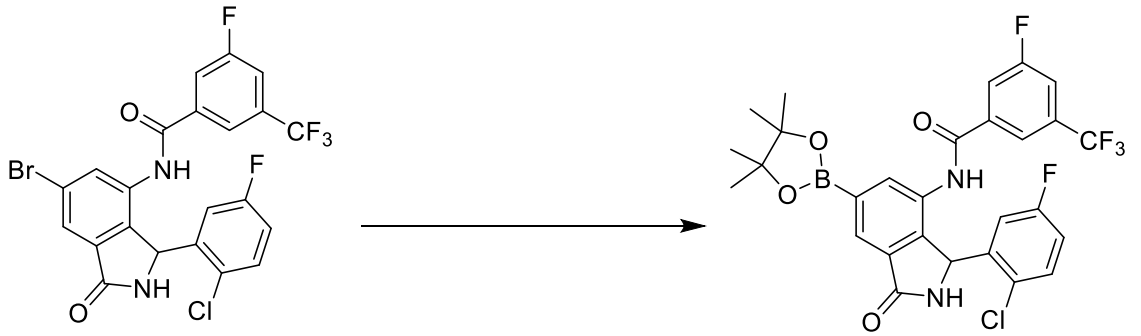
II-1 III-1 .

[0006m] In a further aspect of the present disclosure, there is provided a process for preparing a compound of Formula III-1, comprising a step of coupling compound 2 with compound 3, thereby forming compound III-1:



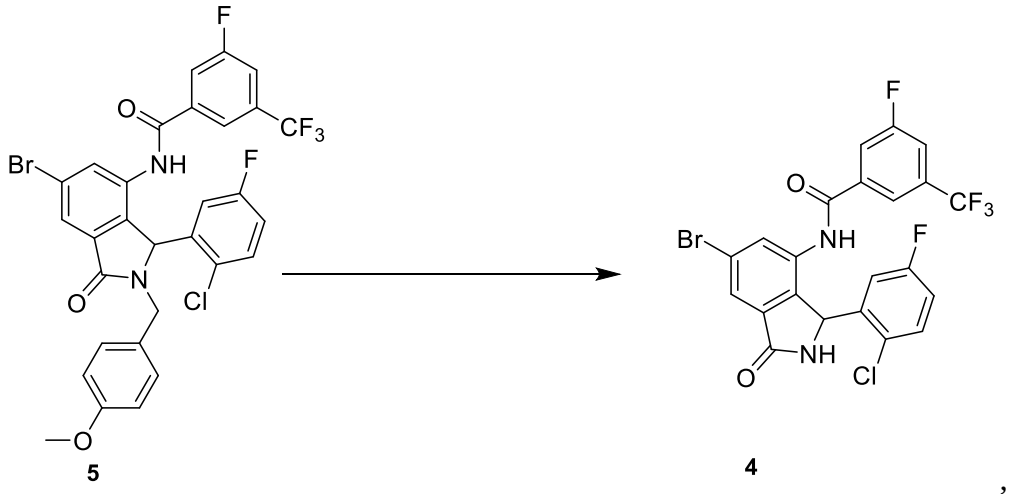
3 2 III-1 ,

optionally further comprising a step of converting compound 4 to compound 3:

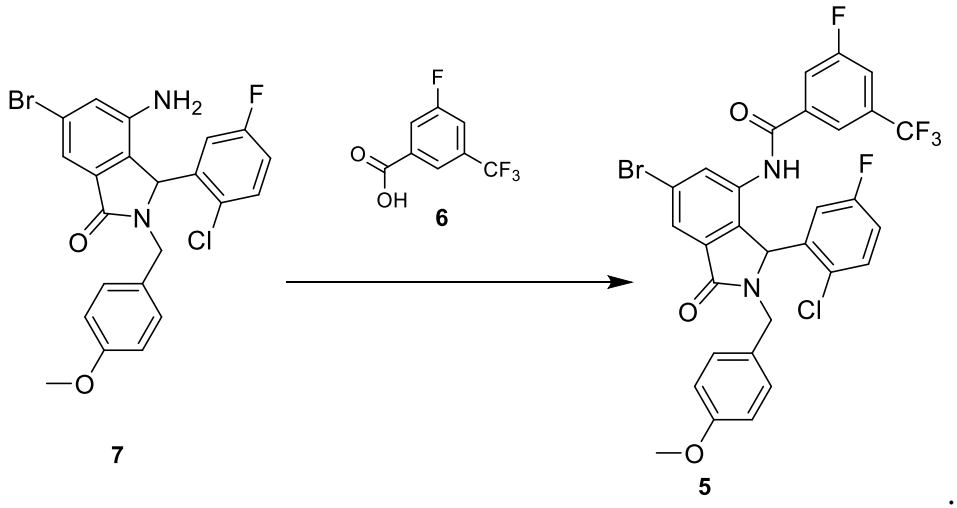


4 3 ,

further optionally comprising a step of converting compound 5 to compound 4:



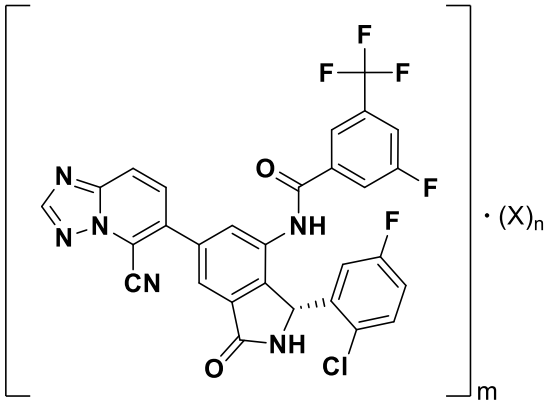
, further optionally comprising a step of coupling compound 6 with compound 7, thereby forming compound 5:



.

