

**METHODS OF PREPARING COMPOUNDS FOR TREATING PAIN AND SOLID FORMS
THEREOF**

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] This application claims the benefit of U.S. Provisional Application No. 63/592,507, filed October 23, 2023, and U.S. Provisional Application No. 63/592,556, filed October 23, 2023, each of which is incorporated by reference in its entirety.

FIELD

[2] Disclosed herein are process and methods of making a voltage-gated sodium channel (Na_v) inhibitor, solid forms thereof, pharmaceutical compositions thereof, methods of treating pain therewith, and processes for making the solid forms.

BACKGROUND

[3] Pain is a protective mechanism that allows healthy animals to avoid tissue damage and to prevent further damage to injured tissue. Nonetheless, there are many conditions where pain persists beyond its usefulness, or where patients would benefit from inhibition of pain. Acute and chronic pain are two common pain states and can be distinguished by the duration of the pain. Acute pain can arise for many reasons (e.g., a hospital procedure) and treatment options are generally limited by poor efficacy and/or adverse events. Like acute pain, chronic pain can arise for many reasons and treatment options are limited by poor efficacy and/or adverse events.

[4] Neuropathic pain is a form of chronic pain caused by an injury to the sensory nerves (Dieleman, J.P., et al., Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*, 2008. **137**(3): p. 681-8). Neuropathic pain can be divided into two categories, pain caused by generalized metabolic damage to the nerve and pain caused by a discrete nerve injury. The metabolic neuropathies include post-herpetic neuropathy, diabetic neuropathy, and drug-induced neuropathy. Discrete nerve injury indications include post-amputation pain, post-surgical nerve injury pain, and nerve entrapment injuries like neuropathic back pain.

[5] Voltage-gated sodium channels (Na_vs) are involved in pain signaling. Na_vs are biological mediators of electrical signaling as they mediate the rapid upstroke of the action potential of many excitable cell types, for example, neurons, skeletal myocytes, cardiac myocytes (Hille, Bertil, *Ion Channels of Excitable Membranes*, Third ed. (Sinauer Associates, Inc., Sunderland, MA, 2001)). The evidence for the role of these channels in normal physiology, the pathological states arising from mutations in sodium

channel genes, preclinical work in animal models, and the clinical pharmacology of known sodium channel modulating agents all point to the central role of Navs in pain sensation (Rush, A.M. and T.R. Cummins, *Painful Research: Identification of a Small-Molecule Inhibitor that Selectively Targets Nav1.8 Sodium Channels*. Mol. Interv., 2007. 7(4): p. 192-5); England, S., Voltage-gated sodium channels: the search for subtype-selective analgesics. *Expert Opin. Investig. Drugs* 17 (12), p. 1849-64 (2008); Krafte, D. S. and Bannon, A. W., Sodium channels and nociception: recent concepts and therapeutic opportunities. *Curr. Opin. Pharmacol.* 8 (1), p. 50-56 (2008)). Because of the role Navs play in the initiation and propagation of neuronal signals, antagonists that reduce Nav currents can prevent or reduce neural signaling and Nav channels have been considered likely targets to reduce pain in conditions where hyper-excitability is observed (Chahine, M., Chatelier, A., Babich, O., and Krupp, J. J., Voltage-gated sodium channels in neurological disorders. *CNS Neurol. Disord. Drug Targets* 7 (2), p. 144-58 (2008)). Several clinically useful analgesics have been identified as inhibitors of Nav channels. The local anesthetic drugs such as lidocaine block pain by inhibiting Nav channels, and other compounds, such as carbamazepine, lamotrigine, and tricyclic antidepressants that have proven effective at reducing pain have also been suggested to act by sodium channel inhibition (Soderpalm, B., Anticonvulsants: aspects of their mechanisms of action. *Eur. J. Pain* 6 Suppl. A, p. 3-9 (2002); Wang, G. K., Mitchell, J., and Wang, S. Y., Block of persistent late Na⁺ currents by antidepressant sertraline and paroxetine. *J. Membr. Biol.* 222 (2), p. 79-90 (2008)).

[6] The Navs form a subfamily of the voltage-gated ion channel super-family and comprises 9 isoforms, designated Nav1.1 – Nav1.9. The tissue localizations of the nine isoforms vary. Nav1.4 is the primary sodium channel of skeletal muscle, and Nav1.5 is primary sodium channel of cardiac myocytes. Navs 1.7, 1.8 and 1.9 are primarily localized to the peripheral nervous system, while Navs 1.1, 1.2, 1.3, and 1.6 are neuronal channels found in both the central and peripheral nervous systems. The functional behaviors of the nine isoforms are similar but distinct in the specifics of their voltage-dependent and kinetic behavior (Catterall, W. A., Goldin, A. L., and Waxman, S. G., International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol. Rev.* 57 (4), p. 397 (2005)).

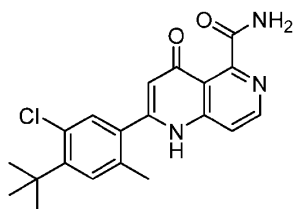
[7] Upon their discovery, Nav1.8 channels were identified as likely targets for analgesia (Akopian, A.N., L. Sivilotti, and J.N. Wood, A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature*, 1996. 379(6562): p. 257-62). Since then, Nav1.8 has been shown to be a carrier of the sodium current that maintains action potential firing in small dorsal root ganglia (DRG) neurons (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na⁺ current, TTX-resistant Na⁺ current, and Ca²⁺ current in the action potentials of nociceptive sensory neurons. *J. Neurosci.*, 2002. 22(23): p. 10277-90). Nav1.8 is involved in spontaneous firing in damaged neurons, like those that drive neuropathic pain (Roza, C., et al., The tetrodotoxin-resistant Na⁺ channel Nav1.8 is essential for the expression of

spontaneous activity in damaged sensory axons of mice. *J. Physiol.*, 2003. **550**(Pt 3): p. 921-6; Jarvis, M.F., et al., A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc. Natl. Acad. Sci. U S A*, 2007. **104**(20): p. 8520-5; Joshi, S.K., et al., Involvement of the TTX-resistant sodium channel Nav1.8 in inflammatory and neuropathic, but not post-operative, pain states. *Pain*, 2006. **123**(1-2): pp. 75-82; Lai, J., et al., Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8. *Pain*, 2002. **95**(1-2): p. 143-52; Dong, X.W., et al., Small interfering RNA-mediated selective knockdown of Nav1.8 tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. *Neuroscience*, 2007. **146**(2): p. 812-21; Huang, H.L., et al., Proteomic profiling of neuromas reveals alterations in protein composition and local protein synthesis in hyper-excitible nerves. *Mol. Pain*, 2008. **4**: p. 33; Black, J.A., et al., Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas. *Ann. Neurol.*, 2008. **64**(6): p. 644-53; Coward, K., et al., Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states. *Pain*, 2000. **85**(1-2): p. 41-50; Yiangou, Y., et al., SNS/PN3 and SNS2/NaN sodium channel-like immunoreactivity in human adult and neonate injured sensory nerves. *FEBS Lett.*, 2000. **467**(2-3): p. 249-52; Ruangsri, S., et al., Relationship of axonal voltage-gated sodium channel 1.8 (Nav1.8) mRNA accumulation to sciatic nerve injury-induced painful neuropathy in rats. *J. Biol. Chem.* **286**(46): p. 39836-47). The small DRG neurons where Nav1.8 is expressed include the nociceptors involved in pain signaling, where Nav1.8 mediates large amplitude action potentials (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na⁺ current, TTX-resistant Na⁺ current, and Ca²⁺ current in the action potentials of nociceptive sensory neurons. *J. Neurosci.*, 2002. **22**(23): p. 10277-90). Nav1.8 is necessary for rapid repetitive action potentials in nociceptors, and for spontaneous activity of damaged neurons. (Choi, J.S. and S.G. Waxman, Physiological interactions between Nav1.7 and Nav1.8 sodium channels: a computer simulation study. *J. Neurophysiol.* **106**(6): p. 3173-84; Renganathan, M., T.R. Cummins, and S.G. Waxman, Contribution of Na(v)1.8 sodium channels to action potential electrogenesis in DRG neurons. *J. Neurophysiol.*, 2001. **86**(2): p. 629-40; Roza, C., et al., The tetrodotoxin-resistant Na⁺ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J. Physiol.*, 2003. **550**(Pt 3): p. 921-6). In depolarized or damaged DRG neurons, Nav1.8 appears to be a driver of hyper-excitability (Rush, A.M., et al., A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc. Natl. Acad. Sci. USA*, 2006. **103**(21): p. 8245-50). In some animal pain models, Nav1.8 mRNA expression levels have been shown to increase in the DRG (Sun, W., et al., Reduced conduction failure of the main axon of polymodal nociceptive C-fibers contributes to painful diabetic neuropathy in rats. *Brain*, **135**(Pt 2): p. 359-75; Strickland, I.T., et al., Changes in the expression of Nav1.7, Nav1.8 and Nav1.9 in a distinct population of dorsal root ganglia innervating the rat knee joint in a model of chronic inflammatory joint pain. *Eur. J. Pain*, 2008. **12**(5): p. 564-72; Qiu, F., et

al., Increased expression of tetrodotoxin-resistant sodium channels $\text{Na}_V1.8$ and $\text{Na}_V1.9$ within dorsal root ganglia in a rat model of bone cancer pain. *Neurosci. Lett.*, **512**(2): p. 61-6).

[8] The inventors have discovered that some voltage-gated sodium channel inhibitors have limitations as therapeutic agents due to, for example, a poor therapeutic window (e.g., due to a lack of Na_V isoform selectivity, low potency, and/or other reasons). Accordingly, there remains a need to develop selective voltage-gated sodium channel inhibitors, such as selective $\text{Na}_V1.8$ inhibitors.

[9] Compound I, 2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4-oxo-1*H*-1,6-naphthyridine-5-carboxamide, is a Na_V inhibitor and thus useful in treating pain. Compound I has the following structure:

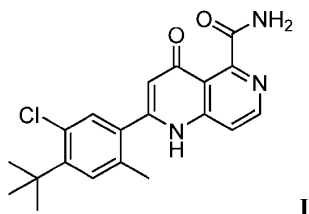


[10] Compound I is disclosed in PCT International Application No. PCT/US2023/066065. Solid (e.g., crystalline or amorphous) forms are of interest in the pharmaceutical industry, where the control of the form(s) of the active ingredient may be desirable or even required. Reproducible processes for producing a compound with a particular form in high purity may be desirable for compounds intended to be used in pharmaceuticals, as different forms may possess different properties. For example, different solid (e.g., crystalline or amorphous) forms may possess different chemical, physical, and/or pharmaceutical properties. In some embodiments, one or more crystalline forms disclosed herein may exhibit a higher level of purity, chemical stability, and/or physical stability compared to the forms produced in PCT/US2023/066065. Certain crystalline forms (e.g., crystalline free form, crystalline salt, crystalline salt solvate, and crystalline salt hydrate forms of Compound I (collectively referred to as “crystalline forms”)) may exhibit lower hygroscopicity than any preexisting forms. Thus, the solid (e.g., crystalline or amorphous) forms of this disclosure may provide advantages during drug substance manufacturing, storage, and handling over the amorphous forms produced in PCT/US2023/066065. Thus, pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms of Compound I may be particularly useful for the production of drugs for the treatment of pain.

[11] In addition, there remains a need for more efficient processes for the synthesis of Compound I that deliver this compound, or pharmaceutically acceptable salts thereof, for example, in higher yield, with higher selectivity, and/or with higher purity relative to known processes.

BRIEF SUMMARY

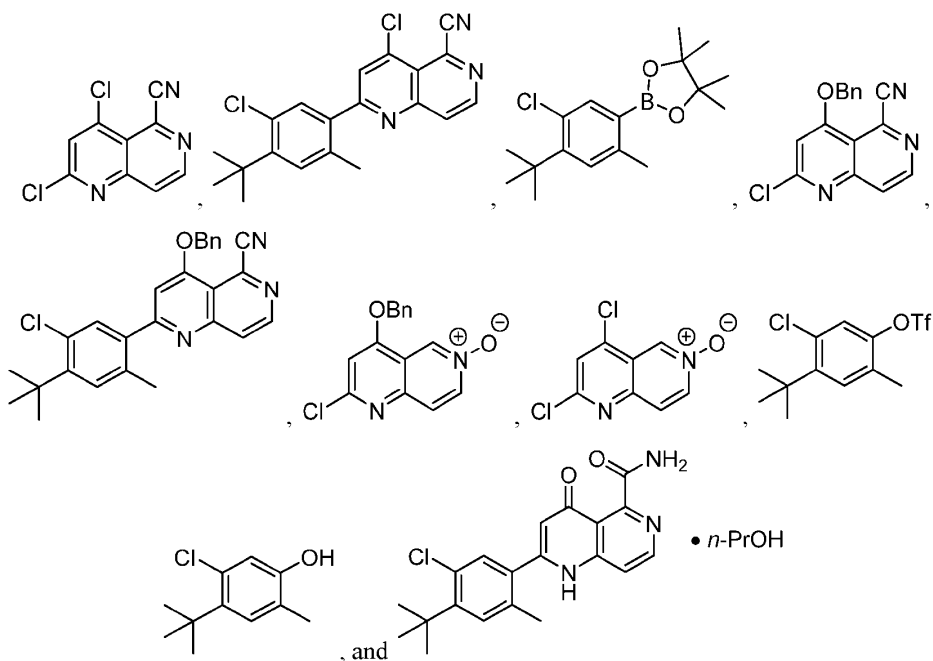
[12] In one aspect, the invention relates to a method of preparing Compound I



or a solvate or a tautomer or a pharmaceutically acceptable salt thereof.

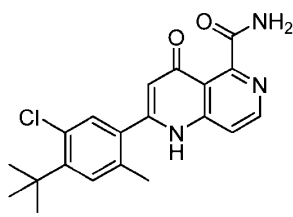
[13] In some embodiments, the method comprises converting any of compounds of formulae A₁, A₁₋₁, A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, A₃, A₃₋₁, A₃₋₂, B₁, B₁₋₁, B₁₋₂, B₁₋₃, B₂, C₁, C₂, and C₃ to Compound I or a solvate thereof or a tautomer or a pharmaceutically acceptable salt thereof following the reaction steps described herein.

[14] In another aspect, compounds are selected from:



pharmaceutically acceptable salts thereof and tautomers thereof and combinations thereof.

[15] In another aspect, the invention provides solid forms of Compound I



wherein the solid forms of Compound I include Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, Compound I TFA Salt A, and Amorphous Compound I.

[16] In other aspects, the invention provides a pharmaceutical composition comprising such solid forms, medical uses of such solid forms, and methods of preparing such solid forms.

BRIEF DESCRIPTION OF THE FIGURES

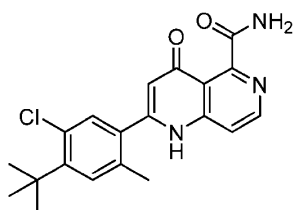
- [17] **Figure 1** provides the X-ray powder diffraction (XRPD) pattern of crystalline Compound B₁.
- [18] **Figure 2** provides the X-ray powder diffraction (XRPD) pattern of crystalline Compound A₂.
- [19] **Figure 3** provides the X-ray powder diffraction (XRPD) pattern of Compound C₂ Form A.
- [20] **Figure 4** provides the X-ray powder diffraction (XRPD) pattern of Compound C₂ Form B.
- [21] **Figure 5** provides the X-ray powder diffraction (XRPD) pattern of Compound C₄ HCl salt, AcOH solvate.
- [22] **Figure 6** provides the X-ray powder diffraction (XRPD) pattern of Compound C₄ Hydrate Form A.
- [23] **Figure 7** provides the X-ray powder diffraction (XRPD) pattern of Compound C₄ Benzenesulfonic Acid Salt Form A.
- [24] **Figure 8** provides the X-ray powder diffraction (XRPD) pattern of Compound I Neat Form A.
- [25] **Figure 9A** provides the ¹³C solid-state NMR (SSNMR) spectrum of Compound I Neat Form A.
- [26] **Figure 9B** provides a comparison of ¹³C solid-state NMR (SSNMR) spectra of Compound I Neat Form A samples at different conditions.
- [27] **Figure 10** provides the X-ray powder diffraction (XRPD) pattern of Compound I Neat Form B.

- [28] Figure 11 provides the ^{13}C solid-state NMR (SSNMR) spectrum of Compound I Neat Form B.
- [29] Figure 12 provides the X-ray powder diffraction (XRPD) pattern of Compound I Neat Form C.
- [30] Figure 13 provides the ^{13}C solid-state NMR (SSNMR) spectrum of Compound I Neat Form C.
- [31] Figure 14 provides the XRPD pattern of Compound I Hemi-Hydrate.
- [32] Figure 15 provides the ^{13}C SSNMR spectrum of Compound I Hemi-Hydrate.
- [33] Figure 16 provides the XRPD pattern of Compound I Monohydrate.
- [34] Figure 17 provides the XRPD pattern of Compound I Methanol Solvate.
- [35] Figure 18 provides the ^{13}C SSNMR spectrum of Compound I Methanol Solvate.
- [36] Figure 19 provides the XRPD pattern of Compound I nPA Solvate Mixture A.
- [37] Figure 20 provides a ^{13}C SSNMR spectrum of Compound I nPA Solvate Mixture A.
- [38] Figure 21 provides a ^{13}C SSNMR spectrum of Compound I nPA Solvate Mixture A.
- [39] Figure 22 provides the XRPD pattern of Compound I nPA Solvate B.
- [40] Figure 23 provides the ^{13}C SSNMR spectrum of Compound I nPA Solvate B.
- [41] Figure 24 provides the XRPD pattern of Compound I nPA Solvate C.
- [42] Figure 25 provides the XRPD pattern of Compound I Na Hemi Salt nPA Solvate.
- [43] Figure 26 provides the ^{13}C SSNMR spectrum of Compound I Na Hemi Salt nPA Solvate.
- [44] Figure 27 provides the XRPD pattern of Compound I nPA Solvate J.
- [45] Figure 28 provides the XRPD pattern of Compound I 2-MeTHF Solvate A.
- [46] Figure 29 provides the XRPD pattern of Compound I 2-MeTHF Solvate Mixture A.
- [47] Figure 30 provides the XRPD pattern of Compound I 2-MeTHF Solvate Mixture C.
- [48] Figure 31 provides the XRPD pattern of Compound I Mandelic Acid Cocrystal.
- [49] Figure 32 provides the XRPD pattern of Compound I Oxalic Acid Cocrystal.
- [50] Figure 33 provides the ^{13}C SSNMR spectrum of Compound I Oxalic Acid Cocrystal.
- [51] Figure 34 provides the XRPD pattern of Compound I TFA Salt A.
- [52] Figure 35 provides the ^{13}C SSNMR spectrum of Compound I TFA Salt A.
- [53] Figure 36 provides the XRPD pattern of Amorphous Compound I.
- [54] Figure 37 provides the ^{13}C SSNMR spectrum of Amorphous Compound I.

DETAILED DESCRIPTION*Definitions*

[55] The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings.

[56] “Compound I” as used throughout this disclosure refers to 2-[2-(3,4-difluoro-2-methylphenoxy)-4-methyl-5-(trifluoromethyl)-3-pyridyl]-4-oxo-1*H*-1,6-naphthyridine-5-carboxamide, and has the following structure:



number which differs from the atomic mass or mass number of the most abundant isotope of the specified element ("isotope-labeled" compounds and salts). Examples of stable isotopes which are commercially available and suitable for the invention include without limitation isotopes of hydrogen, carbon, nitrogen, oxygen, and phosphorus, for example ^2H , ^{13}C , ^{15}N , ^{18}O , ^{17}O , and ^{31}P , respectively. For example, as used in the specification and claims, "H" refers to hydrogen and includes any stable isotope of hydrogen, namely ^1H and D.

[62] The term the "compound of formula" followed by a number (typically Roman number) and the term "compound" followed by the same number (Roman or otherwise) may interchangeably be used. For example, the "compound of formula V" and "compound V" denote the same compound.

[63] The term "reacting," when referring to a chemical reaction, means to add or mix two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

[64] The term "conducted in a solvent," when referring to a reaction, means that the substrate(s) and reagent(s) are dissolved or suspended in the specified solvent or in a mixture of solvents comprising the specified solvent.

[65] The term "chromatographic purification" refers to any method of purification based on differential retention by a stationary phase. Methods of chromatographic purification include flash chromatography, medium pressure liquid chromatography, preparative thin layer chromatography, and high performance liquid chromatography.

[66] The terms "converting" and "transforming" as used herein refer to a step of converting a first compound or salt to a second compound or salt, and refers to a process of transforming the first compound or salt to the second compound or salt in one or more chemical steps.

[67] The term "acid" refers to a chemical species having a pKa (in water) of less than 7. The term includes inorganic (mineral) acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid, and the like. The term also includes organic acids such as acetic acid, propionic acid, *n*-butyric acid, *i*-butyric acid, *n*-valeric acid, *i*-valeric acid, *n*-hexanoic acid, succinic acid, glutaric acid, adipic acid, aspartic acid, formic acid, citric acid, *o*-chlorobenzoic acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, nicotinic acid, lactic acid, oxalic acid, picric acid, picolinic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, phthalic acid, isophthalic acid, terephthalic acid, maleic acid, malonic acid, and the like.

[68] The term “base” refers to a chemical species whose conjugate acid has a pKa (in water) of greater than 7. The term includes “inorganic bases,” such as sodium hydroxide, potassium hydroxide, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, cesium carbonate, potassium phosphate (mono-, di-, or tri-basic), sodium hydride, and potassium hydride. The term also includes “anionic organic bases,” such as methyl lithium, butyl lithium, lithium diisopropyl amide, and sodium acetate. The term also includes “neutral organic bases,” such as trimethylamine, dimethylethylamine, diethylmethylamine, triethylamine, di-n-propylmethylamine, dimethylcyclohexylamine, diisopropylethylamine, tri-n-propylamine, diisopropylisobutylamine, dimethyl-n-nonylamine, tri-n-butylamine, di-n-hexylmethylamine, dimethyl-n-dodecylamine, tri-n-pentylamine, 1,4-diazabicyclo[2.2.2] octane (DABCO), dimethylaminopyridine (DMAP), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine, 2,6-lutidine, 3,4-lutidine, 3,5-lutidine, 2,3,4-collidine, 2,4,5-collidine, 2,5,6-collidine, 2,4,6-collidine, 3,4,5-collidine, and 3,5,6-collidine.

[69] The term “alcohol protecting group” refers to a chemical moiety suitable to protect an alcohol group against undesirable side reactions during synthetic procedures. Common alcohol protecting groups include methyl, ethyl, isopropyl, benzyl, 2-tetrahydropyranyl, acetyl, trifluoroacetyl, trialkylsilyl, arylalkylsilyl, alkylarylsilyl, or triarylsilyl. Other alcohol protecting groups also are well known in the art. See, e.g., P.G.M. Wuts et al., *Greene’s Protective Groups in Organic Synthesis* (4th ed. 2006).

[70] The term “deprotecting” refers to a step of reacting a compound or salt containing a protecting group, such as an alcohol protecting group, under conditions suitable to remove the protecting group and reveal the protected moiety. For example, where a compound or salt contains an alcohol protecting group, the term “deprotecting” refers to reacting the compound or salt under conditions suitable to remove the alcohol protecting group and reveal the alcohol. Conditions for removing various protecting groups are well known in the art. See, e.g., P.G.M. Wuts et al., *Greene’s Protective Groups in Organic Synthesis* (4th ed. 2006).

[71] The term “hydrogenation catalyst” refers to any homogeneous or heterogeneous catalyst that catalyzes the hydrogenolysis of benzylic carbon-oxygen single bonds. Suitable hydrogenation catalysts are well-known in the art and include, for example, palladium on activated carbon, platinum oxide, and Raney Nickel.

[72] The term “coupling,” when referring to a reaction between a carboxylic acid or acid halide and an amine, refers to a net transformation linking the carboxylic acid or acid halide and the amine to form an amide. The term includes a direct reaction between the carboxylic acid and the amine, as well as

a reaction between an activated derivative of the carboxylic acid (such as the derivative formed by the reaction between the carboxylic acid and a coupling reagent) and the amine.

[73] The term “coupling reagent” refers to a reagent suitable to react with a carboxylic acid to activate the carboxylic acid for coupling with an amine to form an amide bond. Coupling reagents are well known in the art. Coupling reagents include, but are not limited to, thionyl chloride, oxalyl chloride, 1,1'-carbonylbis-(4,5-dicyanoimidazole) (CBDCI), 1,1'- carbonyldiimidazole (CDI), propylphosphonic anhydride (T3P), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N, N'-dicyclohexylcarbodiimide (DCC), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), and 1-hydroxybenzotriazole (HOBt).

[74] The term “monovalent cation” refers to any cation with a charge of +1, such as alkali metal cations, NH_4^+ , and tetraalkylammonium.

[75] The term “alkali metal cation” refers to a cation derived from a Group I metal atom, including without limitation lithium (Li^+), sodium (Na^+), potassium (K^+), rubidium (Rb^+), and cesium (Cs^+).

[76] The term “substituted benzyl” refers to a benzyl group that is substituted with 1-3 substituents selected from the group consisting of C_1 - C_3 alkyl, C_1 - C_3 alkoxy, halogen, and cyano.

[77] The term “ketone solvent” refers to a compound having the formula $\text{C}_n\text{H}_{2n+1}\text{C}(\text{O})\text{C}_m\text{H}_{2m+1}$, wherein n and m are each independently an integer between 1 and 6. The $\text{C}_n\text{H}_{2n+1}$ and $\text{C}_m\text{H}_{2m+1}$ groups may be linear or branched and each may be substituted with up to 3 halogens. Ketone solvents include without limitation acetone, methyl ethyl ketone, 3-pentanone, and methyl *tert*-butyl ketone.

[78] The term “etheral solvent” refers to an organic solvent having at least one ether moiety. Etheral solvents include without limitation tetrahydrofuran, dimethoxyethane, dioxane, and dialkyl ethers such as diethyl ether and methyl isobutyl ether.

[79] The term “ester solvent” refers to a compound having the formula $\text{C}_n\text{H}_{2n+1}\text{OC}(\text{O})\text{C}_m\text{H}_{2m+1}$, wherein n and m are each independently an integer between 1 and 6. The $\text{C}_n\text{H}_{2n+1}$ and $\text{C}_m\text{H}_{2m+1}$ groups may be linear or branched and each may be substituted with up to 3 halogens. Ester solvents include without limitation ethyl acetate, isopropyl acetate, butyl acetate, and ethylpropionate.

[80] The term “halogenated solvent” refers to a C_1 - C_6 alkane or C_2 - C_6 alkene substituted with up to six halogens. Halogenated solvents include without limitation dichloromethane, dichloroethane, chloroform, tetrachloroethylene, and carbon tetrachloride.

[81] The term “aromatic solvent” refers to a C_{6-10} aromatic hydrocarbon. The aromatic hydrocarbon may be substituted with up to six halogens. Aromatic solvents include without limitation benzene, trifluoromethylbenzene, xylene, and toluene.

[82] The term “about” means that the stated number can vary from that value by $\pm 10\%$. Where the term defines a temperature, the stated temperature can vary by $\pm 10\%$. For example, about 80°C means between 72°C and 88°C . Where the term defines pressure, the term “about” means the pressure can vary by $\pm 10\%$. Thus, about 100 bars means between 90 and 110 bars. Where the term defines quantity (such as equivalents or weight), the term means the quantity can vary by $\pm 10\%$. For example, about 1 equivalent means between 0.9 and 1.1 equivalents. Where the term defines time, the term means the stated time can vary by $\pm 10\%$. For example, about 1 hour means between 0.9 and 1.1 hours.

[83] The term “leaving group” is a chemical group that is readily displaced by a desired incoming chemical moiety. Thus, the choice of the specific suitable leaving group is predicated upon its ability to be readily displaced by the incoming chemical moiety such as a CN group. Suitable leaving groups are well known in the art, e.g., see, “Advanced Organic Chemistry,” Jerry March, 5th Ed., pp. 351-357, John Wiley and Sons, N.Y.

[84] As used here, the term “cyanating agent” refers to a reagent, such as trimethylsilyl cyanide (TMSCN), diethylaluminum cyanide, KCN, NaCN, TBACN, HCN and the like, useful in the synthesis of compounds disclosed herein, e.g., compound A₁, A₂, and A₃. In one embodiment, the cyanating agent (e.g., trimethylsilyl cyanide) may be combined with a Lewis acid. In some embodiments, the Lewis acid is trifluoromethanesulfonic anhydride (Tf₂O), boron trifluoride ethyl etherate (BF₃OEt₂), TiCl₄, InCl₃, AgSbF₆, iodine, ZnBr₂, Al(OiPr)₃, MgCl₂, Mn(acac)₂, MnCl₂, TMSOTf, SnCl₄, and the like. In further embodiments, the Lewis acid is trifluoromethanesulfonic anhydride (Tf₂O). The cyanation reaction may be conducted in an organic solvent, for example toluene, dichloromethane, 2-methyl THF, acetonitrile, methanol, 1,2-dichloroethane, nitromethane, and the like.

[85] As used herein, the term “active pharmaceutical ingredient” (“API”) or “therapeutic agent” refers to a biologically active compound.

[86] The terms “patient” and “subject” are used interchangeably and refer to an animal including humans.

[87] The terms “effective dose” and “effective amount” are used interchangeably herein and refer to that amount of a compound that produces the desired effect for which it is administered (e.g., improvement in pain or a symptom of pain, or lessening the severity of pain or a symptom of pain). The exact amount of an effective dose will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[88] As used herein, the terms “treatment,” “treating,” and the like generally mean the improvement of pain or one or more of its symptoms or lessening the severity of pain or one or more of its symptoms in

a subject. "Treatment," as used herein, includes, but is not limited to, the following: Chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., bunionectomy pain, herniorrhaphy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia. Improvements in or lessening the severity of any of these symptoms can be readily assessed according to standard methods and techniques known in the art.

[89] As used herein, the term "in combination with," when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to the patient prior to, concurrently with, or subsequent to each other.

[90] "Selected from" and "chosen from" are used interchangeably herein.

[91] As used herein, the term "ambient conditions" means room temperature, open air condition and uncontrolled humidity condition. As used herein, the terms "room temperature" and "ambient temperature" mean 15 °C to 30 °C.

[92] As used herein, the term "solvent" refers to any liquid in which the product is at least partially soluble (solubility of product > 1 g/L).

[93] The term "stable," as used herein, refers to compounds or solid forms that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein.

[94] The term "chemically stable," as used herein, means that the solid form of Compound I does not decompose into one or more different chemical compounds when subjected to specified conditions, e.g., 40 °C/75% relative humidity, for a specific period of time, e.g., 1 day, 2 days, 3 days, 1 week, 2 weeks, or longer. In some embodiments, less than 25% of the solid form of Compound I decomposes. In some embodiments, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, less than about 1 %, less than about 0.5% of the form of Compound I decomposes under the conditions specified. In some embodiments, no detectable amount of the solid form of Compound I decomposes.

[95] The term "physically stable," as used herein, means that the solid form of Compound I does not change into one or more different physical forms of Compound I (e.g., different solid forms as measured by XRPD, DSC, etc.) when subjected to specific conditions, e.g., 40 °C/75 % relative humidity, for a specific period of time, e.g., 1 day, 2 days, 3 days, 1 week, 2 weeks, or longer. In some embodiments, less than 25% of the solid form of Compound I changes into one or more different physical forms when subjected to specified conditions. In some embodiments, less than about 20%, less than about 15%, less

than about 10%, less than about 5%, less than about 3%, less than about 1 %, less than about 0.5% of the solid form of Compound I changes into one or more different physical forms of Compound I when subjected to specified conditions. In some embodiments, no detectable amount of the solid form of Compound I changes into one or more physically different solid forms of Compound I.

[96] As used herein, the term "hydrate" refers to any crystalline Compound I that contains water in its crystal lattice. The stoichiometry of a Compound I hydrate can vary. For example, a hydrate of Compound I can be a quarter hydrate, hemihydrate, monohydrate, dihydrate, or a partially dehydrated form.

[97] As used herein, the term "pharmaceutically acceptable solid form" refers to a solid form of Compound I of this disclosure wherein the solid form (e. g. , crystalline free form, crystalline salt, crystalline salt solvate, crystalline salt hydrate, and amorphous form) of Compound I is nontoxic and suitable for use in pharmaceutical compositions.

[98] As used herein, the term "amorphous" refers to a solid material having no long-range order in the position of its molecules. Amorphous solids are generally rather isotropic, i.e., exhibit similar properties in all directions. Amorphous solids do not have definite melting points. Amorphous solids are generally glasses or supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, e.g., molecular packing, and no long-range order. For example, an amorphous material is a solid material having no sharp characteristic crystalline peak(s) in its X-ray power diffraction (XRPD) pattern (i.e., is not crystalline as determined by XRPD). Instead, one or several broad peaks (e.g., halos) appear in its XRPD pattern. Broad peaks are characteristic of an amorphous solid. See US 2004/0006237 for a comparison of XRPDs of an amorphous material and crystalline material. In some embodiments, a solid material may comprise an amorphous compound, and the material may, for example, be characterized by a lack of sharp characteristic crystalline peak(s) in its XRPD spectrum (i.e., the material is not crystalline, but is amorphous, as determined by XRPD). Instead, one or several broad peaks (e.g., halos) may appear in the XRPD pattern of the material. See US 2004/0006237 for a comparison of XRPDs of an amorphous material and crystalline material. A solid material, comprising an amorphous compound, may be characterized by, for example, a wider temperature range for the melting of the solid material, as compared to the range for the melting of a pure crystalline solid. Other techniques, such as, for example, solid state NMR may also be used to characterize crystalline or amorphous forms.

[99] As used herein, the terms "crystal form," "crystalline form," and "Form" interchangeably refer to a crystal structure (or polymorph) having a particular molecular packing arrangement in the crystal lattice. Crystalline forms can be identified and distinguished from each other by one or more characterization techniques including, for example, X-ray powder diffraction (XRPD), single crystal X-ray diffraction, and ¹³C solid state nuclear magnetic resonance (¹³C SSNMR). Accordingly, as used herein, the terms "crystalline Form [X] of Compound (I)" and "crystalline Form [C] potassium salt of Compound (I)"

refer to unique crystalline forms that can be identified and distinguished from each other by one or more characterization techniques including, for example, XRPD, single crystal X-ray diffraction, and ^{13}C SSNMR. In some embodiments, the novel crystalline forms are characterized by an X-ray powder diffractogram having one or more signals at one or more specified degree two-theta values ($^{\circ}2\theta$).

[100] As used herein, the term "free form" refers to a non-ionized version of the compound in the solid state. Examples of free forms include free bases and free acids.

[101] As used herein, the term "neat form" refers to an unsolvated and unhydrated free form version of a compound in the solid state.

[102] As used herein, the term "solvate" refers to a crystal form comprising one or more molecules of a compound of the present disclosure and, incorporated into the crystal lattice, one or more molecules of a solvent or solvents in stoichiometric or nonstoichiometric amounts. When the solvent is water, the solvate is referred to as a "hydrate."

[103] As used herein, the term "hydrate" refers to any crystalline Compound I that contains water in its crystal lattice. The stoichiometry of a Compound I hydrate can vary, i.e., Compound I can be a variable hydrate. For example, a hydrate of Compound I can be a quarter hydrate, hemihydrate, monohydrate, dihydrate, or a partially dehydrated form.

[104] In some embodiments, a solid material may comprise a mixture of crystalline solids and amorphous solids. A solid material comprising an amorphous compound may also, for example, contain up to 30% of a crystalline solid. In some embodiments, a solid material prepared to comprise an amorphous compound may also, for example, contain up to 25%, 20%, 15%, 10%, 5%, or 2% of a crystalline solid. In embodiments wherein the solid material contains a mixture of crystalline solids and amorphous solids, the characterizing data, such as XRPD, may contain indicators of both crystalline and amorphous solids. In some embodiments, a crystalline form of this disclosure may contain up to 30% amorphous compound. In some embodiments, a crystalline preparation of Compound I may contain up to 25%, 20%, 15%, 10%, 5%, or 2% of an amorphous solid.

[105] As used herein, the term "substantially amorphous" refers to a solid material having little or no long-range order in the position of its molecules. For example, substantially amorphous materials have less than 15% crystallinity (e.g., less than 10% crystallinity, less than 5% crystallinity, or less than 2% crystallinity). It is also noted that the term "substantially amorphous" includes the descriptor, "amorphous," which refers to materials having no (0%) crystallinity.

[106] As used herein, the term "substantially crystalline" refers to a solid material having little or no amorphous molecules. For example, substantially crystalline materials have less than 15% amorphous molecules (e.g., less than 10% amorphous molecules, less than 5% amorphous molecules, or less than 2%

amorphous molecules). It is also noted that the term "substantially crystalline" includes the descriptor "crystalline," which refers to materials that are 100% crystalline form.

[107] As used herein, a crystalline form is "substantially pure" when it accounts for an amount by weight equal to or greater than 90% of the sum of all solid form(s) in a sample as determined by a method in accordance with the art, such as quantitative XRPD. In some embodiments, the solid form is "substantially pure" when it accounts for an amount by weight equal to or greater than 95% of the sum of all solid form(s) in a sample. In some embodiments, the solid form is "substantially pure" when it accounts for an amount by weight equal to or greater than 99% of the sum of all solid form(s) in a sample.

[108] As used herein, the terms "X-ray powder diffractogram," "X-ray powder diffraction pattern," "XRPD pattern," "XRPD spectrum" interchangeably refer to an experimentally obtained pattern plotting signal positions (on the abscissa) versus signal intensities (on the ordinate).

[109] A "signal" or "peak" as used herein refers to a point in the XRPD pattern where the intensity as measured in counts is at a local maximum. An XRPD peak is identified by its angular value as measured in degrees 2 θ ($^{\circ}2\theta$), depicted on the abscissa of an X-ray powder diffractogram, which may be expressed, for example, as "a signal at ... degrees two-theta," "a signal at [a] two-theta value(s) of ... " and/or "a signal at at least ... two-theta value(s) selected from "

[110] The repeatability of the measured angular values is in the range of $\pm 0.2^{\circ} 2\theta$, i.e., the angular value can be at the recited angular value $+0.2$ degrees two-theta, the angular value -0.2 degrees two-theta, or any value between those two end points (angular value $+0.2$ degrees two-theta and angular value -0.2 degrees two-theta).

[111] One of ordinary skill in the art would recognize that one or more signals (or peaks) in an XRPD pattern may overlap and may, for example, not be apparent to the naked eye. Indeed, one of ordinary skill in the art would recognize that some art-recognized methods are capable of and suitable for determining whether a signal exists in a pattern, such as Rietveld refinement.

[112] The terms "signal intensities" and "peak intensities" interchangeably refer to relative signal intensities within a given X-ray powder diffractogram. Factors that can affect the relative signal or peak intensities include sample thickness and preferred orientation (e.g., the crystalline particles are not distributed randomly).

[113] As used herein, an X-ray powder diffractogram is "substantially similar to that in [a particular] Figure" when at least 90%, such as at least 95%, at least 98%, or at least 99%, of the signals in the two diffractograms overlap. In determining "substantial similarity," one of ordinary skill in the art will understand that there may be variation in the intensities and/or signal positions in XRPD diffractograms even for the same crystalline form. Thus, those of ordinary skill in the art will understand that the signal

maximum values in XRPD diffractograms (in degrees two-theta) generally mean that value is identified as ± 0.2 degrees two-theta of the reported value, an art-recognized variance.

[114] As used herein, the term "glass transition temperature" or "T_g" refers to the temperature above which a hard and brittle "glassy" amorphous solid becomes viscous or rubbery supercooled liquid.

[115] As used herein, the term "melting temperature", "melting point", or "T_m" refers to the temperature at which a crystalline material is in equilibrium with liquid phase.

[116] As used herein, the term "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g., colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include a crystalline drug (dispersed phase) in an amorphous polymer (continuous phase); or alternatively, an amorphous drug (dispersed phase) in an amorphous polymer (continuous phase). In some embodiments, a solid dispersion includes the polymer constituting the dispersed phase, and the drug constitute the continuous phase or, a solid dispersion includes the drug constituting the dispersed phase, and the polymer constituting the continuous phase.

Methods for Synthesis of Compound I

[117] Compound I can be prepared from known materials by the methods described herein, including in the Examples, by other similar methods, and by other methods known to one skilled in the art. As one skilled in the art would appreciate, the functional groups of the intermediate compounds may need to be protected by suitable protecting groups. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art. The use of protecting groups is described in detail in T.G.M. Wuts et al., *Greene's Protective Groups in Organic Synthesis* (4th ed. 2006).

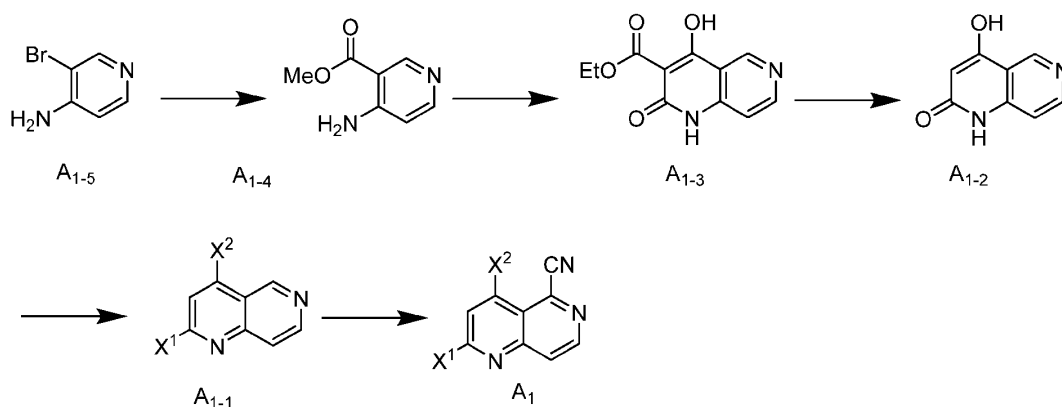
[118] In one embodiment, the skilled artisan could start with any compounds of formulae A₁, A₁₋₁, A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, A₃, A₃₋₁, A₃₋₂, B₁, B₁₋₁, B₁₋₂, B₁₋₃, B₂, C₁, C₂, and C₃ to prepare Compound I or any of the intermediate compounds of formulae A₁, A₁₋₁, A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, A₃, A₃₋₁, A₃₋₂, B₁, B₁₋₁, B₁₋₂, B₁₋₃, B₂, C₁, C₂, and C₃ by following the reactions illustrated in Schemes 1-11.

[119] The method steps described herein may refer to conversion of a starting compound of formulae A₁, A₁₋₁, A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, A₃, A₃₋₁, A₃₋₂, B₁, B₁₋₁, B₁₋₂, B₁₋₃, B₂, C₁, C₂, and C₃ to Compound I. The skilled artisan would understand that such methods can also be used to prepare any intermediate between any starting compound and Compound I. For example, conversion of the compound

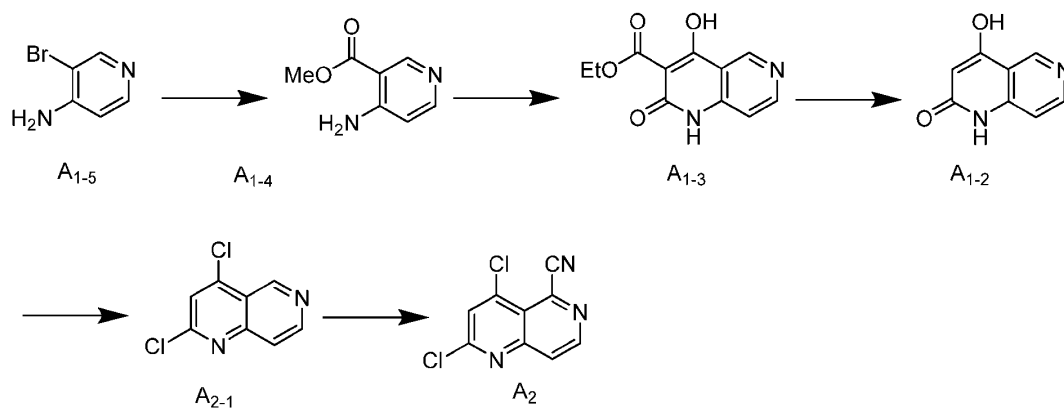
of formula A₁₋₂ to Compound I goes through intermediate compound C₂. As such, the skilled artisan would understand that the methods described for converting the compound of formula A₁₋₂ to Compound I can be used to prepare intermediate compounds A₂₋₁, A₂, and C₂ from the compounds of formula A₁₋₂.

[120] Similarly, conversion of the compound of formula A₃₋₂ to Compound I goes through preparation of intermediate compounds A₃₋₁, A₃, and C₃. As such, the skilled artisan would understand that the methods described for converting the compound of formula A₃₋₂ to Compound I can be used to prepare any of intermediate compounds A₃₋₁, A₃, and C₃ starting with the compound of formula A₃₋₂ or any intermediate compound can be converted to the desired intermediate compound using the methods described herein. Thus, the present application contemplates preparing intermediate compounds A₁, A₁₋₁, A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, A₃, A₃₋₁, A₃₋₂, B₁, B₁₋₁, B₁₋₂, B₁₋₃, B₂, C₁, C₂, and C₃ starting with any intermediate or starting material that precedes the intermediate that is being prepared. For example, intermediate compound C₂ may be prepared starting with any of compounds A₁₋₂, A₁₋₃, A₁₋₄, A₁₋₅, A₂, A₂₋₁, B₁, B₁₋₁, B₁₋₂, B₁₋₃, and B₂. Similarly, compound A₂₋₁ may be prepared starting with any of compounds A₁₋₂, A₁₋₃, A₁₋₄, and A₁₋₅.

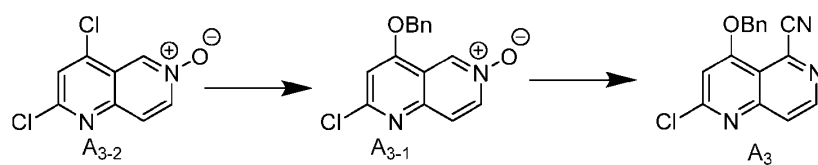
Scheme 1



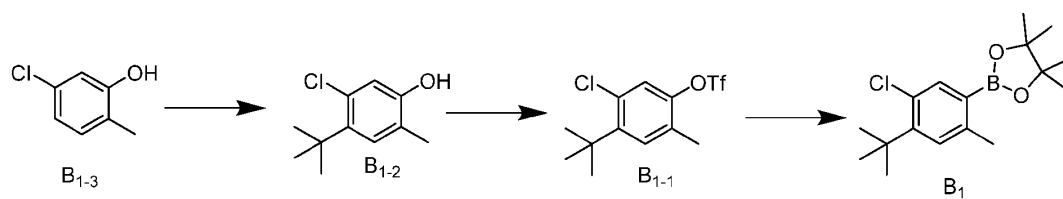
Scheme 2



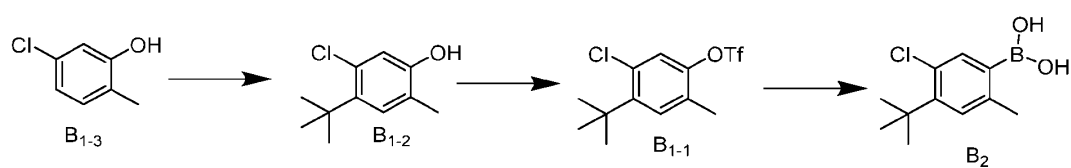
Scheme 3



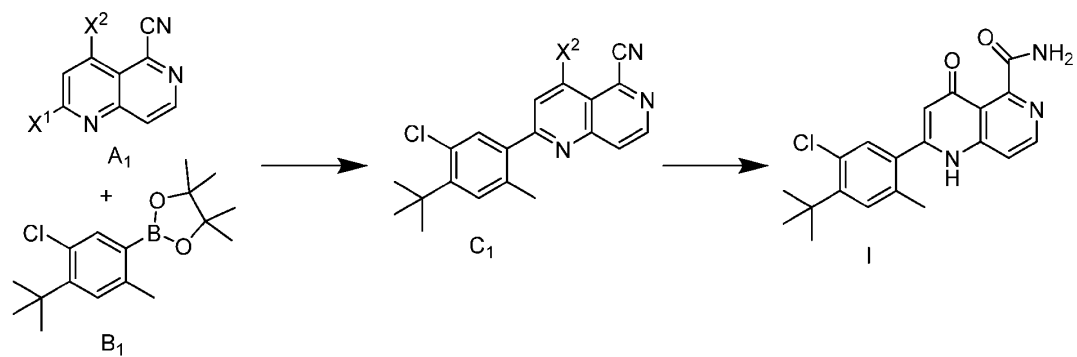
Scheme 4



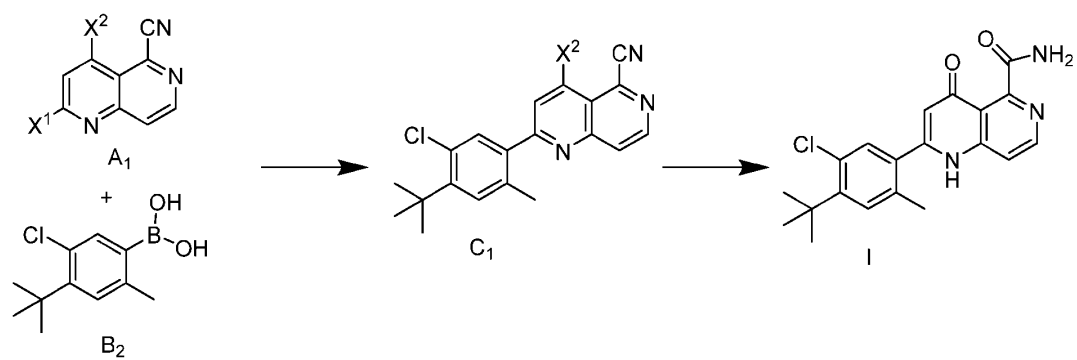
Scheme 5



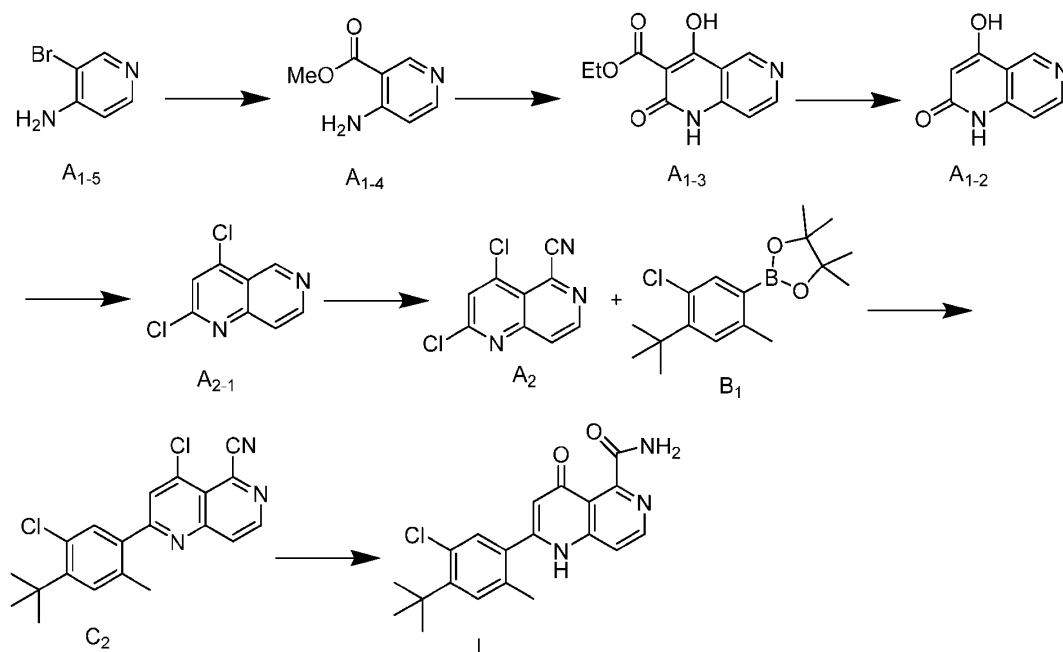
Scheme 6



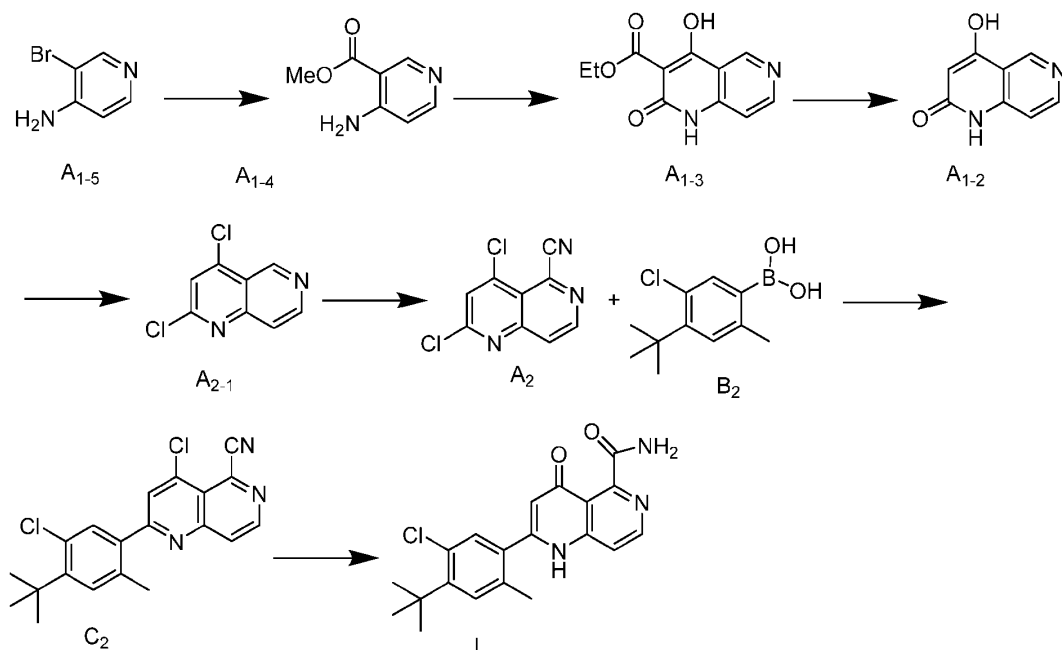
Scheme 7



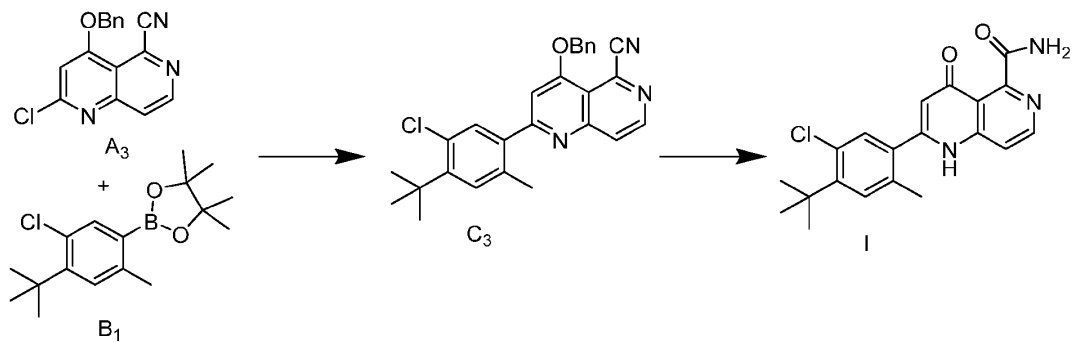
Scheme 8



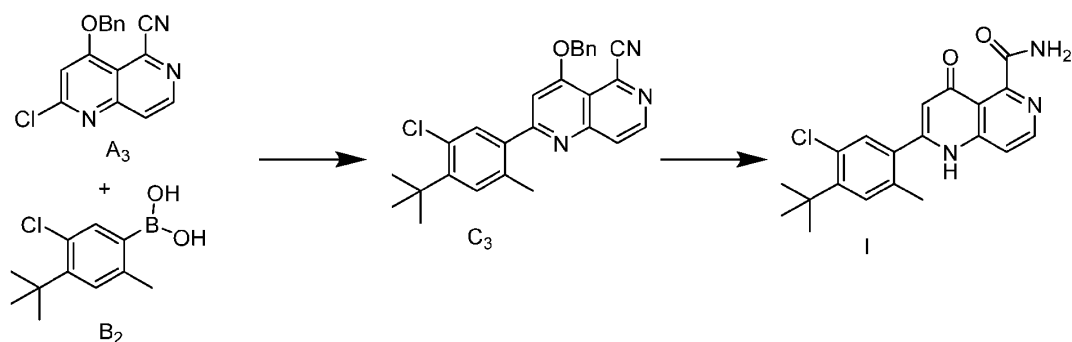
Scheme 9



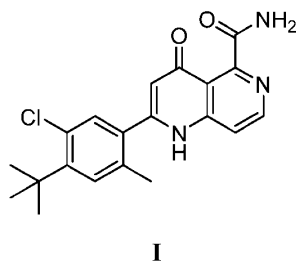
Scheme 10



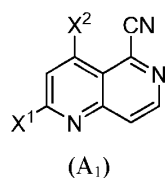
Scheme 11



[121] In one embodiment, the present application provides a process for preparing Compound I and solvates thereof:



comprising transforming a compound of formula (A₁):

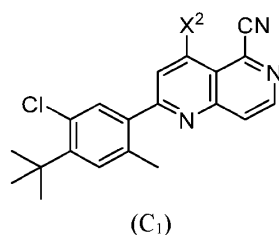


to Compound I; wherein each of X¹ and X² are independently selected from halogen.

