SOLID FORMS OF AN EPIDERMAL GROWTH FACTOR RECEPTOR KINASE INHIBITOR

CROSS REFERENCE TO RELATED CASES

[0001] The present application claims priority to United States provisional application serial number 61/611,376, filed March 15, 2012, the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention provides solid forms of a compound useful as mutant-selective inhibitors of epidermal growth factor receptor (EGFR) kinase. The invention also provides pharmaceutically acceptable compositions comprising solid forms of the present invention and methods of using the compositions in the treatment of various disorders.

[0003] Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to a tyrosine residue located on a protein substrate. Receptor tyrosine kinases act to transmit signals from the outside of a cell to the inside by activating secondary messaging effectors via a phosphorylation event. A variety of cellular processes are promoted by these signals, including proliferation, carbohydrate utilization, protein synthesis, angiogenesis, cell growth, and cell survival.

[0004] There is strong precedent for involvement of the EGFR in human cancer because over 60% of all solid tumors overexpress at least one of these proteins or their ligands. Overexpression of EGFR is commonly found in breast, lung, head and neck, bladder tumors.

[0005] Activating mutations in the tyrosine kinase domain of EGFR have been identified in patients with non-small cell lung cancer (Lin, N. U.; Winer, E. P., Breast Cancer Res 6: 204-210, 2004). The reversible inhibitors Tarceva (erlotinib) and Iressa (gefitinib) currently are first-line therapy for non-small cell lung cancer patients with activating mutations. The most common activating mutations are L858R and delE746-A750.

[0006] Additionally, in the majority of patients that relapse, acquired drug resistance, such as by mutation of gatekeeper residue T790M, has been detected in at least half of such clinically resistant patients. Moreover, T790M may also be pre-existing; there may be an independent, oncogenic role for the T790M mutation. For example, there are patients with

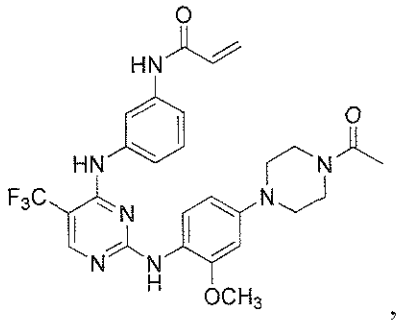
the L858R/T790M mutation who never received gefitinib treatment. In addition, germline EGFR T790M mutations are linked with certain familial lung cancers.

[0007] Current drugs in development, including second-generation covalent inhibitors, such as BIBW2992, HKI-272 and PF-0299804, are effective against the T790M resistance mutation but exhibit dose-limiting toxicities due to concurrent inhibition of WT EGFR. Accordingly, there remains a need to find mutant-selective EGFR kinase inhibitors useful as therapeutic agents.

SUMMARY

[0007] It has now been found that the novel solid forms of the present disclosure, and compositions thereof, are useful as mutant-selective inhibitors of one or more EGFR kinases and exhibits desirable characteristics for the same. In general, these solid forms, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of diseases or disorders as described in detail herein.

[0007a] In a first aspect of the present disclosure, there is provided a solid form of Compound **1**:



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wherein Compound **1** is a free base.

[0007b] In a second aspect of the present disclosure, there is provided a composition comprising the solid form as described herein and a pharmaceutically acceptable carrier or excipient.

[0007c] In a third aspect of the present disclosure, there is provided a method for inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR (WT EGFR) in a biological sample, comprising contacting the biological sample with a solid form as described herein, or a composition thereof.

[0007d] In a fourth aspect of the present disclosure, there is provided a use of a solid form as described herein, or a composition thereof, in the manufacture of a medicament for

inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR (WT EGFR), in a biological sample or in a patient.

[0007e] In a fifth aspect of the present disclosure, there is provided a use of a composition as described herein, in the manufacture of a medicament for treating a mutant EGFR-mediated disorder or condition in a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] **Figure 1** depicts the x-ray powder diffraction (XRPD) pattern for Form A of Compound **1**.

[0009] **Figure 2** depicts the thermogravimetric analysis/differential thermal analyser (TGA/DTA) pattern for Form A of Compound **1**.

[0010] **Figure 3** depicts the differential scanning calorimetry (DSC) pattern for Form A of Compound **1**.

[0011] **Figure 4** depicts the infrared (IR) spectrum for Form A of Compound **1**.

[0012] **Figure 5** depicts the dynamic vapour sorption (DVS) pattern for Form A of Compound **1**.

[0013] **Figure 6** depicts the XRPD pattern for Form B of Compound **1**.

[0014] **Figure 7** depicts the TGA/DTA pattern for Form B of Compound **1**.

[0015] **Figure 8** depicts the DSC pattern for Form B of Compound **1**.

[0016] **Figure 9** depicts the IR spectrum for Form B of Compound **1**.

[0017] **Figure 10** depicts the DVS pattern for Form B of Compound **1**.

[0018] **Figure 11** depicts the change in the XRPD pattern for Form B of Compound **1** when heated to 120°C and 160°C, respectively, as compared to Forms A and B at ambient temperature.

[0019] **Figure 12** depicts the XRPD pattern for Form C of Compound **1**.

[0020] **Figure 13** depicts the TGA/DTA pattern for Form C of Compound **1**.

[0021] **Figure 14** depicts the DSC pattern for Form C of Compound **1**.

[0022] **Figure 15** depicts the IR spectrum for Form C of Compound **1**.

[0023] **Figure 16** depicts the DVS pattern for Form C of Compound **1**.

[0024] **Figure 17** depicts the change in the XRPD pattern for Form C of Compound **1** when stored at 40°C/75%RH for 1 week or 2 weeks, respectively, as compared to the initial forms of Form A and Form C.

[0025] **Figure 18** depicts the change in the XRPD pattern for Form C of Compound **1** when heated to 40 °C and 120 °C, as compared to Forms A and C prior to drying.

[0026] **Figure 19** depicts the XRPD pattern for Form D of Compound **1**, which is present in a mixture with Form B.

[0027] **Figure 20A and B** depict TGA/DTA patterns for Form D of Compound **1**.

[0028] **Figure 21** depicts the DSC pattern for Form D of Compound **1**.

[0029] **Figure 22** depicts the IR spectrum for Form D of Compound **1**.

[0030] **Figure 23** depicts the DVS pattern for Form D of Compound **1**.

[0031] **Figure 24** depicts the change in the XRPD pattern for Form D of Compound **1** when stored at 40°C/75%RH for 1 week or 2 weeks, respectively, as compared to the initial forms of Form A and Form D.

[0032] **Figure 25** depicts the XRPD pattern for Form E of Compound **1**.

[0033] **Figure 26** depicts the TGA/DTA pattern for Form E of Compound **1**.

[0034] **Figure 27** depicts the DSC pattern for Form E of Compound **1**.

[0035] **Figure 28** depicts the IR spectrum for Form E of Compound **1**.

[0036] **Figure 29** depicts the DVS pattern for Form E of Compound **1**.

[0037] **Figure 30** depicts the change in the XRPD pattern for Form E of Compound **1** when stored at 40°C/75%RH for 1 week or 2 weeks, respectively, as compared to the initial forms of Form A and Form E.

[0038] **Figure 31** depicts the change in the XRPD pattern for Form E of Compound **1** when heated to 40 °C and 120 °C, as compared to Forms A and E prior to drying.

[0039] **Figure 32** depicts the XRPD pattern for Form F of Compound **1**.

[0040] **Figure 33** depicts the TGA/DTA pattern for Form F of Compound **1**.

[0041] **Figure 34** depicts the DSC pattern for Form F of Compound **1**.

[0042] **Figure 35** depicts the IR spectrum for Form F of Compound **1**.

[0043] **Figure 36** depicts the DVS pattern for Form F of Compound **1**.

[0044] **Figure 37** depicts the change in the XRPD pattern for Form F of Compound **1** when stored at 40 °C/75%RH for 1 week or 2 weeks, respectively, as compared to the initial forms of Form A and Form F.

[0045] **Figure 38** depicts the change in the XRPD pattern for Form F of Compound **1** when heated to 40 °C and 120 °C, as compared to Forms A and F prior to drying.

[0046] **Figure 39** depicts the XRPD pattern for Form G of Compound **1**.

[0047] **Figures 40A, 40B and 40C** depict TGA/DTA patterns for Form G of Compound **1**.

[0048] **Figure 41** depicts the DSC pattern for Form G of Compound **1**.

[0049] **Figure 42** depicts the IR spectrum for Form G of Compound **1**.

[0050] **Figure 43** depicts the DVS pattern for Form G of Compound **1**.

[0051] **Figure 44** depicts the change in the XRPD pattern for Form G of Compound **1** when stored at 40°C/75%RH for 1 week or 2 weeks, respectively, as compared to the initial forms of Form A and Form G.

[0052] **Figure 45** depicts the change in the XRPD pattern for Form G of Compound **1** when heated to 40 °C and 80 °C, as compared to Forms A and G prior to drying.

[0053] **Figure 46** depicts the XRPD pattern for Form H of Compound **1**.

[0054] **Figure 47** depicts the TGA/DTA pattern for Form H of Compound **1**.

[0055] **Figure 48** depicts the XRPD pattern for Form H of Compound **1** after heating to 115°C.

[0056] **Figure 49** depicts the DSC pattern for Form H of Compound **1**.

[0057] **Figure 50** depicts the TGA/DTA pattern for Form H of Compound **1** when heated to 115°C.

[0058] **Figure 51** depicts the TGA/DTA pattern for Form H of Compound **1** leaving the heated material on a bench for approximately one hour.

[0059] **Figure 52** depicts the XRPD for Form I of Compound **1**.

[0060] **Figure 53** depicts the IR spectra for Form I of Compound **1**.

[0061] **Figure 54** depicts the ^{1}H NMR spectrum for Form I of Compound **1**.

[0062] **Figure 55** depicts the TGA/DTA thermogram for Form I of Compound **1** following 3 days of drying under vacuum.

[0063] **Figure 56** depicts the TGA/DTA thermogram for Form I of Compound **1** after drying and standing at ambient for *ca.* 1 hour.

[0064] **Figure 57** depicts the DSC thermogram for Form I of Compound **1**.

[0065] **Figure 58** depicts the DVS analysis for Form I of Compound **1**.

[0066] **Figure 59** depicts the Post DVS XRPD analysis for Form I of Compound **1**.

[0067] **Figure 60** depicts the HPLC analysis for Form I of Compound **1**.