[0006n] In another aspect of the present disclosure, there is provided a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

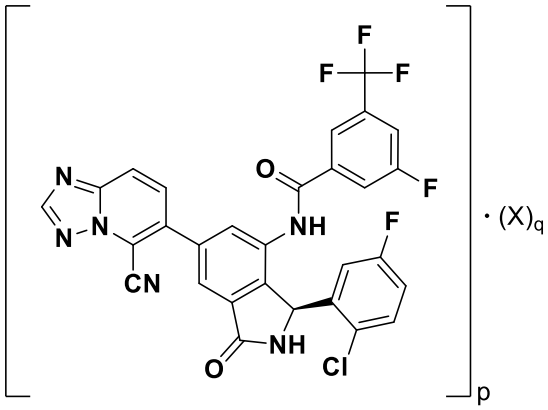
[0007] In some examples, the present disclosure provides a compound of Formula (I):



(I)

or a solvate thereof, wherein each of X, m, and n is independently as defined and described in examples herein. In some examples, a compound of Formula (I), or a solvate thereof, is a crystalline form as described herein.

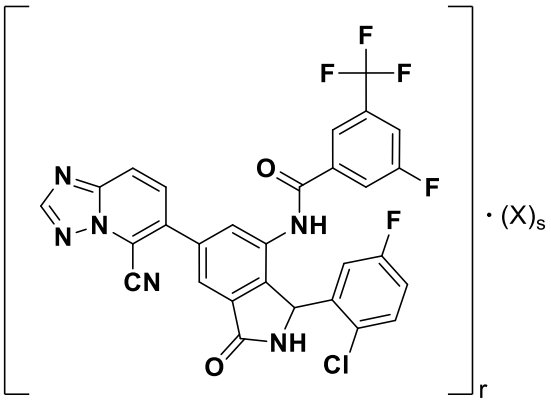
[0008] In another example, provided herein is a compound of Formula (II):



(II)

or a solvate thereof, wherein each of X, p, and q is independently as defined and described in examples herein. In some examples, a compound of Formula (II), or a solvate thereof, is a crystalline form as described herein.

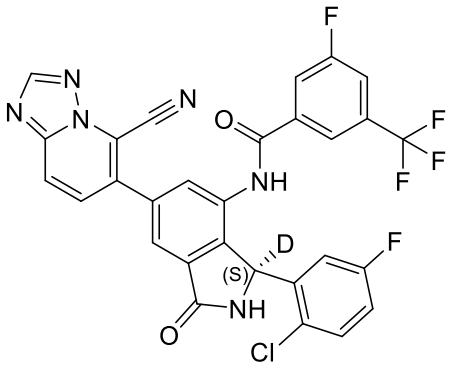
[0009] In another example, provided herein is a compound of Formula (III):



(III),

or a solvate thereof, wherein each of X, r, and s is independently as defined and described in examples herein. In some examples, a compound of Formula (III), or a solvate thereof, is a crystalline form as described herein.

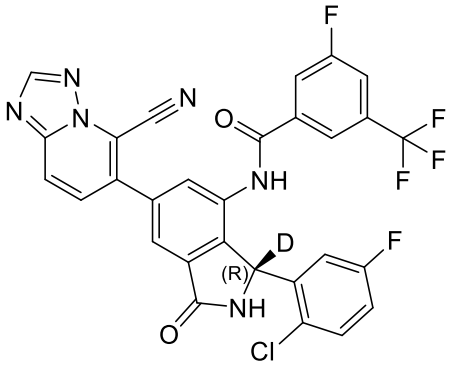
[0010] In one example, provided herein is a compound of Formula (IV-1)



(IV-1),

or a pharmaceutically acceptable salt thereof.

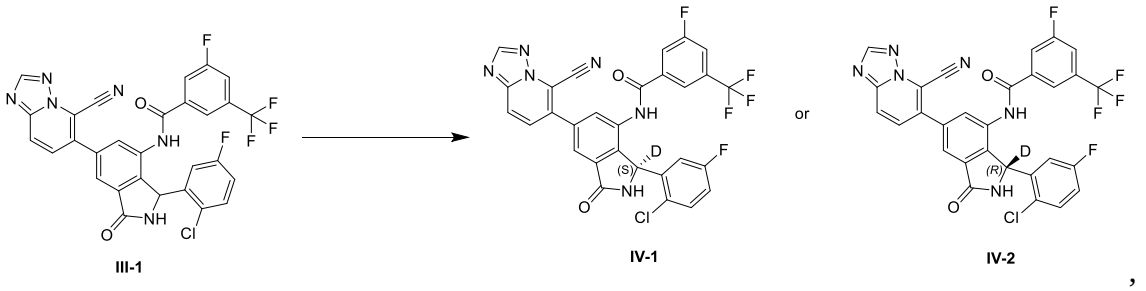
[0011] In another example, provided herein is a compound of Formula (IV-2)



(IV-2),

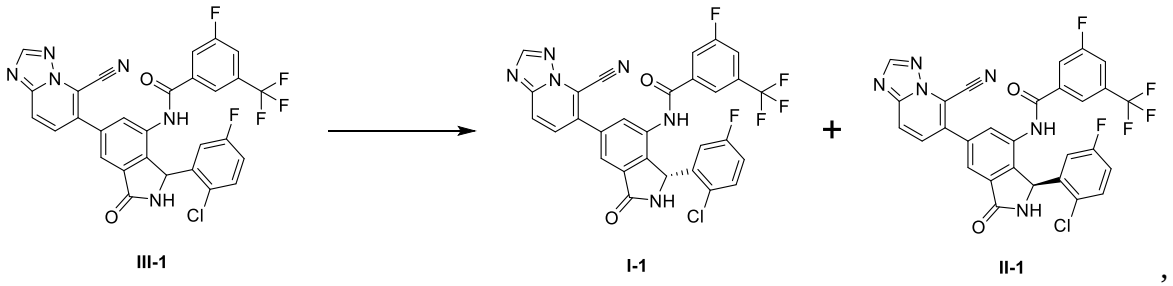
or a pharmaceutically acceptable salt thereof.