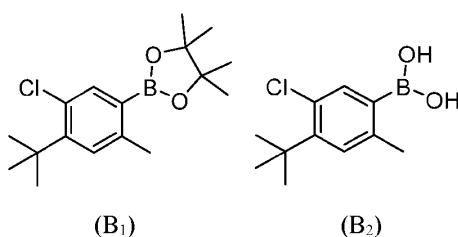
[122] In some embodiments, X¹ and X² are the same. In some embodiments, each of X¹ and X² are fluoro. In some embodiments, each of X¹ and X² are chloro. In some embodiments, each of X¹ and X² are bromo. In some embodiments, each of X¹ and X² are iodo.

[123] In some embodiments, X¹ and X² are different.

[124] In some embodiments, the step of transforming the compound of formula (A₁) to Compound I comprises transforming the compound of formula (A₁) to a compound of formula (C₁):



[125] In some embodiments, the step of transforming the compound of formula (A₁) to the compound of formula (C₁) comprises contacting the compound of formula (A₁) with a compound of formula (B₁) or (B₂):



[126] In some embodiments, the step of transforming the compound of formula (A₁) to the compound of formula (C₁) comprises contacting the compound of formula (A₁) with a compound of formula (B₁). In some embodiments, the step of transforming the compound of formula (A₁) to the compound of formula (C₁) comprises contacting the compound of formula (A₁) with a compound of formula (B₂).

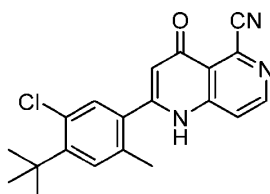
[127] In some embodiments, the step of contacting the compound of formula (A₁) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

[128] In some embodiments, the first palladium catalyst is a palladium-phosphine complex. In some embodiments, the palladium catalyst is PdCl₂(PPh₃)₂.

[129] In some embodiments, the first base is selected from potassium phosphate and potassium carbonate. In some embodiments, the first base is potassium phosphate. In some embodiments, the first base is potassium carbonate.

[130] In some embodiments, the step of transforming the compound of formula (A₁) to Compound I further comprises transforming the compound of formula (C₁) to Compound I. In some embodiments, the step of transforming the compound of formula (C₁) to Compound I comprises treating the compound of formula (C₁) with a first acid. In some embodiments, the first acid is selected from trifluoroacetic acid, sulfuric acid, phosphoric acid, and methane sulfonic acid. In some embodiments, the first acid is trifluoroacetic acid. In some embodiments, the first acid is sulfuric acid. In some embodiments, the first acid is methane sulfonic acid.

[131] In some embodiments, the step of transforming the compound of formula (C₁) to Compound I comprises transforming the compound of formula (C₁) to a compound of formula (C₄):

(C₄)

; and

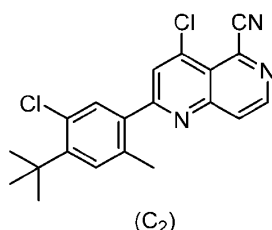
transforming the compound of formula (C₄) to Compound I. In some embodiments, the compound of formula (C₄) is obtained as a salt. In some embodiments, the salt is an HCl salt or a benzenesulfonic acid salt. In some embodiments, the compound of formula (C₄) is obtained as a solvate. In some embodiments, the solvate is an AcOH solvate. In some embodiments, the compound of formula (C₄) is obtained as an HCl salt, AcOH solvate. In some embodiments, the compound of formula (C₄) is obtained as a hydrate.

[132] In some embodiments, the step of transforming the compound of formula (C₁) to the compound of formula (C₄) comprises treating the compound of formula (C₁) with an acid to afford the compound of formula (C₄). In some embodiments, the acid is a Bronsted acid. In some embodiments, the acid is selected from acetic acid, formic acid, sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, *para*-toluenesulfonic acid, and trifluoroacetic acid. In some embodiments, the compound of formula (C₁) is treated with an acid in the presence of water. In some embodiments, the compound of formula (C₁) is treated with an acid in a solvent selected from dimethylsulfoxide (DMSO), toluene, *N*-methylpyrrolidone (NMP), and 1,2-dichloroethane (DCE). In some embodiments, the compound of formula (C₁) is treated with an acid at a temperature of 60-100 °C, e.g., about 100 °C. In some embodiments, the compound of formula (C₁) is the limiting reagent, and the acid is present in excess. In some embodiments, the compound of formula (C₁) is the limiting reagent, the acid is acetic acid (in excess), and the reaction is conducted at a temperature of 60-100 °C, e.g., about 100 °C.

[133] In some embodiments, the step of transforming the compound of formula (C₁) to the compound of formula (C₄) comprises treating the compound of formula (C₁) with a base to afford the compound of formula (C₄). In some embodiments, the base is potassium acetate. In some embodiments, the compound of formula (C₁) is treated with base in the presence of water. In some embodiments, the compound of formula (C₁) is treated with a base in *N,N*-dimethylformamide as a solvent. In some embodiments, the compound of formula (C₁) is treated with a base at a temperature of 80-100 °C. In some embodiments, the compound of formula (C₁) is the limiting reagent, and the base is present in

excess. In some embodiments, the compound of formula (C₁) is the limiting reagent, the base is potassium acetate (in excess), and the reaction is conducted at a temperature of 80-100 °C.

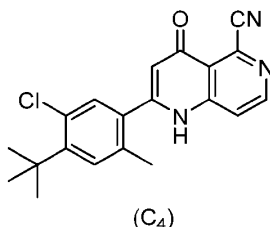
[134] In some embodiments, the compound of formula (C₁) is a compound of formula (C₂), i.e., X² is chloro:



Thus, in these embodiments, the step of transforming the compound of formula (C₁) to Compound I comprises transforming the compound of formula (C₂) to Compound I (see, e.g., Schemes 8 and 9).

[135] In some embodiments, the step of transforming the compound of formula (C₂) to Compound I comprises treating the compound of formula (C₂) with a first acid to afford Compound I. In some embodiments, the first acid is selected from trifluoroacetic acid, sulfuric acid, phosphoric acid, and methanesulfonic acid. In some embodiments, the first acid is trifluoroacetic acid. In some embodiments, the first acid is sulfuric acid. In some embodiments, the first acid is methanesulfonic acid.

[136] In some embodiments, the step of transforming the compound of formula (C₂) to Compound I comprises transforming the compound of formula (C₂) to a compound of formula (C₄):



; and

transforming the compound of formula (C₄) to Compound I.

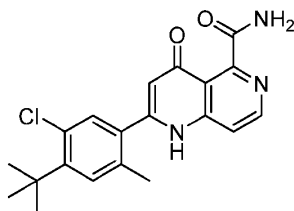
[137] In some embodiments, the step of transforming the compound of formula (C₂) to the compound of formula (C₄) comprises treating the compound of formula (C₂) with an acid to afford the compound of formula (C₄). In some embodiments, the acid is a Bronsted acid. In some embodiments, the acid is selected from acetic acid, formic acid, sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, *para*-toluenesulfonic acid, and trifluoroacetic acid. In some embodiments, the compound of formula (C₂) is treated with an acid in the presence of water. In some embodiments, the compound of formula (C₂) is treated with an acid in a solvent selected from dimethylsulfoxide (DMSO), toluene, *N*-methylpyrrolidone (NMP), and 1,2-dichloroethane (DCE). In

some embodiments, the compound of formula (C₂) is treated with an acid at a temperature of 60-100 °C, e.g., about 100 °C. In some embodiments, the compound of formula (C₂) is the limiting reagent, and the acid is present in excess. In some embodiments, the compound of formula (C₂) is the limiting reagent, the acid is acetic acid (in excess), and the reaction is conducted at a temperature of 60-100 °C, e.g., about 100 °C.

[138] In some embodiments, the step of transforming the compound of formula (C₂) to the compound of formula (C₄) comprises treating the compound of formula (C₂) with a base to afford the compound of formula (C₄). In some embodiments, the base is potassium acetate. In some embodiments, the compound of formula (C₂) is treated with base in the presence of water. In some embodiments, the compound of formula (C₂) is treated with a base in *N,N*-dimethylformamide as a solvent. In some embodiments, the compound of formula (C₂) is treated with a base at a temperature of 80-100 °C. In some embodiments, the compound of formula (C₂) is the limiting reagent, and the base is present in excess. In some embodiments, the compound of formula (C₂) is the limiting reagent, the base is potassium acetate (in excess), and the reaction is conducted at a temperature of 80-100 °C.

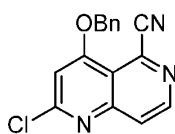
[139] In some embodiments, the step of transforming the compound of formula (C₄) to Compound I comprises treating the compound of formula (C₄) with an acid to afford Compound I. In some embodiments, the acid is a Bronsted acid. In some embodiments, the acid is selected from sulfuric acid, phosphoric acid, and oxalic acid. In some embodiments, the compound of formula (C₄) is treated with an acid in the presence of water. In some embodiments, the compound of formula (C₄) is treated with an acid in a solvent selected from toluene, acetic acid, anisole, γ -valerolactone, and sulfolane. In some embodiments, the compound of formula (C₄) is treated with an acid at a temperature of 20-100 °C, e.g., about 60 °C. In some embodiments, the compound of formula (C₄) is the limiting reagent, and the acid is present in excess. In some embodiments, the compound of formula (C₄) is the limiting reagent, the acid is sulfuric acid (in excess), and the reaction is conducted at a temperature of 20-100 °C, e.g., about 60 °C, in toluene. In some embodiments, the acid is a Lewis acid. In some embodiments, the acid is selected from Cu(OTf)₂, Cu(OAc)₂, In(OTf)₃, InCl₃, WOCl₄, VCl₃, and Sc(OTf)₃. In some embodiments, the compound of formula (C₄) is treated with an acid in the presence of water. In some embodiments, the compound of formula (C₄) is treated with an acid in a solvent or cosolvent selected from toluene, acetic acid, anisole, γ -valerolactone, sulfolane, 2-methyltetrahydrofuran, cyclopentyl methyl ether, *N,N*-dimethylacetamide, isobutyl acetate, *N*-methylcaprolactam, and water. In some embodiments, the compound of formula (C₄) is treated with an acid at a temperature of 20-100 °C, e.g., about 100 °C. In some embodiments, the compound of formula (C₄) is the limiting reagent. In some embodiments, the compound of formula (C₄) is the limiting reagent, the acid is Cu(OTf)₂, acetic acid is present in excess, and the reaction is conducted at a temperature of 20-100 °C, e.g., about 60 °C.

[140] In one embodiment, the present application provides a process for preparing Compound I:



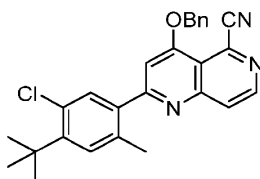
I

comprising transforming a compound of formula (A₃):

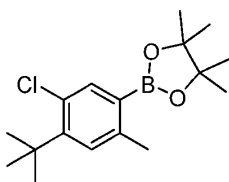
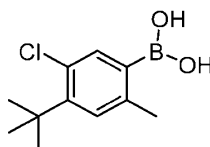
(A₃)

to Compound I.

[141] In some embodiments, the step of transforming the compound of formula (A₃) to Compound I comprises transforming the compound of formula (A₃) to a compound of formula (C₃):

(C₃)

[142] In some embodiments, the step of transforming the compound of formula (A₃) to the compound of formula (C₃) comprises contacting the compound of formula (A₃) with a compound of formula (B₁) or (B₂):

(B₁)(B₂)

[143] In some embodiments, the step of transforming the compound of formula (A₃) to the compound of formula (C₃) comprises contacting the compound of formula (A₃) with a compound of formula (B₁). In some embodiments, the step of transforming the compound of formula (A₃) to the

compound of formula (C₃) comprises contacting the compound of formula (A₃) with a compound of formula (B₂).

[144] In some embodiments, the step of contacting the compound of formula (A₃) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

[145] In some embodiments, the first palladium catalyst is a palladium-phosphine complex. In some embodiments, the first palladium catalyst is PdCl₂(dtbdfp).

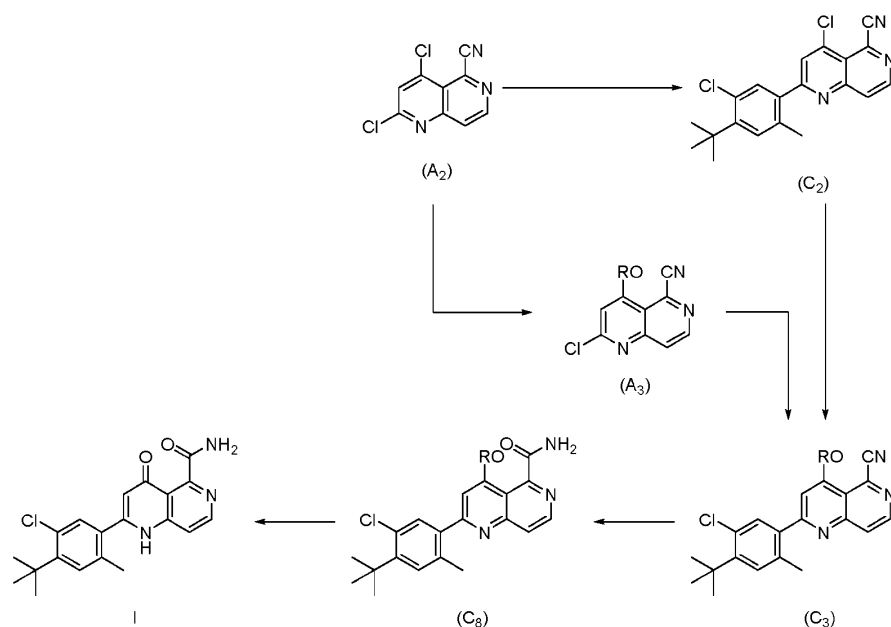
[146] In some embodiments, the first base is selected from potassium phosphate and potassium carbonate. In some embodiments, the first base is potassium phosphate. In some embodiments, the first base is potassium carbonate.

[147] In some embodiments, the step of transforming the compound of formula (A₃) to Compound I further comprises transforming the compound of formula (C₃) to Compound I.

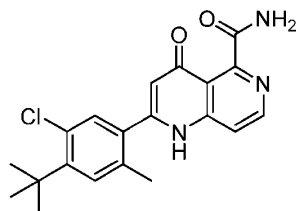
[148] In some embodiments, the step of transforming the compound of formula (C₃) to Compound I comprises treating the compound of formula (C₃) with a first acid. In some embodiments, the first acid is selected from trifluoroacetic acid, sulfuric acid, phosphoric acid, and methane sulfonic acid. In some embodiments, the first acid is trifluoroacetic acid. In some embodiments, the first acid is sulfuric acid. In some embodiments, the first acid is methane sulfonic acid.

[149] In another aspect, the invention relates to a process for preparing Compound I according to Scheme 12.

Scheme 12

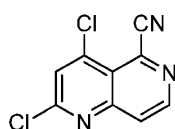


[150] In one embodiment, the invention relates to a process for preparing Compound I:



I

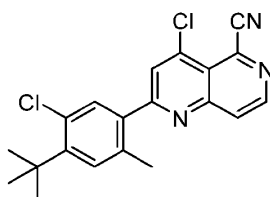
comprising transforming a compound of formula (A₂):



(A₂)

to Compound I.

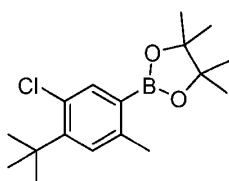
[151] In some embodiments, the step of transforming the compound of formula (A₂) to Compound I comprises transforming the compound of formula (A₂) to a compound of formula (C₂):



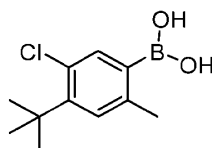
(C₂)

; and

transforming the compound of formula (C₂) to Compound I. In some embodiments, transforming the compound of formula (A₂) to the compound of formula (C₂) comprises treating the compound of formula (A₂) with a compound of formula (B₁) or (B₂):



(B₁)



(B₂)

[152] In some embodiments, the step of transforming the compound of formula (A₂) to the compound of formula (C₂) comprises treating the compound of formula (A₂) with a compound of formula

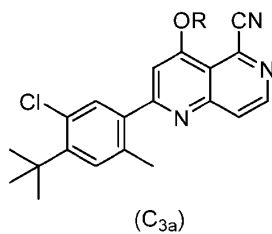
(B₁). In some embodiments, the step of transforming the compound of formula (A₂) to the compound of formula (C₂) comprises treating the compound of formula (A₂) with a compound of formula (B₂).

[153] In some embodiments, the step of treating the compound of formula (A₂) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

[154] In some embodiments, the first palladium catalyst is a palladium-phosphine complex. In some embodiments, the palladium catalyst is PdCl₂(PPh₃)₂.

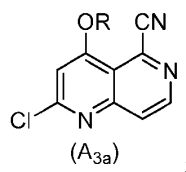
[155] In some embodiments, the first base is selected from potassium phosphate and potassium carbonate. In some embodiments, the first base is potassium phosphate. In some embodiments, the first base is potassium carbonate.

[156] In some embodiments, the step of transforming the compound of formula (C₂) to Compound I comprises transforming the compound of formula (C₂) to a compound of formula (C_{3a}):



wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{3a}) to Compound I. In some embodiments, R is ethyl, isopropyl, *tert*-amyl, or *tert*-butyl. In some embodiments, transforming the compound of formula (C₂) to the compound of formula (C_{3a}) comprises treating the compound of formula (C₂) with NaOR to afford the compound of formula (C_{3a}). For example, in some embodiments where R is ethyl, transforming the compound of formula (C₂) to the compound of formula (C_{3a}) comprises treating the compound of formula (C₂) with NaOEt in ethanol at room temperature. In some embodiments, transforming the compound of formula (C₂) to the compound of formula (C_{3a}) comprises treating the compound of formula (C₂) with ROH and acetic acid at elevated temperature, e.g., 80-100 °C.

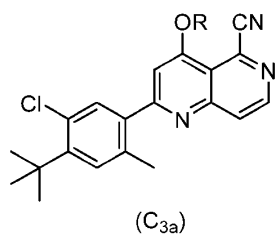
[157] In some embodiments, the step of transforming the compound of formula (A₂) to Compound I comprises transforming the compound of formula (A₂) to a compound of formula (A_{3a}):



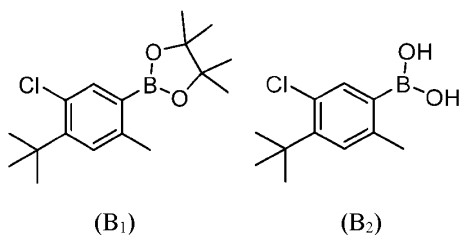
wherein R is C₁-C₆ alkyl; and transforming the compound of formula (A_{3a}) to Compound I. In some embodiments, R is ethyl, isopropyl, *tert*-amyl, or *tert*-butyl. In some embodiments, transforming the

compound of formula (A₂) to the compound of formula (A_{3a}) comprises treating the compound of formula (A₂) with NaOR to afford the compound of formula (A_{3a}). For example, in some embodiments where R is ethyl, transforming the compound of formula (A₂) to the compound of formula (A_{3a}) comprises treating the compound of formula (A₂) with NaOEt in ethanol at room temperature. In some embodiments, transforming the compound of formula (A₂) to the compound of formula (A_{3a}) comprises treating the compound of formula (A₂) with ROH and acetic acid at elevated temperature, e.g., 80-100 °C.

[158] In some embodiments, the step of transforming the compound of formula (A_{3a}) to Compound I comprises transforming the compound of formula (A_{3a}) to a compound of formula (C_{3a}):



wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{3a}) to Compound I. In some embodiments, transforming the compound of formula (A_{3a}) to the compound of formula (C_{3a}) comprises treating the compound of formula (A_{3a}) with a compound of formula (B₁) or (B₂):



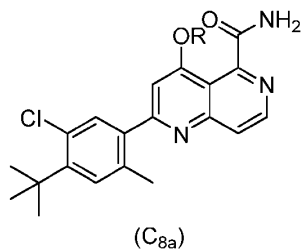
[159] In some embodiments, the step of transforming the compound of formula (A_{3a}) to the compound of formula (C_{3a}) comprises treating the compound of formula (A_{3a}) with a compound of formula (B₁). In some embodiments, the step of transforming the compound of formula (A_{3a}) to the compound of formula (C_{3a}) comprises treating the compound of formula (A_{3a}) with a compound of formula (B₂).

[160] In some embodiments, the step of treating the compound of formula (A_{3a}) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

[161] In some embodiments, the first palladium catalyst is a palladium-phosphine complex. In some embodiments, the palladium catalyst is PdCl₂(PPh₃)₂.

[162] In some embodiments, the first base is selected from potassium phosphate and potassium carbonate. In some embodiments, the first base is potassium phosphate. In some embodiments, the first base is potassium carbonate.

[163] In some embodiments, the step of transforming the compound of formula (C_{3a}) to Compound I comprises transforming the compound of formula (C_{3a}) to a compound of formula (C_{8a}):

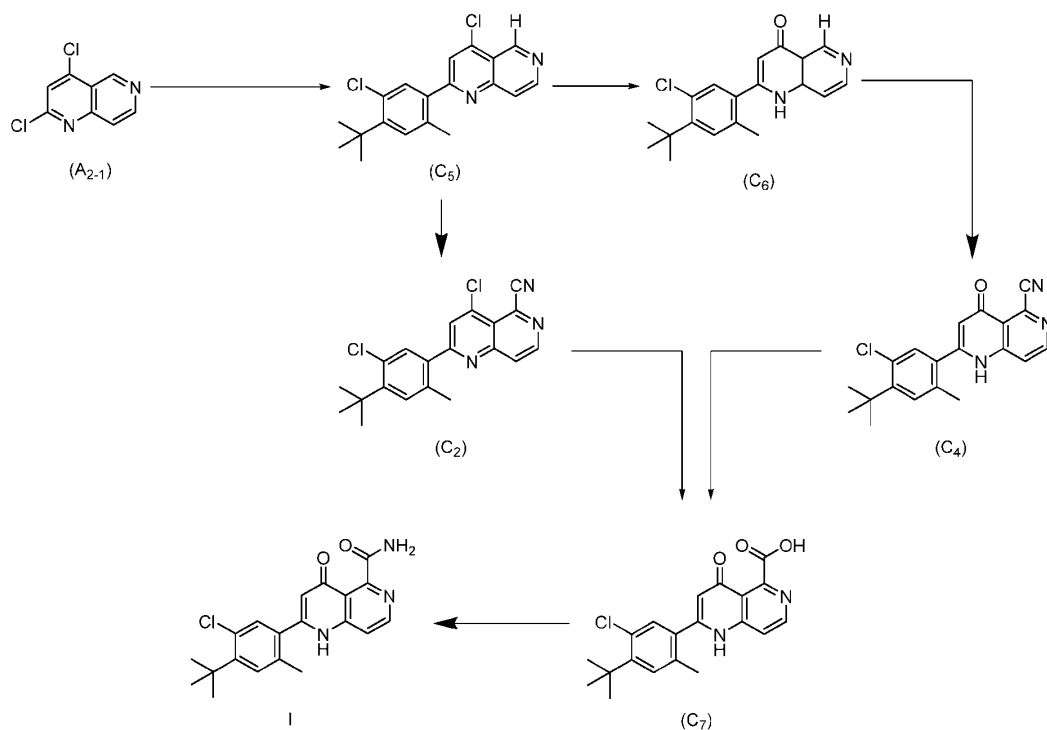


wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{8a}) to Compound I. In some embodiments, transforming the compound of formula (C_{3a}) to the compound of formula (C_{8a}) comprises treating the compound of formula (C_{3a}) with trifluoroacetic acid in the presence of water to afford the compound of formula (C_{8a}).

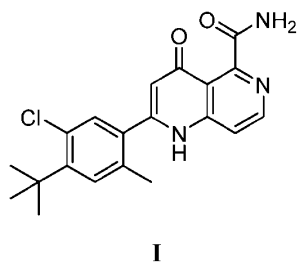
[164] In some embodiments, the step of transforming the compound of formula (C_{8a}) to Compound I comprises treating the compound of formula (C_{8a}) with BBr₃ to afford Compound I.

[165] In another aspect, the invention relates to a process for preparing Compound I according to Scheme 13.

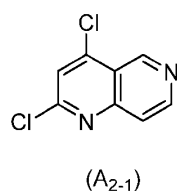
Scheme 13



[166] In one embodiment, the invention relates to a process for preparing Compound I:

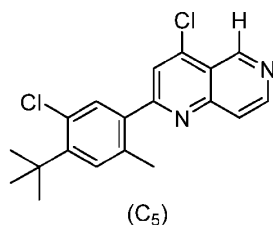


comprising transforming a compound of formula (A₂₋₁):



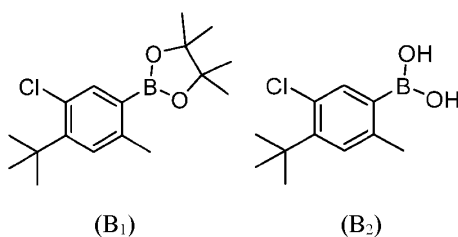
to Compound I.

[167] In some embodiments, the step of transforming the compound of formula (A₂₋₁) to Compound I comprises transforming the compound of formula (A₂₋₁) to a compound of formula (C₅):



; and

transforming the compound of formula (C₅) to Compound I. In some embodiments, transforming the compound of formula (A₂₋₁) to the compound of formula (C₅) comprises treating the compound of formula (A₂₋₁) with a compound of formula (B₁) or (B₂):



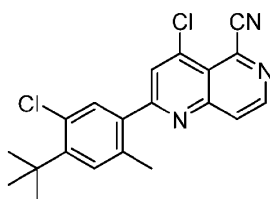
[168] In some embodiments, the step of transforming the compound of formula (A₂₋₁) to the compound of formula (C₅) comprises treating the compound of formula (A₂₋₁) with a compound of formula (B₁). In some embodiments, the step of transforming the compound of formula (A₂₋₁) to the compound of formula (C₅) comprises treating the compound of formula (A₂₋₁) with a compound of formula (B₂).

[169] In some embodiments, the step of treating the compound of formula (A₂₋₁) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

[170] In some embodiments, the first palladium catalyst is a palladium-phosphine complex. In some embodiments, the palladium catalyst is PdCl₂(PPh₃)₂.

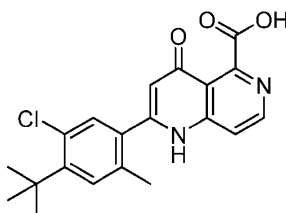
[171] In some embodiments, the first base is selected from potassium phosphate and potassium carbonate. In some embodiments, the first base is potassium phosphate. In some embodiments, the first base is potassium carbonate.

[172] In some embodiments, the step of transforming the compound of formula (C₅) to Compound I comprises transforming the compound of formula (C₅) to a compound of formula (C₂):

(C₂) ; and

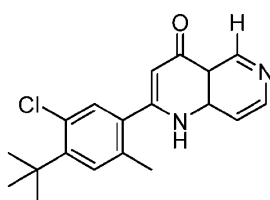
transforming the compound of formula (C₂) to Compound I. In some embodiments, transforming the compound of formula (C₅) to the compound of formula (C₂) comprises treating the compound of formula (C₅) with a cyanating agent (e.g., TMS-CN) and a Lewis acid (e.g., Tf₂O) to afford the compound of formula (C₂).

[173] In some embodiments, the step of transforming the compound of formula (C₂) to Compound I comprises transforming the compound of formula (C₂) to a compound of formula (C₇):

(C₇) ; and

transforming the compound of formula (C₇) to Compound I. In some embodiments, transforming the compound of formula (C₂) to the compound of formula (C₇) comprises treating the compound of formula (C₂) with aqueous base (e.g., NaOH, KOH) to afford the compound of formula (C₇).

[174] In some embodiments, the step of transforming the compound of formula (C₅) to Compound I comprises transforming the compound of formula (C₅) to a compound of formula (C₆):

(C₆) ; and

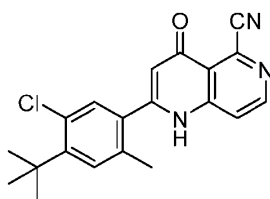
transforming the compound of formula (C₆) to Compound I.

[175] In some embodiments, the step of transforming the compound of formula (C₅) to the compound of formula (C₆) comprises treating the compound of formula (C₅) with an acid to afford the compound of formula (C₆). In some embodiments, the acid is a Bronsted acid. In some embodiments, the

acid is selected from acetic acid, formic acid, sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, *para*-toluenesulfonic acid, and trifluoroacetic acid. In some embodiments, the compound of formula (C₅) is treated with an acid in the presence of water. In some embodiments, the compound of formula (C₅) is treated with an acid in a solvent selected from dimethylsulfoxide (DMSO), toluene, *N*-methylpyrrolidone (NMP), and 1,2-dichloroethane (DCE). In some embodiments, the compound of formula (C₅) is treated with an acid at a temperature of 60-100 °C, e.g., about 100 °C. In some embodiments, the compound of formula (C₅) is the limiting reagent, and the acid is present in excess. In some embodiments, the compound of formula (C₅) is the limiting reagent, the acid is acetic acid (in excess), and the reaction is conducted at a temperature of 60-100 °C, e.g., about 100 °C.

[176] In some embodiments, the step of transforming the compound of formula (C₅) to the compound of formula (C₆) comprises treating the compound of formula (C₅) with a base to afford the compound of formula (C₆). In some embodiments, the base is potassium acetate. In some embodiments, the compound of formula (C₅) is treated with base in the presence of water. In some embodiments, the compound of formula (C₅) is treated with a base in *N,N*-dimethylformamide as a solvent. In some embodiments, the compound of formula (C₅) is treated with a base at a temperature of 80-100 °C. In some embodiments, the compound of formula (C₅) is the limiting reagent, and the base is present in excess. In some embodiments, the compound of formula (C₅) is the limiting reagent, the base is potassium acetate (in excess), and the reaction is conducted at a temperature of 80-100 °C.

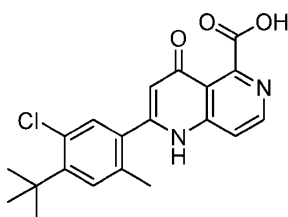
[177] In some embodiments, the step of transforming the compound of formula (C₆) to Compound I comprises transforming the compound of formula (C₆) to a compound of formula (C₄):



(C₄) ; and

transforming the compound of formula (C₄) to Compound I. In some embodiments, transforming the compound of formula (C₆) to the compound of formula (C₄) comprises treating the compound of formula (C₆) with a cyanating agent (e.g., TMSCN) and a Lewis acid (e.g., Tf₂O) to afford the compound of formula (C₄).

[178] In some embodiments, the step of transforming the compound of formula (C₄) to Compound I comprises transforming the compound of formula (C₄) to a compound of formula (C₇):

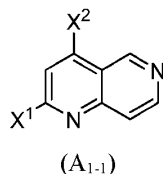
(C₇) ; and

transforming the compound of formula (C₇) to Compound I. In some embodiments, transforming the compound of formula (C₄) to the compound of formula (C₇) comprises treating the compound of formula (C₄) with aqueous base (e.g., NaOH, KOH) to afford the compound of formula (C₇).

[179] In some embodiments, the step of transforming the compound of formula (C₇) to Compound I comprises treating the compound of formula (C₇) with a peptide coupling reagent (e.g., T3P or CDI) and ammonia to afford Compound I.

Preparation of Compound of Formula (A₁)

[180] In some embodiments, the process of preparing Compound I further comprises the step of transforming a compound of formula (A₁₋₁):

(A₁₋₁)

to the compound of formula (A₁).

[181] In some embodiments, the step of transforming a compound of formula (A₁₋₁) to the compound of formula (A₁) comprises the steps of:

treating the compound of formula (A₁₋₁) with trifluoromethanesulfonic anhydride to form a triflyl intermediate;

treating the triflyl intermediate with a cyanation reagent;

treating the cyanated intermediate with a second base to form a cyanated triflyl intermediate; and

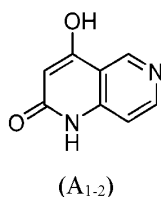
treating the cyanated triflyl intermediate with an aqueous base to form the compound of formula (A₁).

[182] In some embodiments, the cyanation reagent is selected from trimethylsilyl cyanide, sodium cyanide, and potassium cyanide. In some embodiments, the cyanation reagent is trimethylsilyl cyanide. In some embodiments, the cyanation reagent is sodium cyanide. In some embodiments, the cyanation reagent is potassium cyanide.

[183] In some embodiments, the second base is selected from 4-methylmorpholine, triethylamine, and Hunig's base. In some embodiments, the second base is 4-methylmorpholine. In some embodiments, the second base is triethylamine. In some embodiments, the second base is Hunig's base.

[184] In some embodiments, the aqueous base is aqueous sodium bicarbonate.

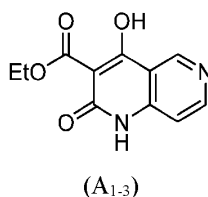
[185] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A_{1.2}):



to the compound of formula (A_{1.1}).

[186] In some embodiments, the step of transforming the compound of formula (A_{1.2}) to the compound of formula (A_{1.1}) comprises treating the compound of formula (A_{1.2}) with a chlorinating reagent. In some embodiments, the chlorinating reagent is selected from HCl, oxalyl chloride, trichloroacetic anhydride/phosgene, triphenylphosphine dichloride, phenylphosphonic dichloride, phosphorous trichloride, phosphorous pentachloride, phosphorous oxychloride, thionyl chloride, p-toluenesulfonyl chloride, and methanesulfonyl chloride. In some embodiments, the chlorinating reagent is phosphorous oxychloride. In some embodiments, the chlorinating reagent is selected from Cl₂ (with/without oxidant), HCl/Cl₂ - plus oxidant, N-chlorosuccinimide (NCS)/dichlorodimethylhydantoin (DCDMH)/trichloroisocyanuric acid (TCCA) sodium dichloroisocyanurate NaDCC, NaOCl, SO₂Cl₂, and CCl₄/C₂Cl₆. In some embodiments, the chlorinating reagent is selected from phosphorus oxychloride and phosphorus pentachloride. In some embodiments, the chlorinating reagent is phosphorus oxychloride.

[187] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A_{1.3}):



to the compound of formula (A_{1.2}).

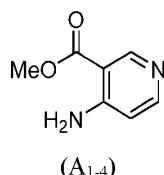
[188] In some embodiments, the step of transforming a compound of formula (A_{1.3}) to the compound of formula (A_{1.2}) comprises treating the compound of formula (A_{1.3}) with a second acid. In

some embodiments, the second acid is a monoprotic acid selected from aqueous hydrochloric acid, acetic acid, nitric acid, and benzoic acid. In some embodiments, the second acid is a polyprotic acid. In some embodiments, the second acid is a diprotic acid selected from sulfuric acid, carbonic acid, hydrogen sulfide, chromic acid, sulfurous acid, and oxalic acid. In some embodiments, the second acid is a triprotic acid selected from phosphoric acid and citric acid. In some embodiments, the second acid is aqueous hydrochloric acid.

[189] In some embodiments, the step of transforming a compound of formula (A_{1.3}) to the compound of formula (A_{1.2}) comprises heating the compound of formula (A_{1.3}).

[190] In some embodiments, the step of transforming a compound of formula (A_{1.3}) to the compound of formula (A_{1.2}) comprises treating the compound of formula (A_{1.3}) with aqueous base (e.g., aqueous sodium hydroxide) to afford the compound of formula (A_{1.2}).

[191] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A_{1.4}):

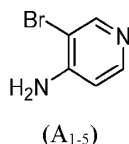


to the compound of formula (A_{1.3}).

[192] In some embodiments, the step of transforming a compound of formula (A_{1.4}) to the compound of formula (A_{1.3}) comprises treating the compound of formula (A_{1.4}) with diethyl malonate in the presence of a third base. In some embodiments, the third base is an alkaline alkoxide. In some embodiments, the third base is an alkaline methoxide. In some embodiments, the third base is selected from lithium methoxide, sodium methoxide, and potassium methoxide. In some embodiments, the third base is lithium methoxide. In some embodiments, the third base is sodium methoxide. In some embodiments, the third base is potassium methoxide. In some embodiments, the third base is an alkaline ethoxide. In some embodiments, the third base is selected from lithium ethoxide, sodium ethoxide, and potassium ethoxide. In some embodiments, the third base is lithium ethoxide. In some embodiments, the third base is sodium ethoxide. In some embodiments, the third base is potassium ethoxide. In some embodiments, the third base is an alkaline tert-butoxide. In some embodiments, the third base is selected from lithium tert-butoxide, sodium tert-butoxide, and potassium tert-butoxide. In some embodiments, the third base is lithium tert-butoxide. In some embodiments, the third base is sodium tert-butoxide. In some embodiments, the third base is potassium tert-butoxide. In some embodiments, third base is an alkaline tert-pentoxide. In some embodiments, the third base is selected from lithium tert-pentoxide, sodium tert-

pentoxide, and potassium tert-pentoxide. In some embodiments, the third base is lithium tert-pentoxide. In some embodiments, the third base is sodium tert-pentoxide. In some embodiments, the third base is potassium tert-pentoxide. In some embodiments, the third base is selected from lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, and potassium bis(trimethylsilyl)amide. In some embodiments, the third base is lithium bis(trimethylsilyl)amide. In some embodiments, the third base is sodium bis(trimethylsilyl)amide. In some embodiments, the third base is potassium bis(trimethylsilyl)amide. In some embodiments, the third base is an alkaline hydride. In some embodiments, the third base is selected from lithium hydride, sodium hydride, and potassium hydride. In some embodiments, the third base is lithium hydride. In some embodiments, the third base is sodium hydride. In some embodiments, the third base is potassium hydride.

[193] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A₁₋₅):



to the compound of formula (A₁₋₄).

[194] In some embodiments, the step of transforming the compound of formula (A₁₋₅) to the compound of formula (A₁₋₄) comprises treating the compound of formula (A₁₋₅) with carbon monoxide in the presence of a fourth base, a second palladium catalyst, and a first suitable ligand.

[195] In some embodiments, the fourth base is selected from triethylamine, Hunig's Base, 4-methylmorpholine, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-Diazabicyclo[2.2.2]octane (DABCO). In some embodiments, the fourth base is triethylamine. In some embodiments, the fourth base is Hunig's Base. In some embodiments, the fourth base is 4-methylmorpholine. In some embodiments, the fourth base is DBU. In some embodiments, the fourth base is DABCO.

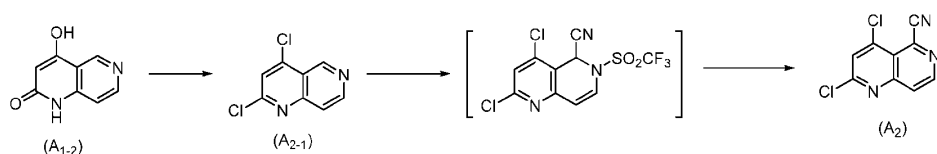
[196] In some embodiments, the second palladium catalyst is Pd(OAc)₂.

[197] In some embodiments, the first suitable ligand is selected from 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), triphenylphosphine (PPh₃), and 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (BINAP). In some embodiments, the first suitable ligand is DPPF. In some embodiments, the first suitable ligand is XantPhos. In some embodiments, the first suitable ligand is PPh₃. In some embodiments, the first suitable ligand is BINAP.

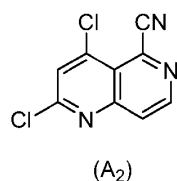
Preparation of Compound of Formula (A₂)

[198] In another aspect, the invention relates to processes for preparing a compound of formula (A₂), as set forth herein. Accordingly, in some embodiments, the invention relates to a process for preparing a compound of formula (A₂), as set forth herein. In other embodiments, the invention relates to a process for preparing Compound I, wherein the compound of formula (A₂) is prepared as set forth herein.

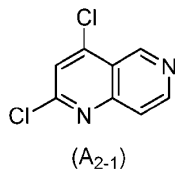
[199] In another aspect, the invention relates to a process for preparing a compound of formula (A₂) according to Scheme 14.

Scheme 14

[200] In one embodiment, the invention relates to a process for preparing a compound of formula (A₂):



comprising transforming a compound of formula (A₂₋₁):

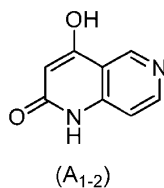


to the compound of formula (A₂). In some embodiments, the step of transforming a compound of formula (A₂₋₁) to the compound of formula (A₂) comprises treating the compound of formula (A₂₋₁) with trifluoromethanesulfonic anhydride, followed by a cyanating agent, to form a cyanated triflyl intermediate; and then treating the cyanated triflyl intermediate with an aqueous base to form the compound of formula (A₂). In some embodiments, the step of transforming a compound of formula (A₂₋₁) to the compound of formula (A₂) comprises treating the compound of formula (A₂₋₁) with a cyanating agent, followed by trifluoromethanesulfonic anhydride, to form a cyanated triflyl intermediate; and then treating the cyanated triflyl intermediate with an aqueous base to form the compound of formula (A₂).

[201] In some embodiments, the cyanating agent is selected from trimethylsilyl cyanide, sodium cyanide, and potassium cyanide. In some embodiments, the cyanation reagent is trimethylsilyl cyanide. In some embodiments, the cyanation reagent is sodium cyanide. In some embodiments, the cyanation reagent is potassium cyanide.

[202] In some embodiments, the aqueous base is aqueous sodium bicarbonate and sodium thiosulfate.

[203] In some embodiments, the process further comprises the step of transforming a compound of formula (A₁₋₂):

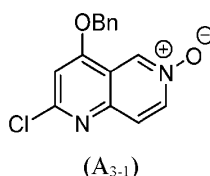


to the compound of formula (A₂₋₁). In some embodiments, the step of transforming the compound of formula (A₁₋₂) to the compound of formula (A₂₋₁) comprises treating the compound of formula (A₁₋₂) with a chlorinating reagent. In some embodiments, the chlorinating reagent is selected from HCl, oxalyl chloride, trichloroacetic anhydride/phosgene, triphenylphosphine dichloride, phenylphosphonic dichloride, phosphorous trichloride, phosphorous pentachloride, phosphorous oxychloride, thionyl chloride, p-toluenesulfonyl chloride, and methanesulfonyl chloride. In some embodiments, the chlorinating reagent is phosphorous oxychloride. In some embodiments, the chlorinating reagent is selected from Cl₂ (with/without oxidant), HCl/Cl⁻ plus oxidant, N-chlorosuccinimide (NCS)/dichlorodimethylhydantoin (DCDMH)/trichloroisocyanuric acid (TCCA) sodium dichloroisocyanurate NaDCC, NaOCl, SO₂Cl₂, and CCl₄/C₂Cl₆. In some embodiments, the chlorinating reagent is selected from phosphorus oxychloride and phosphorus pentachloride. In some embodiments, the chlorinating reagent is phosphorus oxychloride.

[204] In some embodiments, the process further comprises the steps of (1) transforming a compound of formula (A₁₋₃) to the compound of formula (A₁₋₂); and/or (2) transforming a compound of formula (A₁₋₄) to the compound of formula (A₁₋₃); and/or (3) transforming a compound of formula (A₁₋₅) to the compound of formula (A₁₋₄), as set forth above in connection with the preparation of the compound of formula (A₁).

Preparation of Compound of Formula (A₃)

[205] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A₃₋₁):



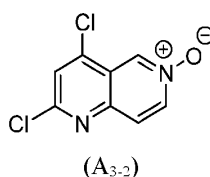
to the compound of formula (A₃).

[206] In some embodiments, the step of transforming a compound of formula (A₃₋₁) to the compound of formula (A₃) comprises treating the compound of formula (A₃₋₁) with a cyanation reagent and a second base.

[207] In some embodiments, the cyanation reagent is selected from trimethylsilyl cyanide, sodium cyanide, and potassium cyanide. In some embodiments, the cyanation reagent is trimethylsilyl cyanide. In some embodiments, the cyanation reagent is sodium cyanide. In some embodiments, the cyanation reagent is potassium cyanide.

[208] In some embodiments, the second base is selected from triethylamine, 4-methylmorpholine, and Hunig's base. In some embodiments, the second base is triethylamine. In some embodiments, the second base is 4-methylmorpholine. In some embodiments, the second base is Hunig's base.

[209] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (A₃₋₂):



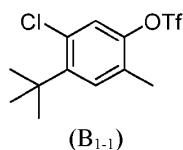
to the compound of formula (A₃₋₁).

[210] In some embodiments, the step of transforming a compound of formula (A₃₋₂) to the compound of formula (A₃₋₁) comprises treating the compound of formula (A₃₋₂) with benzyl alcohol in the presence of a third base. In some embodiments, the third base is an alkaline alkoxide. In some embodiments, the third base is lithium *tert*-butoxide.

Preparation of Compound of Formula (B₁)

[211] In another aspect, the invention relates to processes for preparing a compound of formula (B₁), as set forth herein. Accordingly, in some embodiments, the invention relates to a process for preparing a compound of formula (B₁), as set forth herein. In other embodiments, the invention relates to a process for preparing Compound I, wherein the compound of formula (B₁) is prepared as set forth herein.

[212] In some embodiments, the process for preparing Compound I comprises transforming a compound of formula (B_{1.1}):



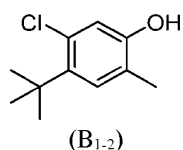
to the compound of formula (B₁).

[213] In some embodiments, the step of transforming the compound of formula (B_{1.1}) to the compound of formula (B₁) comprises treating the compound of formula (B_{1.1}) with bis(pinacolato)diboron in the presence of a third palladium catalyst and a fifth base.

[214] In some embodiments, the third palladium catalyst is selected from Pd(dppf)Cl₂, Pd(PCy₃)₂, and Pd₂dba₃. In some embodiments, the third palladium catalyst is Pd(dppf)Cl₂. In some embodiments, the third palladium catalyst is Pd(PCy₃)₂. In some embodiments, the third palladium catalyst is Pd₂dba₃.

[215] In some embodiments, the fifth base is selected from KOPh, triethylamine, Hunig's Base, KOEt, and KOAc. In some embodiments, the fifth base is KOPh. In some embodiments, the fifth base is triethylamine. In some embodiments, the fifth base is Hunig's Base. In some embodiments, the fifth base is KOEt. In some embodiments, the fifth base is KOAc.

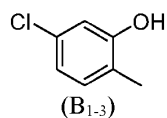
[216] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (B_{1.2}):



to the compound of formula (B_{1.1}).

[217] In some embodiments, the step of transforming the compound of formula (B_{1.2}) to the compound of formula (B_{1.1}) comprises contacting the compound of formula (B_{1.2}) with trifluoromethanesulfonic anhydride, optionally in the presence of a sixth base. In some embodiments, the sixth base is pyridine.

[218] In some embodiments, the process of preparing Compound I comprises transforming a compound of formula (B₁₋₃):

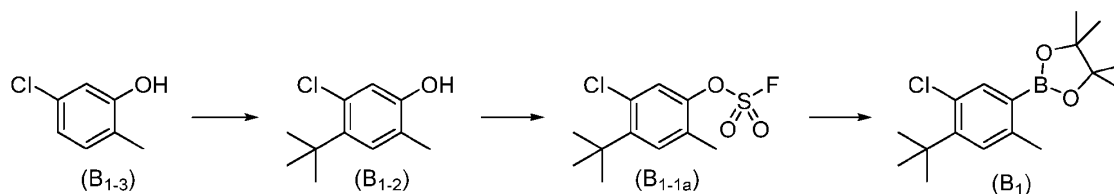


to the compound of formula (B₁₋₂).

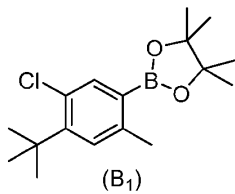
[219] In some embodiments, the step of transforming the compound of formula (B₁₋₃) to the compound of formula (B₁₋₂) comprises treating the compound of formula (B₁₋₃) with *tert*-butanol and a third acid. In some embodiments, the third acid is sulfuric acid.

[220] In another aspect, the invention relates to a process for preparing a compound of formula (B₁) according to Scheme 15.

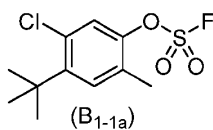
Scheme 15



[221] In one embodiment, the invention relates to a process for preparing a compound of formula (B₁):



comprising transforming a compound of formula (B_{1-1a}):



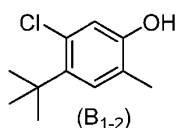
to the compound of formula (B₁). In some embodiments, the step of transforming the compound of formula (B_{1-1a}) to the compound of formula (B₁) comprises treating the compound of formula (B_{1-1a}) with bis(pinacolato)diboron in the presence of a palladium catalyst and a base.

[222] In some embodiments, the palladium catalyst is selected from Pd(OAc)₂ and dppf, Pd(dppf)Cl₂, Pd(PCy₃)₂, and Pd₂dba₃. In some embodiments, the palladium catalyst is Pd(OAc)₂ and

dppf. In some embodiments, the palladium catalyst is Pd(dppf)Cl_2 . In some embodiments, the palladium catalyst is $\text{Pd(PCy}_3)_2$. In some embodiments, the palladium catalyst is Pd_2dba_3 .

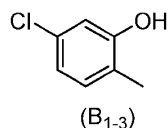
[223] In some embodiments, the base is selected from KOPh, triethylamine, Hunig's Base, KOEt, and KOAc. In some embodiments, the base is KOPh. In some embodiments, the base is triethylamine. In some embodiments, the base is Hunig's Base. In some embodiments, the base is KOEt. In some embodiments, the base is KOAc.

[224] In some embodiments, the process further comprises the step of transforming a compound of formula (B₁₋₂):



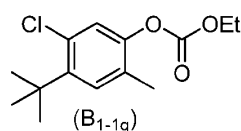
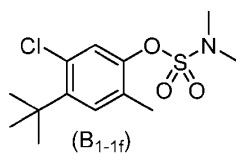
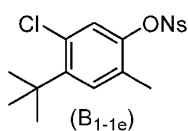
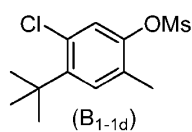
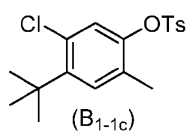
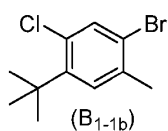
to the compound of formula (B_{1-1a}). In some embodiments, the step of transforming the compound of formula (B₁₋₂) to the compound of formula (B_{1-1a}) comprises treating the compound of formula (B₁₋₂) with sulfonyl fluoride (SO_2F_2) and a base (e.g., trimethylamine) to afford the compound of formula (B_{1-1a}).

[225] In some embodiments, the process further comprises the step of transforming a compound of formula (B₁₋₃):



to the compound of formula (B₁₋₂). In some embodiments, the step of transforming the compound of formula (B₁₋₃) to the compound of formula (B₁₋₂) comprises treating the compound of formula (B₁₋₃) with *tert*-butanol and an acid. In some embodiments, the acid is sulfuric acid.