[0068] **Figure 61** depicts the XRPD analysis of solids remaining after thermodynamic solubility studies of Form I of Compound **1**.

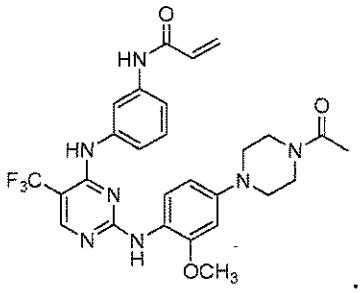
[0069] **Figure 62** depicts the XRPD analysis of 1 week stability tests on Form I of Compound **1** using open containers.

[0070] **Figure 63** depicts the XRPD analysis of 1 week stability tests on Form I of Compound **1** using closed containers.

DETAILED DESCRIPTION OF THE INVENTION

General Description of Certain Aspects of the Invention:

[0071] United States application number 13/286,061 ("the '061 application"), filed October 31, 2011, the entirety of which is hereby incorporated herein by reference, describes certain 2,4-disubstituted pyrimidine compounds which covalently and irreversibly inhibit activity of EGFR kinase. Such compounds include Compound **1**:



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[0072] Compound **1** (*N*-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)) is designated as compound number **I-4** and the synthesis of Compound **1** is described in detail at Example 3 of the '061 application.

[0073] Compound **1** is active in a variety of assays and therapeutic models demonstrating selective covalent, irreversible inhibition of mutant EGFR kinase (in enzymatic and cellular assays). Notably, Compound **1** was found to inhibit human non-small cell lung cancer cell proliferation both *in vitro* and *in vivo*. Accordingly, Compound **1** is useful for treating one or more disorders associated with activity of mutant EGFR kinase.

[0074] It would be desirable to provide a solid form of Compound **1** that, as compared to Compound **1**, imparts characteristics such as improved aqueous solubility, stability and ease of formulation. Accordingly, the present invention provides several solid forms of Compound **1**.

[0075] According to one embodiment, the present invention provides an amorphous form, a crystalline form, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0076] In other embodiments, the present invention provides Compound **1** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include starting materials, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound **1**. In certain embodiments, at least about 90% by weight of Compound **1** is present. In certain embodiments, at least about 95% by weight of Compound **1** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **1** is present.

[0077] According to one embodiment, Compound **1** is present in an amount of at least about 95, 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **1** contains no more than about 5.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **1** contains no more than about 1.0 area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0078] The structure depicted for Compound **1** is also meant to include all tautomeric forms of Compound **1**. Additionally, structures depicted here are also meant to include

compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

Solid Forms of Compound 1:

[0079] It has been found that Compound **1** can exist in a variety of solid forms. Such forms include polymorphs and amorphous forms. The solid forms can be solvates, hydrates and unsolvated forms of Compound **1**. All such forms are contemplated by the present invention. In certain embodiments, the present invention provides Compound **1** as a mixture of one or more solid forms of Compound **1**.

[0080] As used herein, the term "polymorph" refers to the different crystal structures (of solvated or unsolvated forms) in which a compound can crystallize.

[0081] As used herein, the term "solvate" refers to a solid form with either a stoichiometric or non-stoichiometric amount of solvent (e.g., a channel solvate). For polymorphs, the solvent is incorporated into the crystal structure. Similarly, the term "hydrate" refers to a solid form with either a stoichiometric or non-stoichiometric amount of water. For polymorphs, the water is incorporated into the crystal structure.

[0082] As used herein, the term "about", when used in reference to a degree 2-theta value refers to the stated value ± 0.3 degree 2-theta. In certain embodiments, "about" refers to ± 0.2 degree 2-theta or ± 0.1 degree 2-theta.

[0083] In certain embodiments, Compound **1** is a crystalline solid. In other embodiments, Compound **1** is a crystalline solid substantially free of amorphous Compound **1**. As used herein, the term "substantially free of amorphous Compound **1**" means that the compound contains no significant amount of amorphous Compound **1**. In certain embodiments, at least about 90% by weight of crystalline Compound **1** is present, or at least about 95% by weight of crystalline Compound **1** is present. In still other embodiments of the invention, at least about 97%, 98% or 99% by weight of crystalline compound **1** is present.

[0084] In certain embodiments, Compound **1** is a neat or unsolvated crystal form and thus does not have any water or solvent incorporated into the crystal structure. It has been found that Compound **1** can exist in at least two distinct neat (i.e., anhydrous) crystal forms, or polymorphs. In some embodiments, the present invention provides an anhydrous polymorphic form of Compound **1** referred to herein as Form A. In other embodiments, the

present invention provides an anhydrous polymorphic form of Compound **1** referred to herein as Form B.

[0085] In certain embodiments, the present invention provides Form A of Compound **1**. According to one embodiment, Form A of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 6.73, about 18.30, about 18.96 and about 25.48 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 6.73, about 18.30, about 18.96 and about 25.48 degrees 2-theta. In certain embodiments, Form A of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 6.73, about 18.30, about 18.96 and about 25.48 degrees 2-theta. In particular embodiments, Form A of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 6.73, 14.24, 16.13, 18.30, 18.96, 20.59, 21.02, 21.23, 23.99 and 25.48 degrees 2-theta. In an exemplary embodiment, Form A of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about

°2-Theta	°2-Theta	°2-Theta	°2-Theta
5.21	13.89	20.43	27.68
5.42	14.24	20.59	30.32
6.73	15.08	21.02	30.65
8.67	15.47	21.23	31.41
9.47	15.88	22.18	32.31
10.59	16.13	22.93	33.62
10.93	17.57	23.99	34.01
12.07	18.30	24.22	37.93
13.00	18.51	25.48	38.66
13.06	18.96	26.18	39.78
13.64	19.80	26.50	45.41

[0086] According to one aspect, Form A of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 1**. According to another aspect, Form A of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 2**. Accordingly to yet another aspect, Form A of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 3**. According to a further embodiment, Form A of Compound **1** has a infrared spectrum substantially similar to that depicted in **Figure 4**. According to another embodiment, Form A

of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 5**. Form A of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[0087] In certain embodiments, the present invention provides Form B of Compound **1**. According to another embodiment, Form B of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 10.67, about 12.21, about 18.11, about 19.24 and about 21.53 degrees 2-theta. In some embodiments, Form B of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 10.67, about 12.21, about 18.11, about 19.24 and about 21.53 degrees 2-theta. In certain embodiments, Form B of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 10.67, about 12.21, about 18.11, about 19.24 and about 21.53 degrees 2-theta. In particular embodiments, Form B of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 8.96, 10.67, 12.21, 14.56, 16.49, 17.74, 18.11, 19.24, 19.90, 21.53 and 23.93 degrees 2-theta. In an exemplary embodiment, Form B of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.03	14.56	22.25	32.58
4.74	15.29	23.93	33.41
5.01	15.59	24.63	34.38
6.91	16.49	24.87	36.19
7.59	16.98	25.30	39.13
8.23	17.42	26.34	40.01
8.96	17.74	27.66	41.81
10.67	18.11	29.31	45.49
12.21	19.24	30.57	48.16
13.31	19.90	31.21	
14.28	21.53	32.39	

[0088] According to one aspect, Form B of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 6**. According to another aspect, Form B of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 7**. Accordingly to yet another aspect, Form B of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 8**. According to a further embodiment, Form B of Compound **1** has an infrared spectrum

substantially similar to that depicted in **Figure 9**. According to another embodiment, Form B of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 10**. Form B of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[0089] In certain embodiments, Compound **1** is a dimethylformamide (DMF) solvate crystal form. In some embodiments, the present invention provides a DMF solvate polymorphic form of Compound **1** referred to herein as Form C.

[0090] In certain embodiments, the present invention provides Form C of Compound **1**. According one embodiment, Form C of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 16.32, about 18.82, about 20.26, about 22.58 and about 25.36 degrees 2-theta. In some embodiments, Form C of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 16.32, about 18.82, about 20.26, about 22.58 and about 25.36 degrees 2-theta. In certain embodiments, Form C of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 16.32, about 18.82, about 20.26, about 22.58 and about 25.36 degrees 2-theta. In particular embodiments, Form C of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 8.14, 14.45, 15.37, 16.33, 18.16, 18.82, 20.26, 22.58, 22.96, 24.33, 25.36 and 26.36 degrees 2-theta. In an exemplary embodiment, Form C of compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
4.11	17.03	25.36	34.51
5.95	17.57	26.36	35.25
6.30	18.16	27.02	35.65
7.40	18.37	27.37	36.92
7.80	18.82	27.81	38.42
8.14	19.35	28.44	39.28
9.21	19.72	29.12	39.89
10.09	20.26	29.45	41.64
11.01	20.62	29.80	42.14
11.87	21.02	30.28	44.15
12.57	21.56	30.66	44.54
13.59	22.10	31.24	45.35
14.45	22.58	31.79	46.02
15.37	22.96	32.65	46.44
15.94	23.99	33.04	48.42
16.33	24.33	34.03	49.16
16.67	24.62	34.16	

[0091] According to one aspect, Form C of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 12**. According to another aspect, Form C of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 13**. Accordingly to yet another aspect, Form C of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 14**. According to a further embodiment, Form C of Compound **1** has a infrared spectrum substantially similar to that depicted in **Figure 15**. According to another embodiment, Form C of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 16**. Form C of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[0092] In certain embodiments, Compound **1** is a 1,4-dioxane solvate crystal form. In some embodiments, the present invention provides a 1,4-dioxane solvate polymorphic form of Compound **1** referred to herein as Form D.

[0093] In certain embodiments, the present invention provides Form D of Compound **1**. According one embodiment, Form D of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 18.40, about 19.31, about 20.14, about 20.53 and about 25.25 degrees 2-theta. In some embodiments, Form D of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 18.40, about 19.31, about 20.14, about 20.53 and about 25.25 degrees 2-theta. In certain embodiments, Form D of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 18.40, about 19.31, about 20.14, about 20.53 and about 25.25 degrees 2-theta. In particular embodiments, Form D of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 13.51, 16.97, 17.86, 18.40, 19.31, 20.14, 20.53, 21.04, 22.50, 24.98 and 25.25 degrees 2-theta. In an exemplary embodiment, Form D of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.03	11.36	18.40	25.64
3.30	12.22	18.77	26.35
5.49	13.51	19.31	26.60
6.60	14.61	20.14	26.82
6.86	14.92	20.53	27.21
7.21	15.26	21.04	28.19
7.56	16.15	21.52	28.90
8.93	16.45	22.50	29.86
9.87	16.61	23.80	
10.11	16.97	24.98	
10.68	17.86	25.25	

[0094] According to one aspect, Form D of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 19**. According to another aspect, Form D of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 20A** or **20B**. Accordingly to yet another aspect, Form D of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 21**. According to a further embodiment, Form D of Compound **1** has an infrared spectrum substantially similar to that depicted in **Figure 22**. According to another embodiment, Form D of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 23**. Form D of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[0095] In certain embodiments, Compound **1** is a methyl ethyl ketone (MEK) crystal form. In some embodiments, the present invention provides a MEK solvate polymorphic form of Compound **1** referred to herein as Form E.