[0012] In another example, provided herein is a method comprising deuteration of compound III-1 followed by a purification step to separate the enantiomers, thereby forming compounds IV-1 and IV-2:



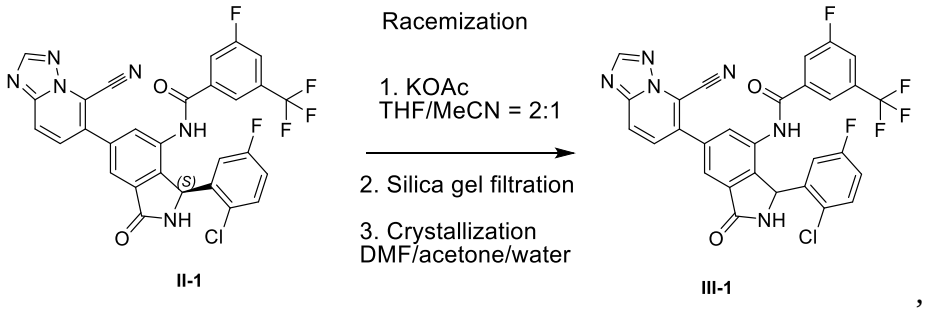
for example, as described in Example 3-A.

[0013] In another example, provided herein is a method for preparing compounds I-1 and II-1 by subjecting compound III-1 to a SMB separation:



for example, as described in Example 1-A.

[0014] In another example, provided herein is a method for preparing compound III-1 by a racemization of compound II-1:



for example, as described in Example 2-A.

[0015] In another example, provided herein is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a crystalline form, as described herein, and a pharmaceutically acceptable excipient. In another example, provided herein is a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof, as described herein, and a pharmaceutically acceptable excipient.

[0016] In another example, provided herein is a method of using a compound or a solvate thereof, or a crystalline form, or a pharmaceutical composition thereof, as described herein, for inhibiting PI3Kα activity and for treating a disorder, disease, and/or condition as described herein. In another example, provided herein is a method of using a compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as described herein, for inhibiting PI3Kα activity and for treating a disorder, disease, and/or condition as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1A depicts an XRPD pattern of I-1 Form A.

[0018] FIG. 1B depicts a DSC thermogram of I-1 Form A (heating rate: 10°C/min).

[0019] FIG. 1C depicts a DSC thermogram of I-1 Form A (heating rate: 2°C/min).

[0020] FIG. 1D depicts a DSC thermogram of I-1 Form A (heating rate: 2°C/min).

[0021] FIG. 1E depicts a TGA thermogram of I-1 Form A.

[0022] FIG. 2A depicts an XRPD pattern of I-1 Form B.

[0023] FIG. 2B depicts a DSC thermogram of I-1 Form B.

[0024] FIG. 2C depicts a TGA thermogram of I-1 Form B.

[0025] FIG. 3A depicts an XRPD pattern of I-1 Form C.

[0026] FIG. 3B depicts a DSC thermogram of I-1 Form C.

[0027] FIG. 3C depicts a TGA thermogram of I-1 Form C.

[0028] FIG. 4A depicts an XRPD pattern of III-1 Form A.

[0029] FIG. 4B depicts a DSC thermogram of III-1 Form A.

[0030] FIG. 4C depicts a TGA thermogram of III-1 Form A.

[0031] FIG. 5A depicts an XRPD pattern of III-1 Form B.

[0032] FIG. 5B depicts a DSC thermogram of III-1 Form B.

[0033] FIG. 6A depicts an XRPD pattern of III-1 Form C.

[0034] FIG. 6B depicts a DSC thermogram of III-1 Form C.

[0035] FIG. 6C depicts a TGA thermogram of III-1 Form C.

[0036] FIG. 7A depicts an XRPD pattern of III-1 Form D.

[0037] FIG. 7B depicts a DSC thermogram of III-1 Form D.

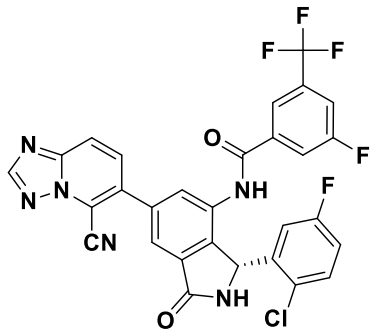
[0038] FIG. 7C depicts a TGA thermogram of III-1 Form D.

[0039] FIG. 8 depicts an XRPD pattern of III-1 Form E.

[0040] FIG. 9A depicts an XRPD pattern of III-1 Form F.

CLAIMS

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

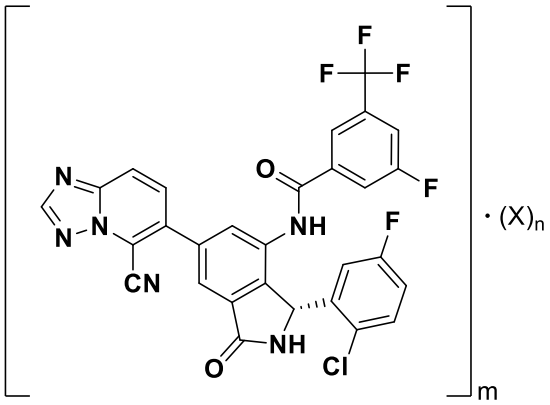


I-1,

or a solvate thereof.

2. The compound in solid form of claim 1, wherein the compound is amorphous or crystalline, optionally:
wherein the solid form is Form A, Form B or Form C.