[226] In some embodiments, the compound of formula (B_{1-1a}) may be replaced in the foregoing process with any one of the compounds of formulas (B_{1-1b}), (B_{1-1c}), (B_{1-1d}), (B_{1-1e}), (B_{1-1f}), and (B_{1-1g}), which may be used in the foregoing process under conditions similar to those used with the compound of formula (B_{1-1a}):

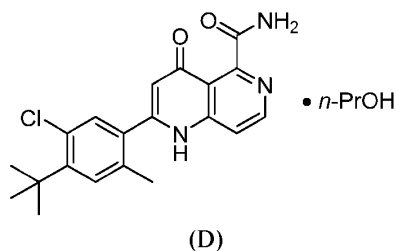


Preparation of Solid Forms of Compound I

[227] In some embodiments, the process of preparing Compound I further comprises transforming Compound I to a solvate of Compound I.

[228] In some embodiments, the step of transforming Compound I to the solvate of Compound I comprises recrystallizing Compound I from an appropriate solvent. In some embodiments, the appropriate solvent is 1-propanol.

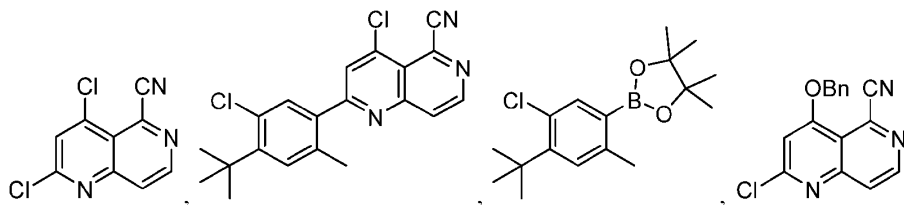
[229] In some embodiments, the solvate of Compound I is a compound of formula (D):

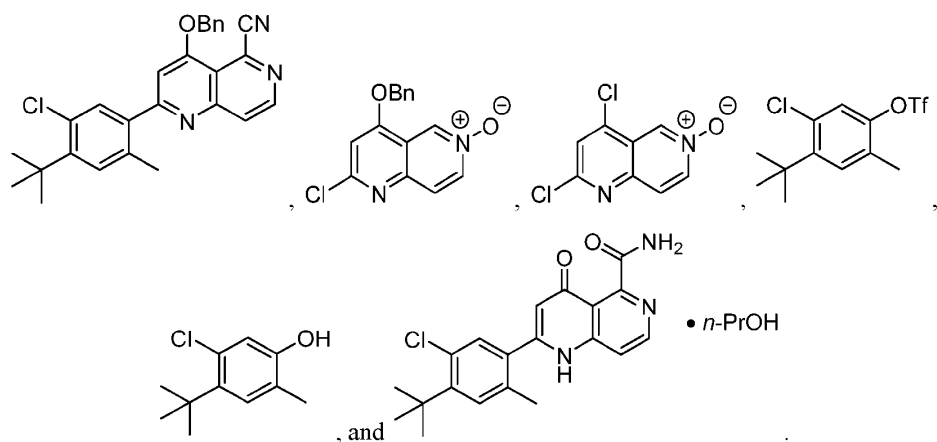


[230] In some embodiments, the process of preparing Compound I comprises transforming the solvate of Compound I to Form A of Compound I.

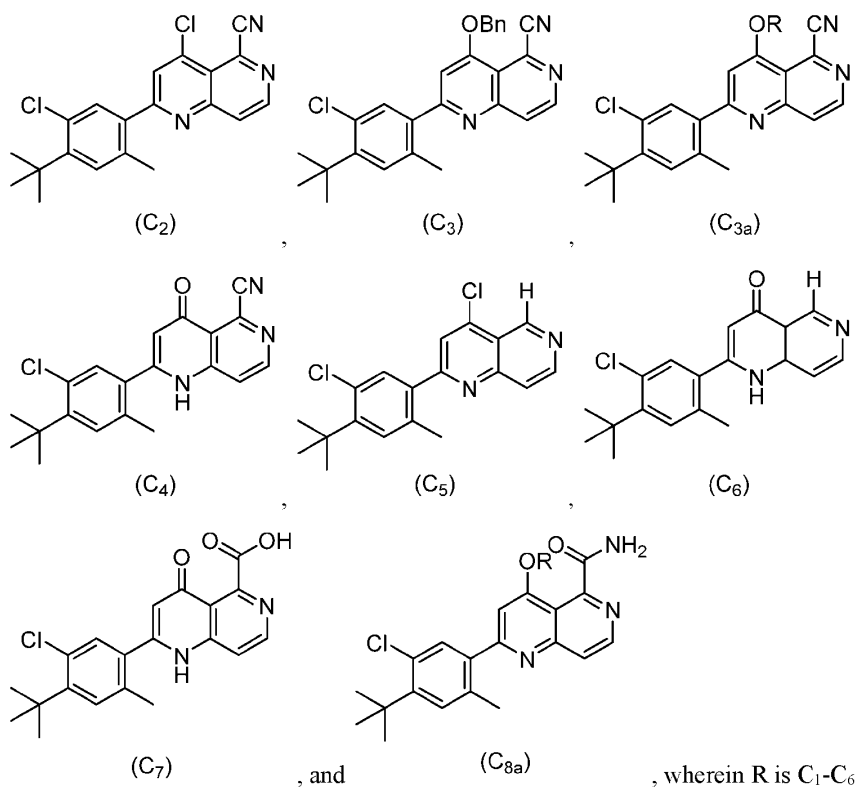
[231] In some embodiments, the step of transforming the solvate of Compound I to Form A of Compound I comprises a methanol solvent exchange and drying.

[232] In one aspect, the invention relates to a compound selected from:



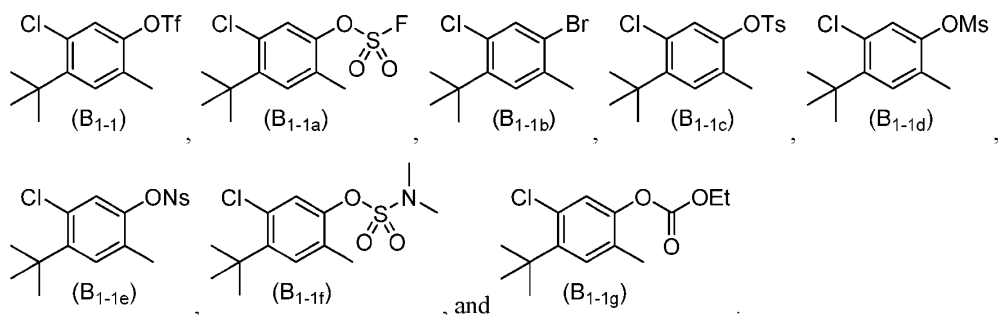


[233] In another aspect, the invention relates to a compound selected from:

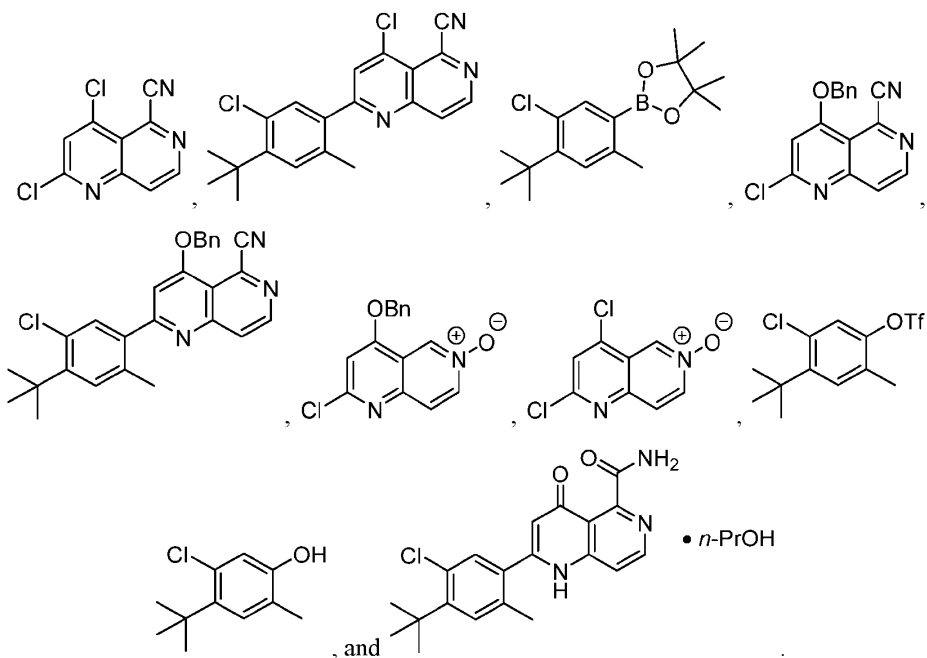


(C₇) , and (C_{8a}) , wherein R is C₁-C₆ alkyl. In some embodiments, R is ethyl, isopropyl, *tert*-amyl, or *tert*-butyl.

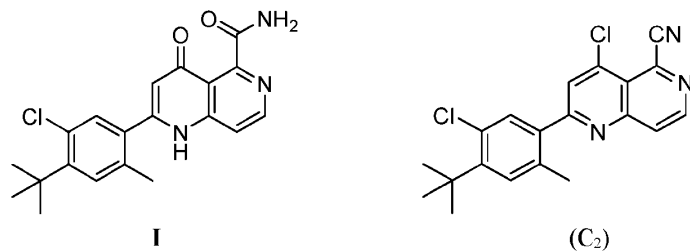
[234] In another aspect, the invention relates to a compound selected from:



[235] In another aspect of the present disclosure, a composition comprising one or more compounds is disclosed, the compounds selected from:

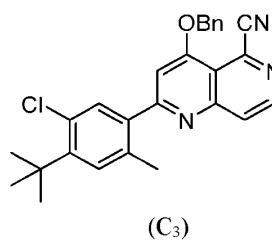
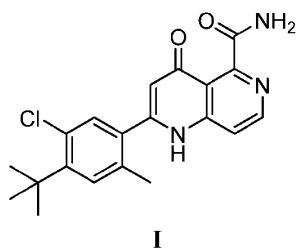


[236] In another aspect of the present disclosure, a composition is disclosed comprising Compound I and a compound of formula (C₂):



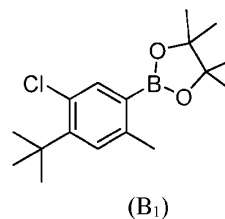
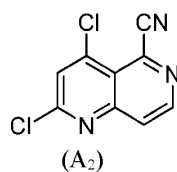
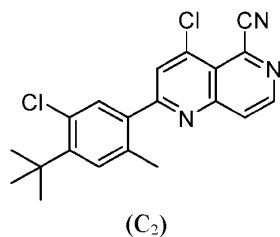
[237] In some embodiments, the composition comprising Compound I and a compound of formula (C₂) further comprises an acid. In some embodiments, the acid is trifluoroacetic acid.

[238] In another aspect of the present disclosure, a composition is disclosed comprising Compound I and a compound of formula (C₃):

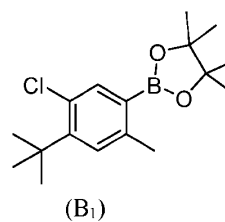
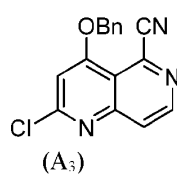
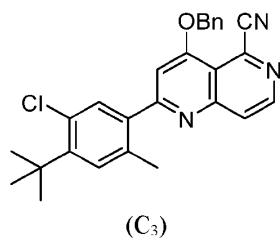


[239] In some embodiments, the composition comprising Compound I and a compound of formula (C₃) further comprises an acid. In some embodiments, the acid is trifluoroacetic acid.

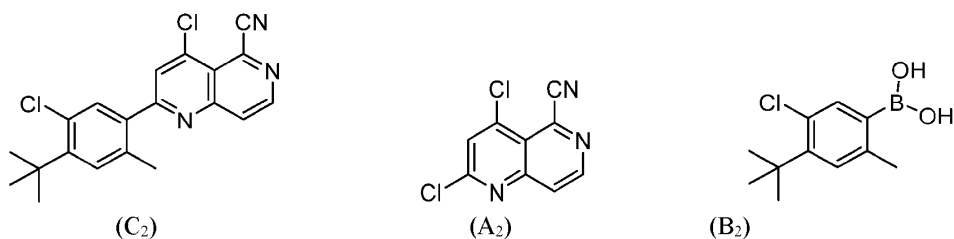
[240] In another aspect of the present disclosure, a composition is disclosed comprising a compound of formula (C₂), a compound of formula (A₁), and a compound of formula (B₁):



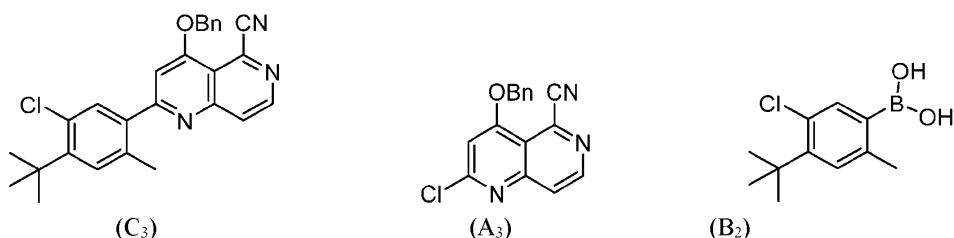
[241] In another aspect of the present disclosure, a composition is disclosed comprising a compound of formula (C₃), a compound of formula (A₃), and a compound of formula (B₁):



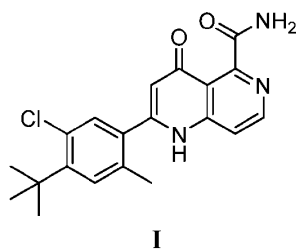
[242] In another aspect of the present disclosure, a composition is disclosed comprising a compound of formula (C₂), a compound of formula (A₂), and a compound of formula (B₂):



[243] In another aspect of the present disclosure, a composition is disclosed comprising a compound of formula (C₃), a compound of formula (A₃), and a compound of formula (B₂):



[244] In another aspect of the present disclosure, a composition is disclosed comprising Compound I:



or a solvate thereof or a pharmaceutically acceptable salt thereof, prepared by any of the processes disclosed herein.

Solid Forms of Compound I

[245] Another aspect of the disclosure provides solid forms of Compound I (e.g., amorphous forms, crystalline forms, solvates, hydrates, and cocrystals), which can be used in the methods of treatment and pharmaceutical compositions described herein. In some embodiments, the invention provides neat crystalline forms of Compound I. In some embodiments, the invention provides solvate crystalline forms of Compound I. In some embodiments, the invention provides hydrate crystalline forms of Compound I.

In some embodiments, the invention provides hemihydrate crystalline forms of Compound I. In some embodiments, the invention provides cocrystal crystalline forms of Compound I. In some embodiments, the invention provides amorphous forms of Compound I.

A. Crystalline Compound I Neat Form A

[246] In some embodiments, the invention provides neat crystalline forms of Compound I. In some embodiments, the invention provides crystalline Compound I Neat Form A.

[247] In some embodiments, Compound I Neat Form A is substantially pure. In some embodiments, Compound I Neat Form A is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Neat Form A is substantially 100% crystalline. In some embodiments, Compound I Neat Form A is 100% crystalline.

[248] In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having a signal at 5.5 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having a signal at 9.0 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having a signal at 10.4 ± 0.2 degrees two-theta.

[249] In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 12.8 ± 0.2 degrees two-theta, 16.0 ± 0.2 degrees two-theta, and 20.4 ± 0.2 degrees two-theta.

[250] In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 12.8 ± 0.2 degrees two-theta, 16.0 ± 0.2 degrees two-theta, and 20.4 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 8.0 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta.

[251] In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram having signals at 5.5 ± 0.2 degrees two-theta, 8.0 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, 11.1 ± 0.2 degrees two-theta, 11.7 ± 0.2 degrees two-theta, 12.8 ± 0.2 degrees two-theta, 16.0 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.7 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.9 ± 0.2 degrees two-theta, 27.4 ± 0.2

degrees two-theta, 27.7 ± 0.2 degrees two-theta, 29.5 ± 0.2 degrees two-theta, and 29.9 ± 0.2 degrees two-theta.

[252] In some embodiments, Compound I Neat Form A is characterized by an X-ray powder diffractogram substantially similar to FIG. 8.

[253] In some embodiments, Compound I Neat Form A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm. In some embodiments, Compound I Neat Form A is characterized by a ^{13}C SSNMR spectrum having peaks at 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm.

[254] In some embodiments, Compound I Neat Form A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.8 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.7 ± 0.2 ppm, 168.3 ± 0.2 ppm, 156.0 ± 0.2 ppm, 153.1 ± 0.2 ppm, 152.4 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.4 ± 0.2 ppm, 148.3 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.8 ± 0.2 ppm, 135.7 ± 0.2 ppm, 134.6 ± 0.2 ppm, 132.8 ± 0.2 ppm, 130.9 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.5 ± 0.2 ppm, 36.4 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.7 ± 0.2 ppm, and 20.5 ± 0.2 ppm. In some embodiments, Compound I Neat Form A is characterized by a ^{13}C SSNMR spectrum having peaks at 178.8 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.7 ± 0.2 ppm, 168.3 ± 0.2 ppm, 156.0 ± 0.2 ppm, 153.1 ± 0.2 ppm, 152.4 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.4 ± 0.2 ppm, 148.3 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.8 ± 0.2 ppm, 135.7 ± 0.2 ppm, 134.6 ± 0.2 ppm, 132.8 ± 0.2 ppm, 130.9 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.5 ± 0.2 ppm, 36.4 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.7 ± 0.2 ppm, and 20.5 ± 0.2 ppm.

[255] In some embodiments, Compound I Neat Form A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.7 ± 0.2 ppm, 178.8 ± 0.2 ppm, 177.6 ± 0.2 ppm, 174.8 ± 0.2 ppm, 169.8 ± 0.2 ppm, 168.3 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.9 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.4 ± 0.2 ppm, 151.1 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm,

146.8 $\pm$ 0.2 ppm, 145.7 $\pm$ 0.2 ppm, 144.7 $\pm$ 0.2 ppm, 135.6 $\pm$ 0.2 ppm, 135.0 $\pm$ 0.2 ppm, 132.8 $\pm$ 0.2 ppm, 131.0 $\pm$ 0.2 ppm, 116.3 $\pm$ 0.2 ppm, 115.1 $\pm$ 0.2 ppm, 113.5 $\pm$ 0.2 ppm, 111.4, 36.3 $\pm$ 0.2 ppm, 30.3 $\pm$ 0.2 ppm, 29.6 $\pm$ 0.2 ppm, and 20.5 $\pm$ 0.2 ppm. In some embodiments, Compound **I** Neat Form A is characterized by a ^{13}C SSNMR spectrum having peaks at 179.7 $\pm$ 0.2 ppm, 178.8 $\pm$ 0.2 ppm, 177.6 $\pm$ 0.2 ppm, 174.8 $\pm$ 0.2 ppm, 169.8 $\pm$ 0.2 ppm, 168.3 $\pm$ 0.2 ppm, 155.9 $\pm$ 0.2 ppm, 154.9 $\pm$ 0.2 ppm, 153.0 $\pm$ 0.2 ppm, 152.4 $\pm$ 0.2 ppm, 151.1 $\pm$ 0.2 ppm, 149.2 $\pm$ 0.2 ppm, 147.8 $\pm$ 0.2 ppm, 146.8 $\pm$ 0.2 ppm, 145.7 $\pm$ 0.2 ppm, 144.7 $\pm$ 0.2 ppm, 135.6 $\pm$ 0.2 ppm, 135.0 $\pm$ 0.2 ppm, 132.8 $\pm$ 0.2 ppm, 131.0 $\pm$ 0.2 ppm, 116.3 $\pm$ 0.2 ppm, 115.1 $\pm$ 0.2 ppm, 113.5 $\pm$ 0.2 ppm, 111.4, 36.3 $\pm$ 0.2 ppm, 30.3 $\pm$ 0.2 ppm, 29.6 $\pm$ 0.2 ppm, and 20.5 $\pm$ 0.2 ppm.

[256] In some embodiments, Compound **I** Neat Form A is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 9A. In some embodiments, it is characterized by a ^{13}C SSNMR spectrum substantially similar to the bottom/lower trace of FIG. 9B, which was collected when a sample of Compound **I** Neat Form A was maintained at ambient conditions. In some embodiments, it is characterized by a ^{13}C SSNMR spectrum substantially similar to the middle trace of FIG. 9B, which was collected when a sample of Compound **I** Neat Form A was dried at 80°C for 3 hours. In some embodiments, it is characterized by a ^{13}C SSNMR spectrum substantially similar to the top/upper trace of FIG. 9B, which was collected when a sample of Compound **I** Neat Form A was dried at 80°C for 3 hours and then re-humidified at 75% relative humidity at room temperature for 12 hours.

[257] In some embodiments, Compound **I** Neat Form A is characterized by triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation (λ =1.54178 Å) of:

a	11.0 $\pm$ 0.1 Å	α	98.0 $\pm$ 0.1°
b	11.2 $\pm$ 0.1 Å	β	93.1 $\pm$ 0.1°
c	15.9 $\pm$ 0.1 Å	γ	95.8 $\pm$ 0.1°

In some embodiments, the diffractometer is a Bruker diffractometer.

[258] In some embodiments, the invention provides a method of making Compound **I** Neat Form A, comprising (i) suspending Compound **I** amorphous material in methanol, (ii) shaking at room temperature for 1 hour, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound **I** Neat Form A.

B. Crystalline Compound I Neat Form B

[259] In some embodiments, the invention provides Compound **I** Neat Form B.

[260] In some embodiments, Compound **I** Neat Form B is substantially pure. In some embodiments, Compound **I** Neat Form B is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in

amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Neat Form B is substantially 100% crystalline. In some embodiments, Compound I Neat Form B is 100% crystalline.

[261] In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, and 9.8 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having a signal at 5.8 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having a signal at 9.5 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having a signal at 9.8 ± 0.2 degrees two-theta.

[262] In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, and 9.8 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 7.7 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, and 21.2 ± 0.2 degrees two-theta.

[263] In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, and 9.8 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 7.7 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, and 21.2 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta; and (c) one, two or three signals selected from 12.5 ± 0.2 degrees two-theta, 15.7 ± 0.2 degrees two-theta, and 17.4 ± 0.2 degrees two-theta.

[264] In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram having signals at 5.8 ± 0.2 degrees two-theta, 7.7 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, 12.5 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, 15.4 ± 0.2 degrees two-theta, 15.7 ± 0.2 degrees two-theta, 16.8 ± 0.2 degrees two-theta, 17.4 ± 0.2 degrees two-theta, 18.4 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 21.2 ± 0.2 degrees two-theta, 23.3 ± 0.2 degrees two-theta, 23.8 ± 0.2 degrees two-theta, 25.3 ± 0.2 degrees two-theta, 25.6 ± 0.2 degrees two-theta, and 27.7 ± 0.2 degrees two-theta.

[265] In some embodiments, Compound I Neat Form B is characterized by an X-ray powder diffractogram substantially similar to FIG. 10.

[266] In some embodiments, Compound I Neat Form B is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm, 176.6 ± 0.2 ppm, 174.4 ± 0.2 ppm, 169.7 ± 0.2 ppm, 157.5 ± 0.2 ppm, 152.8 ± 0.2 ppm, 151.6 ± 0.2 ppm, 150.2 ± 0.2 ppm, 149.4 ± 0.2 ppm, 147.5 ± 0.2 ppm, 145.2 ± 0.2 ppm, 134.5 ± 0.2 ppm, 133.8 ± 0.2 ppm,

133.4 $\pm$ 0.2 ppm, 132.4 $\pm$ 0.2 ppm, 131.1 $\pm$ 0.2 ppm, 130.6 $\pm$ 0.2 ppm, 115.5 $\pm$ 0.2 ppm, 114.2 $\pm$ 0.2 ppm, 113.9 $\pm$ 0.2 ppm, 111.4 $\pm$ 0.2 ppm, 36.3 $\pm$ 0.2 ppm, 30.9 $\pm$ 0.2 ppm, 29.1 $\pm$ 0.2 ppm, 19.8 $\pm$ 0.2 ppm, and 18.1 $\pm$ 0.2 ppm. In some embodiments, Compound I Neat Form B is characterized by a ^{13}C SSNMR spectrum having peaks at 177.9 $\pm$ 0.2 ppm, 176.6 $\pm$ 0.2 ppm, 174.4 $\pm$ 0.2 ppm, 169.7 $\pm$ 0.2 ppm, 157.5 $\pm$ 0.2 ppm, 152.8 $\pm$ 0.2 ppm, 151.6 $\pm$ 0.2 ppm, 150.2 $\pm$ 0.2 ppm, 149.4 $\pm$ 0.2 ppm, 147.5 $\pm$ 0.2 ppm, 145.2 $\pm$ 0.2 ppm, 134.5 $\pm$ 0.2 ppm, 133.8 $\pm$ 0.2 ppm, 133.4 $\pm$ 0.2 ppm, 132.4 $\pm$ 0.2 ppm, 131.1 $\pm$ 0.2 ppm, 130.6 $\pm$ 0.2 ppm, 115.5 $\pm$ 0.2 ppm, 114.2 $\pm$ 0.2 ppm, 113.9 $\pm$ 0.2 ppm, 111.4 $\pm$ 0.2 ppm, 36.3 $\pm$ 0.2 ppm, 30.9 $\pm$ 0.2 ppm, 29.1 $\pm$ 0.2 ppm, 19.8 $\pm$ 0.2 ppm, and 18.1 $\pm$ 0.2 ppm.

[267] In some embodiments, Compound I Neat Form B is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 11.

[268] In some embodiments, Compound I Neat Form B is characterized by triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	11.1 $\pm$ 0.1 Å	α	87.6 $\pm$ 0.1°
b	11.5 $\pm$ 0.1 Å	β	88.2 $\pm$ 0.1°
c	15.0 $\pm$ 0.1 Å	γ	88.9 $\pm$ 0.1°

In some embodiments, the diffractometer is a Bruker diffractometer.

[269] In some embodiments, the invention provides a method of making Compound I Neat Form B, comprising (i) suspending Amorphous Compound I in nitromethane to form a mixture, (ii) agitating the mixture at room temperature for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours.

C. Crystalline Compound I Neat Form C

[270] In some embodiments, the invention provides Compound I Neat Form C.

[271] In some embodiments, Compound I Neat Form C is substantially pure. In some embodiments, Compound I Neat Form C is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Neat Form C is substantially 100% crystalline. In some embodiments, Compound I Neat Form C is 100% crystalline.

[272] In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.0 $\pm$ 0.2 degrees two-theta, 13.9 $\pm$ 0.2 degrees two-theta, and 19.7 $\pm$ 0.2 degrees two-theta. In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having a signal at 6.0 $\pm$ 0.2 degrees two-theta. In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having a signal

at 13.9 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having a signal at 19.7 ± 0.2 degrees two-theta.

[273] In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.0 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 15.4 ± 0.2 degrees two-theta, 15.6 ± 0.2 degrees two-theta, and 18.3 ± 0.2 degrees two-theta.

[274] In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.0 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 15.4 ± 0.2 degrees two-theta, 15.6 ± 0.2 degrees two-theta, and 18.3 ± 0.2 degrees two-theta; and (c) one, two or three signals selected from 9.3 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, and 17.2 ± 0.2 degrees two-theta.

[275] In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having one, two, three, four, five, six, seven, eight, nine, ten, or more signals selected from 6.0 ± 0.2 degrees two-theta, 9.3 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 11.3 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, 15.4 ± 0.2 degrees two-theta, 15.6 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.8 ± 0.2 degrees two-theta, 21.6 ± 0.2 degrees two-theta, 22.3 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.1 ± 0.2 degrees two-theta, 23.4 ± 0.2 degrees two-theta, 24.1 ± 0.2 degrees two-theta, 24.8 ± 0.2 degrees two-theta, 25.2 ± 0.2 degrees two-theta, 26.4 ± 0.2 degrees two-theta, 26.8 ± 0.2 degrees two-theta, and 28.8 ± 0.2 degrees two-theta. In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram having signals at 6.0 ± 0.2 degrees two-theta, 9.3 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 11.3 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, 15.4 ± 0.2 degrees two-theta, 15.6 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.8 ± 0.2 degrees two-theta, 21.6 ± 0.2 degrees two-theta, 22.3 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.1 ± 0.2 degrees two-theta, 23.4 ± 0.2 degrees two-theta, 24.1 ± 0.2 degrees two-theta, 24.8 ± 0.2 degrees two-theta, 25.2 ± 0.2 degrees two-theta, 26.4 ± 0.2 degrees two-theta, 26.8 ± 0.2 degrees two-theta, and 28.8 ± 0.2 degrees two-theta.

[276] In some embodiments, Compound I Neat Form C is characterized by an X-ray powder diffractogram substantially similar to FIG. 12.

[277] In some embodiments, Compound I Neat Form C is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm,

176.5 $\pm$ 0.2 ppm, 173.9 $\pm$ 0.2 ppm, 169.3 $\pm$ 0.2 ppm, 157.8 $\pm$ 0.2 ppm, 153.9 $\pm$ 0.2 ppm, 151.5 $\pm$ 0.2 ppm, 149.8 $\pm$ 0.2 ppm, 148.4 $\pm$ 0.2 ppm, 147.8 $\pm$ 0.2 ppm, 145.6 $\pm$ 0.2 ppm, 135.4 $\pm$ 0.2 ppm, 134.5 $\pm$ 0.2 ppm, 133.0 $\pm$ 0.2 ppm, 131.3 $\pm$ 0.2 ppm, 130.4 $\pm$ 0.2 ppm, 115.6 $\pm$ 0.2 ppm, 115.4 $\pm$ 0.2 ppm, 114.5 $\pm$ 0.2 ppm, 114.1 $\pm$ 0.2 ppm, 111.4 $\pm$ 0.2 ppm, 36.5 $\pm$ 0.2 ppm, 36.3 $\pm$ 0.2 ppm, 31.3 $\pm$ 0.2 ppm, 30.2 $\pm$ 0.2 ppm, 20.9 $\pm$ 0.2 ppm, and 17.9 $\pm$ 0.2 ppm. In some embodiments, Compound I Neat Form C is characterized by a ^{13}C SSNMR spectrum having peaks at 177.9 $\pm$ 0.2 ppm, 176.5 $\pm$ 0.2 ppm, 173.9 $\pm$ 0.2 ppm, 169.3 $\pm$ 0.2 ppm, 157.8 $\pm$ 0.2 ppm, 153.9 $\pm$ 0.2 ppm, 151.5 $\pm$ 0.2 ppm, 149.8 $\pm$ 0.2 ppm, 148.4 $\pm$ 0.2 ppm, 147.8 $\pm$ 0.2 ppm, 145.6 $\pm$ 0.2 ppm, 135.4 $\pm$ 0.2 ppm, 134.5 $\pm$ 0.2 ppm, 133.0 $\pm$ 0.2 ppm, 131.3 $\pm$ 0.2 ppm, 130.4 $\pm$ 0.2 ppm, 115.6 $\pm$ 0.2 ppm, 115.4 $\pm$ 0.2 ppm, 114.5 $\pm$ 0.2 ppm, 114.1 $\pm$ 0.2 ppm, 111.4 $\pm$ 0.2 ppm, 36.5 $\pm$ 0.2 ppm, 36.3 $\pm$ 0.2 ppm, 31.3 $\pm$ 0.2 ppm, 30.2 $\pm$ 0.2 ppm, 20.9 $\pm$ 0.2 ppm, and 17.9 $\pm$ 0.2 ppm.

[278] In some embodiments, Compound I Neat Form C is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 13.

[279] In some embodiments, Compound I Neat Form C is characterized by triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	11.3 $\pm$ 0.1 Å	α	84.3 $\pm$ 0.1°
b	11.5 $\pm$ 0.1 Å	β	68.8 $\pm$ 0.1°
c	15.2 $\pm$ 0.1 Å	γ	89.0 $\pm$ 0.1°

In some embodiments, the diffractometer is a Bruker diffractometer.

[280] In some embodiments, Compound I Neat Form C is characterized by triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 298K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	11.4 $\pm$ 0.1 Å	α	84.2 $\pm$ 0.1°
b	11.6 $\pm$ 0.1 Å	β	69.6 $\pm$ 0.1°
c	15.3 $\pm$ 0.1 Å	γ	88.9 $\pm$ 0.1°

In some embodiments, the diffractometer is a Bruker diffractometer.

[281] In some embodiments, the invention provides a method of making Compound I Neat Form C, comprising (i) suspending Compound I Neat Form A in 2-MeTHF to form a mixture, (ii) stirring the mixture at about 20 °C for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours.

D. Crystalline Compound I Hemi-Hydrate

[282] In some embodiments, the invention provides Compound I Hemi-Hydrate.

[283] In some embodiments, Compound I Hemi-Hydrate is substantially pure. In some embodiments, Compound I Hemi-Hydrate is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Hemi-Hydrate is substantially 100% crystalline. In some embodiments, Compound I Hemi-Hydrate is 100% crystalline.

[284] In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta. In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having a signal at 5.1 ± 0.2 degrees two-theta. In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having a signal at 10.2 ± 0.2 degrees two-theta. In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having a signal at 12.3 ± 0.2 degrees two-theta.

[285] In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 14.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.6 ± 0.2 degrees two-theta.

[286] In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 14.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.6 ± 0.2 degrees two-theta; and (c) one or two signals selected from 11.1 ± 0.2 degrees two-theta and 21.3 ± 0.2 degrees two-theta.

[287] In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram having signals at 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 11.1 ± 0.2 degrees two-theta, 12.3 ± 0.2 degrees two-theta, 14.2 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.6 ± 0.2 degrees two-theta.

[288] In some embodiments, Compound I Hemi-Hydrate is characterized by an X-ray powder diffractogram substantially similar to FIG. 14.

[289] In some embodiments, Compound I Hemi-Hydrate is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.1 ± 0.2 ppm, 169.2 ± 0.2 ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm. In some embodiments, Compound I Hemi-Hydrate is characterized by a ^{13}C SSNMR spectrum having peaks at 178.1 ± 0.2 ppm, 169.2 ± 0.2

ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm.

[290] In some embodiments, Compound I Hemi-Hydrate is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 15.

[291] In some embodiments, the invention provides a method of making Compound I Hemi-Hydrate, comprising (i) suspending Compound I in water, (ii) shaking at 40°C for at least 1 week, at least 2 weeks, at least three weeks, or at least 4 weeks, (iii) collecting the solids, and (iv) drying under vacuum at 40°C to afford Compound I Hemi-Hydrate.

E. Crystalline Compound I Monohydrate

[292] In some embodiments, the invention provides Compound I Monohydrate.

[293] In some embodiments, Compound I Monohydrate is substantially pure. In some embodiments, Compound I Monohydrate is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Monohydrate is substantially 100% crystalline. In some embodiments, Compound I Hemi-Hydrate is 100% crystalline.

[294] In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta. In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having a signal at 5.0 ± 0.2 degrees two-theta. In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having a signal at 10.2 ± 0.2 degrees two-theta.

[295] In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 12.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.5 ± 0.2 degrees two-theta.

[296] In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 12.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.5 ± 0.2 degrees two-theta; and (c) one or two signals selected from 17.1 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, and 23.5 ± 0.2 degrees two-theta.

[297] In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram having signals at 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees

two-theta, 14.2 ± 0.2 degrees two-theta, 17.1 ± 0.2 degrees two-theta, 17.8 ± 0.2 degrees two-theta, 18.1 ± 0.2 degrees two-theta, 20.3 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, 23.5 ± 0.2 degrees two-theta, 26.5 ± 0.2 degrees two-theta, 27.4 ± 0.2 degrees two-theta, and 31.7 ± 0.2 degrees two-theta.

[298] In some embodiments, Compound I Monohydrate is characterized by an X-ray powder diffractogram substantially similar to FIG. 16.

[299] In some embodiments, the invention provides a method of making Compound I Monohydrate, comprising (i) suspending Compound I in water, (ii) shaking at 40 °C for no more than 48 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Monohydrate.

F. Crystalline Compound I Methanol Solvate

[300] In some embodiments, the invention provides Compound I Methanol Solvate.

[301] In some embodiments, Compound I Methanol Solvate is substantially pure. In some embodiments, Compound I Methanol Solvate is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Methanol Solvate is substantially 100% crystalline. In some embodiments, Compound I Methanol Solvate is 100% crystalline.

[302] In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta. In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having a signal at 6.6 ± 0.2 degrees two-theta. In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having a signal at 8.4 ± 0.2 degrees two-theta. In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having a signal at 10.6 ± 0.2 degrees two-theta.

[303] In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 20.9 ± 0.2 degrees two-theta.

[304] In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 20.9 ± 0.2 degrees two-theta; and (c) one, two, or three

signals selected from 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.

[305] In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram having signals at 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.

[306] In some embodiments, Compound I Methanol Solvate is characterized by an X-ray powder diffractogram substantially similar to FIG. 17.

[307] In some embodiments, Compound I Methanol Solvate is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2 ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm. In some embodiments, Compound I Methanol Solvate is characterized by a ^{13}C SSNMR spectrum having peaks at 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2 ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm.

[308] In some embodiments, Compound I Methanol Solvate is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 18.

[309] In some embodiments, Compound I Methanol Solvate is characterized by triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	12.3 ± 0.1 Å	α	$100.4 \pm 0.1^{\circ}$
b	14.1 ± 0.1 Å	β	$105.3 \pm 0.1^{\circ}$
c	14.4 ± 0.1 Å	γ	$107.5 \pm 0.1^{\circ}$

In some embodiments, the diffractometer is a Bruker diffractometer.

[310] In some embodiments, the invention provides a method of making Compound I Methanol Solvate, comprising (i) suspending Compound I amorphous material in methanol, (ii) shaking at 40°C for 1 hour, and (iii) collecting the solids to afford Compound I Methanol Solvate.

G. Crystalline Compound I nPA Solvate Mixture A

[311] In some embodiments, the invention provides Compound I nPA Solvate Mixture A.

[312] In some embodiments, Compound I nPA Solvate Mixture A is substantially pure. In some embodiments, Compound I nPA Solvate Mixture A is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I nPA Solvate Mixture A is substantially 100% crystalline. In some embodiments, Compound I nPA Solvate Mixture A is 100% crystalline.

[313] In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having a signal at 5.3 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having a signal at 8.8 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having a signal at 10.6 ± 0.2 degrees two-theta.

[314] In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 10.1 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta.

[315] In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 10.1 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 13.5 ± 0.2 degrees two-theta, 14.3 ± 0.2 degrees two-theta, and 25.5 ± 0.2 degrees two-theta.

[316] In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 10.1 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.5 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, 14.3 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 18.4 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.3 ± 0.2 degrees two-theta, 25.5 ± 0.2 degrees two-theta, and 26.1 ± 0.2 degrees two-theta.

[317] In some embodiments, Compound I nPA Solvate Mixture A is characterized by an X-ray powder diffractogram substantially similar to **FIG. 19**.

[318] In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm. In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum having peaks at 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm.

[319] In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 20**.

[320] In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm, 36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm. In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum having peaks at 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm, 36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm.

[321] In some embodiments, Compound I nPA Solvate Mixture A is characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 21**.

[322] In some embodiments, Compound I nPA Solvate Mixture A is characterized by monoclinic crystal system, $C2/c$ space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation ($\lambda=1.54178$ Å) of:

a	19.9 ± 0.1 Å	α	90
b	6.9 ± 0.1 Å	β	$93.9 \pm 0.1^\circ$
c	32.6 ± 0.1 Å	γ	90

In some embodiments, the diffractometer is a Bruker diffractometer.

[323] In some embodiments, the invention provides a method of making Compound I nPA Solvate Mixture A, comprising (i) suspending Compound I nPA Solvate B and NaTFA in nPA, (ii) mixing at room temperature for 6-18 hours, (iii) collecting the solids, and (iv) air-drying for 15-45 minutes to afford Compound I nPA Solvate Mixture A.

H. Crystalline Compound I nPA Solvate B

[324] In some embodiments, the invention provides Compound I nPA Solvate Mixture B.

[325] In some embodiments, Compound I nPA Solvate Mixture B is substantially pure. In some embodiments, Compound I nPA Solvate Mixture B is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I nPA Solvate Mixture B is substantially 100% crystalline. In some embodiments, Compound I nPA Solvate Mixture B is 100% crystalline.

[326] In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having a signal at 5.3 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having a signal at 8.8 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having a signal at 10.6 ± 0.2 degrees two-theta.

[327] In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 9.9 ± 0.2 degrees two-theta, 13.2 ± 0.2 degrees two-theta, and 14.8 ± 0.2 degrees two-theta.

[328] In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 9.9 ± 0.2 degrees two-theta, 13.2 ± 0.2 degrees two-theta, and 14.8 ± 0.2 degrees two-theta; and (c) one or two signals selected from 18.9 ± 0.2 degrees two-theta and 21.4 ± 0.2 degrees two-theta.

[329] In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 9.9 ± 0.2

degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.2 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, 17.5 ± 0.2 degrees two-theta, 18.0 ± 0.2 degrees two-theta, 18.9 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, 22.6 ± 0.2 degrees two-theta, 22.9 ± 0.2 degrees two-theta, 24.6 ± 0.2 degrees two-theta, 25.7 ± 0.2 degrees two-theta, 26.1 ± 0.2 degrees two-theta, 26.5 ± 0.2 degrees two-theta, and 28.1 ± 0.2 degrees two-theta.

[330] In some embodiments, Compound I nPA Solvate Mixture B is characterized by an X-ray powder diffractogram substantially similar to FIG. 22.

[331] In some embodiments, Compound I nPA Solvate Mixture B is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, and 20.7 ± 0.2 ppm. In some embodiments, Compound I nPA Solvate Mixture B is characterized by a ^{13}C SSNMR spectrum having peaks at 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm.

[332] In some embodiments, Compound I nPA Solvate Mixture B is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 23.

[333] In some embodiments, Compound I nPA Solvate Mixture B is characterized by triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	6.8 ± 0.1 Å	α	$93.8 \pm 0.1^{\circ}$
b	10.5 ± 0.1 Å	β	$92.9 \pm 0.1^{\circ}$
c	16.4 ± 0.1 Å	γ	$105.8 \pm 0.1^{\circ}$

In some embodiments, the diffractometer is a Bruker diffractometer.

[334] In some embodiments, the invention provides a method of making Compound I nPA Solvate B, comprising (i) suspending Compound I nPA amorphous material in nPA, (ii) mixing at room temperature for 18-30 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I nPA Solvate B.

I. Crystalline Compound I nPA Solvate C

[335] In some embodiments, Compound I nPA Solvate C.

[336] In some embodiments, Compound I nPA Solvate C is substantially pure. In some embodiments, Compound I nPA Solvate C is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I nPA Solvate C is substantially 100% crystalline. In some embodiments, Compound I nPA Solvate C is 100% crystalline.

[337] In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having a signal at 6.1 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having a signal at 11.8 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having a signal at 12.2 ± 0.2 degrees two-theta.

[338] In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 7.2 ± 0.2 degrees two-theta, 14.6 ± 0.2 degrees two-theta, and 15.8 ± 0.2 degrees two-theta.

[339] In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 7.2 ± 0.2 degrees two-theta, 14.6 ± 0.2 degrees two-theta, and 15.8 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 5.4 ± 0.2 degrees two-theta, 8.7 ± 0.2 degrees two-theta, and 10.2 ± 0.2 degrees two-theta.

[340] In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 6.1 ± 0.2 degrees two-theta, 7.2 ± 0.2 degrees two-theta, 8.7 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees two-theta, 14.6 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 17.5 ± 0.2 degrees two-theta, 19.1 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, and 20.5 ± 0.2 degrees two-theta.

[341] In some embodiments, Compound I nPA Solvate C is characterized by an X-ray powder diffractogram substantially similar to FIG. 24.

[342] In some embodiments, the invention provides a method of making Compound I nPA Solvate C, comprising (i) dissolving Compound I in nPA, (ii) mixing at 90-100 °C for 1-2 hours, (iii) mixing at room temperature for 6-30 hours, and (iv) collecting the solids to afford Compound I nPA Solvate C.

J. Crystalline Compound I Na Hemi Salt nPA Solvate

[343] In some embodiments, the invention provides Compound I Na Hemi Salt nPA Solvate.

[344] In some embodiments, Compound I Na Hemi Salt nPA Solvate is substantially pure. In some embodiments, Compound I Na Hemi Salt nPA Solvate is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Na Hemi Salt nPA Solvate is substantially 100% crystalline. In some embodiments, Compound I Na Hemi Salt nPA Solvate is 100% crystalline.

[345] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta. In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having a signal at 6.7 ± 0.2 degrees two-theta. In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having a signal at 14.1 ± 0.2 degrees two-theta. In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having a signal at 14.9 ± 0.2 degrees two-theta.

[346] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 13.4 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta.

[347] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 13.4 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta; and (c) one, two or three signals selected from 5.2 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.3 ± 0.2 degrees two-theta.

[348] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram having signals at 5.2 ± 0.2 degrees two-theta, 6.7 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 9.8 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 13.4 ± 0.2 degrees two-theta, 13.6 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, 14.2 ± 0.2 degrees two-theta, 14.9 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 18.7 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 20.6 ± 0.2 degrees two-theta, 21.0 ± 0.2

degrees two-theta, 24.6 ± 0.2 degrees two-theta, 26.4 ± 0.2 degrees two-theta, 26.6 ± 0.2 degrees two-theta, and 28.4 ± 0.2 degrees two-theta.

[349] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by an X-ray powder diffractogram substantially similar to FIG. 25.

[350] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 114.0 ± 0.2 ppm, 111.6 ± 0.2 ppm, 65.1 ± 0.2 ppm, 62.6 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.7 ± 0.2 ppm, 26.2 ± 0.2 ppm, 24.8 ± 0.2 ppm, 21.4 ± 0.2 ppm, and 20.8 ± 0.2 ppm. In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by a ^{13}C SSNMR spectrum having peaks at 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 114.0 ± 0.2 ppm, 111.6 ± 0.2 ppm, 65.1 ± 0.2 ppm, 62.6 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.7 ± 0.2 ppm, 26.2 ± 0.2 ppm, 24.8 ± 0.2 ppm, 21.4 ± 0.2 ppm, and 20.8 ± 0.2 ppm.

[351] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 26.

[352] In some embodiments, Compound I Na Hemi Salt nPA Solvate is characterized by triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	10.3 ± 0.1 Å	α	$94.2 \pm 0.1^{\circ}$
b	13.3 ± 0.1 Å	β	$91.0 \pm 0.1^{\circ}$
c	16.7 ± 0.1 Å	γ	$104.0 \pm 0.1^{\circ}$

In some embodiments, the diffractometer is a Bruker diffractometer.

[353] In some embodiments, the invention provides a method of making Compound I Na Hemi Salt nPA Solvate, comprising (i) treating 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile with water and TFA, (ii) mixing at 60°C for 18-30 hours, (iii) treating the mixture with water and sodium hydroxide at room temperature, (iv) washing the mixture with aqueous sodium chloride, (v) diluting the mixture with 2-MeTHF and subsequently concentrating, (vi) treating the mixture with nPA and subsequently concentrating, (vii) heating the mixture to 90°C and subsequently holding the mixture at 50°C for 6-18 hours, (viii) cooling the mixture to room temperature, (ix) collecting

the solids, and (s) drying under vacuum at 40 °C for 6-18 hours to afford Compound I Na Hemi Salt nPA Solvate.

K. Crystalline Compound I nPA Solvate J

[354] In some embodiments, the invention provides Compound I nPA Solvate J.

[355] In some embodiments, Compound I nPA Solvate J is substantially pure. In some embodiments, Compound I nPA Solvate J is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I nPA Solvate J is substantially 100% crystalline. In some embodiments, Compound I nPA Solvate J is 100% crystalline.

[356] In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, and 19.0 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having a signal at 5.3 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having a signal at 10.4 ± 0.2 degrees two-theta. In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having a signal at 19.0 ± 0.2 degrees two-theta.

[357] In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, and 19.0 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 8.8 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 13.4 ± 0.2 degrees two-theta.

[358] In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, and 19.0 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 8.8 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 13.4 ± 0.2 degrees two-theta; (c) one, two, or three signals selected from 14.1 ± 0.2 degrees two-theta, 19.2 ± 0.2 degrees two-theta, and 26.0 ± 0.2 degrees two-theta.

[359] In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram having signals at 3.1 ± 0.2 degrees two-theta, 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 10.0 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.4 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 19.0 ± 0.2 degrees two-theta, 19.2 ± 0.2 degrees two-theta, 26.0 ± 0.2 degrees two-theta, and 26.4 ± 0.2 degrees two-theta.

[360] In some embodiments, Compound I nPA Solvate J is characterized by an X-ray powder diffractogram substantially similar to FIG. 27.

[361] In some embodiments, the invention provides a method of making Compound I nPA Solvate J, comprising (i) treating a mixture of Compound I and 2-MeTHF with nPA, (ii) concentrating the mixture at 20-30 °C, (iii) treating the mixture with nPA and subsequently concentrating the mixture at 20-30 °C, (iv) heating the mixture to 80-100 °C, (v) cooling the mixture to room temperature over 8-16 hours, (vi) collecting the solids, and (vi) drying under vacuum at 45 °C to afford Compound I nPA Solvate J.

L. Crystalline Compound I 2-MeTHF Solvate A

[362] In some embodiments, the invention provides Compound I 2-MeTHF Solvate A.

[363] In some embodiments, Compound I 2-MeTHF Solvate A is substantially pure. In some embodiments, Compound I 2-MeTHF Solvate A is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I 2-MeTHF Solvate A is substantially 100% crystalline. In some embodiments, Compound I 2-MeTHF Solvate A is 100% crystalline.

[364] In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta. In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having a signal at 5.8 ± 0.2 degrees two-theta. In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having a signal at 9.4 ± 0.2 degrees two-theta. In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having a signal at 14.0 ± 0.2 degrees two-theta.

[365] In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 9.8 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, and 15.4 ± 0.2 degrees two-theta.

[366] In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 9.8 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, and 15.4 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 17.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, and 20.8 ± 0.2 degrees two-theta.

[367] In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram having signals at 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, 9.8 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 14.0 ± 0.2 degrees two-theta, 15.4 ± 0.2 degrees two-theta, $15.7 \pm$

0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.8 ± 0.2 degrees two-theta, 24.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.

[368] In some embodiments, Compound I 2-MeTHF Solvate A is characterized by an X-ray powder diffractogram substantially similar to FIG. 28.

[369] In some embodiments, the invention provides a provides a method of making Compound I 2-MeTHF Solvate A, comprising (i) treating Compound I Form A with 2-MeTHF, (ii) agitating the mixture for 24 hours at about 22 °C, and (iii) isolating the solids.

M. Crystalline Compound I 2-MeTHF Solvate Mixture A

[370] In some embodiments, the invention provides Compound I 2-MeTHF Solvate Mixture A.

[371] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is substantially pure. In some embodiments, Compound I 2-MeTHF Solvate Mixture A is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I 2-MeTHF Solvate Mixture A is substantially 100% crystalline. In some embodiments, Compound I 2-MeTHF Solvate A is 100% crystalline.

[372] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is characterized by an X-ray powder diffractogram having a signal at 4.6 ± 0.2 degrees two-theta.

[373] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is characterized by an X-ray powder diffractogram having (a) a signal at 4.6 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 15.8 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.

[374] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is characterized by an X-ray powder diffractogram having (a) a signal at 4.6 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 15.8 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 12.4 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.

[375] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is characterized by an X-ray powder diffractogram having signals at 4.6 ± 0.2 degrees two-theta, 12.4 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 19.4 ± 0.2 degrees two-theta, 21.9 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.

[376] In some embodiments, Compound I 2-MeTHF Solvate Mixture A is characterized by an X-ray powder diffractogram substantially similar to FIG. 29.

[377] In some embodiments, the invention provides a method of making Compound I 2-MeTHF Solvate Mixture A, comprising (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I 2-MeTHF Solvate Mixture A.

N. Crystalline Compound I 2-MeTHF Mixture C

[378] In some embodiments, the invention provides Compound I 2-MeTHF Mixture C.

[379] In some embodiments, Compound I 2-MeTHF Mixture C is substantially pure. In some embodiments, Compound I 2-MeTHF Mixture C is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I 2-MeTHF Mixture C is substantially 100% crystalline. In some embodiments, Compound I 2-MeTHF Mixture C is 100% crystalline.

[380] In some embodiments, Compound I 2-MeTHF Mixture C is characterized by an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta.

[381] In some embodiments, Compound I 2-MeTHF Mixture C is characterized by an X-ray powder diffractogram having (a) a signal at 4.9 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 8.2 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, and 18.5 ± 0.2 degrees two-theta.

[382] In some embodiments, Compound I 2-MeTHF Mixture C is characterized by an X-ray powder diffractogram having (a) a signal at 4.9 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 8.2 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, and 18.5 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 15.3 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, and 23.1 ± 0.2 degrees two-theta.

[383] In some embodiments, Compound I 2-MeTHF Mixture C is characterized by an X-ray powder diffractogram having signals at 4.9 ± 0.2 degrees two-theta, 8.2 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 11.3 ± 0.2 degrees two-theta, 15.3 ± 0.2 degrees two-theta, 15.7 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 23.1 ± 0.2 degrees two-theta, 25.0 ± 0.2 degrees two-theta, and 25.2 ± 0.2 degrees two-theta.

[384] In some embodiments, Compound I 2-MeTHF Mixture C is characterized by an X-ray powder diffractogram substantially similar to FIG. 30.

[385] In some embodiments, the invention provides a method of making Compound I 2-MeTHF Solvate Mixture C, comprising (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the

solution to obtain a slurry, (iii) warming the slurry to 90 °C to dissolve solids, (iv) cooling to 25 °C, (v) collecting the solids, and (iv) drying at 50 °C to afford Compound I 2-MeTHF Solvate Mixture C.

O. Crystalline Compound I Mandelic Acid Cocrystal

[386] In some embodiments, the invention provides Compound I Mandelic Acid Cocrystal.