[0096] In certain embodiments, the present invention provides Form E of Compound **1**. According one embodiment, Form E of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 5.78, about 12.57, about 15.34, about 19.10 and about 24.80 degrees 2-theta. In some embodiments, Form E of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 5.78, about 12.57, about 15.34, about 19.10 and about 24.80 degrees 2-theta. In certain embodiments, Form E of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 5.78, about 12.57, about 15.34, about 19.10 and about 24.80 degrees 2-theta. In particular embodiments, Form E of Compound **1** is characterized by substantially all of the peaks in its X-ray powder

diffraction pattern selected from those at about 5.78, 12.38, 12.57, 14.14, 15.34, 18.22, 19.10, 20.05, 24.36 and 24.80 degrees 2-theta. In an exemplary embodiment, Form E of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.96	13.92	20.05	29.70
5.78	14.14	20.81	30.13
7.32	15.34	21.04	30.70
8.05	15.66	22.23	32.37
9.06	16.28	23.12	33.06
9.34	16.84	24.36	33.43
10.09	17.56	24.80	34.37
10.66	17.97	26.45	35.75
11.67	18.22	27.20	39.30
12.38	18.84	28.68	41.13
12.57	19.10	29.37	47.08

[0097] According to one aspect, Form E of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 25**. According to another aspect, Form E of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 26**. Accordingly to yet another aspect, Form E of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 27**. According to a further embodiment, Form E of Compound **1** has a infrared spectrum substantially similar to that depicted in **Figure 28**. According to another embodiment, Form E of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 29**. Form E of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[0098] In certain embodiments, Compound **1** is a N-methyl-2-pyrrolidone (NMP) solvate crystal form. It has been found that Compound **1** can exist in at least two distinct NMP crystal forms, or polymorphs. In some embodiments, the present invention provides a NMP solvate polymorphic form of Compound **1** referred to herein as Form F. In other embodiments, the present invention provides a NMP solvate polymorphic form of Compound **1** referred to herein as Form G.

[0099] In certain embodiments, the present invention provides Form F of Compound **1**. According one embodiment, Form F of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 15.51, about 16.86, about 18.80, about 20.97 and about 23.32 degrees 2-theta. In some embodiments, Form F of

Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 15.51, about 16.86, about 18.80, about 20.97 and about 23.32 degrees 2-theta. In certain embodiments, Form F of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 15.51, about 16.86, about 18.80, about 20.97 and about 23.32 degrees 2-theta. In particular embodiments, Form F of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 5.64, 10.32, 12.97, 13.54, 15.51, 16.39, 16.86, 18.80, 19.16, 20.97, 23.32 and 24.55 degrees 2-theta. In an exemplary embodiment, Form F of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.68	16.39	25.71	36.70
3.87	16.86	26.22	37.60
5.10	17.36	26.40	38.68
5.64	18.80	26.64	39.55
5.81	19.16	27.07	40.14
7.34	19.68	27.76	40.87
8.21	20.08	28.98	41.96
9.81	20.97	30.11	44.15
10.32	21.93	30.95	44.69
12.97	22.64	31.16	45.38
13.54	23.32	31.46	48.22
14.12	23.87	34.04	
15.00	24.55	34.56	
15.51	25.25	35.72	

[00100] According to one aspect, Form F of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 32**. According to another aspect, Form F of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 33**. Accordingly to yet another aspect, Form F of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 34**. According to a further embodiment, Form F of Compound **1** has a infrared spectrum substantially similar to that depicted in **Figure 35**. According to another embodiment, Form F of Compound **1** has a dynamic vapour sorption pattern substantially similar to that depicted in **Figure 36**. Form F of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[00101] In certain embodiments, the present invention provides Form G of Compound **1**. According to another embodiment, Form G of Compound **1** is characterized by one or more

peaks in its powder X-ray diffraction pattern selected from those at about 6.79, about 17.86, about 19.43, about 19.98 and about 22.35 degrees 2-theta. In some embodiments, Form G of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 6.79, about 17.86, about 19.43, about 19.98 and about 22.35 degrees 2-theta. In further embodiments, Form G of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 6.79, about 17.86, about 19.43, about 19.98 and about 22.35 degrees 2-theta. In particular embodiments, Form G of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 6.79, 6.89, 16.50, 17.86, 19.43, 19.98, 22.35, 23.77 and 24.06 degrees 2-theta. In an exemplary embodiment, Form G of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.70	19.43	29.18	38.48
4.38	19.98	29.59	39.37
6.79	20.66	30.08	39.94
6.89	21.06	30.43	41.00
8.60	21.56	31.29	41.97
9.85	22.35	32.36	42.64
12.28	23.77	32.68	43.69
13.48	24.06	33.49	44.91
14.52	25.03	34.40	45.35
15.35	26.06	34.82	46.20
16.08	26.22	35.27	47.43
16.50	26.79	36.01	48.53
17.16	27.56	36.40	48.75
17.86	28.07	37.02	49.48
18.67	28.74	38.03	

[00102] According to one aspect, Form G of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 39**. According to another aspect, Form G of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in any of **Figure 40A**, **40B** or **40C**. Accordingly to yet another aspect, Form G of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 41**. According to a further embodiment, Form G of Compound **1** has an infrared spectrum substantially similar to that depicted in **Figure 42**. According to another embodiment, Form G of Compound **1** has a dynamic vapour sorption pattern substantially

similar to that depicted in **Figure 43**. Form G of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[00103] In certain embodiments, Compound **1** is a hydrated crystal form. It has been found that Compound **1** can exist in at least two distinct hydrated crystal forms, or polymorphs. In some embodiments, the present invention provides a hydrated polymorphic form of Compound **1** referred to herein as Form H. In some embodiments, the present invention provides a hydrated polymorphic form of Compound **1** referred to herein as Form I.

[00104] In certain embodiments, the present invention provides Form H of Compound **1**. According one embodiment, Form H of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 10.82, about 11.08, about 18.45, about 22.85 and about 25.06 degrees 2-theta. In some embodiments, Form H of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 10.82, about 11.08, about 18.45, about 22.85 and about 25.06 degrees 2-theta. In certain embodiments, Form H of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 10.82, about 11.08, about 18.45, about 22.85 and about 25.06 degrees 2-theta. In particular embodiments, Form H of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about 10.14, 10.82, 11.08, 18.45, 22.85, 24.33, 25.06 and 26.54 degrees 2-theta. In an exemplary embodiment, Form H of Compound **1** is characterized by substantially all of the peaks in its X-ray powder diffraction pattern selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
3.56	11.92	19.16	26.02
5.34	13.60	20.02	26.54
6.42	14.22	20.42	27.36
8.57	15.50	21.56	27.45
8.82	16.28	22.85	27.79
9.79	16.55	23.31	28.31
10.14	17.25	24.33	29.15
10.82	18.07	25.06	29.45
11.08	18.45	25.91	

[00105] According to one aspect, Form H of Compound **1** has a powder X-ray diffraction pattern substantially similar to that depicted in **Figure 46**. According to another aspect, Form H of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 47**. Accordingly to yet another aspect, Form H of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 49**. In some embodiments, Form H of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 50** or **Figure 51**. Form H of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[00106] In certain embodiments, the present invention provides Form I of Compound **1**. According to one embodiment, Form I of Compound **1** is characterized by one or more peaks in its powder X-ray diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta. In some embodiments, Form I of Compound **1** is characterized by two or more peaks in its powder X-ray diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta. In some embodiments, Form I of Compound **1** is characterized by three or more peaks in its powder X-ray diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta. In some embodiments, Form I of Compound **1** is characterized by four or more peaks in its powder X-ray diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta. In some embodiments, Form I of Compound **1** is characterized by substantially all of the peaks in its powder X-ray diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta. In some embodiments, Form I of Compound **1** is characterized by substantially all of the peaks selected from those at about:

°2-Theta	°2-Theta	°2-Theta	°2-Theta
5.39	14.56	20.36	25.78
6.13	15.08	21.16	27.95
7.65	15.31	21.90	28.92
9.33	15.91	22.64	29.47
10.18	16.47	23.26	
12.22	18.35	23.75	
12.72	18.88	24.55	
12.98	19.65	24.95	

[00107] According to one aspect, Form I of Compound **1** has a X-ray powder diffraction pattern substantially similar to that depicted in **Figure 52**. In some embodiments, Form I of Compound **1** has an infrared spectrum substantially similar to that depicted in **Figure 53**. In some embodiments, Form I of Compound **1** has a ^{1}H NMR spectrum substantially similar to that depicted in **Figure 54**. According to another aspect, Form I of Compound **1** has a thermogravimetric analysis pattern substantially similar to that depicted in **Figure 55** or **Figure 56**. Accordingly to yet another aspect, Form I of Compound **1** has a differential scanning calorimetry pattern substantially similar to that depicted in **Figure 57**. In some embodiments, Form I of Compound **1** has an dynamic vapour sorption substantially similar to that depicted in **Figure 58**. Form I of Compound **1** can be characterized by substantial similarity to two or more of these figures simultaneously.

[00108] It will be appreciated that any of the above-described polymorph forms can be characterized, for example, by reference to any of the peaks in their respective X-ray diffraction patterns. Accordingly, in some embodiments, a polymorph described herein is characterized by one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty or more XRPD peaks (°2Θ). According to another embodiment, the present invention provides compound **1** as an amorphous solid. Amorphous solids are well known to one of ordinary skill in the art and are typically prepared by such methods as lyophilization, melting, and precipitation from supercritical fluid, among others.

