

SALT AND SOLID FORMS OF AN EGFR INHIBITOR**RELATED APPLICATION**

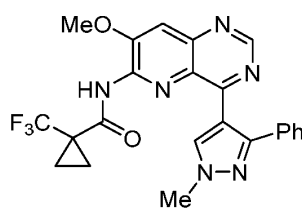
This application claims the benefit of U.S. Provisional Application No. 63/543,598, filed on October 11, 2023, the entire contents of which are incorporated herein by reference.

BACKGROUND

EGFR (Epidermal Growth Factor Receptor) is a member of the erbB receptor family, which includes transmembrane protein tyrosine kinase receptors. By binding to its ligand, such as epidermal growth factor (EGF), EGFR can form a homodimer on the cell membrane or form a heterodimer with other receptors in the family, such as erbB2, erbB3, or erbB4. The formation of these dimers can cause the phosphorylation of key tyrosine residues in EGFR cells, thereby activating a number of downstream signaling pathways in cells. These intracellular signaling pathways play an important role in cell proliferation, survival and anti-apoptosis. Disorders of EGFR signal transduction pathways, including increased expression of ligands and receptors, EGFR gene amplification and alterations such as mutations, deletions and the like, can promote malignant transformation of cells and play an important role in tumor cell proliferation, invasion, metastasis and angiogenesis. For example, alterations such as mutations and deletions in the EGFR gene are found in non-small lung cancer (NSCLC) tumors. The two most frequent EGFR alterations found in NSCLC tumors are short in-frame deletions in exon 19 (del19) and L858R, a single missense mutation in exon 21 (Cancer Discovery 2016 6(6) 601). These two alterations, referred to as sensitizing mutations, cause ligand-independent EGFR activation and are referred to as primary or activating mutations in EGFR mutant NSCLC (EGFR M+). Clinical experience shows an objective response rate (ORR) of approximately 60-85% in EGFR M+ NSCLC patients treated first line (1L) with EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, afatinib and osimertinib (Lancet Oncol. 2010 Vol. 11, 121; Lancet Oncol. 2016 Vol. 17, 577; N. Engl. J. Med. 2017 Nov 18 Doi:10.1056/NEJMoa1713137; Lancet Oncol. 2011 Vol. 12, 735), thus demonstrating that EGFR mutant NSCLC tumors depend on oncogenic EGFR activity for survival and proliferation and establishing del19 and L858R mutated EGFR as oncogenic drivers of disease and thus, validating drug targets and biomarkers for the treatment of NSCLC.

Osimertinib is a covalent third (3rd) generation EGFR TKI that is now the approved standard of care (SOC) in first line (1L) for the treatment of NSCLC harboring del19 and L858R mutations. With a progression-free survival (PFS) of 18.9 mo (JC Soria et al - NEJM, 2018 Jan; 378(2):113-125), it shows a transformative outcome for patients compared to first generation TKIs. However, after an average of 10-12 months of treatment, resistance has been observed in almost all NSCLC patients (Lancet Oncol. 2010 Feb;11(2):121-8.; Lancet Oncol. 2016 May;17(5):577-89; Lancet Oncol. 2011 Aug;12(8):735-42). Additional 3rd generation TKIs are being used in front line (e.g. lazertinib) and relay on the same covalent mechanism of binding to EGFR. The most prominent on-target resistance mechanism is due to the secondary mutation in EGFR of C797X (where “X” can be an “S” or a “G” or an “N” or a “Y” or a “T” or a “D”), which occurs in 7 % to 22 % of patients progressing on 3rd generation EGFR inhibitors used in front line (Blakely, 2012; Kobayashi, 2005). This secondary C797S mutation reduces the affinity of the drug with the target, thereby producing drug resistance, and resulting in tumor recurrence or disease progression. The resulting “double mutant” tumors, that harbors the sensitizing mutations del19 or L858R and the resistance mutation C797X (e.g., C797S), are no longer sensitive to 2nd and 3rd generation TKIs. There is no approved drug to treat the double mutant patients. 1st generation TKIs (gefitinib and erlotinib) are active against C797X (e.g., C797S) but they are poorly tolerated due to activity associated with wild-type EGFR inhibition, and do not control brain disease due to their low ability to cross the blood brain barrier (BBB).

The structure of one of the inhibitors, referred to herein as “Compound (I)” is shown below:



Compound (I)

Compound (I) is a highly selective inhibitor of EGFR TKI that inhibits with high selectivity EGFR mutants with a double mutation, e.g., L858R or exon 19 deletion mutation, and C797X (e.g., C797S) mutation, while at the same time having no or low activity to wild-type EGFR.

The successful development of pharmaceutically active agents, such as Compound (I), typically requires the identification of solid forms with properties that enable ready isolation

and purification following synthesis, that are amendable to large scale manufacture, that can be stored for extended periods of time with minimal absorption of water, decomposition or transformation into other solid forms, that are suitable for formulation.

SUMMARY

It has been found that the free base of Compound (I) has multiple crystalline forms. Form D and Form E exhibit extended physical stability when subjected to heat and humidity.

In one aspect, the present disclosure provides a free base of Compound (I) Form D.

In yet another aspect, the present disclosure provides a free base of Compound (I) Form E.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the free base of Compound (I) disclosed herein and a pharmaceutically acceptable carrier or diluent.

Provided herein are new methods of making and purifying the Compound of Formula (I).

The present disclosure provides a method of inhibiting certain mutant forms of epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein. Mutant forms of EGFR include for example, EGFR with LRCS mutation (the exon 19 deletion (del19) or exon 21 (L858R) substitution mutation, and C797X (e.g., C797S) mutation). Subjects “in need of inhibiting EGFR” are those having a disease for which a beneficial therapeutic effect can be achieved by inhibiting at least one mutant EGFR, e.g., a slowing in disease progression, alleviation of one or more symptoms associated with the disease or increasing the longevity of the subject in view of the disease.

In some embodiments, the disclosure provides a method of treating a disease/condition/or cancer associated with or modulated by mutant EGFR, wherein the inhibition of the mutant EGFR is of therapeutic benefit, including but not limited to the treatment of cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein.

In another embodiment, the disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein. Cancers to be treated according to the disclosed methods include lung cancer, colon cancer, urothelial cancer, breast cancer, prostate cancer, brain cancers, ovarian cancer, gastric cancer, pancreatic cancer, head and neck cancer, bladder cancer, and mesothelioma, including metastasis (in particular brain metastasis) of all cancers listed. Typically, the cancer is characterized by at one or more EGFR mutations described herein. In a specific embodiment, the cancer has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. In a specific embodiment, the disease has progressed on or after first line 3rd generation TKI, e.g. osimertinib. In a specific embodiment, the cancer was not previously treated.

In another aspect, the present disclosure provides a process to produce high purity of free base of Compound (I) Form E.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows the X-ray Powder Diffraction (XRPD) Form of Free Base of Compound (I) Form D from 2–40 °2θ.

Figure 1B shows the Differential Scanning Calorimetry Analysis (DSC) thermogram of Free Base of Compound (I) Form D, 10°C/minute heating ramp.

Figure 1C shows the Thermogravimetric Analysis (TGA) thermogram of Free Base of Compound (I) Form D.

Figure 2A1 shows the X-ray Powder Diffraction (XRPD) Form of Free Base of Compound (I) Form E from Preparation 1 from 2–40 °2θ.

Figure 2A2 shows the X-ray Powder Diffraction (XRPD) Form of Free Base of Compound (I) Form E from Preparation 2 from 2–40 °2θ.

Figure 2A3 shows the X-ray Powder Diffraction (XRPD) Form of Free Base of Compound (I) Form E from Preparation 3 from 2–40 °2θ.

Figure 2A4 shows the X-ray Powder Diffraction (XRPD) Form of Free Base of Compound (I) Form E from Preparation 4 from 2–40 °2θ.

Figure 2B shows the Differential Scanning Calorimetry Analysis (DSC) thermogram of Free Base of Compound (I) Form E, 10°C/minute heating ramp.