3. A compound in solid form, wherein the compound is a compound of Formula (I):



(I),

or a solvate thereof;

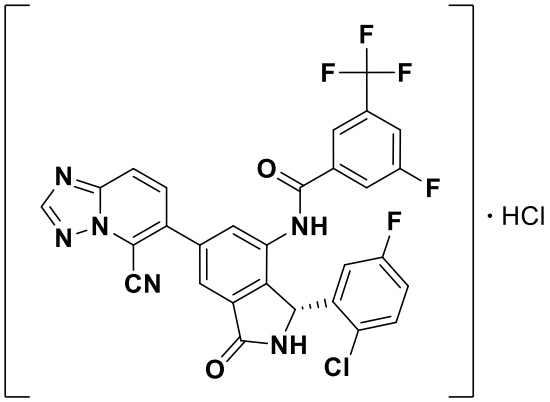
wherein:

m is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

n is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid.

4. The compound in solid form of claim 3, wherein the compound is Compound I-2:



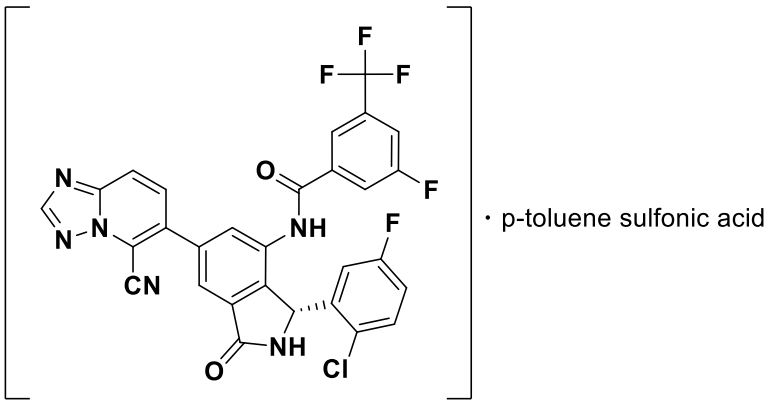
I-2,

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or

wherein the solid form is Form A.

5. The compound in solid form of claim 3, wherein the compound is Compound I-3:



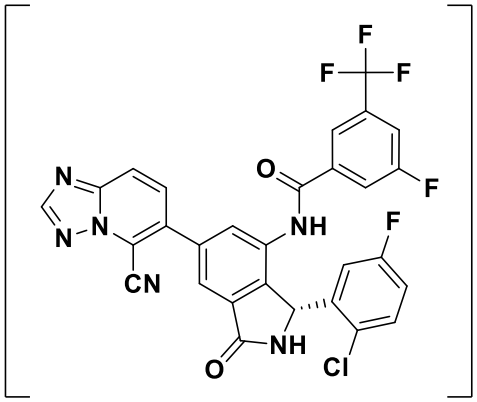
I-3,

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or

wherein the solid form is Form A or Form B.

6. The compound in solid form of claim 3, wherein the compound is Compound I-4:



· methane sulfonic acid

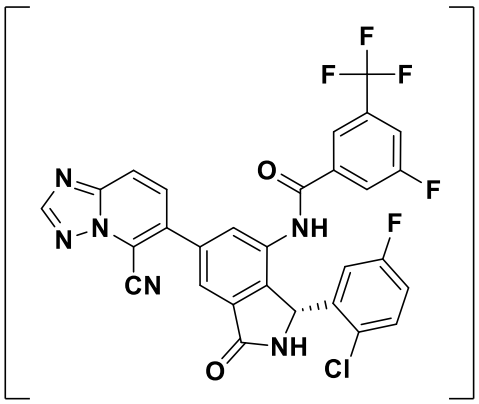
I-4,

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or,

wherein the solid form is Form A.

7. The compound in solid form of claim 3, wherein the compound is Compound I-5:



· naphthalene-1,5-disulfonic acid

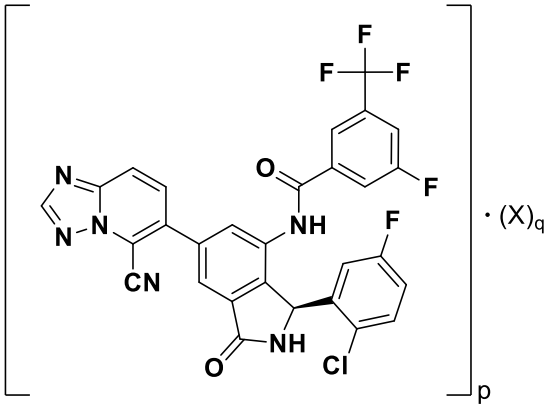
I-5,

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or

wherein the solid form is Form A or Form B.

8. A compound in solid form, wherein the compound is of Formula (II)



(II),

or a solvate thereof,

wherein:

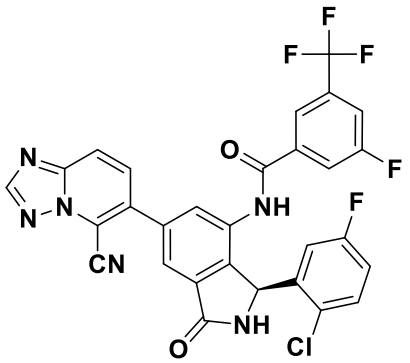
p is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

q is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid; optionally,

wherein the compound is amorphous or crystalline.