General Methods of Providing Compound 1:

[00109] Compound **1** is prepared according to the methods described in detail in the '061 application, the entirety of which is hereby incorporated herein by reference. The various solid forms of Compound **1** can be prepared by dissolving compound **1** in various suitable solvents and then causing Compound **1** to return to the solid phase. Specific combinations of solvents and conditions under which Compound **1** return to the solid phase are discussed in greater detail in the Examples.

[00110] A suitable solvent may solubilize Compound **1**, either partially or completely. Examples of suitable solvents useful in the present invention are a protic solvent, a polar aprotic solvent, or mixtures thereof. In certain embodiments, suitable solvents include an ether, an ester, an alcohol, a ketone, or a mixture thereof. In certain embodiments, the suitable solvent is methanol, ethanol, isopropanol, or acetone wherein said solvent is

anhydrous or in combination with water, methyl tert-butyl ether (MTBE) or heptane. In other embodiments, suitable solvents include tetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylsulfoxide, glyme, diglyme, methyl ethyl ketone, N-methyl-2-pyrrolidone, methyl t-butyl ether, t-butanol, n-butanol, and acetonitrile. In another embodiment, the suitable solvent is anhydrous ethanol. In some embodiments, the suitable solvent is MTBE.

[00111] According to another embodiment, the present invention provides a method for preparing a solid form of Compound **1**, comprising the steps of dissolving Compound **1** with a suitable solvent and optionally heating to form a solution thereof; and isolating Compound **1**.

[00112] As described generally above, Compound **1** is dissolved in a suitable solvent, optionally with heating. In certain embodiments Compound **1** is dissolved at about 50 to about 60 °C. In other embodiments, Compound **1** is dissolved at about 50 to about 55 °C. In still other embodiments, Compound **1** is dissolved at the boiling temperature of the solvent. In other embodiments, Compound **1** is dissolved without heating (e.g., at ambient temperature, approximately 20-25 °C).

[00113] In certain embodiments, Compound **1** precipitates from the mixture. In another embodiment, Compound **1** crystallizes from the mixture. In other embodiments, Compound **1** crystallizes from solution following seeding of the solution (i.e., adding crystals of Compound **1** to the solution).

[00114] Crystalline Compound **1** can precipitate out of the reaction mixture, or be generated by removal of part or all of the solvent through methods such as evaporation, distillation, filtration (e.g., nanofiltration, ultrafiltration), reverse osmosis, absorption and reaction, by adding an anti-solvent (e.g., water, MTBE and/or heptane), by cooling (e.g., crash cooling) or by different combinations of these methods.

[00115] As described generally above, Compound **1** is optionally isolated. It will be appreciated that Compound **1** may be isolated by any suitable physical means known to one of ordinary skill in the art. In certain embodiments, precipitated solid Compound **1** is separated from the supernatant by filtration. In other embodiments, precipitated solid Compound **1** is separated from the supernatant by decanting the supernatant.

[00116] In certain embodiments, precipitated solid Compound **1** is separated from the supernatant by filtration.

[00117] In certain embodiments, isolated Compound **1** is dried in air. In other embodiments isolated Compound **1** is dried under reduced pressure, optionally at elevated temperature.

Uses, Formulation and Administration

Pharmaceutically Acceptable Compositions

[00118] According to another embodiment, the invention provides a composition comprising Compound **1** and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of Compound **1** in compositions of this invention is such that it is effective to measurably inhibit a protein kinase, particularly an EGFR kinase, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00119] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00120] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, Vitamin E polyethylene glycol succinate (d-alpha tocopheryl polyethylene glycol 1000 succinate), sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat.

[00121] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions

are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be an aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00122] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00123] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous and non-aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is typically combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00124] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00125] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00126] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00127] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of Compound **1** include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00128] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00129] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00130] In some embodiments, pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[00131] The amount of Compound **1** that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the

particular mode of administration. In certain embodiments, provided compositions are formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of Compound **1** can be administered to a patient receiving these compositions.

[00132] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00133] Compound **1** and compositions described herein are generally useful for the inhibition of protein kinase activity of one or more enzymes. Examples of kinases that are inhibited by Compound **1** and compositions described herein and against which the methods described herein are useful include EGFR kinase or a mutant thereof. It has been found that Compound **1** is a selective inhibitor of at least one mutation of EGFR, as compared to wild-type ("WT") EGFR. In certain embodiments, an at least one mutation of EGFR is T790M. In certain embodiments, the at least one mutation of EGFR is a deletion mutation. In some embodiments, the at least one mutation of EGFR is an activating mutation. In certain embodiments, Compound **1** selectively inhibits at least one resistant mutation and at least one activating mutation as compared to WT EGFR. In some embodiments, Compound **1** selectively inhibits at least one deletion mutation and/or at least one point mutation, and is sparing as to WT EGFR inhibition.

[00134] A mutation of EGFR can be selected from T790M (resistant or oncogenic), L858R (activating), delE746-A750 (activating), G719S (activating), or a combination thereof.

[00135] As used herein, the term "selectively inhibits," as used in comparison to inhibition of WT EGFR, means that Compound **1** inhibits at least one mutation of EGFR (i.e., at least one deletion mutation, at least one activating mutation, at least one restistant mutation, or a combination of at least one deletion mutation and at least one point mutation) in at least one assay described herein (e.g., biochemical or cellular). In some embodiments, the term "selectively inhibits," as used in comparison to WT EGFR inhibition means that Compound **1** is at least 50 times more potent, at least 45 times, at least 40, at least 35, at least 30, at least

25, or at least 20 times more potent as an inhibitor of at least one mutation of EGFR, as defined and described herein, as compared to WT EGFR.

[00136] As used herein, the term "sparing as to WT EGFR" means that a selective inhibitor of at least one mutation of EGFR, as defined and described above and herein, inhibits EGFR at the upper limit of detection of at least one assay, such as those described in the '061 application (e.g., biochemical or cellular as described in detail in Examples 56-58). *In vitro* assays include assays that determine inhibition of the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of activated EGFR (WT or mutant). Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to EGFR (WT or mutant). Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/EGFR (WT or mutant) complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with EGFR (WT or mutant) bound to known radioligands. In some embodiments, the term "sparing as to WT EGFR" means that Compound **1** inhibits WT EGFR with an IC_{50} of at least 10 μM, at least 9 μM, at least 8 μM, at least 7 μM, at least 6 μM, at least 5 μM, at least 3 μM, at least 2 μM, or at least 1 μM.

[00137] In certain embodiments, Compound **1** selectively inhibits (a) at least one activating mutation; and (b) T790M; and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[00138] In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

[00139] Without wishing to be bound by any particular theory, it is believed that administration of Compound **1** to a patient having at least one activating mutation may preempt formation of the T790M resistance mutation. Thus, in certain embodiments, the present invention provides a method for inhibiting an activating mutation in a patient comprising administering to the patient Compound **1** or composition thereof, as described herein.

[00140] One of ordinary skill in the art will appreciate that certain patients have an oncogenic form of the T790M mutation, i.e., the T790M mutation is present prior to

administrating any EGFR kinase inhibitor to a patient and is therefore oncogenic. Accordingly, in some embodiments, the present invention provides a method for inhibiting oncogenic T790M in a patient comprising administering to the patient a provided compound or composition thereof, as described herein.

[00141] In certain embodiments, the amount of Compound **1** in a composition is effective to measurably inhibit at least one mutant of EGFR selectively as compared to WT EGFR and other protein kinases (e.g., ErbB2, ErbB4, a TEC-kinase, and/or JAK3), in a biological sample or in a patient.

[00142] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00143] Compound **1** is an inhibitor of at least one mutant of EGFR and is therefore useful for treating one or more disorders associated with activity of one of more EGFR mutants (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof). Thus, in certain embodiments, the present invention provides a method for treating a mutant EGFR-mediated disorder comprising the step of administering to a patient in need thereof Compound **1**, or pharmaceutically acceptable composition thereof.

[00144] As used herein, the term "mutant EGFR-mediated" disorders or conditions as used herein means any disease or other deleterious condition in which at least one mutant of EGFR is known to play a role. In certain embodiments, an at least one mutant of EGFR is T790M. In some embodiments, the at least one mutant of EGFR is a deletion mutation. In certain embodiments, the at least one mutant of EGFR is an activating mutation. In some embodiments, the at least one mutant of EGFR is L858R and/or T790M. In certain embodiments, Compound **1** selectively inhibits (a) at least one activating mutation, (b) T790M, and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some

embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[00145] Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which at least one mutant of EGFR is known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from a proliferative disorder, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

[00146] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from a cancer. In some embodiments, the cancer is associated with a solid tumor. In certain embodiments, the cancer is breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, or non-small cell lung cancer. In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, or pancreatic cancer.

[00147] In certain embodiments, the present invention provides a method for treating or lessening the severity of neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms (e.g. MPNST's), or Schwannomas.

[00148] Compound **1** and compositions thereof, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compound **1** is preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration,

and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[00149] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, Compound **1** may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 0.5 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00150] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to Compound **1**, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, polyethylene glycol (e.g., PEG 200, PEG 400, PEG 1000, PEG 2000), propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, Vitamin E polyethylene glycol succinate (d-alpha tocopheryl polyethylene glycol 1000 succinate), polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. The liquid forms above can also be filled into a soft or hard capsule to form a solid dosage form. Suitable capsules can be formed from, for example, gelatin, strach and cellulose derivatives (e.g., hydroxycellulose, hydropropylmethylcellulose).

[00151] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or

suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00152] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00153] In order to prolong the effect of Compound **1** of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00154] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing Compound **1** of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00155] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, Compound **1** is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption

accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00156] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00157] Compound **1** can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00158] Dosage forms for topical or transdermal administration of Compound **1** include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation,

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

[00159] According to another embodiment, the invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutations, or combination thereof) activity in a biological sample comprising the step of contacting said biological sample with Compound **1**, or a composition comprising the compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) activity in a biological sample comprising the step of contacting the biological sample with Compound **1**, or a composition comprising the compound.

[00160] In certain embodiments, Compound **1** selectively inhibits in a biological sample (a) at least one activating mutation, (b) T790M, and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[00161] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00162] Inhibition of at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ transplantation, biological specimen storage, and biological assays.

[00163] Another embodiment of the present invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) activity in a patient comprising the step of administering to

the patient Compound **1** or a composition comprising the compound. In certain embodiments, the present invention provides a method for inhibiting (a) at least one activating mutation, and (b) T790M in a patient, and (c) is sparing as to WT, wherein the method comprises administering to the patient Compound **1** or composition thereof. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is delE746-A750. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is L858R. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is G719S.