[387] In some embodiments, Compound I Mandelic Acid Cocrystal is substantially pure. In some embodiments, Compound I Mandelic Acid Cocrystal is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Mandelic Acid Cocrystal is substantially 100% crystalline. In some embodiments, Compound I Mandelic Acid Cocrystal is 100% crystalline.

[388] In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta. In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 6.6 ± 0.2 degrees two-theta. In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 10.6 ± 0.2 degrees two-theta. In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 21.1 ± 0.2 degrees two-theta.

[389] In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta; and (b) one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta.

[390] In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta; (b) one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta; and (c) one, two, or three signals selected from 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, and 20.9 ± 0.2 degrees two-theta.

[391] In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram having signals at 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.

[392] In some embodiments, Compound I Mandelic Acid Cocrystal is characterized by an X-ray powder diffractogram substantially similar to FIG. 31.

[393] In some embodiments, the invention provides a method of making Compound I Mandelic Acid Cocrystal, comprising (i) combining Compound I and Mandelic acid, (ii) diluting the mixture in DCM, (iii) agitating the mixture for at least 1 hour, (iv) collecting the resulting solid material, and (v) drying the collected solid material in a vacuum oven at 50 °C to afford Compound I Mandelic Acid Cocrystal. In some embodiments, the agitation comprises sonication. In some embodiments, the agitation comprises stirring. In some embodiments, the agitation comprises sonication followed by stirring.

P. Crystalline Compound I Oxalic Acid Cocrystal

[394] In some embodiments, the invention provides Compound I Oxalic Acid Cocrystal.

[395] In some embodiments, Compound I Oxalic Acid Cocrystal is substantially pure. In some embodiments, Compound I Oxalic Acid Cocrystal is substantially crystalline (i.e., wherein less than 15% of Compound I is in amorphous form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form). In some embodiments, Compound I Oxalic Acid Cocrystal is substantially 100% crystalline. In some embodiments, Compound I Oxalic Acid Cocrystal is 100% crystalline.

[396] In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta. In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 8.9 ± 0.2 degrees two-theta. In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 11.6 ± 0.2 degrees two-theta. In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having a signal at 14.5 ± 0.2 degrees two-theta.

[397] In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta; and (b) one or two signals selected from 5.7 ± 0.2 degrees two-theta and 20.1 ± 0.2 degrees two-theta.

[398] In some embodiments, Compound I Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta; (b) one or two signals selected from 5.7 ± 0.2 degrees two-theta and 20.1 ± 0.2 degrees two-theta; and (c) one, two or three signals selected from 10.6 ± 0.2 degrees two-theta, 13.8 ± 0.2 degrees two-theta, and 22.9 ± 0.2 degrees two-theta.

[399] In some embodiments, Compound **I** Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram having signals at 5.7 ± 0.2 degrees two-theta, 8.9 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, 13.8 ± 0.2 degrees two-theta, 14.5 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, and 22.9 ± 0.2 degrees two-theta.

[400] In some embodiments, Compound **I** Oxalic Acid Cocrystal is characterized by an X-ray powder diffractogram substantially similar to FIG. 32.

[401] In some embodiments, Compound **I** Oxalic Acid Cocrystal is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm. In some embodiments, Compound **I** Oxalic Acid Cocrystal is characterized by a ^{13}C SSNMR spectrum having peaks at 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm.

[402] In some embodiments, Compound **I** Oxalic Acid Cocrystal is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 33.

[403] In some embodiments, the invention provides a method of making Compound **I** Oxalic Acid Cocrystal, comprising (i) suspending Compound **I** and oxalic acid (1:1) in DCM, (ii) stirring the resulting slurry at room temperature, (iii) collecting the solids, and (iv) drying under vacuum at 50°C to afford Compound **I** Oxalic Acid Cocrystal.

Q. Crystalline Compound I TFA Salt A

[404] In some embodiments, the invention provides Compound **I** TFA Salt A.

[405] In some embodiments, Compound **I** TFA Salt A is substantially pure. In some embodiments, Compound **I** TFA Salt A is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form). In some embodiments, Compound **I** TFA Salt A is substantially 100% crystalline. In some embodiments, Compound **I** TFA Salt A is 100% crystalline.

[406] In some embodiments, Compound **I** TFA Salt A is characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta. In some embodiments, Compound **I** TFA Salt A is

characterized by an X-ray powder diffractogram having a signal at 8.4 ± 0.2 degrees two-theta. In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram having a signal at 15.1 ± 0.2 degrees two-theta. In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram having a signal at 19.7 ± 0.2 degrees two-theta.

[407] In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and (b) one or two signals selected from 4.4 ± 0.2 degrees two-theta and 11.4 ± 0.2 degrees two-theta.

[408] In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram having (a) one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; (b) one or two signals selected from 4.4 ± 0.2 degrees two-theta and 11.4 ± 0.2 degrees two-theta; and (c) one, two or three signals selected from 17.3 ± 0.2 degrees two-theta, 23.8 ± 0.2 degrees two-theta, and 26.3 ± 0.2 degrees two-theta.

[409] In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram having signals at 4.4 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, 11.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 23.8 ± 0.2 degrees two-theta, and 26.3 ± 0.2 degrees two-theta.

[410] In some embodiments, Compound I TFA Salt A is characterized by an X-ray powder diffractogram substantially similar to FIG. 34.

[411] In some embodiments, Compound I TFA Salt A is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm. In some embodiments, Compound I TFA Salt A is characterized by a ^{13}C SSNMR spectrum having peaks at 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm.

[412] In some embodiments, Compound I TFA Salt A is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 35.

[413] In some embodiments, the invention provides a method of making Compound I TFA Salt A, comprising (i) suspending Compound I in DCM, (ii) treating the suspension with TFA, (iii) stirring at room

temperature for 15-45 minutes, (iv) collecting the solids, and (v) drying at room temperature to afford Compound I TFA Salt A.

R. Amorphous Compound I

[414] In some embodiments, the invention provides Amorphous Compound I.

[415] In some embodiments, Amorphous Compound I is substantially pure. In some embodiments, Amorphous Compound I is substantially amorphous (i.e., wherein less than 15% of Compound I is in crystalline form, wherein less than 10% of Compound I is in crystalline form, wherein less than 5% of Compound I is in crystalline form). In some embodiments, Amorphous Compound I is substantially 100% amorphous. In some embodiments, Amorphous Compound I is 100% amorphous.

[416] In some embodiments, Amorphous Compound I is characterized by an X-ray powder diffractogram substantially similar to FIG. 36.

[417] In some embodiments, Amorphous I is characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.6 ± 0.2 ppm, 172.0 ± 0.2 ppm, 164.0 ± 0.2 ppm, 155.5 ± 0.2 ppm, 151.3 ± 0.2 ppm, 147.1 ± 0.2 ppm, 133.2 ± 0.2 ppm, 131.7 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 36.1 ± 0.2 ppm, 30.0 ± 0.2 ppm, 20.1 ± 0.2 ppm, 9.3 ± 0.2 ppm, 8.3 ± 0.2 ppm, and 7.6 ± 0.2 ppm. In some embodiments, Amorphous Compound I is characterized by a ^{13}C SSNMR spectrum having peaks at 177.6 ± 0.2 ppm, 172.0 ± 0.2 ppm, 164.0 ± 0.2 ppm, 155.5 ± 0.2 ppm, 151.3 ± 0.2 ppm, 147.1 ± 0.2 ppm, 133.2 ± 0.2 ppm, 131.7 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 36.1 ± 0.2 ppm, 30.0 ± 0.2 ppm, 20.1 ± 0.2 ppm, 9.3 ± 0.2 ppm, 8.3 ± 0.2 ppm, and 7.6 ± 0.2 ppm.

[418] In some embodiments, Amorphous Compound I is characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 37.

[419] In some embodiments, the invention provides a method of making Amorphous Compound I, comprising (i) combining Compound I and t-butanol to form a mixture, (ii) stirring the mixture at about 70 °C for about 1 hour, (iii) adding water to the mixture, (iv) freezing the mixture, and (v) isolating the solid material.

Methods of Treatment

[420] Compound I, in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein, acts as a voltage-gated sodium channel inhibitor. In some aspects, the voltage-gated sodium channel is $\text{Na}_v1.8$. Accordingly, in another aspect, the disclosure features a method of inhibiting a voltage-gated sodium channel in a subject comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms

disclosed herein or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is Nav1.8.

[421] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject Compound I or a solvate thereof or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[422] In another aspect, the disclosure relates to a method of treating or lessening the severity of pain in a subject, comprising administering to the subject Compound I, or a pharmaceutically acceptable salt thereof.

[423] In another aspect, the disclosure relates to a method of treating or lessening the severity of pain in a subject, comprising administering to the subject Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[424] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., bunionectomy pain, herniorrhaphy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[425] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, herniorrhaphy pain, bunionectomy pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, or cardiac arrhythmia comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[426] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain, irritable bowel syndrome, endometriosis, polycystic ovarian disease, salpingitis, cervicitis or interstitial cystitis pain wherein said method comprises administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[427] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of neuropathic pain comprising administering an effective amount of Compound I in any one of the

pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some aspects, the neuropathic pain comprises post-herpetic neuralgia, small fiber neuropathy, diabetic neuropathy, or idiopathic small-fiber neuropathy. In some aspects, the neuropathic pain comprises diabetic neuropathy (e.g., diabetic peripheral neuropathy). As used herein, the phrase “idiopathic small-fiber neuropathy” shall be understood to include any small fiber neuropathy.

[428] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton’s neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, HIV-induced neuropathy; post spinal cord injury pain, spinal stenosis pain, small fiber neuropathy, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia wherein said method comprises administering an effective amount of Compound **I** in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[429] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of musculoskeletal pain comprising administering an effective amount of Compound **I** in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some aspects, the musculoskeletal pain comprises osteoarthritis pain.

[430] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain wherein said method comprises administering an effective amount of Compound **I** in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[431] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain, ankylosing spondylitis or vulvodinia wherein said method comprises administering an effective amount of Compound **I** in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[432] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain wherein said method comprises administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[433] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain wherein said method comprises administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[434] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises reflex sympathetic dystrophy pain, wherein said method comprises administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[435] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of pathological cough wherein said method comprises administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[436] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of acute pain comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some aspects, the acute pain comprises acute post-operative pain.

[437] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, hemorrhoidectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain) comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[438] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of bunionectomy pain comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[439] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of shoulder arthroplasty pain or shoulder arthroscopy pain comprising administering an effective amount of a compound of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[440] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of herniorrhaphy pain comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[441] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of abdominoplasty pain comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[442] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of visceral pain comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some aspects, the visceral pain comprises visceral pain from abdominoplasty.

[443] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of a neurodegenerative disease comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some aspects, the neurodegenerative disease comprises multiple sclerosis. In some aspects, the neurodegenerative disease comprises Pitt Hopkins Syndrome (PTHS).

[444] In yet another aspect, the disclosure features a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with an effective of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some embodiments, the additional therapeutic agent is a sodium channel inhibitor.

[445] In another aspect, the disclosure features a method of inhibiting a voltage-gated sodium channel in a biological sample comprising contacting the biological sample with an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is Nav1.8.

[446] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of acute pain, sub-acute and chronic pain, nociceptive pain, neuropathic pain, inflammatory pain,

nociceptive pain, arthritis, migraine, cluster headaches, tension headaches, and all other forms of headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, central neuropathic pain of multiple sclerosis and irritable bowel syndrome, incontinence, pathological cough, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, unspecific chronic back pain, head pain, neck pain, moderate pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), cancer pain including chronic cancer pain and breakthrough cancer pain, stroke (e.g., post stroke central neuropathic pain), whiplash associated disorders, fragility fractures, spinal fractures, ankylosing spondylitis, pemphigus, Raynaud's Disease, scleroderma, systemic lupus erythematosus, Epidermolysis bullosa, gout, juvenile idiopathic arthritis, melorheostosis, polymyalgia reumatica, pyoderma gangrenosum, chronic widespread pain, diffuse idiopathic skeletal hyperostosis, disc degeneration/herniation pain, radiculopathy, facet joint syndrome, failed back surgery syndrome, burns, carpal tunnel syndrome, Paget's disease pain, spinal canal stenosis, spondylodyscitis, transverse myelitis, Ehlers-Danlos syndrome, Fabry's disease, mastocytocytosis, neurofibromatosis, ocular neuropathic pain, sarcoidosis, spondylolysis, spondylolisthesis, chemotherapy induced oral mucositis, Charcot neuropathic osteoarthropathy, temporomandibular joint disorder, painful joint arthroplasties, non-cardiac chest pain, pudendal neuralgia, renal colic, biliary tract diseases, vascular leg ulcers, pain in Parkinson's disease, pain in Alzheimer's disease, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility, comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[447] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache; cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie-Tooth neuropathy; hereditary sensory neuropathy; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; persistent/chronic post-surgical pain (e.g., post amputation, post-thoracotomy, post-cardiac surgery), post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; phantom pain

(e.g., following removal of lower extremity, upper extremity, breast); intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury pain; exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory pain, burn pain, trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain; sinusitis pain; dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease; urinary incontinence, pathological cough; hyperactive bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I, complex regional pain syndrome (CRPS) type II; widespread pain, paroxysmal extreme pain, pruritus, tinnitus, or angina-induced pain, comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[448] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of trigeminal neuralgia, migraines treated with botox, cervical radiculopathy, occipital neuralgia, axillary neuropathy, radial neuropathy, ulnar neuropathy, brachial plexopathy, thoracic radiculopathy, intercostal neuralgia, lumbrosacral radiculopathy, iliolingual neuralgia, pudendal neuralgia, femoral neuropathy, meralgia paresthetica, saphenous neuropathy, sciatic neuropathy, peroneal neuropathy, tibial neuropathy, lumbosacral plexopathy, traumatic neuroma stump pain or postamputation pain, comprising administering an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof.

[449] In some embodiments, the method of treating, or lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Compound I in any one of the pharmaceutically acceptable crystalline (e.g., crystalline or amorphous) forms disclosed herein. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I neat Form A. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I Neat Form B. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I Neat Form C. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I hemi-hydrate. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I monohydrate. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I methanol solvate. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I nPA solvate mixture A. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is

Compound I nPA solvate B. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I nPA solvate C. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I Na hemi salt nPA solvate. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I nPA solvate J. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I 2-Me THF Solvate A. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I 2-Me THF Solvate Mixture A. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I 2-Me THF Mixture C. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I mandelic acid cocrystal. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I DL-oxalic acid cocrystal. In some embodiments the pharmaceutically acceptable crystalline form of Compound I is Compound I TFA Salt A. In some embodiments, the method of treating, or lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Amorphous Compound I, as disclosed herein.

[450] In some embodiments, the method of treating, or lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof. In some embodiments, the method of treating, or lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Amorphous Compound I as disclosed herein or a pharmaceutical composition thereof.

[451] In some embodiments, the method of treating, lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Compound I as any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein in combination with at least one additional active pharmaceutical ingredient. In some embodiments, the method of treating, lessening the severity of, or symptomatically treating pain in a patient comprises administering to the patient an effective amount of Compound I as a solid form selected from Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, and Compound I TFA Salt A, in combination with at least one additional active pharmaceutical ingredient. In some embodiments, the method of treating, lessening the severity of, or symptomatically treating pain in a patient

comprises administering to the patient an effective amount of Amorphous Compound I as disclosed herein in combination with at least one additional active pharmaceutical ingredient.

[452] In some embodiments, the disclosure features Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof for use in any of the foregoing methods.

[453] In some embodiments, the disclosure features the use of Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof for the manufacture of a medicament for use in any of the foregoing methods.

[454] In some embodiments, the disclosure features Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein or a pharmaceutical composition thereof for use as a medicament.

Additional Therapeutic Agents

[455] It will also be appreciated that Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein, and pharmaceutically acceptable compositions of the invention can be employed in combination therapies, that is, the compound in any one of the pharmaceutically acceptable solid forms, and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.” For example, exemplary additional therapeutic agents include, but are not limited to: non-opioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and

Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiologic (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., 2011, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[456] In another embodiment, additional appropriate therapeutic agents are selected from the following:

[457] (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine, or difelikefalin;

[458] (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen (including without limitation intravenous ibuprofen (e.g., Caldolor®)), indomethacin, ketoprofen, ketorolac (including without limitation ketorolac tromethamine (e.g., Toradol®)), meclofenamic acid, mefenamic acid, meloxicam, IV meloxicam (e.g., Anjeso®), nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

[459] (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal or thiopental;

[460] (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[461] (5) a histamine (H₁) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[462] (6) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;

[463] (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;

[464] (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine,

memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1- piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(lH)-quinolinone};

[465] (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1, 2,3,4- tetrahydroisoquinolin-2-yl)-5-(2-pyridyl) quinazoline;

[466] (10) a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

[467] (11) an anticonvulsant, e.g. carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate;

[468] (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11 -tetrahydro-9-methyl-5-(4- methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5- [[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

[469] (13) a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[470] (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[471] (15) a coal-tar analgesic, in particular paracetamol;

[472] (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;

[473] (17) a vanilloid receptor agonist (e.g. resiniferatoxin or civamide) or antagonist (e.g. capsazepine, GRC-15300);

[474] (18) a beta-adrenergic such as propranolol;

[475] (19) a local anesthetic such as mexiletine;

[476] (20) a corticosteroid such as dexamethasone;

[477] (21) a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[478] (22) a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

[479] (23) a cholinergic (nicotinic) analgesic, such as ispronidine (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

[480] (24) Tramadol®, Tramadol ER (Ultram ER®), IV Tramadol, Tapentadol ER (Nucynta®);

[481] (25) a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

[482] (26) an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, ([1alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

[483] (27) a cannabinoid such as KHK-6188;

[484] (28) metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;

[485] (29) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;

[486] (30) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

[487] (31) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;

[488] (32) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamide, NXN-462, or guanidinoethyldisulfide;

[489] (33) an acetylcholinesterase inhibitor such as donepezil;

[490] (34) a prostaglandin E2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

[491] (35) a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;

[492] (36) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (CV-6504);

[493] (37) a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate;

[494] (38) a Na_v1.7 blocker, such as XEN-402, XEN403, TV-45070, PF-05089771, CNV1014802, GDC-0276, RG7893 BIIB-074 (Vixotrigine), BIIB-095, ASP-1807, DSP-3905, OLP-1002, RQ-00432979, FX-301, DWP-1706, DWP-17061, IMB-110, IMB-111, IMB-112 and such as those disclosed in WO2011/140425 (US2011/306607); WO2012/106499 (US2012196869); WO2012/112743 (US2012245136); WO2012/125613 (US2012264749), WO2012/116440 (US2014187533),

WO2011026240 (US2012220605), US8883840, US8466188, WO2013/109521 (US2015005304), WO2020/117626, WO2021/252822, WO2021/252818, WO2021/252820, WO2014/201173, WO2012/125973, WO2013/086229, WO2013/134518, WO2014/201206, or WO2016/141035, and CN111217776, the entire contents of each application hereby incorporated by reference;

[495] (38a) a Nav1.7 blocker such as (2-benzylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl)-(4-isopropoxy-3-methyl-phenyl)methanone, 2,2,2-trifluoro-1-[1'-(3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(4-isobutoxy-3-methoxy-phenyl)methanone, 1-(4-benzhydryl)piperazin-1-yl]-3-[2-(3,4-dimethylphenoxy)ethoxy]propan-2-ol, (4-butoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(5-isopropoxy-6-methyl-2-pyridyl)methanone, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 5-[2-methyl-4-[2-methyl-6-(2,2,2-trifluoroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carbonyl]phenyl]pyridine-2-carbonitrile, (4-isopropoxy-3-methyl-phenyl)-[6-(trifluoromethyl)spiro[3,4-dihydro-2H-pyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-3,3-dimethyl-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopentyloxy-pyridine-2-carbonyl)-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, (4-isopropoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopentyloxy-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[(3S)-2,3-dimethyl-1'-[4-(3,3,3-trifluoropropoxymethyl)benzoyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2,2-trifluoro-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[3-methoxy-4-[(1R)-1-methylpropoxy]phenyl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[1'-[4-methoxy-3-(trifluoromethyl)benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2-dimethyl-propan-1-one, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [2-methyl-6-(1-methylcyclopropanecarbonyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[4-(3,3,3-trifluoropropoxymethyl)phenyl]methanone, 4-bromo-N-(4-bromophenyl)-3-[(1-methyl-2-oxo-4-

piperidyl)sulfamoyl]benzamide or (3-chloro-4-isopropoxy-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone.

[496] (39) a NaV1.8 blocker, such as PF-04531083, PF-06372865 and such as those disclosed in WO2008/135826 (US2009048306), WO2006/011050 (US2008312235), WO2013/061205 (US2014296313), US20130303535, WO2013131018, US8466188, WO2013114250 (US2013274243), WO2014/120808 (US2014213616), WO2014/120815 (US2014228371) WO2014/120820 (US2014221435), WO2015/010065 (US20160152561), WO2015/089361 (US20150166589), WO2019/014352 (US20190016671), WO2018/213426, WO2020/146682, WO2020/146612, WO2020/014243, WO2020/014246, WO2020/092187, WO2020/092667 (US2020140411), WO2020/261114, WO2020/140959, WO2020/144375, WO2020/151728, WO2021/032074, WO2021/257490, WO2021/257420, WO2021/257418, WO2022/263498, WO2022/235558, WO2022/235859, WO2023/138599, CN112390745, CN111808019, CN112225695, CN112457294, CN112300051, CN112300069, CN112441969, CN112479996 (WO2021/047622), and CN114591293, the entire contents of each application hereby incorporated by reference;

[497] (39a) a NaV1.8 blocker such as 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-((5-fluoro-2-hydroxybenzyl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide, 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1H-pyridin-4-yl)-4-(trifluoromethyl)benzamide, [4-[[2-(4-fluoro-2-methylphenoxy)-4-

(trifluoromethyl)benzoyl]amino]-2-oxo-1-pyridyl]methyl dihydrogen phosphate, 2-(4-fluoro-2-(methyl-
d₃)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, (4-(2-(4-fluoro-2-(methyl-
d₃)phenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2H)-yl)methyl dihydrogen phosphate, 3-(4-
fluoro-2-methoxyphenoxy)-N-(3-(methylsulfonyl)phenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-
fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-methoxyphenoxy)-N-
(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(4-chloro-2-methoxyphenoxy)-N-(3-
sulfamoylphenyl)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-
carboxamido)picolinic acid, 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 2-
(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 3-(2,4-difluorophenoxy)-
N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-sulfamoylphenyl)-2-(4-
(trifluoromethoxy)phenoxy)quinoline-3-carboxamide, N-(3-sulfamoylphenyl)-3-(4-
(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamide, 3-(4-chloro-2-methylphenoxy)-N-(3-
sulfamoylphenyl)quinoxaline-2-carboxamide, 5-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-
carboxamido)picolinic acid, 3-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-2,3-dihydro-1H-
benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide, 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-4-
yl)quinoxaline-2-carboxamide, 3-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide,
N-(3-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, N-(4-carbamoylphenyl)-
3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 4-(3-(4-
(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)benzoic acid, N-(4-cyanophenyl)-3-(4-fluoro-2-
methoxyphenoxy)quinoxaline-2-carboxamide, 5-(4,5-dichloro-2-(4-fluoro-2-
methoxyphenoxy)benzamido)picolinic acid, 5-(2-(2,4-dimethoxyphenoxy)-4,6-
bis(trifluoromethyl)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-
methoxyphenoxy)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4,6-
bis(trifluoromethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methoxyphenoxy)-4-
(perfluoroethyl)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4-
(perfluoroethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-
(trifluoromethyl)benzamido)benzoic acid, 5-(4,5-dichloro-2-(4-fluoro-2-
methoxyphenoxy)benzamido)picolinic acid, 4-(2-(2-chloro-4-fluorophenoxy)-4-
(perfluoroethyl)benzamido)benzoic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-
(perfluoroethyl)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-
(trifluoromethoxy)phenoxy)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-chloro-2-
methylphenoxy)benzamido)benzoic acid, 5-(4-(*tert*-butyl)-2-(4-fluoro-2-
methoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-
(trifluoromethoxy)phenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-

methylphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-difluorophenoxy)benzamido)picolinic acid, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide, N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzamide, 4-[[2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, 4-[[3-chloro-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-3-(difluoromethyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-

(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[2-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methyl-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2,3,4-trifluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, N-(2-carbamoyl-4-pyridyl)-3-fluoro-5-[2-methoxy-4-(trifluoromethoxy)phenoxy]-2-(trifluoromethyl)pyridine-4-carboxamide, 4-[[6-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(4-carbamoyl-3-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[3-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-5-(1,1,2,2,2-pentafluoroethyl)benzamide, 4-[[4-(difluoromethoxy)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[4-cyclopropyl-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-5-fluoro-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzamide, 5-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-(4-fluorophenoxy)-3-(trifluoromethyl)benzamide, or 4-[[2-fluoro-6-[3-fluoro-2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide;

[498] (40) a combined Nav1.7 and Nav1.8 blocker, such as DSP-2230, Lohocla201 or BL-1021;

[499] (41) a 5-HT₃ antagonist, such as ondansetron;

[500] (42) a TPRV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof;

[501] (43) a nicotinic receptor antagonist, such as varenicline;

[502] (44) an N-type calcium channel antagonist, such as Z-160;

[503] (45) a nerve growth factor antagonist, such as tanezumab;

[504] (46) an endopeptidase stimulant, such as senrebotase;

[505] (47) an angiotensin II antagonist, such as EMA-401;

[506] (48) acetaminophen (including without limitation intravenous acetaminophen (e.g., Ofirmev®));

[507] (49) bupivacaine (including without limitation bupivacaine liposome injectable suspension (e.g., Exparel®) bupivacaine ER (Posimir), bupivacaine collagen (Xaracoll) and transdermal bupivacaine (Eladur®)); and

[508] (50) bupivacaine and meloxicam combination (e.g., HTX-011).

[509] In one embodiment, the additional appropriate therapeutic agents are selected from V-116517, Pregabalin, controlled release Pregabalin, Ezogabine (Potiga®), Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007), Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561 or ARC-4558.

[510] In another embodiment, the additional appropriate therapeutic agents are selected from N-(6-amino-5-(2,3,5-trichlorophenyl)pyridin-2-yl)acetamide; N-(6-amino-5-(2-chloro-3-methoxyphenyl)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxamide; or 3-((4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-amine.

[511] In another embodiment, the additional therapeutic agent is selected from a GlyT2/5HT2 inhibitor, such as Operanserin (VVZ149), a TRPV modulator such as CA008, CMX-020, NEO6860, FTABS, CNTX4975, MCP101, MDR16523, or MDR652, a EGR1 inhibitor such as Brivoglidge (AYX1), an NGF inhibitor such as Tanezumab, Fasinumab, ASP6294, MEDI7352, a Mu opioid agonist such as Cebranopadol, NKTR181 (oxycodogol), a CB-1 agonist such as NEO1940 (AZN1940), an imidazoline 12 agonist such as CR4056 or a p75NTR-Fc modulator such as LEVI-04.

[512] In another embodiment, the additional therapeutic agent is oliceridine or ropivacaine (TLC590).

[513] In another embodiment, the additional therapeutic agent is a Nav1.7 blocker such as ST-2427, ST-2578 and/or those disclosed in WO2010/129864, WO2015/157559, WO2017/059385, WO2018/183781, WO2018/183782, WO2020/072835, and WO2022/036297 the entire contents of each application hereby incorporated by reference.

[514] In another embodiment, the additional therapeutic agent is selected from ASP18071, CC-8464, ANP-230, ANP-231, NOC-100, NTX-1175, ASN008, NW3509, AM-6120, AM-8145, AM-0422, BL-017881, NTM-006, Opiranserin (UnafrTM), brivoglidge, SR419, NRD.E1, LX9211, LY3016859, ISC-17536, NFX-88, LAT-8881, AP-235, NYX 2925, CNTX-6016, S-600918, S-637880, RQ-00434739, KLS-2031, MEDI 7352, and XT-150.

[515] In another embodiment, the additional therapeutic agent is selected from Olinvyk, Zynrelef, Seglentis, Neumentum, Nevakar, HTX-034, CPL-01, ACP-044, HRS-4800, Tarlige, BAY2395840,

LY3526318, Eliapixant, TRV045, RTA901, NRD1355-E1, MT-8554, LY3556050, AP-325, tetrodotoxin, Otenaproxesul, CFTX-1554, Funapide, iN1011-N17, JMKX000623/ODM-111, ETX-801, OLP-1002, ANP-230/DSP-2230, iN1011-N17, DSP-3905 and ACD440.

[516] In another embodiment, the additional therapeutic agent is selected from HRS4800, ODM-111/JMKX000623, LX9211, LY3556050, LY3857210, CFTX01554/CFTX-1554, MEDI7352, MEDI0618, BAY3178275, BAY2395840, GSK3858279, STC-004, HALNEURON, OLP-1002, ATX01, ANP230, CC-8464, iN1011-N17, ST-2427, MSD199, FZ008, VYNAV-01, BL-017881, Profervia (Cilnidipine), LS-04, vixotrigine, FX301/PCRX-301, PF-04531083, PF-01247324, and DSP-3905.

[517] In another embodiment, the additional therapeutic agent is a sodium channel inhibitor (also known as a sodium channel blocker), such as the $\text{Na}_v1.7$ and $\text{Na}_v1.8$ blockers identified above.

[518] The amount of additional therapeutic agent present in the compositions of this invention may be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions may range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[519] Compound **I** in any one of the pharmaceutically acceptable solid forms disclosed herein or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the invention, in another aspect, includes a composition for coating an implantable device comprising Compound **I** in any one of the pharmaceutically acceptable solid forms described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the invention includes an implantable device coated with a composition comprising Compound **I** in any one of the pharmaceutically acceptable solid forms described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[520] Another aspect of the invention relates to inhibiting $\text{Na}_v1.8$ activity in a biological sample or a subject, which method comprises administering to the subject, or contacting said biological sample with Compound **I** in any one of the pharmaceutically acceptable solid forms disclosed herein, or a

pharmaceutical composition thereof. 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.

[521] Inhibition of $\text{Na}_v1.8$ 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, the study of sodium channels in biological and pathological phenomena; and the comparative evaluation of new sodium channel inhibitors.

Pharmaceutical Compositions

[522] Another aspect of the invention provides pharmaceutical compositions comprising Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein. In some embodiments, the pharmaceutical composition comprises Compound I in a solid form selected from Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Amorphous Compound I, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, and Compound I TFA Salt A.

[523] In some embodiments, the invention provides a pharmaceutical composition comprising (a) Compound I in any one of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein, and (b) at least one pharmaceutically acceptable carrier.

[524] In some embodiments, the invention provides pharmaceutical compositions comprising (a) Compound I in a solid form selected from Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Amorphous Compound I, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, and Compound I TFA Salt A and (b) at least one pharmaceutically acceptable carrier.

[525] As described herein, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth

Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers 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, or 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, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Radiolabeled Analogs of Compound I

[526] In another aspect, the invention relates to radiolabeled analogs of Compound I. The radiolabeled analogs may be in any of the pharmaceutically acceptable solid (e.g., crystalline or amorphous) forms disclosed herein and may be prepared by any of the methods described herein.

[527] As used herein, the term "radiolabeled analogs of Compound I" refers to compounds that are identical to Compound I, as described herein, except that one or more atoms has been replaced with a radioisotope of the atom present in Compound I.

[528] As used herein, the term "radioisotope" refers to an isotope of an element that is known to undergo spontaneous radioactive decay. Examples of radioisotopes include ^3H , ^{14}C , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and the like, as well as the isotopes for which a decay mode is identified in V.S. Shirley & C.M. Lederer,

Isotopes Project, Nuclear Science Division, Lawrence Berkeley Laboratory, Table of Nuclides (January 1980).

[529] The radiolabeled analogs can be used in a number of beneficial ways, including in various types of assays, such as substrate tissue distribution assays. For example, tritium (^3H)- and/or carbon-14 (^{14}C)-labeled compounds may be useful for various types of assays, such as substrate tissue distribution assays, due to relatively simple preparation and excellent detectability.

[530] In another aspect, the invention relates to pharmaceutically acceptable salts of the radiolabeled analogs, in accordance with any of the embodiments described herein in connection with Compound I.

[531] In another aspect, the invention relates to pharmaceutical compositions comprising the radiolabeled analogs, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle, in accordance with any of the embodiments described herein in connection with Compound I.

[532] In another aspect, the invention relates to methods of inhibiting voltage-gated sodium channels and methods of treating or lessening the severity of various diseases and disorders, including pain, in a subject comprising administering an effective amount of the radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, in accordance with any of the embodiments described herein in connection with Compound I.

[533] In another aspect, the invention relates to radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, for use, in accordance with any of the embodiments described herein in connection with Compound I.

[534] In another aspect, the invention relates to the use of the radiolabeled analogs, or pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, for the manufacture of medicaments, in accordance with any of the embodiments described herein in connection with Compound I.

[535] In another aspect, the radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, can be employed in combination therapies, in accordance with any of the embodiments described herein in connection with Compound I.

Non-Limiting Exemplary Embodiments

[536] Further embodiments of the disclosure are set out in the following numbered clauses:

1. Compound I Neat Form A.

2. The Compound **I** Neat Form A of Embodiment 1, wherein the Compound **I** Neat Form A is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
3. The Compound **I** Neat Form A according to Embodiment 1 or 2, wherein the Compound **I** Neat Form A is substantially 100% crystalline.
4. The Compound **I** Neat Form A according to any one of Embodiments 1-3, wherein the Compound **I** Neat Form A is 100% crystalline.
5. The Compound **I** Neat Form A according to any one of Embodiments 1-4, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta.
6. The Compound **I** Neat Form A according to Embodiment 5, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 12.8 ± 0.2 degrees two-theta, 16.0 ± 0.2 degrees two-theta, and 20.4 ± 0.2 degrees two-theta.
7. The Compound **I** Neat Form A according to Embodiment 6, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.0 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta.
8. The Compound **I** Neat Form A according to any one of Embodiments 1-4, characterized by an X-ray powder diffractogram having signals at 5.5 ± 0.2 degrees two-theta, 8.0 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, 11.1 ± 0.2 degrees two-theta, 11.7 ± 0.2 degrees two-theta, 12.8 ± 0.2 degrees two-theta, 16.0 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.7 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.9 ± 0.2 degrees two-theta, 27.4 ± 0.2 degrees two-theta, 27.7 ± 0.2 degrees two-theta, 29.5 ± 0.2 degrees two-theta, and 29.9 ± 0.2 degrees two-theta.
9. The Compound **I** Neat Form A according to any one of Embodiments 1-4, characterized by an X-ray powder diffractogram substantially similar to **FIG. 8**.
10. The Compound **I** Neat Form A according to any one of Embodiments 1-9, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, and 169.6 ± 0.2 ppm.

ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm.

11. The Compound **I** Neat Form A according to any one of Embodiments 1-9, characterized by a ^{13}C SSNMR spectrum having peaks at 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm.
12. The Compound **I** Neat Form A according to any one of Embodiments 1-9, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 9A**.
13. The Compound **I** Neat Form A according to any one of Embodiments 1-12, characterized by triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation ($\lambda=1.54178$ Å) of:

a	11.0 ± 0.1 Å	α	$98.0 \pm 0.1^\circ$
b	11.2 ± 0.1 Å	β	$93.1 \pm 0.1^\circ$
c	15.9 ± 0.1 Å	γ	$95.8 \pm 0.1^\circ$
14. Compound **I** Hemi-Hydrate.
15. The Compound **I** Hemi-Hydrate of Embodiment 14, wherein the Compound **I** Hemi-Hydrate is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
16. The Compound **I** Hemi-Hydrate according to Embodiment 14 or 15, wherein the Compound **I** Hemi-Hydrate is substantially 100% crystalline.
17. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-16, wherein the Compound **I** Hemi-Hydrate is 100% crystalline.

18. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-17, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta.
19. The Compound **I** Hemi-Hydrate according to Embodiment 18, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 14.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.6 ± 0.2 degrees two-theta.
20. The Compound **I** Hemi-Hydrate according to Embodiment 19, characterized by an X-ray powder diffractogram having one or two signals selected from 11.1 ± 0.2 degrees two-theta and 21.3 ± 0.2 degrees two-theta.
21. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-17, characterized by an X-ray powder diffractogram having signals at 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 11.1 ± 0.2 degrees two-theta, 12.3 ± 0.2 degrees two-theta, 14.2 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.6 ± 0.2 degrees two-theta.
22. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-17, characterized by an X-ray powder diffractogram substantially similar to **FIG. 14**.
23. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-22, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.1 ± 0.2 ppm, 169.2 ± 0.2 ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm.
24. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-22, characterized by a ^{13}C SSNMR spectrum having peaks at 178.1 ± 0.2 ppm, 169.2 ± 0.2 ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm.
25. The Compound **I** Hemi-Hydrate according to any one of Embodiments 14-22, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 15**.
26. Compound **I** Monohydrate.

27. The Compound **I** Monohydrate of Embodiment 26, wherein the Compound **I** Monohydrate is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
28. The Compound **I** Monohydrate according to Embodiment 26 or 27, wherein the Compound **I** Monohydrate is substantially 100% crystalline.
29. The Compound **I** Monohydrate according to any one of Embodiments 26-28, wherein the Compound **I** Hemi-Hydrate is 100% crystalline.
30. The Compound **I** Monohydrate according to any one of Embodiments 26-29, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta.
31. The Compound **I** Monohydrate according to Embodiment 30, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 12.2 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, and 26.5 ± 0.2 degrees two-theta.
32. The Compound **I** Monohydrate according to Embodiment 31, characterized by an X-ray powder diffractogram having one or two signals selected from 17.1 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, and 23.5 ± 0.2 degrees two-theta.
33. The Compound **I** Monohydrate according to any one of Embodiments 26-29, characterized by an X-ray powder diffractogram having signals at 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees two-theta, 14.2 ± 0.2 degrees two-theta, 17.1 ± 0.2 degrees two-theta, 17.8 ± 0.2 degrees two-theta, 18.1 ± 0.2 degrees two-theta, 20.3 ± 0.2 degrees two-theta, 21.3 ± 0.2 degrees two-theta, 22.0 ± 0.2 degrees two-theta, 23.5 ± 0.2 degrees two-theta, 26.5 ± 0.2 degrees two-theta, 27.4 ± 0.2 degrees two-theta, and 31.7 ± 0.2 degrees two-theta.
34. The Compound **I** Monohydrate according to any one of Embodiments 26-29, characterized by an X-ray powder diffractogram substantially similar to **FIG. 16**.
35. Compound **I** Methanol Solvate.
36. The Compound **I** Methanol Solvate of Embodiment 35, wherein the Compound **I** Methanol Solvate is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form,

wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form).

37. The Compound I Methanol Solvate according to Embodiment 35 or 36, wherein the Compound I Methanol Solvate is substantially 100% crystalline.
38. The Compound I Methanol Solvate according to any one of Embodiments 35-37, wherein the Compound I Methanol Solvate is 100% crystalline.
39. The Compound I Methanol Solvate according to any one of Embodiments 35-38, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta.
40. The Compound I Methanol Solvate according to Embodiment 39, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 20.9 ± 0.2 degrees two-theta.
41. The Compound I Methanol Solvate according to Embodiment 40, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.
42. The Compound I Methanol Solvate according to any one of Embodiments 35-38, characterized by an X-ray powder diffractogram having signals at 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.
43. The Compound I Methanol Solvate according to any one of Embodiments 35-38, characterized by an X-ray powder diffractogram substantially similar to **FIG. 17**.
44. The Compound I Methanol Solvate according to any one of Embodiments 35-43, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2

ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm.

45. The Compound **I** Methanol Solvate according to any one of Embodiments 35-43, characterized by a ^{13}C SSNMR spectrum having peaks at 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2 ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm.

46. The Compound **I** Methanol Solvate according to any one of Embodiments 35-43, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 18**.

47. The Compound **I** Methanol Solvate according to any one of Embodiments 35-46, characterized by triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation ($\lambda=1.54178 \text{ \AA}$) of:

a	$12.3 \pm 0.1 \text{ \AA}$	α	$100.4 \pm 0.1^\circ$
b	$14.1 \pm 0.1 \text{ \AA}$	β	$105.3 \pm 0.1^\circ$
c	$14.4 \pm 0.1 \text{ \AA}$	γ	$107.5 \pm 0.1^\circ$

48. Compound **I** Neat Form B in any of the embodiments set forth above in Section B.

49. Compound **I** Neat Form C in any of the embodiments set forth above in Section C.

50. Amorphous Compound **I** in any of the embodiments set forth above in Section R.

51. Compound **I** nPA Solvate Mixture A.

52. The Compound **I** nPA Solvate Mixture A of Embodiment 51, wherein the Compound **I** nPA Solvate Mixture A is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).

53. The Compound **I** nPA Solvate Mixture A according to Embodiment 51 or 52, wherein the Compound **I** nPA Solvate Mixture A is substantially 100% crystalline.

54. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-53, wherein the Compound **I** nPA Solvate Mixture A is 100% crystalline.
55. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-54, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta.
56. The Compound **I** nPA Solvate Mixture A according to Embodiment 55, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 10.1 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta.
57. The Compound **I** nPA Solvate Mixture A according to Embodiment 56, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 13.5 ± 0.2 degrees two-theta, 14.3 ± 0.2 degrees two-theta, and 25.5 ± 0.2 degrees two-theta.
58. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-54, characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 10.1 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.5 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, 14.3 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 18.4 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, 22.8 ± 0.2 degrees two-theta, 23.3 ± 0.2 degrees two-theta, 25.5 ± 0.2 degrees two-theta, and 26.1 ± 0.2 degrees two-theta.
59. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-54, characterized by an X-ray powder diffractogram substantially similar to **FIG. 19**.
60. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm.
61. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum having peaks at 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm,

134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm.

62. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 20**.

63. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm, 36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm.

64. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum having peaks at 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm, 36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm.

65. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-59, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 21**.

66. The Compound **I** nPA Solvate Mixture A according to any one of Embodiments 51-65, characterized by monoclinic crystal system, $C2/c$ space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178 \text{ \AA}$) of:

a	19.9 ± 0.1 Å	α	90.
b	6.9 ± 0.1 Å	β	93.9 ± 0.1°
c	32.6 ± 0.1 Å	γ	90

67. Compound **I** nPA Solvate Mixture B.

68. The Compound **I** nPA Solvate Mixture B of Embodiment 67, wherein the Compound **I** nPA Solvate Mixture B is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous

form, wherein less than 10% of Compound I is in amorphous form, wherein less than 5% of Compound I is in amorphous form).

69. The Compound I nPA Solvate Mixture B according to Embodiment 67 or 68, wherein the Compound I nPA Solvate Mixture B is substantially 100% crystalline.
70. The Compound I nPA Solvate Mixture B according to any one of Embodiments 67-69, wherein the Compound I nPA Solvate Mixture B is 100% crystalline.
71. The Compound I nPA Solvate Mixture B according to any one of Embodiments 67-70, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta.
72. The Compound I nPA Solvate Mixture B according to Embodiment 71, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 9.9 ± 0.2 degrees two-theta, 13.2 ± 0.2 degrees two-theta, and 14.8 ± 0.2 degrees two-theta.
73. The Compound I nPA Solvate Mixture B according to Embodiment 72, characterized by an X-ray powder diffractogram having one or two signals selected from 18.9 ± 0.2 degrees two-theta and 21.4 ± 0.2 degrees two-theta.
74. The Compound I nPA Solvate Mixture B according to any one of Embodiments 67-70, characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 9.9 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.2 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, 17.5 ± 0.2 degrees two-theta, 18.0 ± 0.2 degrees two-theta, 18.9 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, 22.6 ± 0.2 degrees two-theta, 22.9 ± 0.2 degrees two-theta, 24.6 ± 0.2 degrees two-theta, 25.7 ± 0.2 degrees two-theta, 26.1 ± 0.2 degrees two-theta, 26.5 ± 0.2 degrees two-theta, and 28.1 ± 0.2 degrees two-theta.
75. The Compound I nPA Solvate Mixture B according to any one of Embodiments 67-70, characterized by an X-ray powder diffractogram substantially similar to **FIG. 22**.
76. The Compound I nPA Solvate Mixture B according to any one of Embodiments 67-75, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6

± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, and 20.7 ± 0.2 ppm.

77. The Compound **I** nPA Solvate Mixture B according to any one of Embodiments 67-75, characterized by a ^{13}C SSNMR spectrum having peaks at 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm.

78. The Compound **I** nPA Solvate Mixture B according to any one of Embodiments 67-75, characterized by a ^{13}C SSNMR spectrum substantially similar to FIG. 23.

79. The Compound **I** nPA Solvate Mixture B according to any one of Embodiments 67-78, characterized by triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	6.8 ± 0.1 Å	α	$93.8 \pm 0.1^{\circ}$
b	10.5 ± 0.1 Å	β	$92.9 \pm 0.1^{\circ}$
c	16.4 ± 0.1 Å	γ	$105.8 \pm 0.1^{\circ}$

80. Compound **I** nPA Solvate C.

81. The Compound **I** nPA Solvate C of Embodiment 80, wherein the Compound **I** nPA Solvate C is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).

82. The Compound **I** nPA Solvate C according to Embodiment 80 or 81, wherein the Compound **I** nPA Solvate C is substantially 100% crystalline.

83. The Compound **I** nPA Solvate C according to any one of Embodiments 80-82, wherein the Compound **I** nPA Solvate C is 100% crystalline.

84. The Compound **I** nPA Solvate C according to any one of Embodiments 80-83, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta.

85. The Compound **I** nPA Solvate C according to Embodiment 84, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 7.2 ± 0.2 degrees two-theta, 14.6 ± 0.2 degrees two-theta, and 15.8 ± 0.2 degrees two-theta.
86. The Compound **I** nPA Solvate C according to Embodiment 85, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.4 ± 0.2 degrees two-theta, 8.7 ± 0.2 degrees two-theta, and 10.2 ± 0.2 degrees two-theta.
87. The Compound **I** nPA Solvate C according to any one of Embodiments 80-83, characterized by an X-ray powder diffractogram having signals at 5.3 ± 0.2 degrees two-theta, 6.1 ± 0.2 degrees two-theta, 7.2 ± 0.2 degrees two-theta, 8.7 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, 12.2 ± 0.2 degrees two-theta, 14.6 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 17.5 ± 0.2 degrees two-theta, 19.1 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 21.4 ± 0.2 degrees two-theta, and 20.5 ± 0.2 degrees two-theta.
88. The Compound **I** nPA Solvate C according to any one of Embodiments 80-83, characterized by an X-ray powder diffractogram substantially similar to **FIG. 24**.
89. Compound **I** Na Hemi Salt nPA Solvate.
90. The Compound **I** Na Hemi Salt nPA Solvate of Embodiment 89, wherein the Compound **I** Na Hemi Salt nPA Solvate is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
91. The Compound **I** Na Hemi Salt nPA Solvate according to Embodiment 89 or 90, wherein the Compound **I** Na Hemi Salt nPA Solvate is substantially 100% crystalline.
92. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-91, wherein the Compound **I** Na Hemi Salt nPA Solvate is 100% crystalline.
93. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-92, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta.

94. The Compound **I** Na Hemi Salt nPA Solvate according to Embodiment 93, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 13.4 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, and 18.7 ± 0.2 degrees two-theta.
95. The Compound **I** Na Hemi Salt nPA Solvate according to Embodiment 94, characterized by an X-ray powder diffractogram having one, two or three signals selected from 5.2 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.3 ± 0.2 degrees two-theta.
96. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-92, characterized by an X-ray powder diffractogram having signals at 5.2 ± 0.2 degrees two-theta, 6.7 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 9.8 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 13.4 ± 0.2 degrees two-theta, 13.6 ± 0.2 degrees two-theta, 13.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, 14.2 ± 0.2 degrees two-theta, 14.9 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 18.7 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 20.6 ± 0.2 degrees two-theta, 21.0 ± 0.2 degrees two-theta, 24.6 ± 0.2 degrees two-theta, 26.4 ± 0.2 degrees two-theta, 26.6 ± 0.2 degrees two-theta, and 28.4 ± 0.2 degrees two-theta.
97. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-92, characterized by an X-ray powder diffractogram substantially similar to **FIG. 25**.
98. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-97, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 114.0 ± 0.2 ppm, 111.6 ± 0.2 ppm, 65.1 ± 0.2 ppm, 62.6 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.7 ± 0.2 ppm, 26.2 ± 0.2 ppm, 24.8 ± 0.2 ppm, 21.4 ± 0.2 ppm, and 20.8 ± 0.2 ppm.
99. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-97, characterized by a ^{13}C SSNMR spectrum having peaks at 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm,

115.9 $\pm$ 0.2 ppm, 114.4 $\pm$ 0.2 ppm, 114.0 $\pm$ 0.2 ppm, 111.6 $\pm$ 0.2 ppm, 65.1 $\pm$ 0.2 ppm, 62.6 $\pm$ 0.2 ppm, 36.5 $\pm$ 0.2 ppm, 30.7 $\pm$ 0.2 ppm, 26.2 $\pm$ 0.2 ppm, 24.8 $\pm$ 0.2 ppm, 21.4 $\pm$ 0.2 ppm, and 20.8 $\pm$ 0.2 ppm.

100. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-97, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 26**.

101. The Compound **I** Na Hemi Salt nPA Solvate according to any one of Embodiments 89-100, characterized by triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178$ Å) of:

a	10.3 $\pm$ 0.1 Å	α	94.2 $\pm$ 0.1°
b	13.3 $\pm$ 0.1 Å	β	91.0 $\pm$ 0.1°
c	16.7 $\pm$ 0.1 Å	γ	104.0 $\pm$ 0.1°

102. Compound **I** nPA Solvate J.

103. The Compound **I** nPA Solvate J of Embodiment 102, wherein the Compound **I** nPA Solvate J is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).

104. The Compound **I** nPA Solvate J according to Embodiment 102 or 103, wherein the Compound **I** nPA Solvate J is substantially 100% crystalline.

105. The Compound **I** nPA Solvate J according to any one of Embodiments 102-104, wherein the Compound **I** nPA Solvate J is 100% crystalline.

106. The Compound **I** nPA Solvate J according to any one of Embodiments 102-105, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.3 $\pm$ 0.2 degrees two-theta, 10.4 $\pm$ 0.2 degrees two-theta, and 19.0 $\pm$ 0.2 degrees two-theta.

107. The Compound **I** nPA Solvate J according to Embodiment 106, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.8 $\pm$ 0.2 degrees two-theta, 10.6 $\pm$ 0.2 degrees two-theta, and 13.4 $\pm$ 0.2 degrees two-theta.

108. The Compound **I** nPA Solvate **J** according to Embodiment 107, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 14.1 ± 0.2 degrees two-theta, 19.2 ± 0.2 degrees two-theta, and 26.0 ± 0.2 degrees two-theta.
109. The Compound **I** nPA Solvate **J** according to any one of Embodiments 102-105, characterized by an X-ray powder diffractogram having signals at 3.1 ± 0.2 degrees two-theta, 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, 10.0 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.4 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 19.0 ± 0.2 degrees two-theta, 19.2 ± 0.2 degrees two-theta, 26.0 ± 0.2 degrees two-theta, and 26.4 ± 0.2 degrees two-theta.
110. The Compound **I** nPA Solvate **J** according to any one of Embodiments 102-105, characterized by an X-ray powder diffractogram substantially similar to **FIG. 27**.
111. Compound **I** 2-MeTHF Solvate **A**.
112. The Compound **I** 2-MeTHF Solvate **A** of Embodiment 111, wherein the Compound **I** 2-MeTHF Solvate **A** is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
113. The Compound **I** 2-MeTHF Solvate **A** according to Embodiment 111 or 112, wherein the Compound **I** 2-MeTHF Solvate **A** is substantially 100% crystalline.
114. The Compound **I** 2-MeTHF Solvate **A** according to any one of Embodiments 111-113, wherein the Compound **I** 2-MeTHF Solvate **A** is 100% crystalline.
115. The Compound **I** 2-MeTHF Solvate **A** according to any one of Embodiments 111-114, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta.
116. The Compound **I** 2-MeTHF Solvate **A** according to Embodiment 115, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 9.8 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, and 15.4 ± 0.2 degrees two-theta.

117. The Compound **I** 2-MeTHF Solvate A according to Embodiment 116, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 17.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, and 20.8 ± 0.2 degrees two-theta.
118. The Compound **I** 2-MeTHF Solvate A according to any one of Embodiments 111-114, characterized by an X-ray powder diffractogram having signals at 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, 9.8 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 14.0 ± 0.2 degrees two-theta, 15.4 ± 0.2 degrees two-theta, 15.7 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 18.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, 20.8 ± 0.2 degrees two-theta, 24.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.
119. The Compound **I** 2-MeTHF Solvate A according to any one of Embodiments 111-114, characterized by an X-ray powder diffractogram substantially similar to **FIG. 28**.
120. Compound **I** 2-MeTHF Solvate Mixture A.
121. The Compound **I** 2-MeTHF Solvate Mixture A of Embodiment 120, wherein the Compound **I** 2-MeTHF Solvate Mixture A is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
122. The Compound **I** 2-MeTHF Solvate Mixture A according to Embodiment 120 or 121, wherein the Compound **I** 2-MeTHF Solvate Mixture A is substantially 100% crystalline.
123. The Compound **I** 2-MeTHF Solvate Mixture A according to any one of Embodiments 120-122, wherein the Compound **I** 2-MeTHF Solvate A is 100% crystalline.
124. The Compound **I** 2-MeTHF Solvate Mixture A according to any one of Embodiments 120-123, characterized by an X-ray powder diffractogram having a signal at 4.6 ± 0.2 degrees two-theta.
125. The Compound **I** 2-MeTHF Solvate Mixture A according to Embodiment 124, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 15.8 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.