Figure 2C shows the Thermogravimetric Analysis (TGA) thermogram of Free Base of Compound (I) Form E.

DETAILED DESCRIPTION

The present disclosure is directed to: i) novel solid forms of the free base of Compound (I); and ii) methods of use and preparation of the solid forms of the free base of Compound (I).

Free base of Compound (I) Form D

In some embodiments, the present disclosure provides crystalline Form D free base of Compound (I). The XRPD Form and peaks are shown in Figure 1A. The Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry Analysis (DSC) thermograms are shown in Figures 1B and 1C.

Table 1. Peak list for Compound (I) free base Form D.

2-theta (deg)	d-Spacing (Å)
5.7	15.58
10.2	8.65
11.8	7.51
14.3	6.17
16.9	5.25
18.7	4.74
20.6	4.32
21.4	4.16
23.1	3.84
23.8	3.74
25.9	3.44
26.5	3.36
29.3	3.04

Table 2. Peak list for Compound (I) free base Form D.

2-theta (deg)	d-Spacing (Å)
5.7	15.58
10.2	8.65
11.8	7.51
14.3	6.17
16.9	5.25
20.6	4.32

In some embodiments, the crystalline Compound (I) Form D free base is characterized by an X-ray powder diffraction pattern which comprises three or more peaks listed in Table 1 or 2.

In some embodiments, the crystalline Form D free base is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, or at least six peaks chosen from 5.7°, 10.2°, 11.8°, 14.3°, 16.9°, and 20.6° ± 0.2 in 2θ. In some embodiments, the crystalline Form D free base is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.7°, 10.2°, 11.8°, 14.3°, 16.9°, and 20.6° ± 0.2 in 2θ.

In some embodiments, the crystalline Form D is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks selected from 5.7°, 10.2°, 11.8°, 14.3°, 16.9°, 18.7°, 20.6°, 21.4°, 23.1°, 23.8°, 25.9°, 26.5°, and 29.3° ± 0.2 in 2θ. In some embodiments, the crystalline Form D is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.7°, 10.2°, 11.8°, 14.3°, 16.9°, 18.7°, 20.6°, 21.4°, 23.1°, 23.8°, 25.9°, 26.5°, and 29.3° ± 0.2 in 2θ.

In some embodiments, the crystalline Form D free base is characterized by an X-ray powder diffraction pattern substantially similar to Figure 1A.

As used herein, an X-ray powder diffraction pattern is “substantially similar to Figure 1A” or “substantially similar to any one of Figure 2A1, Figure 2A2, Figure 2A3, or Figure 2A4” means that for comparison purposes, at least 90% of the peaks shown in Figure 1A, Figure 2A1, Figure 2A2, Figure 2A3, or Figure 2A4 are present. It is to be further understood that for comparison purposes some variability in peak position from those shown in Figure 1A, Figure 2A1, Figure 2A2, Figure 2A3, or Figure 2A4 are allowed, such as ±0.2 degrees.

In some embodiments, the crystalline Form D free base is characterized by a differential scanning calorimeter (DSC) substantially similar to Figure 1B. In some embodiments, the crystalline is Form D free base characterized by a differential scanning calorimeter (DSC) having an endotherm with an onset peak at 224 ± 2 °C. In some embodiments, the crystalline is Form D free base characterized by a differential scanning calorimeter (DSC) having an endotherm with an onset peak at 224 ± 2 °C (at 10°C/minute).

In some embodiments, the crystalline Form D free base is characterized by a thermogravimetric analysis (TGA) substantially similar to Figure 1C. Compound (I) Form D free base is anhydrous, with 0.06% weight loss between approx. 50 to 200 °C, following the onset of decomposition up to 4.0 wt% by approx. 250 °C.

In some embodiments, crystalline Form D is at least 70%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, 99.5% or 99.9% pure. The purity of Form D is determined by dividing the weight of crystalline Form D in a composition comprising free base compound (I) over the total weight of the compound in the composition. In one embodiment, the present invention provides a composition comprising free base compound (I), wherein at least 70%, 80%, 85%, 90%, 95%, 97%, 99%, 99.5% or 99.9% by weight of the compound in the composition is crystalline Form D of the compound.

Free base of Compound (I) Form E

In some embodiments, the present disclosure provides crystalline Compound (I) Form E free base. The XRPD Form and peaks are shown in Figure 2A1, 2A2, 2A3, and 2A4. The Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry Analysis (DSC) thermograms are shown in Figures 2B and 2C, respectively.

Form E exhibits preferred orientation based on particle size and sample preparation; therefore, the order of peaks via relative intensity is subject to variability in addition to peak broadening/splitting.

Table 3 XRPD Peak list of Compound (I) Form E free base

2-theta (deg)	d-Spacing (ang.)
5.9	15.08
10.2	8.68
11.8	7.49
23.8	3.73

Table 4 XRPD Peak list of Compound (I) Form E free base

2-theta (deg)	d-Spacing (ang.)
5.9	15.08
10.2	8.68
11.8	7.49
17.8	4.98
21.7	4.09
22.1	4.02

2-theta (deg)	d-Spacing (ang.)
22.7	3.92
23.8	3.73
26.4	3.38
26.7	3.34

Table 5 XRPD Peak list of Compound (I) Form E free base

2-theta (deg)	d-Spacing (ang.)
5.9	15.08
10.2	8.68
11.3	7.82
11.8	7.49
13.8	6.40
14.5	6.09
17.8	4.98
21.7	4.09
22.1	4.02
22.7	3.92
23.8	3.73
26.4	3.38
26.7	3.34

In some embodiments, the crystalline Compound (I) Form E free base is characterized by an X-ray powder diffraction pattern which comprises three or more peaks listed in Table 3, 4, or 5.

In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks selected from 5.9°, 10.2°, 11.8°, and 23.8° ± 0.2 in 2θ. In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.9°, 10.2°, 11.8°, and 23.8° ± 0.2 in 2θ.

In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten peaks selected from 5.9°, 10.2°, 11.8°, 17.8°, 21.7°, 22.1°, 22.7°, 23.8°, 26.4°, and 26.7° ± 0.2 in 2θ. In some embodiments, the

crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.9°, 10.2°, 11.8°, 17.8°, 21.7°, 22.1°, 22.7°, 23.8°, 26.4°, and 26.7° ± 0.2 in 2θ.

In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks at 5.9°, 10.2°, 11.8°, and 23.8° and at least one, at least two, at least three, at least four, at least five, or at least six peaks selected from 17.8°, 21.7°, 22.1°, 22.7°, 26.4°, and 26.7° ± 0.2 in 2θ. In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.9°, 10.2°, 11.8°, and 23.8° and at least one, at least two, at least three, at least four, at least five, or at least six peaks selected from 17.8°, 21.7°, 22.1°, 22.7°, 26.4°, and 26.7° ± 0.2 in 2θ.

In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks selected from 5.9°, 10.2°, 11.3°, 11.8°, 13.8°, 14.5°, 17.8°, 21.7°, 22.1°, 22.7°, 23.8°, 26.4°, and 26.7° ± 0.2 in 2θ. In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.9°, 10.2°, 11.3°, 11.8°, 13.8°, 14.5°, 17.8°, 21.7°, 22.1°, 22.7°, 23.8°, 26.4°, and 26.7° ± 0.2 in 2θ.

In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks at 5.9°, 10.2°, 11.8°, and 23.8° and at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight or at least nine peaks selected from 11.3°, 13.8°, 14.5°, 17.8°, 21.7°, 22.1°, 22.7°, 26.4°, and 26.7° ± 0.2 in 2θ. In some embodiments, the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises peaks at 5.9°, 10.2°, 11.8°, and 23.8° and at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight or at least nine peaks selected from 11.3°, 13.8°, 14.5°, 17.8°, 21.7°, 22.1°, 22.7°, 26.4°, and 26.7° ± 0.2 in 2θ.

In some embodiments, the crystalline Form E free base is characterized by an X-ray powder diffraction pattern substantially similar to any one of Figure 2A1, Figure 2A2, Figure 2A3, or Figure 2A4.