[00164] According to another embodiment, the invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) activity in a patient comprising the step of administering to the patient Compound **1** or a composition comprising the compound. According to certain embodiments, the invention relates to a method of irreversibly inhibiting at least one mutant of EGFR activity (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) in a patient comprising the step of administering to said patient Compound **1** or a composition comprising the compound. In certain embodiments, the present invention provides a method for irreversibly inhibiting (a) at least one activating mutation, and (b) T790M in a patient, and (c) is sparing as to WT, wherein said method comprises administering to the patient Compound **1** or composition thereof. In some embodiments, an irreversibly inhibited at least one activating mutation is a deletion mutation. In some embodiments, an irreversibly inhibited at least one activating mutation is a point mutation. In some embodiments, the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is delE746-A750. In some embodiments, the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is L858R. In some embodiments, the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is G719S.

[00165] In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) in a patient in need thereof, comprising the step of administering to said patient Compound **1** or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00166] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may also be present in the compositions of this invention or as part of a treatment regimen including Compound **1**. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease or condition being treated."

[00167] For example, Compound **1** or a pharmaceutically acceptable composition thereof is administered in combination with chemotherapeutic agents to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane (e.g., paclitaxel), vinca alkaloids (e.g., vinblastine), anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), cisplatin, an mTOR inhibitor (e.g., a rapamycin), methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents (e.g., chlorambucil), 5-fluorouracil, campthothecin, cisplatin, metronidazole, and Gleevec™, among others. In other embodiments, Compound **1** is administered in combination with a biologic agent, such as Avastin or VECTIBIX.

[00168] In certain embodiments, Compound **1** or a pharmaceutically acceptable composition thereof is administered in combination with an antiproliferative or chemotherapeutic agent selected from any one or more of abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate,

histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, or zoledronic acid.

[00169] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as donepezil hydrochloride (Aricept®) and rivastigmine (Exelon®); treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), glatiramer acetate (Copaxone®), and mitoxantrone; treatments for asthma such as albuterol and montelukast (Singulair®); agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00170] In certain embodiments, Compound 1 or a pharmaceutically acceptable composition thereof is administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00171] The additional agents may be administered separately from a Compound **1**-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with Compound **1** in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another (e.g., one hour, two hours, six hours, twelve hours, one day, one week, two weeks, one month).

[00172] As used herein, the terms "combination," "combined," and related terms refer to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, Compound **1** may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising Compound **1**, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00173] The amount of Compound **1** and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of Compound **1** can be administered.

[00174] In those compositions that include an additional therapeutic agent, that additional therapeutic agent and Compound **1** may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions may be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions, a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00175] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range *from about 50% to 100% of the amount normally present in a composition comprising that* agent as the only therapeutically active agent.

[00176] Compound **1** or pharmaceutical compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial

valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with Compound **1** are another embodiment of the present invention.

[00177] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

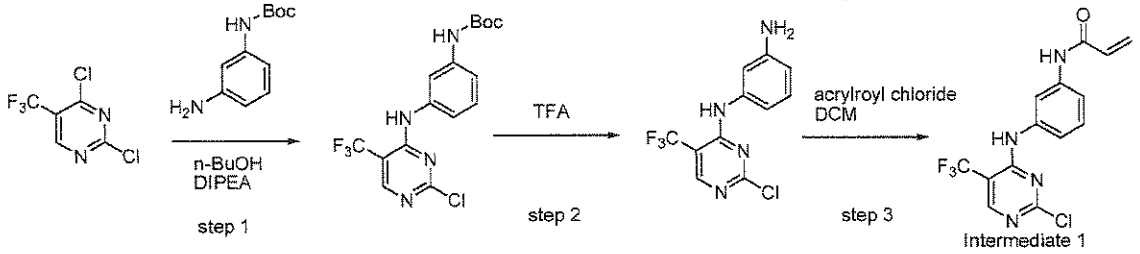
[00178] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXEMPLIFICATION

[00179] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

Preparation of Compound 1

[00180] The synthesis of Compound **1** is described in detail at Example 3 of the '061 application.



Step 1:

[00181] In a 25 mL 3-neck round-bottom flask previously equipped with a magnetic stirrer, Thermo pocket and $CaCl_2$ guard tube, N-Boc-1,3-diaminobenzene (0.96 g) and n-butanol (9.00 mL) were charged. The reaction mixture was cooled to 0 °C. 2,4-Dichloro-5-trifluoromethylpyrimidine (1.0 g) was added dropwise to the above reaction mixture at 0 °C. Diisopropylethylamine (DIPEA) (0.96 mL) was dropwise added to the above reaction

mixture at 0 °C and the reaction mixture was stirred for 1 hr at 0 °C to 5 °C. Finally, the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for another 4 hrs at room temperature. Completion of reaction was monitored by TLC using hexane: ethyl acetate (7: 3). The solid precipitated out was filtered off and washed with 1-butanol (2 mL). The solid was dried under reduced pressure at 40 °C for 1 hr. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.48 (S, 9 H), 7.02 (m, 1 H), 7.26 (m, 2 H), 7.58 (S, 1 H), 8.57 (S, 1 H), 9.48 (S, 1 H), 9.55 (S, 1 H).

Step 2:

[00182] To the above crude (3.1 g) in dichloromethane (DCM) (25 mL) was added trifluoroacetic acid (TFA) (12.4 mL) slowly at 0 °C. The reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for another 10 min at room temperature. The crude was concentrated under reduced pressure.

Step 3:

[00183] The concentrated crude was dissolved in DIPEA (2.0 mL) and dichloromethane (25 mL), and then cooled to -30 °C. To the reaction mixture was slowly added acryloyl chloride (0.76 g) at -30 °C. The reaction mass was warmed to room temperature stirred at room temperature for 1.0 hr. The reaction was monitored on TLC using hexane: ethyl acetate (7:3) as mobile phase. The reaction was completed after 1 hr. Step 3 yielded intermediate 1.

Step 4:

[00184] To obtain a salt of compound **1**, a mixture of intermediate 1 (16 mg) and 2-methoxy-4-(4-acetylpiperazinyl)aniline in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give compound **1** as a TFA salt. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 10.2 (S, 1 H), 8.2 (br, 1 H), 8.30 (S, 1 H), 7.73 (br, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.26 (J = 8.2 Hz, 1 H), 7.14 (be, 1 H), 6.60 (S, 1 H), 6.42 (dd, J = 11.4, 16.9 Hz, 1 H), 6.24 (d, J = 16.9 Hz, 1 H), 5.75 (d, J = 11.4 Hz, 1 H), 3.76 (S, 3 H), 3.04 (br, 4 H), 2.04 (S, 3 H); calculated mass for $C_{27}H_{28}F_3N_7O_3$: 555.2, found: 556.2 ($M+H^+$).

Step 5:

[00185] To obtain the free base form of Compound **1** from the TFA salt, the salt was added to DCM and cooled to 0 °C. Na_2CO_3 solution (9.6% w/w) was added at 0 °C. The mixture was warmed to 20 °C and stirred for 35 min. The pH of the aqueous layer was > 8. The layers were separated. Extraction of the aqueous layer was performed using DCM. The

organic layers were combined and washed with brine. The organic layer was collected and evaporated to yield a solid of Compound **1**.

General Procedures

[00186] X-ray powder diffraction (XRPD) analysis was carried out on a Siemens D5000, scanning the samples between 3 and 30 or 50°2-theta. For samples <100 mg, *ca.* 5-10 mg of sample was gently compressed onto a glass slide which fitted into the sample holder. For samples >100 mg, *ca.* 100 mg of sample was gently compressed into a plastic sample holder, so that the sample surface was smooth and just above the level of the sample holder. Measurements were made as follows:

step size	0.02 °2-theta
scan step time	1 s
offset	0 °2-theta
divergence slit type	fixed
divergence slit size	2.0000 °
receiving slit size	0.2 mm
temperature	20° C
anode material	copper
K-Alpha1	1.54060 Angstroms
K-Alpha2	1.54443 Angstroms
K-Beta	1.39225 Angstroms
K-A2/K-A1 Ratio	0.50000
Geneator settings	40 mA, 40 kV
goniometer radius	217.50

[00187] In polarized light microscopy (PLM), the presence of crystallinity (birefringence) was determined using an Olympus BX50 polarising microscope, equipped with a Motic camera and image capture software (Motic Images Plus 2.0). All images were recorded using the 20x objective, unless otherwise stated.

[00188] For thermogravimetric analysis (TGA), approximately 5-10 mg of material was accurately weighed into an open aluminium pan and loaded into a simultaneous thermogravimetric/differential thermal analyser (TG/DTA) and held at room temperature. The sample was then heated at a rate of 10 °C/min from 25 °C to 300 °C during which time

the change in sample weight was recorded along with any differential thermal events (DTA). Nitrogen was used as the purge gas, at a flow rate of 100 cm^3/min.

[00189] For differential scanning calorimetry (DSC), approximately 5-10 mg of material was weighed into an aluminium DSC pan and sealed non-hermetically with a pierced aluminium lid. The sample pan was then loaded into a Seiko DSC6200 (equipped with a cooler) cooled and held at 25 °C. Once a stable heat-flow response was obtained, the sample and reference were heated to *ca.* 260 °C at scan rate of 10 °C/min and the resulting heat flow response monitored.

[00190] ^{1}H-NMR experiments were performed on a Bruker AV400 (^{1}H frequency: 400 MHz). ^{1}H experiments of each sample were performed in deuterated DMSO and each sample was prepared to *ca.* 10 mg concentration.

[00191] For dynamic vapour sorption (DVS), approximately 10 mg of sample was placed into a wire mesh vapour sorption balance pan and loaded into a DVS-1 dynamic vapour sorption balance by Surface Measurement Systems. The sample was subjected to a ramping profile from 20 – 90 % relative humidity (RH) at 10 % increments, maintaining the sample at each step until a stable weight had been achieved (99.5 % step completion). After completion of the sorption cycle, the sample was dried using the same procedure, but all the way down to 0 % RH and finally taken back to the starting point of 20 % RH. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined.

[00192] Infrared spectroscopy (IR) was carried out on a Bruker ALPHA P spectrometer. Sufficient material was placed onto the centre of the plate of the spectrometer and the spectra were obtained using the following parameters: resolution – 4 cm^{-1}, background scan time – 16 scans, sample scan time – 16 scans, data collection 4000 to 400 cm^{-1}, result spectrum – transmittance.