126. The Compound **I** 2-MeTHF Solvate Mixture A according to Embodiment 125, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 12.4 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.
127. The Compound **I** 2-MeTHF Solvate Mixture A according to any one of Embodiments 120-124, characterized by an X-ray powder diffractogram having signals at 4.6 ± 0.2 degrees two-theta, 12.4 ± 0.2 degrees two-theta, 14.8 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 19.4 ± 0.2 degrees two-theta, 21.9 ± 0.2 degrees two-theta, and 25.3 ± 0.2 degrees two-theta.
128. The Compound **I** 2-MeTHF Solvate Mixture A according to any one of Embodiments 120-124, characterized by an X-ray powder diffractogram substantially similar to **FIG. 29**.
129. Compound **I** 2-MeTHF Mixture C.
130. The Compound **I** 2-MeTHF Mixture C of Embodiment 129, wherein the Compound **I** 2-MeTHF Mixture C is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
131. The Compound **I** 2-MeTHF Mixture C according to Embodiment 129 or 130, wherein the Compound **I** 2-MeTHF Mixture C is substantially 100% crystalline.
132. The Compound **I** 2-MeTHF Mixture C according to any one of Embodiments 129-131, wherein the Compound **I** 2-MeTHF Mixture C is 100% crystalline.
133. The Compound **I** 2-MeTHF Mixture C according to any one of Embodiments 129-132, characterized by an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta.
134. The Compound **I** 2-MeTHF Mixture C according to Embodiment 133, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.2 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, and 18.5 ± 0.2 degrees two-theta.
135. The Compound **I** 2-MeTHF Mixture C according to Embodiment 134, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 15.3 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, and 23.1 ± 0.2 degrees two-theta.

136. The Compound **I** 2-MeTHF Mixture C according to any one of Embodiments 129-132, characterized by an X-ray powder diffractogram having signals at 4.9 ± 0.2 degrees two-theta, 8.2 ± 0.2 degrees two-theta, 10.3 ± 0.2 degrees two-theta, 11.3 ± 0.2 degrees two-theta, 15.3 ± 0.2 degrees two-theta, 15.7 ± 0.2 degrees two-theta, 15.8 ± 0.2 degrees two-theta, 17.2 ± 0.2 degrees two-theta, 18.5 ± 0.2 degrees two-theta, 19.6 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 23.1 ± 0.2 degrees two-theta, 25.0 ± 0.2 degrees two-theta, and 25.2 ± 0.2 degrees two-theta.
137. The Compound **I** 2-MeTHF Mixture C according to any one of Embodiments 129-1329, characterized by an X-ray powder diffractogram substantially similar to **FIG. 30**.
138. Compound **I** Mandelic Acid Cocrystal.
139. The Compound **I** Mandelic Acid Cocrystal of Embodiment 138, wherein the Compound **I** Mandelic Acid Cocrystal is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
140. The Compound **I** Mandelic Acid Cocrystal according to Embodiment 138 or 139, wherein the Compound **I** Mandelic Acid Cocrystal is substantially 100% crystalline.
141. The Compound **I** Mandelic Acid Cocrystal according to any one of Embodiments 138-140, wherein the Compound **I** Mandelic Acid Cocrystal is 100% crystalline.
142. The Compound **I** Mandelic Acid Cocrystal according to any one of Embodiments 138-141, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.
143. The Compound **I** Mandelic Acid Cocrystal according to Embodiment 142, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, and 18.8 ± 0.2 degrees two-theta.
144. The Compound **I** Mandelic Acid Cocrystal according to Embodiment 143, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, and 20.9 ± 0.2 degrees two-theta.
145. The Compound **I** Mandelic Acid Cocrystal according to any one of Embodiments 138-141, characterized by an X-ray powder diffractogram having signals at 6.6 ± 0.2 degrees two-theta, 8.4

± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 13.3 ± 0.2 degrees two-theta, 15.9 ± 0.2 degrees two-theta, 17.6 ± 0.2 degrees two-theta, 18.8 ± 0.2 degrees two-theta, 20.9 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta.

146. The Compound **I** Mandelic Acid Cocrystal according to any one of Embodiments 138-141, characterized by an X-ray powder diffractogram substantially similar to **FIG. 31**.

147. Compound **I** Oxalic Acid Cocrystal.

148. The Compound **I** Oxalic Acid Cocrystal of Embodiment 147, wherein the Compound **I** Oxalic Acid Cocrystal is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).

149. The Compound **I** Oxalic Acid Cocrystal according to Embodiment 147 or 148, wherein the Compound **I** Oxalic Acid Cocrystal is substantially 100% crystalline.

150. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-149, wherein the Compound **I** Oxalic Acid Cocrystal is 100% crystalline.

151. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-150, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta.

152. The Compound **I** Oxalic Acid Cocrystal according to Embodiment 151, characterized by an X-ray powder diffractogram having one or two signals selected from 5.7 ± 0.2 degrees two-theta and 20.1 ± 0.2 degrees two-theta.

153. The Compound **I** Oxalic Acid Cocrystal according to Embodiment 152, characterized by an X-ray powder diffractogram having one, two or three signals selected from 10.6 ± 0.2 degrees two-theta, 13.8 ± 0.2 degrees two-theta, and 22.9 ± 0.2 degrees two-theta.

154. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-150, characterized by an X-ray powder diffractogram having signals at 5.7 ± 0.2 degrees two-theta, 8.9 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, 13.8 ± 0.2 degrees two-theta, 14.5 ± 0.2 degrees two-theta, 20.1 ± 0.2 degrees two-theta, and 22.9 ± 0.2 degrees two-theta.

155. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-150, characterized by an X-ray powder diffractogram substantially similar to **FIG. 32**.
156. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-155, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm.
157. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-155, characterized by a ^{13}C SSNMR spectrum having peaks at 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm.
158. The Compound **I** Oxalic Acid Cocrystal according to any one of Embodiments 147-155, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 33**.
159. Compound **I** TFA Salt A.
160. The Compound **I** TFA Salt A of Embodiment 159, wherein the Compound **I** TFA Salt A is substantially crystalline (i.e., wherein less than 15% of Compound **I** is in amorphous form, wherein less than 10% of Compound **I** is in amorphous form, wherein less than 5% of Compound **I** is in amorphous form).
161. The Compound **I** TFA Salt A according to Embodiment 159 or 160, wherein the Compound **I** TFA Salt A is substantially 100% crystalline.
162. The Compound **I** TFA Salt A according to any one of Embodiments 159-161, wherein the Compound **I** TFA Salt A is 100% crystalline.
163. The Compound **I** TFA Salt A according to any one of Embodiments 159-162, characterized by an X-ray powder diffractogram having one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta.

164. The Compound **I** TFA Salt A according to Embodiment 163, characterized by an X-ray powder diffractogram having one or two signals selected from 4.4 ± 0.2 degrees two-theta and 11.4 ± 0.2 degrees two-theta.
165. The Compound **I** TFA Salt A according to Embodiment 164, characterized by an X-ray powder diffractogram having one, two or three signals selected from 17.3 ± 0.2 degrees two-theta, 23.8 ± 0.2 degrees two-theta, and 26.3 ± 0.2 degrees two-theta.
166. The Compound **I** TFA Salt A according to any one of Embodiments 159-162, characterized by an X-ray powder diffractogram having signals at 4.4 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, 11.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, 17.3 ± 0.2 degrees two-theta, 19.7 ± 0.2 degrees two-theta, 20.4 ± 0.2 degrees two-theta, 23.8 ± 0.2 degrees two-theta, and 26.3 ± 0.2 degrees two-theta.
167. The Compound **I** TFA Salt A according to any one of Embodiments 159-162, characterized by an X-ray powder diffractogram substantially similar to **FIG. 34**.
168. The Compound **I** TFA Salt A according to any one of Embodiments 159-167, characterized by a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm.
169. The Compound **I** TFA Salt A according to any one of Embodiments 159-167, characterized by a ^{13}C SSNMR spectrum having peaks at 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm.
170. The Compound **I** TFA Salt A according to any one of Embodiments 159-167, characterized by a ^{13}C SSNMR spectrum substantially similar to **FIG. 35**.
171. A pharmaceutical composition comprising the Compound **I** according to any one of Embodiments 1-170.

172. The pharmaceutical composition according to Embodiment 171, further comprising one or more additional therapeutic agents.
173. The Compound I according to any one of Embodiments 1-170, or the pharmaceutical composition according to Embodiment 198 or 199, for use in treating or lessening the severity in a subject of pain.
174. The Compound I or pharmaceutical composition for use according to Embodiment 173, wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.
175. The Compound I or pharmaceutical composition for use according to Embodiment 174, wherein the pain comprises neuropathic pain.
176. The Compound I or pharmaceutical composition for use according to Embodiment 175, wherein the neuropathic pain comprises post-herpetic neuralgia.
177. The Compound I or pharmaceutical composition for use according to Embodiment 175, wherein the neuropathic pain comprises small-fiber neuropathy.
178. The Compound I or pharmaceutical composition for use according to Embodiment 175, wherein the neuropathic pain comprises idiopathic small-fiber neuropathy.
179. The Compound I or pharmaceutical composition for use according to Embodiment 175, wherein the neuropathic pain comprises diabetic neuropathy.
180. The Compound I or pharmaceutical composition for use according to Embodiment 179, wherein the diabetic neuropathy comprises diabetic peripheral neuropathy.
181. The Compound I or pharmaceutical composition for use according to Embodiment 173, wherein the pain comprises musculoskeletal pain.
182. The Compound I or pharmaceutical composition for use according to Embodiment 181, wherein the musculoskeletal pain comprises osteoarthritis pain.

183. The Compound I or pharmaceutical composition for use according to Embodiment 173, wherein the pain comprises acute pain.
184. The Compound I or pharmaceutical composition for use according to Embodiment 183, wherein the acute pain comprises acute post-operative pain.
185. The Compound I or pharmaceutical composition for use according to Embodiment 173, wherein the pain comprises postsurgical pain.
186. The Compound I or pharmaceutical composition for use according to Embodiment 185, wherein the postsurgical pain comprises bunionectomy pain.
187. The Compound I or pharmaceutical composition for use according to Embodiment 185, wherein the postsurgical pain comprises abdominoplasty pain.
188. The Compound I or pharmaceutical composition for use according to Embodiment 185, wherein the postsurgical pain comprises hemiorrhaphy pain.
189. The Compound I or pharmaceutical composition for use according to Embodiment 173, wherein the pain comprises visceral pain.
190. The Compound I or pharmaceutical composition for use according to any one of Embodiments 173-189, wherein the Compound or pharmaceutical composition is for administration in combination with one or more additional therapeutic agents.
191. The Compound I or pharmaceutical composition for use according to Embodiment 190, wherein the one or more additional therapeutic agents comprise one or more additional pain modulating compounds.
192. Use of the Compound I according to any one of Embodiments 1-170, or the pharmaceutical composition according to Embodiment 171 or 172, in the manufacture of a medicament for treating or lessening the severity in a subject of pain.
193. The use according to Embodiment 192, wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

194. The use according to Embodiment 193, wherein the pain comprises neuropathic pain.
195. The use according to Embodiment 194, wherein the neuropathic pain comprises post-herpetic neuralgia.
196. The use according to Embodiment 194, wherein the neuropathic pain comprises small-fiber neuropathy.
197. The use according to Embodiment 194, wherein the neuropathic pain comprises idiopathic small-fiber neuropathy.
198. The use according to Embodiment 194, wherein the neuropathic pain comprises diabetic neuropathy.
199. The use according to Embodiment 198, wherein the diabetic neuropathy comprises diabetic peripheral neuropathy.
200. The use according to Embodiment 193, wherein the pain comprises musculoskeletal pain.
201. The use according to Embodiment 200, wherein the musculoskeletal pain comprises osteoarthritis pain.
202. The use according to Embodiment 193, wherein the pain comprises acute pain.
203. The use according to Embodiment 202, wherein the acute pain comprises acute post-operative pain.
204. The use according to Embodiment 193, wherein the pain comprises postsurgical pain.
205. The use according to Embodiment 204, wherein the postsurgical pain comprises bunionectomy pain.
206. The use according to Embodiment 204, wherein the postsurgical pain comprises abdominoplasty pain.
207. The use according to Embodiment 204, wherein the postsurgical pain comprises herniorrhaphy pain.
208. The use according to Embodiment 193, wherein the pain comprises visceral pain.

209. The use according to any one of Embodiments 192-208, wherein the medicament is for administration in combination with one or more additional therapeutic agents.
210. The use according to Embodiment 209, wherein the one or more additional therapeutic agents comprise one or more additional pain modulating compounds.
211. A method of treating or lessening the severity in a subject of pain comprising administering the Compound I according to any one of Embodiments 1-170, or the pharmaceutical composition according to Embodiment 171 or 172, to the subject.
212. The method according to Embodiment 211, wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.
213. The method according to Embodiment 212, wherein the pain comprises neuropathic pain.
214. The method according to Embodiment 213, wherein the neuropathic pain comprises post-herpetic neuralgia.
215. The method according to Embodiment 213, wherein the neuropathic pain comprises small-fiber neuropathy.
216. The method according to Embodiment 213, wherein the neuropathic pain comprises idiopathic small-fiber neuropathy.
217. The method according to Embodiment 213, wherein the neuropathic pain comprises diabetic neuropathy.
218. The method according to Embodiment 217, wherein the diabetic neuropathy comprises diabetic peripheral neuropathy.
219. The method according to Embodiment 212, wherein the pain comprises musculoskeletal pain.
220. The method according to Embodiment 219, wherein the musculoskeletal pain comprises osteoarthritis pain.

221. The method according to Embodiment 212, wherein the pain comprises acute pain.
222. The method according to Embodiment 221, wherein the acute pain comprises acute post-operative pain.
223. The method according to Embodiment 212, wherein the pain comprises postsurgical pain.
224. The method according to Embodiment 223, wherein the postsurgical pain comprises bunionectomy pain.
225. The method according to Embodiment 223, wherein the postsurgical pain comprises abdominoplasty pain.
226. The method according to Embodiment 223, wherein the postsurgical pain comprises herniorrhaphy pain.
227. The method according to Embodiment 212, wherein the pain comprises visceral pain.
228. The method according to any one of Embodiments 211-227, wherein the medicament is for administration in combination with one or more additional therapeutic agents.
229. The method according to Embodiment 228, wherein the one or more additional therapeutic agents comprise one or more additional pain modulating compounds.
230. A method of making Compound I Neat Form A, comprising (i) suspending Compound I amorphous material in methanol, (ii) shaking at room temperature for 1 hour, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Neat Form A.
231. A method of making Compound I Neat Form B, comprising (i) suspending Amorphous Compound I in nitromethane to form a mixture, (ii) agitating the mixture at room temperature for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form B.
232. A method of making Compound I Neat Form C, comprising (i) suspending Compound I Neat Form A in 2-MeTHF to form a mixture, (ii) stirring the mixture at about 20 °C for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form C.

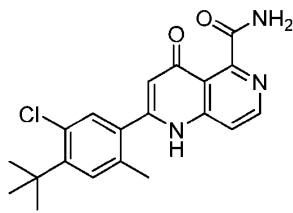
233. A method of making Compound I Hemi-Hydrate, comprising (i) suspending Compound I in water, (ii) shaking at 40 °C for at least 1 week, at least 2 weeks, at least three weeks, or at least 4 weeks, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Hemi-Hydrate.
234. A method of making Compound I Monohydrate, comprising (i) suspending Compound I in water, (ii) shaking at 40 °C for no more than 48 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Monohydrate.
235. A method of making Compound I Methanol Solvate, comprising (i) suspending Compound I amorphous material in methanol, (ii) shaking at 40 °C for 1 hour, and (iii) collecting the solids to afford Compound I Methanol Solvate.
236. A method of making Compound I nPA Solvate Mixture A, comprising (i) suspending Compound I nPA Solvate B and NaTFA in nPA, (ii) mixing at room temperature for 6-18 hours, (iii) collecting the solids, and (iv) air-drying for 15-45 minutes to afford Compound I nPA Solvate Mixture A.
237. A method of making Compound I nPA Solvate B, comprising (i) suspending Compound I nPA amorphous material in nPA, (ii) mixing at room temperature for 18-30 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I nPA Solvate B.
238. A method of making Compound I nPA Solvate C, comprising (i) dissolving Compound I in nPA, (ii) mixing at 90-100 °C for 1-2 hours, (iii) mixing at room temperature for 6-30 hours, and (iv) collecting the solids to afford Compound I nPA Solvate C.
239. A method of making Compound I Na Hemi Salt nPA Solvate, comprising (i) treating 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile with water and TFA, (ii) mixing at 60 °C for 18-30 hours, (iii) treating the mixture with water and sodium hydroxide at room temperature, (iv) washing the mixture with aqueous sodium chloride, (v) diluting the mixture with 2-MeTHF and subsequently concentrating, (vi) treating the mixture with nPA and subsequently concentrating, (vii) heating the mixture to 90 °C and subsequently holding the mixture at 50 °C for 6-18 hours, (viii) cooling the mixture to room temperature, (ix) collecting the solids, and (s) drying under vacuum at 40 °C for 6-18 hours to afford Compound I Na Hemi Salt nPA Solvate.

240. A method of making Compound I nPA Solvate J, comprising (i) treating a mixture of Compound I and 2-MeTHF with nPA, (ii) concentrating the mixture at 20-30 °C, (iii) treating the mixture with nPA and subsequently concentrating the mixture at 20-30 °C, (iv) heating the mixture to 80-100 °, (v) cooling the mixture to room temperature over 8-16 hours, (v) collecting the solids, and (vi) drying under vacuum at 45 °C to afford Compound I nPA Solvate J.
241. A method of making Compound I 2-MeTHF Solvate A comprising (i) treating Compound I Form A with 2-MeTHF, (ii) agitating the mixture for 24 hours at about 22 °C, and (iii) isolating the solids to afford Compound I 2-MeTHF Solvate A.
242. A method of making Compound I 2-MeTHF Solvate Mixture A, comprising (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I 2-MeTHF Solvate Mixture A.
243. A method of making Compound I 2-MeTHF Solvate Mixture C, comprising (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) warming the slurry to 90 °C to dissolve solids, (iv) cooling to 25 °C, (v) collecting the solids, and (iv) drying at 50 °C to afford Compound I 2-MeTHF Solvate Mixture C.
244. A method of making Compound I Mandelic Acid Cocrystal, comprising (i) combining Compound I and Mandelic acid, (ii) diluting the mixture in DCM, (iii) agitating the mixture for at least 1 hour, (iv) collecting the resulting solid material, and (v) drying the collected solid material in a vacuum oven at 50 °C to afford Compound I Mandelic Acid Cocrystal.
245. A method of making Compound I Oxalic Acid Cocrystal, comprising (i) suspending Compound I and oxalic acid (1:1) in DCM, (ii) stirring the resulting slurry at room temperature, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I Oxalic Acid Cocrystal.
246. A method of making Compound I TFA Salt A, comprising (i) suspending Compound I in DCM, (ii) treating the suspension with TFA, (iii) stirring at room temperature for 15-45 minutes, (iv) collecting the solids, and (v) drying at room temperature to afford Compound I TFA Salt A.
247. A method of making Amorphous Compound I, comprising (i) combining Compound I and t-butanol to form a mixture, (ii) stirring the mixture at about 70 °C for about 1 hour, (iii) adding

water to the mixture, (iv) freezing the mixture, and (v) isolating the solid material to afford Amorphous Compound I.

[537] Still further embodiments of the disclosure are set out in the following numbered clauses:

1. A substantially crystalline Compound I

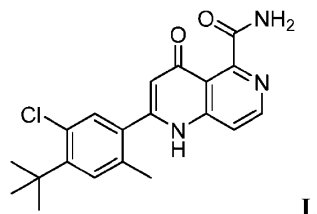


wherein the substantially crystalline Compound I is selected from Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, and Compound I TFA Salt A.

2. The substantially crystalline Compound I according to Embodiment 1, wherein less than 15% of Compound I is in amorphous form.
3. The substantially crystalline Compound I according to Embodiment 1, wherein less than 10% of Compound I is in amorphous form.
4. The substantially crystalline Compound I according to Embodiment 1, wherein less than 5% of Compound I is in amorphous form.
5. The substantially crystalline Compound I according to Embodiment 1, wherein 100% of Compound I is crystalline.
6. The substantially crystalline Compound I according to any one of Embodiments 1-5, characterized by crystal lattice parameters.
7. The substantially crystalline Compound I according to any one of Embodiments 1-6, characterized by an X-ray powder diffractogram (XRPD).

8. The substantially crystalline Compound I according to any one of Embodiments 1-7, characterized by ^{13}C solid-state nuclear magnetic resonance (^{13}C SSNMR) spectrum.

9. An amorphous Compound I



10. The amorphous Compound I according to Embodiment 9, characterized by an X-ray powder diffractogram (XRPD).

11. The amorphous Compound I according to Embodiment 9 or 10, characterized by ^{13}C solid-state nuclear magnetic resonance (^{13}C SSNMR) spectrum.

12. A pharmaceutical composition comprising the substantially crystalline Compound I according to any one of Embodiments 1-8 or the amorphous Compound I according to any one of Embodiments 9-11.

13. The pharmaceutical composition according to Embodiment 12, further comprising one or more additional therapeutic agents.

14. The substantially crystalline Compound I according to any one of Embodiments 1-8, the amorphous Compound I according to any one of Embodiments 9-11, or the pharmaceutical composition according to Embodiment 12 or 13, for use in treating or lessening the severity in a subject of pain.

15. The substantially crystalline Compound I, amorphous compound I, or pharmaceutical composition for use according to Embodiment 14, wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

16. Use of the substantially crystalline Compound I according to any one of Embodiments 1-8, the amorphous Compound I according to any one of Embodiments 9-11, or the pharmaceutical composition according to Embodiment 12 or 13, in the manufacture of a medicament for treating or lessening the severity in a subject of pain.

17. A method of treating or lessening the severity in a subject of pain comprising administering the substantially crystalline Compound I according to any one of Embodiments 1-8, the amorphous Compound I according to any one of Embodiments 9-11, or the pharmaceutical composition according to Embodiment 12 or 13, to the subject.

18. The compound or composition for use of Embodiment 14 or 15, the use of Embodiment 16, or the method of Embodiment 17, wherein the substantially crystalline Compound I according to any one of Embodiments 1-8, the amorphous Compound I according to any one of Embodiments 9-11, or the composition according to Embodiment 12 or 13 is administered in combination with one or more additional therapeutic agents.

19. The compound or composition for use, the use, or the method of Embodiment 18, wherein the one or more additional therapeutic agents comprise one or more additional pain modulating compounds.

20. A method of preparing a solid form of Compound I, comprising:

(a) (i) suspending Compound I amorphous material in methanol, (ii) shaking at room temperature for 1 hour, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Neat Form A;

(b) (i) suspending Amorphous Compound I in nitromethane to form a mixture, (ii) agitating the mixture at room temperature for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form B;

(c) (i) suspending Compound I Neat Form A in 2-MeTHF to form a mixture, (ii) stirring the mixture at about 20 °C for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form C;

(d) (i) suspending Compound I in water, (ii) shaking at 40 °C for at least 1 week, at least 2 weeks, at least three weeks, or at least 4 weeks, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Hemi-Hydrate;

(e) (i) suspending Compound I in water, (ii) shaking at 40 °C for no more than 48 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Monohydrate;

(f) (i) suspending Compound I amorphous material in methanol, (ii) shaking at 40 °C for 1 hour, and (iii) collecting the solids to afford Compound I Methanol Solvate;

(g) (i) suspending Compound I nPA Solvate B and NaTFA in nPA, (ii) mixing at room temperature for 6-18 hours, (iii) collecting the solids, and (iv) air-drying for 15-45 minutes to afford Compound I nPA Solvate Mixture A;

(h) (i) suspending Compound I nPA amorphous material in nPA, (ii) mixing at room temperature for 18-30 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I nPA Solvate B;

(i) (i) dissolving Compound I in nPA, (ii) mixing at 90-100 °C for 1-2 hours, (iii) mixing at room temperature for 6-30 hours, and (iv) collecting the solids to afford Compound I nPA Solvate C;

(j) (i) treating 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile with water and TFA, (ii) mixing at 60 °C for 18-30 hours, (iii) treating the mixture with water and sodium hydroxide at room temperature, (iv) washing the mixture with aqueous sodium chloride, (v) diluting the mixture with 2-MeTHF and subsequently concentrating, (vi) treating the mixture with nPA and subsequently concentrating, (vii) heating the mixture to 90 °C and subsequently holding the mixture at 50 °C for 6-18 hours, (viii) cooling the mixture to room temperature, (ix) collecting the solids, and (s) drying under vacuum at 40 °C for 6-18 hours to afford Compound I Na Hemi Salt nPA Solvate;

(k) (i) treating a mixture of Compound I and 2-MeTHF with nPA, (ii) concentrating the mixture at 20-30 °C, (iii) treating the mixture with nPA and subsequently concentrating the mixture at 20-30 °C, (iv) heating the mixture to 80-100 °, (v) cooling the mixture to room temperature over 8-16 hours, (v) collecting the solids, and (vi) drying under vacuum at 45 °C to afford Compound I nPA Solvate J;

(l) (i) treating Compound I Form A with 2-MeTHF, (ii) agitating the mixture for 24 hours at about 22 °C, and (iii) isolating the solids to afford Compound I 2-MeTHF Solvate A;

(m) (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I 2-MeTHF Solvate Mixture A;

(n) (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) warming the slurry to 90 °C to dissolve solids, (iv) cooling to 25 °C, (v) collecting the solids, and (iv) drying at 50 °C to afford Compound I 2-MeTHF Solvate Mixture C;

(o) (i) combining Compound I and Mandelic acid, (ii) diluting the mixture in DCM, (iii) agitating the mixture for at least 1 hour, (iv) collecting the resulting solid material, and (v) drying the collected solid material in a vacuum oven at 50 °C to afford Compound I Mandelic Acid Cocrystal;

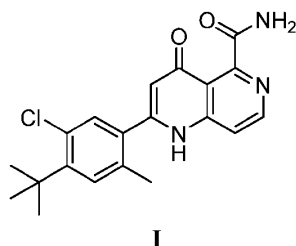
(p) (i) suspending Compound I and oxalic acid (1:1) in DCM, (ii) stirring the resulting slurry at room temperature, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I Oxalic Acid Cocrystal;

(q) (i) suspending Compound I in DCM, (ii) treating the suspension with TFA, (iii) stirring at room temperature for 15-45 minutes, (iv) collecting the solids, and (v) drying at room temperature to afford Compound I TFA Salt A; or

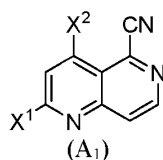
(r) (i) combining Compound I and t-butanol to form a mixture, (ii) stirring the mixture at about 70 °C for about 1 hour, (iii) adding water to the mixture, (iv) freezing the mixture, and (v) isolating the solid material to afford Amorphous Compound I.

[538] Still further embodiments of the disclosure are set out in the following numbered clauses:

1. A process for preparing Compound I or solvates or pharmaceutically acceptable salts thereof:



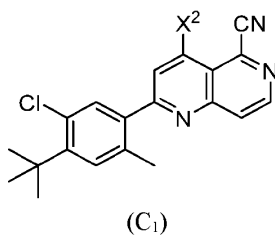
comprising transforming a compound of formula (A₁):



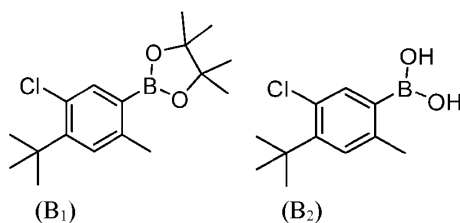
to Compound I;

wherein each of X¹ and X² are independently selected from halogen.

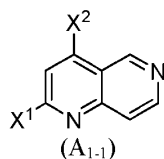
2. The process of Embodiment 1, wherein transforming the compound of formula (A₁) to Compound I comprises transforming the compound of formula (A₁) to a compound of formula (C₁):



3. The process of Embodiment 2, wherein transforming the compound of formula (A₁) to the compound of formula (C₁) comprises contacting the compound of formula (A₁) with a compound of formula (B₁) or (B₂):



4. The process of Embodiment 3, wherein contacting the compound of formula (A₁) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.
5. The process of Embodiment 4, wherein the first palladium catalyst is a palladium-phosphine complex.
6. The process of any one of Embodiments 4 and 5, wherein the first palladium catalyst is PdCl₂(PPh₃)₂.
7. The process of any one of Embodiments 4-6, wherein the first base is selected from potassium phosphate and potassium carbonate.
8. The process of any one of Embodiments 2 to 7, wherein transforming the compound of formula (A₁) to Compound I further comprises transforming the compound of formula (C₁) to Compound I.
9. The process of Embodiment 8, wherein transforming the compound of formula (C₁) to Compound I comprises treating the compound of formula (C₁) with a first acid.
10. The process of Embodiment 8, wherein transforming the first acid is selected from trifluoroacetic acid, sulfuric acid, phosphoric acid, and methane sulfonic acid.
11. The process of any one of Embodiments 1 to 10, further comprising transforming a compound of formula (A₁₋₁):



to the compound of formula (A₁).

12. The process of Embodiment 11, wherein transforming a compound of formula (A₁₋₁) to the compound of formula (A₁) comprises the steps of:

treating the compound of formula (A₁₋₁) with trifluoromethanesulfonic anhydride to form a triflyl intermediate;

treating the triflyl intermediate with a cyanation reagent;

treating the cyanated intermediate with a second base to form a cyanated triflyl intermediate; and

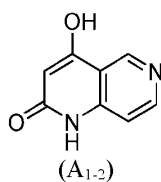
treating the cyanated triflyl intermediate with an aqueous base to form the compound of formula (A₁).

13. The process of Embodiment 12, wherein the cyanation reagent is selected from trimethylsilyl cyanide, sodium cyanide, and potassium cyanide.

14. The process of Embodiment 12 or 13, wherein the second base is selected from 4-methylmorpholine, triethylamine, and Hunig's base.

15. The process of any one of Embodiments 12 to 14, wherein the aqueous base is aqueous sodium bicarbonate.

16. The process of any one of Embodiments 11 to 15, further comprising transforming a compound of formula (A₁₋₂):

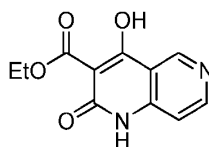


to the compound of formula (A₁₋₁).

17. The process of Embodiment 16, wherein transforming the compound of formula (A₁₋₂) to the compound of formula (A₁₋₁) comprises treating the compound of formula (A₁₋₂) with a chlorinating reagent.

18. The process of Embodiment 17, wherein the chlorinating reagent is selected from phosphorus pentachloride and phosphorous oxychloride.

19. The process of any one of Embodiments 16 to 18, further comprising transforming a compound of formula (A₁₋₃):



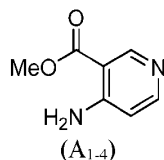
(A₁₋₃)

to the compound of formula (A₁₋₂).

20. The process of Embodiment 19, wherein transforming a compound of formula (A₁₋₃) to the compound of formula (A₁₋₂) comprises treating the compound of formula (A₁₋₃) with a second acid.

21. The process of Embodiment 20, wherein the second acid is selected from aqueous hydrochloric acid and aqueous sulfuric acid.

22. The process of any one of Embodiments 19 to 21, further comprising transforming a compound of formula (A₁₋₄):



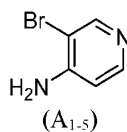
to the compound of formula (A₁₋₃).

23. The process of Embodiment 22, wherein transforming a compound of formula (A₁₋₄) to the compound of formula (A₁₋₃) comprises treating the compound of formula (A₁₋₄) with diethyl malonate in the presence of a third base.

24. The process of Embodiment 23, wherein the third base is an alkaline alkoxide.

25. The process of Embodiment 23 or Embodiment 24, wherein the third base is sodium ethoxide.

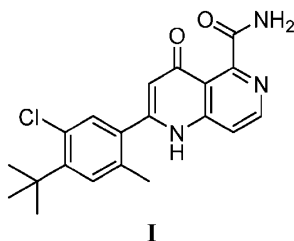
26. The process of any one of Embodiments 22 to 25, further comprising transforming a compound of formula (A₁₋₅):



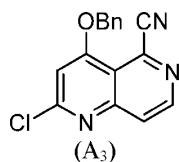
to the compound of formula (A₁₋₄).

27. The process of Embodiment 26, wherein transforming the compound of formula (A₁₋₅) to the compound of formula (A₁₋₄) comprises treating the compound of formula (A₁₋₅) with carbon monoxide in the presence of a fourth base, a second palladium catalyst, and a first suitable ligand.

28. The process of Embodiment 27, wherein the fourth base is selected triethylamine, Hunig's Base, 4-methylmorpholine, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-Diazabicyclo[2.2.2]octane (DABCO).
29. The process of Embodiment 27 or 28, wherein the second palladium catalyst is Pd(OAc)₂.
30. The process of any one of Embodiments 27 to 29, wherein the first suitable ligand is selected from 1,1'-bis(diphenylphosphino)ferrocene (DPPF), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), triphenylphosphine (PPh₃), and 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (BINAP).
31. The process of any one of Embodiments 1-30, wherein X₁ and X₂ are both chloro.
32. A process for preparing Compound I:

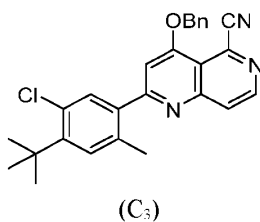


comprising transforming a compound of formula (A₃):

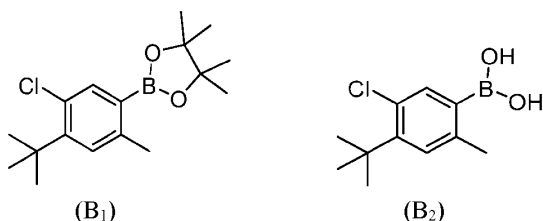


to Compound I.

33. The process of Embodiment 32, wherein transforming the compound of formula (A₃) to Compound I comprises transforming the compound of formula (A₃) to a compound of formula (C₃):



34. The process of Embodiment 33, wherein transforming the compound of formula (A₃) to the compound of formula (C₃) comprises contacting the compound of formula (A₃) with a compound of formula (B₁) or (B₂):



35. The process of Embodiment 34, wherein contacting the compound of formula (A₃) with a compound of formula (B₁) or (B₂) is performed in the presence of a first palladium catalyst and a first base.

36. The process of Embodiment 35, wherein the first palladium catalyst is a palladium-phosphine complex.

37. The process of Embodiment 35 or Embodiment 36 wherein the first palladium catalyst is PdCl₂(dtbdpf).

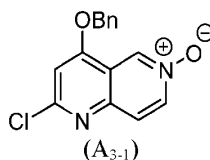
38. The process of any one of Embodiments 35-37, wherein the first base is selected from potassium phosphate and potassium carbonate.

39. The process of any one of Embodiments 32-38, wherein transforming the compound of formula (A₃) to Compound I further comprises transforming the compound of formula (C₃) to Compound I.

40. The process of Embodiment 39, wherein transforming the compound of formula (C₃) to Compound I comprises treating the compound of formula (C₃) with a first acid.

41. The process of Embodiment 36, wherein the first acid is selected from trifluoroacetic acid, sulfuric acid, phosphoric acid, and methane sulfonic acid.

42. The process of any one of Embodiments 32-41, further comprising transforming a compound of formula (A₃₋₁):



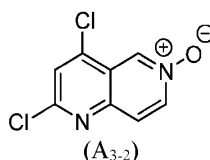
to the compound of formula (A₃).

43. The process of Embodiment 42, wherein transforming a compound of formula (A₃₋₁) to the compound of formula (A₃) comprises treating the compound of formula (A₃₋₁) with a cyanation reagent and a second base.

44. The process of Embodiment 43, wherein the cyanation reagent is selected from trimethylsilyl cyanide, sodium cyanide, and potassium cyanide.

45. The process of Embodiment 43 or 44, wherein the second base is selected from triethylamine, 4-methylmorpholine, and Hunig's base.

46. The process of any one of Embodiments 42-45, further comprising transforming a compound of formula (A₃₋₂):



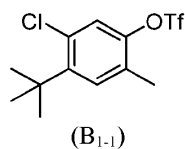
to the compound of formula (A₃₋₁).

46. The process of Embodiment 46, wherein transforming a compound of formula (A₃₋₂) to the compound of formula (A₃₋₁) comprises treating the compound of formula (A₃₋₂) with benzyl alcohol in the presence of a third base.

47. The process of Embodiment 46, wherein the third base is an alkaline alkoxide.

48. The process of Embodiment 46 or 47, wherein the third base is lithium *tert*-butoxide.

49. The process of any one of Embodiments 3-31 and 34-48, further comprising transforming a compound of formula (B₁₋₁):



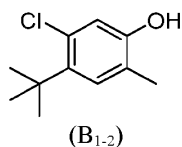
to the compound of formula (B₁).

50. The process of Embodiment 49, wherein transforming the compound of formula (B₁₋₁) to the compound of formula (B₁) comprises treating the compound of formula (B₁₋₁) with bis(pinacolato)diboron in the presence of a third palladium catalyst and a fifth base.

51. The process of Embodiment 50, wherein the third palladium catalyst is selected from Pd(dppf)Cl₂, Pd(PCy₃)₂, and Pd₂dba₃.

52. The process of Embodiment 50 or 51, wherein the fifth base is selected from KOPh, triethylamine, Hunig's Base, KOEt, and KOAc.

53. The process of any one of Embodiments 49-52, further comprising transforming a compound of formula (B₁₋₂):

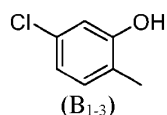


to the compound of formula (B₁₋₁).

54. The process of Embodiment 53, wherein transforming the compound of formula (B₁₋₂) to the compound of formula (B₁₋₁) comprises contacting the compound of formula (B₁₋₂) with trifluoromethanesulfonic anhydride and a sixth base.

55. The process of Embodiment 54, wherein the sixth base is pyridine.

56. The process of Embodiment 54 or 55, further comprising transforming a compound of formula (B₁₋₃):



to the compound of formula (B₁₋₂).

57. The process of Embodiment 56, wherein transforming the compound of formula (B₁₋₃) to the compound of formula (B₁₋₂) comprises treating the compound of formula (B₁₋₃) with *tert*-butanol and a third acid.

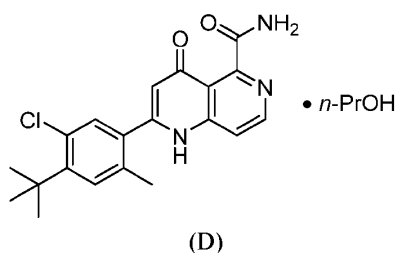
58. The process of Embodiment 57, wherein the third acid is sulfuric acid.

59. The process of any one of Embodiments 1 to 58, further comprising transforming Compound **I** to a solvate of Compound **I**.

60. The process of Embodiment 59, wherein transforming Compound **I** to the solvate of Compound **I** comprises recrystallizing Compound **I** from an appropriate solvent.

61. The process of Embodiment 60, wherein the appropriate solvent is 1-propanol.

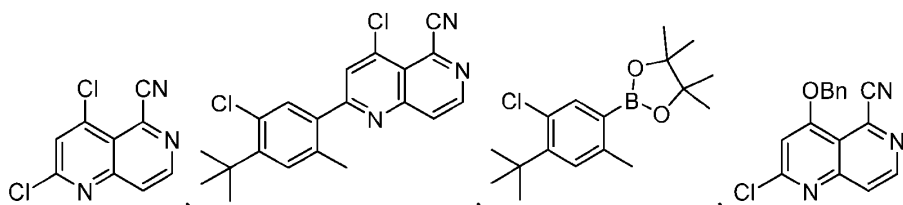
62. The process of any one of Embodiments 59-61, wherein the solvate of Compound **I** is a compound of formula (D):

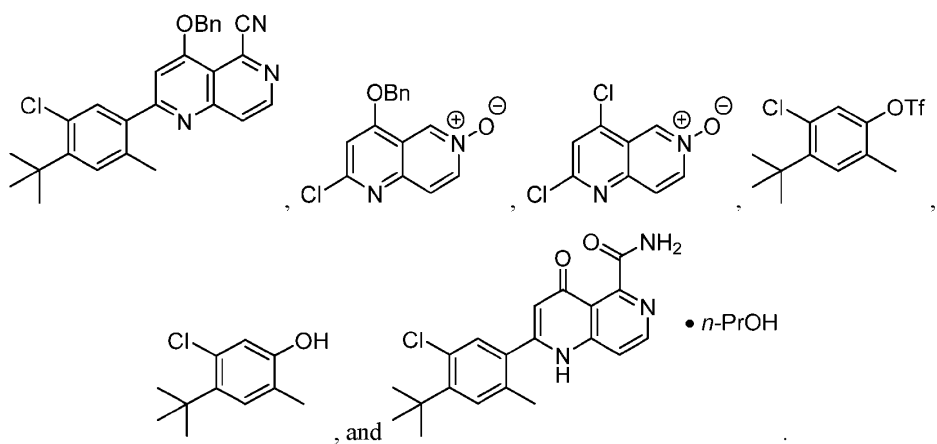


63. The process of any one of Embodiments 59-62, further comprising transforming the solvate of Compound **I** to Form A of Compound **I**.

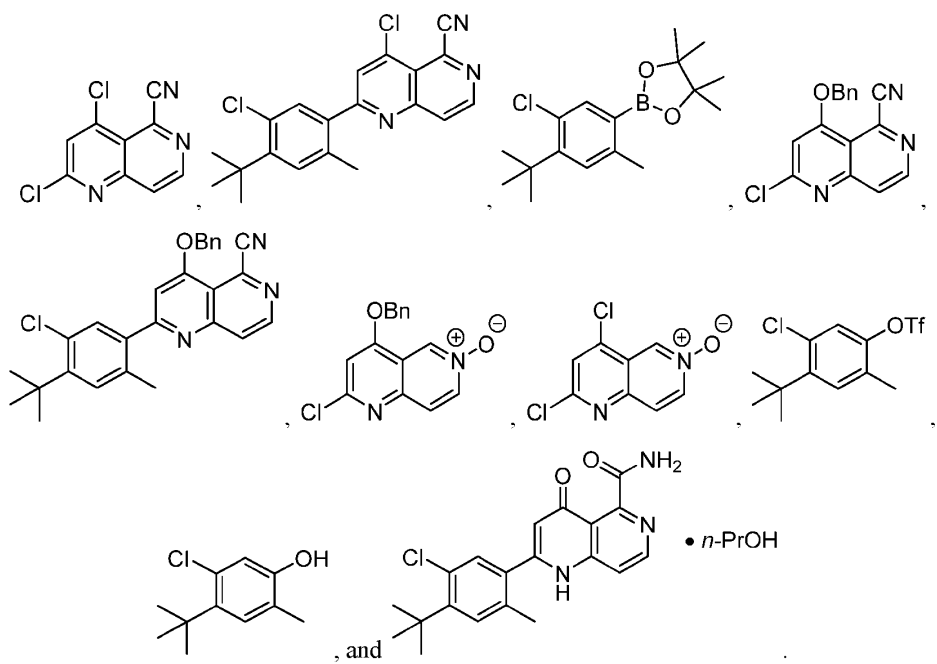
64. The process of Embodiment 63, wherein transforming the solvate of Compound **I** to Form A of Compound **I** comprises a methanol solvent exchange and drying.

65. A compound selected from:

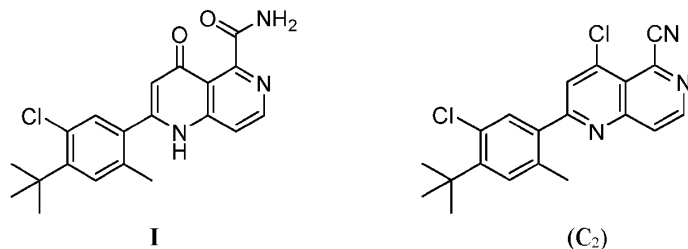




66. A composition comprising one or more compounds selected from:



67. A composition comprising Compound **I** and a compound of formula (C₂):



68. The composition of Embodiment 67, further comprising an acid.

69. The composition of Embodiment 68, wherein the acid is trifluoroacetic acid.

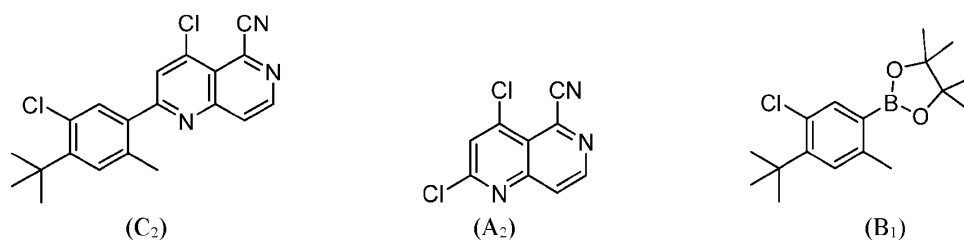
70. A composition comprising Compound **I** and a compound of formula (C₃):



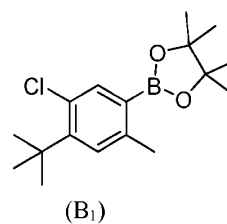
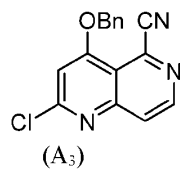
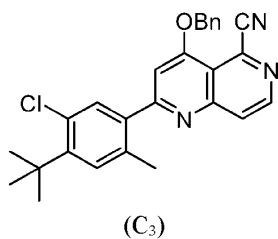
71. The composition of Embodiment 70, further comprising an acid.

72. The composition of Embodiment 71, wherein the acid is trifluoroacetic acid.

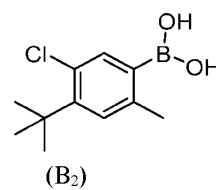
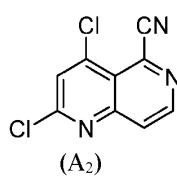
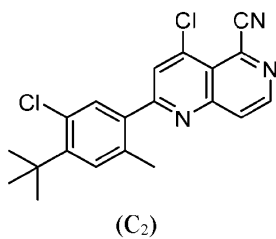
73. A composition comprising a compound of formula (C₂), a compound of formula (A₂), and a compound of formula (B₁):



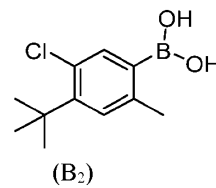
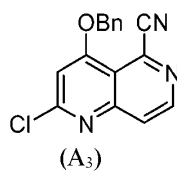
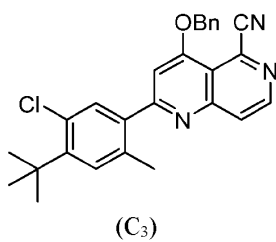
74. A composition comprising a compound of formula (C₃), a compound of formula (A₃), and a compound of formula (B₁):



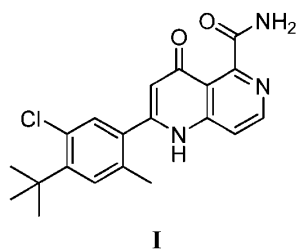
75. A composition comprising a compound of formula (C₂), a compound of formula (A₂), and a compound of formula (B₂):



76. A composition comprising a compound of formula (C₃), a compound of formula (A₃), and a compound of formula (B₂):



77. Compound I:



or a solvate thereof or a pharmaceutically acceptable salt thereof, prepared by the process of any one of Embodiments 1 to 64.

EXAMPLES

[539] Unless otherwise noted, or where the context dictates otherwise, the following abbreviations shall be understood to have the following meanings:

<u>Abbreviation</u>	<u>Meaning</u>
NMR	Nuclear magnetic resonance
HPLC	High performance liquid chromatography
SSNMR	Solid-state Nuclear magnetic resonance
XRPD	X-ray powder diffraction
LC	Liquid chromatography
LC/MS	Liquid chromatography-mass spectrometry
UPLC	Ultra performance liquid chromatography
HPLC/MS/MS	High performance liquid chromatography/tandem mass spectrometry
IS	Internal standard
SFC	Supercritical fluid chromatography
MDAP	Mass directed auto purification
g	Grams
mg	Milligrams
kg	Kilograms
L	Liter(s)
mL	Milliliters
μL	Microliters
nL	Nanoliters
mol	Moles
mmol	Millimoles
hr, h	Hours
min	Minutes
s	Seconds
ms	Millisecond
mm	Millimeters
μm	Micrometers
nm	Nanometer
MHz	megahertz
kHz	kilohertz
Hz	Hertz
Å	Angstrom
rpm	Revolutions per minute
N	Normal (concentration)
M	Molar (concentration)
mM	Millimolar (concentration)
μM	Micromolar (concentration)
ppm	Parts per million
% w/v	Weight-volume concentration
% w/w	Weight-weight concentration
equiv	equivalents
V or Vols	Volumes
T _j	Temperature of the jacket
T _r	Temperature of the reactor
DI	Deionized

<u>Abbreviation</u>	<u>Meaning</u>
DCM	Dichloromethane
EtOH	Ethanol
EtOAc	Ethyl acetate
MeOH	Methanol
2-MeTHF	2-Methyltetrahydrofuran
NaOH	Sodium hydroxide
NaCl	Sodium chloride
NaHCO ₃	Sodium Bicarbonate
Na ₂ SO ₄	Sodium Sulfate
nPA	n-propanol
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
NaTFA	Sodium trifluoroacetate
RT	Room temperature
ca.	Circa (approximately)
tBuOH	<i>tert</i> -butyl alcohol
nBuAc	n-butyl acetate
CPME	Cyclopentyl methyl ether
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
IPA	Isopropyl alcohol
T3P	Propylphosphonic anhydride, i.e., 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide
MTBE	Methyl <i>tert</i> -butyl ether
MSA	methane sulfonic acid
Mn(acac) ₂	manganese(II) acetylacetonate
TEA	triethylamine
RB(F)	Round bottom (flask)
TFT	α,α,α -Trifluorotoluene
TMSOTf	trimethylsilyl trifluoromethanesulfonate
DIPEA	N,N-diisopropylethyl amine
NMM	N-methylmorpholine
TBD	Triazabicyclodecene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-diazabicyclo[2.2.2] octane
MTBD	7-Methyl-1,5,7-triazabicyclo [4.4.0]dec-5-ene
LiHMDS	Lithium hexamethyldisilazide (LiN(SiMe ₃) ₂)

General Experimental Details

Solution Phase NMR

[540] ¹H NMR (400 MHz) and ¹⁹F NMR (376 MHz) spectra were obtained as solutions in an appropriate deuterated solvent such as dimethyl sulfoxide-*d*₆ (DMSO-*d*₆).

Liquid Chromatography

[541] Exemplary LC Method #1: HPLC analysis was conducted using an Agilent 1260 HPLC utilizing an Agilent Poroshell EC-C18 column (4.6 x 150 mm, 2.7 μ m particle) guard column (pn: 693975-902), and a dual gradient run from 5-95% mobile phase B over 45 min. Mobile phase A = 0.1% (v/v) phosphoric acid in water. Mobile phase B = 0.1% (v/v) Phosphoric Acid in Acetonitrile. Flow rate = 1.0 mL/min, injection volume = 5 μ L, and column temperature = 35 °C.

[542] Exemplary LC Method #2: HPLC analysis was conducted using an Agilent 1260 HPLC utilizing an Agilent Poroshell EC-C18 column (4.6 x 150 mm, 2.7 μ m particle) guard column (pn: 693975-902), and a dual gradient run from 5-95% mobile phase B over 15 min. Mobile phase A = 0.1% (v/v) phosphoric acid in water. Mobile phase B = 0.1% (v/v) Phosphoric Acid in Acetonitrile. Flow rate = 1.0 mL/min, injection volume = 5 μ L, and column temperature = 35 °C.

[543] Exemplary LC Method #3: LC analysis was conducted using an Acquity UPLC BEH C8 column (50 $\times$ 2.1 mm, 1.7 μ m particle) made by Waters (pn: 186002877) with a (2.1 $\times$ 5 mm, 1.7 μ m particle) guard column (pn: 186003978), and a dual gradient run from 2-98% mobile phase B over 4.45 minutes. Mobile phase A = H₂O (10 mM ammonium formate with 0.05 % ammonium hydroxide). Mobile phase B = acetonitrile. Flow rate = 0.6 mL/min, injection volume = 2 μ L, and column temperature = 45 °C.

Solid State NMR

[544] Bruker-Biospin 400 MHz wide-bore spectrometer equipped with Bruker-Biospin 4mm HFX probe was used. Samples were packed into 4mm ZrO₂ rotors and spun under Magic Angle Spinning (MAS) condition with spinning speed typically set to 12.5 kHz. The proton relaxation time was measured using ¹H MAS T₁ saturation recovery relaxation experiment in order to set up proper recycle delay of the ¹³C cross-polarization (CP) MAS experiments. The CP contact time of carbon CPMAS experiments was set to 2 ms. A CP proton pulse with linear ramp (from 50% to 100%) was employed. The carbon Hartmann-Hahn match was optimized on external reference sample (glycine). All carbon spectra were recorded with proton decoupling using TPPM15 or SPINAL64 decoupling sequence with the field strength of approximately 100 kHz.

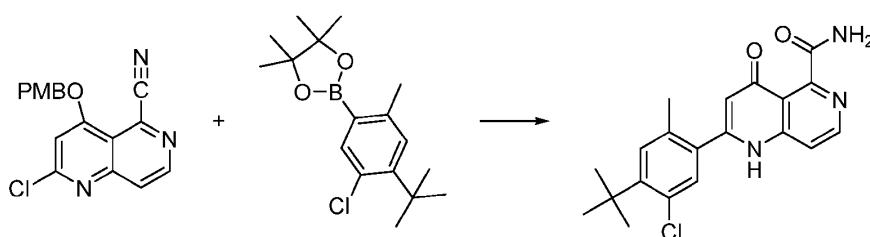
X-ray Powder Diffraction

[545] X-ray powder diffraction (XRPD) spectra were recorded at room temperature in transmission mode using a PANalytical Empyrean system equipped with a sealed tube source and a PIXcel 1D Medipix-2 detector (Malvern PANalytical Inc, Westborough, Massachusetts). The X-Ray generator operated at a voltage of 45 kV and a current of 40 mA with copper radiation (1.54060 Å). The powder sample was

placed in a back filled sample holder and loaded into the instrument. The sample was scanned over the range of about 3° to about 40° 2 θ with a step size of 0.0131303° and 49.725s per step.