9. The compound in solid form of claim 8, wherein the compound is compound II-1:



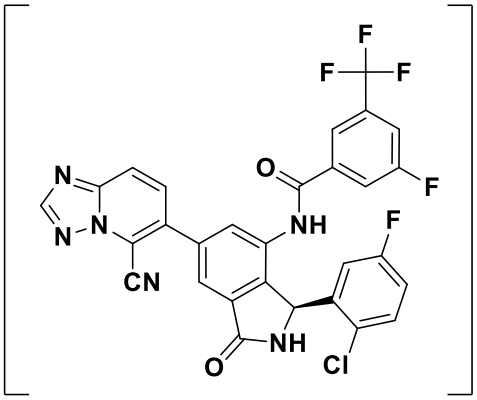
(II-1),

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or

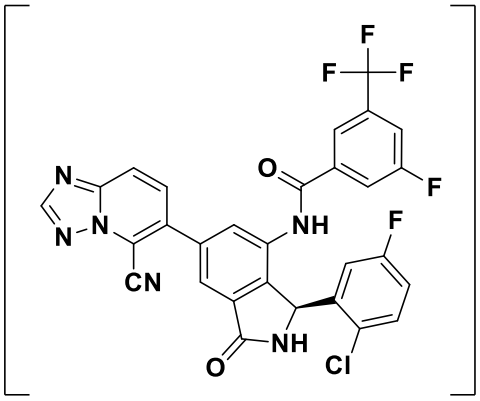
wherein the solid form is Form A, Form B, or Form C.

10. The compound in solid form of claim 8, wherein the compound is compound II-2, II-3, II-4, II-5, or II-6:



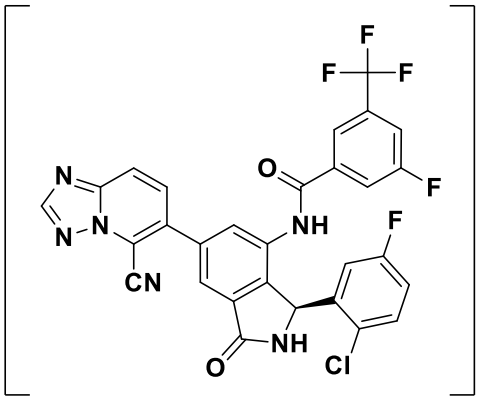
· HCl

II-2



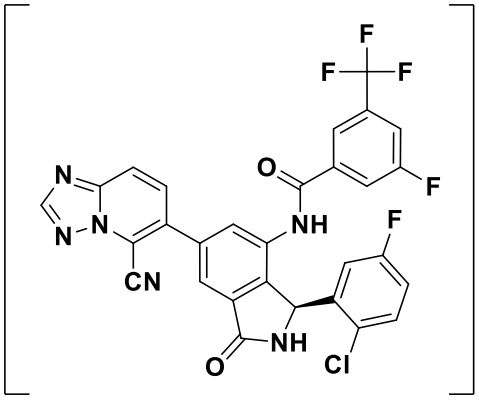
· p-toluene sulfonic acid

II-3



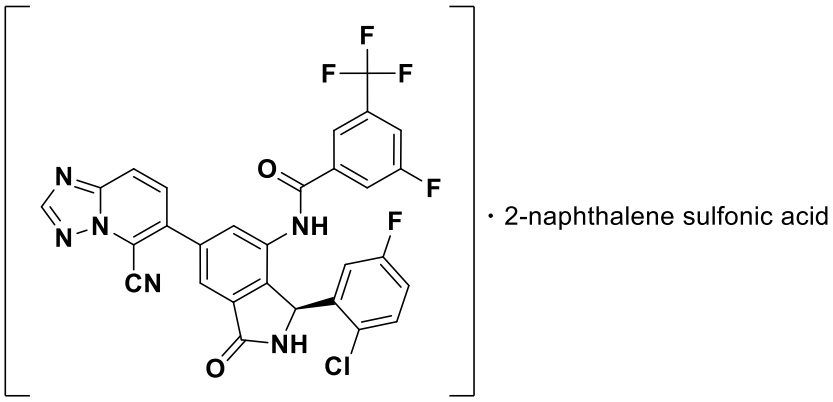
· methane sulfonic acid

II-4



· naphthalene-1,5-disulfonic acid

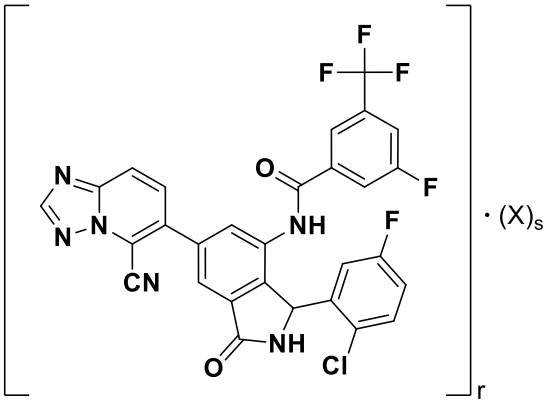
II-5,



II-6,

or a solvate thereof.

11. A compound in solid form, wherein the compound is of Formula III:



III,

or a solvate thereof,

wherein:

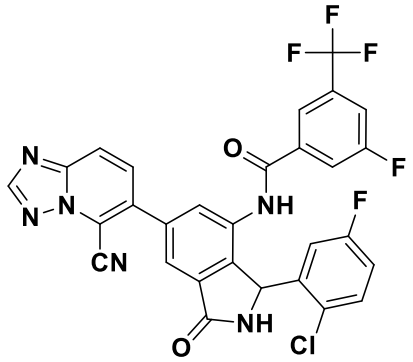
r is 1, 2, 3, 4, 5, 6, 7, 8, or 9;

s is 0, 0.5, 1, 1.5, 2, 2.5, or 3; and

X is hydrochloric acid, *p*-toluene sulfonic acid, methane sulfonic acid, naphthalene-1,5-disulfonic acid, or 2-naphthalene sulfonic acid; optionally,

wherein the compound is amorphous or crystalline.