[00193] For Karl Fischer (KF) Coulometric titration, 10-15 mg of solid material was accurately weighed into a vial. The solid was then manually introduced into the titration cell of a Mettler Toledo C30 Compact Titrator. The vial was back-weighed after the addition of the solid and the weight of the added solid entered on the instrument. Titration was initiated once the sample had fully dissolved in the cell. The water content was calculated automatically by the instrument as a percentage and the data printed.

[00194] Reverse-phase gradient high performance liquid chromatography (HPLC) was performed on an Agilent 1100 instrument fitted with a C18, 3.0 x 100 mm x 3.5 μm column. The detection wavelength was 240 nm.

[00195] A Sotax AT7 dissolution bath (USP 2, EP 2 apparatus) was used for the dissolution study in which paddles were used to stir the media. All tests were carried out at 37°C and a paddle speed of 100 rpm.

[00196] Samples of each form were exposed to an environment of 40 °C/75%RH for 1 week and 2 week periods to determine stability. Resulting solids were analysed by XRPD and HPLC to establish if any changes had occurred.

[00197] Slurries of all each polymorphic form were created in deionised water and shaken for *ca.* 24 hours. The resulting solid was then analysed by HPLC to determine the concentration of material dissolved.

Example 1

Preparation of Form A

[00198] *ca.* 120 mg of Compound **1** was weighed into a vial and slurried in *ca.* 2 ml of acetonitrile. This was temperature cycled between *ca.* 0°C and ambient (*ca.* 22°C) whilst stirring in 2 hour cycles for a period of 2-3 days. Overnight, the sample was kept at *ca.* 2-5°C. Solid material was isolated and left to dry under vacuum for 7 days.

[00199] XRPD analysis (**Figure 1**) showed the material to be crystalline. PLM analysis (not shown) indicated very fine, birefringent needle-like crystals. TGA/DTA (**Figure 2**) showed a 0.4% weight loss from the outset to *ca.* 150 °C likely due to unbound solvent. No significant weight losses seen prior to degradation. DSC analysis (**Figure 3**) showed a single endotherm at onset *ca.* 203.2 °C (peak 207.5 °C) due to the melt. IR analysis (**Figure 4**) corresponds with the input freebase material. ^{1}H NMR (not shown) carried out in deuterated DMSO showed a spectrum which corresponded with the input freebase. Acetonitrile does not appear to be present. DVS analysis (**Figure 5**) showed a water uptake of 0.87% between 20 and 70% RH, indicating a non-hygroscopic material. Post DVS XRPD indicated that the material remained Form A (data not shown). No polymorphic form changes were evident. Some loss in crystallinity was observed. KF analysis did not detect the presence of water. HPLC purity analysis indicated a purity of *ca.* 97.6%. Form A could not be detected by HPLC analysis for the aqueous solubility. The aqueous solubility is therefore poor.

[00200] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material to still be consistent with Form A, with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 97.5%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material to still be consistent with Form A, however, it became poorly crystalline. HPLC analysis indicated a purity of *ca.* 96.3%.

Example 2

Preparation of Form B

[00201] *ca.* 120 mg of Compound **1** was weighed into a vial and slurried in *ca.* 2 ml tetrahydrofuran. This was temperature cycled between *ca.* 0 °C and ambient (*ca.* 22 °C) whilst stirring in 2 hour cycles for a period of 2-3 days. Overnight, the sample was kept at *ca.* 2-5 °C. Solid material was isolated and left to dry under vacuum at ambient for 7 days and at 40 °C for a further 2 days.

[00202] XRPD analysis (**Figure 6**) showed the material produced to be crystalline. PLM analysis (not shown) indicated birefringent, rod-like crystals. TGA/DTA (**Figure 7**) showed no significant weight losses prior to degradation after drying for 7 days at ambient under vacuum, and a further 2 days at 40 °C. DSC analysis (**Figure 8**) showed an endotherm at onset 153.6 °C (peak 157.6°) directly followed by an exotherm at peak 161.3 °C indicating a polymorphic transition. A further small endotherm is present at peak 186.0 °C, followed by a final endotherm at onset 203.9 °C (peak 207.9 °C) which appears to correspond with the Form A melt. IR analysis (**Figure 9**) showed a significant number of differences and shifts in comparison to Form A. ^{1}H NMR (not shown) carried out in deuterated DMSO showed a spectrum which corresponded with the input freebase. Traces of THF appear to be present. DVS analysis (**Figure 10**) showed a water uptake of 0.74% between 20 and 70% RH, indicating a non-hygroscopic material. Post DVS XRPD (not shown) indicated that the material remained Form B. No polymorphic form changes were evident. KF (not shown) analysis indicated the presence of *ca.* 0.97% water. HPLC purity analysis indicated a purity of *ca.* 97.0%. Form B could not be detected by HPLC analysis for the aqueous solubility. The aqueous solubility is therefore poor.

[00203] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material to be predominantly amorphous. HPLC analysis indicated a purity of *ca.* 96.8%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material to be predominantly amorphous. HPLC analysis indicated a purity of *ca.* 95.9%.

[00204] In order to determine the relationship between Forms A and B, a sample of Form B was heated to 120 °C and then XRPD analysis was carried out. The XRPD showed a mixture of Form B and Form A, indicating that as Form B is heated, it starts to convert to Form A. Form B was also heated to 160 °C (temperature above phase transition seen in DSC) and then XRPD analysis was carried out which indicated that the material converted predominantly to Form A at this temperature. The comparative XRPD results are shown in **Figure 11**.

Example 3

Preparation of Form C

[00205] *ca.* 120 mg of Compound **1** was weighed into a vial and slurried in *ca.* 100 µl of DMF. This was temperature cycled between *ca.* 0 °C and ambient (*ca.* 22 °C) whilst stirring in 2 hour cycles. After *ca.* 2 hours, a further 300µl of DMF was added. The temperature cycling was continued for a period of 2-3 days. Overnight, the sample was kept at *ca.* 2-5 °C. Solid material was isolated and left to dry under vacuum at ambient for 7 days and at 40 °C for a further 2 days.

[00206] XRPD analysis (**Figure 12**) showed the material to be crystalline. PLM analysis (not shown) indicated birefringent, rod-like crystals. TGA/DTA (**Figure 13**) showed a weight loss of *ca.* 8.2%. (11.6 wt% DMF required for a mono solvate) after drying for 7 days at ambient under vacuum and a further 2 days at 40 °C. DSC analysis (**Figure 14**) showed a broad endotherm between 85-125 °C, corresponding with the weight loss in the TGA. A final endotherm is seen at onset *ca.* 204.4 °C (peak 208.3 °C) corresponding with the Form A melt. IR analysis (**Figure 15**) showed some differences and shifts in comparison with Form A. ^{1}H NMR (not shown) carried out in deuterated DMSO showed a spectrum which corresponds with the input freebase with some DMF present (*ca.* 3:1 API: DMF). DVS analysis (**Figure 16**) corresponded with the TGA data where the material is seen to contain solvent, which is lost as the relative humidity is increased. Post DVS XRPD (not shown) indicated that the material converted to Form A during DVS analysis. KF analysis (not shown) indicated the presence of *ca.* 0.01% water. HPLC purity analysis indicated a purity of *ca.* 97.3%. Form C could not be detected by HPLC analysis for the aqueous solubility. The solubility is therefore poor.

[00207] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material converted to Form A with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 97.1%. XRPD analysis after 2 week storage (open container) at 40°C/75%RH showed the material to be poorly crystalline with the peaks present corresponding with Form A. HPLC analysis indicated a purity of *ca.* 96.8%. The comparative XRPD results are shown in **Figure 17**.

[00208] To determine whether Form C remains the same after losing the solvent present, a sample of Form C was heated to 120°C (*i.e.*, just past the temperature at which the solvent is removed) and then XRPD analysis was carried out. The XRPD showed that the material had converted to Form A. Similarly, after drying at ambient temperature under vacuum for 7 days and then for a further 2 days at 40 °C, Form C showed some loss in crystallinity and converted to Form A. The comparative XRPD results are shown in **Figure 18**.

Example 4

Preparation of Form D

[00209] *ca.* 120 mg of Compound **1** was weighed into a vial and slurried in *ca.* 2 ml of 1,4-dioxane. This was temperature cycled between *ca.* 0 °C and ambient (*ca.* 22 °C) whilst stirring in 2 hour cycles for a period of 2-3 days. Overnight, the sample was kept at *ca.* 2-5 °C. Solid material was isolated and left to dry under vacuum at ambient for 7 days and at 40 °C for a further 2 days.

[00210] XRPD analysis showed that the preparation of Form D provided above resulted in a mixture of Form B and Form D (**Figure 19**). PLM analysis indicated birefringent, rod-like crystals (not shown). TGA/DTA (**Figure 20A**) showed a weight loss of *ca.* 5.5% between 60-100 °C after drying for 7 days at ambient under vacuum. After drying for 7 days at ambient under vacuum, and a further 2 days at 40°C, the TGA (**Figure 20B**) showed a weight loss of *ca.* 1.4% between 100-150 °C. DSC analysis after 40°C drying (**Figure 21**) showed a very small exotherm at *ca.* 146 °C. A final endotherm was then seen at onset *ca.* 202.6 °C (peak 207.4 °C) corresponding with the Form A melt. IR analysis (**Figure 22**) corresponded with the spectrum of Form B, with small 1,4-dioxane peaks present. ^{1}H-NMR (not shown) carried out in deuterated DMSO after 7 days of drying at ambient temperature under vacuum showed a spectrum which corresponds with the input free base with some 1,4-dioxane present (*ca.* 2:1 API: 1,4-Dioxane). DVS analysis (**Figure 23**) corresponded with the TGA data

where the material is seen to contain solvent which is lost as the relative humidity is increased. Post DVS XRPD (not shown) indicated that the material converted completely to Form B during DVS analysis. KF analysis (not shown) indicated the presence of *ca.* 1.1% water. HPLC purity analysis indicated a purity of *ca.* 96.6%. Form D could not be detected by HPLC analysis for the aqueous solubility. The solubility is therefore extremely poor.

[00211] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material converted completely to Form B with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 96.5%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material to be poorly crystalline with the peaks present corresponding with Form B. HPLC analysis indicated a purity of *ca.* 95.5%. The comparative XRPD results are shown in **Figure 24**.