In some embodiments, the crystalline Form E free base is characterized by a differential scanning calorimeter (DSC) substantially similar to Figure 2B.

In some embodiments, the crystalline is Form E free base characterized by a differential scanning calorimeter (DSC) having endotherms with onset peaks at 180 ± 2 °C and 225 ± 2 °C. In some embodiments, the crystalline is Form E free base characterized by a

differential scanning calorimeter (DSC) having endotherms with onset peaks at 180 ± 2 °C and 225 ± 2 °C (at 10°C/minute).

In some embodiments, the crystalline Form E free base is characterized by a thermogravimetric analysis (TGA) substantially similar to Figure 2C. Compound (I) Form E free base is anhydrous, with 0.03% weight loss between approx. 50 to 200 °C, following the onset of decomposition up to 0.5 wt% by approx. 250 °C.

In some embodiments, crystalline Form E is at least 70%, 80%, 85%, 90%, 95%, 97%, 99%, 99.5% or 99.9% pure. The purity of Form E is determined by dividing the weight of crystalline Form E in a composition comprising free base compound (I) over the total weight of the compound in the composition. In one embodiment, the present invention provides a composition comprising free base compound (I), wherein at least 70%, 80%, 85%, 90%, 95%, 97%, 99%, 99.5% or 99.9% by weight of the compound in the composition is crystalline Form E of the compound.

Methods of Purifying compound of formula (I) free base

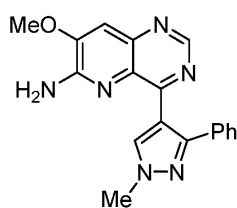
In one aspect, the compound of formula (I) can be purified by recrystallizing in a solvent system, for example, in a solvent system comprising 2-MeTHF. For example, the compound of formula (I) can be dissolved in 2-MeTHF and water mixture, optionally with heating, and optionally, activated charcoal may be added, optionally with cooling. In one aspect, the compound of formula (I) can be purified by recrystallizing in a solvent system, for example, comprising i) dissolving the compound of formula (I) in a solvent mixture at an elevated temperature, and ii) distill to induce (i.e., reduce the volume of the solvent mixture) the crystallization of the compound of formula (I). The solvent mixture is selected from THF/H₂O, 2-MeTHF/H₂O, 2-MeTHF/MeOH, MEK/H₂O, EtOAc/H₂O, and CH₃CN/H₂O. In one aspect, the compound of formula (I) is obtained from the methods described above or in the Exemplification and is isolated from the reaction as, for example, a wet cake. The product obtained from this recrystallization process is crystalline and is referred to herein as “crystalline form E” or “crystalline form D”. In one aspect, the water content of the product obtained from this recrystallization process is no more than (NMT) 0.1%-w/w and the product is Form E.

In some embodiments, the compound of formula (I) can be dissolved in 2-MeTHF and water at an elevated temperature (e.g., between 50-70 °C, between 60-70 °C or between 60-65 °C) to form a solution of the compound in 2-MeTHF and water and crystallizing the compound by distilling and cooling the solution (e.g., to 15-25 °C). In some embodiments,

the water content in the solution following the distillation is not more than 0.1% w/w (i.e., weight percentage) to form crystalline Form E of the compound. In some embodiments, the compound of formula (I) can be dissolved in ethyl acetate (EtOAc) and water at an elevated temperature (e.g., between 60-80 °C, between 65-75 °C or about 70 °C (i.e., ± 2 °C) to form a solution of the compound in EtOAc and water and crystallizing the compound by distilling and cooling the solution (e.g., to 15-25 °C).

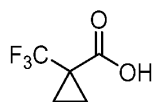
Methods of preparing compound of formula (I) free base

Disclosed herein are methods of preparing the compound of formula (I). The method comprises reacting a first starting material of formula (Ic):



(Ic) or a salt thereof with a second starting material of formula

(Id):



(Id) or a salt thereof.

The reaction of the starting material of formula (Ic) with the starting material of formula (Id) is in one aspect carried out in the presence of a coupling agent. A “coupling agent” is an agent activates the carboxylic acid group of formula (Id) to react with the amino group of formula (Ic) to form an amide bond. In one embodiment, the coupling agent is selected from Ghosez’s reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine), TCFH (Chloro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate), and CDI (1,1'-carbonyldiimidazole)]. Alternatively, coupling reagents can be also be selected from DMC (2-chloro-4,5-dihydro-1,3-dimethyl-1H-imidazolium chloride), T₃P (propanephosphonic acid anhydride), EDCI [1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide], SOCl₂, POCl₃, (COCl)₂, HATU {1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate}, TBTU [2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate], HBTU [*N,N,N',N'*-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate], and COMU [(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate].

In one embodiment, the reaction of the starting material of formula (Ic) with the starting material of formula (Id) is carried out in the presence of Ghosez's reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine). In one embodiment, the reaction of the starting material of formula (Ic) with the starting material of formula (Id) is carried out in the presence of Ghosez's reagent and a base. In one embodiment, the base is *N*-methyldmorpholine. Any suitable solvent or solvent mixture can be used. In one embodiment, the reaction is carried out in THF. The reaction can be carried out at a suitable temperature, for example, in the range of 20-80 °C, 30-70 °C, 40 -60 °C or 51-61 °C or at a temperature about 56 °C (i.e., ± 2 °C). In some embodiments, excess amount of the second starting material of formula (Id) relative to the first starting material of formula (Ic) is used in the reaction. In one embodiment, the molar ratio of the first starting material of formula (Ic) to the second starting material of formula (Id) is between 1:1 and 1:10, between 1:1 and 1:5, between 1:1 and 1:2, between 1:1.5 and 1:2 or between 1:1.7 and 1:1.9. In one embodiment, the molar ratio of the first starting material to the second starting material is 1:1.8. In some embodiments, excess amount of the Ghosez's reagent relative to the first starting material of formula (Ic) is used in the reaction. In one embodiment, the molar ratio of the first starting material to the Ghosez's reagent is between 1:1 and 1:5, between 1:1 and 1:2, between 1:1 and 1:1.5 or between 1:1.3 and 1:1.4. In one embodiment, the molar ratio of first starting material to the Ghosez's reagent is 1:1.35.

Pharmaceutical Compositions

Pharmaceutical compositions of the disclosure (also referred to herein as the "disclosed pharmaceutical compositions") comprise one or more pharmaceutically acceptable carrier(s) or diluent(s) and a compound of the disclosure (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof.

"Pharmaceutically acceptable carrier" and "pharmaceutically acceptable diluent" refer to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the pharmaceutical compositions of the disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers and/or diluents include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch,

hydroxymethylcellulose, fatty acid esters, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical excipients are suitable for use with disclosed compounds or pharmaceutically acceptable salts thereof.

The pharmaceutical compositions of the disclosure optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents, sweeteners, and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

Methods of Treatment

The present disclosure provides a method of inhibiting certain mutant forms of epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein. Mutant forms of EGFR include for example, EGFR with LRCS mutation (the exon 19 deletion (del19) or exon 21 (L858R) substitution mutation, and C797X (e.g., C797S) mutation). Subjects "in need of inhibiting EGFR" are those having a disease for which a beneficial therapeutic effect can be achieved by inhibiting at least one mutant EGFR, e.g., a slowing in disease progression, alleviation of one or more symptoms associated with the disease or increasing the longevity of the subject in view of the disease.

In some embodiments, the disclosure provides a method of treating a disease/condition/or cancer associated with or modulated by mutant EGFR, wherein the

inhibition of the mutant EGFR is of therapeutic benefit, including but not limited to the treatment of cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein.

In another embodiment, the disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein. Cancers to be treated according to the disclosed methods include lung cancer, colon cancer, urothelial cancer, breast cancer, prostate cancer, brain cancers, ovarian cancer, gastric cancer, pancreatic cancer, head and neck cancer, bladder cancer, and mesothelioma, including metastasis (in particular brain metastasis) of all cancers listed. Typically, the cancer is characterized by at least one or more EGFR mutations described herein. In a specific embodiment, the cancer has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. In a specific embodiment, the disease has progressed on or after first line 3rd generation TKI, e.g. osimertinib. In a specific embodiment, the cancer was not previously treated.