Preparation of Compound I – Preparation 1

2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4-oxo-1*H*-1,6-naphthyridine-5-carboxamide (Compound I)

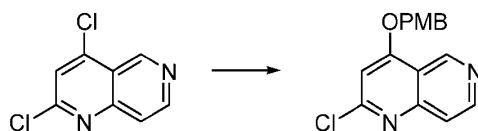


[546] A microwave reaction vial charged with 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine-5-carbonitrile (100 mg, 0.31 mmol), 2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (130 mg, 0.32 mmol), SPhos Pd G3 (36 mg, 0.05 mmol), potassium phosphate (170 mg, 0.80 mmol), dioxane (1.5 mL) and water (150 μ L) was flushed with nitrogen for 60 seconds, capped and heated for 1 hour at 50 °C. The reaction mixture was diluted with water and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The PMB-protected intermediate was taken up in toluene (2 mL) and TFA (2 mL) and stirred at 60 °C for 6 hours. The solvent was evaporated and the crude material purified by silica gel chromatography using 0-100% ethyl acetate in DCM, followed by a second purification by reverse phase chromatography using 0-40% acetonitrile in water (5 mM HCl) to obtain 2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4-oxo-1*H*-1,6-naphthyridine-5-carboxamide (32 mg, 28%). ESI-MS m/z calc. 369.12, found 370.4 ($M+1$)⁺. ¹H NMR (400 MHz, DMSO- d_6) δ (ppm) 12.04 (s, 1H), 8.56 (d, J = 5.8 Hz, 1H), 7.58 (s, 1H), 7.55 (s, 2H), 7.50 (d, J = 5.8 Hz, 1H), 7.37 (s, 1H), 6.19 (s, 1H), 2.37 (s, 3H), 1.55 (s, 9H).

Preparation of Starting Materials

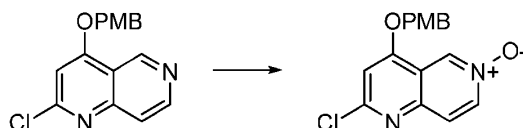
2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine-5-carbonitrile

[547] **Step 1:** 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine



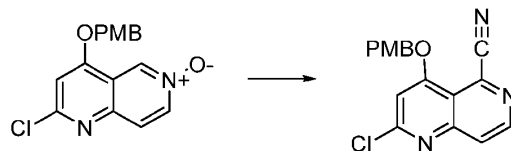
[548] To a mixture at 0 °C of 2,4-dichloro-1,6-naphthyridine (3.29 g, 16.5 mmol) and (4-methoxyphenyl)methanol (2.28 g, 2.05 mL, 16.47 mmol) in DMF (33 mL) and 2-MeTHF (33 mL) was added sodium hydride (715 mg, 60% in mineral oil, 17.88 mmol) portionwise. The mixture was stirred at 0 °C for 1 h, then gradually warmed to room temperature and stirred for 19.5 h. The mixture was poured into a stirring mixture of 0.1 M aqueous HCl (100 mL) and 2-MeTHF (100 mL). The layers were separated and the aqueous layer extracted with additional 2-MeTHF (2 x 100 mL). The organic layers were combined and washed with water (2 x 50 mL), 1:1 water/brine (50 mL) and brine (50 mL). The solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (5-100% ethyl acetate/heptanes) provided 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine (1.95 g, 39%) as a pale yellow solid. ESI-MS *m/z* calc. 300.06, found 301.2 (M+1)⁺. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.44 (s, 1H), 8.74 (d, *J* = 5.9 Hz, 1H), 7.72 - 7.67 (m, 1H), 7.48 - 7.42 (m, 2H), 7.09 (s, 1H), 6.97 - 6.88 (m, 2H), 5.50 (s, 2H), 3.83 (s, 3H). ESI-MS *m/z* calc. 300.06, found 301.2 (M+1)⁺.

[549] **Step 2:** 2-chloro-4-[(4-methoxyphenyl)methoxy]-6-oxido-1,6-naphthyridin-6-ium



[550] A solution of 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine (5 g, 16.6 mmol) in DCM (100 mL) was cooled to 0 °C and treated with solid 3-chlorobenzenecarboperoxoic acid (4.7 g, 21 mmol). The reaction was warmed to room temperature and stirred for 4 h. The mixture was quenched with saturated aqueous sodium bicarbonate (100 mL) and the layers were separated. The aqueous layer was extracted with additional DCM (3 x 25 mL). The combined organic layers were washed with brine (20 mL x 2), dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to obtain 2-chloro-4-[(4-methoxyphenyl)methoxy]-6-oxido-1,6-naphthyridin-6-ium (5.1 g, 97%). ESI-MS *m/z* calc. 316.06, found 317.2 (M+1)⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.66 (d, *J* = 2.1 Hz, 1H), 8.40 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.41 (s, 1H), 7.05 - 6.95 (m, 2H), 5.39 (s, 2H), 3.78 (s, 3H).

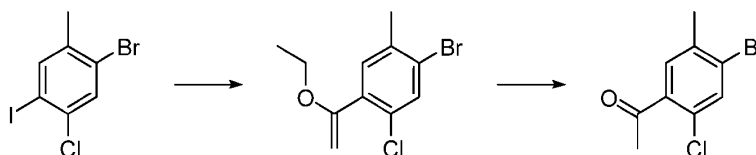
[551] **Step 3:** 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine-5-carbonitrile



[552] To a solution of 2-chloro-4-[(4-methoxyphenyl)methoxy]-6-oxido-1,6-naphthyridin-6-ium (6.1 g, 19.3 mmol) in DCM (50 mL) under an atmosphere of nitrogen was added trimethylsilyl cyanide (6.8 mL, 51 mmol), followed by the addition of TEA (8 mL, 57.4 mmol). The mixture was stirred for 20 h at room temperature. The reaction was quenched with water and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (0-100% ethyl acetate/DCM) provided 2-chloro-4-[(4-methoxyphenyl)methoxy]-1,6-naphthyridine-5-carbonitrile (5.5 g, 88%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.90 (d, J = 5.8 Hz, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.61 (s, 1H), 7.60 - 7.52 (m, 2H), 7.03 - 6.95 (m, 2H), 5.52 (s, 2H), 3.77 (s, 3H).

2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[553] **Step 1:** 1-(4-bromo-2-chloro-5-methyl-phenyl)ethan-1-one



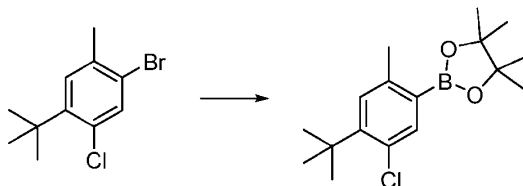
[554] To a microwave vial containing a solution of 1-bromo-5-chloro-4-iodo-2-methyl-benzene (21 g, 63.37 mmol) and tributyl(1-ethoxyvinyl)stannane (21.4 mL, 63.34 mmol) in dioxane (105 mL) was added $\text{PdCl}_2(\text{PPh}_3)_2$ (2.25 g, 3.21 mmol). The reaction mixture was degassed with nitrogen for 30-60 seconds, sealed and heated at 100 °C for 17 hours. The reaction mixture cooled to room temperature and quenched with water. The aqueous layer was extracted with DCM (3x). The combined organic layer was dried over magnesium sulfate, filtered and concentrated to obtain 1-bromo-5-chloro-4-(1-ethoxyvinyl)-2-methyl-benzene. ESI-MS m/z calc. 273.98, found 277.07 ($\text{M}+2$) $^+$. The intermediate was taken up in THF (100 mL) and HCl (95 mL of 1 M, 95 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h. The aqueous layer was extracted with DCM (3x), dried over magnesium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography using 0 to 15% ethyl acetate in Hexanes to obtain 1-(4-bromo-2-chloro-5-methyl-phenyl)ethan-1-one (12.62 g, 80%) as a white solid. ESI-MS m/z calc. 245.94, found 248.95 ($\text{M}+3$) $^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.83 (s, 1H), 7.74 (s, 1H), 2.58 (s, 3H), 2.38 (s, 3H).

[555] Step 2: 1-bromo-4-*tert*-butyl-5-chloro-2-methyl-benzene



[556] To a solution of tetrachlorotitanium in toluene (50 mL of 1 M, 50 mmol) in DCM (35 mL) at $-40\text{ }^{\circ}\text{C}$ was added dimethylzinc in toluene (33 mL of 2 M, 66 mmol) slowly maintaining the temperature below $-40\text{ }^{\circ}\text{C}$ (internal temperature). The reaction mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 30 min and then a solution of 1-(4-bromo-2-chloro-5-methylphenyl)ethanone (6.3 g, 25.45 mmol) in DCM (10 mL) was added dropwise, maintaining the internal temperature below $-40\text{ }^{\circ}\text{C}$. The reaction mixture was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by slowly pouring it into ice and saturated sodium bicarbonate solution. The aqueous phase was acidified with concentrated HCl and then extracted with DCM. The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified via silica gel column chromatography using hexanes to obtain 1-bromo-4-*tert*-butyl-5-chloro-2-methylbenzene (5.8 g, 87%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.60 (s, 1H), 7.42 (s, 1H), 2.33 (s, 3H), 1.41 (s, 9H).

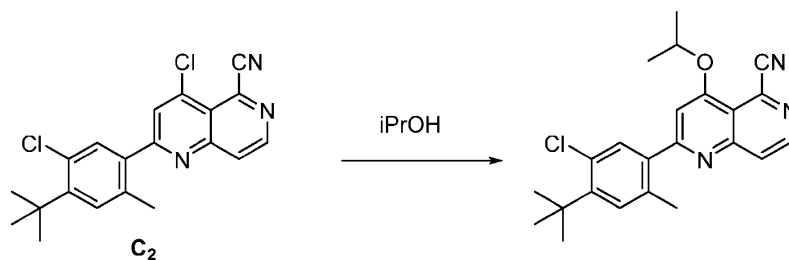
[557] Step 3: 2-(4-*tert*-butyl-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[558] A solution of 1-bromo-4-*tert*-butyl-5-chloro-2-methylbenzene (4.49 g, 17.2 mmol) in 1,4-dioxane (50 mL) was sparged with nitrogen for 20 min then bis(pinacolato)diboron (5.7 g, 22.5 mmol), potassium acetate (5.0 g, 51 mmol) and $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ (1.4 g, 1.7 mmol) were added. The mixture was stirred for 4 h at $100\text{ }^{\circ}\text{C}$. The mixture was cooled to room temperature and additional bis(pinacolato)diboron (1.9 g, 7.5 mmol) and $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ (500 mg, 0.612 mmol) added. The mixture was sparged with nitrogen for 5 min then stirred at $105\text{ }^{\circ}\text{C}$ for 2 h. Once cooled to room temperature, MTBE (50 mL) was added and the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography using 0 to 5% ethyl acetate in heptanes. The resulting material was triturated in methanol (15 mL) and filtered. The solid was rinsed with cold methanol (5 mL) and dried under vacuum to provide 2-(4-*tert*-butyl-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate **B-2**, 3.75 g, 71%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.71 (s, 1H), 7.20 (s, 1H), 2.49 (s, 3H), 1.46 (s, 9H), 1.33 (s, 12H). ESI-MS m/z calc. 308.17, found 309.2 ($\text{M}+1$) $^+$.

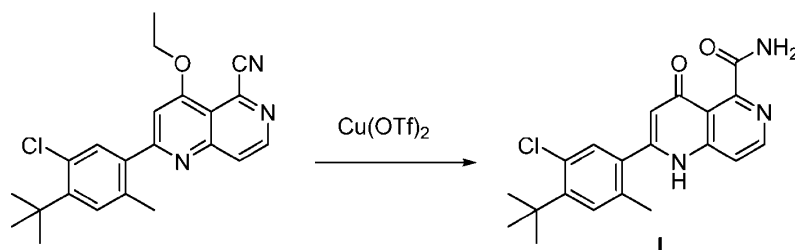
Preparation of Compound I – Preparation 2

2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-isopropoxy-1,6-naphthyridine-5-carbonitrile



[559] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (**C₂**: 20 g, 54 mmol, 1 eq.), which can be prepared as described below, was charged to a reactor at 25° C along with isopropanol (200 mL) and stirred and heated to 80° C. Acetic acid (160 mL) was subsequently added at 60-80° C and stirred for 8 hours.

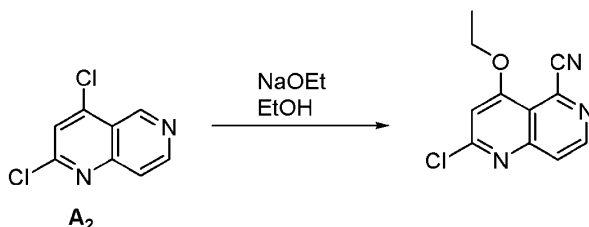
2-(4-*tert*-butyl-5-chloro-2-methyl-phenyl)-4-oxo-1*H*-1,6-naphthyridine-5-carboxamide (**Compound I**)



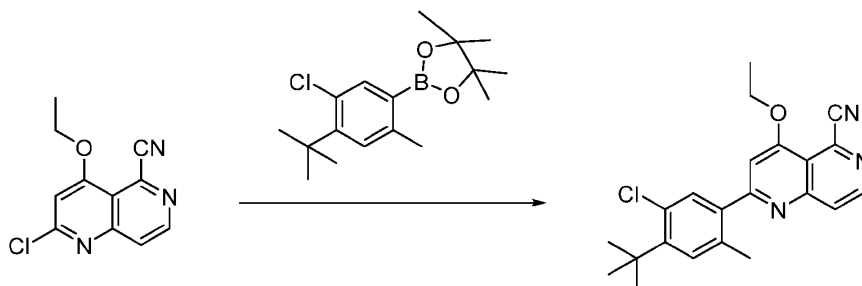
[560] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-ethoxy-1,6-naphthyridine-5-carbonitrile (100 mg, 0.263 mmol, 1 eq) was charged to a reactor at 20 °C. Copper(II) trifluoromethanesulfonate (96.8 mg), MeTHF (2.9 mL), and AcOH (0.98 mL) were added. Stirring was started and the mixture was heated to 60 °C. The mixture was stirred for 30 h, then aqueous HCl (6N, 110 µL) was added. The mixture was stirred at 60 °C for an additional 0.5 h. HPLC analysis indicated formation of **Compound I**.

Preparation of Starting Materials

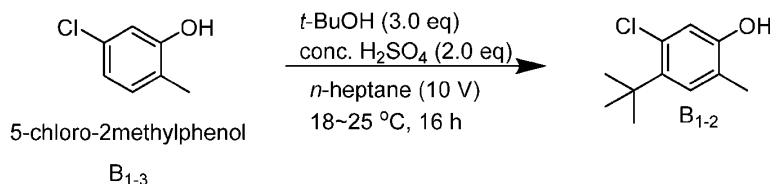
2-chloro-4-ethoxy-1,6-naphthyridine-5-carbonitrile



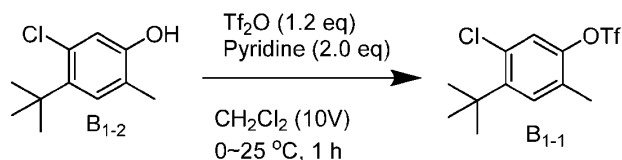
[561] 2,4-dichloro-1,6-naphthyridine (A₂; 0.56 g, 2.5 mmol, 1.0 eq), which can be prepared as described below, and EtOH (20 mL) were charged to a dry reactor. Stirring was started and the mixture was kept at 25 °C. 21% NaOEt in EtOH (0.85 g, 2.62 mmol, 1.05 eq) was charged and the mixture was stirred at 25 °C for 4 h. The slurry was filtered. The filter cake was dissolved in DCM and purified by flash chromatography eluted with DCM/MeOH to give 2-chloro-4-ethoxy-1,6-naphthyridine-5-carbonitrile as a white solid (0.50 g, 86% yield).

[562] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-ethoxy-1,6-naphthyridine-5-carbonitrile

[563] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-ethoxy-1,6-naphthyridine-5-carbonitrile can be prepared in a manner analogous to 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂), described below.

*Preparation of Compound I – Preparation 3***[564] Synthesis of B₁****[565] Step 1: Synthesis of 4-(tert-butyl)-5-chloro-2-methylphenol (B₁₋₂)**

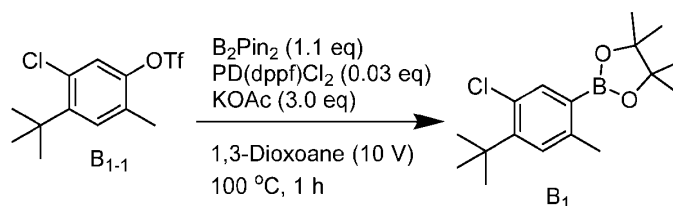
[566] 5-chloro-2-methylphenol (40.4 kg, 1.0 eq.) (B₁₋₃) was charged to a clean and dry reactor. *n*-Heptane (275.7 kg, 10 V) and *t*-BuOH (63.02 kg, 3 eq.) were charged to the reactor followed by conc. H₂SO₄ (55.75 kg, 2 eq). The reaction mixture was stirred at 18-25 °C. After reaction completion, as determined by HPLC, the reaction mixture was cooled to 0-10 °C. H₂O (282.8 kg, 7 V) was charged and the layers were separated. The organic layer was collected in a clean container. The aqueous layer was back extracted with *n*-heptane (55.3 kg, 2 V). The combined organic layers were washed with 10% NaCl (81 kg) and the organic layer was dried over anhydrous MgSO₄ (22.2 kg). The organic layer was filtered. The filtrate was concentrated under reduced pressure to afford 4-(tert-butyl)-5-chloro-2-methylphenol (B₁₋₂) as a brown oil (78.1 kg, 92% isolated yield, 93% pure by HPLC). ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9 H), 2.20 (s, 3 H), 6.80 (s, 1 H), 7.13 (s, 1 H). The crude 4-(tert-butyl)-5-chloro-2-methylphenol (B₁₋₂) was used directly in the next step without further purification.

[567] Step 2: Synthesis of 4-(tert-butyl)-5-chloro-2-methylphenyl trifluoromethanesulfonate (B₁₋₁)

[568] 4-(tert-butyl)-5-chloro-2-methylphenol (B₁₋₂) (53 kg, 1.0 eq.) and toluene (401.21 kg) were charged to a reactor. Pyridine (42.4 kg, 2 eq.) and Tf₂O (90.63 kg, 1.2 eq.) were charged to the resulting mixture at 0-10 °C. The reaction mixture was stirred at 0-10 °C. After reaction completion, as determined by HPLC, the mixture was treated with 1 M HCl (107.4 kg). The layers were separated. The organic layer was washed with 10% KHCO₃ (530 kg). The organic phase was washed with 10% NaCl (106 kg) and then treated with activated carbon (8.48 kg). The charcoal was filtered off and the filtrate was concentrated to afford 4-(tert-butyl)-5-chloro-2-methylphenyl trifluoromethanesulfonate (B₁₋₁) as a light-yellow oil (89 kg, 100% yield, 92.4% purity by HPLC). ¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 9 H), 2.35

(s, 3 H), 7.25 (s, 1 H), 7.33 (s, 1 H); ^{19}F NMR (376 MHz, CDCl_3) δ -73.75. The crude 4-(tert-butyl)-5-chloro-2-methylphenyl trifluoromethanesulfonate (B_{1-1}) was used directly in the next step without further purification.

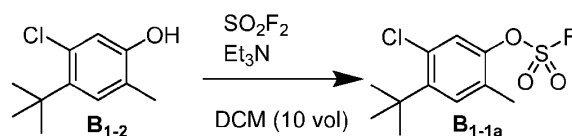
[569] Step 3: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (B_1)



[570] 4-(tert-butyl)-5-chloro-2-methylphenyl trifluoromethanesulfonate (B_{1-1}) (89.3 kg, 1.0 eq.) and 1,4-dioxane (92 kg) were charged to a reactor. Bic(pinacolato)diboron (79.05 kg, 1.1 eq.) and KOAc (66.28 kg, 3.0 eq.) were charged, and the mixture was degassed with nitrogen. $\text{PdCl}_2(\text{dppf})$ (6.43 kg, 0.03 eq.) was charged to the reactor and the resulting mixture was stirred at 100–105 °C. After reaction completion, as determined by HPLC analysis, the mixture was cooled to 20 °C. Activated carbon (17.86 kg) and *n*-heptane (807.82 L) were charged and the reaction mixture was stirred at 20 °C. The mixture was filtered, and the filtrate was concentrated. *N*-heptane (131.35 L) was charged, and the mixture was concentrated. MeOH (113.06 L) was charged, and the mixture was concentrated. The methanol solution was heated to about 50 to about 55 °C and stirred for 2–3 h, and then slowly cooled to about 15 to about 20 °C. The resulting slurry was filtered, and the wet cake was dried under vacuum to afford 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (B_1) as a white solid (72.8 kg, 88% yield). $m/z = [\text{M}+\text{H}]^+$ 309.1; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (s, 12 H), 1.49 (s, 9 H), 2.51 (s, 3 H), 7.22 (s, 1 H), 7.74 (s, 1 H).

[571] Alternative Synthesis of B_1

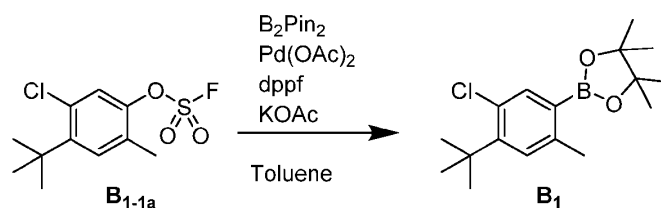
[572] Step 1: Synthesis of 4-(tert-butyl)-5-chloro-2-methylphenyl sulfurofluoridate (B_{1-1a})



[573] To a solution of 4-(tert-butyl)-5-chloro-2-methylphenol (B_{1-2} ; 110 g, 0.554 mol, 1.0 eq) in IPAc (1.1 L, 10 V) was added Et_3N (112.1 g, 1.11 mol, 2.0 eq) at 20 °C. SO_2F_2 (1.2 eq) was introduced by bubbling through the solution at 20–30 °C over 20 hours. After the complete consumption of B_{1-2} as determined by gas chromatography, 1 M HCl (0.5 L) was charged. The mixture was stirred at 25 °C for

about 15 min and the layers were separated. The bottom aq. layer was drained. Saturated aqueous solution of NaHCO_3 (0.5 L) was charged. The mixture was stirred at 25 °C for about 15 min and the layers were separated. The bottom aq. layer was drained. 10% Brine (0.5 L) was charged. The mixture was stirred at 25 °C for about 15 min and the layers were separated. The bottom aq. layer was drained. The organic layer was isolated and concentrated under vacuum to about 0.44 L, which was then cooled to -5 °C and seeded with 4-(tert-butyl)-5-chloro-2-methylphenyl sulfurofluoridate seed crystals. Solid started to form in the solution. The batch was aged at -5 °C for 2 h. Water (110 mL) was charged slowly over 1 h at -5 °C. The slurry was stirred at -5 ~ 0 °C for 10 h then filtered. The cake was rinsed with heptane (110 mL). The wet cake was dried at 25 °C under vacuum to afford 4-(tert-butyl)-5-chloro-2-methylphenyl sulfurofluoridate (B_{1-1a} , 138.4 g, 89% yield) as a white solid. $m/z = [\text{M}+\text{H}]^+$ 279.9; ^1H NMR (400 MHz, CDCl_3) δ 7.35 - 7.33 (m, 2H), 2.35 (s, 3H), 1.48 (s, 9H); ^{19}F NMR (376 MHz, CDCl_3) δ 39.25 (s, 1F).

[574] Step 2: Synthesis of B_1



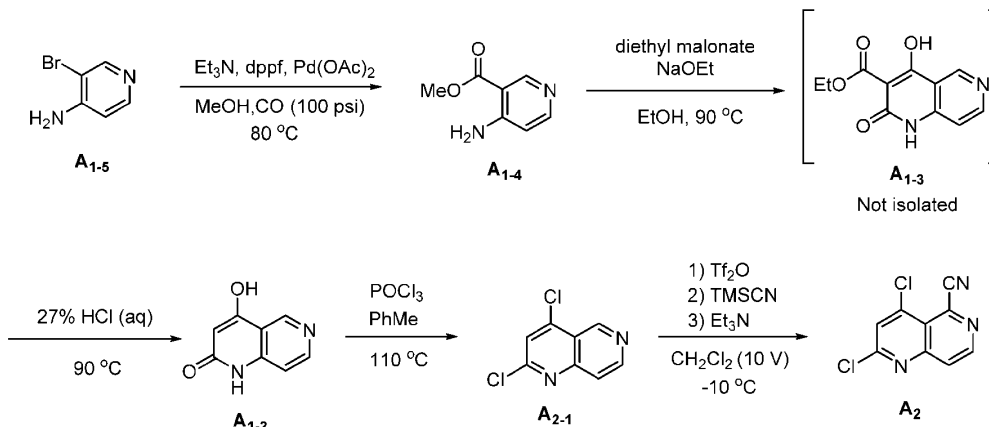
[575] 4-(tert-butyl)-5-chloro-2-methylphenyl sulfurofluoridate (B_{1-1a} , 1.0 kg, 3.56 mol, 1.0 eq), IPAc (9.02 Kg, 10 V), KOAc (0.74 kg, 2.5 eq), B_2Pin_2 (0.885 kg, 1.1 eq) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (72.0 g, 0.03 eq) were charged into a dry and clean Reactor 1. The mixture was degassed with nitrogen. The batch was stirred at 85-95 °C for 15 ~ 17 h. After consumption of the starting materials as determined by HPLC, the batch was cooled to 20 ~ 30 °C. n-Heptane (6.15 kg, 9 V) and activated charcoal (0.2 kg) were charged. The batch was stirred at 20 ~ 30 °C for 3 ~ 4 h and then filtered through a pad of Celite (0.2 kg) to remove insoluble solid. The filter cake was charged to a clean Reactor 2 and n-Heptane (4.1 kg, 6 V) was charged. The batch was stirred at 25 °C for 1 h and filtered. The filter cake was rinsed with n-Heptane (1.36 kg, 2 V). The combined filtrate was concentrated under vacuum at 45 ~ 55 °C until minimum volume (0.9 ~ 1.3 V). n-Heptane (1 kg) was charged and the batch was concentrated until the minimum volume. Methanol (1 kg) was charged and the batch was concentrated until the minimum volume. Methanol (1 kg) was charged and the batch was stirred at 45 ~ 55 °C for 3 ~ 5 h. The batch was then cooled to 15 ~ 20 °C and stirred for 3 ~ 5 h. The batch was filtered and the filter cake was rinsed with cold Methanol (0.4 kg). The filter cake and n-Heptane (4.1 kg, 6 V) were charged to a dry and clean Reactor 3 and the batch was stirred until a clear solution was obtained. Activated carbon (0.1 kg) was charged and the batch was stirred at 45 ~ 55 °C for 3 ~ 5 h. The batch was filtered and the filter cake was rinsed with n-

Heptane (1.37 kg, 2 V). The combined filtrate was concentrated under vacuum at 45 ~55 °C until minimum volume. The batch was cooled to 15~20 °C and stirred for 3 ~ 5 h. The batch was filtered and the filter cake was rinsed with cold Methanol (0.4 kg, 0.5 V). The wet cake was dried under vacuum at 40 ~ 50 °C to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**B₁**) as a white solid (901 g, 82% yield). $m/z = [M+H]^+$ 309.1; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.35 (s, 12 H), 1.49 (s, 9 H), 2.51 (s, 3 H), 7.22 (s, 1 H), 7.74 (s, 1 H).

[576] Compound **B₁** was found to be a neat crystalline solid. The XRPD pattern for crystalline Compound **B₁** was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound **B₁** is provided in **FIG. 1**, and the data are summarized below in **Table 1**.

Table 1. XRPD Signals for Crystalline Compound **B₁**.

No.	Pos. [2θ]	Area [cts* 2θ]	Rel. Int. [%]
1	11.1	402.4	29.4
2	13.1	338.7	18.6
3	15.4	752.6	41.3
4	16.8	1040.5	44.4
5	17.8	1088.5	84.5
6	18.9	198.9	19.1
7	19.9	1562.6	100
8	21.8	371.1	35.6
9	28.2	88.1	11.3

[577] Synthesis of 2,4-dichloro-1,6-naphthyridine-5-carbonitrile (A₂)**[578] Step 1: Synthesis of methyl 4-aminonicotinate (A₁₋₄)**

[579] 3-bromopyridin-4-amine (A₁₋₅) (60 kg, 346.8 mol, 1 eq.), Et₃N (36.77 kg, 364.1 mol, 1.05 eq.), DPPF (317.2 g, 0.57 mol, 0.00165 eq.) and MeOH (225 L) were charged to an autoclave and agitation was started. Pd(OAc)₂ (85.6 g, 0.38 mol, 0.0011 eq) was then charged and the mixture was stirred under CO (100 psi) at 80 °C. After the reaction was completed, as determined by HPLC analysis, the mixture was concentrated in vacuo to give the crude product. H₂O (3.5 V) was charged, and the resulting mixture was stirred at 20 °C. The resulting suspension was filtered, and the wet cake was dried under reduced pressure to give methyl 4-aminonicotinate (A₂₋₄) (42 kg, 276.3 mol, 79.6% yield) as an off-white solid. *m/z* = [M+H]⁺ 153.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (s, 1H), 8.07 (s, 1H), 7.27 (s, 2H), 6.68 (d, *J* = 4.0 Hz, 1H), 3.81 (s, 3H).

[580] Step 2: Synthesis of ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (A₁₋₃)

[581] Methyl 4-aminonicotinate (A₁₋₄) (42 kg, 276.3 mol, 1 eq) and diethyl malonate (53.1 kg, 331.5 mol, 1.2 eq.) were charged to a reactor at 25 °C followed by EtOH (294 L) and EtONa (24.4 kg, 359.2 mol, 1.3 eq.). The mixture was stirred at 90 °C. After the reaction was completed, as determined by HPLC analysis, the reaction mixture was acidified with HCl (1.5 M) to pH 3~4. The mixture was then concentrated in vacuo. The slurry was cooled to 25 °C and filtered. The filter cake was dried under vacuum to afford crude ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (A₁₋₃) (~65 kg), which was used directly in the next step without further purification. *m/z* = [M-OEt]⁺ 189.0; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.02 (s, 1H), 8.78 (s, 1H), 8.20 (d, *J* = 5.4 Hz, 1H), 6.87 (d, *J* = 6.1 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.0 Hz, 3H).

[582] Step 3: Synthesis of 4-hydroxy-1,6-naphthyridin-2(1H)-one (A₁₋₂)

[583] Crude ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (A₁₋₃) (64.8 kg) and toluene (32 L) were charged to a reactor followed by HCl (453 L, 27% w/w% in H₂O). The mixture was stirred at 90 °C. After the reaction was completed, the mixture was cooled to 25 °C and the layers were separated. The aqueous layer was cooled to 0 °C and basified with 30% NaOH to pH 5-6. The resulting slurry was filtered and the filter cake was triturated with MeCN (5 V). The wet cake was dried under vacuum to afford 4-hydroxy-1,6-naphthyridin-2(1H)-one (A₁₋₂) (33.5 kg) as an off-white solid. m/z = [M+H]⁺ 163.0; ¹H NMR (400 MHz, DMSO-d₆) δ 11.97 (s, 1H), 8.97 (s, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 1H).

[584] Step 4: Synthesis of 2,4-dichloro-1,6-naphthyridine (A₂₋₁)

[585] 4-Hydroxy-1,6-naphthyridin-2(1H)-one (A₁₋₂) (33.5 kg, 206.6 mol, 1.0 eq.) and toluene (67 L) were charged to a reactor followed by POCl₃ (88 kg, 574.3 mol, 2.78 eq.). The mixture was stirred at 110 °C. After the reaction was completed, as determined by HPLC analysis, the mixture was concentrated in vacuo. The residue was diluted with CH₂Cl₂ (5 V), quenched into ice water (5 V), and then the resulting mixture was poured into sat. NaHCO₃. The resulting mixture was filtered, and the layers of the bi-phasic filtrate were separated. The aqueous phase was extracted with EtOAc. All organic phases were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was triturated with MTBE (2 V) to afford 2,4-dichloro-1,6-naphthyridine (A₂₋₁) (33.6 kg, 168.8 mol, 81.7% yield) as a yellow solid. m/z = [M³⁵Cl³⁵Cl+H]⁺ 199.0; [M³⁵Cl³⁷Cl+H]⁺ 201.0; [M³⁷Cl³⁷Cl+H]⁺ 203.0 (9:6:1 ratio); ¹H NMR (400 MHz, DMSO-d₆) δ 9.57 (s, 1H), 8.91 (d, *J* = 4.0 Hz, 1H), 8.12 (s, 1H), 7.94 (d, *J* = 4.0 Hz, 1H).

[586] Step 5: Synthesis of 2,4-dichloro-1,6-naphthyridine-5-carbonitrile (A₂)

[587] 2,4-Dichloro-1,6-naphthyridine (A₂₋₁) (33.6 kg, 168.8 mol, 1 eq.) and CH₂Cl₂ (336 L) were charged to a reactor. The solution was cooled to -10 °C. Tf₂O (50 kg, 177.2 mol, 1.05 eq.) was charged. After complete addition, TMSCN (17.5 kg, 177.2 mol, 1.05 eq.) was charged followed by Et₃N (22.2 kg, 219.4 mol, 1.3 eq.). After reaction completion, as determined by HPLC analysis, the reaction mixture was diluted with CH₂Cl₂ (7.5 V) and basified to pH 7 with sat. NaHCO₃. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 V). The combined organic layers were washed with water (2 x 5 L) and brine and dried over with anhydrous Na₂SO₄. The organic solution was concentrated under vacuum and the residue was triturated with MeOH (4 V). The slurry was filtered, and the wet cake was dried under vacuum to afford 2,4-dichloro-1,6-naphthyridine-5-carbonitrile (A₂) as a yellow solid (31.21

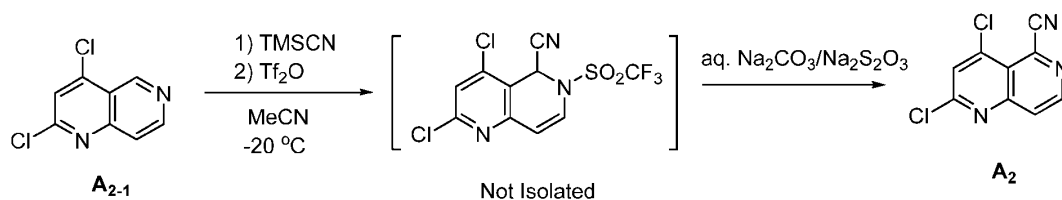
kg). $m/z = [M+H]^+$ 223.9; $^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 9.01 (d, $J = 5.6$ Hz, 1H), 8.32 (s, 1H), 8.29 (d, $J = 5.6$ Hz, 1H).

[588] Compound **A₂** was found to be a neat crystalline solid. The XRPD pattern for crystalline Compound **A₂** was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound **A₂** is provided in **FIG. 2**, and the data are summarized below in **Table 2**.

Table 2. XRPD Signals for Crystalline Compound **A₂**.

No.	Pos. [$^{\circ}2\theta$]	Area [cts $^{\circ}2\theta$]	Rel. Int. [%]
1	9.4	17.6	6.6
2	13.2	21.7	13.3
3	13.4	44.6	21.9
4	17.6	36.5	15.0
5	24.9	22.2	13.6
6	25.1	12.3	10.1
7	26.6	268.1	100
8	26.7	55.1	41.1
9	27.0	13.4	6.7

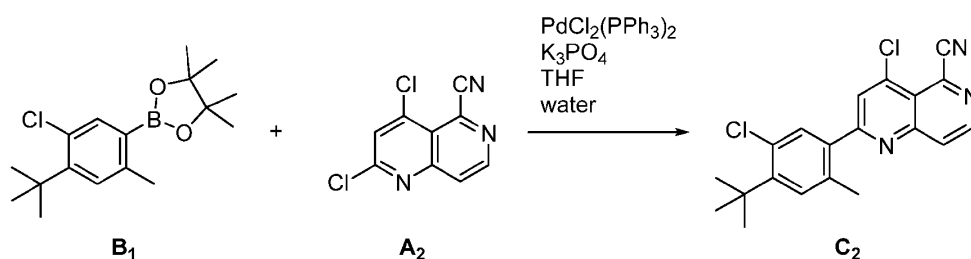
[589] Alternative Synthesis of **A₂ (starting from **A₂₋₁**)**



[590] 2,4-Dichloro-1,6-naphthyridine (**A₂₋₁**; 10.0 g, 49.04 mmol, 1.00 eq.) and MeCN (100 mL) were charged to a reactor. Stirring was started and the mixture was cooled to -20 °C. TMSCN (5.11 g, 51.49 mmol, 1.05 eq.) was charged. The mixture was stirred at -20 °C for 0.5-1 h. TiF_2O (15.22 g, 53.94 mmol, 1.10 eq.) was charged over 1 h to the reactor. The resulting mixture was stirred at -20 °C for 1 h. After complete consumption of **A₂₋₁**, as determined by HPLC analysis, the mixture was quenched into an aqueous solution of Na_2CO_3 (10.395 g, 98.08 mmol, 2.0 eq.) and $\text{Na}_2\text{S}_2\text{O}_3$ (3.10 g, 19.62 mmol, 0.40 eq.) in water (100 mL). The resulting slurry was stirred at 5-10 °C for 3 h. After completion, as determined by HPLC analysis, the batch was filtered and the cake was rinsed with H_2O (20 mL). The wet cake was dried under vacuum at 50 °C to give a yellow solid. The yellow solid was dissolved in CH_2Cl_2 (250 mL) and active charcoal (1.0 g) was added. The mixture was stirred at 20-30 °C for 4 h. The batch was filtered and the filter cake was rinsed with CH_2Cl_2 (50 mL). The filtrate was concentrated under vacuum until minimum volume. Heptane (60 mL) was charged and the mixture was again concentrated under vacuum

to about 40 mL left. The batch was cooled to 20 ~ 25 °C and stirred for 2 h. The batch was filtered and the filter cake was rinsed with heptane (10 mL) to give a yellow solid which was dried under vacuum at 50 °C to afford 2,4-dichloro-1,6-naphthyridine-5-carbonitrile (**A₂**) as a yellow solid (10.17 g, 90% yield). $m/z = [M+H]^+$ 223.9; $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 9.01 (d, $J = 5.6$ Hz, 1H), 8.32 (s, 1H), 8.29 (d, $J = 5.6$ Hz, 1H).

[591] Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂**)**



[592] 2,4-dichloro-1,6-naphthyridine-5-carbonitrile (**A₂**) (30 g, 1 eq.), 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**B₁**) (42.2 g, 1.02 eq.), dichlorobis(triphenylphosphine)-palladium (0.64 g, 0.68 mol%), and THF (270 mL, 9 vol) were charged to a reactor. The mixture was evacuated and purged with nitrogen. The reaction was heated to 45 °C and an aqueous solution of potassium phosphate (71.1 g, 2.5 eq. in 138 mL, 4.6 vol of water) was added to the mixture. After reaction completion, as determined by HPLC analysis, THF (180 mL, 6 vol) was added, and the aqueous layer was separated from the batch. The organic layer was treated with SiliaMetS Thiol resin (6 g, 20 wt%) and stirred for 16 hours at 45 °C. The mixture was cooled to 25 °C and the resin was filtered off. Water was added (60 mL, 2 vol) and the resulting mixture was filtered. The filter cake was isolated and dried under vacuum at 50 °C to afford 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (**C₂**) as a white solid (39.7 g, 80% yield). $m/z = [M+H]^+$ 370.10; $^1\text{H NMR}$ (400 MHz, DMSO) δ 8.99 (d, $J = 5.7$ Hz, 1H), 8.38 – 8.30 (m, 2H), 7.66 (s, 1H), 7.47 (s, 1H), 2.44 (s, 3H), 1.49 (s, 9H).

[593] Compound **C₂** was found to be a neat crystalline solid. The XRPD pattern for crystalline Form A of Compound **C₂** was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Form A of Compound **C₂** is provided in **FIG. 3**, and the data are summarized below in **Table 3**.

Table 3. XRPD Signals for Crystalline Form A of Compound C₂.

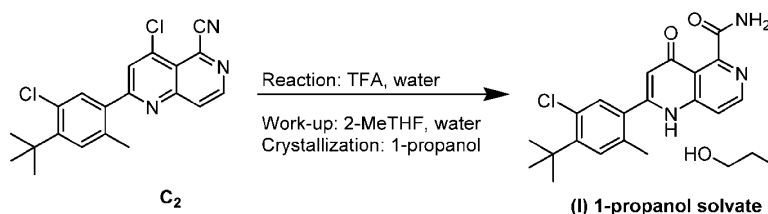
No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	8.0	503.8	100
2	10.8	31.9	7.5
3	11.9	338.0	79.7
4	13.1	254.1	51.4
5	14.3	77.4	13.7
6	15.5	35.5	7.2
7	16.0	149.5	30.2
8	17.0	31.4	7.4
9	17.6	62.5	11.0
10	19.0	71.2	11.2
11	23.6	71.6	12.7
12	25.0	152.0	19.6

[594] Compound C₂ was also found to exist in a second crystalline form: Neat Form B. Neat Crystalline Form B of Compound C₂ is formed by heating Neat Crystalline Form A in a vacuum oven at 135 °C for two days. The XRPD pattern for Neat Crystalline Form B of Compound C₂ was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Neat Crystalline Form B of Compound C₂ is provided in **FIG. 4**, and the data are summarized below in **Table 4**.

Table 4. XRPD Signals for Neat Crystalline Form B of Compound C₂.

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	3.4	50.5	5.81
2	3.7	130.4	15
3	4.1	869.6	100
4	8.7	44.7	3.85
5	9.9	29.6	2.55
6	12.4	98.3	6.28
7	15.9	77.8	3.83
8	17.5	183.8	10.57
9	24.0	0.1	7.48
10	25.0	106.7	7.45

[595] Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide n-propanol solvate (Compound I 1-propanol solvate)

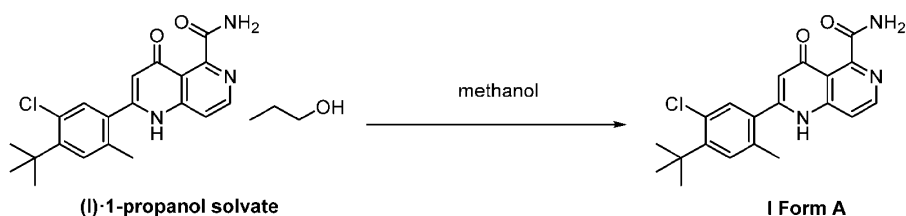


[596] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂) (22 g, 1 eq.), trifluoroacetic acid (132 mL, 6 vol) and water (7 mL, 0.3 vol) were charged to the reactor. The mixture was heated to 60 °C. After reaction completion, as determined by HPLC, the reaction was concentrated and treated with aqueous sodium hydroxide (154 g, 6.5 eq. in 660 mL, 30 vol of water), sodium chloride (116.6 g, 33.6 eq.) and 2-MeTHF (880 mL, 40 vol). The organic layer was isolated and washed with aqueous sodium chloride (15 wt%). The organic layer was then concentrated and swapped into n-propanol. The n-propanol solution was seeded with Formula I n-propanol solvate form B and the resulting slurry filtered. The isolated solid was dried under vacuum at 45 °C to afford 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide n-propanol solvate (Compound I n-propanol solvate, Form B) as a white solid (23.0 g, 90% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 12.01 (bs, 1H), 8.51 (d, *J* = 5.8 Hz, 1H), 7.55 (bs, 1H), 7.49 (s, 2H), 7.46 (d, *J* = 5.8 Hz, 1H), 7.33 (bs, 1H), 6.13 (s, 1H), 4.37 (t, *J* = 4.0 Hz, 1H), 3.3-3.4 (m, 2H), 2.31 (s, 3H), 1.48 (s, 9H), 1.35-1.45 (m, 2H), 0.83 (t, *J* = 4.0 Hz, 3H).

[597] Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide n-Propanol Solvate Form B Seeds

[598] Compound I was charged to a vessel controlled at 20 +/- 5 °C. 1-propanol (4 L/kg based amount of Compound I) was charged and the slurry mixture was stirred at 20 °C for at least 24 h. The solids were filtered and dried in an oven overnight (40 °C, under vacuum, nitrogen bleed) prior to use as seed material in the crystallization.

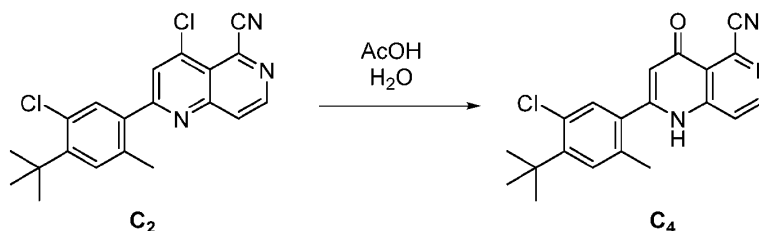
[599] Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide Form A



[600] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide n-propanol solvate (Compound I n-propanol solvate) (3800 g, 1 eq.) and methanol (20.6 L, 5.5 vol) were charged to a reactor and the slurry was stirred at 25 °C. The slurry was filtered, washed with methanol (7.6L, 2 vol) and the isolated solid material was dried at 50 °C under vacuum to afford 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide (Compound I Form A) as a white solid (2909 g, 89% yield). HRMS m/z = $[M+H]^+$ 370.1304; 1H NMR (500 MHz, DMSO- d_6) δ 12.01 (bs, 1H), 8.51 (d, J = 5.8 Hz, 1H), 7.55 (bs, 1H), 7.49 (s, 2H), 7.46 (d, J = 5.8 Hz, 1H), 7.33 (bs, 1H), 6.13 (s, 1H), 2.31 (s, 3H), 1.48 (s, 9H).

Alternate Preparation of Compound I from Compound C₂

[601] Step 1: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄)



[602] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂; 60 g, 162 mmol, 1.0 eq) and AcOH (480 mL) were charged to a reactor at 25 °C. Stirring was started and the mixture was heated to 100 °C. The mixture was stirred at 100 °C for 5 h, and then cooled to 20 °C over 5 h. The batch was stirred at 20 °C for 12 hours and then the batch was filtered, and the cake was rinsed with AcOH (120 mL). The wet cake was dried under vacuum at 50 °C to afford 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) HCl salt, AcOH solvate as an off-white solid (67.8 g, 93% yield).

[603] The XRPD pattern for 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) HCl salt, AcOH solvate was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) HCl salt, AcOH solvate is provided in **FIG. 5**, and the data are summarized below in **Table 5**.

Table 5. XRPD Signals for 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) HCl salt, AcOH solvate.

No.	Pos. [°2 θ]	Area [cts*°2 θ]	Rel. Int. [%]
1	5.7	840.5	100

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
2	8.2	11.6	1.2
3	9.5	62.1	7.1
4	10.5	5.2	1.0
6	13.9	77.7	13.2
7	14.8	60.4	10.3
8	16.5	217.0	31.7
9	18.3	61.4	7.0
10	21.0	48.6	5.5
11	22.2	63.7	6.5
12	23.8	36.7	5.3
13	26.4	260.6	24.2
14	27.1	17.0	3.5

Alternative Step 1: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄)

[604] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂; 15 g, 162 mmol, 1.0 eq) and AcOH (1200 mL) were charged to a reactor at 25 °C. Stirring was started and the mixture was heated to 100 °C. The reaction mixture was stirred at 100 °C for 2 h and was then inversely quenched into water (255 mL) at 80 °C. The resulting slurry was then cooled from 80 °C to 20 °C over 5 hours. The slurry was filtered and the cake washed with water (30 mL) and the wet cake dried under vacuum at 80-85 °C with a nitrogen sweep. This afforded 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) hydrate ("Hydrate Form A") as an off-white solid (~85% yield).

[605] The XRPD pattern for Hydrate Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Hydrate Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) is provided in **FIG. 6**, and the data are summarized below in **Table 6**.

Table 6. XRPD Signals for Hydrate Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄).

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	6.5	72.0	15.9
2	9.3	314.2	55.5
3	11.3	418.3	73.9
4	13.1	128.0	22.6
5	14.4	565.7	100

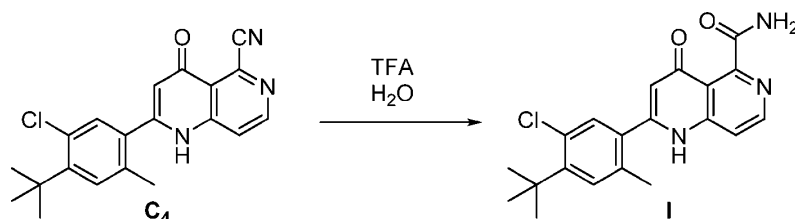
No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
6	16.0	53.6	9.5
7	17.3	34.0	7.5
8	18.2	40.3	5.9
9	19.7	66.8	8.4
10	20.8	96.6	8.5
11	21.7	234.5	34.5
12	23.5	430.5	46.2
13	25.1	138.6	14.9
14	27.1	156.0	20.9

[606] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) was also found to exist as a benzenesulfonic acid salt. Benzenesulfonic Acid Salt Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) was formed by stirring C₄ with 1.1 molar equivalent of benzenesulfonic acid in toluene for 24 hours. The XRPD pattern for Benzenesulfonic Acid Salt Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Benzenesulfonic Acid Salt Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) is provided in **FIG. 7**, and the data are summarized below in **Table 7**.

Table 7. XRPD Signals for Benzenesulfonic Acid Salt Form A of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄).

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	5.9	14.2	30.5
2	6.2	37.3	60.0
3	10.0	16.0	20.6
4	11.3	13.2	21.3
5	13.8	62.1	100
6	14.4	6.8	7.3
9	15.5	10.6	17.1
11	17.0	15.6	14.3

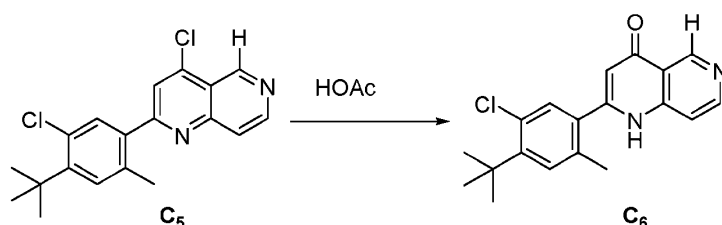
[607] Step 2: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide (Compound I)



[608] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄) HCl salt, AcOH solvate (55 g, 123 mmol, 1.0 eq), water (2.25 g, 1.02 equiv), and TFA (132 mL) were charged to the reactor at 25 °C. Stirring was started and the mixture was heated to 60 °C. The reaction mixture was stirred at 60 °C for 16 h, and then cooled to 20 °C over 2 h. The batch was transferred to a second reactor containing a mixture of NaOH (75.13 g), water (864 mL), and MeTHF (33 mL) at 50 °C. An additional solution of NaOH (1.92 g) in water (22 mL) was added to the batch, followed by MeTHF (1078 mL) and NaCl (56.1 g). The mixture was stirred for 1 hour at 50 °C and then stirring was stopped and the aqueous phase was removed. A solution of NaCl (22.3 g) in water (429 mL) was charged to the organic phase and the mixture was stirred for 1 hour at 50 °C. After 1 hour, the stirring was stopped, and the aqueous phase was removed. A solution of NaCl (22.3 g) in water (429 mL) was charged to the organic phase and the mixture was stirred for 1 hour at 50 °C. After 1 hour, the stirring was stopped, and the aqueous phase was removed. The mixture was distilled under reduced pressure to a volume of 214.5 mL and MeTHF (1166 mL) was charged to the batch. The mixture was heated to 50 °C and the resulting solution was filtered. The mixture was then distilled under reduced pressure to a volume of 302.5 mL. The batch was heated to 75 °C and then slowly cooled to 20 °C over 10 hours. The batch was stirred at 20 °C for 8 h and then filtered. The cake was rinsed with MeTHF (88 mL) and then dried under vacuum at 80 °C to afford *Compound I* as an off-white solid (32.3 g, 71% yield).

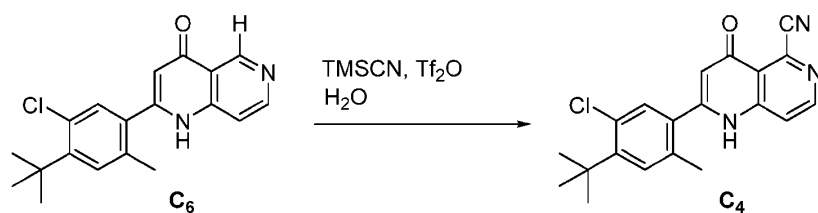
Alternative Preparation of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄)

[609] Step 1: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridin-4(1H)-one (C₆)



[610] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine (C₅, 162 g, 0.47 mol, 1.0 eq) and glacial acetic acid (1.7 L) were charged to a reactor. The solution was heated to 100 °C and stirred for 2.5 hours. After complete consumption of the starting material, as determined by HPLC, the batch was cooled to 22 °C over 4 h and agitated at 22 °C overnight. The beige slurry thus obtained was filtered and the filter cake was washed with 650 mL water. The solids were charged back to the reactor along with 1.62 L of water. The slurry was brought to a pH of 10 using 2 M NaOH. The slurry was agitated for 1.5 h before filtering. The filter cake was washed with 540 mL water. The wet cake was dried under vacuum at 50 °C to constant weight to provide 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridin-4(1H)-one (C₆, 106 g, 69% yield) as a white solid. ¹H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 9.19 (s, 1H), 8.58 (d, J = 5.8 Hz, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.41 (d, J = 5.8 Hz, 1H), 6.14 (d, J = 1.2 Hz, 1H), 2.27 (s, 3H), 1.45 (s, 9H).