Example 5

Preparation of Form E

[00212] *ca.* 120 mg of Compound **1** was weighed into a vial and *ca.* 12 ml of MEK was then added in attempts to dissolve the material. A very thin slurry resulted and this was then filtered to obtain a saturated solution. The solution was placed at *ca.* -18°C for crash cooling for 2-3 days. Solid material was isolated and left to dry under vacuum at ambient for 7 days and at 40°C for a further 2 days.

[00213] XRPD analysis (**Figure 25**) showed the material to be crystalline. PLM analysis (not shown) indicated birefringent, thin, rod-like crystals. TGA/DTA (**Figure 26**) showed a weight loss of *ca.* 5.2% between *ca.* 70-110 °C after drying for 7 days at ambient under vacuum. DSC analysis (**Figure 27**) showed a broad endotherm between 70-110 °C, corresponding with the weight loss in the TGA. A final endotherm is seen at onset *ca.* 198.4° C (peak 203.3 °C). IR analysis (**Figure 28**) showed some small shifts in comparison with Form A. ^{1}H-NMR (not shown) carried out in deuterated DMSO after 7 days of drying at ambient under vacuum showed a spectrum which corresponds with the input free base with a non-stoichiometric amount of MEK present. DVS analysis (**Figure 29**) showed a water uptake of 0.25% between 20 and 70% RH. Post DVS XRPD (not shown) indicated that the material converted to Form A during DVS analysis. KF analysis (not shown) indicated the presence of *ca.* 1.2% water. HPLC purity analysis indicated a purity of *ca.* 97.8%. Form E could not be detected by HPLC analysis for the aqueous solubility. The solubility is therefore extremely poor.

[00214] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material to be predominantly amorphous with visible peaks present corresponding with Form A. HPLC analysis indicated a purity of *ca.* 97.7%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material to be predominantly amorphous with visible peaks present corresponding with Form A. HPLC analysis indicated a purity of *ca.* 97.3%. The comparative XRPD results are shown in **Figure 30**.

[00215] In order to determine whether Form E remains the same after losing the solvent present, a sample of Form E was heated to 120 °C (*i.e.*, just past the temperature at which the solvent is lost) and then XRPD analysis was carried out. The XRPD showed that the material had converted to Form A. Similarly, after drying at ambient under vacuum for 7 days and then for a further 2 days at 40 °C, Form E lost some crystallinity and converted to Form A. The comparative XRPD results are shown in **Figure 31**.

Example 6

Preparation of Form F

[00216] *ca.* 120 mg of Compound **1** was weighed into a vial and *ca.* 200µl of NMP was then added in order to dissolve the material. Anti-solvent addition was then carried out by adding a total of *ca.* 4.5ml of TBME in 500 µl aliquots to obtain a cloudy solution. The sample was then allowed to stand for *ca.* 2 hours before the solid was isolated. The solid material was then left to dry under vacuum at ambient for 7 days and at 40 °C for a further 2 days.

[00217] XRPD analysis (**Figure 32**) showed the material to be crystalline. PLM analysis (not shown) indicated birefringent, very thin, plate-like crystals which appear to grow in clusters. TGA/DTA (**Figure 33**) showed a weight loss of *ca.* 10.2% between 70-120 °C (15.1 wt% NMP required for a mono solvate) after drying for 7 days at ambient temperature under vacuum. DSC analysis (**Figure 34**) showed an endotherm at onset 97 °C (peak 100.9 °C) corresponding with the weight loss in the TGA. A final endotherm is seen at onset *ca.* 204.2 °C (peak 208.3 °C) corresponding with the Form A melt. IR analysis (**Figure 35**) showed some small shifts in comparison with Form A. ^{1}H-NMR (not shown) carried out in deuterated DMSO after 7 days of drying at ambient under vacuum showed a spectrum which corresponds with the input free base with a non-stoichiometric amount of NMP present. DVS analysis (**Figure 36**) corresponded with the TGA data where the material is seen to

contain solvent, which is lost as the relative humidity is increased. Post DVS XRPD (not shown) indicated that the material converted predominantly to Form A (traces of Form F remaining). KF analysis (not shown) indicated the presence of *ca.* 0.87% water. HPLC purity analysis indicated a purity of *ca.* 97.0%. Form F could not be detected by HPLC analysis for the aqueous solubility. The solubility is therefore poor.

[00218] XRPD analysis after 1 week storage (open container) at 40°C/75%RH showed the material converted to Form A, with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 96.8%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material to be partially crystalline with peaks present corresponding with Form A. HPLC analysis indicated a purity of *ca.* 96.3%. The comparative XRPD results are shown in **Figure 37**.

[00219] In order to determine whether Form F remains the same after losing the solvent present, a sample of Form F was heated to 120 °C (*i.e.*, just past the temperature at which the solvent is lost) and then XRPD analysis was carried out. The XRPD showed that the material had converted predominantly to Form A. Similarly, after drying at ambient temperature under vacuum for 7 days and then for a further 2 days at 40 °C, Form F lost some crystallinity and converted predominantly to Form A. The comparative XRPD results are shown in **Figure 38**.

Example 7

Preparation of Form G

[00220] *ca.* 120 mg of Compound **1** was weighed into a vial and slurried in *ca.* 100 µl of NMP. This was temperature cycled between *ca.* 0°C and ambient (*ca.* 22 °C) whilst stirring in 2 hour cycles for a period of 2-3 days. Overnight, the sample was kept at *ca.* 2-5 °C. Solid material was isolated and left to dry under vacuum at ambient for 7 days and at 40 °C for a further 2 days. A portion of the solid was also dried at 80 °C for *ca.* 4 days.

[00221] XRPD analysis (**Figure 39**) showed the material to be crystalline. PLM analysis (not shown) indicated birefringent, plate-like crystals. TGA/DTA (**Figure 40A**) showed weight losses of *ca.* 23.6% and 10.2% after drying for 4 days at ambient temperature under vacuum. After drying for 7 days at ambient temperature under vacuum and a further 2 days at 40°C, the TGA (**Figure 40B**) showed a weight loss of *ca.* 6.3% between *ca.* 70-110 °C. After drying for 4 days at 80 °C, the TGA (**Figure 40C**) showed a weight loss of *ca.* 2.8% between *ca.* 70-110 °C. DSC analysis after drying at 80°C (**Figure 41**) showed an endotherm

at onset *ca.* 205.3 °C (peak 210.0 °C). IR analysis after 4 days of ambient temperature drying (**Figure 42**) showed some shifts in comparison with Form A and also the presence of NMP. ^{1}H-NMR (not shown) carried out in deuterated DMSO after 4 days of drying at ambient temperature under vacuum corresponded with the input free base with a significant amount of NMP present. DVS analysis (**Figure 43**) corresponded with the TGA data, where the material is seen to contain significant amounts of solvent that are lost as the relative humidity is increased. Post DVS XRPD (not shown) indicated that the material converted to Form A. KF analysis (not shown) indicated the presence of *ca.* 0.45% water. HPLC purity analysis indicated a purity of *ca.* 97.0%. Form F in the HPLC chromatogram to determine aqueous solubility was below the limit of quantification. The aqueous solubility is therefore poor.

[00222] XRPD analysis after 1 week storage (open container) at 40 °C/75%RH showed the material converted predominantly to Form A, with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 96.8%. XRPD analysis after 2 week storage (open container) at 40 °C/75%RH showed the material converted predominantly to Form A, with some loss in crystallinity. HPLC analysis indicated a purity of *ca.* 96.2%. The comparative XRPD results are shown in **Figure 44**.

[00223] After drying at ambient under vacuum for 7 days and then for a further 2 days at 40 °C, Form G converted to Form A. After drying at 80 °C for 4 days, Form G converted to Form A. The comparative XRPD results are shown in **Figure 45**.

Example 8

Polymorph Stability Studies

[00224] The results from the competitive slurries carried out at ambient (*ca.* 22 °C) and 60 °C are tabulated below.

Table 1: Competitive Slurry results at ambient and 60°C

Solvent System	Ambient (approx. 22 °C)	60 °C
Dichloromethane	Form B	Form B
Isopropanol	Form A	Form A
Acetone	Form A	Form A
Ethyl Acetate	Form A	Form A
Acetone:Water (80:20)	Form A	Form H

From slurrying at both ambient and 60 °C, the majority of experiments resulted in conversion to Form A, thus indicating that Form A is likely the more stable form in comparison with Form B. Form B has been obtained consistently throughout the study from dichloromethane

and tetrahydrofuran. A new polymorphic form, labelled Form H, was obtained from the competitive slurry carried out in acetone: water (80:20) at 60 °C.

Example 9

Preparation of Form H

[00225] *ca.* 10 mg of Form A and *ca.* 10 mg of Form B were weighed into a vial. *ca.* 200µl of acetone:water (80:20%) was added to the vial to form a slurry. The sample was allowed to stir at *ca.* 50°C for 3 days. The solid material was isolated and left to dry at ambient before analysis was carried out. Further drying was also carried out at 40 °C for 2 days.

[00226] XRPD analysis (**Figure 46**) showed the material to be crystalline, with the diffractogram different from all identified polymorphic forms. PLM analysis (not shown) indicated birefringent, block-like crystals. The material visually appeared yellow in colour. TGA/DTA (**Figure 47**) after 2 days of drying at 40 °C, showed a 4.4% weight loss from the outset up to *ca.* 120 °C. The final endotherm in the DTA trace appears to correspond with the Form A melt. (3.14 wt% is required for 1 mole equivalent of water.)

[00227] To examine whether Form H changes to Form A after heating to 115 °C (point after the solvent loss), the Form H material was heated to 115°C and XRPD analysis and DSC analysis were then carried out. The XRPD diffractogram (**Figure 48**) after heating still corresponded with Form H, with some loss in crystallinity likely due to the harsh heating conditions. The DSC analysis (**Figure 49**) indicated overlapping endotherms between *ca.* 115-135 °C, followed by an exotherm at peak 143.9 °C, likely indicating a polymorphic transition. A final endotherm was present at onset 202.7 °C (peak 206.6 °C) corresponding with the Form A melt.

[00228] To test whether Form H picks up water after desolvating/dehydrating the material by heating to 115 °C, a further test was carried out whereby Form H was heated to 115 °C in a TGA pan. The sample was then removed from the TGA pan and allowed to sit on the bench for *ca.* 1 hour. After 1 hour, another TGA was carried out up to 115 °C. TGA for the sample heated to 115 °C showed a *ca.* 4.2% weight loss of the solvent / water present (**Figure 50**). TGA after leaving the desolvated /dehydrated material on the bench for *ca.* 1 hour, showed a *ca.* 3.7% loss up to 115 °C (**Figure 51**). The material therefore picked up water upon standing at ambient conditions on the bench. This indicates that it is either hygroscopic or rapidly rehydrates following dehydration /desolvation.