In a specific embodiment, the cancer to be treated is lung cancer. In a more specific embodiment, the cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is locally advanced or metastatic NSCLC, NSCLC adenocarcinoma, NSCLC with squamous histology and NSCLC with non-squamous histology. In another embodiment, the lung cancer is NSCLC adenocarcinoma. In another specific embodiment, the lung cancer (or non-small cell lung cancer) has metastasized to the brain.

In another embodiment, the disease/condition/or cancer associated with or modulated by mutant EGFR that is characterized by an EGFR genotype selected from genotypes 1-36 according the Table below (del18 = Exon 18 deletion, specifically, e.g., del E709_T710 insD; and del19 = Exon 19 deletion, specifically, e.g., delE746_A750 (most common), delE746_S752insV, del747_A750insP, delL747_P753insS, and delS752_I759; ex20ins – Exon 20 insertion, specifically, e.g., D761-E762insX, A763-Y764insX, Y764-V765insX, V765-M766insX, A767-S768insX, S768-D769insX, V769-D770insX, N771-P772insX, P772-H773insX, H773-V774insX, and V774-C775insX):

EGFR Genotype

1	EGFR del19
2	EGFR del19 C797S
3	EGFR del19 C797X (C797G or C797N or C797Y or C797T or C797D)
4	EGFR del19 L792X (L792F, L792H or L792Y)
5	EGFR del19 G796R (G796S)
6	EGFR del19 L792R (L792V or L792P)
7	EGFR del19 L718Q (L718V)
8	EGFR del19 G724S
9	EGFR del19 S768I (SV768IL)
10	EGFR del 19 V834L
11	EGFR del19 C797S L718Q (L718V)
12	EGFR del19 L718Q (L718V) A750P
13	EGFR L858R
14	EGFR L858R C797S
15	EGFR L858R C797X (797G or C797N or C797Y or C797T or C797D)
16	EGFR L858R L792X (L792F, L792H or L792Y)
17	EGFR L858R G796R (G796S)
18	EGFR L858R L792R (L792V or L792P)
19	EGFR L858R L718Q (L718V)
20	EGFR L858R G724S
21	EGFR L858R S768I (SV768IL)
22	EGFR L858R V834L
23	EGFR L858R C797S L718Q (L718V)
24	EGFR L858R L718Q (L718V) A750P
25	EGFR L861Q
27	EGFR L861Q C797S/G/N
28	EGFR del18
29	EGFR G719X (G719A, G719S, G719C, G719R, G719D, or G719V)
30	EGFR E709X (E709K, E709H, or E709A)
31	EGFR E709X (E709K, E709H, or E709A) (G719A, G719S, G719C, G719D, G719R, or G719V)

32	EGFR G719X (G719A, G719S, G719C, G719D, G719R, or G719V) S768I
33	EGFR S768I
34	EGFR ex20ins
35	EGFR ex20ins L718Q
36	EGFR ex20ins C797S

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 C797S.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 C797X (C797G or C797N or C797Y or C797T or C797D).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt, or or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 L792X (L792F, L792H or L792Y).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 G796R (G796S).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 L792R (L792V or L792P).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del19 L718Q (L718V).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R C797S.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R C797X (C797G or C797N or C797Y or C797T or C797D).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R L792X (L792F, L792H or L792Y).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R G796R (G796S).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R L792R (L792V or L792P).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt thereof or pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR L858R L718Q (L718V).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR del18.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR G719X (G719A, G719S, G719C, G719R, G719D, or G719V).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR E709X (E709K, E709H, or E709A).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR E709X (E709K, E709H, or E709A) (G719A, G719S, G719C, G719D, G719R, or G719V).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR G719X (G719A, G719S, G719C, G719D, G719R, or G719V) S768I.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR S768I.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR ex20ins.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR ex20ins L718Q.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR comprising EGFR ex20ins C797S.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by an EGFR genotype selected from genotypes 1-36.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to osimertinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical

composition disclosed herein is characterized by EGFR mutations that confer resistance to afatinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to dacomitinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to lazertinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to osimertinib and afatinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to osimertinib and dacomitinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to amivantamab.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to amivantamab and lazertinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to aumolertinib (formerly almonertinib).

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to olmutinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to nazartinib.

In another embodiment, the disease/condition/or cancer (e.g., NSCLC) being treated with a disclosed compound, a pharmaceutically acceptable salt or a pharmaceutical composition disclosed herein is characterized by EGFR mutations that confer resistance to avitinib.

Another embodiment is the treatment a subject with metastatic NSCLC with tumors harboring activating Exon 19 Deletion or L858R EGFR mutations, G719X (A, S, C, D, R, V), S768I and L861Q, as well as a resistance mutation disclosed herein as detected by an approved molecular testing methodology.

Another embodiment is a disclosed compound used in combination with a 2nd or 3rd generation TKI indicated for the treatment of subject with metastatic NSCLC with tumors harboring C797X mutations as detected by an approved test, and whose disease has progressed on or after 1 or 2 prior EGFR TKI therapies.

Another embodiment is a disclosed compound for the treatment of subjects with metastatic NSCLC whose disease with on-target EGFR resistance has progressed on or after any EGFR TKI. In a specific embodiment, the disclosed compound is used in combination with a 2nd or 3rd generation TKI indicated for the treatment of subject with metastatic NSCLC.

Another embodiment is a disclosed compound for the treatment of subjects with metastatic EGFR C797X mutation-positive NSCLC as detected by an approved molecular test, whose disease has progressed on or after first-line or second-line osimertinib. In a specific embodiment, the disclosed compound is used in combination with a 2nd or 3rd generation TKI indicated for the treatment of subject with metastatic NSCLC.

In a particular embodiment, the deletions, mutations, and insertions disclosed herein are detected by an FDA-approved test.

A person of ordinary skill in the art can readily determine the certain EGFR alterations a subject possesses in a cell, cancer, gene, or gene product, e.g., whether a subject has one or more of the mutations or deletions described herein using a detection method selected from those known in the art such as hybridization-based methods, amplification-based methods, microarray analysis, flow cytometry analysis, DNA sequencing, next-

generation sequencing (NGS), primer extension, PCR, in situ hybridization, fluorescent in situ hybridization, dot blot, and Southern blot.

To detect one or more EGFR deletions and/or mutations, a primary tumor sample, circulating tumor DNA (ctDNA), circulating tumor cells (CTC), and/or circulating exosomes may be collected from a subject. The samples are processed, the nucleic acids are isolated using techniques known in the art, then the nucleic acids are sequenced using methods known in the art. Sequences are then mapped to individual exons, and measures of transcriptional expression (such as RPKM, or reads per kilobase per million reads mapped), are quantified. Raw sequences and exon array data are available from sources such as TCGA, ICGC, and the NCBI Gene Expression Omnibus (GEO). For a given sample, individual exon coordinates are annotated with gene identifier information, and exons belonging to kinase domains are flagged. The exon levels are then z-score normalized across all tumors samples.

The compounds of the disclosure, pharmaceutically acceptable salts thereof or pharmaceutical compositions disclosed herein may be used for treating to a subject who has become refractory to treatment with one or more other EGFR inhibitors. "Refractory" means that the subject's cancer previously responded to drugs but later responds poorly or not at all. In some some embodiments, the subject has become refractory to one or more first generation EGFR inhibitors such as erlotinib, gefitinib, icotinib or lapatinib. In some embodiments, the subject has been become refractory to treatment with one or more second generation EGFR inhibitors such as afatinib, dacomitinib, poziotinib, or neratinib. In some embodiments the subject has become refractory to treatment with one or more first generation inhibitors and one or more second generation inhibitors. In some embodiments, the subject has become refractory to treatment with one or more third generation inhibitors such as osimertinib, nazartinib, or avitinib. In one embodiment, the subject has become refractory to treatment with one or more first generation EGFR inhibitors and one or more third generation EGFR inhibitors. In some embodiments, the subject has become refractory to treatment with one or more second generation EGFR inhibitors and one or more third generation EGFR inhibitors. In some embodiments, the subject has become refractory to treatment with one or more first generation inhibitors, and one or more third generation EGFR inhibitors.