[611] Step 2: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C₄)

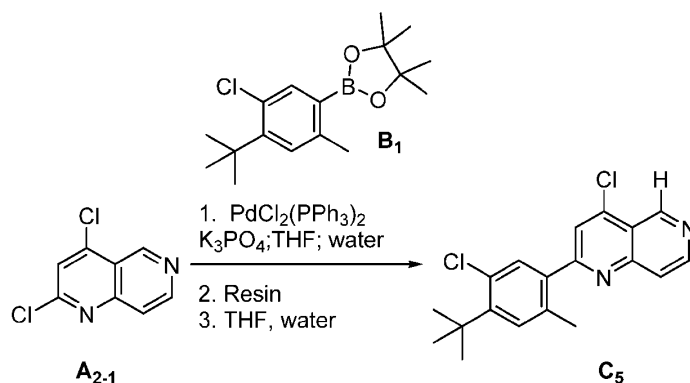


[612] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridin-4(1H)-one (C₆, 0.947 g, 2.9 mmol, 1 eq.) and MeCN (10 mL) were charged to a dry and clean flask. Stirring was started and the mixture was cooled to -20 °C. TMSCN (0.302 g, 0.38 mL, 1.05 eq.) was charged dropwise to the vessel over ~1 min. The resulting mixture was stirred at -22 ~ -15 °C for 1 hour. Tf₂O (1.8 g, 1.08 mL, 2.2 eq) was charged to the reactor over 4 min. After complete consumption of the starting material, as determined by HPLC, the mixture was quenched into a 13 mL solution of K₂CO₃/Na₂S₂O₃ (0.95 M/0.19 M) over ~8

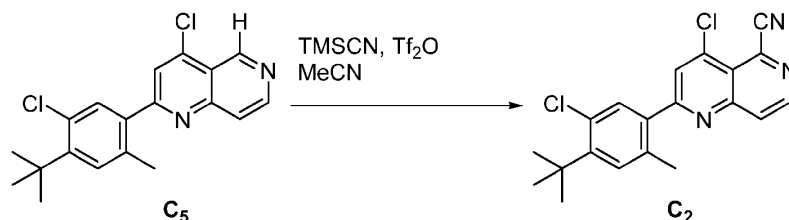
minutes. The yellow suspension was filtered and the filter cake was rinsed with water and then heptane. The crude solid was dissolved in CH_2Cl_2 and purified by flash chromatography eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carbonitrile (C_4 , 0.50 g, 49% yield).

[613] Alternative Preparation of Compound I

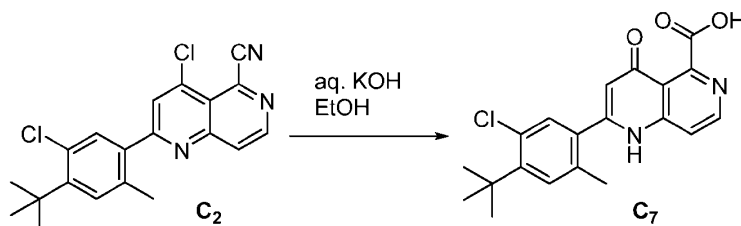
[614] Step 1: 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine (C_5)



[615] 2,4-dichloro-1,6-naphthyridine ($\text{A}_{2.1}$; 50 g, 0.25 mol, 1.0 eq), 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (B_1 ; 85.2 g, 0.276 mol, 1.1 eq) and degassed THF (450 mL) were charged to a clean Reactor 1. Degassed 2 M aq K_3PO_4 (2.5 eq, 307 mL) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1.2 g, 0.007 eq) were charged. The reaction mixture was sparged with N_2 for at least 20 min before heating to 35 °C overnight. After the reaction completion as determined by HPLC, the batch was cooled to 25 °C and the layers were separated. The organic layer was charged back to the Reactor 2 with 10 g thiol resin and agitated at 45 °C overnight. The resin was filtered off hot and rinsed with additional THF (100 mL). The filtrate was concentrated and the residue was purified by flash chromatography eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine (C_5 , 78.5 g, 91% yield) as a white solid. ^1H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 8.89 (d, J = 5.6 Hz, 1H), 8.17 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.62 (s, 1H), 7.46 (s, 1H), 2.42 (s, 3H), 1.50 (s, 9H).

[616] Step 2: Synthesis of C₂

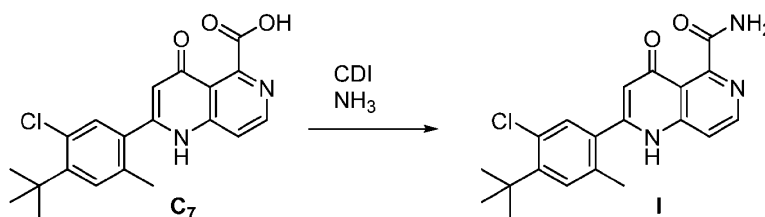
[617] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine (C₅, 10 g, 29 mmol, 1.0 eq) and MeCN (100 mL) were charged to a reactor. Stirring was started and the mixture was cooled to -20 °C. TMS-CN (3.02 g, 30.4 mmol, 1.05 eq.) was charged. The mixture was stirred at -20 °C for 0.5-1 h. Tf₂O (8.99 g, 31.9 mmol, 1.10 eq.) was charged over 1 h to the reactor. The resulting mixture was stirred at -20 °C for 1 h. After complete consumption of the starting material, as determined by HPLC analysis, the mixture was quenched into an aqueous solution of Na₂CO₃ (6.14 g, 57.9 mmol, 2.0 eq.) and Na₂S₂O₃ (1.83 g, 11.6 mmol, 0.40 eq.) in water (100 mL). The resulting slurry was stirred at 5-10 °C for 3 h. After reaction completion as determined by HPLC analysis, the batch was filtered and the cake was rinsed with H₂O (20 mL). The wet cake was dried under vacuum at 50 °C to give an off-white solid. The off-white solid was dissolved in CH₂Cl₂ and purified by flash chromatography eluting with CH₂Cl₂/MeOH to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile as a white solid (C₂; 9.65 g, 90% yield). m/z = [M+H]⁺ 370.10; ¹H NMR (400 MHz, DMSO) δ 8.99 (d, J = 5.7 Hz, 1H), 8.38 – 8.30 (m, 2H), 7.66 (s, 1H), 7.47 (s, 1H), 2.44 (s, 3H), 1.49 (s, 9H).

[618] Step 3: Synthesis of 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid (C₇)

[619] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (C₂; 5.0 g, 13.5 mmol, 1.0 eq) was charged to a reactor. KOH (5.15 g, 81.0 mmol, 6 eq), water (15.0 mL) and EtOH (20 mL) were also charged to the reactor. The resulting mixture was stirred at 70 °C for 30 h. After consumption of the starting material, as determined by HPLC analysis, the mixture was concentrated under vacuum at 50 °C to minimum volume. 2 N HCl (45.0 mL) was added to adjust pH to about 3. A

light-yellow solid precipitated out. The slurry was filtered and the cake was rinsed with water and then heptane to give a light-yellow solid. The solid was dissolved in CH_2Cl_2 and purified by flash chromatography, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid as a pale-yellow solid (C_7 , 4.06 g, 81% yield). $m/z = [\text{M}+\text{H}]^+ 371.1$; $^1\text{H NMR}$ (400 MHz, DMSO) δ 12.16 (s, 1H), 8.54 (d, $J = 5.8$ Hz, 1H), 7.52 (2, 1H), 7.50 (d, $J = 5.8$ Hz, 1H), 7.49 (2, 1H), 6.20 (s, 1H), 2.31 (s, 3H), 1.48 (s, 9H). C_4 can be transformed to C_7 under similar conditions.

[620] Step 4: Synthesis of Compound I



[621] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid (C_7 , 10.0 g, 25.9 mmol, 1.0 eq) was charged to a reactor. 1,1'-Carbonyldiimidazole (10.1 g, 62.1 mmol, 2.4 eq) and CH_2Cl_2 (150 mL) were also charged to the reactor. The resulting mixture was stirred at 25 °C for 22 h. After consumption of the starting materials, as determined by HPLC analysis, ammonia solution in THF (0.4 M, 97.0 mL, 38.8 mmol, 1.5 eq) was charged and the resulting mixture was stirred at 25 °C for 24 h. After consumption of the starting materials, as determined by HPLC analysis, the mixture was concentrated under vacuum at 40 °C to minimum volume. Water (60 mL) was charged and the resulting slurry was stirred at 25 °C for 2 h and then filtered. The filter cake was rinsed with water (10 mL) and then heptane (10 mL) to give a white solid which was dissolved in CH_2Cl_2 and purified by flash chromatography eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-oxo-1,4-dihydro-1,6-naphthyridine-5-carboxamide as a white solid (Compound I; 8.60 g, 90% yield). HRMS $m/z = [\text{M}+\text{H}]^+ 370.1304$; $^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$) δ 12.01 (bs, 1H), 8.51 (d, $J = 5.8$ Hz, 1H), 7.55 (bs, 1H), 7.49 (s, 2H), 7.46 (d, $J = 5.8$ Hz, 1H), 7.33 (bs, 1H), 6.13 (s, 1H), 2.31 (s, 3H), 1.48 (s, 9H).

*Example 1: Compound I Neat Form A**Preparation of Compound I Neat Form A*

[622] Compound I amorphous material (40 mg) was added to a 2 mL glass vial and the vial was crimped. The solids were diluted and suspended in methanol (400 μ L). A stir bar was added and the vial was placed on a shaker block (20 °C, 800 rpm) for 1 hour. The solids were filtered and dried in an oven overnight (40 °C, under vacuum, nitrogen bleed).

X-Ray Powder Diffraction

[623] The XRPD pattern for Compound I neat Form A form was recording using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound I neat Form A is provided in FIG. 8, and the data are summarized below in Table 8.

Table 8: XRPD Signals for Compound I Neat Form A

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.5	282.1	100.0
2	8.0	36.6	15.5
3	9.0	61.0	34.4
4	10.4	81.5	34.6
5	11.1	26.9	10.0
6	11.7	24.1	8.7
7	12.8	72.9	38.6
8	16.0	80.9	36.2
9	17.3	109.4	19.1
10	18.7	85.7	43.4
11	20.4	164.8	64.8
12	22.8	37.8	8.7
13	23.9	35.9	10.3
14	27.4	50.2	11.7
15	27.7	22.4	10.6
16	29.5	31.9	12.5
17	29.9	35.3	12.8

Solid-State ^{13}C NMR

[624] The ^{13}C SSNMR of Compound I neat Form A was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound I neat Form A, collected at ambient condition, is provided in FIG. 9A. FIG. 9B provides a comparison of ^{13}C SSNMR spectra for Compound

I neat Form A, collected at ambient conditions (bottom trace), Compound I neat Form A, collected after the sample was dried at 80°C for 3 hours (middle trace), and Compound I neat Form A, collected after the sample was dried at 80°C for 3 hours and then rehumidified for 12 hours at 75% relative humidity at room temperature (top trace). The ^{13}C SSNMR data for these three traces are summarized in Table 9, below.

Table 9: ^{13}C SSNMR Signals for Compound I Neat Form A

Peak #	Sample at Ambient Condition		Sample Dried at 80°C for 3 hours		Sample dried at 80°C for 3 hours and then rehumidified for 12 hours at 75% relative humidity at room temperature	
	Chemical Shift [ppm]	Intensity [rel]	Chemical Shift [ppm]	Intensity [rel]	Chemical Shift [ppm]	Intensity [rel]
1	179.6	0.4	178.8	3.28	179.7	0.77
2	178.7	3.2	177.5	3.27	178.8	2.42
3	177.5	3.4	174.7	2.68	177.6	3.03
4	174.6	2.2	168.3	2.58	174.8	2.64
5	169.7	0.3	156.0	1.94	169.8	0.63
6	168.2	2.1	153.1	2.69	168.3	2.06
7	155.9	1.7	152.4	3.42	155.9	1.36
8	154.8	0.3	150.9	3.17	154.9	0.51
9	153.0	2.5	149.4	1.34	153.0	2.6
10	152.3	2.6	148.3	1.84	152.4	2.77
11	150.9	2.7	146.8	3.79	151.1	3.21
12	149.1	1.6	145.6	4.17	149.2	2.14
13	147.7	1.8	144.8	5.85	147.8	2.42
14	146.7	3.2	135.7	8.36	146.8	3.16
15	145.6	3.6	134.6	3.29	145.7	3.67
16	144.7	4.9	132.8	5.44	144.7	5.51
17	135.6	7.1	130.9	5.24	135.6	7.88
18	134.7	3.1	129.6	1.46	135.0	3.99
19	132.8	5.0	116.3	2.71	132.8	5.91
20	131.0	4.6	115.1	4.32	131.0	5.68
21	129.7	0.8	113.5	5.69	116.3	2.55
22	116.3	2.4	111.5	3.86	115.1	4.08
23	115.0	4.0	36.4	3.26	113.5	5.42
24	113.6	4.7	30.3	6.82	111.4	2.81
25	113.3	4.7	29.7	10	36.3	3.07
26	111.4	3.6	20.5	8.95	30.3	6.77
27	36.5	2.5			29.6	10
28	36.2	3.0			20.5	9.19
29	30.3	6.0				
30	29.5	10.0				
31	20.4	8.3				

Single Crystal Elucidation of Compound I Neat Form A

[625] Single crystals having the Compound I neat Form A structure were grown by making a slurry of Compound I n-propanol solvate B in 70% propanol/water at 60 °C. X-ray diffraction data were acquired at 100K on a Bruker diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a CPAD detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in the Table 10 below.

Table 10: Single Crystal Elucidation of Compound I Neat Form A

Crystal System	Triclinic
Space Group	P-1
a (Å)	10.9746(2)
b (Å)	11.1748(3)
c (Å)	15.9101(4)
α (°)	97.9880(10)
β (°)	93.0750(10)
γ (°)	95.7750(10)
V (Å ³)	1917.92(8)
Z/Z'	2/2
Temperature (K)	100(2)

Example 2: Compound I Neat Form B*Preparation of Compound I Neat Form B*

[626] Amorphous Compound I (40 mg) was placed in a 2 mL vial, and nitromethane (400 μ L) was added. The mixture was stirred (800 rpm) at 20 °C for 1 hour. The mixture was filtered and the isolated solids were dried in an oven (78 °C, nitrogen bleed under vacuum) for 72 hours.

X-Ray Powder Diffraction

[627] The XRPD pattern for Compound I Neat Form B was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound I Neat Form B is provided in FIG. 10, and the data are summarized below in Table 11.

Table 11: XRPD Signals for Compound I Neat Form B

Peak No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	5.8	211.7	100
2	7.7	28.2	15.7
3	9.5	58.2	31.0
4	9.8	88.2	50.6
5	12.5	16.6	8.9
6	13.7	53.8	29.7
7	15.4	16.0	10.6
8	15.7	61.6	39.4
9	16.8	35.1	16.0
10	17.4	85.3	28.3
11	18.4	14.7	11.6
12	19.7	80.2	42.2
13	21.2	124.0	78.3
14	23.3	18.3	14.5
15	23.8	24.2	12.8
16	25.3	21.7	11.4
17	25.6	44.4	23.3
18	27.7	30.7	10.8

Solid-State ¹³C NMR

[628] The ¹³C SSNMR of Compound I Neat Form B was acquired using the procedure described in the General SSNMR Method. The ¹³C SSNMR spectrum for Compound I Neat Form B is provided in FIG. 11, and the data are summarized below in Table 12.

Table 12: ¹³C SSNMR Signals for Compound I Neat Form B

Peak #	Chem Shift [ppm]	Intensity [rel]
1	177.9	3.58
2	176.6	3.14
3	174.4	1.89

Peak #	Chem Shift [ppm]	Intensity [rel]
4	169.7	1.85
5	157.5	1.6
6	152.8	1.75
7	151.6	2.62
8	150.2	1.51
9	149.4	4.54
10	147.5	4.33
11	145.2	4.24
12	134.5	2.78
13	133.8	5.03
14	133.4	4.94
15	132.4	4.1
16	131.1	7.55
17	130.6	6.25
18	115.5	3.5
19	114.2	6.35
20	113.9	4.59
21	111.4	3.76
22	36.3	4.69
23	30.9	10
24	29.1	8.89
25	19.8	5.11
26	18.1	5.36

Single Crystal Elucidation of Compound I Neat Form B

[629] A single crystal having the Compound I Neat Form B structure was obtained by slow evaporation of a nitromethane solution of Compound I and then holding a resulting crystal under dry nitrogen at 80°C for about 12 hours. X-ray diffraction data were acquired at 100K on a Rigaku diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a hybrid pixel array detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in **Table 13** below.

Table 13. Single Crystal Elucidation of Compound I Neat Form B

Crystal System	Triclinic
Space Group	<i>P</i> -1
a (Å)	11.1474(3)
b (Å)	11.4565(4)
c (Å)	14.9885(6)
α (°)	87.610(3)
β (°)	88.212(3)
γ (°)	88.920(2)
V (Å ³)	1911.29(11)

Z/Z'	2 / 2
Temperature (K)	100(2)

Example 3: Compound I Neat Form C

Preparation of Compound I Neat Form C

[630] Compound I Neat Form A (40 mg) was placed in a 2 mL glass, crimp vial, and 2-MeTHF (400 μ L) was added. The mixture was stirred (800 rpm) at 20 °C for 1 hour. The mixture was filtered and the isolated solids were dried in an oven (78 °C, nitrogen bleed under vacuum) for 72 hours.

X-Ray Powder Diffraction

[631] The XRPD pattern for Compound I Neat Form C was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound I Neat Form C is provided in FIG. 12, and the data are summarized below in Table 14.

Table 14: XRPD Signals for Compound I Neat Form C

Peak No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	6.0	252.5	83.5
2	9.3	141.9	48.4
3	10.3	61.9	63.0
4	11.3	33.9	16.8
5	12.2	20.1	13.3
6	13.9	154.2	56.9
7	15.4	78.4	55.0
8	15.6	30.0	31.2
9	17.2	144.6	100
10	17.6	28.3	22.2
11	18.3	66.2	47.1
12	19.7	148.3	89.8
13	20.1	59.6	51.5
14	20.8	152.1	66.4
15	21.6	45.5	18.0
16	22.3	13.8	12.3
17	22.8	31.8	22.6
18	23.1	22.0	15.3
19	23.4	19.8	16.2

Peak No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
20	24.1	25.3	13.4
21	24.8	70.5	24.9
22	25.2	102.9	18.0
23	26.4	68.4	38.3
24	26.8	27.6	22.5
25	28.8	11.0	13.2

Solid-State ^{13}C NMR

[632] The ^{13}C SSNMR of Compound I Neat Form C was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound I Neat Form C is provided in **FIG. 13**, and the data are summarized below in Table 15.

Table 15: ^{13}C SSNMR Signals for Compound I Neat Form C

Peak #	Chem Shift [ppm]	Intensity [rel]
1	177.9	3.4
2	176.5	3.08
3	173.9	1.97
4	169.3	1.96
5	157.8	1.76
6	153.9	1.66
7	151.5	2.85
8	149.8	3.85
9	148.4	4.35
10	147.8	3.59
11	145.6	4.28
12	135.4	1.12
13	134.5	4.31
14	133.0	4.96
15	131.3	7.39
16	130.4	5.27
17	115.6	2.7
18	115.4	2.73
19	114.5	7.78
20	114.1	4.95
21	111.4	3.93
22	36.5	3.15
23	36.3	3.32
24	31.3	10
25	30.2	9.25

Peak #	Chem Shift [ppm]	Intensity [rel]
26	20.9	5.1
27	17.9	5.26

Single Crystal Elucidation of Compound I Neat Form C

[633] A single crystal having the Compound I Neat Form C structure was obtained by slow evaporation of a methyl ethyl ketone solution of Compound I and then holding a resulting crystal under dry nitrogen at 70°C for about 20 hours.

X-ray diffraction data were acquired on a Rigaku diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a hybrid pixel array detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in **Tables 16** (data collected at 100 K) and **17** (data collected at 298 K) below.

Table 16: Single Crystal Elucidation of Compound I Neat Form C (determined at 100 K)

Crystal System	Triclinic
Space Group	<i>P</i> -1
a (Å)	11.2658(3)
b (Å)	11.5404(3)
c (Å)	15.1706(6)
α (°)	84.308(3)
β (°)	68.773(3)
γ (°)	88.970(2)
V (Å ³)	1829.14(10)
Z/Z'	2 / 2
Temperature (K)	100(2)

Table 17. Single Crystal Elucidation of Compound I Neat Form C (determined at 298 K)

Crystal System	Triclinic
Space Group	<i>P</i> -1
a (Å)	11.3795(6)
b (Å)	11.6019(6)
c (Å)	15.2981(8)
α (°)	84.215(4)
β (°)	69.578(5)
γ (°)	88.887(4)
V (Å ³)	1882.86(16)
Z/Z'	2 / 2
Temperature (K)	298(2)

Example 4: Compound I Hemi-Hydrate*Preparation of Compound I Hemi-Hydrate*

[634] Compound I amorphous material (40 mg) was added to a 2 mL glass vial and the vial was crimped. Compound I was diluted and suspended in water (400 μ L). A stir bar was added and the vial was placed on a shaker block (40 $^{\circ}$ C, 800 rpm) for 1 month. The solids were filtered and dried in an oven overnight (40 $^{\circ}$ C, under vacuum, nitrogen bleed).

X-Ray Powder Diffraction

[635] The XRPD pattern of crystalline Compound I Hemi-Hydrate was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I Hemi-Hydrate is provided in FIG. 14, and the XRPD data are summarized below in Table 18.

Table 18: XRPD Signals for Compound I Hemi-Hydrate

No.	Pos. [$^{\circ}$ 2 θ]	Area [cts* $^{\circ}$ 2 θ]	Rel. Int.[%]
1	5.1	307.3	100.0
2	10.2	210.3	68.4
3	11.1	18.7	5.5
4	12.3	52.4	19.2
5	14.2	99.3	29.1
6	21.3	30.3	11.1
7	22.0	39.0	19.1
8	26.6	43.8	16.0

Solid-State 13 C NMR

[636] The 13 C SSNMR of Compound I Hemi-Hydrate was acquired using the procedure described in the General SSNMR Method. The 13 C SSNMR spectrum for Compound I Hemi-Hydrate is provided in FIG. 15 and the data are summarized below in Table 19.

Table 19: 13 C SSNMR Signals for Compound I Hemi-Hydrate

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	178.1	2.5
2	169.2	2.8
3	155.4	2.3
4	154.0	3.3
5	147.7	3.6
6	146.4	4.1
7	137.6	1.9

Peak #	Chemical Shift [ppm]	Intensity [rel]
8	137.0	1.8
9	133.4	6.4
10	129.0	0.9
11	127.2	3.3
12	116.7	2.2
13	115.6	4.3
14	113.0	3.9
15	35.4	2.6
16	29.6	10.0
17	21.1	6.1

Example 5: Compound I Monohydrate

Preparation of Compound I Monohydrate

[637] Compound I amorphous material (40 mg) was added to a 2 mL glass vial and the vial was crimped. Compound I was diluted and suspended in of water (400 μ L). A stir bar was added and the vial was placed on a shaker block (40 °C, 800 rpm) for 24 hours. The solids were filtered and dried in an oven overnight (40 °C, under vacuum, nitrogen bleed).

X-Ray Powder Diffraction

[638] The XRPD pattern of crystalline Compound I Monohydrate was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I Monohydrate is provided in **FIG. 16**, and the XRPD data are summarized below in Table 20.

Table 20: XRPD Signals for Compound I Monohydrate

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.0	419.3	100.0
2	10.2	264.1	68.5
3	12.2	71.2	20.7
4	14.2	142.8	30.6
5	17.1	29.3	7.8
6	17.8	33.2	4.8
7	18.1	16.1	5.2
8	20.3	16.4	5.0
9	21.3	43.5	12.0
10	22.0	79.5	20.3
11	23.5	30.1	8.1
12	26.5	69.1	17.5
13	27.4	29.1	5.0

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
14	31.7	8.0	2.6

Example 6: Compound I Methanol Solvate

Preparation of Compound I Methanol Solvate

[639] Compound I amorphous material (40 mg) was added to a 2 mL glass vial and the vial was crimped. Compound I was diluted and suspended in methanol (400 μ L). A stir bar was added and the vial was placed on a shaker block (40 $^{\circ}$ C, 800 rpm) for 1 hour. The solids were filtered. The powder sample was taped during filtration and analysis.

X-Ray Powder Diffraction

[640] The XRPD pattern of crystalline Compound I Methanol Solvate was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I Methanol Solvate is provided in FIG. 17, and the XRPD data are summarized below in Table 21.

Table 21: XRPD Signals for Compound I Methanol Solvate

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	6.6	404.7	100.0
2	8.4	103.4	22.2
3	10.6	232.6	56.0
4	13.3	54.9	12.6
5	15.9	36.9	9.5
6	17.6	212.6	28.7
7	18.8	143.0	23.6
8	20.9	103.8	13.6
9	21.1	254.0	41.5

Solid-State ^{13}C NMR

[641] The ^{13}C SSNMR of Compound I Methanol Solvate was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum is provided in FIG. 18, and the data are summarized below in Table 22.

Table 22: ^{13}C SSNMR Signals for Compound I Methanol Solvate

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	178.3	2.8

Peak #	Chemical Shift [ppm]	Intensity [rel]
2	177.4	2.5
3	172.8	1.7
4	170.3	2.0
5	156.9	1.4
6	154.1	1.6
7	151.9	4.5
8	150.0	3.4
9	149.2	2.4
10	147.8	4.1
11	146.4	3.3
12	135.0	3.8
13	134.0	5.1
14	132.9	8.7
15	131.5	4.5
16	129.6	2.7
17	116.2	5.3
18	115.0	2.3
19	114.6	2.8
20	112.0	2.7
21	49.5	4.5
22	49.3	7.4
23	49.0	2.5
24	36.4	2.3
25	35.3	2.1
26	30.2	10.0
27	28.2	6.0
28	19.1	6.2
29	18.8	6.6

Single Crystal Elucidation of Compound I Methanol Solvate

[642] Single crystals having the Compound I methanol solvate structure were grown making a slurry of Compound I in a mixture of 10% water in methanol. X-ray diffraction data were acquired at 100 K on a Bruker diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a CPAD detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in Table 23 below.

Table 23: Single Crystal Elucidation of Compound I Methanol Solvate at 100 K

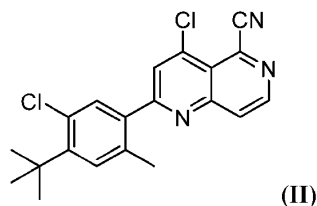
Crystal System	Triclinic
Space Group	P-1

a (Å)	12.3471(4)
b (Å)	14.0898(5)
c (Å)	14.3868(5)
α (°)	100.4428(14)
β (°)	105.3106(13)
γ (°)	107.4906(14)
V (Å ³)	2208.08(13)
Z/Z'	2 / 2
Temperature (K)	100(2)

Example 7: Compound I nPA Solvate Mixture A

Preparation of Compound I nPA Solvate Mixture A

[643] Compound **II** (25 g, 67.52 mmol, 1.0 eq)



was added to a 250 mL round bottom flask followed by DI water (7.5 mL, 0.3 V). TFA (150 mL, 6 V, 223.35 g) was added to the flask followed by stirring at 500 rpm. An orange clear solution was obtained within 2 min at room temperature. The solution was heated to an internal temperature of 60 °C, and stirred for 16 hours. The TFA was quenched using a 0.44 M NaOH solution (0.74 L, 30 V) and the reaction was transferred to a 500 mL round bottom flask. The reaction was concentrated under vacuum (20 mbar, 45-50 °C) to 2 V (77.39 g, 50 mL). The remaining solution was diluted with 2-MeTHF (25 mL, 1 V) to decrease viscosity for transfer to a 5 L reactor. Once transferred, 0.44 M NaOH solution (0.74 L) was added followed by 2-MeTHF (25 mL, 1 V). The solution was agitated and heated to 40 °C. Over 10 minutes, TFA concentrate in 2-MeTHF (25 mL, 1 V) was slowly added to the reactor. The flask containing TFA concentrate was rinsed with 2-MeTHF (1 V) and add into the reactor. Additional 0.44 M NaOH (120 mL) was added to the reactor to adjust to pH 11. A pinkish reaction mixture was obtained. Additional 2-MeTHF (0.925 L, 37 V) was added followed by stirring at 40 °C for 10 min. The reaction was allowed to settle and

the layers were separated. The bottom red-orange aqueous layer (pH ~11) was drained into a 1 L bottle giving a total mass of 986.25 g and 9.45 g of Compound I nPA Solvate A (32.6 % yield determined by HPLC assay). The top organic layer was washed with 15 % w/v NaCl (0.25 L, 10 V). The bottom colorless aqueous layer (pH 7) was drained into a 0.5 L bottle. The top organic layer was washed again with 15 % w/v NaCl (0.25 L, 10 V) followed by the bottom colorless aqueous layer (pH 7) being drained into a 0.5 L bottle. A third 15 % w/v NaCl (0.25 L, 10 V) wash of the top organic layer was done followed by draining the bottom colorless aqueous layer (pH 7) into a 0.5 L bottle. The NaCl washes were combined for a total mass of 892.1 g and 0.080 g of Compound I nPA Solvate A (0.28% yield determined by HPLC assay). The organic layer was concentrated to 10 V under vacuum (180 mbar, T_r (temperature of reaction contents) 35-40 °C, T_j (temperature of reactor jacket) 55 °C) over 3 h. A slurry was obtained. To the slurry, nPA (0.25 L, 10 V) was added followed by concentration to 10 V under vacuum (120 mbar, T_r 35-40 °C, T_j 55 °C) over 3.5 h. A slurry was obtained. To the slurry, nPA (0.25 L, 10 V) was added followed by concentration to 10 V under vacuum (100 mbar, T_r 35-45 °C, T_j 55 °C) over 3.5 h. A slurry was obtained and heated to T_r 95 °C (T_j 100 °C). nPA (40 mL) was added to obtain a clear solution. The solution was stirred at 95 °C for 10 min and slowly cool to 60 °C over 1 h. Compound I nPA Solvate seeds (~0.25 g, ~1 % w/v) were added at 60 °C and stirred at 60 °C for 1 h. The reaction was slowly cooled 20 °C over 10 h and stirred at 20 °C for 5 h. The solids were filtered, rinsed with nPA (2.5 V), and dried on the frit for a few min to give a light-yellow solid (14.341 g). The wet cake was dried overnight at room temperature to give a dry light-yellow solid (13.384 g). HPLC assay showed 99.8% purity and ^1H NMR assay showed 86.0 % w/w Compound I and 13.5 % w/w Compound I nPA Solvate Mixture A (1/0.967 mol/mol).

X-Ray Powder Diffraction

[644] The XRPD pattern of crystalline Compound I nPA Solvate Mixture A was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I nPA Solvate Mixture A is provided in **FIG. 19**, and the XRPD data are summarized below in Table 24.

Table 24: XRPD Signals for Crystalline Compound I nPA Solvate Mixture A

No.	Pos. [2θ]	Area [cts* 2θ]	Rel. Int. [%]
1	5.3	522.9	100.0
2	8.8	195.4	29.3
3	10.1	74.4	11.9
4	10.6	297.7	37.3
5	13.5	102.7	11.8
6	13.7	285.5	25.4
7	14.3	147.1	17.2

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
8	15.8	42.1	5.9
9	18.4	91.3	5.7
10	18.8	433.1	28.7
11	20.4	101.1	8.1
12	21.4	55.1	6.2
13	22.8	51.9	6.5
14	23.3	110.8	10.2
15	25.5	268.7	30.5
16	26.1	238.5	17.4

Solid-State ^{13}C NMR

[645] The ^{13}C SSNMR of Compound **I** nPA Solvate Mixture A was acquired using the procedure described in the General SSNMR Method. Two representative ^{13}C SSNMR spectra for Compound **I** nPA Solvate Mixture A (different lots) are provided in **FIG. 20** and **FIG. 21**, and the data are summarized below in Table 25 (corresponding to **FIG. 20**) and Table 26 (corresponding to **FIG. 21**).

Table 25: ^{13}C SSNMR Signals for Compound **I nPA Solvate Mixture A Spectrum 1**

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	175.2	30.0
2	172.3	21.6
3	155.1	17.8
4	149.7	25.5
5	147.2	23.4
6	145.3	31.6
7	143.5	22.4
8	135.3	41.0
9	134.7	39.7
10	132.6	34.1
11	130.9	35.0
12	117.1	15.8
13	112.9	49.7
14	64.3	47.3
15	36.5	24.8
16	30.4	100.0
17	24.8	48.3
18	20.7	53.9
19	11.9	54.2

Table 26: ^{13}C SSNMR Signals for Compound I nPA Solvate Mixture A Spectrum 2

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	176.5	1.8
2	175.2	2.0
3	171.8	3.7
4	154.3	1.4
5	153.2	0.9
6	150.1	3.0
7	147.6	2.5
8	144.9	3.3
9	143.5	2.2
10	142.2	2.0
11	135.5	4.6
12	134.5	4.7
13	132.6	6.2
14	131.1	4.7
15	117.0	2.3
16	113.6	5.8
17	112.1	1.4
18	64.3	4.7
19	63.9	4.4
20	36.5	4.9
21	29.9	10.0
22	25.9	2.1
23	24.9	4.6
24	20.9	6.8
25	13.4	1.6
26	11.7	4.7

Single Crystal Elucidation of Compound I nPA Solvate Mixture A

[646] Single crystals having the Compound I nPA Solvate Mixture A structure were grown by slowly evaporating a solution of Compound I in a mixture of 80% water in nPA. X-ray diffraction data were acquired at 100 K on a Bruker diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a CPAD/hybrid pixel array detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in Table 27 below.

Table 27: Single Crystal Elucidation of Compound I nPA Solvate Mixture A

Crystal System	monoclinic
Space Group	$C2/c$
a (Å)	19.9097(6)

b (Å)	6.9043(2)
c (Å)	32.6062(10)
α (°)	90
β (°)	93.9113(15)
γ (°)	90
V (Å ³)	4471.7(2)
Z/Z'	8 / 1
Temperature (K)	100(2)

Example 8: Compound I nPA Solvate B

Preparation of Compound I nPA Solvate B

[647] Compound I amorphous material (40 mg) was added to a 2 mL glass vial and the vial was crimped. Compound I was diluted and suspended in nPA (400 μ L). A stir bar was added and the vial was placed on a shaker block (20 °C, 800 rpm) for 24 hours. The solids were filtered and dried in an oven overnight (40 °C, under vacuum, nitrogen bleed).

X-Ray Powder Diffraction

[648] The XRPD pattern of crystalline Compound I nPA Solvate B was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I nPA Solvate B is provided in FIG. 22, and the XRPD data are summarized below in Table 28.

Table 28: XRPD Signals for Crystalline Compound I nPA Solvate B

No.	Pos. [°2 θ]	Area [cts*°2 θ]	Rel. Int. [%]
1	5.3	51.7	100.0
2	8.8	44.9	98.7
3	9.9	18.0	43.8
4	10.6	36.7	62.6
5	13.2	40.8	71.8
6	13.9	22.28	39.5
7	14.8	20.0	35.8
8	17.5	18.7	32.1
9	18.0	6.9	15.8

No.	Pos. [$^{\circ}2\theta$]	Area [cts $^{\circ}2\theta$]	Rel. Int. [%]
10	18.9	68.4	87.1
11	21.4	48.6	37.7
12	22.6	6.8	13.7
13	22.9	5.6	9.4
14	24.6	18.5	33.5
15	25.7	38.3	66.1
16	26.1	31.0	54.0
17	26.5	11.9	14.6
18	28.1	19.4	15.8

Solid-State ^{13}C NMR

[649] The ^{13}C SSNMR of Compound I nPA Solvate B was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound I nPA Solvate B is provided in **FIG. 23** and the data are summarized below in Table 29.

Table 29: ^{13}C SSNMR Signals for Compound I nPA Solvate B

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	175.2	30.0
2	172.3	21.6
3	155.1	17.8
4	149.7	25.5
5	147.2	23.4
6	145.3	31.6
7	143.5	22.4
8	135.3	41.0
9	134.7	39.7
10	132.6	34.1
11	130.9	35.0
12	117.1	15.8
13	112.9	49.7
14	64.3	47.3
15	36.5	24.8
16	30.4	100.0
17	24.8	48.3
18	20.7	53.9
19	11.9	54.2

Single Crystal Elucidation of Compound I nPA Solvent B

[650] X-ray diffraction data were acquired at 100 K on a Bruker diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a CPAD detector. The structure was solved and refined using SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in the Table 30 below.

Table 30: Single Crystal Elucidation of Compound I nPA Solvate B

Crystal System	triclinic
Space Group	<i>P</i> -1
a (Å)	6.8013(9)
b (Å)	10.4633(10)
c (Å)	16.3601(7)
α (°)	93.818(5)
β (°)	92.876(8)
γ (°)	105.779(11)
V (Å ³)	1115.1(2)
Z/Z'	2 / 1
Temperature (K)	100(2)

*Example 9: Compound I nPA Solvate C**Preparation of Compound I nPA Solvate C*

[651] A 50 L jacketed reactor was set to a T_j of 20 °C and Compound **III** (4-(benzyloxy)-2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridine-5-carbonitrile) (987 g, 2233.274 mmol, 1 equiv.) and toluene (9870 mL, 0.226 M, 10 Vols) were added with stirring at 150 rpm. The temperature was set to an internal reaction mixture temperature of 60 °C. The mixture was stirred until the solids dissolved. TFA (12732.232 g, 8545.122 mL, 111663.718 mmol, 50 equiv.) was added to the reactor and stirred for 20 hours. The reaction solution was removed from the reactor, placed in a 20 L round bottom flask, and then concentrated to dryness by rotavap (55 °C, vacuum 6 mbar). The solution was then chased with toluene (4935 mL, 0.453 M, 5 Vols) to remove any remaining TFA. The material was completely dried into a dark

brown oil. The oil was dissolved in 2-MeTHF (19740 mL, 0.113 M, 20 Vols) and transferred back into the 50 L reactor. The organics were washed with saturated aqueous NaHCO_3 (6909 mL, 0.323 M, 7 Vols). The mixture was stirred for 1.5 h. The aqueous layer was removed and the organic layer was washed with saturated aqueous NaHCO_3 (6909 mL, 0.323 M, 7 Vols). The mixture was stirred overnight at room temperature. Product had precipitated overnight so mixture was heated to 35 °C while adding an additional portion of 2-MeTHF (3948 mL, 0.566 M, 4 Vols) to the mixture. Combined aqueous layers were back extracted with 2-MeTHF (3948 mL, 0.566 M, 4 Vols), stirring was stopped, and the layers were allowed to settle. The aqueous layer (bottom) was drained from the reactor. Then both organic layers were combined and washed with 50% saturated aqueous NaCl (3948 mL, 0.566 M, 4 Vols). The mixture was stirred for 30 min, stirring was stopped, and the layers were allowed to settle. The aqueous layer was drained from the reactor and the organic layers were combined and dried with Na_2SO_4 . The organic layers were filtrated and concentrated to dryness by rotary evaporation for a final yield of 2,600 g. The crude material was dissolved in nPA (7680 mL, 0.291 M, 7.781 Vols). The internal temperature of the reactor was increased to 95 °C by controlling the jacket temperature. The temperature was maintained for 1.5 hrs. Jacket temperature was cooled down to 20 °C over 10 hours and then heated to 22 °C for stirring overnight. Prepped 5L glass filter was set-up with a 20L carboy and the filtrate receiver.

X-Ray Powder Diffraction

[652] The XRPD pattern of crystalline Compound I nPA Solvate C was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I nPA Solvate C is provided in **FIG. 24**, and the XRPD data are summarized below in Table 31.

Table 31: XRPD Signals for Crystalline Compound I nPA Solvate C

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.4	1074.9	100.0
2	6.1	54.7	5.1
3	7.2	25.6	2.1
4	8.7	379.3	30.9
5	10.2	251.1	23.4
6	11.8	85.0	6.9
7	12.2	57.3	7.5
8	14.6	159.0	9.4
9	15.8	166.0	12.0
10	17.5	61.4	4.0
11	19.1	91.6	6.6
12	19.6	63.9	5.2

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
13	21.4	5.0	2.8
14	20.5	91.8	7.5

Example 10: Compound I Na Hemi Salt nPA Solvate

Preparation of Compound I Na Salt nPA Solvate

[653] 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile (Compound II, 3 g, 8.102 mmol, 1 equiv), water (0.9 mL, 9.002 M, 0.3 Vols), and TFA (18 mL, 0.45 M, 6 Vols) were added to a 40 mL vial with a magnetic stir bar and sealed with a cap. The vial was placed on a stir plate that had been preheated to 60 °C and aged for 24 hours before being allowed to cool to room temperature. The reaction was then transferred to a 100 mL round bottom flask and concentrated using a rotovap (60 mbar, 50 °C) to 2V (6 mL). The reaction was transferred to a 300 mL Chemglass™ reactor controlled at 20 °C using 2-methyltetrahydrofuran (120 mL, 0.068 M, 40 Vols) to rinse the flask. Using an aqueous quenching solution of water (90 mL, 0.09 M, 30 Vols) and sodium hydroxide (3.33 g), the reaction was quenched over 2-3 minutes. The agitation was stopped, allowing the phases to separate. The pH was measured with a pH strip (target pH: 11.0 - 14.0). An aqueous 15 % w/v sodium chloride was added to the reaction and reaction was heated to 40 °C and the phases were allowed to separate. The aqueous layer was removed. 10 V (30mL) of aqueous 15 % w/v sodium chloride solution was added while adjusting the temperature back to 40 °C. The agitation was paused, allowing the phases to separate. The aqueous layer was removed. 10 V (30 mL) of aqueous 15 % w/v sodium chloride solution was added while adjusting the temperature back to 40 °C. Agitation was paused, allowing the phases to separate. The aqueous layer was removed. 10 V (30mL) of aqueous 15 % w/v sodium chloride solution was added while adjusting the temperature back to 40 °C and holding overnight. The aqueous layer was removed. The reaction was transferred to a 250 mL round bottom flask and distilled down to 20V (60mL) using a rotovap (200 mbar, 50 °C). 2-MeTHF (150 mL, 50 V) was added and the reaction was distilled down to 20 V using a rotovap (200 mbar, 50 °C). 2-MeTHF (60 mL, 20 V) was added and the reaction was heated to 50 °C using a rotovap bath. The solids were filtered through a preheated filter. The solids were dried under vacuum at 35 °C overnight. The solids were transferred to a 250 mL round bottom flask and distilled to 10V (30 mL) using a rotovap (300 mbar, 55 °C). nPA (60 mL, 20 V) was added and distilled down to 10 V using a rotovap (100 mbar, 55 °C). nPA (60mL, 20 V) was added and aged in a bath at 55 °C for 1 hour. The reaction was distilled to 10 V using a rotovap (90 mbar, 60 °C). nPA (60 mL, 20 V) was added and the reaction was distilled down to 10 V using a rotovap (80 mbar, 60 °C). The reaction was transferred to a 100 mL glass EasyMax™ vessel with overhead agitation. The temperature was adjusted to 20 °C followed by a heating

of $T_r = 90\text{ }^{\circ}\text{C}$, a 1 hour cool-down to $T_r = 50\text{ }^{\circ}\text{C}$ and then held at $50\text{ }^{\circ}\text{C}$ overnight. Compound **I** nPA Solvate B seeds (0.03 g) were added and the temperature was held at $50\text{ }^{\circ}\text{C}$ for 1 h. Over 4 h the temperature was cooled to $20\text{ }^{\circ}\text{C}$. The solids were filtered and dried in an oven under vacuum at $40\text{ }^{\circ}\text{C}$ overnight with a nitrogen bleed.

X-Ray Powder Diffraction

[654] The XRPD pattern for Compound **I** Na hemi salt nPA Solvate was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound **I** Na hemi salt nPA Solvate is provided in **FIG. 25**, and the data are summarized below in Table 32.

Table 32: XRPD Signals for Compound **I Na Hemi Salt nPA Solvate**

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.2	144.2	37.5
2	6.7	87.6	18.2
3	8.8	360.0	74.9
4	9.8	35.7	7.4
5	10.2	101.6	35.2
6	10.3	192.3	50.0
7	13.4	269.8	46.8
8	13.6	31.8	11.0
9	13.7	72.7	12.6
10	14.1	175.7	30.5
11	14.2	53.1	13.8
12	14.9	85.1	17.7
13	17.3	52.5	10.9
14	18.3	55.7	19.3
15	18.5	203.7	42.4
16	18.7	673.2	100.0
17	19.6	168.1	25.0
18	20.1	128.4	16.7
19	20.4	107.9	14.0
20	20.6	103.3	17.9
21	21.0	149.3	22.2
22	24.6	221.6	25.6
23	26.4	263.7	30.5
24	26.6	194.4	28.9
25	28.4	128.3	14.8

Solid-State ^{13}C NMR

[655] The ^{13}C SSNMR of Compound I Na Hemi Salt nPA Solvate was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound I Na Hemi Salt nPA Solvate is provided in FIG. 26, and the data are summarized below in Table 33.

Table 33: ^{13}C SSNMR Signals for Compound I Na Hemi Salt nPA Solvate

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	178.0	1.6
2	176.8	1.2
3	175.7	1.4
4	174.2	1.8
5	161.9	1.3
6	152.1	1.3
7	151.1	1.5
8	150.4	1.6
9	147.4	1.3
10	146.1	1.5
11	144.6	1.5
12	142.6	4.2
13	135.4	2.2
14	134.4	3.3
15	133.0	2.0
16	132.0	3.6
17	130.5	2.7
18	119.6	1.1
19	118.8	1.9
20	115.9	0.9
21	114.4	2.1
22	114.0	2.6
23	111.6	1.9
24	65.1	1.3
25	62.6	1.4
26	36.5	2.2
27	30.7	10.0
28	26.2	1.6
29	24.8	1.2
30	21.4	2.3
31	20.8	3.9

Single Crystal Elucidation of Compound I Na Hemi Salt nPA Solvate

[656] X-ray diffraction data were acquired at 100K on a Rigaku diffractometer equipped with Cu K α radiation ($\lambda=1.54178$ Å) and a hybrid pixel array detector. The structure was solved and refined using

SHELX programs (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122) and results are summarized in the Table 34 below.

Table 34: Single Crystal Elucidation of Compound I Na Hemi Salt nPA Solvate

Crystal System	Triclinic
Space Group	<i>P</i> -1
a (Å)	10.3361(7)
b (Å)	13.2991(8)
c (Å)	16.7313(10)
α (°)	94.164(5)
β (°)	90.974(5)
γ (°)	104.044(5)
V (Å ³)	2223.8(2)
Z/Z'	2 / 2
Temperature (K)	100(2)

Example 11: Compound I nPA Solvate J

Preparation of Compound I nPA Solvate J

[657] Compound **II** (10 g, 27.007 mmol, 1 equiv) was added to a reaction vessel with jacket temperature controlled at 25 °C ± 5 °C. Water (3 mL, 9.002 M, 0.3 Vols) was added to the reaction vessel followed by agitation. TFA (60 mL, 0.45 M, 6 Vols) was added to reaction vessel while keeping internal temperature at 40 °C. The reactor was then heated to an internal temperature of 60 °C ± 5 °C and stirred for 15h. The reaction was cooled to an internal temperature of 20 °C ± 5 °C followed by distillation to 2 L/kg while maintaining the internal temperature at 30 °C. The reaction mixture was transferred to flask containing an aqueous 1.7 % w/v sodium hydroxide solution (300 mL, 30 Vols) and 2-methyltetrahydrofuran (50 mL, 0.54 M, 5 Vols) while maintaining the pH of the solution in the range 11-12 and maintaining internal temperature of 50 °C. The reaction was stirred for 30 minutes. The internal temperature was adjusted to 40 ± 5 °C followed by the addition of 2-methyltetrahydrofuran (350 mL, 0.077 M, 35 Vols) while maintaining the internal temperature at 40 ± 5 °C. The reaction was stirred for 30

minutes and the temperature was maintained at 40 ± 5 °C. Sodium chloride (53 g, 906.92 mmol, 33.581 equiv.) was added to the reaction while maintaining the internal temperature at 45 °C. The temperature was then adjusted to 40 ± 5 °C and stirred for 30 minutes. Once complete, the stirring was stopped and the phases were allowed to separate for 30 minutes. The lower aqueous phase was removed followed by an addition of aqueous 15 % w/v sodium chloride solution (10 L/kg) to the organic layer. The solution was stirred for 30 minutes at 40 ± 5 °C followed by a pausing in stirring for the phases to separate. This process of aqueous layer removal, addition of aqueous sodium chloride, and stirring was repeated four additional times. Compound I Form A (0.02 kg/kg Compound I Form A) was seeded to the vessel at a controlled temperature of 20 ± 5 °C and stirred for 24 h. The organic layer was distilled to 20 L/kg while maintaining the internal temperature in the range 20 to 50 °C. 2-methyltetrahydrofuran (20 L/kg) was added to the organic layer via spray ball followed by distilling to 20 L/kg while maintaining the internal temperature in the range 20 to 50 °C. 2-methyltetrahydrofuran (20 L/kg) was added to the organic layer via spray ball followed by an adjustment of the internal temperature to 45 °C and stirring for 30 min. A pressure transfer through tandem filters into the crystallization vessel with a rinse of 2-methyltetrahydrofuran (50 mL, 0.54 M, 5 Vols) to clear any solids in the lines. The reactor was distilled down to 10 L/kg while maintaining internal temperature between 20 °C and 30 °C. nPA (200 mL, 0.135 M, 20 Vols) was added to vessel followed by a distillation down to 10 L/kg while maintaining internal temperature between 20 °C and 30 °C. Compound I nPA solvate seed was added and stirred for 1 h at 20 ± 5 °C. Anhydrous nPA (20 L/kg) was added to the vessel and distilled to 10 L/kg while maintaining internal temperature between 20 °C and 30 °C. This was repeated once followed by raising the internal temperature to 90 °C. The vessel was cooled to 20 °C over 12 hours followed by stirring at 20 °C for 3h. Solids were isolated by filtration and the reactor was rinsed with nPA (25 mL, 1.08 M, 2.5 Vols) and dropped onto the wet cake. The wet cake was dried under vacuum at 45 °C.

X-Ray Powder Diffraction

[658] The XRPD pattern of crystalline Compound I nPA Solvate J was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I nPA Solvate J is provided in FIG. 27, and the XRPD data are summarized below in Table 35.

Table 35: XRPD Signals for Crystalline Compound I nPA Solvate J

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	3.1	13.9	0.40
2	5.3	690.8	100.0
3	8.8	184.1	19.0
4	10.0	105.7	10.9

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
5	10.4	147.8	21.4
6	10.6	199.2	18.0
7	13.4	300.4	16.7
8	14.1	319.9	15.4
9	18.5	81.4	8.4
10	19.0	175.3	21.2
11	19.2	187.1	13.5
12	26.0	116.9	12.1
13	26.4	137.0	11.0

Example 12: Compound I 2-MeTHF Solvate A

Preparation of Compound I 2-MeTHF Solvate A

[659] Compound I Form A (40 mg) was added to a 2 mL glass vial. 2-MeTHF (400 μ L) was added and the vial and sealed. The vial was mixed on a shaker block at 800 rpm at 22 $^{\circ}$ C for 24 hrs. The solid were filtered with a centrifuge filter and allow to air dry for no less than 1 hour and no more than 4 hours.

X-Ray Powder Diffraction

[660] The XRPD pattern of crystalline Compound I 2-MeTHF Solvate A was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I 2-MeTHF Solvate A is provided in **FIG. 28**, and the XRPD data are summarized below in Table 36.

Table 36: XRPD Signals for Crystalline Compound I 2-MeTHF Solvate A

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.8	137.7	100.0
2	9.4	38.7	28.1
3	9.8	27.8	20.2
4	10.3	14.6	24.8
5	14.0	39.0	28.3
6	15.4	27.8	23.6
7	15.7	25.2	21.3
8	17.3	53.1	45.0
9	18.3	21.7	18.4
10	19.7	66.8	42.4
11	20.1	11.9	15.1
12	20.8	87.4	24.7
13	24.8	32.0	10.2

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
14	25.3	33.1	10.5

Example 13: Compound I 2-MeTHF Solvate Mixture A

Preparation of Compound I 2-MeTHF Solvate Mixture A

[661] Compound **III** (4-(benzyloxy)-2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridine-5-carbonitrile) (7 g, 15.839 mmol, 1 equiv.), water (2.1 mL, 7.542 M, 0.3 Vols), and TFA (42 mL, 0.377 M, 6 Vols) was added to a 100 mL EasyMax™ reactor outfitted with overhead agitation and nitrogen purge. The reaction was heated to a T_r of 60 °C over 30min and stirred for 16 h at 60 °C. The reaction was cooled to 20 °C over 1h and distilled to a (28mL, 4 vol) in a 200 mL round-bottom flask in a rotovap (150 mbar, 50 °C). The bath temperature was increased to 60 °C followed by the addition of 2-methyltetrahydrofuran (77 mL, 0.206 M, 11 Vols). The reaction was distilled to 4 vol and the bath temperature was increased to 80 °C and reduced minimum pressure (50 mbar) and held overnight. 2-methyltetrahydrofuran (77 mL, 0.206 M, 11 Vols) was added followed by a distillation to 4 vol in a rotovap (115-60 mbar, 80 °C). 2-methyltetrahydrofuran (77 mL, 0.206 M, 11 Vols) was added and the reaction was transferred to a 250 mL graduated cylinder containing a magnetic stir bar. A saturated aqueous NaHCO₃ solution (49 mL, 7 V) and a saturated NaCl solution (28 mL, 4 V) were added to graduated cylinder and stirred. The aqueous layer was separated. Saturated aqueous NaCl (4 V) was added without temperature control, the mixture was allowed to separate, and the aqueous layer was removed. The mixture was concentrated to 4 V (28 mL), and 98 mL of 2-MeTHF (14 V) was added. The mixture was distilled to 4 V at a bath temperature of 50 °C and a pressure of 500 mbar. The pressure was reduced to 150 mbar very gradually. The resulting slurry was aged at room temperature for 3 days, the slurry was filtered, and the filter cake was washed with 2-MeTHF. The filter cake was dried under vacuum at 50 °C overnight.

X-Ray Powder Diffraction

[662] The XRPD pattern of crystalline Compound **I** 2-MeTHF Solvate Mixture A was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound **I** 2-MeTHF Solvate Mixture A is provided in **FIG. 29**, and the XRPD data are summarized below in Table 37.