Example 10

Preparation of Form I

[00229] Approximately *ca.* 5 mL of acetonitrile: water (10%) was added to *ca.* 1 g of Compound **1** free base to form a slurry. In a separate vial, *ca.* 3 mL of acetonitrile : water (10%) was added to 1 equivalent of hydrobromic acid (48%). The acid solution was then added dropwise over a 1 hour period to the free base slurry whilst stirring and maintaining a temperature between 0-5 °C. After the complete addition of the acid, a further 3 mL of acetonitrile : water (10%) was added. The reaction was stirred for *ca.* 1 day before being isolated and dried under vacuum at ambient (*ca.* 22 °C). A yield of *ca.* 79% was obtained.

[00230] Compound **1** hydrobromide salt material was ground using a Retsch Ball Mill for *ca.* 25 minutes, with a 5 minute break midway to prevent the sample from overheating.

[00231] Approximately 500 mg of amorphous Compound **1** hydrobromide salt material was slurried in *ca.* 18 mL of acetone:water (90:10). The suspension was then temperature cycled between 4 and 25 °C in four hour cycles for *ca.* 2 days, before being isolated and dried under vacuum at ambient (*ca.* 22 °C). The secondary screen analysis was carried out on Form I after drying.

[00232] Form I was scaled-up for further analysis. During the scale-up, a colour change was observed from yellow to a light beige/cream colour. XRPD analysis (**Figure 52**) showed the material produced from scale-up to be crystalline and predominantly consistent with the small scale Form I diffractogram. IR and ^{1}H NMR are depicted in **Figure 53** and **Figure 54**, respectively. PLM analysis indicated birefringent, fibrous, needle-like crystals when wet. Upon drying the material appeared to lose its needle-like morphology, appearing as small particles with no clearly defined morphology. Hot stage microscopy indicated melting at *ca.* 135 °C with some recrystallization occurring at *ca.* 180 °C, followed by complete melting by *ca.* 210 °C. After drying under vacuum for *ca.* 72 hours, the TGA/DTA indicated a weight loss of 2.8% from *ca.* 80 to 120 °C corresponding with an endotherm in the DTA trace (**Figure 55**). An exotherm was observed in the DTA trace at onset *ca.* 149 °C (peak *ca.* 166 °C), followed by a further endotherm at onset *ca.* 197 °C (peak *ca.* 201 °C). After standing at ambient conditions, the TGA/DTA was re-run showing a weight loss of 2.6% from the outset to *ca.* 80 °C, followed by a further weight loss of 2.8% between *ca.* 80 °C and 120 °C corresponding with two endotherms in the DTA trace (**Figure 56**). An exotherm was then observed in the DTA trace at onset *ca.* 155 °C (peak *ca.* 167 °C) followed by a further

endotherm at onset *ca.* 196 °C (peak *ca.* 202 °C). The DSC analysis indicated overlapping endotherms starting from the outset, followed by an exotherm at onset *ca.* 138 °C (peak *ca.* 149 °C) and a further endotherm at onset *ca.* 92 °C (peak *ca.* 200 °C) (**Figure 57**). DVS analysis (**Figure 58**) showed the following observations:

- Cycle 1 – Sorption 20-90%RH
  Sample gradually takes up *ca.* 0.66% mass.
- Cycle 2 – Desorption 90-0%RH
  Between 90-10%RH, sample mass decreases gradually by *ca.* 1.2%.
  A rapid loss of *ca.* 2.7% occurs between 10-0%RH.
- Cycle 3 – Sorption 0-20%RH
  Moisture uptake of *ca.* 2.8% between 0-20%RH.

[00233] The input material containing ca. 5.6% water appeared to be relatively non-hygroscopic. Approximately 1 equivalent of water was lost at the lower RH percentages. Post DVS XRPD analysis indicated that the material remained as Form I (**Figure 59**). No polymorphic form changes were evident. KF analysis indicated the presence of *ca.* 5.4% water. HPLC purity analysis indicated a purity of ca. 99.66% (**Figure 60**). Ion chromatography indicated the presence of 1.64% bromide (*ca.* 12.57% required for 1 equivalent). XRPD analysis carried out on the thermodynamic solubility experiment solids remaining after 24 hours, indicated that for pH 6.6, 4.5 and 3.0 the material remained as Form I (**Figure 61**). For pH 1, the material appeared to be a mixture of Form I and possibly the HCl salt formed during screening.

[00234] From the characterisation carried out on Form I, this form was determined to be a hydrated version of the freebase rather than a bromide salt form. The TGA/DTA and DVS data appear to suggest that this may be either a hygroscopic monohydrate or a dihydrate form.

[00235] ***7 day Stability Studies at 25 °C, 80 °C, 40 °C/75%RH (open and closed conditions).*** Approximately 15 mg of Form I was placed separately into vials and then exposed to 25 °C, 80 °C and 40 °C/75%RH environments (open and closed vials) for 1 week to determine stability. The resulting solids were analysed by XRPD and HPLC to establish if any changes had occurred. Results are presented in Tables 2 and 3 and **Figures 62** and **63**.

Table 2 – 1 week stability studies (Open container)

Condition	Purity	XRPD analysis
40 °C/75% RH	98.9%	Form I
80 °C	98.5%	Form I (some loss in crystallinity)
25 °C	98.7%	Form I

Table 3 – 1 week stability studies (Closed container)

Condition	Purity	XRPD Analysis
40 °C/75% RH	99.3%	Form I (some loss in crystallinity)
80 °C	99.2%	Form I (some loss in crystallinity)
25 °C	99.4%	Form I

[00236] ***Thermodynamic Solubility Studies.*** Slurries of Form I were created in media of various pH (pH 1; pH 3; pH 4.5 and pH 6.6) and shaken for *ca.* 24 hours. After 24 hours, the slurries were filtered and the solution analysed by HPLC in order to determine the solubility at the various pH levels. For the buffer solutions, KCl /HCl was used for pH 1 and citrate / phosphate combinations for pH 3, 4.5 and 6.6 (10mM). The pH of the solutions was also measured prior to HPLC analysis. XRPD analysis was carried out on the remaining solids after 24 hours of shaking. Results are presented in Table 4:

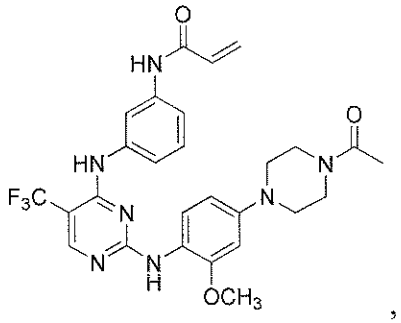
Table 4 – Thermodynamic Solubility studies

Buffer pH	pH prior to analysis	Solubility (mg/mL)
1	0.95	3.266
3	2.26	0.023
4.5	3.38	0.002
6.6	5.04	Not detected

CLAIMS

We claim:

1. A solid form of Compound **1**:



wherein Compound **1** is a free base.

2. The solid form of claim 1, wherein the solid form is amorphous.

3. The solid form of claim 1, wherein the solid form is crystalline.

4. The solid form of claim 3, wherein Compound **1** is unsolvated.

5. The solid form of claim 4, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.73, about 18.30, about 18.96 and about 25.48 degrees 2-theta.

6. The solid form of claim 5, wherein the solid form is Form A.

7. The solid form of claim 4, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 10.67, about 12.21, about 18.11, about 19.24 and about 21.53 degrees 2-theta.

8. The solid form of claim 7, wherein the solid form is Form B.

9. The solid form of claim 3, wherein Compound **1** is a dimethylformamide solvate.

10. The solid form of claim 9, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 16.32, about 18.82, about 20.26, about 22.58 and about 25.36 degrees 2-theta.

11. The solid form of claim 10, wherein the solid form is Form C.

12. The solid form of claim 3, wherein Compound **1** is a 1,4-dioxane solvate.

13. The solid form of claim 12, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 18.40, about 19.31, about 20.14, about 20.53 and about 25.25 degrees 2-theta.

14. The solid form of claim 13, wherein the solid form is Form D.

15. The solid form of claim 3, wherein Compound **1** is a methyl ethyl ketone solvate.

16. The solid form of claim 15, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 5.78, about 12.57, about 15.34, about 19.10 and about 24.80 degrees 2-theta.

17. The solid form of claim 16, wherein the solid form is Form E.

18. The solid form of claim 3, wherein Compound **1** is a N-methyl-2-pyrrolidone solvate.

19. The solid form of claim 18, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 15.51, about 16.86, about 18.80, about 20.97 and about 23.32 degrees 2-theta.

20. The solid form of claim 19, wherein the solid form is Form F.

21. The solid form of claim 18, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.79, about 17.86, about 19.43, about 19.98 and about 22.35 degrees 2-theta.

22. The solid form of claim 21, wherein the solid form is Form G.

23. The solid form of claim 3, wherein Compound **1** is a hydrate.

24. The solid form of claim 23, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 10.82, about 11.08, about 18.45, about 22.85 and about 25.06 degrees 2-theta.

25. The solid form of claim 24, wherein the solid form is Form H.

26. The solid form of claim 23, having one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.13, about 12.22, about 15.91, about 18.35, about 18.88, and about 21.90 degrees 2-theta.

27. The solid form of claim 26, wherein the solid form is Form I.

28. A composition comprising the solid form of claim 1 and a pharmaceutically acceptable carrier or excipient.

29. A method for inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR (WT EGFR) in a biological sample, comprising contacting the biological sample with a solid form according to claim 1, or a composition thereof.

30. The method according to claim 29, wherein said method is sparing for WT EGFR.

31. The method according to claim 29, wherein the at least one mutant is an activating mutant, a deletion mutant, a point mutation, or a mutant selected from T790M, delE746-A750, L858R or G719S.

32. Use of a solid form according to claim 1, or a composition thereof, in the manufacture of a medicament for inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR (WT EGFR), in a biological sample or in a patient.

33. Use of a composition according to claim 28, in the manufacture of a medicament for treating a mutant EGFR-mediated disorder or condition in a patient.

34. The use according to claim 33, wherein the disorder or condition is a cancer.