EXPERIMENTAL

Abbreviations:

Solvents	
Name	Abbreviation
Dichloromethane	DCM
Dimethyl sulfoxide	DMSO
Ethanol	EtOH
Ethyl acetate	EtOAc
Methanol	MeOH
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA

UNITS	
Name	Abbreviation
Ampere Angstrom	Å
Celsius	°C
Degree	°
Equivalent(s)	eq.
Gram	g
Hour	h
Hertz (s ⁻¹)	Hz
Joule	J
Kelvin	K
Milligram	mg
Milliliter	mL
Minute	min
Relative humidity	RH
Room temperature (20–24 °C)	RT
Second	s
Volume	vol.
Watt	W
Weight	wt

Instruments	
Name	Abbreviation
Differential Scanning Calorimetry	DSC
X-ray Powder Diffraction	XRPD
Thermogravimetric Analysis	TGA

Analysis Conditions:

In-process control (IPC) methods are part of the quality control (QC) strategy used to monitor the chemical and biochemical process synthesis of the reaction.

Differential scanning calorimetry

Differential scanning calorimetry was performed via TA Instrument DSC Q2000, using a Tzero aluminum hermetically sealed pan (without a pinhole) with an inner Tzero pan and 3-10 mg of sample. The sample was equilibrated at 20°C followed by a 5-minute isothermal hold. The sample was then heated at 10°C/minute up to 300°C (for Form D) and up to 250°C (for Form E).

Thermogravimetric Analysis (TGA) Method:

Thermogravimetric analysis was performed via TA instrument TGA Q500 using a platinum pan, with a heat ramp from 20°C to 500°C. (Form D and E)

X-Ray Powder Diffraction (XRPD)

XRPD data was obtained via Rigaku MiniFlex using a variable and fixed slit system (5.0 deg. Soller (inc.), 10.0 mm HIS, 1.250 deg. DS, 13.0 mm (open) SS, 5.0 deg. Soller (rec.), 13.0 mm (open) RS, kb filter (x1.5) monochromatization). The scan axis used was theta/2-theta in a continuous 1D scan at 40 kV, 15 mA with sample spinning. Samples were prepared using a front load zero background sample plate (5mm well diameter by 0.22mm well depth),

For Form D: the sample pressed flat and smoothly into the well ensuring a flush level with the edges of the sample well.

Form E exhibits preferred orientation based on particle size and sample preparation. To exemplify this phenomenon, four Form E diffractogram examples are provided with the specific XRPD sample preparation procedure leading to the resultant diffractogram described.

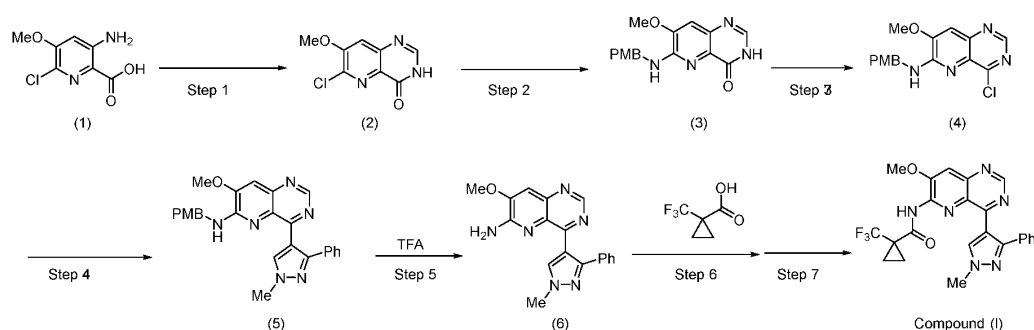
Preparation 1: Form E was pre-ground using a mortar and pestle for approximately 1 to 2 minutes, until a homogenous powder (particle size average <10 µm, no particles >50 µm) was obtained. The sample was then pressed flat and smoothly into the sample plate well ensuring a flush level with the edges of the well. (See Figure 2A1)

Preparation 2: Form E was pre-ground using a mortar and pestle for approximately 1 minute, until a mostly homogenous powder (some particles >50 μm) was obtained. The sample was then pressed flat and smoothly into the sample plate well ensuring a flush level with the edges of the well. (See Figure 2A2)

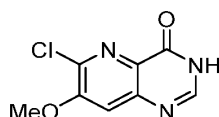
Preparation 3: Form E (native particle size) was pressed flat and smoothly into the sample plate well ensuring a flush level with the edges of the well. (See Figure 2A3)

Preparation 4: Form E was pre-ground using a mortar and pestle for approximately 1 to 2 minutes, until a homogenous powder (particle size average <10 μm , no particles >50 μm) was obtained. The sample was then pressed flat and smoothly into the sample plate well ensuring a flush level with the edges of the well. (See Figure 2A4)

Example 1. Preparation of Freebase Compound (I)



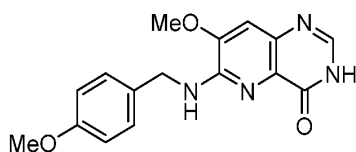
Step 1. Compound (2): 6-chloro-7-methoxypyrido[3,2-d]pyrimidin-4(3H)-one



Formamidine acetate (420 g, 4.04 mol) was added to 3-amino-6-chloro-5-methoxypyridine-4-carboxylic acid (**Compound (1)**, 220 g, 1.01 mol) in EtOH (2.0 L) at rt and the resulting mixture was heated to 90 °C for 24 h. The solids were collected by filtration to afford the title compound as a brown solid (201 g, 94 %). LCMS: $m/z = 212$ $[\text{M}+\text{H}]^+$.

Alternatively, the reaction can be run in ethylene glycol (5 volumes) at 120 °C for 3h and diluted with water (4V). The slurry was filtered and the cake washed with water.

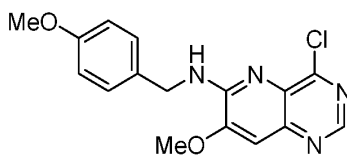
Step 2. Compound (3): 7-methoxy-6-((4-methoxybenzyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one



Representative Procedure 1: 4-methoxybenzylamine (45.2 g, 330 mmol) was added to 6-chloro-7-methoxypyrido[3,2-d]pyrimidin-4(3H)-one (**Compound (2)**, 10 g, 47.2 mmol) in DMSO (50 mL) at rt and the resulting mixture stirred at 100°C for 2h. The mixture was diluted with EtOAc (100 mL) and washed with brine (2x 50 mL). The combined organics were dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography (SiO₂, 25:1 DCM/MeOH) to afford the title compound as a yellow solid (8 g, 54%). LCMS: m/z = 313 [M+H]⁺.

Representative Procedure 2: To stirred mixture of 1,4-dioxane (137.5 L) and **Compound (2)** (25 kg, 118 mol) at 90-110 °C was added 4-methoxybenzylamine (79 kg, 567 mol) and 1,4-dioxane (150 L). The mixture was stirred at 90-110 °C (target 107 °C) until reaction completion as judged by in-process control (IPC). Water (50 L) was added to the mixture at 50-80 °C. The mixture was heated to reflux and distilled 50-125 L at constant volume (by feeding same amount of water). Water (50 L) was added to the mixture at 80-90 °C, followed by cooling to 15-25 °C and filtration. The wet cake was washed with *i*-PrOH/water (v/v 1:1, 88 L), *i*-PrOH (75 L), then dried at 55-65 °C to give **Compound (3)** as a solid (typical yield: ~74%).