Table 37: XRPD Signals for Crystalline Compound I 2-MeTHF Solvate Mixture A

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	4.6	608.5	100.0
2	12.4	87.6	14.4

No.	Pos. [$^{\circ}2\theta$]	Area [cts $^{\circ}2\theta$]	Rel. Int. [%]
3	14.8	91.2	12.9
4	15.8	462.0	45.6
5	18.8	168.0	18.4
6	19.4	105.2	10.4
7	21.9	119.8	11.8
8	25.3	113.9	14.0

Example 14: Compound I 2-MeTHF Mixture C

Preparation of Compound I 2-MeTHF Mixture C

[663] Compound **III** (4-(benzyloxy)-2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-1,6-naphthyridine-5-carbonitrile) (5 g, 11.313 mmol, 1 equiv), water (1.5 mL, 7.542 M, 0.3 Vols), and TFA (30 mL, 0.377 M, 6 Vols) was added to a 100 mL EasyMax™ reactor outfitted with overhead agitation and nitrogen blanket. The temperature was ramped to a T_j of 62 °C over 30 min and held overnight at T_j = 62 °C. The temperature is lowered to T_j = 20 °C and 2-methyltetrahydrofuran (55 mL, 0.206 M, 11 Vols) is added to the reaction. The reaction is distilled to 4vol (20mL) in a 200 mL round-bottom flask in a rotovap (110 mbar, 50-80 °C. 2-methyltetrahydrofuran (55 mL, 0.206 M, 11 Vols) was added and the reaction was distilled to 4 vol. using a rotovap (130 mbar, 70 °C). This addition and distillation was repeated followed by addition of 2-methyltetrahydrofuran (55 mL, 0.206 M, 11 Vols) and transferred to 250 mL graduated cylinder containing a magnetic stir bar. The reaction was washed with 7V (35mL) of sat. aq. NaHCO_3 solution followed by 7V (35mL) of sat. aq. NaCl solution. The phases separated and the aqueous layer was removed. The reaction was washed with 7V (35mL) of sat. aq. NaHCO_3 solution and the phases were allowed to separate with collection of the aqueous layer. A final wash of 7V (35mL) of sat. aq. NaHCO_3 solution followed by 7V (35 mL) of sat. aq. NaCl solution with gentle heating and agitation. The phases were allowed to settle and the aqueous layer was separated. The organic layer was transferred to a 250 mL round bottom flask and distilled to 4vol (20 mL) using a rotovap (500 mbar, 70 °C). The temperature was increased to dissolve solids to 90 °C followed by cooling the bath to 25 °C. Solids were filtered and dried at 40 °C overnight.

X-Ray Powder Diffraction

[664] The XRPD pattern of crystalline Compound **I** 2-MeTHF Mixture C was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound **I** 2-MeTHF Mixture C is provided in **FIG. 30**, and the XRPD data are summarized below in Table 38.

Table 38: XRPD Signals for Crystalline Compound I 2-MeTHF Mixture C

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	4.9	250.4	81.4
2	8.2	109.4	41.5
3	10.3	31.6	10.3
4	11.3	28.7	9.3
5	15.3	97.9	24.8
6	15.7	61.7	23.4
7	15.8	69.1	26.2
8	17.2	395.5	100.0
9	18.5	158.1	32.7
10	19.6	93.7	23.7
11	20.4	72.9	18.4
12	23.1	96.5	24.4
13	25.0	71.0	20.2
14	25.2	59.4	16.9

Example 15: Compound I Mandelic Acid Cocrystal*Preparation of Compound I Mandelic Acid Cocrystal*

[665] Compound I (175.62 mg, 0.48 mmol, 1 equiv.) and Mandelic acid (73.22 mg, 0.48 mmol, 1 equiv.) were added to a 2 mL glass vial. DCM (2 mL, 0.24 M, 87.8 Vols) and was added, and the vial was sealed. The vial was sonicated for 1 hour and allowed to stir at 900 rpm and 25 °C for 1 week. The solids were filtered and dried in a vacuum oven at 50 °C with a nitrogen bleed.

[666]*X-Ray Powder Diffraction*

[667] The XRPD pattern of crystalline Compound I Mandelic Acid Cocrystal was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for crystalline Compound I Mandelic Acid Cocrystal is provided in FIG. 31, and the XRPD data are summarized below in Table 39.

Table 39: XRPD Signals for Crystalline Compound I Mandelic Acid Cocrystal

No.	Pos. [°2θ]	Area [cts*°2θ]	Rel. Int. [%]
1	6.6	404.7	100.0
2	8.4	103.4	22.2
3	10.6	232.6	56.0
4	13.3	54.9	12.6

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
5	15.9	36.9	9.5
6	17.6	212.6	28.7
7	18.8	143.0	23.6
8	20.9	103.8	13.6
9	21.1	254.0	41.5

Example 16: Compound I Oxalic Acid Cocrystal

Preparation of Compound I Oxalic Acid Cocrystal

[668] Compound I (3 g, 8.111 mmol, 1 equiv.), oxalic acid (0.7 g, 8.111 mmol, 1 equiv), and DCM (15 mL, 0.541 M, 5 Vols) were charged to a 20 mL glass vial. The vial was sealed and sonicated for 5 min and allowed to stir at 900 rpm at 25 $^{\circ}\text{C}$ overnight. The slurry was sonicated for an additional 10 minutes until the slurry became free flowing and allowed to stir at 900 rpm at 25 $^{\circ}\text{C}$ for an additional 20 hours. The solids were filtered and dried in a vacuum oven at 50 $^{\circ}\text{C}$ with a nitrogen bleed to give an off white solid.

X-Ray Powder Diffraction

[669] The XRPD pattern for Compound I Oxalic Acid Cocrystal was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound I Oxalic Acid Cocrystal is provided in **FIG. 32**, and the data are summarized below in Table 40.

Table 40: XRPD Signals for Compound I Oxalic Acid Cocrystal

No.	Pos. [$^{\circ}2\theta$]	Area [cts* $^{\circ}2\theta$]	Rel. Int. [%]
1	5.7	154.7	100.0
2	8.9	54.1	23.3
3	10.6	24.5	10.6
4	11.6	42.6	13.8
5	13.8	36.5	13.5
6	14.5	32.3	13.9
7	20.1	53.6	19.8
8	22.9	29.0	12.5

Solid-State ^{13}C NMR

[670] The ^{13}C SSNMR of Compound I Oxalic Acid Cocrystal was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound Oxalic Acid Cocrystal is provided in **FIG. 33**, and the data are summarized below in Table 41.

Table 41: ^{13}C SSNMR Signals for Compound I Oxalic Acid Cocrystal

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	177.5	4.6
2	169.8	1.6
3	169.5	1.8
4	162.4	2.8
5	161.5	2.7
6	154.3	2.0
7	153.7	2.4
8	149.3	1.2
9	148.0	2.3
10	146.4	1.6
11	146.1	1.9
12	134.9	2.5
13	133.0	0.6
14	132.0	3.3
15	130.9	1.6
16	130.0	2.4
17	128.1	0.3
18	117.7	3.5
19	114.6	1.8
20	112.4	3.9
21	36.3	2.7
22	29.3	10.0
23	17.9	3.7

Example 17: Compound I TFA Salt A*Preparation of Compound I TFA Salt A*

[671] Compound I Form A (1.0 g) was placed in a 20 mL vial, and CH_2Cl_2 (5 mL, 5 V) was added. The mixture was stirred at room temperature, and a suspension was obtained. TFA (1.1 eq, 0.23 mL) was added. A clear solution formed, and then a slurry was obtained within 0.5 min. The mixture was stirred at room temperature for 30 min. The slurry was filtered, the wet cake was rinsed with CH_2Cl_2 (~5 mL), and the cake was dried on the frit for 2-3 min to give a white fluffy solid (0.562 g), which was dried at RT for five hours to give a dry slightly fluffy white solid (0.552 g).

X-Ray Powder Diffraction

[672] The XRPD pattern for Compound I TFA Salt A was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Compound I TFA Salt A is provided in FIG. 34, and the data are summarized below in Table 42.

Table 42: XRPD Signals for Compound I TFA Salt A

No.	Pos. [$^{\circ}2\theta$]	Area [cts $^{\circ}2\theta$]	Rel. Int. [%]
1	4.4	1644.5	100.0
2	8.4	139.6	10.9
3	11.4	90.4	11.0
4	15.1	111.0	12.2
5	17.3	184.6	9.2
6	19.7	181.6	11.0
7	20.4	47.1	1.8
8	23.8	200.1	9.1
9	26.3	253.7	11.6

Solid-State ^{13}C NMR

[673] The ^{13}C SSNMR of Compound I TFA Salt A was acquired using the procedure described in the General SSNMR Method. The ^{13}C SSNMR spectrum for Compound TFA Salt A is provided in FIG. 35, and the data are summarized below in Table 43.

Table 43: ^{13}C SSNMR Signals for Compound I TFA Salt A

Peak #	Chemical Shift [ppm]	Intensity [rel]
1	171.9	4.2
2	169.2	3.2
3	160.7	1.7
4	159.5	3.0
5	149.1	2.4
6	147.4	3.3
7	146.8	3.3
8	136.1	3.7
9	133.7	2.6
10	132.1	4.2
11	131.0	3.7
12	118.1	4.0
13	116.0	2.3
14	113.0	3.7
15	36.6	2.4
16	31.3	10.
17	18.4	5.3

Example 18: Amorphous Compound I*Preparation of Amorphous Compound I*

[674] Compound I Neat Form A (40 mg) was added into a glass, crimp vial (2 mL). t-Butanol (1.2 mL) and a stir bar were added. The resulting mixture was stirred (800 rpm) on a shaker block at 70 °C for about 1 hour. Water was then added dropwise until all solids were dissolved. The vial was then sealed with a cap and placed in a -80 °C freezer overnight. The frozen solid was lyophilized using a Labconco FreezeZone 6.

X-Ray Powder Diffraction

[675] The XRPD pattern for Amorphous Compound I was recorded using the procedure described in the General XRPD Method. The XRPD diffractogram for Amorphous Compound I is provided in FIG. 36.

Solid-State ¹³C NMR

[676] The ¹³C SSNMR of Amorphous Compound I was acquired using the procedure described in the General SSNMR Method. The ¹³C SSNMR spectrum for Amorphous Compound I is provided in FIG. 37, and the data are summarized below in Table 44.

Table 44: ¹³C SSNMR Signals for Amorphous Compound I

Peak #	Chem Shift [ppm]	Intensity [rel]
1	177.6	1.64
2	172.0	1.44
3	164.0	0.38
4	155.5	1.22
5	151.3	2.45
6	147.1	4.51
7	133.2	5.67
8	131.7	5.56
9	115.9	2.73
10	114.4	3.26
11	36.1	2.68
12	30.0	10
13	20.1	2.92
14	9.3	0.33
15	8.3	0.33
16	7.6	0.3

Other Embodiments

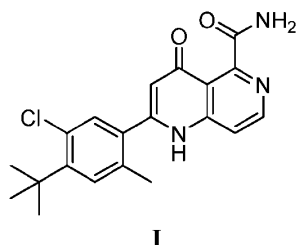
[677] The present disclosure enables one of skill in the relevant art to make and use the inventions provided herein in accordance with multiple and varied embodiments. Various alterations, modifications, and improvements of the present disclosure that readily occur to those skilled in the art, including certain alterations, modifications, substitutions, and improvements are also part of this disclosure. Accordingly, the foregoing description are by way of example to illustrate the discoveries provided herein. Furthermore, the foregoing Description and Examples are exemplary of the present invention and not limiting thereof. The scope of the invention is therefore set out in the appended claims.

[678] Although specific embodiments of the present disclosure are herein illustrated and described in detail, the disclosure is not limited thereto. The above detailed descriptions are provided as exemplary of the present disclosure and should not be construed as constituting any limitation of the disclosure. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the disclosure are intended to be included with the scope of the appended claims.

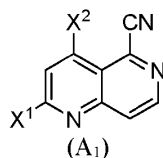
CLAIMS

What is claimed is:

1. A process for preparing Compound I:



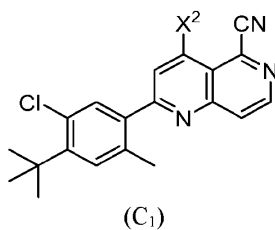
comprising transforming a compound of formula (A₁):



to Compound I;

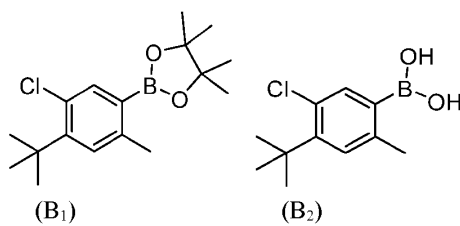
wherein each of X¹ and X² are independently selected from halogen.

2. The process of claim 1, wherein transforming the compound of formula (A₁) to Compound I comprises transforming the compound of formula (A₁) to a compound of formula (C₁):

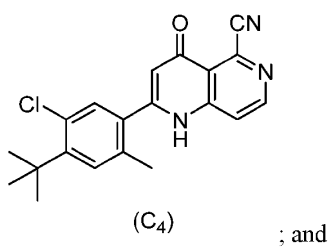


and transforming the compound of formula (C₁) to Compound I.

3. The process of claim 2, wherein transforming the compound of formula (A₁) to the compound of formula (C₁) comprises contacting the compound of formula (A₁) with a compound of formula (B₁) or (B₂):

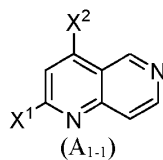


4. The process of claim 2 or 3, wherein transforming the compound of formula (C₁) to Compound I comprises transforming the compound of formula (C₁) to a compound of formula (C₄):



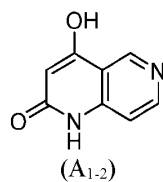
transforming the compound of formula (C₄) to Compound I.

5. The process of any one of claims 1 to 4, further comprising transforming a compound of formula (A₁₋₁):



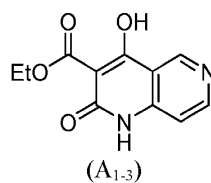
to the compound of formula (A₁).

6. The process of claim 5, further comprising transforming a compound of formula (A₁₋₂):



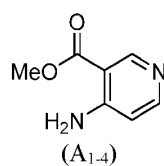
to the compound of formula (A₁₋₁).

7. The process of claim 6, further comprising transforming a compound of formula (A₁₋₃):



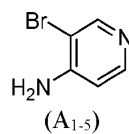
to the compound of formula (A_{1.2}).

8. The process of claim 7, further comprising transforming a compound of formula (A_{1.4}):



to the compound of formula (A_{1.3}).

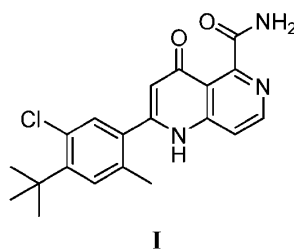
9. The process of claim 8, further comprising transforming a compound of formula (A_{1.5}):



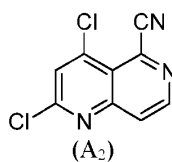
to the compound of formula (A_{1.4}).

10. The process of any one of claims 1 to 9, wherein X₁ and X₂ are both chloro.

11. A process for preparing Compound I:

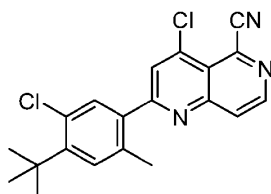


comprising transforming a compound of formula (A₂):



to Compound I.

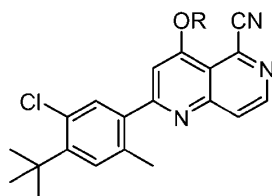
12. The process of claim 11, wherein the step of transforming the compound of formula (A₂) to Compound I comprises transforming the compound of formula (A₂) to a compound of formula (C₂):



(C₂) ; and

transforming the compound of formula (C₂) to Compound I.

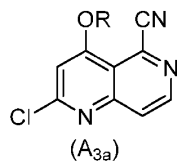
13. The process of claim 12, wherein the step of transforming the compound of formula (C₂) to Compound I comprises transforming the compound of formula (C₂) to a compound of formula (C_{3a}):



(C_{3a}) ;

wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{3a}) to Compound I.

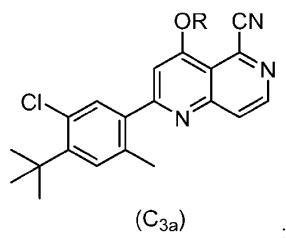
14. The process of claim 11, wherein the step of the step of transforming the compound of formula (A₂) to Compound I comprises transforming the compound of formula (A₂) to a compound of formula (A_{3a}):



(A_{3a}) ;

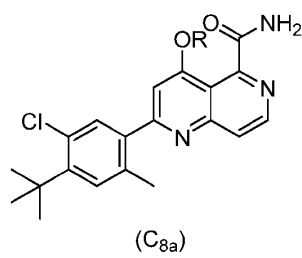
wherein R is C₁-C₆ alkyl; and transforming the compound of formula (A_{3a}) to Compound I.

15. The process of claim 14, wherein the step of transforming the compound of formula (A_{3a}) to Compound I comprises transforming the compound of formula (A_{3a}) to a compound of formula (C_{3a}):



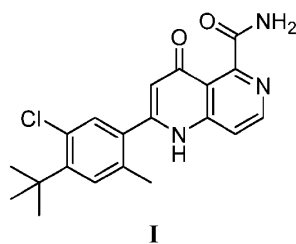
wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{3a}) to Compound I.

16. The process of claim 13 or 15, wherein the step of transforming the compound of formula (C_{3a}) to Compound I comprises transforming the compound of formula (C_{3a}) to a compound of formula (C_{8a}):

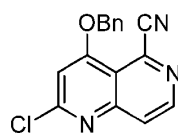


wherein R is C₁-C₆ alkyl; and transforming the compound of formula (C_{8a}) to Compound I.

17. A process for preparing Compound I:



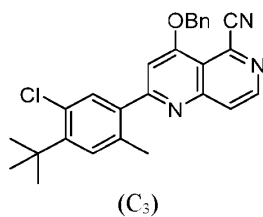
comprising transforming a compound of formula (A₃):



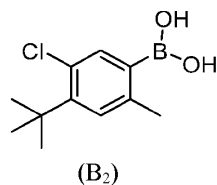
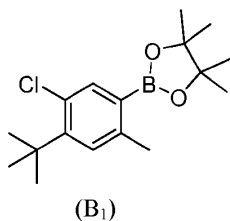
(A₃)

to Compound I.

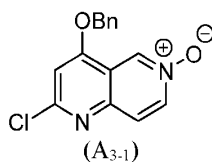
18. The process of claim 17, wherein transforming the compound of formula (A₃) to Compound I comprises transforming the compound of formula (A₃) to a compound of formula (C₃):

and transforming the compound of formula (C₃) to Compound I.

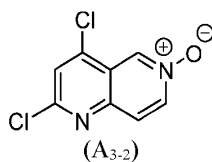
19. The process of claim 18, wherein transforming the compound of formula (A₃) to the compound of formula (C₃) comprises contacting the compound of formula (A₃) with a compound of formula (B₁) or (B₂):



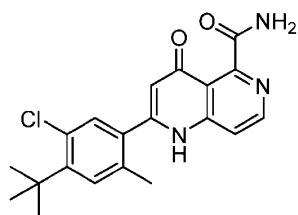
20. The process of any one of claims 17 to 19, further comprising transforming a compound of formula (A₃₋₁):

to the compound of formula (A₃).

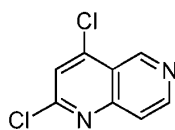
21. The process of claim 20, further comprising transforming a compound of formula (A₃₋₂):

to the compound of formula (A₃₋₁).

22. A process for preparing Compound I:

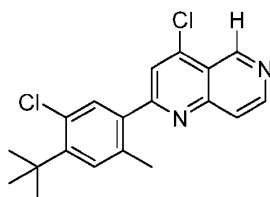
**I**

comprising transforming a compound of formula (A₂₋₁):

(A₂₋₁)

to Compound **I**.

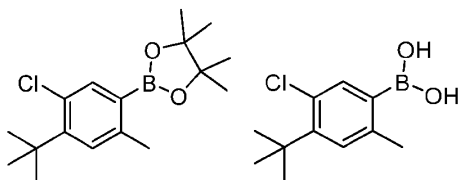
23. The process of claim 22, wherein the step of transforming the compound of formula (A₂₋₁) to Compound **I** comprises transforming the compound of formula (A₂₋₁) to a compound of formula (C₅):

(C₅)

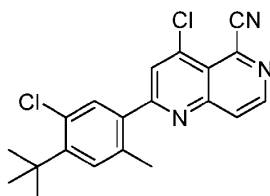
; and

transforming the compound of formula (C₅) to Compound **I**.

24. The process of claim 23, wherein transforming the compound of formula (A₂₋₁) to the compound of formula (C₅) comprises treating the compound of formula (A₂₋₁) with a compound of formula (B₁) or (B₂):

(B₁)(B₂)

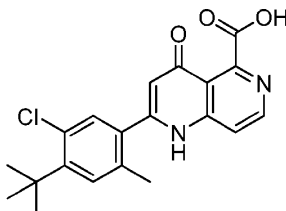
25. The process of claim 23 or 24, wherein the step of transforming the compound of formula (C₅) to Compound I comprises transforming the compound of formula (C₅) to a compound of formula (C₂):



(C₂) ; and

transforming the compound of formula (C₂) to Compound I.

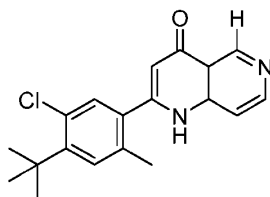
26. The process of claim 25, wherein the step of transforming the compound of formula (C₂) to Compound I comprises transforming the compound of formula (C₂) to a compound of formula (C₇):



(C₇) ; and

transforming the compound of formula (C₇) to Compound I.

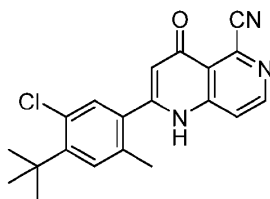
27. The process of claim 23 or 24, wherein the step of transforming the compound of formula (C₅) to Compound I comprises transforming the compound of formula (C₅) to a compound of formula (C₆):



(C₆) ; and

transforming the compound of formula (C₆) to Compound I.

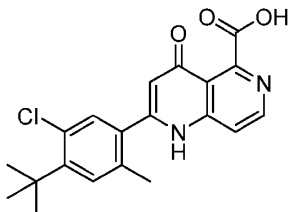
28. The process of claim 27, wherein the step of transforming the compound of formula (C₆) to Compound I comprises transforming the compound of formula (C₆) to a compound of formula (C₄):

(C₄)

; and

transforming the compound of formula (C₄) to Compound I.

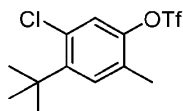
29. The process of claim 28, wherein the step of transforming the compound of formula (C₄) to Compound I comprises transforming the compound of formula (C₄) to a compound of formula (C₇):

(C₇)

; and

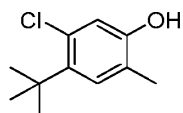
transforming the compound of formula (C₇) to Compound I.

30. The process of any one of claims 3 to 10, 19 to 21, and 24 to 29, further comprising transforming a compound of formula (B₁₋₁):

(B₁₋₁)

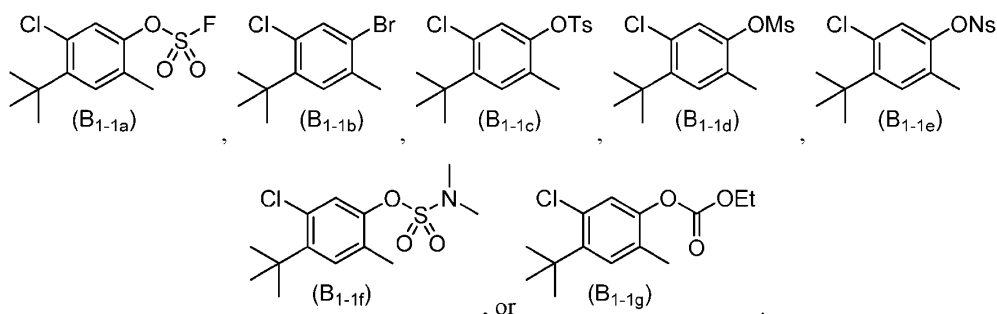
to the compound of formula (B₁).

31. The process of claim 30, further comprising transforming a compound of formula (B₁₋₂):

(B₁₋₂)

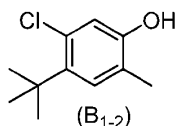
to the compound of formula (B₁₋₁).

32. The process of any one of claims 3 to 10, 19 to 21, and 24 to 29, further comprising transforming a compound of formula (B_{1-1a}), (B_{1-1b}), (B_{1-1c}), (B_{1-1d}), (B_{1-1e}), (B_{1-1f}), or (B_{1-1g}):



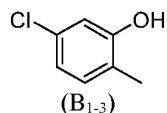
to the compound of formula (B₁).

33. The process of claim 32, further comprising transforming a compound of formula (B₁₋₂):



to the compound of formula (B_{1-1a}), (B_{1-1b}), (B_{1-1c}), (B_{1-1d}), (B_{1-1e}), (B_{1-1f}), or (B_{1-1g}).

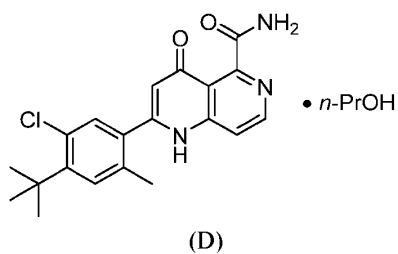
34. The process of claim 31 or 33, further comprising transforming a compound of formula (B₁₋₃):



to the compound of formula (B₁₋₂).

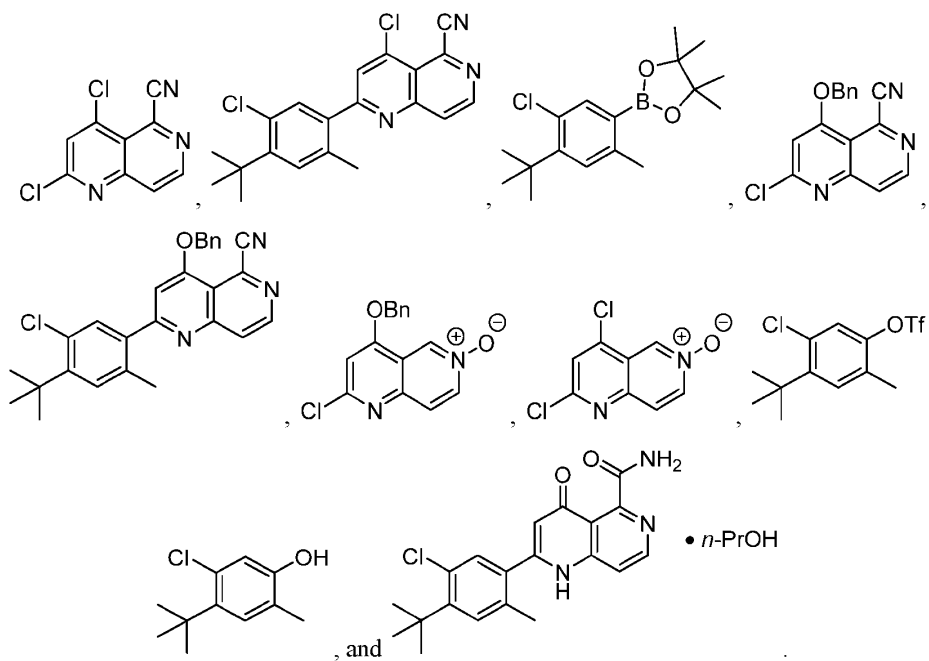
35. The process of any one of claims 1 to 34, further comprising transforming Compound I to a solvate of Compound I.

36. The process of claim 35, wherein the solvate of the compound of formula (I) is a compound of formula (D):

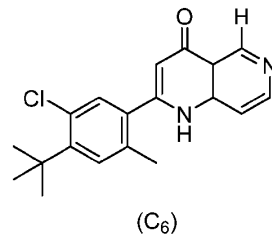
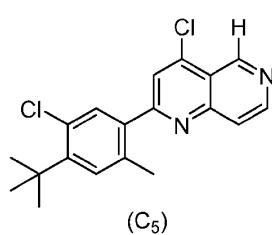
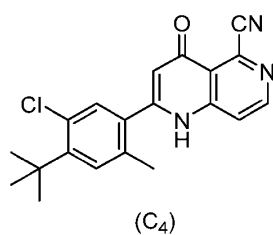
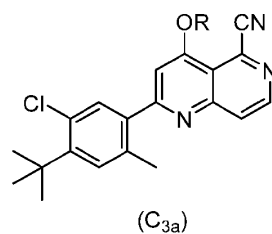
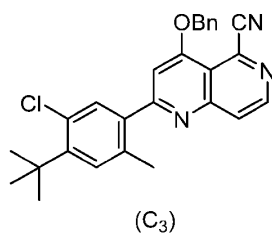
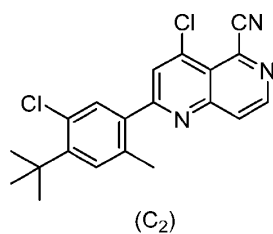


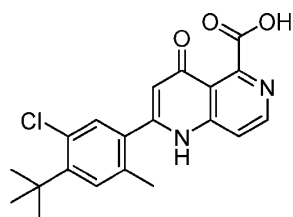
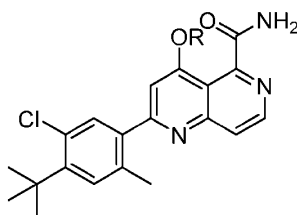
37. The process of claim 35 or 36, further comprising transforming the solvate of Compound I to Form A of Compound I.

38. A compound selected from:



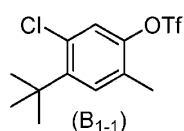
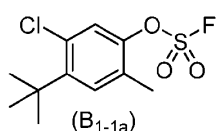
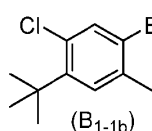
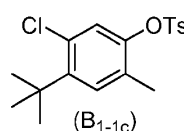
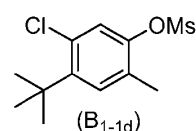
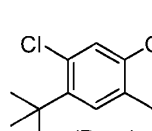
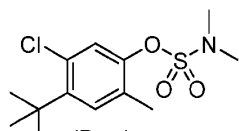
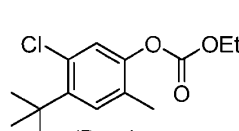
39. A compound selected from:



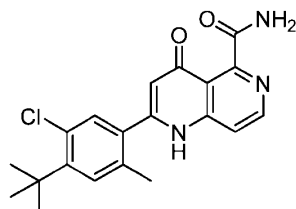
(C₇)(C_{8a})

, and , wherein R is C₁-C₆ alkyl. In some embodiments, R is ethyl, isopropyl, *tert*-amyl, or *tert*-butyl.

40. A compound selected from:

(B₁₋₁)(B_{1-1a})(B_{1-1b})(B_{1-1c})(B_{1-1d})(B_{1-1e})(B_{1-1f})(B_{1-1g})

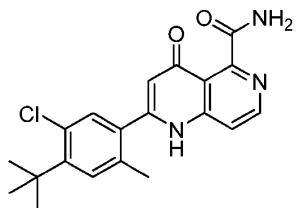
41. Compound I:



I

prepared by the process of any one of claims 1 to 34.

42. A substantially crystalline Compound I



I

wherein the substantially crystalline Compound I is selected from Compound I Neat Form A, Compound I Neat Form B, Compound I Neat Form C, Compound I hemi-hydrate, Compound I monohydrate, Compound I methanol solvate, Compound I nPA solvate mixture A, Compound I nPA solvate B, Compound I nPA solvate C, Compound I Na hemi salt nPA solvate, Compound I nPA solvate J, Compound I 2-Me THF Solvate A, Compound I 2-Me THF Solvate Mixture A, Compound I 2-Me THF Mixture C, Compound I mandelic acid cocrystal, Compound I DL-oxalic acid cocrystal, and Compound I TFA Salt A.

43. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I Neat Form A, optionally wherein Compound I Neat Form A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.5 ± 0.2 degrees two-theta, 9.0 ± 0.2 degrees two-theta, and 10.4 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 8**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.6 ± 0.2 ppm, 178.7 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.6 ± 0.2 ppm, 169.7 ± 0.2 ppm, 168.2 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.8 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.3 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.7 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 129.7 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 113.3 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.2 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.5 ± 0.2 ppm, and 20.4 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.8 ± 0.2 ppm, 177.5 ± 0.2 ppm, 174.7 ± 0.2 ppm, 168.3 ± 0.2 ppm, 156.0 ± 0.2 ppm, 153.1 ± 0.2 ppm, 152.4 ± 0.2 ppm, 150.9 ± 0.2 ppm, 149.4 ± 0.2 ppm, 148.3 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 144.8 ± 0.2 ppm, 135.7 ± 0.2 ppm, 134.6 ± 0.2 ppm, 132.8 ± 0.2 ppm, 130.9 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.5 ± 0.2 ppm, 36.4 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.7 ± 0.2 ppm, and 20.5 ± 0.2 ppm; and/or

(e) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 179.7 ± 0.2 ppm, 178.8 ± 0.2 ppm, 177.6 ± 0.2 ppm, 174.8 ± 0.2 ppm, 169.8 ± 0.2 ppm, 168.3 ± 0.2 ppm, 155.9 ± 0.2 ppm, 154.9 ± 0.2 ppm, 153.0 ± 0.2 ppm, 152.4 ± 0.2 ppm, 151.1 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.8 ± 0.2 ppm, 145.7 ± 0.2 ppm, 144.7 ± 0.2 ppm, 135.6 ± 0.2 ppm, 135.0

± 0.2 ppm, 132.8 ± 0.2 ppm, 131.0 ± 0.2 ppm, 116.3 ± 0.2 ppm, 115.1 ± 0.2 ppm, 113.5 ± 0.2 ppm, 111.4 , 36.3 ± 0.2 ppm, 30.3 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 20.5 ± 0.2 ppm; and/or

(f) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9A**; and/or

(g) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (bottom trace); and/or

(h) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (middle trace); and/or

(i) a ^{13}C SSNMR spectrum substantially similar to **FIG. 9B** (top trace); and/or

(j) a triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	11.0 ± 0.1 Å	α	$98.0 \pm 0.1^{\circ}$
b	11.2 ± 0.1 Å	β	$93.1 \pm 0.1^{\circ}$
c	15.9 ± 0.1 Å	γ	$95.8 \pm 0.1^{\circ}$

44. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I Neat Form B, optionally wherein Compound I Neat Form B is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.5 ± 0.2 degrees two-theta, and 9.8 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 10**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm, 176.6 ± 0.2 ppm, 174.4 ± 0.2 ppm, 169.7 ± 0.2 ppm, 157.5 ± 0.2 ppm, 152.8 ± 0.2 ppm, 151.6 ± 0.2 ppm, 150.2 ± 0.2 ppm, 149.4 ± 0.2 ppm, 147.5 ± 0.2 ppm, 145.2 ± 0.2 ppm, 134.5 ± 0.2 ppm, 133.8 ± 0.2 ppm, 133.4 ± 0.2 ppm, 132.4 ± 0.2 ppm, 131.1 ± 0.2 ppm, 130.6 ± 0.2 ppm, 115.5 ± 0.2 ppm, 114.2 ± 0.2 ppm, 113.9 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 30.9 ± 0.2 ppm, 29.1 ± 0.2 ppm, 19.8 ± 0.2 ppm, and 18.1 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 11**; and/or

(e) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	11.1 ± 0.1 Å	α	$87.6 \pm 0.1^{\circ}$
---	------------------	----------	------------------------

b	$11.5 \pm 0.1 \text{ \AA}$	β	$88.2 \pm 0.1^\circ$
c	$15.0 \pm 0.1 \text{ \AA}$	γ	$88.9 \pm 0.1^\circ$

45. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I Neat Form C, optionally wherein Compound I Neat Form C is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.0 ± 0.2 degrees two-theta, 13.9 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 12**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.9 ± 0.2 ppm, 176.5 ± 0.2 ppm, 173.9 ± 0.2 ppm, 169.3 ± 0.2 ppm, 157.8 ± 0.2 ppm, 153.9 ± 0.2 ppm, 151.5 ± 0.2 ppm, 149.8 ± 0.2 ppm, 148.4 ± 0.2 ppm, 147.8 ± 0.2 ppm, 145.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.5 ± 0.2 ppm, 133.0 ± 0.2 ppm, 131.3 ± 0.2 ppm, 130.4 ± 0.2 ppm, 115.6 ± 0.2 ppm, 115.4 ± 0.2 ppm, 114.5 ± 0.2 ppm, 114.1 ± 0.2 ppm, 111.4 ± 0.2 ppm, 36.5 ± 0.2 ppm, 36.3 ± 0.2 ppm, 31.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 20.9 ± 0.2 ppm, and 17.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 13**; and/or

(e) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178 \text{ \AA}$) of:

a	$11.3 \pm 0.1 \text{ \AA}$	α	$84.3 \pm 0.1^\circ$
b	$11.5 \pm 0.1 \text{ \AA}$	β	$68.8 \pm 0.1^\circ$
c	$15.2 \pm 0.1 \text{ \AA}$	γ	$89.0 \pm 0.1^\circ$

and/or

(f) a triclinic crystal system, a P-1 space group, and unit cell dimensions measured at 298K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178 \text{ \AA}$) of:

a	$11.4 \pm 0.1 \text{ \AA}$	α	$84.2 \pm 0.1^\circ$
b	$11.6 \pm 0.1 \text{ \AA}$	β	$69.6 \pm 0.1^\circ$
c	$15.3 \pm 0.1 \text{ \AA}$	γ	$88.9 \pm 0.1^\circ$

46. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I hemi-hydrate, optionally wherein Compound I hemi-hydrate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.1 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 12.3 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 14**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.1 ± 0.2 ppm, 169.2 ± 0.2 ppm, 155.4 ± 0.2 ppm, 154.0 ± 0.2 ppm, 147.7 ± 0.2 ppm, 146.4 ± 0.2 ppm, 137.6 ± 0.2 ppm, 137.0 ± 0.2 ppm, 133.4 ± 0.2 ppm, 129.0 ± 0.2 ppm, 127.2 ± 0.2 ppm, 116.7 ± 0.2 ppm, 115.6 ± 0.2 ppm, 113.0 ± 0.2 ppm, 35.4 ± 0.2 ppm, 29.6 ± 0.2 ppm, and 21.1 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 15**.

47. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** monohydrate, optionally wherein Compound **I** monohydrate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.0 ± 0.2 degrees two-theta, 10.2 ± 0.2 degrees two-theta, and 14.2 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 16**.

48. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** methanol solvate, optionally wherein Compound **I** methanol solvate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 8.4 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 17**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.3 ± 0.2 ppm, 177.4 ± 0.2 ppm, 172.8 ± 0.2 ppm, 170.3 ± 0.2 ppm, 156.9 ± 0.2 ppm, 154.1 ± 0.2 ppm, 151.9 ± 0.2 ppm, 150.0 ± 0.2 ppm, 149.2 ± 0.2 ppm, 147.8 ± 0.2 ppm, 146.4 ± 0.2 ppm, 135.0 ± 0.2 ppm, 134.0 ± 0.2 ppm, 132.9 ± 0.2 ppm, 131.5 ± 0.2 ppm, 129.6 ± 0.2 ppm, 116.2 ± 0.2 ppm, 115.0 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.0 ± 0.2 ppm, 49.5 ± 0.2 ppm, 49.3 ± 0.2 ppm, 49.0 ± 0.2 ppm, 36.4 ± 0.2 ppm, 35.3 ± 0.2 ppm, 30.2 ± 0.2 ppm, 28.2 ± 0.2 ppm, 19.1 ± 0.2 ppm, and 18.8 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 18**; and/or

(e) a triclinic crystal system, P-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178$ Å) of:

a	12.3 ± 0.1 Å	α	$100.4 \pm 0.1^\circ$
b	14.1 ± 0.1 Å	β	$105.3 \pm 0.1^\circ$
c	14.4 ± 0.1 Å	γ	$107.5 \pm 0.1^\circ$

49. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** nPA solvate mixture A, optionally wherein Compound **I** nPA solvate mixture A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 19**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, 20.7 ± 0.2 ppm, and 11.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 20**; and/or

(e) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 176.5 ± 0.2 ppm, 175.2 ± 0.2 ppm, 171.8 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.2 ± 0.2 ppm, 150.1 ± 0.2 ppm, 147.6 ± 0.2 ppm, 144.9 ± 0.2 ppm, 143.5 ± 0.2 ppm, 142.2 ± 0.2 ppm, 135.5 ± 0.2 ppm, 134.5 ± 0.2 ppm, 132.6 ± 0.2 ppm, 131.1 ± 0.2 ppm, 117.0 ± 0.2 ppm, 113.6 ± 0.2 ppm, 112.1 ± 0.2 ppm, 64.3 ± 0.2 ppm, 63.9 ± 0.2 ppm, 36.5 ± 0.2 ppm, 29.9 ± 0.2 ppm, 25.9 ± 0.2 ppm, 24.9 ± 0.2 ppm, 20.9 ± 0.2 ppm, 13.4 ± 0.2 ppm, and 11.7 ± 0.2 ppm; and/or

(f) a ^{13}C SSNMR spectrum substantially similar to **FIG. 21**; and/or

(g) a monoclinic crystal system, $C2/c$ space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K α radiation ($\lambda=1.54178$ Å) of:

a	19.9 ± 0.1 Å	α	90
b	6.9 ± 0.1 Å	β	$93.9 \pm 0.1^\circ$
c	32.6 ± 0.1 Å	γ	90

50. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** nPA solvate B, optionally wherein Compound **I** nPA solvate B is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 8.8 ± 0.2 degrees two-theta, and 10.6 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 22**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 175.2 ± 0.2 ppm, 172.3 ± 0.2 ppm, 155.1 ± 0.2 ppm, 149.7 ± 0.2 ppm, 147.2 ± 0.2 ppm, 145.3 ± 0.2 ppm, 143.5 ± 0.2 ppm, 135.3 ± 0.2 ppm, 134.7 ± 0.2 ppm, 132.6 ± 0.2 ppm, 130.9 ± 0.2 ppm, 117.1 ± 0.2 ppm, 112.9 ± 0.2 ppm, 64.3 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.4 ± 0.2 ppm, 24.8 ± 0.2 ppm, and 20.7 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 23**; and/or

(e) a triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K $_{\alpha}$ radiation ($\lambda=1.54178$ Å) of:

a	6.8 ± 0.1 Å	α	$93.8 \pm 0.1^{\circ}$
b	10.5 ± 0.1 Å	β	$92.9 \pm 0.1^{\circ}$
c	16.4 ± 0.1 Å	γ	$105.8 \pm 0.1^{\circ}$

51. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** nPA solvate C, optionally wherein Compound **I** nPA solvate C is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.1 ± 0.2 degrees two-theta, 11.8 ± 0.2 degrees two-theta, and 12.2 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 24**.

52. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** Na hemi salt nPA solvate, optionally wherein Compound **I** Na hemi salt nPA solvate is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 6.7 ± 0.2 degrees two-theta, 14.1 ± 0.2 degrees two-theta, and 14.9 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 25**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 178.0 ± 0.2 ppm, 176.8 ± 0.2 ppm, 175.7 ± 0.2 ppm, 174.2 ± 0.2 ppm, 161.9 ± 0.2 ppm, 152.1 ± 0.2 ppm, 151.1 ± 0.2 ppm, 150.4 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 144.6 ± 0.2 ppm, 142.6 ± 0.2 ppm, 135.4 ± 0.2 ppm, 134.4 ± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.5 ± 0.2 ppm, 119.6 ± 0.2 ppm, 118.8 ± 0.2 ppm, 115.9 ± 0.2 ppm, 114.4 ± 0.2 ppm, 114.0 ± 0.2 ppm, 111.6 ± 0.2 ppm, 65.1 ± 0.2 ppm, 62.6 ± 0.2 ppm, 36.5 ± 0.2 ppm, 30.7 ± 0.2 ppm, 26.2 ± 0.2 ppm, 24.8 ± 0.2 ppm, 21.4 ± 0.2 ppm, and 20.8 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 26**; and/or

(e) triclinic crystal system, *P*-1 space group, and unit cell dimensions measured at 100K on a diffractometer utilizing Cu K_α radiation ($\lambda=1.54178 \text{ \AA}$) of:

a	$10.3 \pm 0.1 \text{ \AA}$	α	$94.2 \pm 0.1^\circ$
b	$13.3 \pm 0.1 \text{ \AA}$	β	$91.0 \pm 0.1^\circ$
c	$16.7 \pm 0.1 \text{ \AA}$	γ	$104.0 \pm 0.1^\circ$

53. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** nPA solvate J, optionally wherein Compound **I** nPA solvate J is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.3 ± 0.2 degrees two-theta, 10.4 ± 0.2 degrees two-theta, and 19.0 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 27**.

54. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** 2-Me THF Solvate A, optionally wherein Compound **I** 2-Me THF Solvate A is characterized by:

(a) an X-ray powder diffractogram having one, two, or three signals selected from 5.8 ± 0.2 degrees two-theta, 9.4 ± 0.2 degrees two-theta, and 14.0 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 28**.

55. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I 2-Me THF Solvate Mixture A, optionally wherein Compound I 2-Me THF Solvate Mixture A is characterized by:

- (a) an X-ray powder diffractogram having a signal at 4.6 ± 0.2 degrees two-theta; and/or
- (b) an X-ray powder diffractogram substantially similar to **FIG. 29**.

56. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I 2-Me THF Mixture C, optionally wherein Compound I 2-Me THF Mixture C is characterized by:

- (a) an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta; and/or
- (b) an X-ray powder diffractogram substantially similar to **FIG. 30**.

57. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I mandelic acid cocrystal, optionally wherein Compound I mandelic acid cocrystal is characterized by:

- (a) an X-ray powder diffractogram having one, two, or three signals selected from 6.6 ± 0.2 degrees two-theta, 10.6 ± 0.2 degrees two-theta, and 21.1 ± 0.2 degrees two-theta; and/or
- (b) an X-ray powder diffractogram substantially similar to **FIG. 31**.

58. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound I is Compound I DL-oxalic acid cocrystal, optionally wherein Compound I DL-oxalic acid cocrystal is characterized by:

- (a) an X-ray powder diffractogram having one, two, or three signals selected from 8.9 ± 0.2 degrees two-theta, 11.6 ± 0.2 degrees two-theta, and 14.5 ± 0.2 degrees two-theta; and/or
- (b) an X-ray powder diffractogram substantially similar to **FIG. 32**; and/or
- (c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 177.5 ± 0.2 ppm, 169.8 ± 0.2 ppm, 169.5 ± 0.2 ppm, 162.4 ± 0.2 ppm, 161.5 ± 0.2 ppm, 154.3 ± 0.2 ppm, 153.7 ± 0.2 ppm, 149.3 ± 0.2 ppm, 148.0 ± 0.2 ppm, 146.4 ± 0.2 ppm, 146.1 ± 0.2 ppm, 134.9

± 0.2 ppm, 133.0 ± 0.2 ppm, 132.0 ± 0.2 ppm, 130.9 ± 0.2 ppm, 130.0 ± 0.2 ppm, 128.1 ± 0.2 ppm, 117.7 ± 0.2 ppm, 114.6 ± 0.2 ppm, 112.4 ± 0.2 ppm, 36.3 ± 0.2 ppm, 29.3 ± 0.2 ppm, and 17.9 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 33**.

59. The substantially crystalline Compound according to claim 42, where the substantially crystalline Compound **I** is Compound **I** TFA Salt A, optionally wherein Compound **I** TFA Salt A is characterized by:

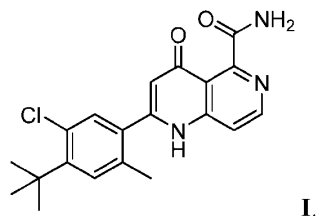
(a) an X-ray powder diffractogram having one, two, or three signals selected from 8.4 ± 0.2 degrees two-theta, 15.1 ± 0.2 degrees two-theta, and 19.7 ± 0.2 degrees two-theta; and/or

(b) an X-ray powder diffractogram substantially similar to **FIG. 34**; and/or

(c) a ^{13}C SSNMR spectrum having one, two, three, four, five, six, seven, eight, nine, ten, or more peaks selected from 171.9 ± 0.2 ppm, 169.2 ± 0.2 ppm, 160.7 ± 0.2 ppm, 159.5 ± 0.2 ppm, 149.1 ± 0.2 ppm, 147.4 ± 0.2 ppm, 146.8 ± 0.2 ppm, 136.1 ± 0.2 ppm, 133.7 ± 0.2 ppm, 132.1 ± 0.2 ppm, 131.0 ± 0.2 ppm, 118.1 ± 0.2 ppm, 116.0 ± 0.2 ppm, 113.0 ± 0.2 ppm, 36.6 ± 0.2 ppm, 31.3 ± 0.2 ppm, and 18.4 ± 0.2 ppm; and/or

(d) a ^{13}C SSNMR spectrum substantially similar to **FIG. 35**.

60. An amorphous Compound **I**



61. A pharmaceutical composition comprising the substantially crystalline Compound **I** according to any one of claims 42 to 59 or the amorphous Compound **I** according to claim 60.

62. The substantially crystalline Compound **I** according to any one of claims 42 to 59, the amorphous Compound **I** according to claim 60, or the pharmaceutical composition according to claim 61, for use in treating or lessening the severity in a subject of pain, optionally wherein the pain comprises chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

63. Use of the substantially crystalline Compound I according to any one of claims 42 to 59, the amorphous Compound I according to claim 60, or the pharmaceutical composition according to claim 61, in the manufacture of a medicament for treating or lessening the severity in a subject of pain.

64. A method of treating or lessening the severity in a subject of pain comprising administering the substantially crystalline Compound I according to any one of claims 42 to 59, the amorphous Compound I according to claim 60, or the pharmaceutical composition according to claim 61, to the subject.

65. A method of preparing a solid form of Compound I, comprising:

(a) (i) suspending Compound I amorphous material in methanol, (ii) shaking at room temperature for 1 hour, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Neat Form A;

(b) (i) suspending Amorphous Compound I in nitromethane to form a mixture, (ii) agitating the mixture at room temperature for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form B;

(c) (i) suspending Compound I Neat Form A in 2-MeTHF to form a mixture, (ii) stirring the mixture at about 20 °C for about 1 hour, (iii) isolating the solids from the mixture, and (iv) drying the solids in an oven for about 72 hours to afford Compound I Neat Form C;

(d) (i) suspending Compound I in water, (ii) shaking at 40 °C for at least 1 week, at least 2 weeks, at least three weeks, or at least 4 weeks, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Hemi-Hydrate;

(e) (i) suspending Compound I in water, (ii) shaking at 40 °C for no more than 48 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I Monohydrate;

(f) (i) suspending Compound I amorphous material in methanol, (ii) shaking at 40 °C for 1 hour, and (iii) collecting the solids to afford Compound I Methanol Solvate;

(g) (i) suspending Compound I nPA Solvate B and NaTFA in nPA, (ii) mixing at room temperature for 6-18 hours, (iii) collecting the solids, and (iv) air-drying for 15-45 minutes to afford Compound I nPA Solvate Mixture A;

(h) (i) suspending Compound I nPA amorphous material in nPA, (ii) mixing at room temperature for 18-30 hours, (iii) collecting the solids, and (iv) drying under vacuum at 40 °C to afford Compound I nPA Solvate B;

(i) (i) dissolving Compound I in nPA, (ii) mixing at 90-100 °C for 1-2 hours, (iii) mixing at room temperature for 6-30 hours, and (iv) collecting the solids to afford Compound I nPA Solvate C;

(j) (i) treating 2-(4-(tert-butyl)-5-chloro-2-methylphenyl)-4-chloro-1,6-naphthyridine-5-carbonitrile with water and TFA, (ii) mixing at 60 °C for 18-30 hours, (iii) treating the mixture with water and sodium hydroxide at room temperature, (iv) washing the mixture with aqueous sodium chloride, (v) diluting the mixture with 2-MeTHF and subsequently concentrating, (vi) treating the mixture with nPA and subsequently concentrating, (vii) heating the mixture to 90 °C and subsequently holding the mixture at 50 °C for 6-18 hours, (viii) cooling the mixture to room temperature, (ix) collecting the solids, and (s) drying under vacuum at 40 °C for 6-18 hours to afford Compound I Na Hemi Salt nPA Solvate;

(k) (i) treating a mixture of Compound I and 2-MeTHF with nPA, (ii) concentrating the mixture at 20-30 °C, (iii) treating the mixture with nPA and subsequently concentrating the mixture at 20-30 °C, (iv) heating the mixture to 80-100 °, (v) cooling the mixture to room temperature over 8-16 hours, (v) collecting the solids, and (vi) drying under vacuum at 45 °C to afford Compound I nPA Solvate J;

(l) (i) treating Compound I Form A with 2-MeTHF, (ii) agitating the mixture for 24 hours at about 22 °C, and (iii) isolating the solids to afford Compound I 2-MeTHF Solvate A;

(m) (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I 2-MeTHF Solvate Mixture A;

(n) (i) obtaining a solution of Compound I in 2-MeTHF, (ii) concentrating the solution to obtain a slurry, (iii) warming the slurry to 90 °C to dissolve solids, (iv) cooling to 25 °C, (v) collecting the solids, and (iv) drying at 50 °C to afford Compound I 2-MeTHF Solvate Mixture C;

(o) (i) combining Compound I and Mandelic acid, (ii) diluting the mixture in DCM, (iii) agitating the mixture for at least 1 hour, (iv) collecting the resulting solid material, and (v) drying the collected solid material in a vacuum oven at 50 °C to afford Compound I Mandelic Acid Cocrystal;

(p) (i) suspending Compound I and oxalic acid (1:1) in DCM, (ii) stirring the resulting slurry at room temperature, (iii) collecting the solids, and (iv) drying under vacuum at 50 °C to afford Compound I Oxalic Acid Cocrystal;

(q) (i) suspending Compound I in DCM, (ii) treating the suspension with TFA, (iii) stirring at room temperature for 15-45 minutes, (iv) collecting the solids, and (v) drying at room temperature to afford Compound I TFA Salt A; or

(r) (i) combining Compound I and t-butanol to form a mixture, (ii) stirring the mixture at about 70 °C for about 1 hour, (iii) adding water to the mixture, (iv) freezing the mixture, and (v) isolating the solid material to afford Amorphous Compound I.