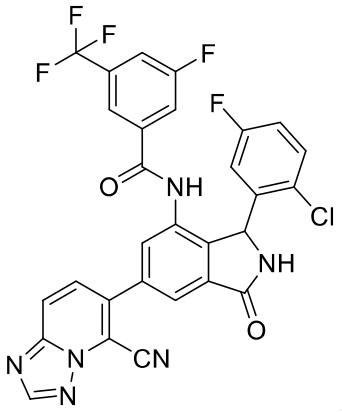
the therapeutic window, enabling sufficient target inhibition in the tumor while avoiding dose-limiting toxicity in cancer patients.

SUMMARY

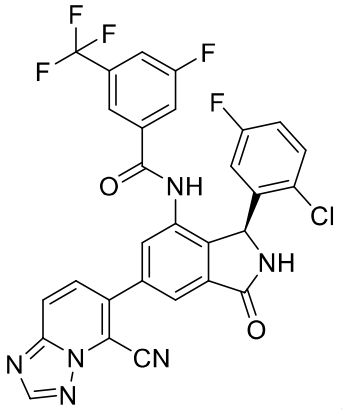
[0005a] In a first aspect of the present disclosure, there is provided a compound, which is:



,

or a pharmaceutically acceptable salt thereof.

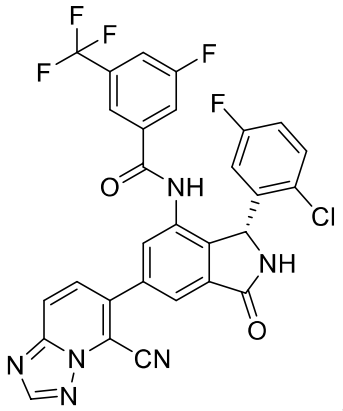
[0005b] In another aspect of the present disclosure, there is provided a compound, which is:



,

or a pharmaceutically acceptable salt thereof.

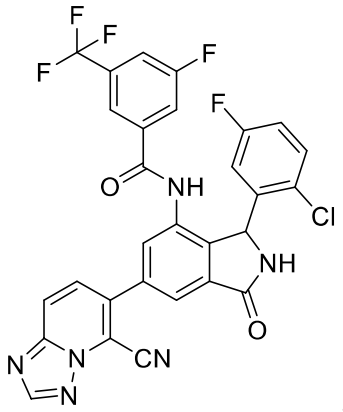
[0005c] In yet another aspect of the present disclosure, there is provided a compound, which is:



,

or a pharmaceutically acceptable salt thereof.

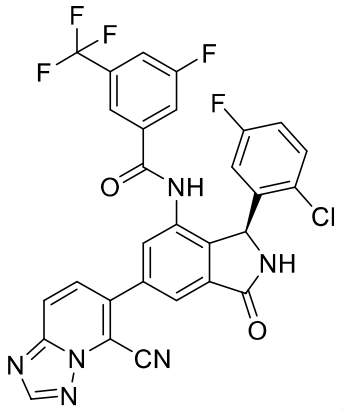
[0005d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

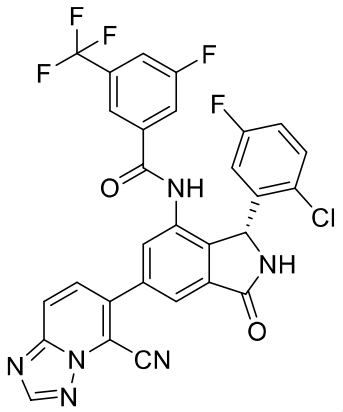
[0005e] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0005f] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound:



,

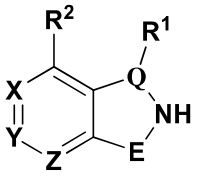
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0005g] In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject in need thereof.

[0005h] In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject in need thereof.

[0005i] In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a cellular proliferative disease in a subject in need thereof.

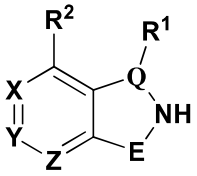
[0006] In some examples, the present disclosure provides a compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, Q, E, X, Y, and Z is as defined in examples and classes and subclasses herein.

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



I

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, Q, E, X, Y, and Z is as defined in examples and classes and subclasses herein.

[0008] In some examples, the present disclosure provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

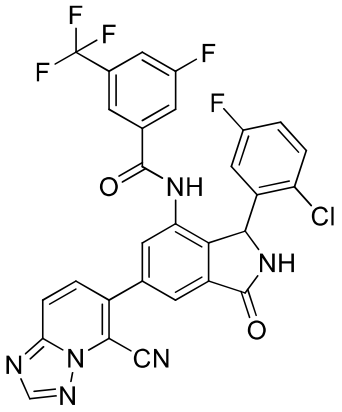
[0009] In some examples, the present disclosure provides a method of treating a PI3Kα-mediated disorder comprising administering to a patient in need thereof a compound of formula I, or composition comprising said compound.