Step 3. Compound (4): 4-chloro-7-methoxy-N-(4-methoxybenzyl)pyrido[3,2-d]pyrimidin-6-amine

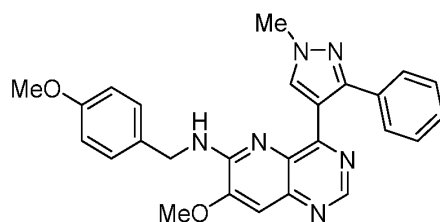


Representative Procedure 1: POCl₃ (15.7 g, 102 mmol) and N,N-diethylaniline (25.7 g, 153 mmol) were added to 7-methoxy-6-((4-methoxybenzyl)amino)pyrido[3,2-d]pyrimidin-4(3H)-one (**Compound (3)**, 8 g, 25.6 mmol) in MeCN (15 mL) at rt and the reaction stirred at 80°C for 2h. The resulting mixture was added to ice-water and the pH adjusted to pH 8 using aq. Na₂CO₃ (1 M) and extracted with EtOAc (2x 500 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue was purified

by silica gel chromatography (10:1 DCM/EtOAc) to afford the title compound as a yellow solid (7g, 83%). LCMS: $m/z = 331$ $[M+H]^+$.

Representative Procedure 2: To an agitated reactor at ambient temperature was charged toluene (152 L), **Compound (3)** (28 kg, 89.6 mol), *N,N*-Diisopropylethylamine (13.9 kg), POCl₃ (18.6 kg) and CH₃CN (18 L). The mixture was stirred at 70-80 °C until reaction completion as judged by IPC. The mixture was cooled to 10-30 °C, then charged to a separate reactor containing 25.4 kg ammonia solution (25%-w/w) and water (224 L) while maintaining the internal temperature at 0-15 °C during addition. The resulting mixture was warmed to 15-25 °C, pH adjusted (target 3-7), then filtered. The filter cake was washed with toluene (98 L), water (112 L), *i*-PrOH (126 L), then dried at 55-65 °C to give Compound (4) as a solid (typical isolation yield: ~85%)

Step 4. Compound (5): 7-methoxy-N-(4-methoxybenzyl)-4-(1-methyl-3-phenyl-1H-pyrazol-4-yl)pyrido[3,2-d]pyrimidin-6-amine

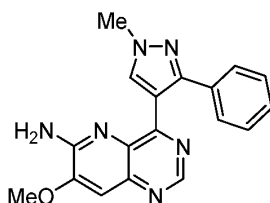


Representative Procedure 1: A mixture of Pd(dppf)Cl₂ (1.76 g, 2.11 mmol), K₂CO₃ (4.36 g, 31.6 mmol), 4-chloro-7-methoxy-N-(4-methoxybenzyl)pyrido[3,2-d]pyrimidin-6-amine (**Compound (4)**, 7 g, 21.1 mmol) and 1-methyl-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.97 g, 31.6 mmol) in H₂O (30 mL) and dioxane (120 mL) was stirred at 80 °C for 2 h under N₂. The mixture was diluted with EtOAc (200 mL) and washed with water (2x 50 mL). The combined organics were dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue was purified by silica gel chromatography (20:1 DCM/MeOH) to afford the title compound as a yellow oil (6.5 g, 68%). LCMS: $m/z = 453$ $[M+H]^+$.

Representative Procedure 2: To an agitated reactor at ambient temperature was added 54 kg of 1,4-dioxane and 7 kg of **Compound (4)** (21.2 mol, 1 equiv.). 1-Methyl-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.6 kg, 1.1 equiv.) was charged to the reactor followed by potassium carbonate, 20% w/w in water (33 kg). The inerted reaction was heated to 60 – 80 °C and Pd(dppf)Cl₂ (0.155 kg, 0.01 equiv.) was charged. The reaction was stirred and warmed to 60 – 80 °C until reaction completion as judged by IPC,

(~5h). The reaction solution was filtered to remove palladium black and the filtrate was treated with *N*-acetyl-*L*-cysteine 3.9 kg (9% w/w in water) for at least 20 minutes. Aqueous layer was removed and the reaction solution was washed with *N*-acetyl-*L*-cysteine 7.7 kg (9% w/w in water) for at least 20 minutes. To the reaction was added seed crystals (35 g) then water (45 kg) was added over ≥ 60 minutes at 40 – 55 °C and the slurry was held for ≥ 30 minutes before cooling to 5 – 15 °C and holding for 8 h. The reaction was filtered and the cake was washed with 14 L of 1,4-dioxane/water (v/v 1:1) and 11 kg of isopropanol respectively. The cake was dried at 55 – 85 °C (typical isolation yield: 85 -90%).

Step 5. Compound (6): 7-methoxy-4-(1-methyl-3-phenyl-1H-pyrazol-4-yl)pyrido[3,2-d]pyrimidin-6-amine

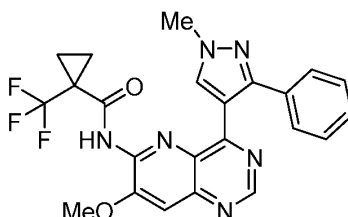


Representative Procedure 1: TFA (5 mL) was added to 7-methoxy-*N*-(4-methoxybenzyl)-4-(1-methyl-3-phenyl-1H-pyrazol-4-yl)pyrido[3,2-d]pyrimidin-6-amine (**Compound (5)**), 3 g, 5.49 mmol) at rt and the mixture stirred at 60°C for 3 h. The mixture was diluted with EtOAc (100 mL), washed with brine (2x 50 mL), dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue was purified by silica gel chromatography (18:1 DCM/MeOH) to afford the title compound as a yellow solid (2.5g). LCMS: *m/z* = 333 [M+H]⁺.

Representative Procedure 2: To an agitated reactor at 30 °C was added anisole (30 L), then **Compound (5)** (15 kg), and trifluoroacetic acid (30 L, 12.2 equiv.) at less than 40 °C. The reaction was warmed to 70 – 80 °C and stirred until reaction completion as judged by IPC, (~5 h). A second agitated reactor was charged with *n*-propanol, (75 L) and completed reaction solution was added to second reactor at 15 – 60 °C. The initial reactor was rinsed with 11.5 kg of trifluoroacetic acid and added to reactor 2. A distillation was performed by warming reactor 2 to reflux, (75 -100 °C) and distilling 75 L of solvent. The distillation was complete when internal temperature was greater than 90 °C. The reaction was cooled to 85 °C and was diluted with 30L of *n*-propanol and warmed back to 90- 100 °C for an additional distillation of 15 L. 30 L of additional 1-propanol was added to the reactor at 90 – 100 °C and finally triethylamine, (1.7 kg, 0.5 equiv.) was added and the slurry was cooled to

60 –100 °C and the pH was determined to be 7 or greater and the slurry was cooled to 20 °C over 2 – 4h. The slurry was filtered and the reactor and cake was washed with 15L, 23L and 15L of 1-propanol successively. The cake was dried at 55 – 65 °C (typical isolation yield: ~90%).

Step 6. Compound (I): *N*-(7-methoxy-4-(1-methyl-3-phenyl-1H-pyrazol-4-yl)pyrido[3,2-d]pyrimidin-6-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide



Representative Procedure 1 (Ghosez/NMM Process):

To an agitated reactor at ambient temperature was added THF (195 L), Ghosez's reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine, 8.1 kg, 1.35 equiv.), 1-(trifluoromethyl)cyclopropanecarboxylic acid (12.5 kg, 1.8 equiv.), *N*-methylmorpholine (9.1 kg, 2.0 equiv.), then **Compound (6)** (15 kg, 45.1 mol, 1 equiv.). The mixture was stirred at 51-61 °C (target 56 °C) until reaction completion as judged by IPC. The resulting mixture was diluted with THF (60 L) at the same temperature, followed by hot filtration and rinsing of filter cake with THF (30 L). The filtration was volume adjusted by distillation to remove 127.5-142.5 L of solvent at internal temperature of 40-55 °C, followed by addition of water (30 L) at 50-60 °C. *i*-PrOH/water (v/v 3:2, 60 L) was added at 37-50 °C. The slurry was cooled to 0-10 °C, then filtered. The wet cake was washed with *i*-PrOH/water (v/v 1:1, 75 L), *i*-PrOH (45 L), then dried at 55 – 65 °C to give crude Compound (I) as a solid (typical isolation yield: ~90%). Representative Procedure 1 provides Compound (I), free base, Form D.