12. The compound in solid form of claim 11, wherein the compound is compound III-1



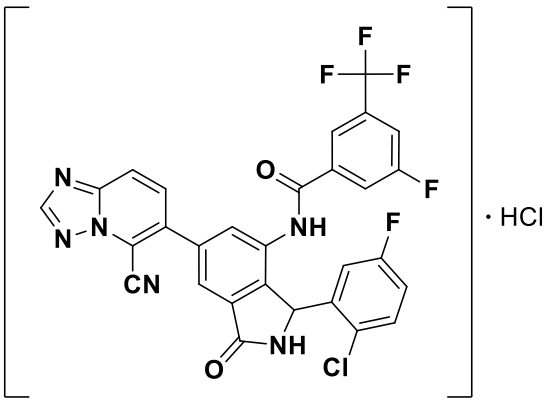
III-1,

or a solvate thereof; optionally,

wherein the compound is amorphous or crystalline; and/or

wherein the solid form is Form A, Form B, Form C, Form D, Form E, or Form F.

13. The compound in solid form of claim 11, wherein the compound is Compound III-2:



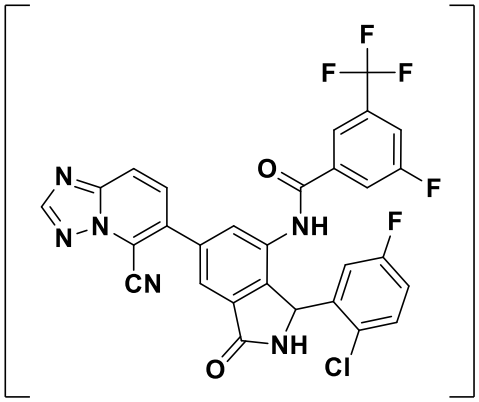
III-2,

or a solvate thereof; optionally,

wherein the compound is amorphous or crystalline; and/or

wherein the solid form is Form A or Form B.

14. The compound in solid form of claim 11, wherein the compound is compound III-6



· 2-naphthalene sulfonic acid

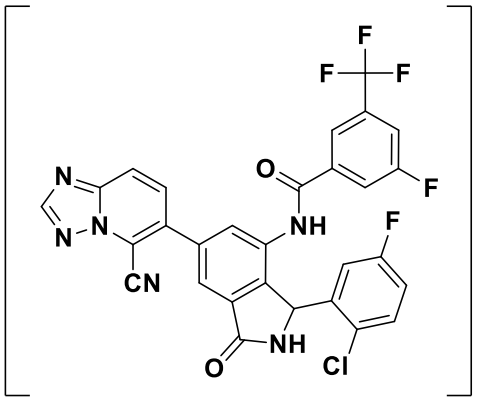
III-6,

or a solvate thereof, optionally,

wherein the compound is amorphous or crystalline; and/or

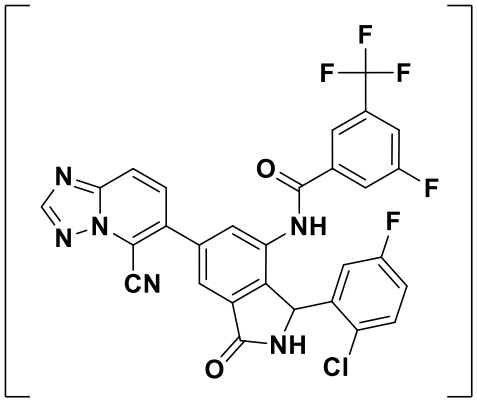
wherein the solid form is Form A.

15. The compound in solid form of claim 11, wherein the compound is compound III-3, III-4, or III-5:



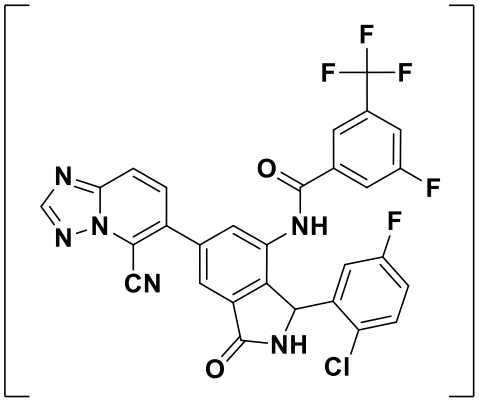
· p-toluene sulfonic acid

III-3,



· methane sulfonic acid

III-4,



· naphthalene-1,5-disulfonic acid

III-5,

or a solvate thereof.

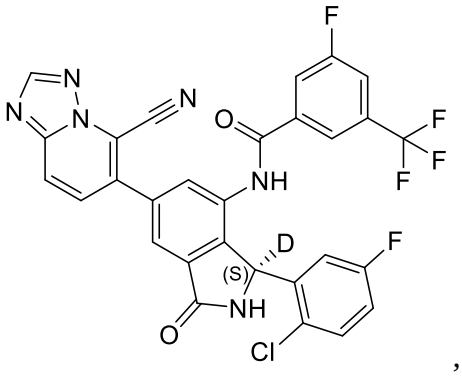
16. A process for preparing:

(a) a crystalline form of a compound of Formula (I), comprising: a) preparing a solution of a compound of Formula (I); b) adjusting the temperature so that solid crystalline form of a compound of Formula (I) precipitates out of the solution; and c) isolating the solid crystalline form; or

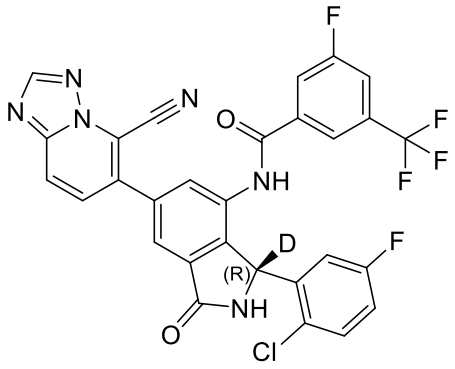
(b) a crystalline form of a compound of Formula (II), comprising: a) preparing a solution of a compound of Formula (II); b) adjusting the temperature so that solid crystalline form of a compound of Formula (II) precipitates out of the solution; and c) isolating the solid crystalline form; or

(c) a crystalline form of a compound of Formula (III), comprising: a) preparing a solution of a compound of Formula (III); b) adjusting the temperature so that solid crystalline form of a compound of Formula (III) precipitates out of the solution; and c) isolating the solid crystalline form.