[0010] In some examples, the present disclosure provides a process for providing a compound of formula I, or synthetic intermediates thereof.

[0011] In some examples, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of formula I.

What is claimed is:

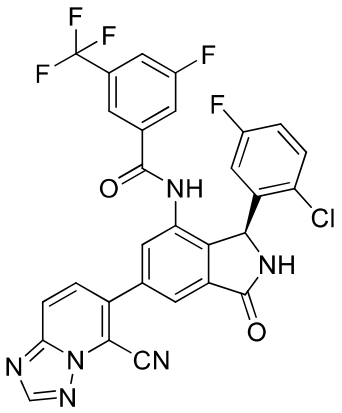
1. A compound, which is:



,

or a pharmaceutically acceptable salt thereof.

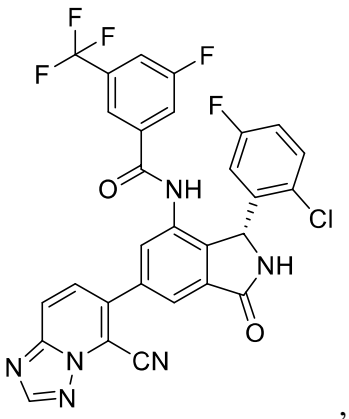
2. A compound, which is:



,

or a pharmaceutically acceptable salt thereof.

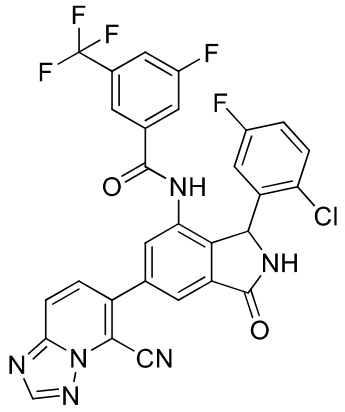
3. A compound, which is:



,

or a pharmaceutically acceptable salt thereof.

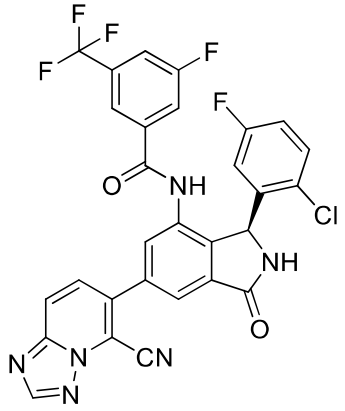
4. A pharmaceutical composition comprising a compound:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

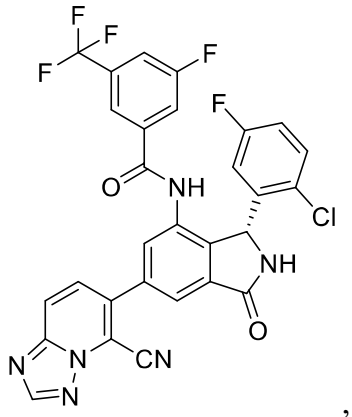
5. A pharmaceutical composition comprising a compound:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

6. A pharmaceutical composition comprising a compound:



,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

7. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 4, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject in need thereof.

8. Use of the compound of claim 2, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 5, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject in need thereof.

9. Use of the compound of claim 3, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 6, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject in need thereof.

10. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 4, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject in need thereof.

11. Use of the compound of claim 2, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 5, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject in need thereof.

12. Use of the compound of claim 3, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 6, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject in need thereof.

13. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 4, in the manufacture of a medicament for treating a cellular proliferative disease in a subject in need thereof.

14. Use of the compound of claim 2, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 5, in the manufacture of a medicament for treating a cellular proliferative disease in a subject in need thereof.

15. Use of the compound of claim 3, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 6, in the manufacture of a medicament for treating a cellular proliferative disease in a subject in need thereof.

16. The use of any one of claims 13-15, wherein the cellular proliferative disease is cancer.

17. The use of claim 16, wherein the cancer is breast cancer.

18. The use of claim 16, wherein the cancer is ovarian cancer.

19. The use of claim 18, wherein the ovarian cancer is clear cell ovarian cancer.

20. The use of claim 16, wherein 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; leukemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; villous colon adenoma; neoplasia; neoplasia of epithelial character; lymphoma; mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; neck; head; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Waldenstrom macroglobulinemia.

21. The use of any one of claim 10-12, wherein the PI3Kα-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 greata, erythema multiforme, dermatitis herpetiformis,

scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, autoimmune haematogical disorders, 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, ulcerative colitis and Crohn's disease, endocrine ophthalmopathy, Graves' disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis such as 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, 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.

22. The use of any one of claims 7-21, wherein the subject has PI3Kα containing at least one of the following mutations: H1047R, E542K, and E545K.