Representative Procedure 2 (TCFH/NMI Process):

To an agitated reactor at ambient temperature was added CH₃CN (60 L), **Compound (6)** (8 kg, 24.1 mol), Chloro-*N,N,N',N'*-tetramethylformamidine hexafluorophosphate (TCFH, 10.1 kg, 36.1 mol), 1-methylimidazole (NMI, 6.9 kg, 84.2 mol) and 1-(trifluoromethyl)cyclopropane-1-carboxamide (5.6 kg, 36.1 mol). The mixture was stirred at 14-45 °C until reaction completion as judged by IPC. Afterwards, the mixture was cooled

to 0-10 °C and filtered. The wet cake was washed with CH₃CN (12 L, then 16 L), and dried at 60 °C to give crude Compound (I) as a solid.

Representative Procedure 3 (CDI Process):

The reaction can be run using **Compound (6)**, (20 g, 60.17 mmol) with 1.4 eq of carbonyl diimidazole, (11.71 g, 72.20 mmol) and 1.4 equiv. of 1-(trifluoromethyl)cyclopropane-1-carboxylic acid, (12.98 g, 84.24 mmol) in 10 V of anisole, (200 mL) at 110°C for 4h. The product was isolated by addition of 50 mL of water and 40 mL of *n*-butanol at 80 °C and a phase separation was done to remove the aqueous and a second aqueous wash, (40 mL, 2 V) was done on the organic phase. A polish filtration was conducted at 80 °C. The organic was distilled back to 10 volumes before slowly cooling to 0 °C and filtering solids, washing with 1.5V of acetone (30mL) and drying product at 60 °C to give 27.1g of (**Compound (I)**), (57.9mmol, 92.9% yield) in 97.6% purity.

Step 7. Example 2. Preparation of Form E, free base

Representative Procedure:

To an agitated reactor was charged 2-MeTHF (214 L) and **Compound (I)** (10.7 kg, 22.8 mol) at ambient temperature. The suspension was heated to 50-70 °C (target 62 °C) and water (9 L) was added. Another 32 L water was charged at the same temperature and the mixture was stirred. Stirring was stopped to allow phase separation. The organic portion was polish filtered at 50-70 °C, followed by rinsing of filtration line with 2 -MeTHF (11 L). The filtrate was volume adjusted by distillation to remove 64-75 L of solvent at normal pressure, followed by constant-volume distillation with 2-MeTHF (59-70 L) at normal pressure. The mixture was cooled to 55-70 °C, and further volume adjusted by distillation at 55-70 °C under reduced pressure to remove 112-123 L solvent, followed by constant-volume distillation with 2-MeTHF (if needed) to achieve water content of not more than (NMT) 0.10%-w/w. The resulting suspension was cooled to 15-25 °C and filtered. The wet cake was washed with 2-MeTHF (13 L, then 11 L), and dried at 55-65 °C to give **Compound (I)** Form E as a solid (typical yield: ~83%).

Example 3. Preparation of Form D, free base

Representative Procedure 1: refer to “Representative Procedure 1” (Ghosez/NMM Process) to make **Compound (I), Form D, free base**

Representative Procedure 2:

Crude **Compound (I)** (20 g) was suspended in 280 mL 2-MeTHF and 12 mL water. The mixture was heated to 70°C to obtain a clear solution. The solution was seeded (0.04 g) and cooled to 55°C, followed by further cooling to 5°C over 60 min and stirred for 60 min at 5 °C. The product was filtered off and washed with 2-MeTHF (2 × 25 mL). The wet product was dried at 60 °C under vacuum. The product was obtained as form D (typical isolation yield: ~90%).

Experimental Data

Biological Example 1. Biochemical EGFR Inhibition assays

Inhibitory effects of the compounds of the disclosure were measured in biochemical assays that measure the phosphorylation activity of EGFR enzyme phosphorylates 2.5 micromolar 5-FAM-EEPLYWSFPAKKK-CONH₂ peptide substrate (ProfilerPro Kinase Peptide Substrate 22, PerkinElmer, Part #760366) in the presence of adenosine-5'-triphosphate (ATP) and varying concentrations of the test compound in 100 mM 2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES), pH 7.5, 10 mM MgCl₂, 0.015% Brij-35, 1 mM dithiothreitol (DTT), 1.0% dimethylsulfoxide (DMSO). Assays were performed at 1.0 mM ATP or at ATP K_m of the EGFR enzymes. Reactions proceeded until between 10% to 20% total peptides were phosphorylated at room temperature (25 °C) and were terminated with 35 mM 2,2',2'',2'''-(ethane-1,2-diylidinitrilo)tetraacetic acid (EDTA). Product was detected using the Caliper mobility shift detection method where the phosphorylated peptide (product) and substrate were electrophoretically separated and measured. Percent activity was plotted against log concentration of compound and points to generate an apparent IC₅₀. The following enzyme forms of EGFR were examples that were used in these assays:

EGFR WT (SignalChem, E10-112G)

EGFR L858R (SignalChem, E10-122BG)

EGFR (d746-750) (SignalChem, E10-122JG)

EGFR L858R C797S (SignalChem, E10-122ZG)

EGFR (d746-750) C797S (SignalChem, E10-122TG)

Biological Example 2. Cellular EGFR Inhibition assaysPC-9/A431 pEGFR AlphaLISA assays

Inhibitory effects of compounds were evaluated in cellular assays that measure level of intracellular phosphorylation of EGFR in PC-9 (ECACC, #90071810, Milipore/Sigma) and A431 cell lines (ATCC, CRL-1555) using AlphaLISA sureFire ultra p-EGFR (Tyr1068) assay kit (PerkinElmer, ALSU-PEGFR-A50K). PC-9 cells were seeded at 3.125×10^5 cells/ml in 40 μ L phenol-free DMEM supplemented with 10% FBS per well of a 384 well plate (Corning, 3764), while A431 were seeded at 3.125×10^5 cells/ml in 40 μ L in phenol-free DMEM with 0.5% FBS. Cells were allowed to adhere overnight at 37°C/5% CO₂. On the next day, compounds were transferred at 4-fold, 10-point serial dilution from compound source plate to cell plates using liquid handler Echo550 and were incubated at 37°C/5% CO₂ for 4 hours. A431 cells were stimulated prior harvesting for 10 min with EGF at final concentration of 30 ng/ml in the incubator. Medium was removed from the plates and cells were lysed with 10 μ L of 1x AlphaLISA lysis buffer (supplemented with 1x protease/phosphatase inhibitor cocktail) followed by shaking at 600rpm for 30 minutes at room temperature. Lysates were transferred to Optiplate (Apricot designs) and 5 μ L of 1x acceptor bead mix (prepared just before use) was added to each well followed by incubation at room temperature for 1.5-2 h in dark. Then 5 μ L of freshly-made donor bead mix is added to each well under subdued lighting or green filters, was mixed well on the shaker and the plate was sealed and left for an overnight incubation at room temperature in dark. On the next day, the plate was read the Envision using standard AlphaLISA settings. Percent of pEGFR inhibition was plotted against log concentration of compounds to generate IC₅₀ values.

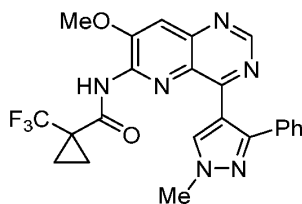
Biological assay data of Compound (I) are provided in the Table A below.

Table A

Example number	Enz EGFR_L858R IC ₅₀ (nM)	Enz EGFR_Exon19- del746-750 IC ₅₀ (nM)	Ext pEGFR_PC-9 Ex19Del IC ₅₀ (nM)
Compound (I)	1.6	0.9	1.2

CLAIMS

1. A crystalline Form E of the free base represented by the following formula:



Compound (I)

wherein said Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks selected from 5.9° , 10.2° , 11.8° , and $23.8^\circ \pm 0.2$ in 2θ .