17. A compound of Formula (IV-1) or Formula (IV-2):



,



(IV-1), (IV-2),

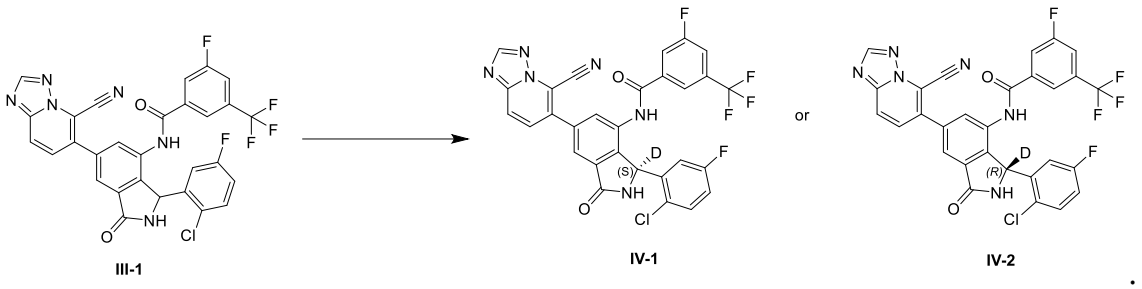
or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound according to any one of claims 1-15 or 17, and a pharmaceutically acceptable carrier.

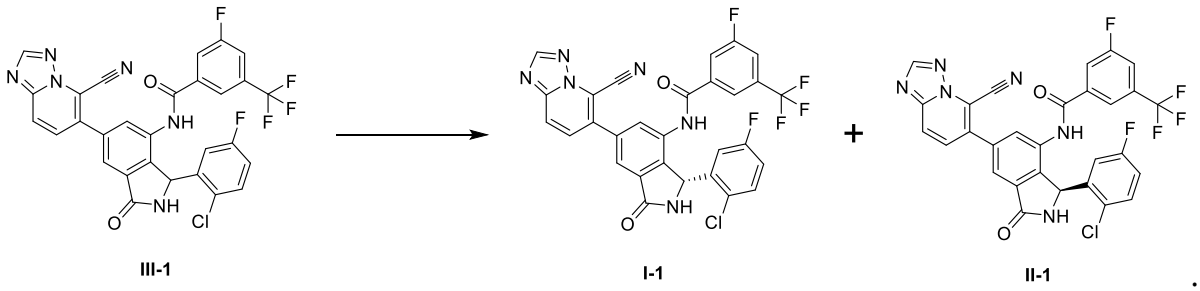
19. Use of a therapeutically effective amount of a compound of any of claims 1-15 or 17, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for inhibiting PI3Kα activity or for treating a cancer in a subject in need thereof, optionally wherein:
the compound or pharmaceutical composition is to be administered with a therapeutically effective amount of an antibody, an antibody-drug conjugate, a kinase inhibitor, an immunomodulator, or a histone deacetylase inhibitor.

20. A kit comprising a compound of any one of claims 1-15 or 17, optionally further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the solid form or compound, and/or written instructions describing how to administer the resulting composition to the patient, further optionally comprising a pharmaceutically acceptable excipient.

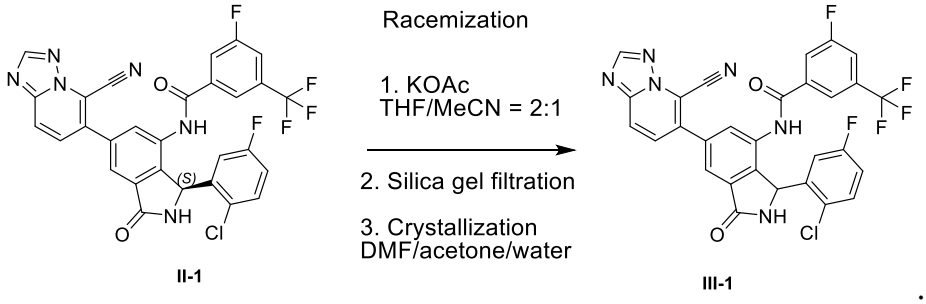
21. A process for preparing a compound of Formula IV-1 and a compound of Formula IV-2, comprising deuteration of compound III-1 followed by a purification step to separate the enantiomers, thereby forming compounds IV-1 and IV-2:



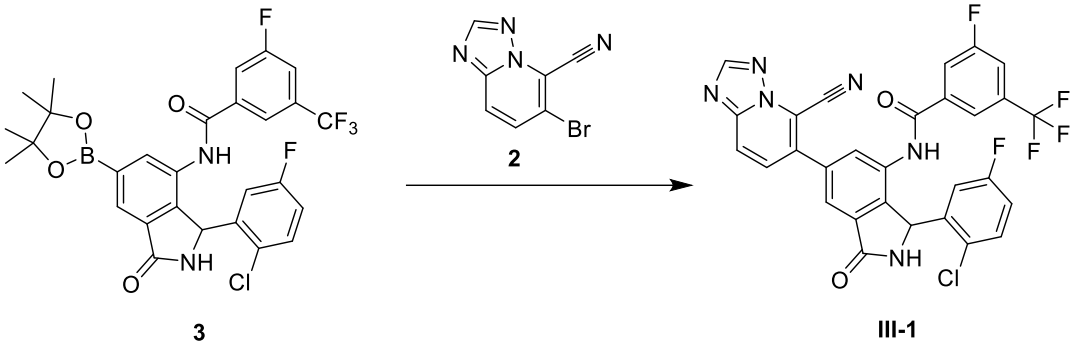
22. A process for preparing a compound of Formula I-1 and a compound of Formula II-1, comprising subjecting compound III-1 to a SMB separation, for example, as described in Example 1-A, thereby forming compounds I-1 and II-1:



23. A process for preparing a compound of Formula III-1, comprising a racemization of compound II-1:

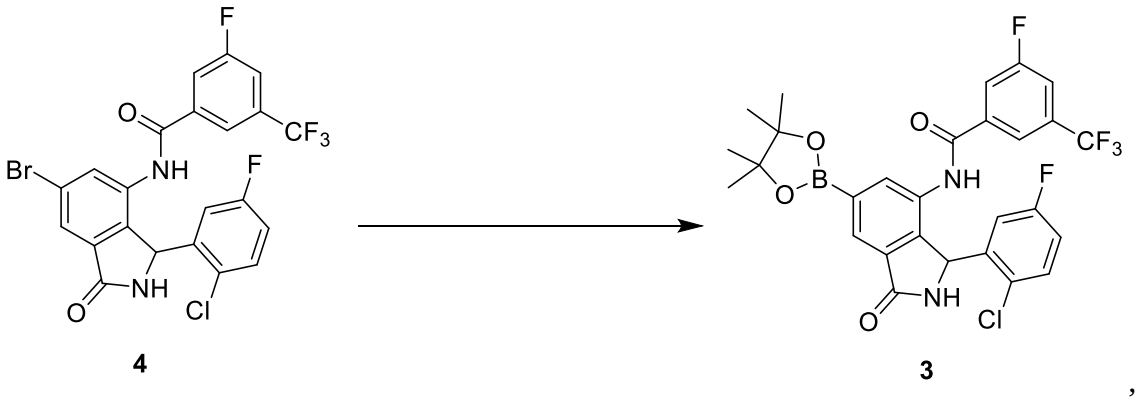


24. A process for preparing a compound of Formula III-1, comprising a step of coupling compound 2 with compound 3, thereby forming compound III-1:



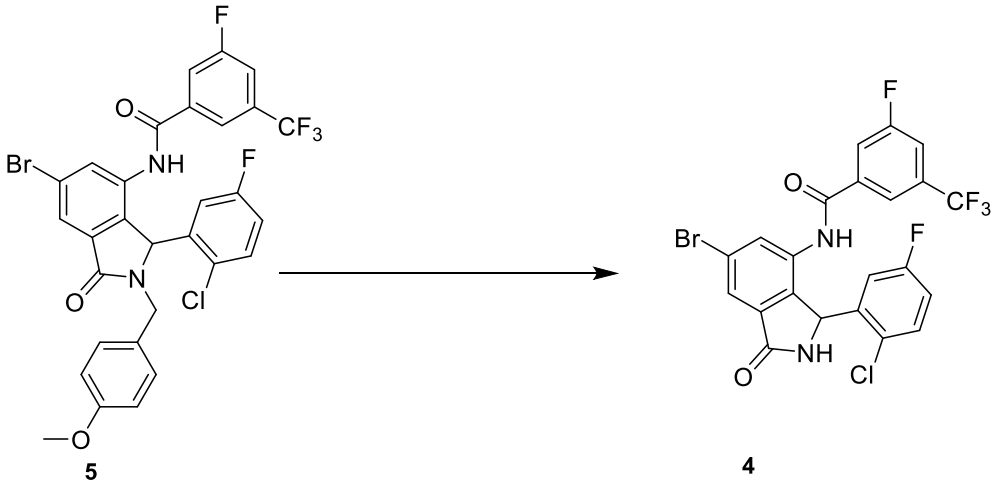
,

optionally further comprising a step of converting compound 4 to compound 3:

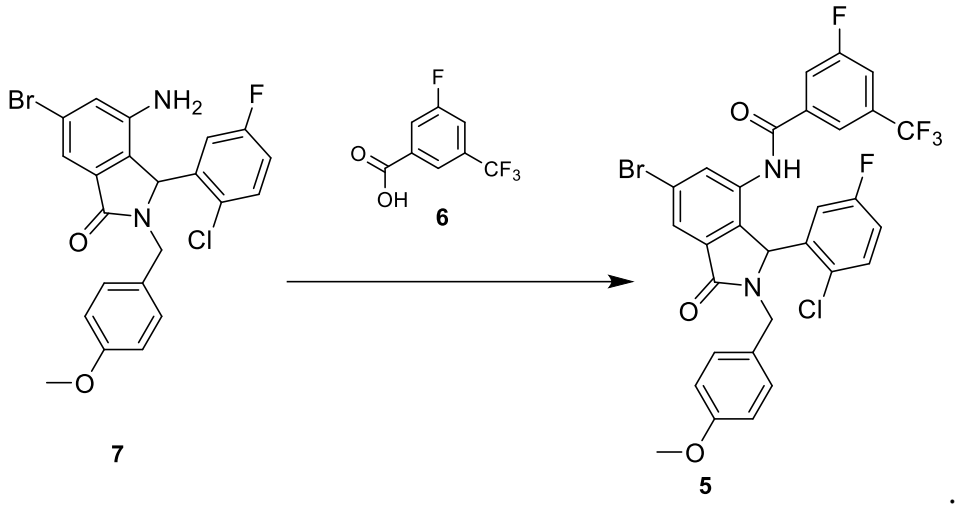


,

further optionally comprising a step of converting compound 5 to compound 4:



, further optionally comprising a step of coupling compound 6 with compound 7, thereby forming compound 5:



25. A therapeutically effective amount of a compound of any of claims 1-15 or 17, or a pharmaceutical composition of claim 18, for use in therapy.