2. The crystalline Form E of claim 1, wherein the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks at 5.9° , 10.2° , 11.8° , and 23.8° and at least one, at least two, at least three, at least four, at least five, or at least six peaks selected from 17.8° , 21.7° , 22.1° , 22.7° , 26.4° , and $26.7^\circ \pm 0.2$ in 2θ .

3. The crystalline Form E of claim 1 or 2, wherein the crystalline Form E is characterized by an X-ray powder diffraction pattern which comprises at least three or at least four peaks at 5.9° , 10.2° , 11.8° , and 23.8° and at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight or at least nine peaks selected from 11.3° , 13.8° , 14.5° , 17.8° , 21.7° , 22.1° , 22.7° , 26.4° , and $26.7^\circ \pm 0.2$ in 2θ .

4. The crystalline Form E of any one of claims 1-3, wherein the crystalline Form E is characterized by an X-ray powder diffraction pattern substantially similar to Figure 2A1, figure 2A2, Figure 2A3, or Figure 2A4.

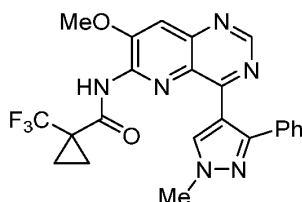
5. The crystalline Form E of any one of claims 1-4, wherein the crystalline Form E is characterized by a differential scanning calorimetry (DSC) substantially similar to Figure 2B.

6. The crystalline Form E of any one of claims 1-5, wherein the crystalline Form E is characterized by a differential scanning calorimeter (DSC) having endotherms with an onset peaks at 180 and $224 \pm 2^\circ\text{C}$.

7. The crystalline Form E of any one of claims 1-6, wherein the crystalline Form E is characterized by a thermogravimetric analysis (TGA) substantially similar to Figure 2C.

8. The crystalline Form E of any one of claims 1-7, wherein the crystalline Form E is anhydrous.

9. A crystalline Form D of the free base represented by the following formula:



Compound (I)

wherein said Form D is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, or at least six peaks chosen from 5.7° , 10.2° , 11.8° , 14.3° , 16.9° , and $20.6^\circ \pm 0.2$ in 2θ .

10. The crystalline form D of claim 9, wherein the crystalline Form D is characterized by an X-ray powder diffraction pattern which comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or at least thirteen peaks selected from 5.7° , 10.2° , 11.8° , 14.3° , 16.9° , 18.7° , 20.6° , 21.4° , 23.1° , 23.8° , 25.9° , 26.5° , and $29.3^\circ \pm 0.2$ in 2θ .

11. The crystalline Form D of claim 9 or 10, wherein the crystalline Form D is characterized by an X-ray powder diffraction pattern substantially similar to Figure 1A.

12. The crystalline Form D of any one of claims 9-11, wherein the crystalline Form D is characterized by a differential scanning calorimetry (DSC) substantially similar to Figure 1B.

13. The crystalline Form D of any one of claims 9-12, wherein the crystalline Form D is characterized by a differential scanning calorimeter (DSC) having an endotherm with an onset peak at $224 \pm 2^\circ\text{C}$.

14. The crystalline Form D of any one of claims 9-13, wherein the crystalline Form D is characterized by a thermogravimetric analysis (TGA) substantially similar to Figure 1C.

15. The crystalline Form D of any one of claims 9-14, wherein the crystalline Form D is anhydrous.

16. A pharmaceutical composition comprising the crystalline Form E of any one of claims

1-8 or the crystalline Form D of any one of claims 9-15, and a pharmaceutically acceptable carrier or diluent.

17. A method of treating a cancer, comprising administering a subject in need thereof an effective amount of the crystalline Form E of any one of claims 1-8 or the crystalline Form D of any one of claims 9-15, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 16.

18. The method of claim 17, wherein the cancer is non-small cell lung cancer.

19. The method of claim 17 or 18, wherein the cancer in the subject in need thereof has metastasized.

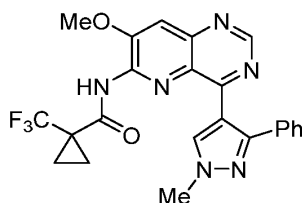
20. The method of any one of claims 17 to 19, wherein the cancer is characterized by: i) epidermal growth factor receptor EGFR L858R mutation or exon 19 deletion; and ii) C797S mutation.

21. The method of claim 20, wherein the cancer is further characterized by epidermal growth factor receptor (EGFR) T790M mutation.

22. The method of any one of claims 17 to 21, further comprises administering the subject in need thereof an effective amount of afatinib or osimertinib.

24. A method of inhibiting epidermal growth factor receptor (EGFR), comprising administering to a subject in need thereof an effective amount of the crystalline Form E of any one of claims 1-8 or the crystalline Form D of any one of claims 9-15, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 16.

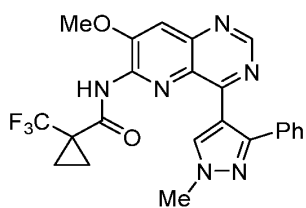
25. A method of purifying a compound of formula (I):



Compound (I)

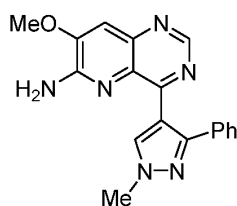
comprising recrystallizing the compound of formula (I) in a solvent system.

26. The method of claim 25, wherein the solvent system is 2-MeTHF and water.
27. The method of claim 25 or claim 26, further comprising dissolving the compound in 2-MeTHF and water at an elevated temperature to form a solution of the compound in 2-MeTHF and crystallizing the compound by distilling and cooling the solution.
28. The method of Claim 27, wherein the water content of the solution following the distillation is not more than 0.1%-w/w.
29. The method of any one of claims 26-28, wherein the compound of formula (I) is isolated as a wet and dry cakes.
30. A method of preparing a compound of formula (I):



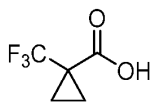
Compound (I)

comprising reacting a first starting material of formula (Ic):



(Ic) or a salt thereof with a second starting material of formula

(Id):



(Id) or a salt thereof.

31. The method of claim 30, wherein the reaction of the starting material of formula (Ic) with the starting material of formula (Id) is carried out in the presence of a coupling agent.

32. The method of claim 31, wherein the coupling agent is selected from Ghosez's reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine), TCFH (Chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate), CDI (1,1'-carbonyldiimidazole), DMC (2-chloro-4,5-dihydro-1,3-dimethyl-1H-imidazolium chloride), T₃P (propanephosphonic acid anhydride), EDCI [1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide], SOCl₂, POCl₃, (COCl)₂, HATU {1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate}, TBTU [2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate], HBTU [*N,N,N',N'*-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate], COMU [(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate].

33. The method of claim 32, wherein the coupling agent is selected from Ghosez's reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine), TCFH (Chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate), and CDI (1,1'-carbonyldiimidazole).

34. The method of claim 32, wherein the coupling agent is Ghosez's reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine).

35. The method of claim 34, wherein the reaction is carried out in THF.

36. The method of claim 34 or 35, wherein the reaction is carried out in the presence of a base.

37. The method of claim 36, wherein the base is N-methylmorpholine.
38. The method of any one of claims 34-37, wherein the molar ratio of first starting material to the Ghosez's reagent is between 1:1 and 1:5, between 1:1 and 1:2, between 1:1 and 1:1.5, between 1:1.3 and 1:1.4 or is 1:1.35.
39. The method of any one of claims 34-38, wherein the molar ratio of the first starting material to the second starting material is between 1:1 and 1:10, between 1:1 and 1:5, between 1:1 and 1:2, between 1:1.5 and 1:2, between 1:1.7 and 1:1.9 or is 1:1.8.
40. The method of any one of claims 34-39, wherein the reaction is carried out at a temperature in the range of 20-80 °C, 30-70 °C, 40 -60 °C or 51-61 °C or at a temperature about 56 °C.